STRUCTURE & REACTIVITY III: REACTIVITY IN ORGANIC, BIOLOGICAL AND INORGANIC CHEMISTRY

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CHAPTER OVERVIEW

1: Thermodynamics

1.1: Introduction

We use energy every day. We plug in our electronic devices, drawing energy that has been converted into electricity, but which originated in a waterfall on a spinning turbine, a wind that turned a windmill, the burning of coal to produce carbon dioxide, a nuclear reaction, or other sources. We drive cars, in which the energy released from a chemical reaction heats gas in a chamber, pushing a piston which drives a crankshaft that ultimately causes the wheels to turn.

Many of our sources of energy depend on chemical processes. Solar power, for example, depends on photochemistry. When a photon from the sun is absorbed by an atom of the right kind of material, an electron hops from one energy level to a higher one. That event leaves behind a "hole", a place where an electron used to be. An electron might move in from a neighbouring atom to occupy that hole. Now the original electron can't fall back to where it came from; it will instead need to drop into a hole on the next atom. We now have electrons moving from one atom to the next. We have electricity.

The burning of gasoline and coal depends on expanding gases which push against a turbine, like wind against a windmill. The gases expand because they get hotter when the combustion, or burning, reaction happens. But why do these reactions produce heat? That's related to the formation of chemical bonds. When chemical bonds are formed, energy is released.

- The formation of a chemical bond always releases energy.

Over the course of a chemical reaction, old bonds are frequently broken and new ones are frequently made. But if energy is always released when bonds are formed, what happens when a bond is broken? When a bond is broken, energy is consumed. It costs energy to break a bond, but the formation of a new bond pays some energy back.

- Breaking a chemical bond always costs energy.

So, if breaking bonds costs energy, and making bonds pays energy, and energy becomes heat, then a reaction will only produce heat if the energy released when the bonds are made is more than the energy consumed when bonds were broken. We need to replace weaker bonds with stronger ones.

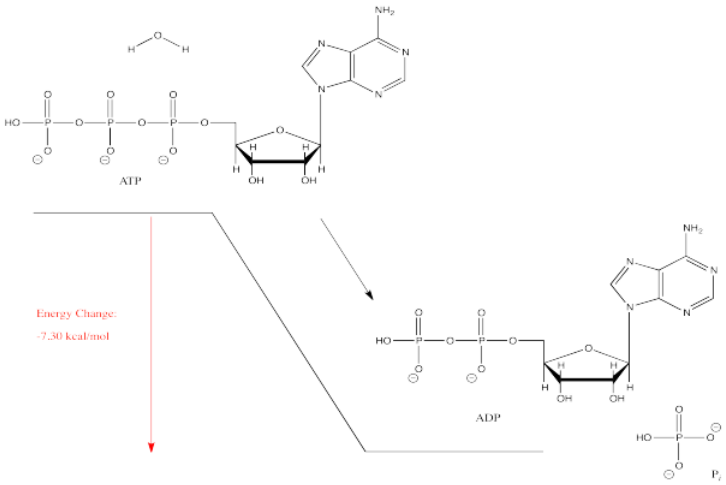
Burning carbon-containing compounds, like wood, coal, or gasoline, is a fantastic way to release energy and make heat. Our ancestors have known that since the stone age. Carbon-containing compounds generally contains lots of carbon-carbon and carbon-hydrogen bonds (which are actually quite strong). When burned, they produce carbon dioxide and water, which contain carbon-oxygen and hydrogen-oxygen bonds, and those bonds are *even stronger than* the carbon-hydrogen and carbon-carbon bonds that were broke. Overall, energy is released.

We can use that energy to warm ourselves on a cold night under the stars, to cook our food, to drive a mill that manufactures steel, or to fly an airplane. We can use that energy to get work done.

Thermodynamics is the study of the relationship between heat (or energy) and work. In other words, thermodynamics looks at how we can put energy into a system (whether it is a machine or a molecule) and make it do work. Alternatively, we might be able to do some work on a system and make it produce energy (like spinning the turbines in a power station to produce electricity).

In chemistry, we sometimes speak more broadly about "energetics" of reactions (rather than thermodynamics), because energy given off during a reaction may simply be lost to the surroundings without doing useful work. Nevertheless, the ideas are the same: energy can be added to a set of molecules in order to produce a reaction, or a reaction can occur between a set of molecules in order to release energy.

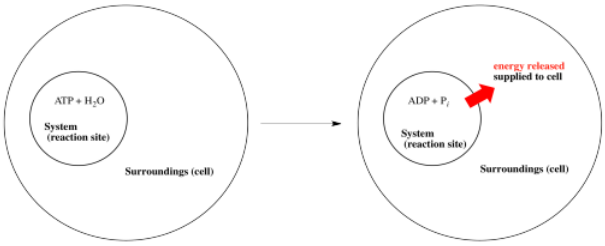
A classic example of reaction energetics is the hydrolysis of ATP to ADP in biology. This reaction is used in the cell as a source of energy; the energy released from the reaction is frequently coupled to other processes that could not occur without the added energy.



The hydrolysis of ATP, or the addition of water to ATP in order to break ATP into two, smaller molecules, gives off energy. That energy can be used by the cell to carry out other processes that would cost energy. One molecule of ADP and one molecule of inorganic phosphate, sometimes abbreviated as P_i, are also produced.

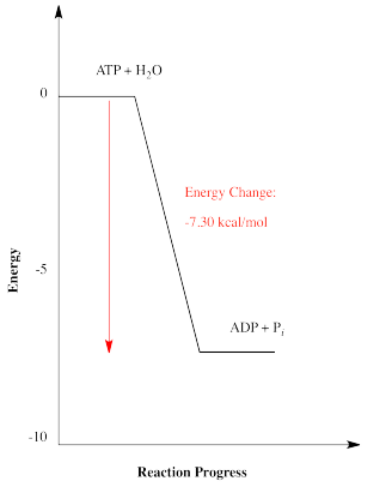
- Energy can be given off by a chemical reaction.
- That energy can be used to power other reactions that require energy.

In the cell, ATP is produced in high levels in the mitochondria. Because it is a relatively small molecule, it can be transported easily to other areas of the cell where energy may be needed. The ATP can be hydrolysed on site, providing energy for the cell to use for other reactions.



Note that the scheme above uses some thermodynamics jargon. The place where the reaction takes place, or the molecules participating in the reaction, are called "the system". Energy is supplied to "the surroundings", meaning places or molecules other than those directly involved in this reaction.

There are a couple of other ways in which energetics of reactions are commonly depicted. The energetic relationship between ATP plus water and ADP plus phosphate shown above is really a simplified graph of energy versus reaction progress (sometimes called reaction coordinate). This type of graph shows changes in energy over the course of a reaction. The energy of the system at the beginning of the reaction is shown on the left, and the energy at the end of the reaction is shown on the right. This type of graph is sometimes referred to as a reaction profile.

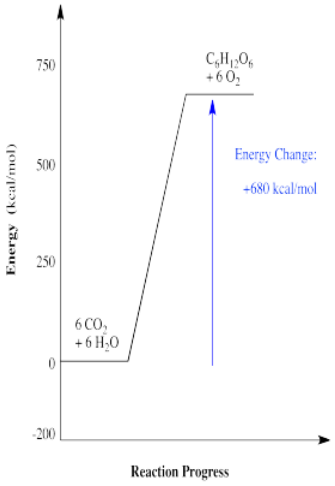


Another common way of discussing energetics is to include energy as a reactant or product in an equation describing the reaction. An equation for a reaction shows what the starting materials were for the reaction, and what they turned into after the reaction. The things that reacted together in the reaction are called the "reactants". They are written on the left hand side of the arrow that says a reaction took place. The things that the reactants turned into are called the "products". They show up on the right hand side of the arrow.

$$ATP + H_2O \rightarrow ADP + P_i + energy$$

For the hydrolysis of ATP, energy is simply included as one of the products of the reaction, since the reaction releases energy.

Alternatively, the energetic observation about ATP can be turned around, since there are evidently some reactions that cost energy. Probably the most well-know reaction of this type is the conversion of carbon dioxide to carbohydrates such as glucose. This conversion actually results from a long series of different reactions that happen one after another. Overall, the process requires a lot of energy. This energy is supplied in part by ATP, generated with assistance from photosystem I and II, which are arrays of molecules that interact with sunlight. A simplified reaction profile for carbohydrate synthesis is shown below.



- Energy can be consumed by a chemical reaction.
- Reactions that consume energy need an energy source in order to occur.

Again, this energetic relationship can be thought of in the form of a balanced reaction.

$$energy + 6CO_2 + 6H_2O \rightarrow C_6H_{12}O_6 + O_2$$

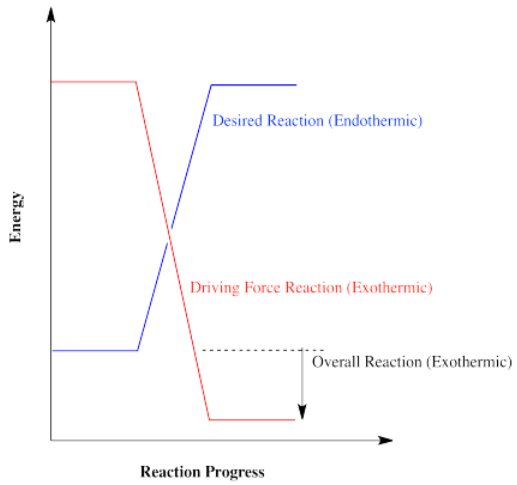
In this case, energy is a reactant, not a product. It is one of the key ingredients needed to make the reaction happen.

Reactions that produce energy, like ATP hydrolysis, are referred to as exothermic reactions (or sometimes exergonic, meaning roughly the same thing). In reaction profiles, these reactions go downhill in energy as the reaction occurs from the left side of the diagram to the right. On the other hand, reactions that cost energy (the ones that go uphill on the reaction profile, like carbohydrate synthesis) are referred to as endothermic (or sometimes endergonic).

It is useful to think of reactions as "going downhill" or "going uphill" because one of these situations should seem inherently easier than the other (especially if you've ever been skiing). Exothermic reactions (the downhill ones) occur very easily; endothermic reactions do not (those are the uphill ones).

- Systems always go to lower energy if possible.

Reactions that are energetically "uphill" cannot happen easily by themselves. Those reactions must be powered by other reactions that are going downhill. The energy traded between these reactions keeps chemical reactions going, in cells and other important places. Sometimes, a process that is used to supply energy for another reaction is thought of as the "driving force" of the reaction. Without the driving force, the desired reaction would not be able to occur.

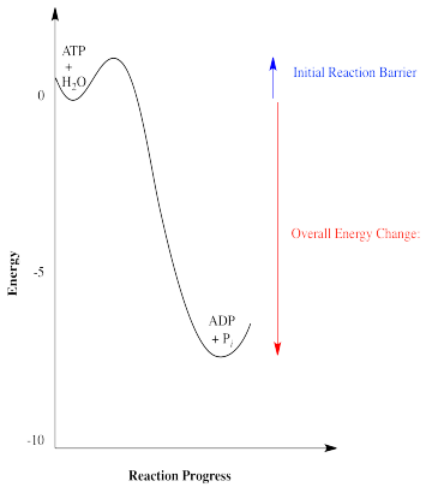


In general, a reaction will occur if more than enough energy is supplied. Excess energy does not hurt on the macroscopic scale. However, if not enough energy is supplied to make up for an endothermic reaction, the reaction is not likely to happen.

Energy is a lot like money. It can be passed from one set of hands to another. Doing so often helps get things done.

There is one problem with the use of chemical reactions as sources of energy. If ATP hydrolysis releases energy, and if the release of energy is always favored, why does not it happen spontaneously? In other words, why don't all the ATP molecules in all the cells in all the organisms in the whole world just slide downhill into ADP right now? What is stopping them?

Fortunately, all reactions have barriers that stop them from happening until they are ready to go. A reaction barrier is an initial investment of energy needed to get things started. Reaction barriers occur for a variety of physical reasons: two molecules may need to get oriented in the right direction to react with each other, or a bond may have to be broken to get the reaction going, costing an initial outlay of energy.

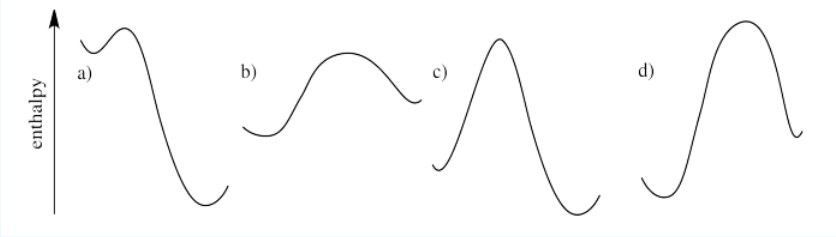


The reaction barriers of reactions influence how quickly reactions happen. High barriers slow reactions down a lot. Low barriers allow them to happen more easily. The study of reaction barriers, and how quickly reactions can occur, is called chemical kinetics.

Thermodynamics, on the other hand, is really concerned with the overall energy change from the beginning of a reaction to the end. It compares the energies of two sets of molecules to each other: the energies of the reactants and the energies of the products.

? Exercise 1.1.1

Which of the following reaction profiles describe reactions that will go forward, as opposed to ones that will probably not occur?

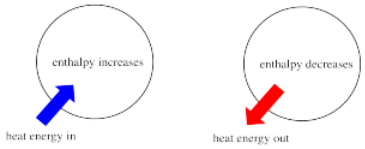


Answer

Reactions that go down in energy will proceed. Reactions that go up in energy will not proceed. If the reaction profile is higher on the left (reactant side) than the right, the reaction will go forward and it will form products. If the reverse is true, the reaction presumably will not occur.

1.2: Enthalpy

Thermodynamics is the study of the relationship between heat (or energy) and work. Enthalpy is a central factor in thermodynamics. It is the heat content of a system. The heat that passes into or out of the system during a reaction is the enthalpy change. Whether the enthalpy of the system increases (i.e. when energy is added) or decreases (because energy is given off) is a crucial factor that determines whether a reaction can happen.



Sometimes, we call the energy of the molecules undergoing change the "internal enthalpy". Sometimes, we call it the "enthalpy of the system". These two phrases refer to the same thing.

Similarly, the energy of the molecules that don't take part in the reaction is called the "external enthalpy" or the "enthalpy of the surroundings".

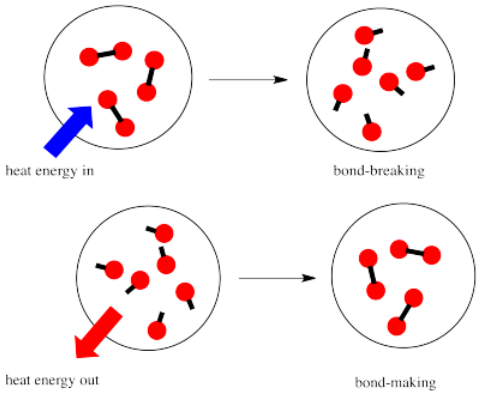
Roughly speaking, the energy changes that we looked at in the introduction to thermodynamics were changes in enthalpy. We will see in the next section that there is another energetic factor, entropy, that we also need to consider in reactions. For now, we will just look at enthalpy.

- Enthalpy is the heat content of a system.
- The enthalpy change of a reaction is roughly equivalent to the amount of energy lost or gained during the reaction.
- A reaction is favored if the enthalpy of the system decreases over the reaction.

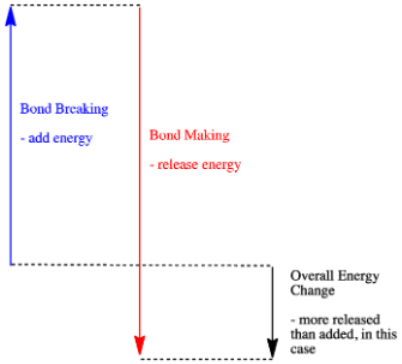
That last statement is a lot like the description of energetics on the previous page. If a system undergoes a reaction and gives off energy, its own energy content decreases. It has less energy left over if it gave some away.

Why does the energy of a set of molecules change when a reaction occurs? To answer that, we need to think about what happens in a chemical reaction.

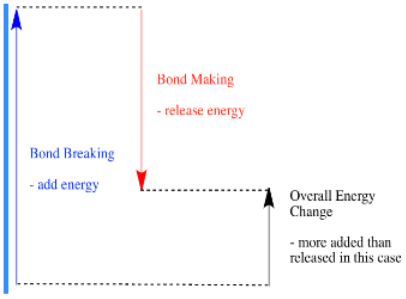
In a reaction, there is a change in chemical bonding. Some of the bonds in the reactants are broken, and new bonds are made to form the products. It costs energy to break bonds, but energy is released when new bonds are made.



Whether a reaction is able to go forward may depend on the balance between these bond-making and bond-breaking steps.



- A reaction is exothermic if more energy is released by formation of new bonds than is consumed by breaking old bonds.
- A reaction is exothermic if weaker bonds are traded for stronger ones.
- A reaction is endothermic if bond-breaking costs more energy than what is provided in bond-making.



one lots of work measuring bond strengths, and they have collected the information in tables, so if you need to know how strong a bond is, you can just look up the information you need.

Bond	Bond Energy (kcal/mol)		Bond	Bond Energy (kcal/mol)
H-H	104		O-H	111
C-C	83		C-H	99
O=O	119		N-H	93
N≡N	226		C=O	180

For example, suppose you wanted to know whether the combustion of methane were an exothermic or endothermic reaction. I am going to guess that it's exothermic, because this reaction (and others like it) is used to provide heat for lots of homes by burning natural gas in furnaces.

The "combustion" of methane means that it is burned in air, so that it reacts with oxygen. The products of burning hydrocarbons are mostly carbon dioxide and water. The carbon atom in methane (CH_4) gets incorporated into a carbon dioxide molecule. The hydrogen atoms get incorporated into water molecules. There are four hydrogen atoms in methane, so that's enough to make two molecules of H_2O.

- Four C-H bonds must be broken in the combustion of methane.
- Four new O-H bonds are made when the hydrogens from methane are added into new water molecules.
- Two new C=O bonds are made when the carbon from methane is added into a CO_2 molecule.

The other piece of the puzzle is the oxygen source for the reaction. Oxygen is present in the atmosphere mostly as O_2. Because we need two oxygen atoms in the CO_2 molecule and two more oxygen atoms for the two water molecules, we need a total of four oxygen atoms for the reaction, which could be provided by two O_2 molecules.

- Two O=O bonds must be broken to provide the oxygen atoms for the products.

Altogether, that's four C-H and two O=O bonds broken, plus two C=O and four O-H bonds made. That's 4 x 99 kcal/mol for the C-H bonds and 2 x 119 kcal/mol for the O=O bonds, a total of 634 kJ/mol added. The reaction releases 2 x 180 kcal/mol for the C=O bonds and 4 x 111 kcla/mol for the OH bonds, totaling 804 kcal/mol. Overall, there is 170 kcal/mol more released than is consumed.

That means the reaction is exothermic, so it produces heat. It's probably a good way to heat your home.

? Exercise 1.2.1

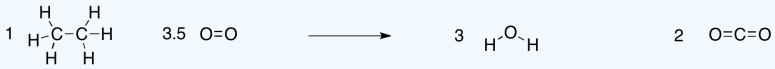
Compare the combustion of ethane to the combustion of methane.

a. Write a reaction for the combustion of ethane, CH_3CH_3, to carbon dioxide and water.
b. How many carbon dioxide molecules would be produced from one molecule of ethane?
c. How many water molecules would be produced from one molecule of ethane?
d. How many oxygen molecules would be needed to provide oxygen atoms to accomplish the steps in questions (b) and (c)?
e. How much energy is consumed / produced by the reaction? Compare this result to the one for methane.

Answer

Answer a

The reaction is given with structures below:



Answer b

Because there are two carbons in ethane, one molecule of ethane will give rise to two molecules of CO_2.

Answer c

Because there are six hydrogens in ethane, one molecule of ethane will give rise to three molecules of H_2O.

Answer d

In order to make two molecules of carbon dioxide (four oxygen atoms) and three water molecules (three oxygen atoms), we would need seven oxygen atoms total. Since oxygen molecules contain pairs of oxygen atoms, we would only need 3.5 oxygen molecules.

Answer e

The energy requirements are laid out in the following table. Overall, the reaction releases 375.5 kcal per mol of ethane burned. The negative sign in the table is often used to denote that this is excess energy released (whereas a positive sign would indicate that energy as consumed overall).

	Bond Breaking	**Costs (kcal/mol)**	**Sum of Cost**	**Bond Making**	**Releases (kcal/mol)**	**Sum of Release**	**Overall (kcal/mol)**
	6 x C-H	6 * 99	594	6 x O-H	6 * 111	666	
	3.5 x O=O	3.5 * 119	416.5	4 x C=O	4 * 180	720	
	1 x C-C	83	83				
total		**breaking:**	1093.5		**making:**	1386	**-292.5**

That's more energy than was produced from a molecule of methane (-170 kcal/mol).

? Exercise 1.2.2

The Haber-Bosch process is used to make ammonia for fertilizer. It employs the reaction of hydrogen gas (H_2) with atmospheric nitrogen (N_2) in a 3:1 ratio to produce ammonia (NH_3).

a. Write a reaction for the Haber-Bosch process.

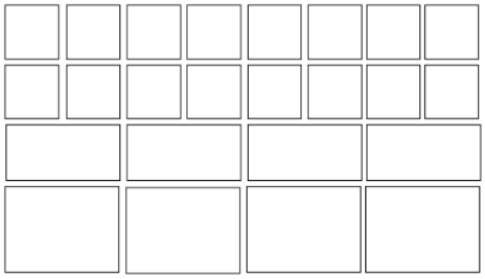
b. How many ammonia molecules would be produced from one molecule of nitrogen?
c. How much energy is consumed / produced by the reaction?

1.3: Entropy

Entropy is another important aspect of thermodynamics. Enthalpy has something to do with the energetic content of a system or a molecule. Entropy has something to do with how that energy is stored.

We sometimes speak of the energy in a system as being "partitioned" or divided into various "states". How this energy is divided up is the concern of entropy.

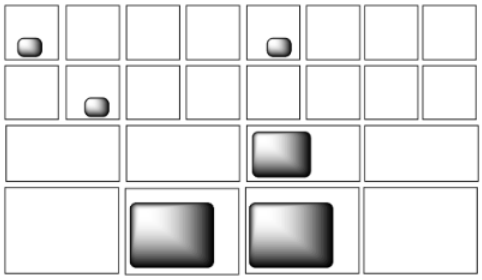
By way of analogy, picture a set of mailboxes. You may have a wall of them in your dormitory or your apartment building. The mailboxes are of several different sizes: maybe there are a few rows of small ones, a couple of rows of medium sized ones, and a row of big mailboxes on the bottom.



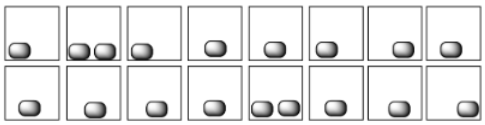
Instead of putting mail in these boxes, we're going to use them to hold little packages of energy. Later on, you might take the energy packages out of your own mailbox and use them to take a trip to the mall or the gym. But how does the mail get to your mailbox in the first place?

The energy packages don't arrive in your molecular dormitory with addresses on them. The packages come in different sizes, because they contain different amounts of energy, but other than that there is no identifying information on them.

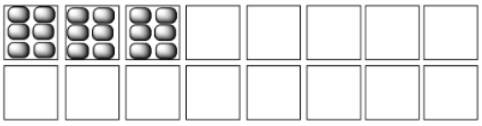
Some of the packages don't fit into some of the mailboxes, because some of the packages are too big and some of the mailboxes are smaller than the others. The energy packages need to go into mailboxes that they will fit into.



Still, there are an awful lot of mailboxes that most of the energy packages could still fit into. There needs to be some system of deciding where to put all of these packages. It turns out that, in the molecular world, there is such a system, and it follows a pretty simple rule. When a whole pile of energy packages arrive, the postmaster does her best to put one package into every mailbox. Then, when every mailbox has one, she starts putting a second one into each box, and so on.



It didn't have to be that way. It could have been the case that all the energy was simply put into the first couple of mailboxes and the rest were left empty. In other words, the rule could have been that all the energy must be sorted into the same place, instead of being spread around. But that's not how it is.



- Energy is always partitioned into the maximum number of states possible.

Entropy is the sorting of energy into different modes or states. When energy is partitioned or sorted into additional states, entropy is said to increase. When energy is bundled into a smaller number of states, entropy is said to decrease. Nature's bias is towards an increase in entropy.

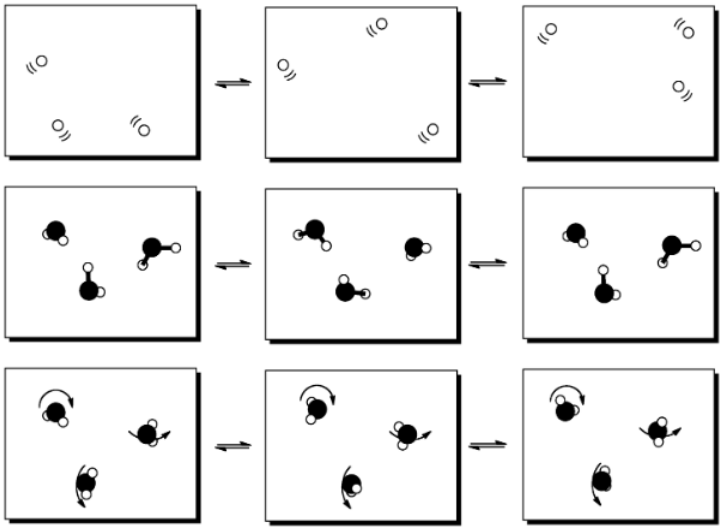
This is a fundamental law of the universe; there is no reason that can be used to explain why nature prefers high entropy to low entropy. Instead, increasing entropy is itself the basic reason for a wide range of things that happen in the universe.

Entropy is popularly described in terms of "disorder". That can be a useful idea, although it does not really describe what is happening energetically.

A better picture of entropy can be built by looking at how a group of molecules might sort some energy that is added to them. In other words, what are some examples of "states" in which energy can be sorted?

If you get more energy -- maybe by eating breakfast -- one of the immediate benefits is being able to increase your physical activity. You have more energy to move around, to run, to jump. A similar situation is true with molecules.

Molecules have a variety of ways in which they can move, if they are given some energy. They can zip around; this kind of motion is usually called translation. They can tumble and roll; this kind of motion is referred to as rotation. Also, they can wiggle, letting their bonds get longer and shorter by moving individual atoms around a little bit. This type of motion is called vibration.

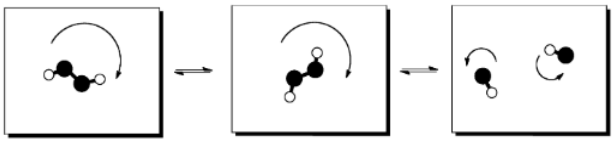


When molecules absorb extra energy, they may be able to sort the energy into rotational, vibrational and translational states. This only works with energy packages of a certain size; other packages would be sorted into other kinds of states. However, these are just a few examples of what we mean by states.

OK, so energy is stored in states, and it is sorted into the maximum possible number of states. But how does entropy change in a reaction? We know that enthalpy may change by breaking or forming certain bonds, but how does the energy get sorted again?

The changes in internal entropy during a reaction are often very small. In other words, the energy remaining at the end of the reaction gets sorted more or less the way it was before the reaction. However, there are some very common exceptions.

The most common case in which internal entropy changes a lot is when the number of molecules involved changes between the start of the reaction and the end of the reaction. Maybe two molecules react together to form one, new molecule. Maybe one molecule splits apart to make two, new molecules.



If one molecule splits apart in the reaction, entropy generally increases. Two molecules can rotate, vibrate and translate (or tumble, wiggle and zip around) independently of each other. That means the number of states available for partitioning energy increases when one molecule splits into two.

- Entropy generally increases when a reaction produces more molecules than it started with.
- Entropy generally decreases when a reaction produces fewer molecules than it started with.

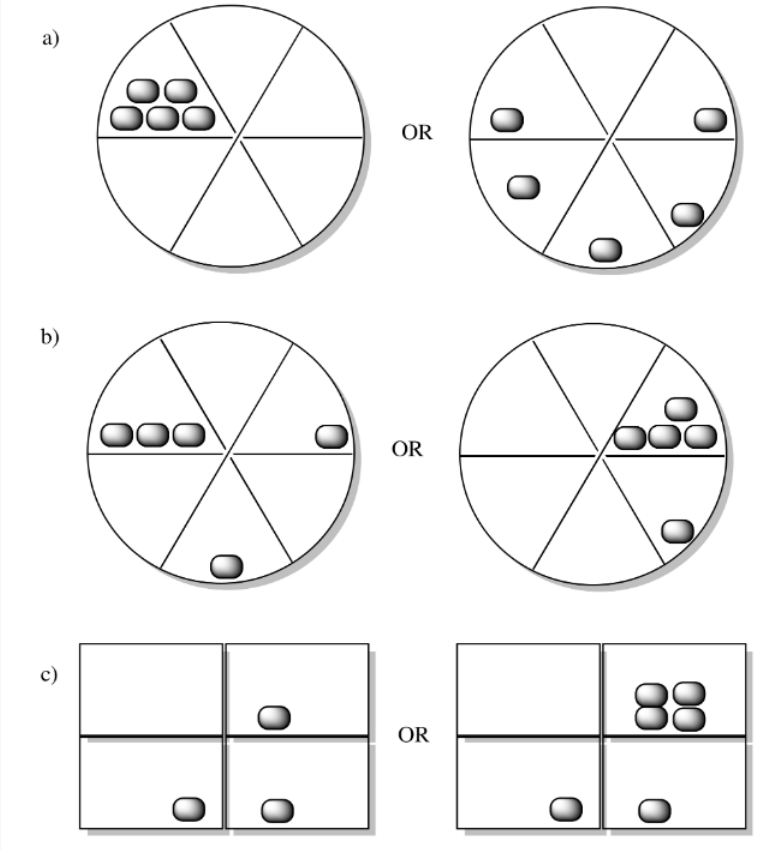
Apart from a factor like a change in the number of molecules involved, internal entropy changes are often fairly subtle. They are not as easy to predict as enthalpy changes.

Nevertheless, there may sometimes be a trade-off between enthalpy and entropy. If a reaction splits a molecule into two, it seems likely that an increase in enthalpy will be involved, so that the bond that held the two pieces together can be broken. That's not favorable. However, when that happens, we've just seen that there will be an increase in entropy, because energy can then be sorted into additional modes in the two, independent molecules.

So we have two different factors to balance. There is a tool we often use to decide which factor wins out. It's called free energy, and we will look at it next.

? Exercise 1.3.1

In each of the following pairs, look at the distribution of energy packages (gray shapes) and decide which system has the highest entropy.

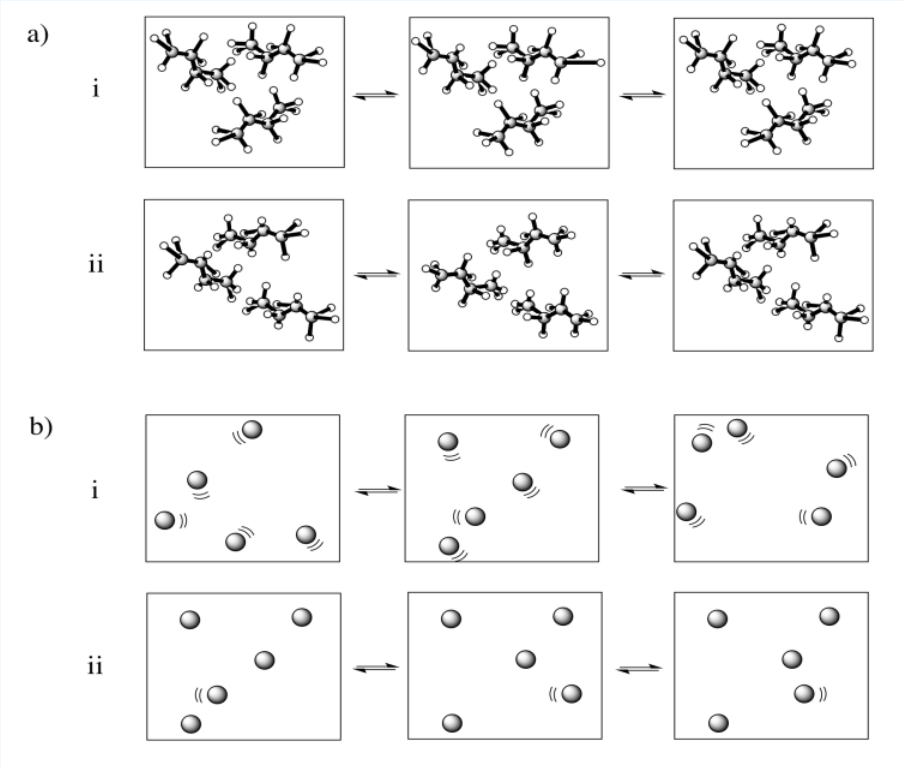


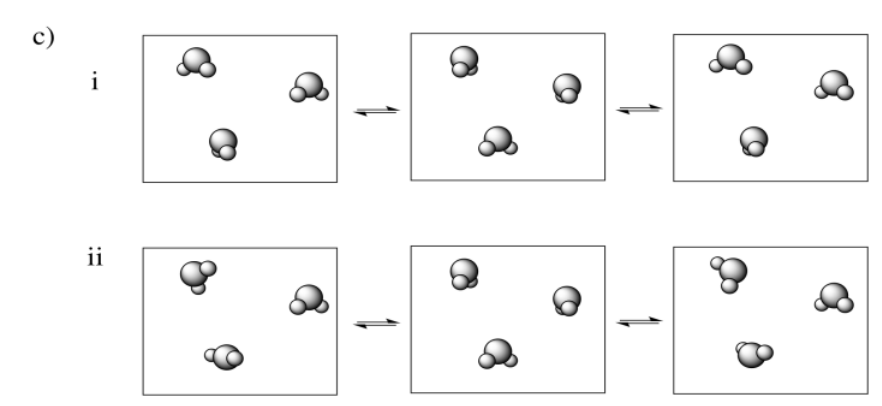
Answer

Entropy is higher if the energy is partitioned into more states. For example, in question (b), the same amount of energy is distributed into three states on the left hand side and only two states on the right. Entropy is higher in the left hand example than the right in that case.

Exercise 1.3.2

In each of the following pairs, select the system (i or ii) that has the highest entropy.





Answer

Examples of "states" into which energy can be partitioned include molecular vibrational, rotational and translational states (which, loosely speaking, correspond to wiggling, spinning and zipping around). Entropy is higher if energy is distributed into more of these states. That might include a greater range of vibrational or rotational states used in (a) and (c), or similar states employed in a greater number of molecules in (b).

Exercise 1.3.3

Based on what you know, would the following reactions be entropically favored or not?

a. The decarboxylation of one molecule of the anti-Parkinson's drug, L-DOPA, to produce one molecule of carbon dioxide and one molecule of the neurotransmitter, dopamine.
b. One molecule of nitrogen and three molecules of hydrogen react to produce two molecules of ammonia?
c. One molecule of methane reacts with two molecules of oxygen to produce two molecules of water and one molecule of carbon dioxide?

Answer

One general observation about internal entropy is that it increases if the number of molecules increases during a reaction and decreases if the number of molecules decreases during a reaction. It's just a matter of counting how many things on the left get turned into how many things on the right. For example, in question (a), one molecule produces two new molecules in the decarboxylation reaction, so the reaction is entropically favored.

1.4: Free Energy

Entropy and enthalpy are two of the basic factors of thermodynamics. Enthalpy has something to do with the energetic content of a system or a molecule. Entropy has something to do with how that energy is stored.

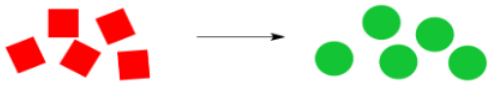
There is a bias in nature toward decreasing enthalpy in a system. Reactions can happen when enthalpy is transferred to the surroundings.

- A reaction is favored if enthalpy decreases.

There is also a bias in nature toward increasing entropy in a system. Reactions can happen when entropy increases.

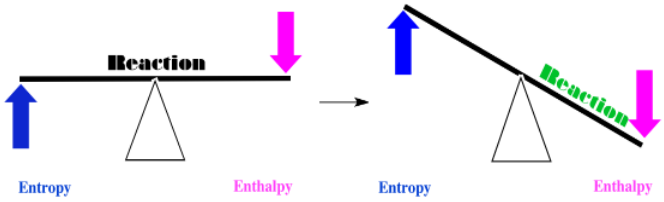
- A reaction is favored if entropy increases.

Consider the cartoon reaction below. Red squares are being converted to green circles, provided the reaction proceeds from left to right as shown.

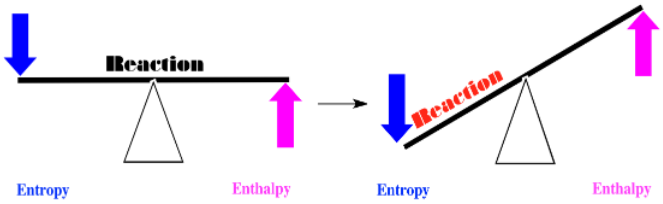


Whether or not the reaction proceeds to the right depends on the balance between enthalpy and entropy. There are several combinations possible.

In one case, maybe entropy increases when the red squares turn into green circles, and the enthalpy decreases. If we think of the balance between these two factors, we come to a simple conlusion. Both factors tilt the balance of the reaction to the right. In this case, the red squares will be converted into green circles.

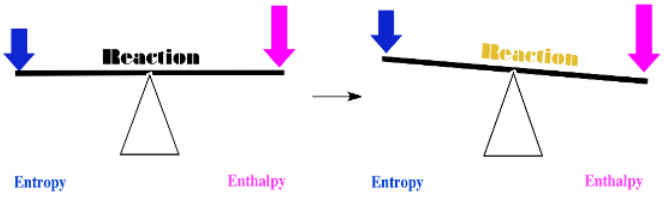


Alternatively, maybe entropy decreases when the red squares turn into green circles, and enthalpy increases. If we think of the balance between these two factors, we come to another simple conlusion. Both factors tilt the balance of the reaction to the left. In this case, the red squares will remain just as they are.



Having two factors may lead to complications. For example, what if enthalpy decreases, but so does entropy? Does the reaction happen, or does not it?

In that case, we may need quantitation to make a decision. How much does the enthalpy decrease? How much does the entropy decrease? If the effect of the enthalpy decrease is greater than that of the entropy decrease, the reaction may still go forward.



The combined effects of enthalpy and entropy are often combined in what is called "free energy". Free energy is just a way to keep track of the sum of the two effects. Mathematically, the symbol for the internal enthalpy change is " ΔH" and the symbol for the internal entropy change is "ΔS". Free energy is symbolized by "ΔG", and the relationship is given by the following expression:

$$\Delta G = \Delta H - T\Delta S$$

(note: that may look like "?G" = "?H" - "?S" in some web browsers, rather than ΔG = ΔH - TΔS; the ? will show up as a Greek delta in Safari or Firefox)

The letter T in this expression stands for the temperature (in Kelvin, rather than Celsius or Fahrenheit). The temperature acts as a scaling factor in the expression, putting the entropy and enthalpy on equivalent footing so that their effects can be compared directly.

How do we use free energy? It works the same way we were using enthalpy earlier (that's why the free energy has the same sign as the enthalpy in the mathematical expression, whereas the entropy has an opposite sign). If free energy decreases, the reaction can proceed. If the free energy increases, the reaction can't proceed.

- A reaction is favored if the free energy of the system decreases.
- A reaction is not favored if the free energy of the system increases.

Because free energy takes into consideration both the enthalpy and entropy changes, we don't have to consider anything else to decide if the reaction occurs. Both factors have already been taken into account.

Remember the terms "endothermic" and "exothermic" from our discussion of enthalpy. Exothermic reactions were favores (in which enthalpy decreases). Endothermic ones were not. In free energy terms, we say that *exergonic* reactions are favored (in which free energy decreases). *Endergonic* ones (in which free energy increases) are not.

? Exercise 1.4.1

Imagine a reaction in which the effects of enthalpy and entropy are opposite and almost equally balanced, so that there is no preference for whether the reaction proceeds or not. Looking at the expression for free energy, how do you think the situation will change under the following conditions:

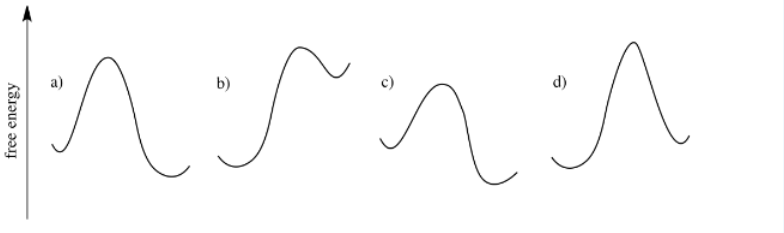
a. the temperature is very cold (0.09 K)
b. the temperature is very warm (500 K)

Answer

The expression ΔG = ΔH - TΔS includes both an enthalpy contribution and an enthalpy contribution and balances them against each other. However, the effect of entropy is *multiplied by* the temperature. The greater the temperature, the greater will be the influence of entropy (and therefore the smaller the influence of enthalpy). The lower the temperature, the smaller will be the influence of entropy (and therefore the greater the influence of enthalpy).

? Exercise 1.4.2

Which of the following reaction profiles describe reactions that will proceed? Which ones describe reactions that will not proceed?



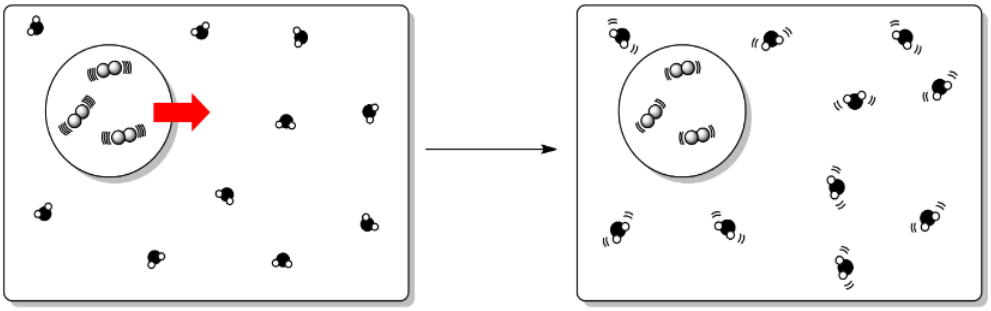
Answer

See problem Exercise 1.1.1

How Entropy Rules Thermodynamics

Sometimes it is said that entropy governs the universe.

As it happens, enthalpy and entropy changes in a reaction are partly related to each other. The reason for this relationship is that if energy is added to or released from the system, it has to be partitioned into new states. Thus, an enthalpy change can also have an effect on entropy.

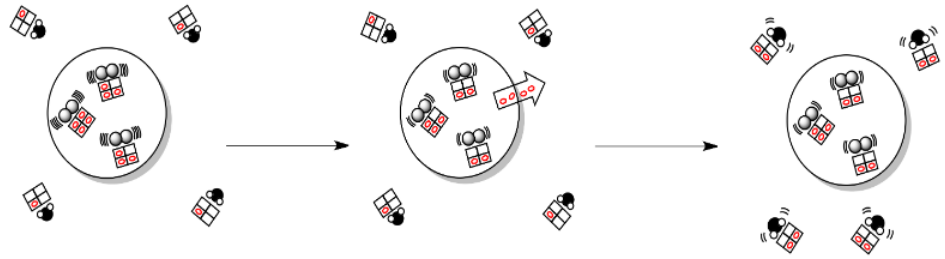


Specifically, the internal enthalpy change that we discussed earlier has an effect on the entropy of the surroundings. So far, we have just considered internal entropy changes.

- In an exothermic reaction, the external entropy (entropy of the surroundings) increases.
- In an endothermic reaction, the external entropy (entropy of the surroundings) decreases.

Free energy takes into account both the entropy of the system and the entropy changes that arise because of heat exchange with the surroundings. Together, the system and the surroundings are called "the universe". That's because the system is just everything involved in the reaction, and the surroundings are everything that isn't involved in the reaction.

Enthalpy changes in the system lead to additional partitioning of energy. We might visualize that with the mailbox analogy we used for entropy earlier. In this case, each molecule has its own set of mailboxes, into which it sorts incoming energy.



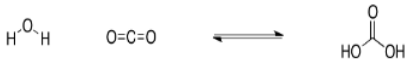
Looked at in this way, thermodynamics boils down to one major consideration, and that is the combined entropy of both the system and its surroundings (together known as the universe).

- For a reaction to proceed, the entropy of the universe must increase.

1.5: Reversibility and Le Chatelier

Sometimes, there is not a big difference in energy between reactants and products of a reaction. What happens then? Does the reaction go forward, because it will not cost a lot of energy? Or does it not proceed, because there isn't enough driving force?

For example, one simple reaction that occurs all the time is the reaction of water with carbon dioxide. This is a reaction that happens when carbon dioxide dissolves in lakes, rivers and oceans. It even happens in your own bloodstream.



Water reacts with carbon dioxide to form carbonic acid.

However, carbonic acid also decomposes spontaneously in water. It reacts to form carbon dioxide and water.

In other words, this is a reaction that can go either direction. It can go forwards or backwards. It is an example of an equilibrium reaction. An equilibrium reaction is one that is energetically balanced, so that it really isn't favored to go in either direction.

Equilibrium reactions are extremely important in nature, partly because of the forward and reverse capabilities that they offer. In essence, they are reactions with an "undo" button. The reaction can proceed in one direction when needed, and it can proceed in the other direction when needed.

However, there are some inherent limitations involved. Frequently, equilibrium reactions only proceed "partway". That is, a group of molecules will start to produce products. However, at some point those products will begin reverting to the starting materials again. Eventually the system will settle out as a mixture of reactants and products.

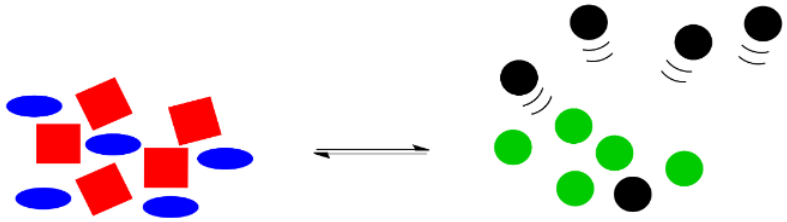
What if it's really important that we have the products of the reaction at one point, with none of the reactants? And if later on we need the reactants, but not any of the products? It would be useful if there were a way to control the direction of an equilibrium reaction, so that we could "push" it to one side or the other.

Control of equilibrium reactions can be remarkably simple. It follows a rule that was observed by Henri le Chatelier (ah-REE luh shah-tell-YAY), a French industrial chemist, around 1900. Le Chaletelier noticed that equilibrium reactions often shift direction if the conditions of the reaction are changed.

In general, adding any product of the reaction shifts the balance back toward the reactants. If any product of the reaction is added, the reaction makes more starting materials. Thus, adding more carbonic acid to a carbon dioxide - water - carbonic acid mixture would result in reverse reaction, producing more water and carbon dioxide. Adding more carbon dioxide, on the other hand, would lead to production of more carbonic acid.

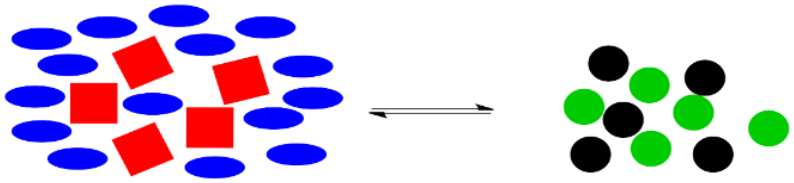
Here is a cartoon illustration of "le Chatelier's Principle" at work. Suppose red squares and blue ovals can react together to make black circles and green circles. Maybe there is a natural equilibrium in this reaction, so that the two piles of shapes are roughly equal in size.

What would happen if something knocked this system off balance? For example, maybe black circles are highly elusive, and they just wander away as soon as they are formed. The system won't be in equilibrium anymore, because without those black circles, the balance will be upset, with not enough things on the right side for the number of things on the left.

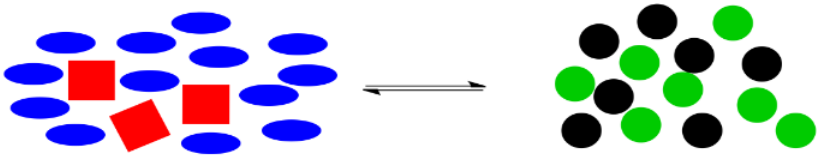


Le Chatelier noticed that nature automatically corrects for such changes. If some of the black circles disappear, the reaction will kick into action again, using up some red squares and blue ellipses to produce more green and black circles. The exact numbers of shapes won't return to exactly the same as before, because some of the black circles have still gone missing, but the system will have shifted to use up more reactants on the left and to produce more products on the right, so that the overall ratio between right and left is restored.

Alternatively, maybe we found a way to make the black circles stay where they are. Instead, we have dumped in a bunch of extra blue ellipses. Once again, the system is knocked off balance. This time, there is too much stuff on the left, compared to the amount on the right side.



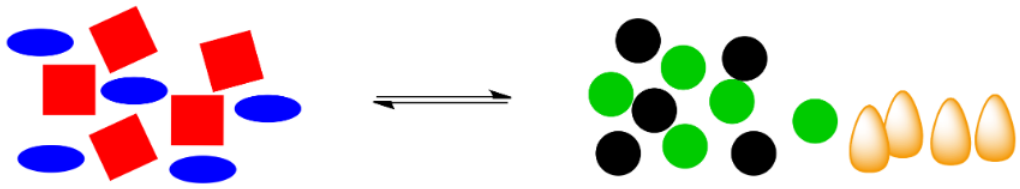
The reaction goes into action again. It uses up some of those extra blue ellipses (and, at the same time, some of the red squares) to produce more black and green circles, bringing the system back to the original ratio of right side shapes to left side shapes.



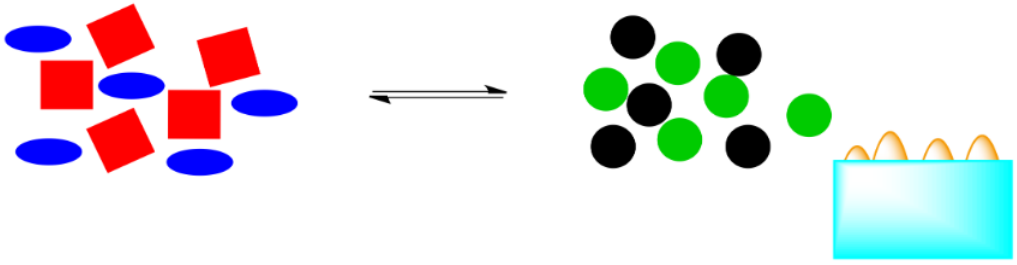
In general, if molecules are added to a system, the reaction will shift to bring the system back into equilibrium. If molecules are removed from the system, the reaction will also shift to bring the system back into equilibrium.

Furthermore, because heat can be consumed by (or produced by) reactions, temperature can sometimes be used to shift equilibria. If a reaction is exothermic, heat is a product of the reaction. Adding more heat will result in the reaction shifting to produce more reactants. Cooling the reaction (removing heat) would do the opposite: the reaction would shift to produce more heat, and more products.

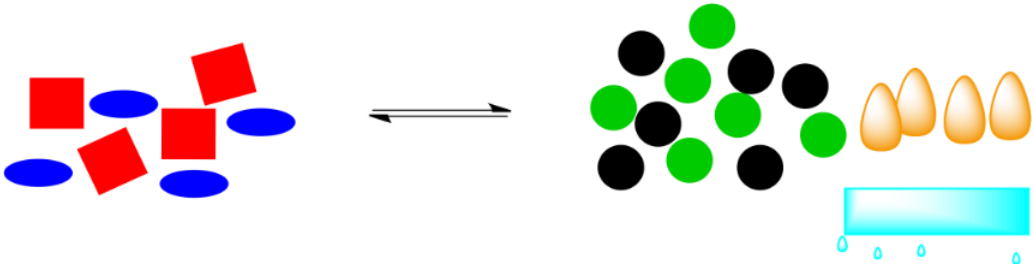
In the cartoon, we have a shape-shifting reaction again, but this time the reaction releases energy (those are orange flames, symbolic of the heat produced).



What happens if that energy is removed? For example, if heat is removed through addition of a pale blue ice cube, what will be the effect on the system?

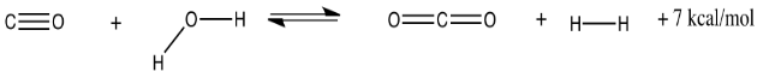


Those orange energy shapes (the "flames") were a part of the system. If they are removed, the system will have to shift in order to restore them. If the reaction pushes to the right again, more energy will be released, bringing the system back into equilibrium.



? Exercise 1.5.1

The water-gas shift reaction involves the production of hydrogen gas from steam and carbon monoxide. It is important both for the commercial production of hydrogen gas and for its application in fuel cells. At 300 K, the reaction (and an approximate energy produced) is shown below:



Explain what would happen if this gas-phase reaction is already at equilibrium and the following changes take place:

a. The pressure of steam injected into the reaction is doubled.
b. The temperature is raised to 450 K.
c. The CO_2 produced is "captured" and removed as carbonate.
d. The temperature is lowered to 250 K.
e. The pressure of CO added is cut in half.

Answer
Answer

The removal of any item produced on the right side of the reaction will shift the reaction to the right in order to restore equilibrium. On the other hand, adding any more of any of the items on the right will shift the reaction to the left.

Items on the left side will work in the opposite way. Adding more of anything on the left will shift the reaction to the right, to use up the newly added materials. Removing anything from the left will shift the reaction further left, to replace the items that were removed.

Answer a

The amount of water increases, moving the reaction to the right. More products are made.

Answer b

The amount of energy increases, moving the reaction to the left. Fewer products are made.

Answer c

The amount of carbon dioxide decreases, shifting the reaction to the right. More products are made.

Answer d

The amount of energy decreases, shifting the reaction to the right. More products are made.

Answer e

The amount of carbon monoxide decreases, shifting the reaction to the left. Fewer products are made.

? Exercise 1.5.2

Hydrochlorination of acetylene (ethyne) is another gas-phase reaction. It is used to produce vinyl chloride, the starting material for the polyvinyl chloride commonly used to make the pipes in household plumbing. At 300 K, the reaction (and an approximate energy produced) is shown below:

Explain what would happen if the system is at equilibrium and the following changes take place:

a. The temperature is raised to 350 K.
b. The pressure of HCl is doubled.
c. The pressure of acetylene is cut in half.
d. The temperature is dropped to 250 K.
e. The overall pressure in the system is increased from one atmosphere to two atmospheres.

Answer
Answer a

The amount of energy increases, moving the reaction to the left. Fewer products are made.

Answer b

The amount of hydrogen chloride increases, shifting the reaction to the right. More products are made.

Answer c

The amount of acetylene decreases, shifting the reaction to the left. Fewer products are made.

Answer d

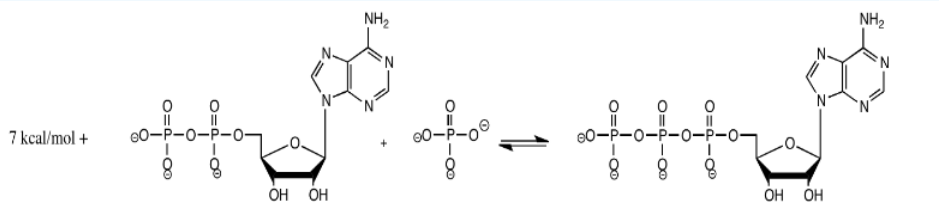
The amount of energy decreases, shifting the reaction to the right. More products are made.

Answer e

This question doesn't follow the pattern. However, because the products and reactants are all gases, we can think about the effect they would have on pressure if the reaction moved one way or the other. Because fewer gas molecules are produced on the right than the left, pressure would decrease on going from left to right (and increase on going from right to left). Thus, we can pencil in "pressure" as an item on the left side of the reaction. That means increasing pressure will shift the reaction to the right, making more products.

Exercise 1.5.3

Production of ATP in the cell proceeds according to the reaction below, with an approximate energy indicated at 310 K.



If the system is already at equilibrium, explain what happens when the following changes take place:

a. The temperature is raised to 320 K (It's OK. This organism is really hardy and it can handle the temperature change).
b. The temperature is lowered to 300 K.
c. The supply of inorganic phosphate is doubled.

Answer

Answer a

The amount of energy increases, shifting the reaction to the right. More products are made.

Answer b

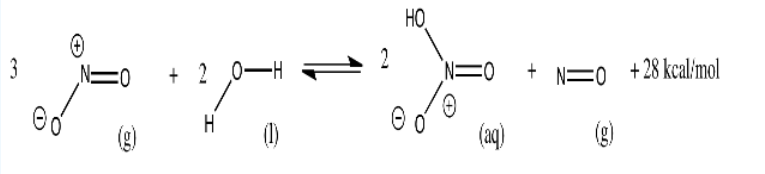
The amount of energy decreases, moving the reaction to the left. Fewer products are made.

Answer c

The amount of phosphate increases, shifting the reaction to the right. More products are made.

Exercise 1.5.4

Nitric acid, HNO_3, is a common industrial chemical. For example, it is used to make azo dyes that are employed in paints. Nitric acid production involves the following reaction, with an approximate energy change indicated at 300 K.



Note that this is a multi-phase reaction: it involves gases (g), liquids (l) and aqueous solutions (aq, something dissolved in water). Explain what would happen if production were run under the following conditions:

a. The NO_2 gas is introduced into a chamber that contains a tank of water. After reacting for a while, the gas is released and the water, containing the aqueous solution of nitric acid, is drained from the tank.
b. The NO_2 gas is introduced into a chamber that contains a tank of water. Periodically, the water is drained from the tank, and new water is introduced, without releasing any gases.
c. The NO_2 gas is continually introduced into a chamber, and there is a vent that slowly releases gases from the chamber at all times. There is also a constant flow of water into and out of the chamber.

Answer

Answer a

The nitric acid would build up in the water, and the NO gas would build up, until equilibrium is reached. The nitric acid in the water would be limited by that equilibrium point.

Answer b

Periodically removing the nitric acid solution and adding fresh water would help to shift the reaction further to the right, although the eventual buildup of NO gas might prevent the reaction from shifting too far.

Answer c

A constant source of both water and nitrogen dioxide (nitric oxide) would help to push the reaction to the right. Although allowing gases to vent would limit the amount of nitrogen dioxide in the system, it would also prevent a buildup of nitrogen monoxide (nitrous oxide), which would otherwise push the reaction to the left, eventually.

1.6: Free Energy and Equilibrium

The balance between reactants and products in a reaction will be determined by the free energy difference between the two sides of the reaction. The greater the free energy difference, the more the reaction will favor one side or the other. The smaller the free energy difference, the closer the mixture will get to equal parts reactants and products (loosely speaking).

Exactly where the balance lies in an equilibrium reaction is described by the equilibrium constant. The equilibrium constant is just the ratio of products to reactants, once the reaction has settled out at equilibrium. That's the point at which the forward and reverse reactions are balanced, so that the ratio of products to reactants is stable.

- A reaction has reached equilibrium when the reaction has stopped progressing, so that the amount of reactants that have turned into products remains constant, and the amount of reactants left over stays constant.
- The equilibrium constant is the ratio of products to reactants when the reaction has reached equilibrium.

The equilibrium constant could be a large number (like a thousand). That means that there are much more products than reactants at equilibrium. It could also be a very small fraction (like one millionth). That would indicate that the reaction does not proceed very far, producing only a tiny amount of products at equilibrium.

- Every reaction has an equilibrium constant.
- A very large equilibrium constant (in the millions or bazillions) means the reaction goes "to completion", with all reactants essentially converted into products.
- A tiny equilibrium (very close to zero) constant means the reaction hardly moves forward at all.
- A modest equilibrium constant (close to one, or as close to one as numbers like 0.01 or 100) is considered to be a true equilibrium reaction, in which there is a significant amount of both products and reactants.

The equilibrium constant is related to the free energy change of the reaction by the expression:

$$K = e^{(\frac{-\Delta G}{RT})}$$

or $lnK = \frac{-DeltaG}{RT}$

in which T is the temperature in Kelvin and R is the "gas constant" (1.986 cal/K mol). Remember, e is just a number that occurs frequently in mathematical relationships in nature (sort of like π); it has a value of about 2.718. This expression for K does make some assumptions about the conditions that we won't worry about; we are using a slightly simplified model.

? Exercise 1.6.1

Arrange the following series of numbers from the largest quantity to the smallest, from left to right.

a. 10^5 10^4 10^6
b. 2^3 2^6 2^2
c. 3^3 3^0 3^2
d. e^2 e^1 e^4
e. 10^{-1} 10^{-5} 10^{-3}
f. 1 / 10 1 / 25 1 / 50
g. $2^{0.5}$ $2^{0.1}$ $2^{0.9}$

Answer

The exponent is the number of times the base number is multiplied by itself. For example, 10^3 = 10 x 10 x 10. The higher the exponent, the larger the resulting mathematical product.

The same is true with the magnitude of a negative exponent, but the negative sign means that we are dealing with the inverse of the base number. For example, $10^{-2} = \frac{1}{10} \times \frac{1}{10} = \frac{1}{10 \times 10}$

Let's look at the form of this relationship between free energy and the equilibrium constant. First, we will see how we deal with endergonic versus exergonic reactions. The free energy changes in opposite directions in these two cases, and we usually deal with opposites by giving one quantity a positive sign and one quantity a negative sign. A reaction in which the *free energy increases* is

given a *positive* value for its free energy. On the other hand, if *free energy decreases* over the course of the reaction, we show that by using a *negative* number for the value of the free energy.

If ΔG is negative, the exponent in the relationship becomes positive (because it is multiplied by -1 in the expression). Since e to a positive power will usually be a number greater than one, the relationship suggests there are more products than reactants. That's good, because the reaction is exergonic, and we expect the reaction to go forward. What's more, the larger the value of ΔG, the more product-favored the reaction will be.

- $10^{\text{large number}}$ is a large number.
- $10^{\text{small number}}$ is a smaller number.

However, if ΔG is a positive number, then the exponent in the relationship becomes negative. An number with a negative exponent, by the rules of exponents, is the same as the inverse of the number with a positive exponent of the same size.

In other words, $10^{-2} = 1 / 10^{2}$.

- $10^{\text{negative number}}$ is a fraction.

That means if ΔG is positive, the equilibrium constant becomes a fraction. That's because that positive value of ΔG is multiplied by -1 in the expression, becoming negative, and then it's placed in the exponent.

That's good, because a positive value of ΔG corresponds to an endergonic reaction, and that's not supposed to favor product formation.

? Exercise 1.6.2

Given the following free energy differences, arrange the corresponding equilibrium constants from largest to smallest.

a. 25 kcal/mol 17 kcal/mol 9 kcal/mol
b. 16 kcal/mol 19 kcal/mol 21 kcal/mol
c. 7 kcal/mol 22 kcal/mol 13 kcal/mol
d. -17 kcal/mol -3 kcal/mol -8 kcal/mol
e. -17 kcal/mol 3 kcal/mol -8 kcal/mol

Answer

The greater (and more positive) the free energy change, the smaller the equilibrium constant.

However, the greater (and more negative) the free energy change, the larger the equilibrium constant.

Equilibrium constants, from largest to smallest, would have associated free energies as follows:

(large K) big, negative ΔG > small, negative ΔG > small, positive ΔG > large, positive ΔG (small K)

There are other factors in the expression relating ΔG to the equilibrium constant. One of them, R, is just a "fudge factor"; it's the number that, when placed in the expression, makes the relationship agree with reality. And it's a constant, so it does not change.

The other factor is temperature. It does change. That means that the equilibrium constant may change with different temperatures.

Overall, the effect of temperature is to make the exponent in the expression a smaller number. That's because the free energy is divided by the temperature and the gas constant; the resulting number becomes the exponent in the relationship. At the extreme, a high temperature could make the exponent into a very, very small number, something close to zero. What happens then?

- $10^{0} = 1$
- $e^{0} = 1$

As the exponent gets smaller and smaller, the equilibrium constant could approach 1. That means there would be more or less equal amounts of products and reactants in our simplified approach.

However, the fact that there is a temperature factor in the expression for ΔG itself means that there is a limit to how small K will get as the temperature increases. At some point, the two values for temperature cancel out altogether and the expression becomes K

= e $^{(\Delta S/R)}$. At that point, the equilibrium constant is independent of temperature and is based only on internal entropy differences between the two sides of the reaction.

This relationship is useful because of its predictive value. Qualtitatively, it confirms ideas we had already developed about thermodynamics.

- Highly exergonic reactions (large, negative/decreasing ΔG) favor products.
- Highly endergonic reactions (large, positive/increasing ΔG) favor reactants.
- Reactions with small free energy changes lead to equilibrium mixtures of both products and reactants.

Exercise 1.6.3

What is the value of the equilibrium constant at 300K in the following cases?

What is the value of the equilibrium constant in the following cases? (1 kcal = 1000 cal)

a. ΔG = 3 kcal /mol
b. ΔG = -2 kcal/mol
c. ΔG = -5 kcal /mol
d. ΔG = 15 kcal/mol
e. ΔG = -10 kcal/mol
f. The free energy increases by 8 kcal/mol over the reaction.
g. The free energy decreases by 1 kcal/mol over the reaction.

Answer

This is just an algorithm problem, but don't forget to convert kcal to cal.

For example, in (a), \(K = e^\

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= e^{-5.035} = 0.0065\)

Exercise 1.6.4

In which of the cases in Exercise 1.6.3 do you think there would be significant amounts of both products and reactants at equilibrium?

Answer

Remember, the closer K gets to 1, the closer the system gets to an equal mix of reactants and products. That's a slight approximation, because the value of K when there is an equal amount of reactants and products may be more or less than one depending on how many molecules (or moles) of each species are involved in the reaction.

Exercise 1.6.5

The mathematical expression for the equilibrium constant says that K will get smaller at higher temperatures. Explain this phenomenon without the mathematical expression in terms of what you know about temperature and energy.

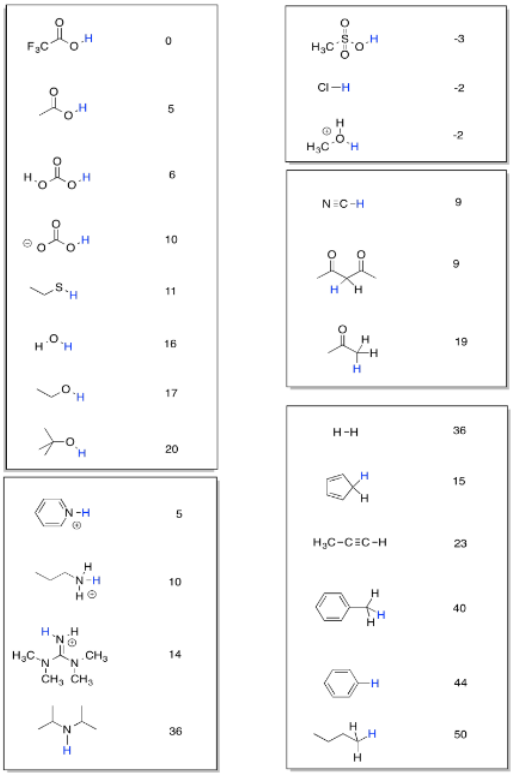
Answer

There are a couple of reasons, but one involves the enthalpy requirement compared to the available energy. Temperature is an index of how much energy is available in the surroundings. The more energy is available from the surroundings, the more likely energy can be supplied to overcome a deficit in enthalpy, for either the forward or the reverse reaction. Thus at high temperature, the equilibrium is just as likely to sit on the high energy side of the reaction as it is on the low energy side.

Another way of looking at things is that the external entropy change is relatively small at high temperature, because the additional distribution of energy resulting from the reaction is very small compared to the pre-existing distribution of external energy when there is already a lot of energy in the surroundings. That leaves only the internal entropy change to govern the equilibrium.

1.7: Equilibrium and pKa

Proton transfer reactions are very common. It's useful to be able to tell whether a proton is likely to be transferred from one position to another. Researchers have worked very hard to work out information that will give them some insight into that problem. The resulting data is often compiled into a pKa table, like the one below.



The table is organised into columns of compounds. On each compound, there is a hydrogen colored in blue. The pK_a value listed next to the compound is an index of how tightly that hydrogen is held by the compound. The bigger the pK_a, the more tightly that proton is held.

- A low pK_a means the proton is given up easily. The compound is very acidic.
- A high pK_a means the proton is held very tightly. The compound is not very acidic.

For example, methanesulfonic acid, CH_3SO_3H, is quite acidic. It has a low pK_a. In this table, its approximate pK_a is listed as -3. What does that mean exactly? Well, the equilibrium constant for the ionisation of any compound is 10^{-pKa}. The equlibrium constant for the ionisation of methanesulfonic acid is 10^3, or 1000. That's the equilibrium constant for the reaction:

$CH_3SO_2O\text{-}H = CH_3SO_2O^- + H^+$

Of course, you may already know that a proton is not likely to wander around on its own. It is normally bound to a lone pair. In some studies, the lone pair is on a water molecule. Then the reaction would really look like this:

$CH_3SO_2O\text{-}H + H_2O = CH_3SO_2O^- + H_3O^+$

In other studies, the lone pair is on another solvent molecule, such as DMSO, $(CH_3)_2SO$. Then the reaction would really look like this:

$CH_3SO_2O\text{-}H + (CH_3)_2SO = CH_3SO_2O^- + (CH_3)_2SOH^+$

The actual value of the pK_a varies depending on the conditions of the measurement. For example, a pK_a measured in water is a little different from a pK_a measured in DMSO, but the trends are generally the same.

We can use the pK_a table to compare the acidity of different compounds. Methanesulfonic acid is much, much more acidic than butane, $CH_3CH_2CH_2CH_3$, which has a pK_a of about 50. In addition, we can use the table to predict the direction of a reaction, or

the equilibrium of a reaction. If a proton is being transferred from one position to another, a comparison of pKa values will tell us whether the reaction will proceed or not.

For example, consider the transfer of a proton from ethane thiol, CH_3CH_2SH, to pyridine, C_5H_5N (it looks like a benzene with one carbon replaced by a nitrogen). The pK_a of the ethane thiol is 11. If the pyridine accepts the proton, it will form a pyridinium ion, $C_5H_5NH^+$, with a pK_a of 5. Qualitatively, we can already predict that the reaction will not proceed that well. The ethane thiol has a higher pK_a than the pyridinium ion, so it will keep its proton, not give it away. However, the difference between the numbers isn't that large. Maybe there will be a measurable equilibrium, meaning an equilibrium in which there are measurable amounts of both products and reactants.

It can be shown that the equilibrium constant for a proton transfer reaction is $K = 10^{(pKa2-pKa1)}$, in which pK_a2 is the pK_a of the acid on the product side and pK_a1 is the pK_a of the acid on the reactant side. The acid is simply the species on either side that might give up its proton.

In this case,

$K = 10^{(5-11)} = 10^{-6}$.

The equilibrium constant is really defined as the ratio of the product concentrations to the reactant concentrations.

$$K = \frac{[products]}{[reactants]}$$

K = [products]/[reactants]

In this case,

$$K = \frac{[CH_3CH_2S^-][C_5H_5NH^+]}{[CH_3CH_2SH][C_5H_5N]}$$

We have two numbers multiplied together in the numerator and two numbers multiplied together in the denominator. Each time an ethane thiol and a pyridine react together and transfer a proton, we will get a thiolate anion and a pyridinium cation. In a simple case, we can think of an equal number of thiolate anions and pyridinium cations forming (since the same proton went from one to the other).

Then the equilibrium constant has a slightly simpler form:

$$K = \frac{x^2}{y^2}$$

in which x = the concentration of either the thiolate or the pyridinium and y = the concentration of either the thiol or the pyridine.

In that case, the ratio of products to reactants, x/y, is equal to the square root of the equilibrium constant. In this case, the ratio is the square root of 0.000001. So the ratio of the products to the reactants is 0.001.

? Exercise 1.7.1

a) Predict the equilibrium constant for the reaction of pentane-2,4-dione, $CH_3COCH_2COCH_3$, with sodium tert-butoxide, $NaOC(CH_3)_3$.

Answer

$K = 10^{20-9} = 10^{11}$

The table can often be used even if you don't see the compound you are looking for. Often, you can see something that looks pretty similar to what you are interested in and you can estimate the pK_a that you need.

? Exercise 1.7.2

a) Predict the equilibrium constant for the reaction of 2-pentanone, $CH_3CH_2COCH_2CH_3$, with sodium methoxide, $NaOCH_3$.

Answer

$K = 10^{17-19} = 10^{-2}$

Note that this pK_a table is organised so that similar sorts of structures are placed in a box together. That arrangement is supposed to make it easier for you to look for trends and understand what kinds of factors make a proton more tightly held or more easily released.

? Exercise 1.7.3

a. Compare a pair of compounds in the box of nitrogen compounds and explain why one has a higher pKa than the other.
b. Compare a pair of compounds in the box of hydrocarbons and explain why one has a higher pKa than the other.
c. Compare a pair of compounds in the box of O-H containing compounds and explain why one has a higher pKa than the other.

1.8: Hess' Law

Sometimes we can use available information about the energetics of reactions to predict the energetics of a new reaction. To see how, we'll look at a relatively simple reaction: the combustion of carbon.

A couple of things could happen when we burn some carbon. Burning typically results in the combination of the elements in a material with oxygen. So we are just talking about combining carbon with oxygen to make a new compound. There are two possibilities. Either the reaction forms carbon monoxide, or it forms carbon dioxide.

The first reaction is:

$$2\,\mathrm{C} + \mathrm{O_2} \rightarrow 2\,\mathrm{CO} \tag{1.8.1}$$

That reaction is exothermic. It releases about 25 kcal per mol of CO produced.

Note that the reaction has been balanced to keep track of the exact numbers of atoms involved in the transaction. Because only one oxygen atom is needed, and the oxygen molecules comes with two oxygen atoms, the oxygen molecule can actually convert two carbon atoms into carbon monoxide.

The second reaction is:

$$\mathrm{C} + \mathrm{O_2} \rightarrow \mathrm{CO_2} \tag{1.8.2}$$

That reaction is also exothermic. It releases about 90 kcal per mol of CO_2 produced.

Because energy is released, or produced, by each reaction, we can think about the energy as another product of the reaction. We'll just list it on the product side of the equation with the other products.

$$2\,\mathrm{C} + \mathrm{O_2} \rightarrow 2\,\mathrm{CO} + 50\,\frac{\mathrm{kcal}}{\mathrm{mol}} \tag{1.8.3}$$

and

$$\mathrm{C} + \mathrm{O_2} \rightarrow \mathrm{CO_2} + 90\,\frac{\mathrm{kcal}}{\mathrm{mol}} \tag{1.8.4}$$

There's a third reaction that is related to these two reactions. It's the combustion of carbon monoxide.

$$2CO + O_2 \rightarrow 2CO_2 \tag{1.8.5}$$

Again, the reaction is exothermic, releasing about 65 kcal per mole of CO_2 produced. It would release 130 kcal for the reaction as written, because we are showing the production of two moles of CO_2. Rewriting the equation to include the energy produced:

$$2CO + O_2 \rightarrow 2CO_2 + 130\frac{kcal}{mol} \tag{1.8.6}$$

What if we conducted this reaction in stages? What if we combusted the carbon to carbon monoxide, then took the carbon monoxide and allowed it to react further to get carbon dioxide?

$$2C + O_2 \rightarrow 2CO + 50\frac{kcal}{mol} \tag{1.8.7}$$

$$2CO + O_2 \rightarrow 2CO_2 + 130\frac{kcal}{mol} \tag{1.8.8}$$

Imagine this is a pair of algebraic equations. What would happen if we added them together?

$$2C + O_2 = 2CO + 50\frac{kcal}{mol} \tag{1.8.9}$$

$$2CO + O_2 = 2CO_2 + 130\frac{kcal}{mol} \tag{1.8.10}$$

Sum: $2C + 2CO + 2O_2 = 2CO + 2CO_2 + 180\frac{kcal}{mol}$

Note that the CO appears on both sides and would cancel.

$$2C + 2O_2 = 2CO_2 + 180\frac{kcal}{mol} \tag{1.8.11}$$

We can drop the factor of 2:

$$C + O_2 = CO_2 + 90\frac{kcal}{mol} \tag{1.8.12}$$

So two reactions, one after the other, would add up to a third. In addition, the energies of those two reactions, added together, give the energy of the third.

This result is a pretty important aspect of thermodynamics. Enthalpy is a state function. that means it does not matter how a reaction is performed. Whether we convert carbon directly into carbon dioxide or we convert it to carbon monoxide, then continue, the e nergy involved is the same overall. That's because the energy of the reaction is a property of the products and the reactants only. It is independent of how we get from one to the other.

One more note on the reactions above. The enthalpies for these reactions, if measured in the correct way, are sometimes called the heats of formation of the compounds. The heat of formation refers to the energy change when the compounds are formed from the elements under standard conditions. We're not going too deeply into what those standard conditions are here. However, because C is the elemental form of carbon and O_2 is the elemental form of oxygen, we would loosely consider the energies listed above to be heats of formation.

- When you hear the phrase "heat of formation", we're just talking about the formation of the compound from the elements.

? Exercise 1.8.1

a. If the heat of formation of potassium chloride, KCl, is -104 kcal/mol, and the heat of formation or potassium chlorite, $KClO_2$, is -95 kcal/mol, then what is the heat of reaction when potassium chloride reacts with oxygen to produce potassium chlorite?
b. If the heat of formation of tantalum(IV) oxide, TaO_2, is -40 kcal/mol, and the heat of formation of tantalum(V) oxide, Ta_2O_5, is -490 kcal/mol, then what is the heat of reaction for the combustion of TaO_2 to Ta_2O_5?
c. If the heat of formation of carbon monoxide, CO, is -25 kcal/mol and the heat of formation of tetracarbonyl nickel, $Ni(CO)_4$, is -145 kcal/mol, then what is the heat of reaction for the formation of tetracarbonyl nickel from nickel and carbon monoxide?

Answer
Answer a

We could write the equations for the reactions, including the energy change involved:

K + 0.5 Cl_2 → KCl + 104 kcal/mol

There is a 0.5 in front of the Cl_2. Although chlorine is diatomic in its elemental state, we only need half the number of Cl_2 molecules as we need potassium atoms if we are to form potassium chloride.

K + 0.5 Cl_2 + O_2 → $KClO_2$ + 95 kcal/mol

In both cases, the heat of formation is negative, so we are writing that energy as a product of the reaction.

If we write the first reaction in reverse,

104 kcal/mol + KCl → K + 0.5 Cl_2

then we are saying that the reverse reaction would require the input of energy.

We will combine those two equations by adding them together:

K + 0.5 Cl_2 + O_2 → $KClO_2$ + 95 kcal/mol

104 kcal/mol + KCl → K + 0.5 Cl_2

Sum:

104 kcal/mol + KCl + K + 0.5 Cl_2 + O_2 → K + 0.5 Cl_2 + $KClO_2$ + 95 kcal/mol

Simplifying (the 0.5 chlorine molecules and potassium atoms appear on both sides, so they cancel):

104 kcal/mol + KCl + O_2 → $KClO_2$ + 95 kcal/mol

Now we use more algebra and combine the numerical part together:

104 kcal/mol - 95 kcal/mol + KCl + O_2 → $KClO_2$ + 95 kcal/mol - 95 kcal/mol

Which leaves:

9 kcal/mol + KCl + O_2 → $KClO_2$

The energy is added on the left. It is needed for the reaction. The heat of reaction, ΔH_{rxn} = + 9 kcal/mol. It's an endothermic reaction.

1.9: Solutions to Selected Problems

Exercise 1.1.1:

Reactions that go down in energy will proceed. Reactions that go up in energy will not proceed. If the reaction profile is higher on the left (reactant side) than the right, the reaction will go forward and it will form products. If the reverse is true, the reaction presumably will not occur.

Exercise 1.2.1:

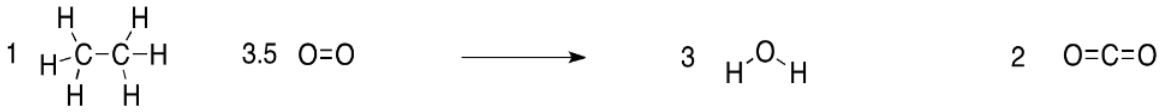
b) Because there are two carbons in ethane, one molecule of ethane will give rise to two molecules of CO_2.

c) Because there are six hydrogens in ethane, one molecule of ethane will give rise to three molecules of H_2O.

d) In order to make two molecules of carbon dioxide (four oxygen atoms) and three water molecules (three oxygen atoms), we would need seven oxygen atoms total. Since oxygen molecules contain pairs of oxygen atoms, we would only need 3.5 oxygen molecules.

In principle, three and a half molecules is a problem. Where are we going to get a half of a molecule? In practice, it's nothing to worry about. We can't really do reactions with single molecules anyway. We are always working with vast numbers of molecules, but we have to make sure we keep them in the right ratio. Instead of using one molecule of ethane, we might use one billion ethane molecules, and 3.5 billion oxygen molecules.

a) The reaction is given with structures below:



e) The energy requirements are laid out in the following table. Overall, the reaction releases 375.5 kcal per mol of ethane burned. The negative sign in the table is often used to denote that this is excess energy released (whereas a positive sign would indicate that energy as consumed overall).

Bond Breaking	**Costs (kcal/mol)**	**Sum of Cost**	**Bond Making**	**Releases (kcal/mol)**	**Sum of Release**	**Overall (kcal/mol)**	
	6 x C-H	6 * 99	594	6 x O-H	6 * 111	666	
	3.5 x O=O	3.5 * 119	416.5	4 x C=O	4 * 180	720	
	1 x C-C	83	83				
total		**breaking:**	1093.5		**making:**	1386	**-292.5**

That's more energy than was produced from a molecule of methane (-170 kcal/mol).

Exercise 1.3.1:

Entropy is higher if the energy is partitioned into more states. For example, in question (b), the same amount of energy is distributed into three states on the left hand side and only two states on the right. Entropy is higher in the left hand example than the right in that case.

Exercise 1.3.2:

Examples of "states" into which energy can be partitioned include molecular vibrational, rotational and translational states (which, loosely speaking, correspond to wiggling, spinning and zipping around). Entropy is higher if energy is distributed into more of these states. That might include a greater range of vibrational or rotational states used in (a) and (c), or similar states employed in a greater number of molecules in (b).

Exercise 1.3.3:

One general observation about internal entropy is that it increases if the number of molecules increases during a reaction and decreases if the number of molecules decreases during a reaction. It's just a matter of counting how many things on the left get turned into how many things on the right. For example, in question (a), one molecule produces two new molecules in the decarboxylation reaction, so the reaction is entropically favored.

Exercise 1.4.1:

The expression $\Delta G = \Delta H - T\Delta S$ includes both an enthalpy contribution and an enthalpy contribution and balances them against each other. However, the effect of entropy is *multiplied by* the temperature. The greater the temperature, the greater will be the influence of entropy (and therefore the smaller the influence of enthalpy). The lower the temperature, the smaller will be the influence of entropy (and therefore the greater the influence of enthalpy).

Exercise 1.4.2:

See problem 1.1.1

Exercise 1.5.1:

The removal of any item produced on the right side of the reaction will shift the reaction to the right in order to restore equilibrium. On the other hand, adding any more of any of the items on the right will shift the reaction to the left.

Items on the left side will work in the opposite way. Adding more of anything on the left will shift the reaction to the right, to use up the newly added materials. Removing anything from the left will shift the reaction further left, to replace the items that were removed.

a. The amount of water increases, moving the reaction to the right. More products are made.
b. The amount of energy increases, moving the reaction to the left. Fewer products are made.
c. The amount of carbon dioxide decreases, shifting the reaction to the right. More products are made.
d. The amount of energy decreases, shifting the reaction to the right. More products are made.
e. The amount of carbon monoxide decreases, shifting the reaction to the left. Fewer products are made.

Exercise 1.5.2:

a. The amount of energy increases, moving the reaction to the left. Fewer products are made.
b. The amount of hydrogen chloride increases, shifting the reaction to the right. More products are made.
c. The amount of acetylene decreases, shifting the reaction to the left. Fewer products are made.
d. The amount of energy decreases, shifting the reaction to the right. More products are made.
e. This question does not follow the pattern. However, because the products and reactants are all gases, we can think about the effect they would have on pressure if the reaction moved one way or the other. Because fewer gas molecules are produced on the right than the left, pressure would decrease on going from left to right (and increase on going from right to left). Thus, we can pencil in "pressure" as an item on the left side of the reaction. That means increasing pressure will shift the reaction to the right, making more products.

Exercise 1.5.3:

a. The amount of energy increases, shifting the reaction to the right. More products are made.
b. The amount of energy decreases, moving the reaction to the left. Fewer products are made.
c. The amount of phosphate increases, shifting the reaction to the right. More products are made.

Exercise 1.5.4:

a. The nitric acid would build up in the water, and the NO gas would build up, until equilibrium is reached. The nitric acid in the water would be limited by that equilibrium point.
b. Periodically removing the nitric acid solution and adding fresh water would help to shift the reaction further to the right, although the eventual buildup of NO gas might prevent the reaction from shifting too far.
c. A constant source of both water and nitrogen dioxide (nitric oxide) would help to push the reaction to the right. Although allowing gases to vent would limit the amount of nitrogen dioxide in the system, it would also prevent a buildup of nitrogen monoxide (nitrous oxide), which would otherwise push the reaction to the left, eventually.

Exercise 1.6.1:

The exponent is the number of times the base number is multiplied by itself. For example, 10^3 = 10 x 10 x 10. The higher the exponent, the larger the resulting mathematical product.

The same is true with the magnitude of a negative exponent, but the negative sign means that we are dealing with the inverse of the base number. For example, $10^{-2} = \frac{1}{10} \times \frac{1}{10} = \frac{1}{(10 \times 10)}$

Exercise 1.6.2:

The greater (and more positive) the free energy change, the smaller the equilibrium constant.

However, the greater (and more negative) the free energy change, the larger the equilibrium constant.

Equilibrium constants, from largest to smallest, would have associated free energies as follows:

(large K) big, negative ΔG > small, negative ΔG > small, positive ΔG > large, positive ΔG (small K)

Exercise 1.6.3:

This is just an algorithm problem, but don't forget to convert kcal to cal.

For example, in (a), $K = e^{-\frac{3000 cal\ mol^{-1}}{1.986 cal\ K^{-1}\ mol^{-1} \times 300 K}} = e^{-5.035} = 0.0065$

Exercise 1.6.4:

Remember, the closer K gets to 1, the closer the system gets to an equal mix of reactants and products. That's a slight approximation, because the value of K when there is an equal amount of reactants and products may be more or less than one depending on how many molecules (or moles) of each species are involved in the reaction.

Exercise 1.6.5:

There are a couple of reasons, but one involves the enthalpy requirement compared to the available energy. Temperature is an index of how much energy is available in the surroundings. The more energy is available from the surroundings, the more likely energy can be supplied to overcome a deficit in enthalpy, for either the forward or the reverse reaction. Thus at high temperature, the equilibrium is just as likely to sit on the high energy side of the reaction as it is on the low energy side.

Another way of looking at things is that the external entropy change is relatively small at high temperature, because the additional distribution of energy resulting from the reaction is very small compared to the pre-existing distribution of external energy when there is already a lot of energy in the surroundings. That leaves only the internal entropy change to govern the equilibrium.

Exercise 1.7.1:

a) K = $10^{20\text{-}9} = 10^{11}$

Exercise 1.7.2:

a) K = $10^{17\text{-}19} = 10^{-2}$

Exercise 1.8.1:

a) We could write the equations for the reactions, including the energy change involved:

$$K + 0.5Cl_2 \rightarrow KCl + 104\frac{kcal}{mol}$$

There is a 0.5 in front of the Cl_2. Although chlorine is diatomic in its elemental state, we only need half the number of Cl_2 molecules as we need potassium atoms if we are to form potassium chloride.

$$K + 0.5Cl_2 + O_2 \rightarrow KClO_2 + 95\frac{kcal}{mol}$$

In both cases, the heat of formation is negative, so we are writing that energy as a product of the reaction.

If we write the first reaction in reverse,

$$104\frac{kcal}{mol} + KCl \rightarrow K + 0.5Cl_2$$

then we are saying that the reverse reaction would require the input of energy.

We will combine those two equations by adding them together:

$$K + 0.5Cl_2 + O_2 \rightarrow KClO_2 + 95\frac{kcal}{mol}$$

$$104\frac{kcal}{mol} + KCl \rightarrow K + 0.5Cl_2$$

Sum:

$$\boxed{104 \frac{kcal}{mol} + KCl + K + 0.5Cl_{2} + O_{2} \rightarrow K + 0.5Cl_{2} + KClO_{2} \_ 95 \frac{kcal}{mol} \nonumber}$$

Simplifying (the 0.5 chlorine molecules and potassium atoms appear on both sides, so they cancel):

$$104\frac{kcal}{mol} + KCl + O_2 \rightarrow KClO_2 + 95\frac{kcal}{mol}$$

Now we use more algebra and combine the numerical part together:

$$104\frac{kcal}{mol} - 95\frac{kcal}{mol} + KCl + O_2 \rightarrow KClO_2 + 95\frac{kcal}{mol} - 95\frac{kcal}{mol}$$

Which leaves:

$$9\frac{kcal}{mol} + KCl + O_2 \rightarrow KClO_2$$

The energy is added on the left. It is needed for the reaction. The heat of reaction, ΔH_{rxn} = + 9 kcal/mol. It's an endothermic reaction.

CHAPTER OVERVIEW

2: Ligand Binding in Coordination Complexes and Organometallic Compounds

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2.1: Introduction

> **Note**
>
> A general introduction to coordination compounds is given in the context of Lewis acids and bases on another page.

Much of reactivity can be understood in Lewis acidity terms. Perhaps the simplest examples of reactions are the formation of Lewis acid-base complexes. In a Lewis acid-base complex, a Lewis base has simply shared a pair of electrons with a Lewis acid, forming a new bond.

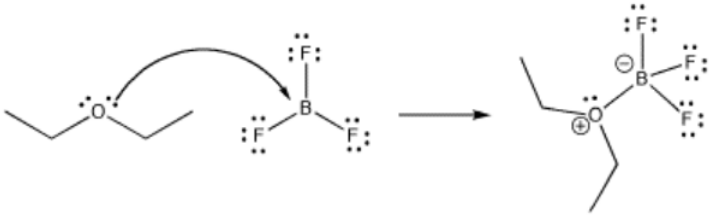


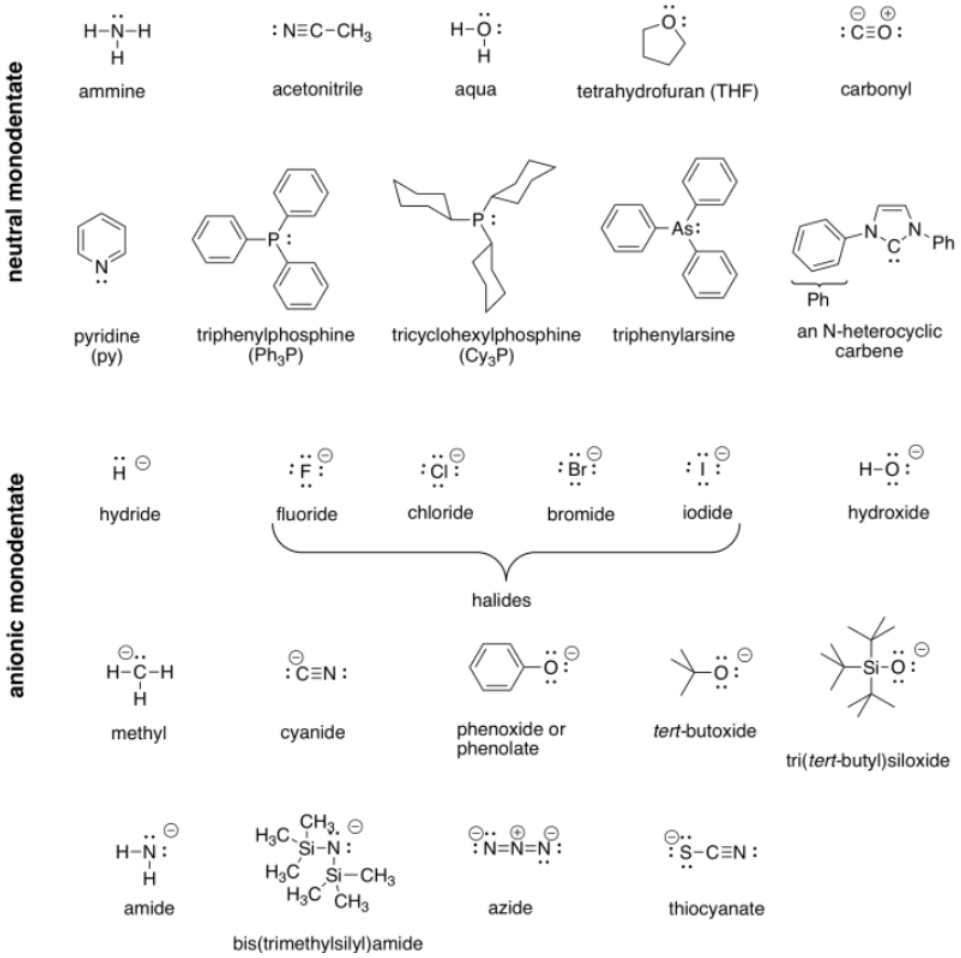
Figure 2.1.1: Formation of a Lewis acid-base complex, boron trifluoride etherate.

Frequently, metal atoms or ions act as Lewis acids. They can often accept electrons from a number of different Lewis bases at once, forming "complexes" or "complex ions" ("complex" meaning they are formed from individual parts that connect together). These Lewis bases (also called "ligands") are said to be "coordinated" to the metal, meaning they are stuck to the metal via the electron pair that they share with it.

Figure 2.1.2: Coordination of ammonia to complete the formation of *cis*-platin, an important antitumour drug.

A number of examples of ligands (compounds with lone pairs that can bind to metals) are shown in the following table.

Table 2.1.1: Some Common Ligands.



"Coordination complexes" play important roles in biology as well as economically important processes. Probably the most familiar coordination complex in biology is hemoglobin. It can coordinate with an additional dioxygen molecule and carry the oxygen through the bloodstream, delivering oxygen to tissues much more efficiently.

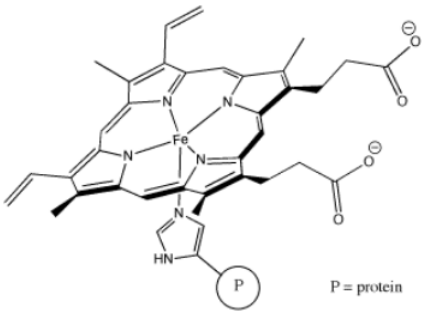


Figure 2.1.3: Hemoglobin, a biologically important coordination complex.

A very common coordination complex in industrial use is Wilkinson's catalyst, $(PPh_3)_3RhCl$. Wilkinson's catalyst is used to make a number of transformations more efficient; most notably, it is used in hydrogenation reactions. Chemical transformations of this sort are commonly used in making pharmaceuticals and other high-demand materials.

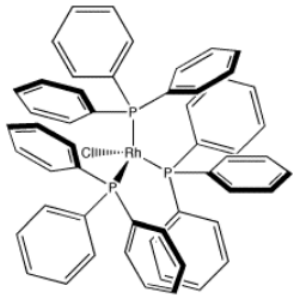


Figure 2.1.4: Wilkinson's Catalyst.

Because coordination compounds can sometimes be anions or cations, there is a convention used to tell the reader which part of the formula is connected together, and which part is the counterion(s). The part listed in square brackets consists of ligands bonding to a central metal; the part outside the brackets is the counterion(s). For example, $[(H_2O)_6Co]Cl_2$ consists of a Co2+ ion bound to six waters. Two separate chloride anions are found nearby.

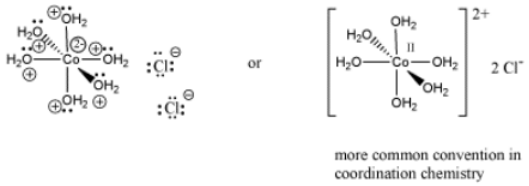


Figure 2.1.5: Structural drawings for the formula $[(H_2O)_6Co]Cl_2$.

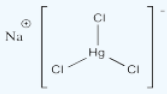
? Exercise 2.1.1

Draw structures for the following coordination compounds.

a. $K_2[PtCl_6]$
b. $K_3[Fe(CN)_6]$
c. $[(NH_3)_4CoCl_2]Cl$ (two isomers)
d. $[(NH_3)_3CoCl_3]$ (two isomers)
e. $[(NH_3)_2Ag]PF_6$ (it's Ag^+; that's a single PF_6^- counterion)
f. $Na[HgCl_3]$
g. $Cd(NH_3)_4Cl_2$ (two isomers)
h. $Li_2[CoCl_4]$
i. $K[Rh(CO)_2I_2]$
j. $[Fe(OH_2)_6])NO_3)_2$
k. $[Cu(NH_3)_4](SO_4)_2$
l. $Na_2[Ni(CN)_4]$
m. $[Fe(OH_2)_6])NO_3)_2$ (repeat of j.)
n. $K_3[Fe(SCN)_6]$
o. $K_2[Zn(OH)_4]$
p. $Pt(NH_3)_2Cl_2$ (two isomers)
q. $[Ru(NH_3)_5Cl]Cl_2$
r. $Li[Sn(OH)_3]$
s. $K_4[Mn(CN)_6]$
t. $Ni(CO)_4$
u. $[Co(NH_3)_5NO_2](NO_2)_2$ (two isomers based on how the ligand connects to the metal)
v. $[Co(NH_3)_5SCN]Cl_2$ (two isomers possible)
w. $[VO]SO_4$ (challenge: why might you draw the V-O bond differently than the other metal-ligand bonds so far?)
x. $[VO_2]PF_6$
y. $Na_2[HgS_2]$
z. $K[MnO_4]$

Answer

f)



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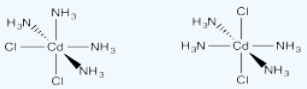

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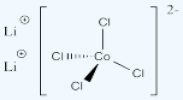

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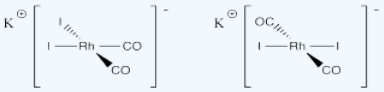

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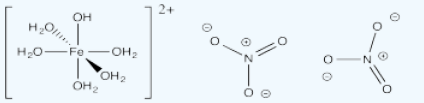

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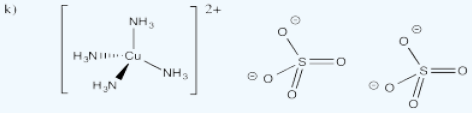

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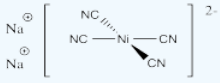

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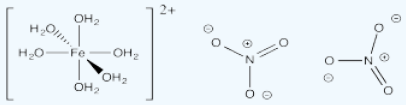

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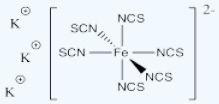

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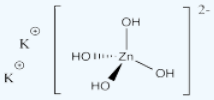

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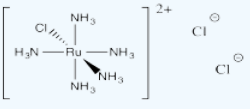

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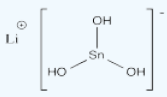

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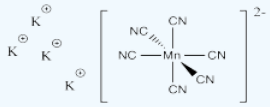

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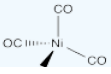
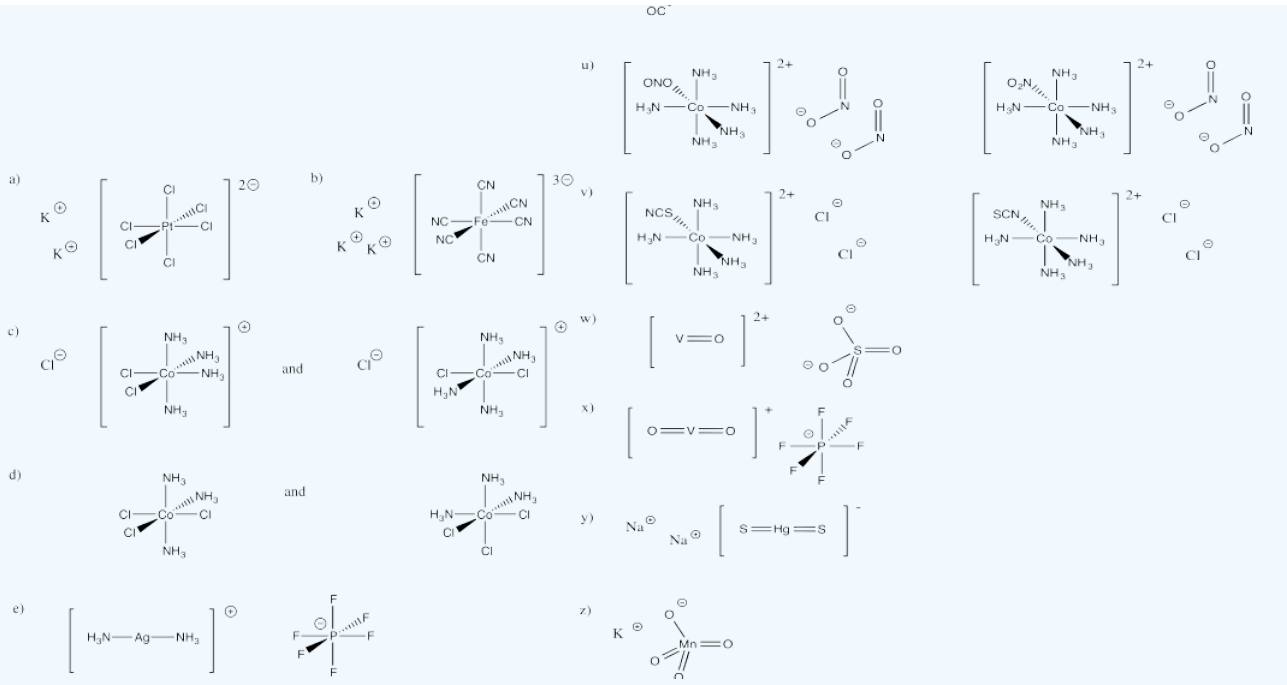




Exercise 2.1.2

Identify the geometries of each of the complexes in Exercise 2.1.1

Note:

Some of the complexes in Exercise 2.1.1 (Problem CC1.1.) have interesting stories. For example, problem (a) was reported many years ago by Alexander Shilov to be capable of breaking C-H bonds. This reaction has the potential to convert methane, routinely burned off in petroleum fields because it is a safety hazard, into useful products. All of that methane is currently being converted directly into greenhouse gases, and that's a real problem. (Astronauts have reported that, at night on Earth, the petroleum fields of the Middle East shine brighter than major cities.) This reaction has recently received intensive study in the lab of John Bercaw at Caltech.

Problem (i) is an economically important catalyst, used in the production of acetic acid in the Monsanto Process, originally developed by BASF but improved upon by Monsanto. These days, it is being supplanted by the same complex with iridium instead of rhodium; that complex drives the more environmentally-friendly Cativa Process. The new process was developed by BP. Acetic acid is a sort of heavy-duty worker molecule used in the production of paints, plastics, pharmaceuticals and other commodities.

Problem (p) is a member of a class of potent anti-cancer drugs that are particularly effective against testicular and ovarian tumours. Exactly how they worked was the subject of study for many years, and was finally deduced by Steve Lippard (MIT) and Amy Rosenzweig (Northwestern).

Problem (t) is used in the Mond Process for the purification of nickel ores. We use nickel principally in making steel, but also in other alloys.

Vanadyl salts such as (w) are sometimes found in minerals such as cavansite, giving them an intense blue color.

2.2: How Tightly Do Ligands Bind?

All Lewis acid-base complexes form reversibly. That means that, just as the Lewis base can donate its electrons to the acid, it can take them back again.

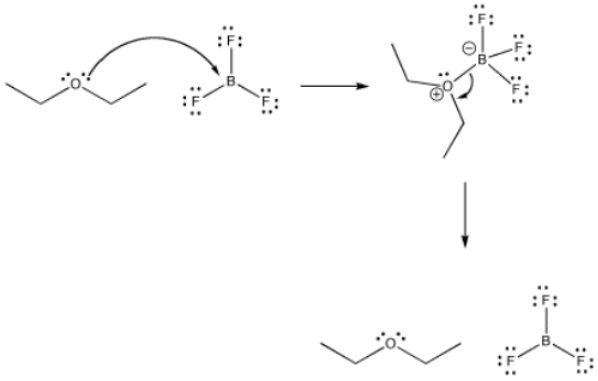


Figure 2.2.1: Reversible binding in a Lewis acid-base complex.

Exactly how reversible are these bonds? How tightly is a ligand bound in a coordination complex? There are many factors that affect the answer to this question, including the nature of the metal, the ligand, the environment or solvent, the temperature, and so on. However, in general, the answer could be found in any specific case by looking at an equilibrium constant.

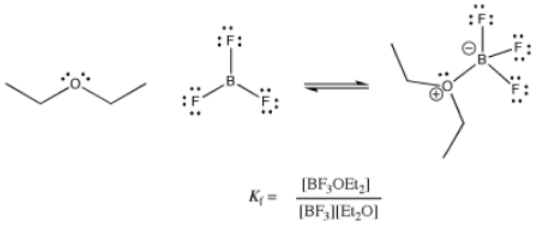


Figure 2.2.2: The equilibrium constant in a Lewis acid-base complex.

This equilibrium constant, which compares the ratio of complex to free Lewis acid and Lewis base, is sometimes called the formation constant or the binding constant. It is a measure of how tightly the ligand is bound. The same thing expressed in reverse, $K = \frac{[BF_3][Et_2O]}{[BF_3OEt_2]}$, is called the dissociation constant. Of course, it really measures the same thing from the opposite point of view: how easily is the ligand given up? Numerically, it is just the inverse, 1 / Kf.

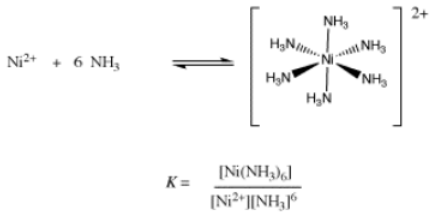


Figure 2.2.3: Formation of a hexaammine nickel ion.

If there are many ligands bound to the ion, as in the formation of hexaammine nickel ion, then the formation constant becomes more complicated. It is really a combination of six different binding constant: the constant for the first ammonia with nickel ion, the constant for the second ammonia with the ammine nickel ion, and so on. When all of these individual constants are combined, we arrive at an ammonia concentration raised to the sixth power in the expression for the formation constant.

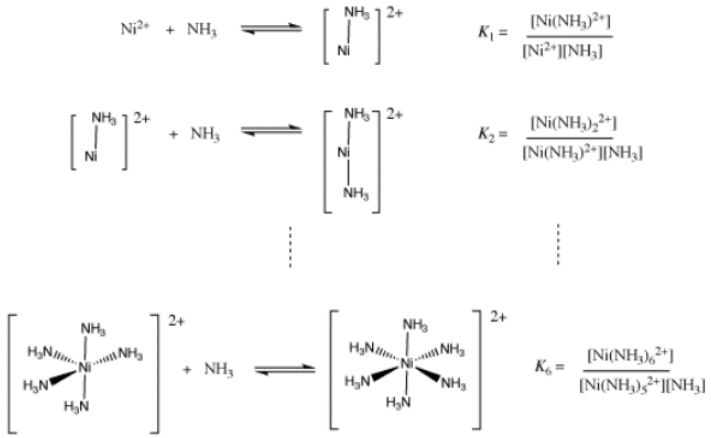


Figure 2.2.4: Stepwise formation of a hexaammine nickel ion.

Exercise 2.2.1

Show that the overall equilibrium constant for formation of $Ni(NH_3)_6^{2+}$ is a product of the equilibrium constants for individual ammonia binding steps, K_1 x K_2 x ... x K_6.

Answer

$$K_6 = \frac{[Ni(NH_3)_6^{2+}]}{[Ni(NH_3)_5^{2+}]\,[NH_3]}$$

but $$K_5 = \frac{[Ni(NH_3)_5^{2+}]}{[Ni(NH_3)_4^{2+}]\,[NH_3]}$$ or $$K_5\,[Ni(NH_3)_4^{2+}][NH_3] = [Ni(NH_3)_5^{2+}]$$

so $$K_6 = \frac{[Ni(NH_3)_6^{2+}]}{K_5\,[Ni(NH_3)_4^{2+}][NH_3][NH_3]}$$ or $$K_5\,K_6 = \frac{[Ni(NH_3)_6^{2+}]}{[Ni(NH_3)_4^{2+}][NH_3]^2}$$

and so on until $$K_1K_2K_3K_4K_5K_6 = \frac{[Ni(NH_3)_6^{2+}]}{[Ni^{2+}][NH_3]^6} = K$$

Determining an equilibrium constant requires that the concentrations of the individual species can be measured, such as $[Ni^{2+}]$, $[NH_3]$ and $[Ni(NH_3)_6^{2+}]$. This measurement might be accomplished using spectroscopic or electrochemical techniques. This measurement has been done for this example at 25 ° C in water, and the value of K = 1.0 x 10^8 M^{-6}.

Exercise 2.2.2

The numerical values for individual binding constants for ammonia with nickel at 25 ° C in water are as follows:

K_1: 4.7 x 10^2 K_2: 1.3 x 10^2 K_3: 41 K_4: 12 K_5: 4.2 K_6: 0.81

a) Use these values to confirm the value of the complex formation constant for $[Ni(NH_3)_6^{2+}]$.

b) What explanations can you offer for the trend in individual K values?

Answer
Answer a

$K = K_1$ x K_2 x K_3 x K_4 x K_5 x K_6

= 470 x 130 x 41 x 12 x 4.2 x 0.81

= 1.03 x 10^8

Answer b

As the nickel binds ammonia ligands, it becomes more electronically saturated. That means it becomes less Lewis acidic. It does not have as strong an attraction for additional ligands.

The reality of the experimental determination of the binding constant is more complex than illustrated in these figures. For example, a Ni^{2+} ion does not really exist on its own. First of all, there must be counterions involved. If the counterions are not selected carefully, they might affect the measurements. For example, if the counterions are chlorides, maybe they could form $NiCl_2$ or other chloride species. Chloride is a Lewis base and it could compete with ammonia as an alternative nucleophile or ligand. Other counterions are called "non-coordinating" because they do not generally bind with Lewis acids; these include BF_4^-, PF_6^- and ClO_4^-.

In addition, the fact that the experiment was done in water means that Ni^{2+} ion was not really involved. Water is a nucleophile, too. That means that the real starting species was $[Ni(OH_2)_6^{2+}]$. Instead of just binding to a bare nickel ion, the ammonia was replacing the water molecules, one at a time.

Exactly how one nucleophile substitutes for another in a coordination complex is the subject of another chapter.

? Exercise 2.2.3

Explain the differences between formation constants for the following of complexes at 25 ° C:

a) $[Zn(NH_3)_4^{2+}]$: 7.8 x 10^8 and $[Zn(CN)_4^{2-}]$: 4.7 x 10^{19}

b) $[Fe(CN)_6^{4-}]$: 1.0 x 10^{24} and $[Fe(CN)_6^{3-}]$: 1.0 x 10^{31}

Answer

Answer a

This is a Zn^{2+} ion binding to either NH_3 or CN^- ligands. The zinc cation is more strongly attracted to the anionic cyanide ligands than the neutral ammonia ligand, so the binding constant with cyanide is higher than with ammonia.

Answer b

Both cases involve cyanide ions. In one case, the CN^- binds to Fe^{2+}, whereas the other case involves Fe^{3+}. The ligand is more attracted to the more highly charged ion, so the binding constant is higher.

2.3: Electron Counting in Transition Metal Complexes

Electron counting is always important in chemistry, especially when reactions are occurring. Because reactions involve the transfer of electrons from one atom to another during the making and breaking of chemical bonds, we need to keep track of where the electrons are going.

Counting electrons on a transition metal in a coordination compound can be a little tricky. Instead of an eight-electron rule or octet, transition metals obey an eighteen electron rule. The easiest way to count electrons is to take the complex apart and count the electrons in pieces. First, we give the donated electrons back to the individual ligands.

- Deconstruct the complex: give lone pairs back to ligands

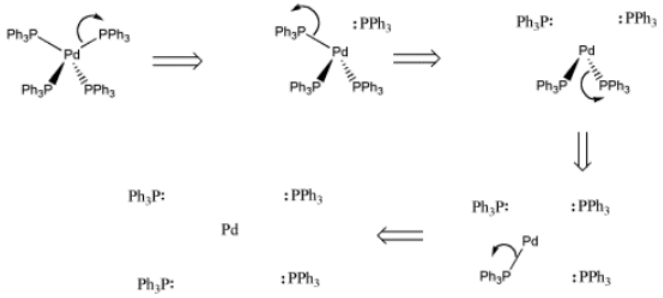


Figure 2.3.1: Giving each pair of donor electrons back to the ligands in a coordination complex.

Once the complex has been deconstructed, we count a pair of electrons for each ligand, since they are each donating a pair to the metal in the complex. Also, we must count the valence electrons that the metal brings itself. The total is the electron count in the metal in the complex. It often equals eighteen.

- Count one pair of electrons per ligand
- Count the valence electrons on the metal

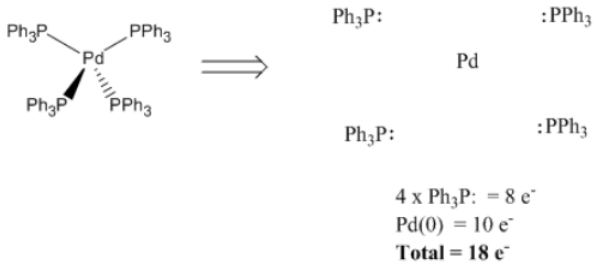


Figure 2.3.2: Counting electrons on the ligands and the metal.

There is a wrinkle in this process if charges are involved. For example, if the free ligands are not neutral, but charged, you need to adjust the electron count on the metal. The metal may be an ion, not an atom, so the electron count will be lower. If donor atoms have formal charges, adjust the charge on the metal atom or ion to balance the overall charge on the complex. In many cases, the overall charge is zero, so the metal charge is just the sum of charges on ligands.

If you don't remember anything about formal charges, review here.

- Check for formal charges on free ligand donor atoms
- Adjust charge on metal so that the overall charge of (ligands + metal) equals the charge on the complex

For example, in *cis*-platin, two of the ligands are chlorides, which have negative charges. Since *cis*-platin is neutral overall, the platinum must have a two plus charge. As a result, it does not have ten electrons. It only has eight. The total electron count on the metal in the complex is sixteen.

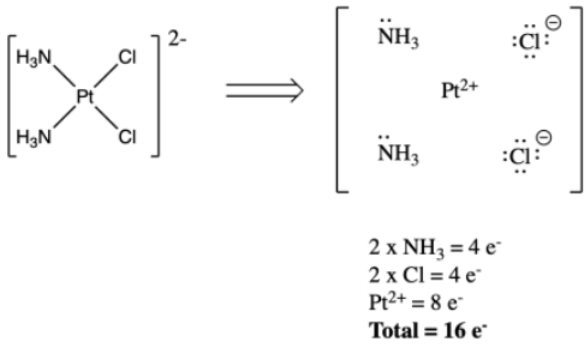


Figure 2.3.3: Counting electrons on the anionic ligands and the metal ion.

A further wrinkle occurs if there is an overall charge on the complex. In main group, covalent compounds, we always adjust the electron count to reflect an overall charge on the structure. We don't have to do that here, because we already make the adjustment when we decide the "oxidation state" or charge on the metal.

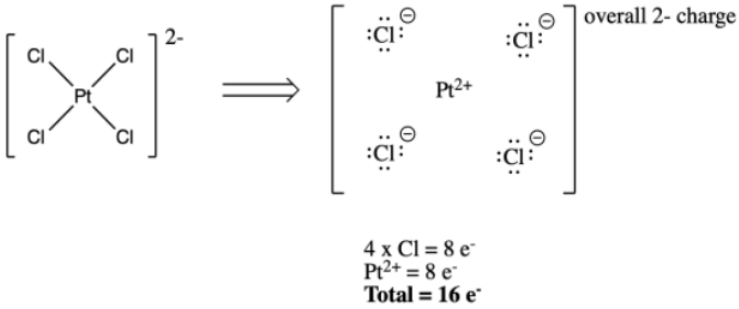
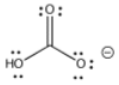
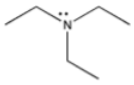
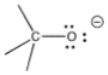
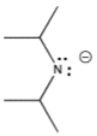


Figure 2.3.4: Counting electrons on the ligands and the metal ion in an overall anionic complex.

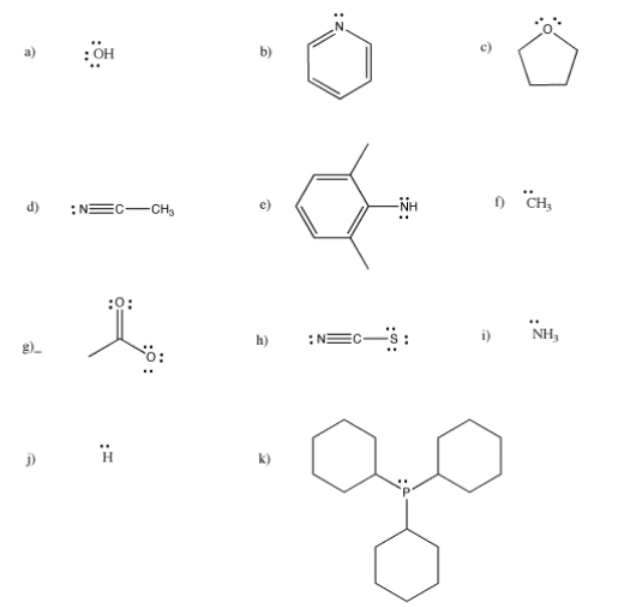
Anionic ligands are often prepared by deprotonating a neutral molecule. Some common bases used in synthetic chemistry are shown below. A range of base strengths are needed to ensure complete removal of proton from a variety of reactants. On the other hand, very large pKa differences between the acid reactant and the conjugate acid produced in the reaction, can cause highly exothermic reactions and lead to fires.

Table CC 2.3.1: Some bases commonly used in synthetic chemistry.

Base (counterions omitted)	Approximate pKa of conjuga
	5
	7
	9
	11
	15
	17
	35
	36
	45

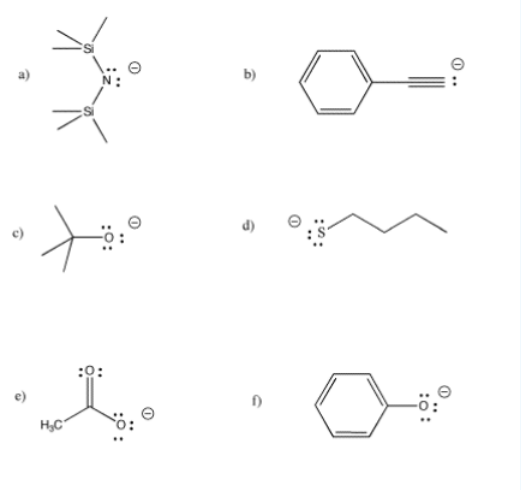
Exercise 2.3.1

Which of the following ligands are anionic, and which ones are neutral?



Exercise 2.3.2

For the following ligands, show the corresponding neutral (the conjugate acid). Select an appropriate base to deprotonate it, and justify your choice.



Exercise 2.3.3

Draw structures for the following complexes (or complex ions), then deconstruct them into ligands and metal atoms (or ions).

a) $[Co(NH_3)_4Cl_2]^+$ b) $[Fe(CN)_6]^{3-}$ c) $[Co(NH_3)_6]^{2+}$

d) $[MnO_4]^-$ e) $Fe(CO)_5$ f) $[PtCl_6]^{2-}$

g) $Mo(CO)_6$ h) $[WO_4]^{2-}$ i) $(PPh_3)_3RhCl$

j) $[RuO_3]^{2-}$ k) $PCy_3Ir(H)(CO)Cl$ (Cy = cyclohexyl)

Exercise 2.3.4

For each complex in the previous problem, what is the valence electron count at the metal in the complex?

Answer a

Metal valence count: 9

Metal with charge: 6

Donated by ligands: 6 x 2 = 12

Total: 18

Answer b

Metal valence count: 8

Metal with charge: 5

Donated by ligands: 6 x 2 = 12

Total: 17

Answer c

Metal valence count: 9

Metal with charge: 7

Donated by ligands: 6 x 2 = 12

Total: 19

Answer d

Metal valence count: 7

Metal with charge: 0

Donated by ligands: 4 x 4 = 16

Total: 16

Answer e

Metal valence count: 8

Metal with charge: 8

Donated by ligands: 5 x 2 = 10

Total: 18

Answer f

Metal valence count: 10

Metal with charge: 6

Donated by ligands: 6 x 2 = 12

Total: 18

Answer g

Metal valence count: 6

Metal with charge: 6

Donated by ligands: 6 x 2 = 12

Total: 18

Answer h

Metal valence count: 6

Metal with charge: 0

Donated by ligands: 4 x 4 = 16

Total: 16

Answer i

Metal valence count: 9

Metal with charge: 8

Donated by ligands: 4 x 2 = 8

Total: 16

Answer j

Metal valence count: 8

Metal with charge: 4

Donated by ligands: 3 x 4 = 12

Total: 16

Answer k

Metal valence count: 9

Metal with charge: 7

Donated by ligands: 4 x 2 = 8

Total: 15

Charge on metal is often represented as a Roman number in parentheses. This number is formally called the oxidation state. Oxidation state refers to how many electrons an atom has lost (or gained). In cases like this one, the oxidation state is the same thing as the charge on an ion. For example, Ta(V) means a Ta^{5+} ion.

? Exercise 2.3.5

How many valence electrons are found on the following metal ions?

a) Fe(II) b) Ni(II) c) Mn(II) d) Fe(III)

e) Zn(II) f) Mn(IV) g) Cu(I) h) Au(0)

i) Cr(IV) j) Cu(II) k) Fe(IV)

Answer

Answer a

6

Answer b

8

Answer c

5

Answer d

5

Answer e

10

Answer f

1

Answer g

10

Answer h

12

Answer i

2

Answer j

9

Answer k

4

Coordination complexes most often have 18 electrons on the metal atom. That's because, for transition metals, eighteen is the number of electrons in the nearest noble gas configuration, which includes s + p + d electrons. (The second and third row of transition metals have f electrons, too, but we usually simplify and don't worry about those electrons for electron counting purposes; we treat them like core electrons, not valence electrons.) Frequent exceptions include 16 electron complexes, which are especially common in late metals such as copper, nickel and palladium. There are molecular orbital considerations that contribute to these exceptions.

Occasionally, electron counts can be as low as eight electrons. These cases often occur in early transition metals, such as titanium or tantalum. These metals have a long way to go to get to eighteen electrons, and sometimes they cannot fit that many ligands in their "coordination sphere". Hence, steric factors can prevent metals from reaching eighteen electrons.

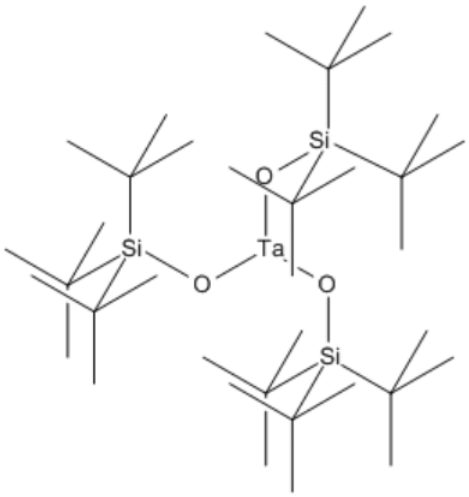


Figure 2.3.7: $(Silox)_3Ta$, or $(^tBu_3SiO)_3Ta$, an electronically unsaturated metal complex.

Complexes that do not have eighteen electrons are sometimes called "electronically unsaturated". Like six electron complexes in main group chemistry, they often react with donors in order to increase the electron count at the metal atom.

? Exercise 2.3.6

Deconstruct $(silox)_3Ta$ into ligands and metal atom (or ion) and confirm the electron count on tantalum

? Exercise 2.3.7

Draw the following low-valent compounds, and determine the number of valence electrons at the metal in each one.

a) Me_3TaCl_2 b) $[(Me_3Si)_2N]_3Fe$ c) $W(CH_3)_6$

Because steric crowding is one of the reasons that metals in coordination complexes may remain "electronically unsaturated" (meaning not enough electrons) or "coordinatively unsaturated" (because there aren't enough donors), it is important to pay attention to how much space a ligand will occupy. The parameter used to describe this factor is called a "cone angle". This is just the angle at the nose of the imaginary cone where the ligand attaches to the metal. The breadth of the cone, and thus the cone angle, is detarmined by how large the ligand is. A large cone angle indicates a large ligand; a small cone angle is associated with a smaller ligand.

For example, trimethylphosphine, $P(CH_3)_3$, has a cone angle of 118^0. Triethylphosphine, $P(CH_2CH_3)_3$, is slightly larger, with a cone angle of 132^0.

? Exercise 2.3.8

Predict which of the following pairs will have the larger cone angle.

a) PF_3 or PH_3

b) PH_3 or $P(CH_3)_3$ (also abbreviated PMe_3)

c) PMe_3 or $P(C(CH_3)_3)_3$ (also abbreviated P^tBu_3)

d) P^tBu_3 or $P(cyclic\text{-}C_6H_6)_3$ (also abbreviated PPh_3)

Answer
Answer a

PF_3 (104^o vs 87^o)

Answer b

PMe_3 (118^o vs 87^o)

Answer c

P^tBu_3 (182^o vs 118^o)

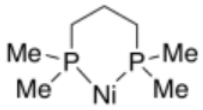
Answer d

P^tBu_3 (182^o vs 145^o)

2.4: Chelation

Monodentate ligands bind through only one donor atom. Monodentate means "one-toothed". The halides, phosphines, ammonia and amines seen previously are monodentate ligands.

Bidentate ligands bind through two donor sites. Bidentate means "two-toothed". An example of a bidentate ligand is bis(dimethylphosphino)propane. It can bind to a metal via two donor atoms at once: it uses one lone pair on each phosphorus atom.

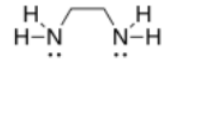


an example of a bidentate donor coordinating to a metal

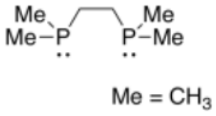
More examples of bidentate ligands are shown below. They all have at least two different atoms with lone pairs. In some cases, there are additional atoms with lone pairs, but only two of them are able to face the metal at one time. Oxalate and glycinate would act as bidentate donors, donating up to two sets of lone pairs at the same time.

Table CC 2.4.1 Some common bidentate ligands

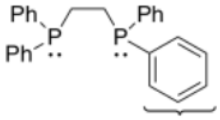
neutral bidentate



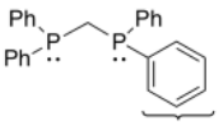
ethylenediamine (en)



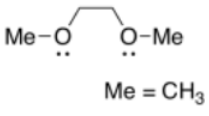
1,2-bis (dimethylphosphino) ethane (dmpe)



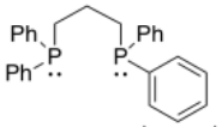
1,2-bis (diphenylphosphino) ethane (dppe) or diphos



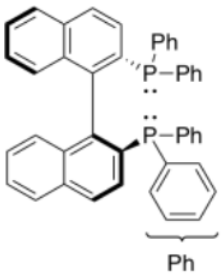
1,2-bis (diphenylphosphino) methane (dpm)



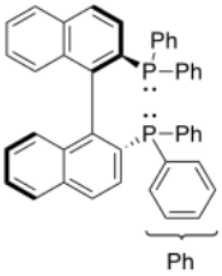
dimethoxyethane (dme)



1,2-bis (diphenylphosphino) propane (dppp)



(*S*)-BINAP



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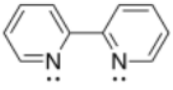
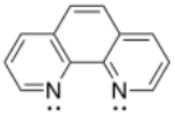
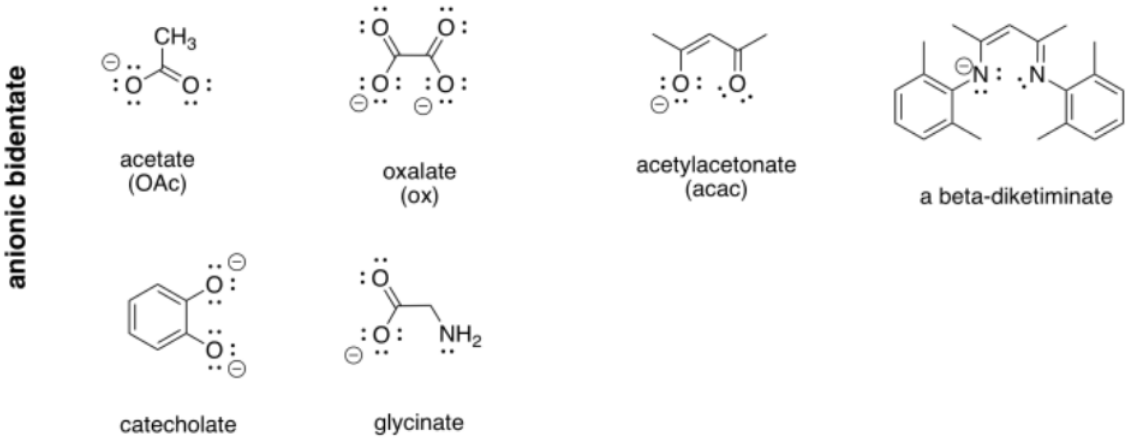


bipyridyl (bpy)



phenanthroline (phen)



Bidentate binding allows a ligand to bind more tightly. Tridentate ligands, which bind through three donors, can bind even more tightly, and so on. This phenomenon is generally called the "chelate effect". This term comes from the Greek chelos, meaning "crab". A crab does not have any teeth at all, but it does have two claws for tightly holding onto something.for a couple of reasons. A very simple analogy is that, if you are holding something with two hands rather than one, you are not as likely to drop it.

- Multidentate ligands bind more tightly because of the chelate effect

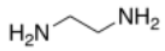
The chemical reasons for the chelate effect involve relative enthalpy and entropy changes upon binding a multidentate ligand. In terms of enthalpy, in order to completely remove a bidentate ligand, two coordinate bonds must be broken. That costs more energy than breaking one coordinate bond for a monodentate ligand.

In terms of entropy, which deals with the distribution of energy within a system, it is generally thought that bringing two molecules together (a bidentate ligand and a metal complex) costs less than bringing three molecules together (two monodentate ligands and a metal complex). That's because individual molecules are free to move around, tumble and vibrate independently. Once they come together, they have to do all these things together. Since these different types of motion represent different ways of distributing energy, if the system becomes more restricted, energy can't be distributed in as many states.

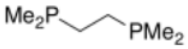
- Energy is lowered even more by two bonding interactions
- Compared to two separate donors, bidentate donation is entropically favored

? Exercise 2.4.1

Draw metal complexes using the ligands below, binding to Ni(2+) in a bidentate mode.

a) 

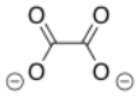
ethylenediamine (en)

b) 

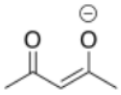
dimethylphoshinoethane (dmpe)

c) 

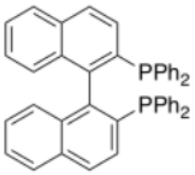
acetate (OAc)

d) 

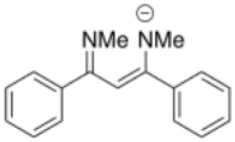
oxalate (ox)

e) 

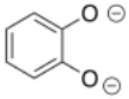
acetylacetonate (acac)

f) 

BINAP

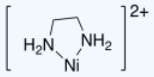
g) 

beta-diketiminate

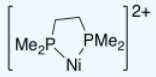
h) 

catecholate

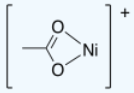
Answer

a) 

ethylenediamine (en)

b) 

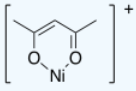
dimethylphoshinoethane (dmpe)

c) 

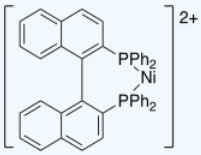
acetate (OAc)

d) 

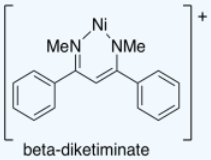
oxalate (ox)

e) 

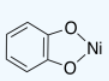
acetylacetonate (acac)

f) 

BINAP

g) 

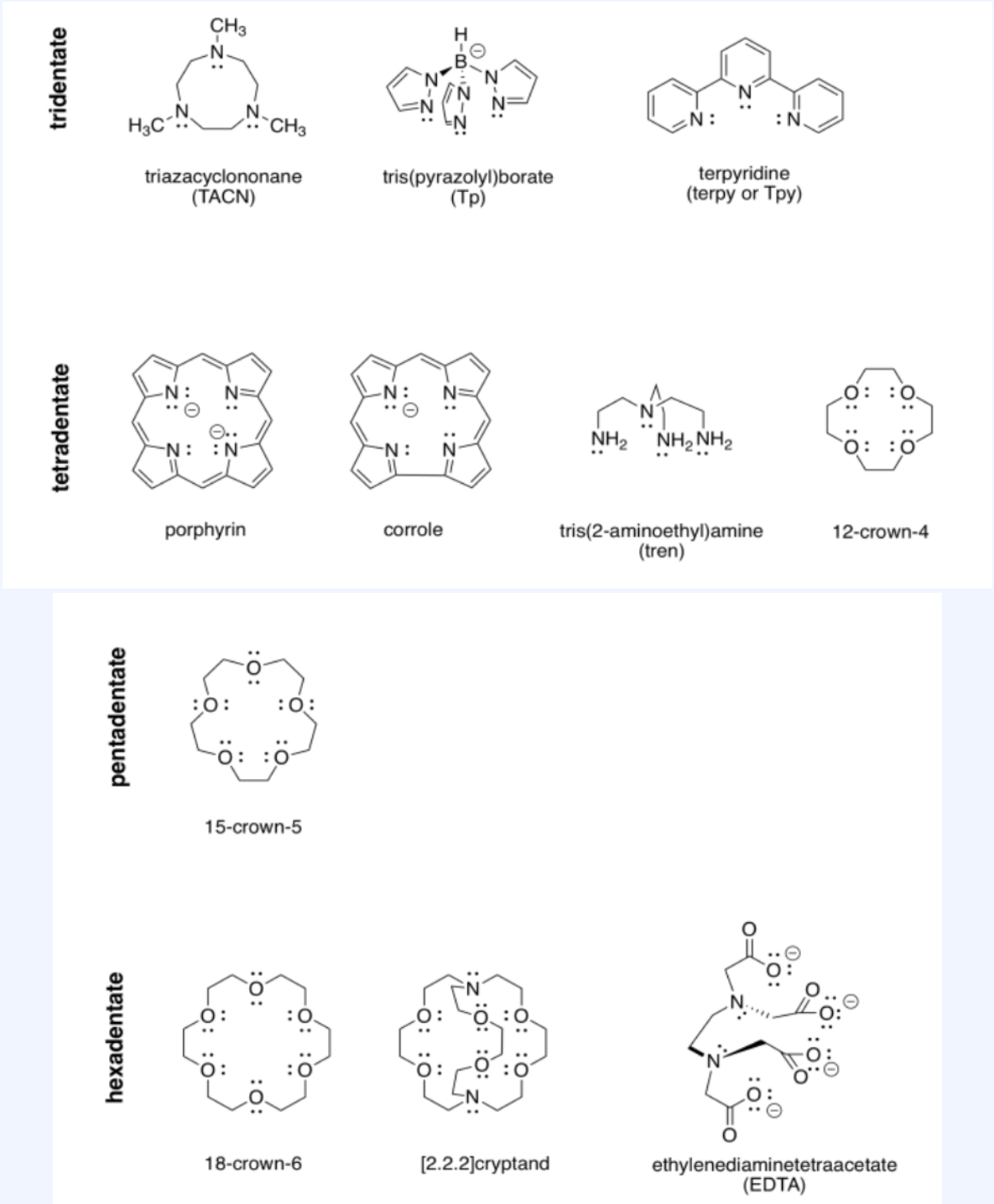
beta-diketiminate

h) 

catecholate

A ligand could be monodentate, meaning it binds through a lone pair on a single atom. It could be bidentate, meaning it binds through lone pairs on two different atoms. It could even be tridentate, with three atoms bearing their own lone pairs, tetradentate, and so on.

Table CC 2.4.2 Examples of polydentate ligands.



There is a symbol for denticity, κ (it's a Greek letter, pronounced "kappa"), which simply describes how many atoms are bound to the metal. For example, in ethylenediamine or 1,2-diaminoethane, $NH_2CH_2CH_2NH_2$, the two nitrogen atoms can be bound to the metal at the same time, although none of the other atoms in between would be directly attached to the metal. This

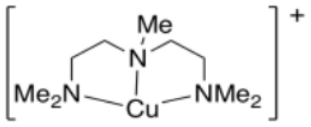
donor is capable of binding in a κ^2 mode. However, if for some reason one of the nitrogen atoms lets go of the metal so that the ethylenediamine is hanging on by only one nitrogen, we would say that the ligand is binding in κ^1 mode.

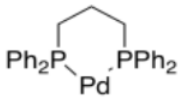
Exercise 2.4.2

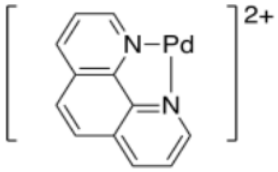
In each of the following cases,

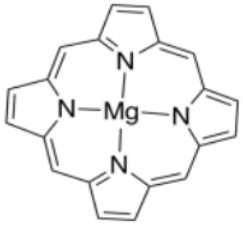
i) describe the denticity;

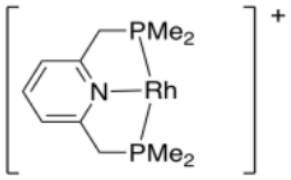
ii) indicate the charge on the ligand and on the metal.

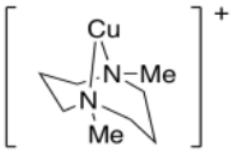
a) 

b) 

c) 

d) 

e) 

f) 

Answer

Answer a

tridentate or κ^3; ligand = 0; metal = 1+

Answer b

bidentate or κ^2; ligand = 1-; metal = 0

Answer c

bidentate or κ^2; ligand = 0; metal = 2+

Answer d

tetradentate or κ^4; ligand = 2-; metal = 2+

Answer e

tridentate or κ^3; ligand = 0; metal = 1+

Answer f

bidentate or κ^2; ligand = 0; metal = 1+

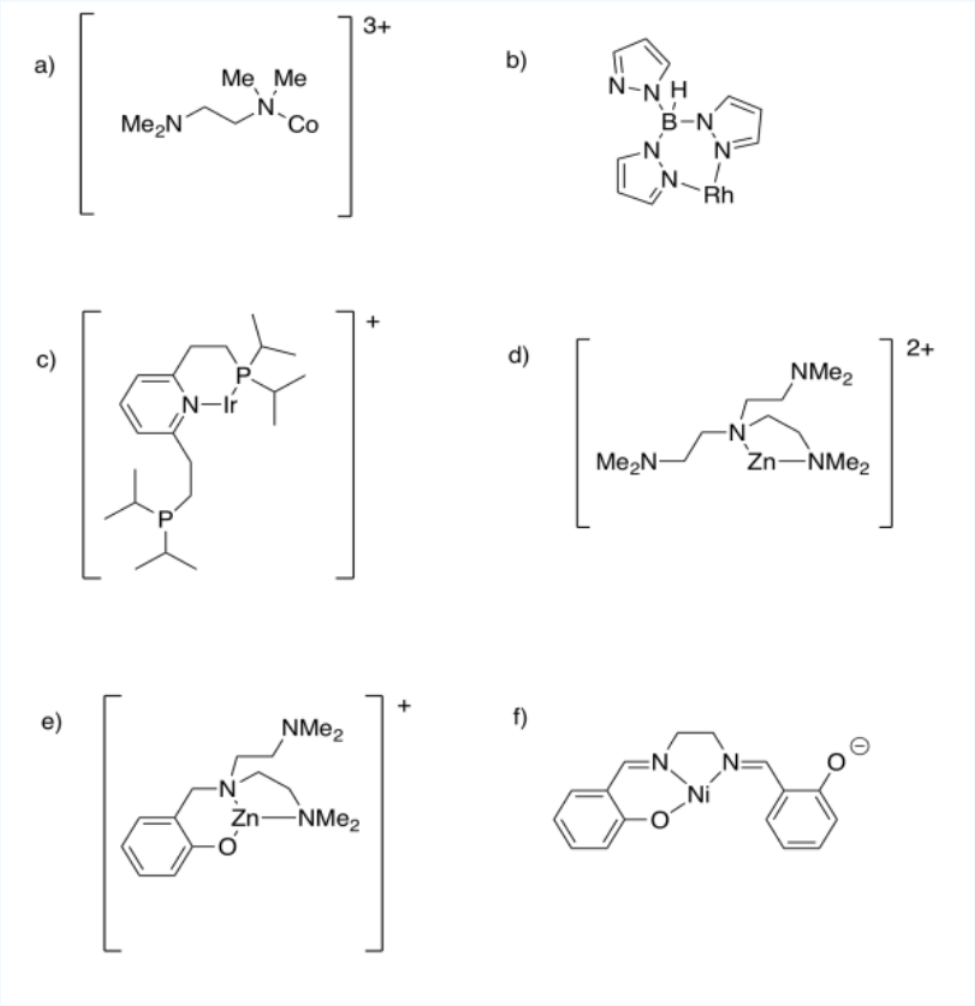
Exercise 2.4.3

In the following cases, the ligand has slipped, so that it isn't binding as tightly as it possibly could. In each case,

i) describe the denticity as drawn;

ii) state the maximum denticity possible;

iii) indicate the charge on the ligand and on the metal



Answer

Answer a

monodentate or κ^1; maximum bidentate or κ^2; ligand = 0; metal = 2+

Answer b

bidentate or κ^2; maximum tridentate or κ^3; ligand = 1-; metal = 1+

Answer c

bidentate or κ^2; maximum tridentate or κ^3; ligand = 0; metal = 1+

Answer d

bidentate or κ^2; maximum tetradentate or κ^4; ligand = 0; metal = 2+

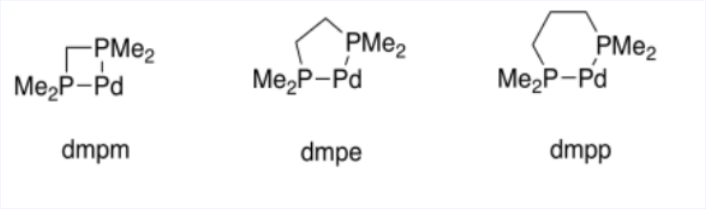
Answer e

tridentate or κ^3; maximum tetradentate or κ^4; ligand = 1-; metal = 2+

Answer f

tridentate or κ^3; maximum tetradentate or κ^4; ligand = 2-; metal = 2+

There are more subtle aspects of chelation. For example, two different bidentate ligands may not necessarily bind to the metal in exactly the same way. In the drawing below, it's apparent that the three bidentate phosphine ligands, bis(dimethylphosphino)methane, bis(dimethylphosphino)ethane, and bis(dimethylphosphino)propane, do not all bind the metal with the same geometry. In each case, the metal forms a different angle with the two phosphines.

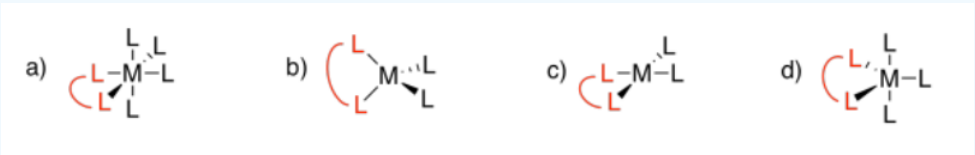


The term "bite angle" is frequently used to describe how different bidentate ligands will attach to metals at different angles. In the picture, the P-Pd-P angle appears to be about 90 degrees when dmpm is bound; in reality it is even smaller. With dmpe, the bite angle appears larger in the picture than the one for dmpm, and in reality it is larger, although not quite as large as it appears here. Two different ligands that bind with two different bite angles will have different influences on the complex that forms. In fact, chemists often use these differences to "tune" the behavior of transition metals that are used as catalysts for important properties. They might add similar ligands with different bite angles to see which one best promotes the desired catalytic reaction.

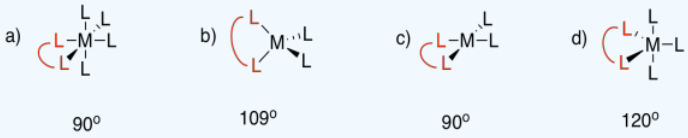
Many factors can influence the bite angle, including structural features of the bidentate ligand itself, the metal, and other ligands bound to the metal. However, a particular ligand will usually have a normal range of bite angles that it will be able to adopt under different circumstances.

Exercise 2.4.4

Certain ligands may have natural bite angles that work better in some cases than in others. Propose the optimum bite angle in each of the following geometries.



Answer

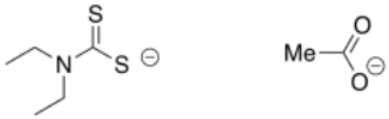


Exercise 2.4.5

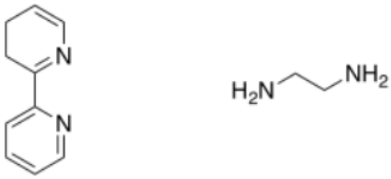
Certain ligands tend to give a certain range of bite angles. Use the suggested criterion to predict which ligand in each pair would give the larger bite angle.

a) nitrate vs. oxalate, based on **ring size**

b) dithiocarbamatre vs. acetate, based on **bond lengths**



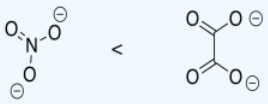
c) bipyridyl vs. ethylenediamine, based on **hybridization / bond angles**



Answer

Answer a

a) nitrate vs. oxalate, based on **ring size**



180° 360° 540° 720°

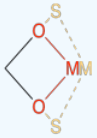
3 x 60° = 180° 4 x 90° = 360° 5 x 108° = 540° 6 x 120° = 720°

The total of the interior angles of a regular polyhedron is given by $(n\text{-}2)180^{o}$, in which n is the number of sides in the polyhedron. Assuming the ring formed by the bidentate ligand and the metal is a regular polyhedron (it won't be, but we are simplifying), then nitrate gives a triangle with 60° angles, including a 60° O-M-O bite angle. Oxalate gives a square with a larger, 90° bite angle.

In reality, the bite angle for nitrate varies with the complex that is formed, but it is usually somewhere around sixty degrees, whereas oxalate usually gives somewhere around eighty five degrees (see, for example, Alvarez, *Chem. Rev.* **2015**, *115*, 13447-13483). The smaller ring size gives a smaller bite angle.

Answer b

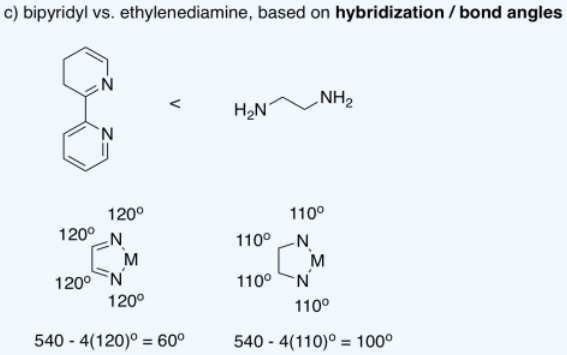
b) dithiocarbamatre vs. acetate, based on **bond lengths**



Sulfur is larger than oxygen, so its bonds will be a little longer. As a result, you can imagine those two sides of the square being a little longer with sulfur than with oxygen. From the perspective of the metal, the gap between the two donor atoms widens out a little.

Acetate forms bite angles of around sixty degrees, but dithiocarbamate forms larger bite angles of seventy or seventy five degrees.

Answer c

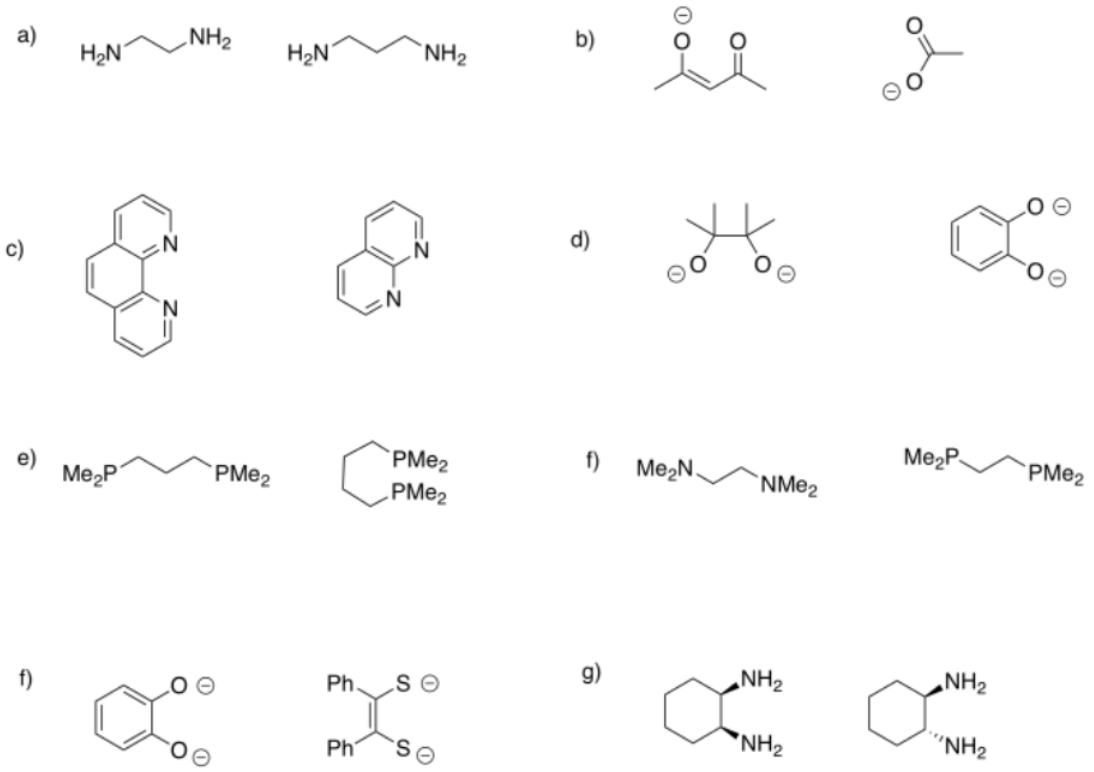


There are lots of differences between these two ligands, but if we simplify and only consider bond angle, we can make a prediction. If the atoms in bipridyl can be considered sp^2 hybridised, then they form 120° bond angles. The atoms in ethylenediamine could be considered sp^3 hybridised, forming approximately 110° angles. The angle N-M-N still has to complete the shape of the regular pentagon, so if all of the other angles are bigger in the bipyridyl complex, we would expect the bite angle to be smaller.

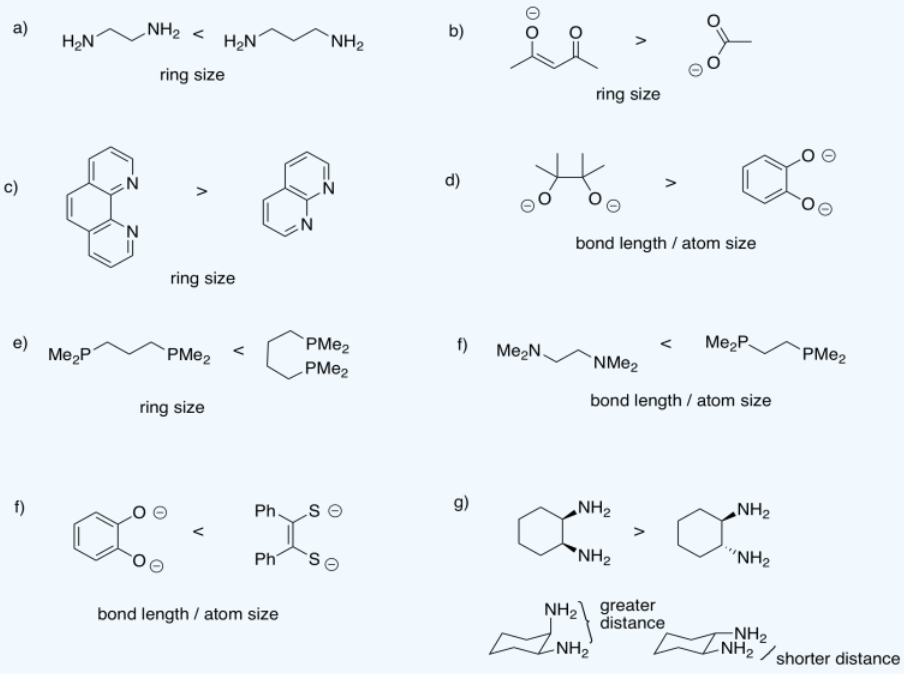
Really, the bite angles are much closer than this rough estimate suggests. Bipyridyl forms average bite angles of around eighty degrees, whereas ethylenediamine forms average bite angles of around eighty-five degrees. Keep in mind that those are just averages, though. These two values are close enough that their ranges overlap; lots of bipyridyl complexes would have bite angles smaller than ethylenediamine complexes.

? Exercise 2.4.6

Suggest which ligand in each pair would have the larger bite angle, and why.



Answer



2.5: Pi Coordination- Donation from Alkenes

Lone pairs are the most common electron donors in coordination complexes. Chloride ions, ammonia and phosphines all donate a lone pair to metals to form complexes. Lone pairs are not stabilized by bonding interactions already. Forming a bond lowers the energy of the lone pair electrons. On the other hand, bonding pairs are already lower in energy and so they are less likely to be donated.

However, pi bonds can also donate to Lewis acids. Donation from sigma bonds is still much less likely, though. Sigma bonds are buried between atoms and are hard to reach.

- Pi bonds are often higher in energy than corresponding sigma bonds
- Pi bonds are more accessible spatially than sigma bonds

A simple example of donation from a pi bond is the treatment of silver(I) salts with alkenes, shown in figure 2.5.1.

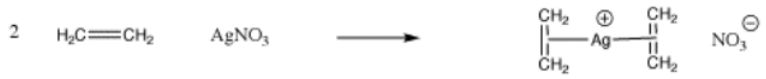


Figure 2.5.1: Formation of a silver alkene complex or "silver olefin" complex.

Strictly speaking, if an alkene donates its pi bonding electrons to a metal, we might draw it as shown in Figure CC4.2. The electrons are shared between two carbon atoms in the alkene. Since a bond is generally thought of as a pair of electrons shared between two atoms, then once the pi electrons are donated to the metal, they are shared between the metal and one of the carbons, but not both. If you are keeping track of electrons carefully, that leaves one of the carbons short on electrons. It must be a cation. Of course, either carbon could be the cationic one, so we can draw resonance structures showing both possible states.

- donation of pi electrons to a metal can "activate" an alkene
- the alkene can become positive and electrophilic

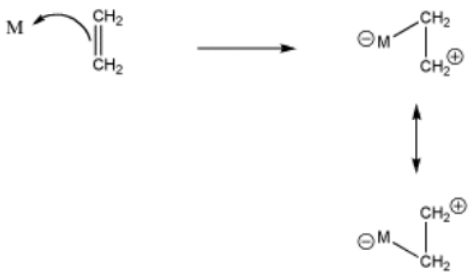


Figure 2.5.2: Donation of a pair of pi-bonding electrons to a transition metal.

However, if a metal has valence electrons of its own, it could donate these electrons back to the "cation" that is forming on one of the alkene carbons. The alkene complex can be thought of as a "metallacycle" or a "metallacyclopropane", a three-membered ring containing two carbons and the transition metal atom.

- alkene coordination also involves metal-to-alkene donation

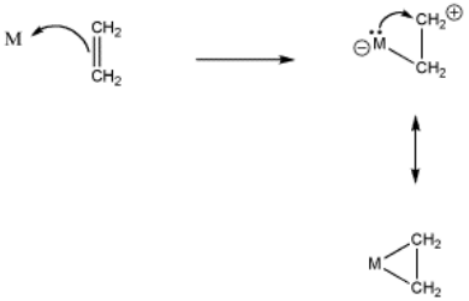


Figure 2.5.3: "Back-donation" of electrons from the metal to the alkene, in a Lewis sense.

The idea of back-donation is also supported from a molecular orbital point of view. The alkene pi bond can donate electrons into an empty orbital on the metal, such as a p orbital. In turn, an occupied metal d orbital has the correct symmetry to overlap with a pi* orbital on the alkene. In doing so, we would think of the pi bond as breaking. We would also think of two pairs of bonding electrons between the metal and alkenes. This situation fits the picture of a metallacyle pretty well.

- alkene-to-metal donation and metal-to-alkene donation are supported by molecular orbital calculations
- without both components, alkenes do not bind very well to metals
- nevertheless, the sigma bond formed by donation from the alkene is still the principle bond-forming event.

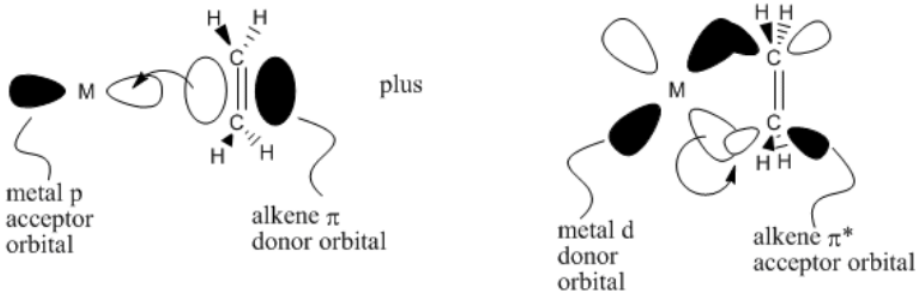


Figure 2.5.4: "Back-donation" of electrons from the metal to the alkene, in an MO sense.

Remember that formalisms can be complicated in coordination complexes. For one thing, we do not usually draw positive formal charges on the donor atom or negative formal charges on the metal atom in the complex (unless specifically illustrating a point). In alkene complexes, bonding is usually illustrated with a line between the pi bond and the metal, as in Figure CC4.5. That line could be read as a pair of electrons, but it isn't, really. The pair of electrons is in the pi bond. They are being shared with the metal.

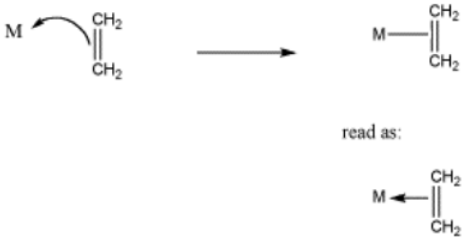
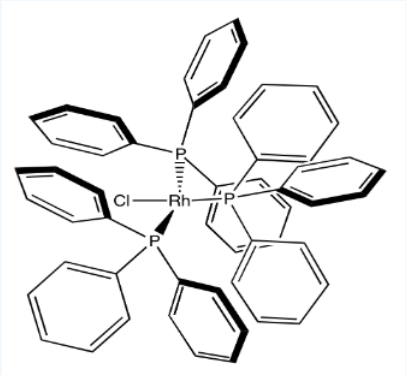


Figure 2.5.5: Typical representation of alkene complexes.

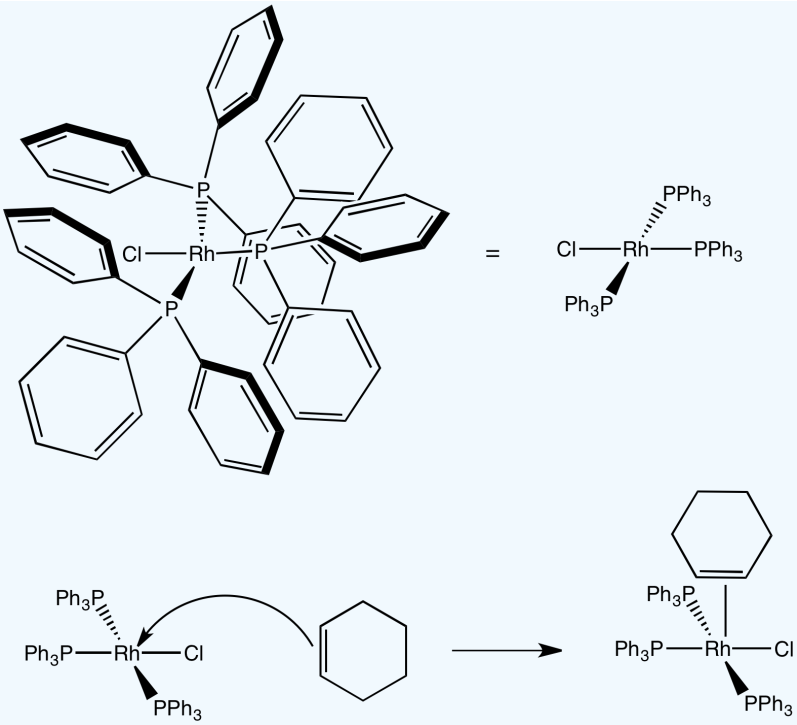
? Exercise 2.5.1

Alkene binding is one of the first steps performed by hydrogenation catalysts such as Wilkinson's catalyst, which catalyze the addition of dihydrogen across an alkene double bond to form an alkane.



Show, with arrows, the coordination of cyclohexene to Wilkinson's catalyst, $(PPh_3)_3RhCl$.

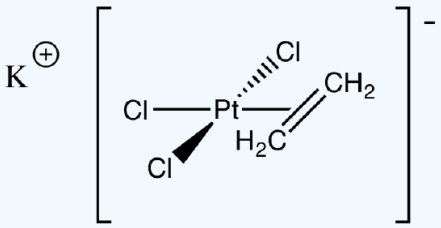
Answer



Exercise 2.5.2

The first example of an alkene coordinated to a transition metal was prepared by pharmaceutical chemist W. C. Ziese at the University of Copenhagen in 1827. Its structure was confirmed by x-ray diffraction about a century later. Its formula is $K[PtCl_3(CH_2CH_2)]$. Draw the structure.

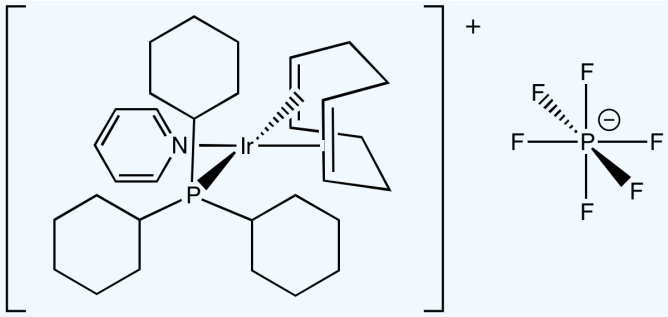
Answer



Exercise 2.5.3

Crabtree's catalyst is a hydrogenation catalyst with formula $[(COD)(py)(PCy_3)Ir]\ PF_6$. Note that COD = 1,4-cyclooctadiene; py = pyridine; Cy = cyclohexyl. Draw the structure of this square planar iridium complex.

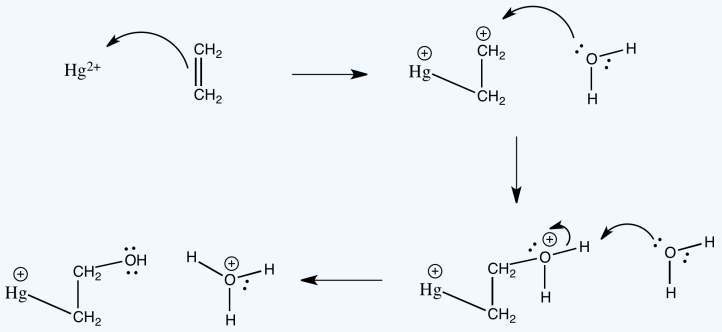
Answer



Exercise 2.5.4

Treatment of alkenes with Hg(II) in water results in addition of a solvent molecule (a nucleophile) to one end of the "activated" alkene. Draw, with arrows, the mechanism for the formation of a hydroxyethylmercury ion, $HgCH_2CH_2OH^+$, from ethene under these conditions.

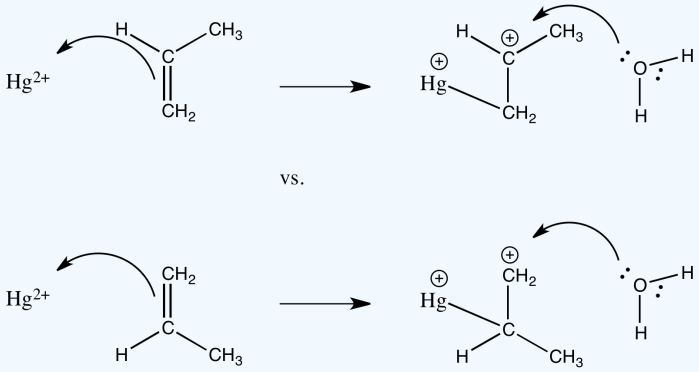
Answer



Exercise 2.5.5

Treatment of 2-methylpropene with Hg(II) in water results in formation of the ion, $HgCH_2C(CH_3)_2OH^+$. A second product of solvent addition is possible, but is not observed. Show the other possible product and provide a possible explanation for the selectivity of the reaction.

Answer



Exercise 2.5.6

Alkenes coordinate to many metals tightly enough that alkene complexes can be isolated and characterized. However, although early metal ions such as Zr(IV) are believed to bind alkenes, they do not coordinate tightly enough to form stable compounds that can be isolated and characterized. Explain why.

Answer

Zr(IV) or Zr^{4+} has no valence d electrons. That means that, although an alkene could certainly donate its pi bond to the zirconium atom, the zirconium has no electrons with which it can stabilize the alkene complex via "back-donation" to the pi antibonding orbital on the alkene.

Nevertheless, d^0 metals such as Zr(IV) and Ti(IV) can be used as alkene polymerization catalysts to make common plastics such as HDPE, LDPE and polypropylene. That means that, although an alkene complex isn't directly observed with these metal ions, these metals can evidently bind alkenes briefly and get them to react with other alkenes to form long chains. Even so, most industrial olefin polymerization catalysts use Ti(III).

Exercise 2.5.7

Alkynes can also coordinate to metal atoms. Draw the molecular orbitals involved in:

a) alkyne donation to the metal

b) metal donation to the alkyne

Answer

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Exercise 2.5.8

Explain the differences seen in the equilibrium constants for the formation of silver(I) complexes with the following alkenes:

a) CH_2CH_2: K = 22.3

b) cis-$CH_3CHCHCH_2CH_2CH_3$: K = 3.1

c) trans-$CH_3CHCHCH_2CH_2CH_3$: K = 0.8

Answer

We will use (a), the binding constant between Ag(I) and ethylene or ethene (CH_2=CH_2), as our baseline value. Other constants will be compared with this one in order to look for a trend.

In (b), the binding constant is much smaller, so the silver ion binds *cis*-2-hexene much less tightly than it does ethene. This is just another alkene, like ethene, but instead of having just hydrogen atoms attached to the C=C unit, *cis*-2-hexene has some other stuff. Maybe this other stuff causes some problem for alkene binding. The obvious difference between hydrogen atoms and this other stuff is that this *other stuff is bigger*. Maybe the complex gets *too crowded* when the *cis*-2-hexene binds to the silver ion.

Very often when we see metal ions on paper, we are not dealing with bare metal ions in reality. The ion often has other ligands already attached to it at the beginning, such as water molecules, and what we are sometimes looking at is replacement of an old ligand with a new ligand. Other ligands attached to the silver could make crowding problems even worse.

There is an alternative explanation as well. If you compare two alkenes that differ only in the number of hydrogens attached to the double bond, such as 1-butene, CH_2=$CHCH_2CH_3$, and 2-butene, CH_3CH=$CHCH_3$, you invariably find that the alkene with fewer hydrogens attached to the double bond (and more other stuff) is more stable. "Terminal alkenes", with double bonds at the ends of the chain, are always less stable than "internal alkenes", with double bonds somewhere along the middle of the chain. This difference can be explained by looking at some quantum mechanical calculations, but we're not going to do that right now.

The point is, the difference in this reaction might be caused, not by the alkene complexes, but by the alkenes themselves, on the other side of the reaction profile. It's important to remember that equilibrium constants always compare two sides of a reaction. Ethene, having fewer substituents on the double bond than *cis*-2-hexene ("substituents" is a four syllable word for "other stuff"), may simply be less stable and more reactive.

Do either of these ideas hold up in the other examples?

In (c), *trans*-2-hexene is bound even less tightly than *cis*-2-hexene. We could argue that in a *cis*-2-hexene complex, the substituents, which are on the same side of the double bond, might both be held away from other ligands on the metal that may exacerbate crowding problems. That would be more difficult to do with *trans*-2-hexene, since one substituent is on either side of the double bond. Getting one substituent away from the crowding may be possible, but probably not both.

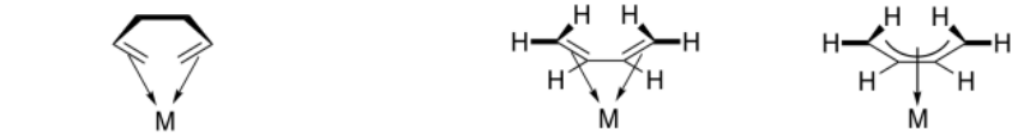
Once again, the alternative explanation holds up here, too. *cis*-2-Hexene is less stable than *trans*-2-hexene, because the substituents on the double bond crowd each other in *cis*-2-hexene, but are held away from each other in *trans*-2-hexene. So maybe *cis*-2-hexene binds to silver ion more easily because it is more reactive.

2.6: Hapticity

When a lone pair is bonded to a transition metal, then the atom with the lone pair is forming a bond to the metal. When a pi bond is coordinated, which atom is bonded to the metal? Both of them. Three atoms are involved in this bonding situation, instead of just two. Both carbons that form the original pi bond are now donating that pi bond to the metal.

When ligands are bound to a metal via a conjugated pi-system, describing the mode of binding might seem even trickier. If there are two double bonds in a row, then all four of the atoms that form those two pi bonds are donating to the metal. Furthermore, because the bond is conjugated, we can think of this as one long pi bond. The bond from the pi bond to the metal involves all four donor atoms, plus the metal atom.

Contrast that situation with two separate pi bonds that are not conjugated. If a ligand contains two separate pi bonds, it is a bidentate donor. Bidentate ligands bind through two donor sites. We think of a ligand like 1,2-ethanediamine as binding through the lone pairs on both nitrogen atoms. We would think of 1,5-hexadiene as binding through the pi bond at either end of the chain. However, 1,3-butadiene is a little different, because of the participation of all four carbons in bonding to the metal through one conjugated bond.



bidentate diene (not conjugated) conjugated diene

The term used to describe the participation of multiple atoms simultaneously during pi coordination is hapticity. A regular alkene, like ethene or propene, is a dihaptic donor; two carbons participate in donation of one bond to the metal. A conjugated alkene, like 1,3-butadiene, is a tetrahaptic donor. Four carbons participate in donation of a conjugated pi bond to the metal. Of course, this conjugated diene can donate four electrons at once, forming something a little like a double bond to the metal.

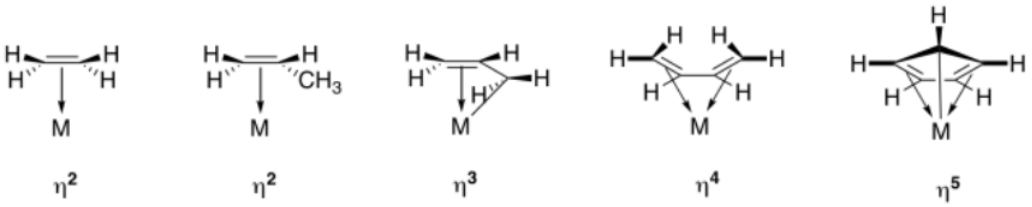


Figure 2.6.1: Some common multihaptic ligands.

In the drawings above, the symbols, η^2 or η^3, etc. (read "eta-two" or "eta-three") refer to the hapticity of the ligand. An η^2 ligand is dihaptic, with two atoms sharing in the donation from the pi system; an η^3 ligand is trihaptic, with three atoms sharing in the donation from the conjugated pi system.

? Exercise 2.6.1

The following alkenes form complexes with silver. Describe their probable mode of binding as η^2, etc.:

a. $CH_2CHCHCH_2$
b. $CH_2CHCH_2CHCH_2$
c. $CH_2CHCH_2CH_2CHCH_2$
d. $CH_2CHCHCHCHCH_2$

Answer a

There are two double bonds here, and they are conjugated: CH_2=CH-CH=CH_2. The conjugated double bond would allow the ligand to bind η^4.

Answer b

There are two double bonds here, but they are not conjugated: CH_2=CH-CH_2-CH=CH_2. Each double bond would bind η^2, and the ligand would be able to bind in a bidentate fashion, but since the double bonds are not conjugated and binding all in a row, we would not describe binding as η^4. It would most commonly be described as η^2,η^2; that simply means each double bond is an η^2-donor, and there are two of them. It could also be considered a κ^2 donor because of its denticity.

Answer c

This is another non-conjugated case: CH_2=CH-CH_2-CH_2-CH=CH_2. In terms of hapticity, it could be described as η^2,η^2.

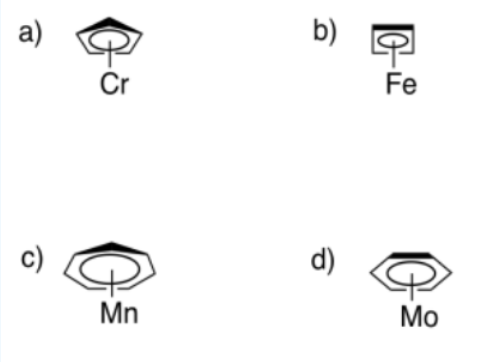
Answer d

There are three double bonds here, and they are conjugated: CH_2=CH-CH=CH-CH=CH_2. The conjugated double bond would allow the ligand to bind η^6.

? Exercise 2.6.2

Cyclic, conjugated systems make good ligands for transition metals. In each of the following cases,

i. describe the hapticity.
ii. indicate the number of electrons donated to the metal.
iii. indicate the charge on the ligand.



Answer a

The ligand is bound η^5; it donates 6 electrons, from two double bonds and one lone pair; the ligand has a charge of -1.

Answer b

The ligand is bound η^4; it donates 4 electrons, from two double bonds; the ligand has no charge.

Answer c

The ligand is bound η^7; it donates 8 electrons, from three double bonds and one lone pair; the ligand has a charge of -1.

Answer d

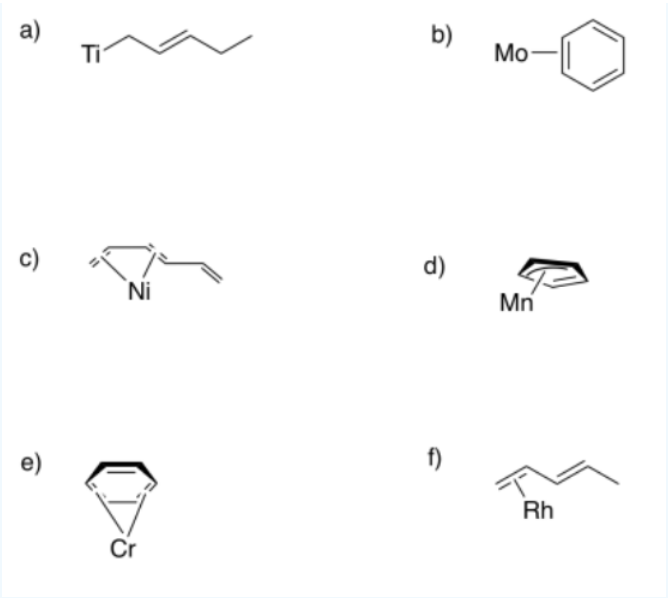
The ligand is bound η^6; it donates 6 electrons, from three double bonds; the ligand has no charge.

? Exercise 2.6.3

Sometimes, conjugated ligands might "slip", donating fewer than the maximum number of electrons to the metal. In the following cases, indicate:

i) the hapticity shown in the picture.

ii) the maximum hapticity possible with the ligand.



Answer a

The ligand is bound η^1; it donates one lone pair; however, it could donate an additional pi bond and then it would bind η^3.

Answer b

The ligand is bound η^2; it donates one pi bond; however, it could donate two more pi bonds and then it would bind η^6.

Answer c

The ligand is bound η^4; it donates two pi bonds; however, it could donate one more pi bond and then it would bind η^6.

Answer d

The ligand is bound η^3; it donates one lone pair and one pi bond; however, it could donate an additional pi bond and then it would bind η^5.

Answer e

The ligand is bound η^4; it donates two pi bonds; however, it could donate one more pi bond and then it would bind η^6.

Answer f

The ligand is bound η^2; it donates one pi bond; however, it could donate one more pi bond and then it would bind η^4.

? Exercise 2.6.4

One of the most common multidentate ligands is the cyclopentadienyl anion, often abbreviated Cp.

a. CpH is easily deprotonated to form Cp^-. Explain why.
b. How many electrons does Cp donate to a metal?
c. The archetypal Cp complex is ferrocene, Cp_2Fe, the structure of which was determined by Geoff Wilkinson, in work that led to him being awarded the Nobel Prize in 1973. Draw the structure of ferrocene.
d. Count the electrons on the iron in ferrocene.

Answer a

The resulting anion has aromatic stability. It is cyclic, fully conjugated, flat and has an odd number of electron pairs.

Answer b

Cp anion could bind to a metal through just one pair or through two pairs, but in most cases it will bind via three pairs of electrons.

Answer d

Valence count on metal: 8

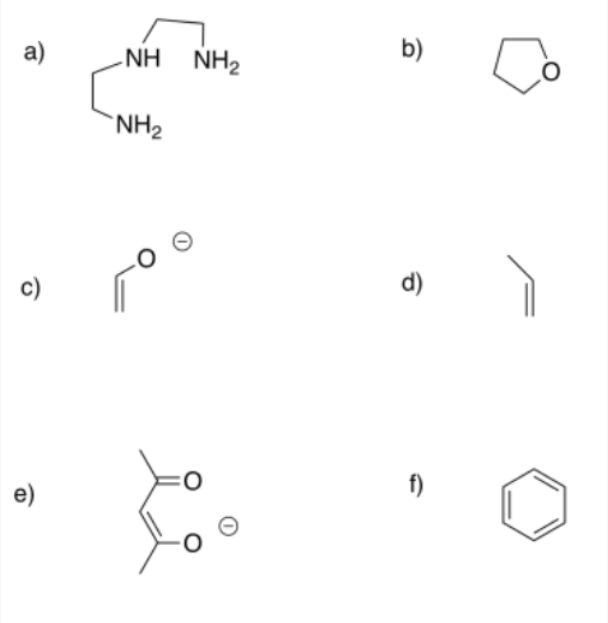
Count on metal, correcting for +2 charge: 6

Donated from ligands: 2 x 6 = 12

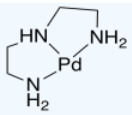
Total: 18

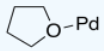
Exercise 2.6.5

Predict the most probable binding modes of the following ligands (monodentate, trihaptic, etc.).



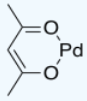
Answer

a)  tridentate, κ^3

b)  monodentate, κ^1

c)  monodentate, κ^1 OR  η^3

d)  η^2

e)  bidentate, κ^2 OR  η^5

f)  η^6

Exercise 2.6.6

Using ideas from denticity, explain the differences seen in the equilibrium constants for the formation of silver(I) complexes of the following alkenes:

a. CH_2=CHCH=CH_2; K = 4.2
b. CH_2=$CHCH_2CH$=CH_2; K = 10.2
c. CH_2=$CHCH_2CH_2CH$=CH_2; K = 28.8

Answer

This problem deals with the "bite angle" of the ligand. Remember, a chain of atoms becomes more flexible the longer it gets, because of the possibility for rotation around each bond along the chain. As the two double bonds move further apart from each other (one bond apart in (a), two bonds apart in (b) and three bonds apart in (c), the chain can "open up" and bind with a more optimal overlap with the metal.

2.7: Hard and Soft Acid and Base Concepts

Not all metals form coordination complexes with all possible ligands. Some metals are more likely to form compounds with certain ligands. This observation has eventually led to a classification system called Hard and Soft Acids and Bases (HSAB).

In a nutshell, smaller or more highly charged metal ions are called **hard acids**. They are more likely to bind to hard bases, which typically have small donor atoms such as oxygen or nitrogen. Typical hard acids are titanium(IV), tantalum(V), magnesium(II) and lithium(I). Oxide, hydroxide and carbonate (CO_3^{2-}) are some typical hard bases.

Larger, more polarizable metal ions with lower charges are called **soft acids**. "Polarizable" means they have large, easily distorted clouds of electrons. They are more likely to bind to soft bases, which are typically large anions such as sulfide or selenide.

- "hard" acids are small or highly charged
- "soft" acids are larger or more polarizable or have lower charge
- "hard" bases contain smaller, less polarizable donor atoms, usually oxygen or nitrogen
- "soft" bases contain larger, more polarizable donor atoms, such as sulfur or phosphorus
- hard ions tend to bind well together; soft ions tend to bind well together

? Exercise 2.7.1

Suggest which of the following ions is harder.

a) zinc(II) or mercury(II) b) potassium(I) or copper(I) c) iron(II) or iron(III)

Answer a

Zn(II), because it is smaller and less polarizable.

Answer b

K^+, because it is less electronegative.

Answer c

Fe(III), because of the higher charge.

? Exercise 2.7.2

Suggest which of the following bases is softer.

a) Me_3P or Me_3N b) chloride or iodide c) amide (NH_2^-) or azide (N_3^-)

Answer a

Me_3P, because phosphorus is larger and more polarizable than nitrogen.

Answer b

Iodide, which is larger and more polarizable than chloride.

Answer c

Azide, which has a more polarizable, delocalized pi bonding system.

There are some obvious HSAB applications in metallurgy and geology. Some common minerals of hard metals are rutile (titanium oxide, TiO_2), dolomite (magnesium and calcium carbonate $CaMg(CO_3)_2$) and chromite (iron chromium oxide, $FeCrO_4$). Fluoride, carbonates, oxides, phosphates and sulfates are examples of hard bases.

Some prevalent minerals of soft metals are galena (lead sulfide, PbS_2) and cinnabar (mercury sulfide, HgS). Sulfides are the most common soft bases in geology, although the larger halides, like bromide and iodide, are also soft.

Some metals can pair with either hard or soft bases, particularly those metals from the middle of the transition metal group. For example, iron(III) is often found as hematite (iron oxide, Fe_2O_3), whereas iron(II) can also be found as pyrite (iron sulfide, FeS).

Molybdenum(VI) can be found as powellite (calcium molybdenum oxide, $CaMoO_4$), but the most commonly mined ore contains molybdenum(IV), found in molybdenite (MoS_2).

Exercise 2.7.3

Propose a formula for a plausible mineral containing each of the following ions.

a) zirconium(IV) b) cadmium(II) c) tungsten(VI)

d) zinc(II) e) copper(I)

Answer a

ZrO_2

Answer b

CdS

Answer c

WO_3

Answer d

ZnS

Answer e

Cu_2S

In biology, metals display aspects of hard & soft acid & base chemistry. Relatively hard potassium ions bind to oxygen atoms in DNA to help stabilize the helix structure. Calmodulin, used to aid in calcium uptake, uses hard oxygen donors in aspartate and glutamate to bind to the Ca^{2+}.

On the other hand, copper(I) is a soft acid. In poplar plastocyanin, which aids in transferring electrons during reactions in the plant cell, the copper ion is coordinated to two nitrogen-donating histidines and two sulfur donors, a cysteine and a methionine.

Many biologically important metal ions fall under the "borderline" category between hard and soft. Iron is one of the most abundant elements on earth, and many iron compounds play important roles in biology. Many biological compounds contain iron(II), which is able to bind well to both hard and soft ligands. Consequently, it is found with anionic oxygen carboxylate donors in methane monooxygenase, neutral and anionic nitrogen porphyrin donors in heme proteins, and sulfur cysteines and sulfides in ferridoxins and other iron-sulfur clusters.

Hard and soft acid and base phenomena have been studied using molecular orbital theory and other quantitative approaches. In MO theory, it has been shown that interactions between hard anions and cations are characterized by large HOMO-LUMO separations, whereas interactions between soft anions and cations are characterized by small HOMO-LUMO separations. In other words, hard acid-base interactions are dominated by more strongly ionic character, but soft acid-base interactions are dominated by more strongly covalent character.

Exercise 2.7.4

Mercury ions, Hg(I) and Hg(II), are particularly poisonous. They can displace other metals from enzymes, so that the enzymes stop working.

a) are these ions hard or soft?

b) what amino acid residues would most likely bind to them?

Answer a

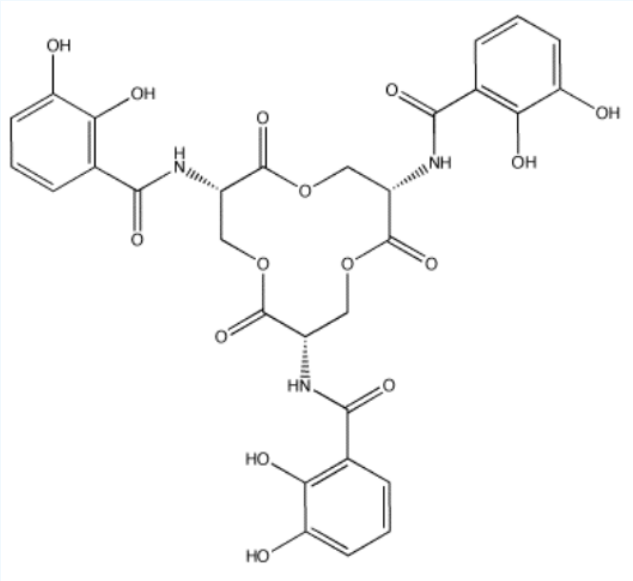
Hg(I) and Hg(II) are both large, polarizable ions. They are soft cations and should bind well to soft donors.

Answer b

The most common soft donor is a sulfur atom or sulfide ion; in amino acids, that suggests cysteine or methionine.

Exercise 2.7.5

Enterobactin (below) is a molecule used by certain bacteria to bind iron(III) and transport it into the cell. The formation constant for the iron(III)-enterobactin complex is about 10^{49}. Provide reasons why the formation constant is so high.



Answer

Fe(III) is a hard cation and should bind well to oxygen donors. Enterobactin has several oxygen donors it could provide to the iron. In fact, there is a pair of OH groups on each of the benzene rings in enterobactin. These benzene rings with two OH groups next to each other are called "catechols". Because there are three of these groups in enterobactin, and there is enough space in between for the groups to fold around a central atom, enterobactin is a chelating (hexadentate) donor with a high binding constant.

Attribution

- Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

2.8: Ligand Field Theory

Concepts from molecular orbital theory are useful in understanding the reactivity of coordination compounds. One of the basic ways of applying MO concepts to coordination chemistry is in Ligand Field Theory. Ligand Field Theory looks at the effect of donor atoms on the energy of d orbitals in the metal complex.

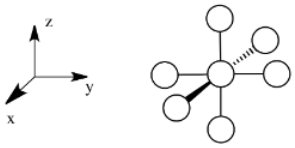
There are two ways in which we sometimes think about the effect of ligands on the d electrons on a metal. On the basis of simple electron-electron repulsion, donation of a lone pair might raise an occupied d orbital in energy. Alternatively, we can think about bonding interactions between ligand orbitals and d orbitals. This second way of thinking about things is a little bit more useful, and that's the approach we'll focus on, here.

Either way, there are interactions between ligand electrons and d electrons, that usually end up raising the d electrons in energy. The effect depends on the coordination geometry of the ligands. Ligands in a tetrahedral coordination sphere will have a different effect than ligands in an octahedral coordination sphere, because they will interact with the different d orbitals in different ways.

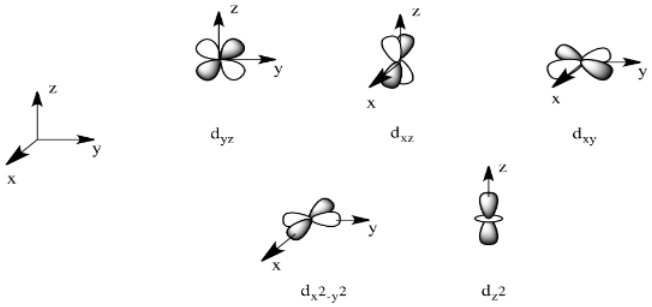
> *Ligand Field Theory looks at the effect of donor atoms on the energy of d orbitals in the metal complex. The effect depends on the coordination geometry geometry of the ligands.*

Octahedral case

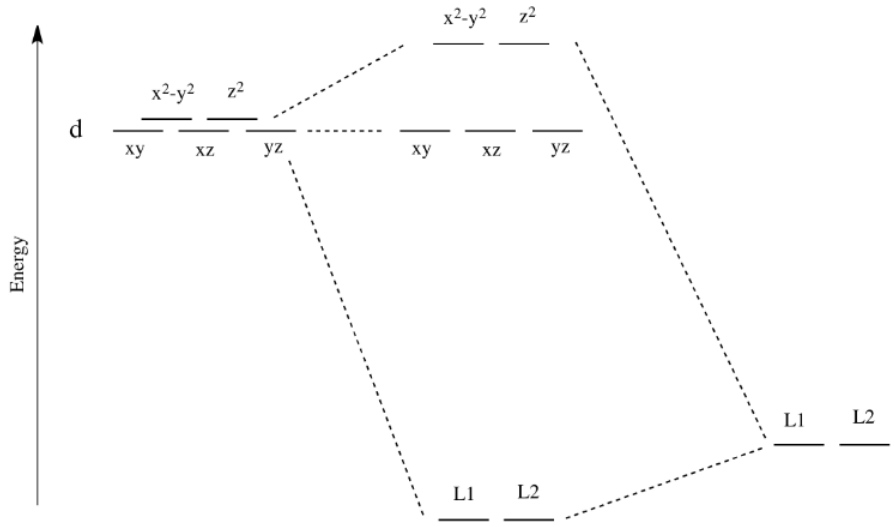
Suppose a complex has an octahedral coordination sphere. Assume the six ligands all lie along the x, y and z axes.



There are two d orbitals that will interact very strongly with these ligands: the $d_{x^2-y^2}$, which lies directly on the x and y axes, and the d_{z^2}, which lies directly on the z axis. Together, these two metal orbitals and the ligand orbitals that interact with them will form new bonding and antibonding molecular orbitals.



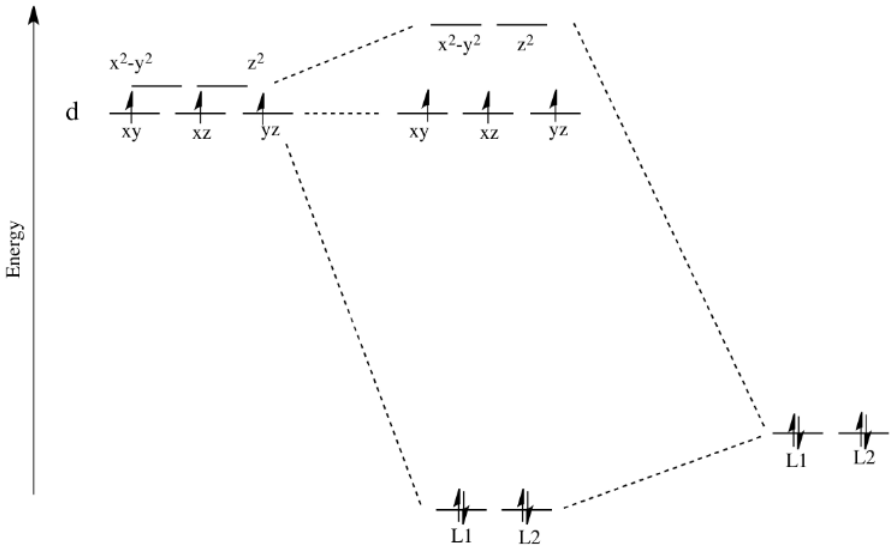
The drawing below is simplified. The ligands will also interact with s and p orbitals, but for the moment we're not going to worry about them. We also won't worry about interactions from the other four ligands with the d orbitals (possible by symmetry considerations, but also a more complicated picture).



Now, remember that metals usually have d electrons that are much higher in energy than those on typical donor atoms (like oxygen, sulfur, nitrogen or phosphorus). That means the antibonding combinations will be much closer in energy to the original d orbitals, because both are relatively high in energy. The bonding combination will be much closer in energy to the original ligand orbitals, because these ones are all relatively low in energy.

That energetic similarity generally translates into a similarity in shape and location as well. In other words, the antibonding combination between a d orbital and a ligand orbital is a lot like the original d orbital. The bonding combination is more like the original ligand orbital than the original d orbital. Because of those similarities, inorganic chemists often refer to those antibonding orbitals as if they were still the original d orbitals.

These two orbitals will be raised relatively high in energy by sigma bonding interactions with the donor orbitals. If there are electrons in the picture, it might look something like this:



- Assume the six ligands all lie along the x, y and z axes.
- The $d_{x^2-y^2}$ and the d_{z^2} orbitals lie along the bond axes.
- These two orbitals will be raised relatively high in energy.
- These orbitals are like antibonding levels.
- These orbitals are sometimes called the "**e_g**" set of orbitals. The term "e_g" comes from the mathematics of symmetry.

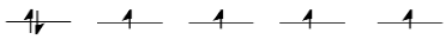
On the other hand, the other three d orbitals, the d_{xy}, d_{xz} and d_{yz}, all lie *between* the donor ligands, rather than hitting them head-on. These orbitals will interact less strongly with the donor electrons.

- The d_{xy}, d_{xz} and d_{yz} orbitals all lie between the bond axes.
- These three orbitals will be changed in energy only a little.
- These orbitals are more like non-bonding orbitals.
- These orbitals are sometimes called the "$\mathbf{t_{2g}}$" set of orbitals.

Remember, only the energy of the electrons affects the overall energy of the system. The unoccupied d orbitals are raised in energy, but the occupied orbitals go down in energy (or else stay the same).

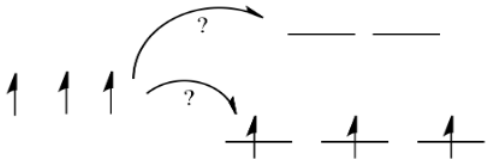
Apart from the stabilization of the complex, there is another consequence of this picture. What we are left with is two distinct sets of d energy levels, one lower than the other. That will have an effect on the electron configuration at the metal atom in the complex. That means there will be cases where electrons could be paired or unpaired, depending on how these orbitals are occupied.

Take the case of the biologically important iron(II) ion. It has a d^6 valence electron configuration. In less formal parlance of inorganic chemistry, "iron(II) is d^6". In an iron(II) ion all alone in space, all the d-obitals would have the same energy level. We would put one electron in each orbital, and have one left. It would need to pair up in one of the d orbitals. (Notice that, in the chemistry of transition metal *ions*, the valence s and p orbitals are always assumed to be unoccupied).

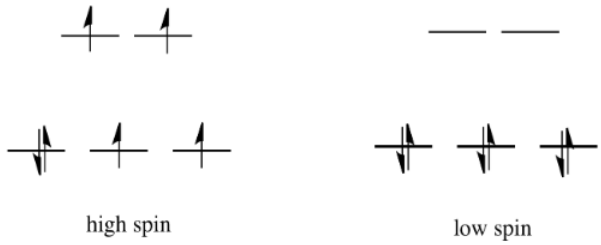


Things are very different in an octahedral complex, like $K_4[Fe(CN)_6]$. In that case, the d orbitals are no longer at the same energy level. There are two possible configurations to consider.

In one case, one electron would go into each of the lower energy d orbitals. A choice would be made for the fourth electron. Does it go into the higher energy d orbital, or does it pair up with one of the lower energy d electrons? The choice depends on how much higher in energy the upper d orbitals are, compared to how much energy it costs to put two electrons in the same d orbital.

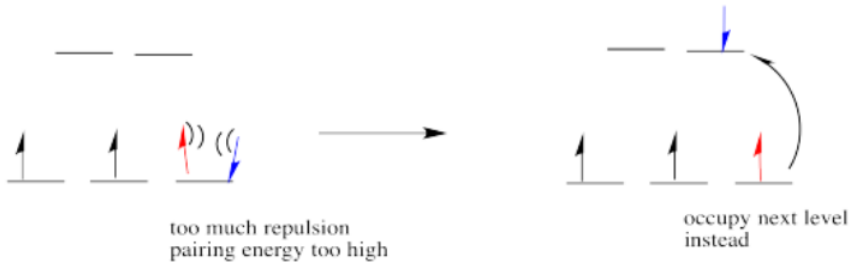


If the "d orbital splitting energy" is pretty low, so that the two sets of d orbitals are still pretty similar in energy, the next electron can go into a higher orbital. Pairing would not be required until the final electron. Overall, that would leave four unpaired electrons, just like in the case of a lone metal ion in space. This is called the "high-spin" case, because electrons can easily go into the higher orbital.

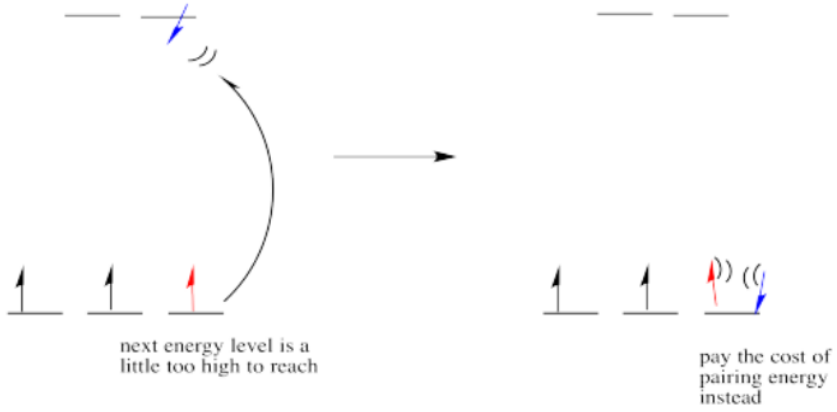


If the d orbital splitting energy is too high, the next electron must pair up in a lower orbital. All three remaining electrons pair up, and so there are no unpaired electrons in the complex. This is called the "low-spin" case, because electrons more easily pair up in the orbital.

So the overall rule is that if the energy to pair up the electrons is greater than the energy needed to get to the next level, the electron will go ahead and occupy the next level.



However, if the energy it takes to get to the next level is more than it would cost to pair up, the electrons will just pair up instead.



> *The electron configuration can be "high spin" or "low-spin", depending on how large the energy splitting is between the two sets of d orbitals.*

The difference between the high-spin case and the low-spin case is significant, because unpaired electrons affect the magnetic properties of a material. The low-spin case would be diamagnetic, resulting in no interaction with a magnetic field. However, the high-spin case would be paramagnetic, and would be attracted to a magnetic field.

It turns out $K_4[Fe(CN)_6]$ is diamagnetic. Thus, it is pretty clear that it is a low-spin complex. The energy difference between the two d orbital levels is relatively large in this case.

In addition to influencing magnetic properties, whether a complex is high- or low-spin also influences reactivity. Compounds with high-energy d electrons are generally more labile, meaning they let go of ligands more easily.

- electron configuration influences magnetic properties
- electron configuration influences lability (how easily ligands are released)

Reasons for Low-spin vs. High-spin: The Effect of the Metal Ion

There are a few factors that determine the magnitude of the d orbital splitting, and whether an electron can occupy the higher energy set of orbitals, rather than pairing up. It is based partly on ligand field strength, which is explored on the next page. It also depends on the charge on the metal ion, and whether the metal is in the first, second or third row of the transition metals.

The higher the charge on the metal, the greater the splitting between the d orbital energy levels. For example, Fe(II) is usually high spin. It has a smaller splitting between the lower and higher d orbital levels, so electrons can more easily go to the higher level rather than pair up un the lower level.

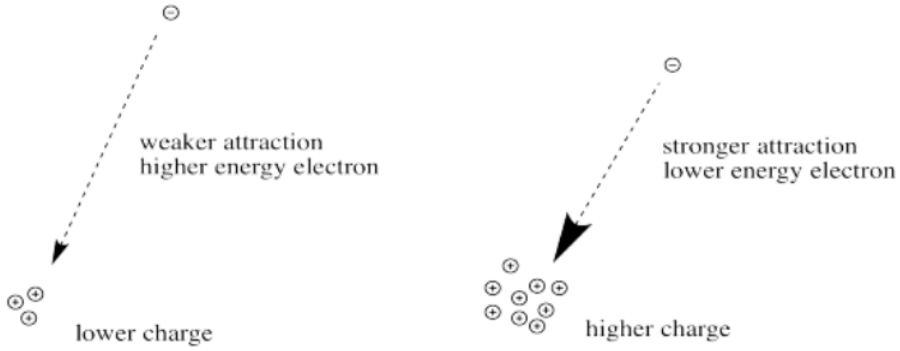
On the other hand, Fe(III) is usually low spin. It has a larger splitting between the d levels. In that case, it costs less energy for electrons to pair up in the lower level than to go up to the higher level.

- High-spin versus low-spin cases involve a trade-off between the d orbital splitting energy and the pairing energy.
- 2nd and 3rd row transition metals are usually low spin
- 1st row transition metals are often high spin
- However, 1st row transition metals and be low spin if they are very positive (usually 3+ or greater)

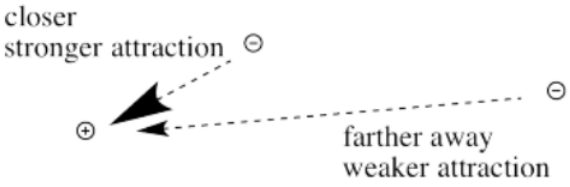
There is a lot going on in metal ions, but we'll take a simplified view of things. Thinking only about electrostatics, we can try to imagine what happens to those electrons when the charge on the metal ion changes.

First we need to know about Coulomb's law. Coulomb's law states that the force of attraction between the electron and the nucleus depends on only two factors: the amount of positive charge in the nucleus, and the distance between the nucleus and the electron.

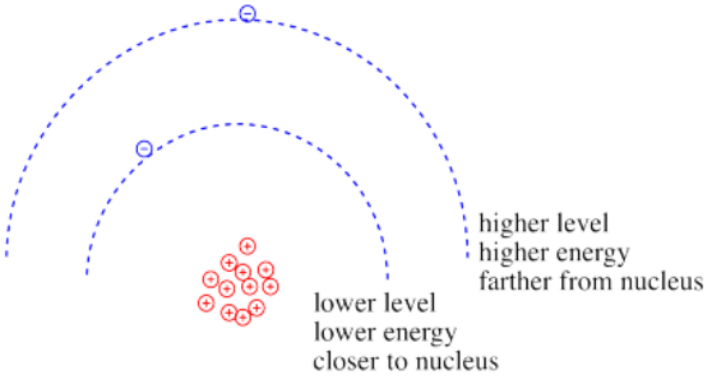
The greater the charge on the nucleus, the greater the attraction between the electron and the nucleus.



The farther an electron is from the nucleus, the weaker the attraction between the electron and the nucleus.

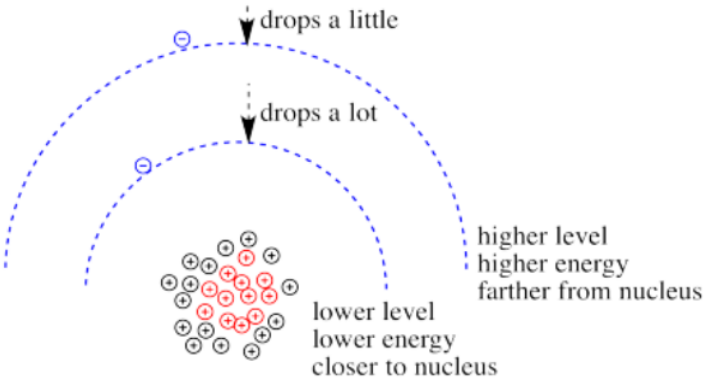


Coulomb's law can be used to evaluate the potential energy of the electron. It is one of the factors that determines how high or low those electronic energy levels are that we see in energy level diagrams for atoms, ions and molecules. The energy of the electron varies in a roughly similar way: the greater the charge on the nucleus, the lower the energy of the electron. Also, the closer the electron is to the nucleus, the lower its energy.



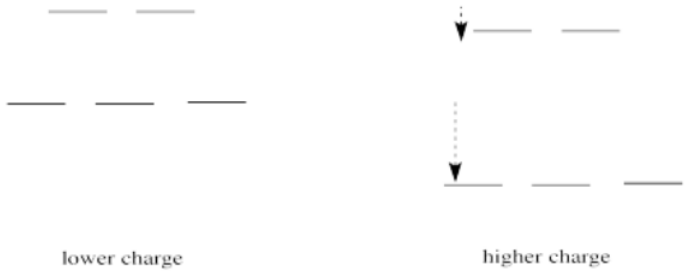
Roughly speaking, electrons at higher energy are farther from the nucleus. Electrons at lower energy are closer to the nucleus.

What happens if the charge increases? Maybe a lot more protons are added to the nucleus. Maybe some electrons are lost, so that to the remaining electrons it just *feels like* the charge of the nucleus has increased. Then the electrons should be more attracted to the nucleus. They get a little closer. Their potential energy drops.



Of course, if one electron is closer to the nucleus already, it feels that increase in positive charge more strongly than an electron that is farther away. Consequently, it drops further in energy than an electron that is further away.

If we translate that idea into a picture of the d orbital energy levels in an octahedral geometry, it looks like this:



When the charge on the metal ion is increased, both the higher and the lower levels drop in energy. However, the lower level drops more. Thus, the gap between the levels gets wider.

Metals in the second and third row of the periodic table almost never form high-spin complexes. The d orbital energy splitting in these cases is larger than for first row metals. From a very simple point of view, these metals have many more protons in their nuclei than the first row transition metals, dropping that lower set of d electrons lower with respect to the higher set.

That isn't the whole picture for the second and third row transition metals, however. Remember, we are simplifying, and there are factors we won't go into. However, it is important to know that metal-ligand bond strengths are much greater in the second and third row than in the first. We'll look at the whole interaction diagram for an octahedral complex now, including contributions form metal s and p orbitals.

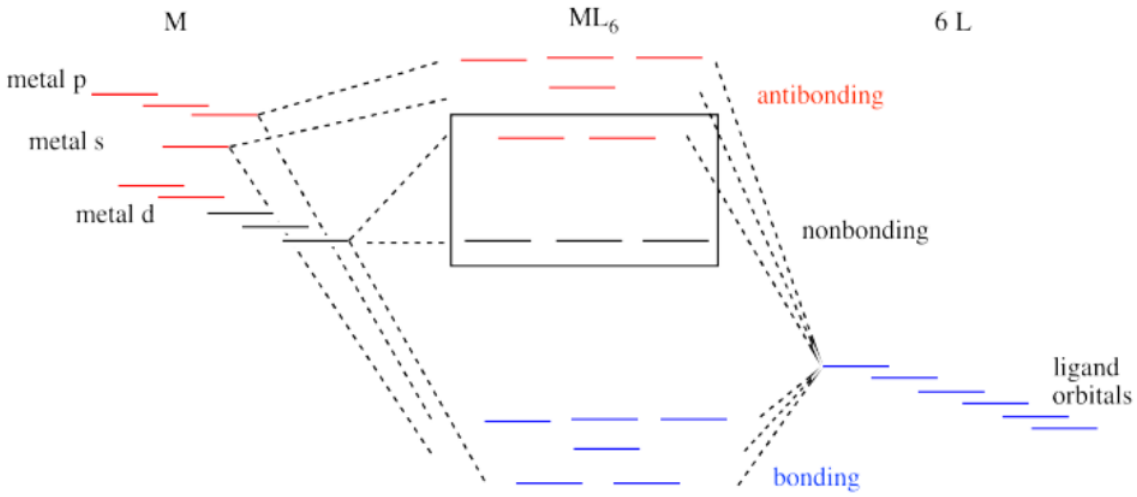
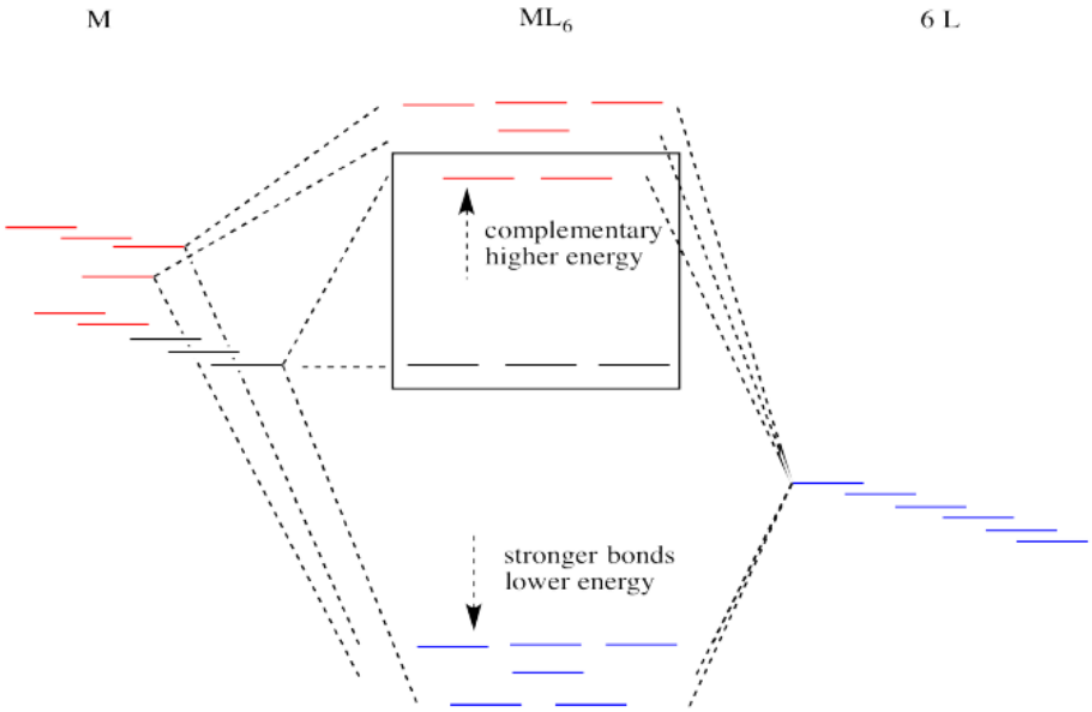


Figure 2.8.15:

Like all ligand-metal interaction diagrams, the energy levels of the ligands by themselves are shown on one side. The metal's electronic energy levels are shown on the other side. The result of their interaction, a metal-ligand complex, is shown in the middle. The d orbital splitting diagram is shown in a box.

Suppose the diagram above is for a first row transition metal. The diagram for a second or third row metal is similar, but with stronger bonds.



If the bonding interaction is stronger between the metal and ligand, then so is the antibonding interaction. The antibonding levels are bumped higher in energy as the bonding levels sink lower. Generally that's OK, because when the electrons are filled in, they will be found preferentially at the lower levels, not the higher ones. There will be a net lowering of electronic energy.

Why do second and third row transition metals form such strong bonds? Bond strengths are very complicated. In general, there is greater covalency between these metals and their ligands because of increased spatial and energetic overlap. Rather than go into those factors, we'll just think about all those extra protons in the nucleus that are attracting the ligand electrons more strongly.

There is one more important distinction that makes second and third row transition metals low spin. In addition, the pairing energy is lower in these metals because the orbitals are larger. There is more room for two electrons in one orbital, with less repulsion. As a result, electrons are much more likely to pair up than to occupy the next energy level.

- 2nd and 3rd row transition metals have stronger bonds, leading to a larger gap between d orbital levels
- 2nd and 3rd row transition metals have more diffuse orbitals, leading to a lower pairing energy

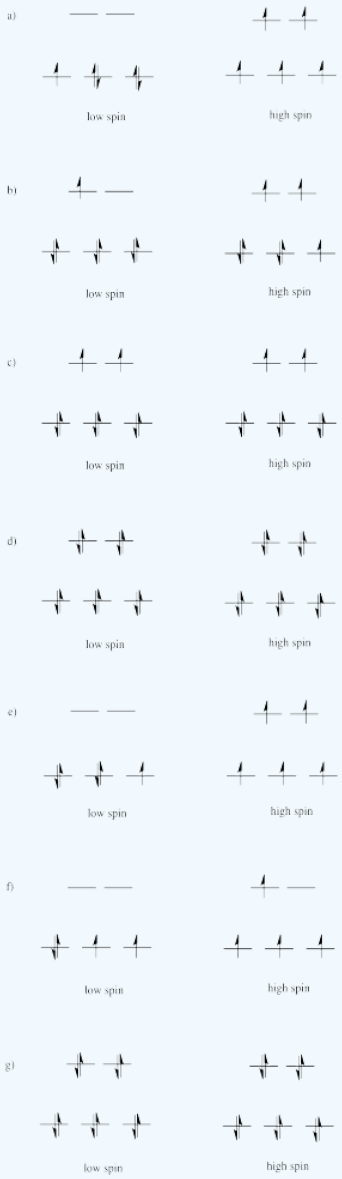
It is significant that most important transition metal ions in biology are from the first row of the transition block and are pretty labile. That fact plays an important role in the ease of formation and deconstruction of transition-metal containing proteins. In terms of formation, if the metal is more easily released by its previous ligands (either water or some compound that delivers the metal to the site of protein construction), it can form the necessary protein more quickly. However, even if a metal-containing enzyme plays a useful role, it should not be too stable, because we need to be able to regulate the level of protein concentration for optimum activity, or disassemble protein if it becomes damaged. Thus, it is important that the metal ion can be removed easily.

? Exercise 2.8.1

Draw both high spin and low spin d-orbital splitting diagrams for the following ions in an octahedral environment and determine the number of unpaired electrons in each case.

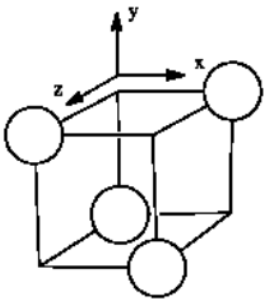
a) Mn^{2+} b) Co^{2+} c) Ni^{2+} d) Cu^{+} e) Fe^{3+} f) Cr^{2+} g) Zn^{2+}

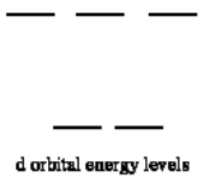
Answer



Exercise 2.8.2

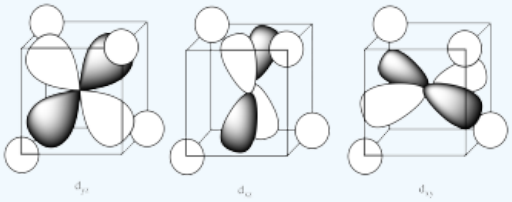
The d orbital splitting diagram for a tetrahedral coordination environment is shown below. Given this diagram, and the axes in the accompanying picture, identify which d orbitals are found at which level. In the picture, the metal atom is at the center of the cube, and the circle represent the ligands.



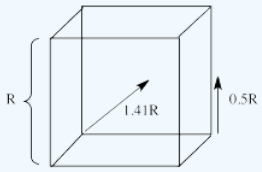


Answer

The three orbitals shown above interact a little more strongly with the ligands. The three orbitals shown below interact a little more weakly.



The reason for the difference in the interaction has to do with how close the nearest lobe of a d orbital comes to a ligand. There are really two possible positions: the face of a cube or the edge of a cube. If the ligands are at alternating corners of the cube, then the orbitals pointing at the edges are a little closer than those pointing at the faces of the cube.



$$\sqrt{R^2 + R^2} = 0.5\sqrt{2R^2} = 0.705R$$

Exercise 2.8.3

Typically, the d orbital splitting energy in the tetrahedral case is only about 4/9 as large as the splitting energy in the analogous octahedral case. Explain why it is smaller for the tetrahedral case.

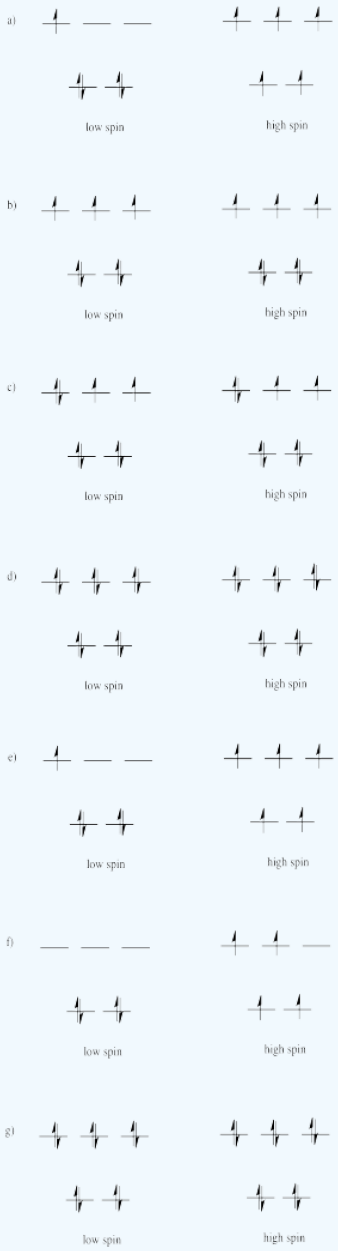
Answer

The ligands do not overlap with the d orbitals as well in tetrahedral complexes as they do in octahedral complexes. Thus, there is a weaker bonding interaction in the tetrahedral case. That means the antibonding orbital involving the d electrons is not raised as high in energy, so the splitting between the two d levels is smaller.

Exercise 2.8.4

Suppose each of the ions in Exercise 2.8.1 (CC8.1) were in tetrahedral, rather than octahedral, coordination environments. Draw the d orbital diagrams for the high spin and the low spin case for each ion.

Answer



Exercise 2.8.5

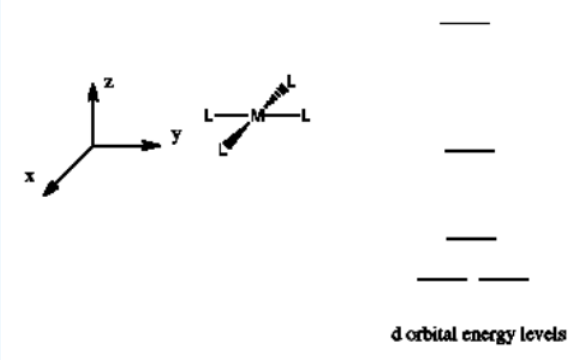
Usually, tetrahedral ions are high spin rather than low spin. Explain why.

Answer

Because the d orbital splitting is much smaller in the tetrahedral case, it is likely that the energy required to pair two electrons in the same orbital will be greater than the energy required to promote an electron to the next energy level. In most cases, the complex will be high spin.

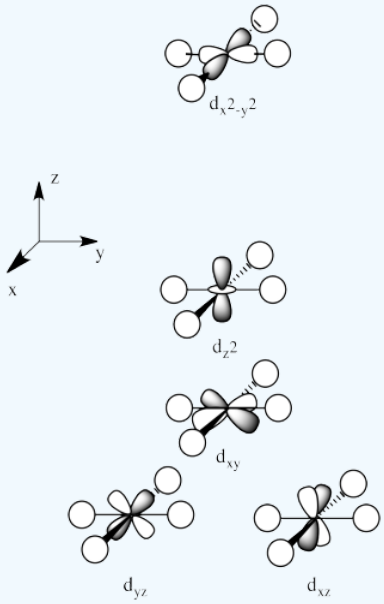
Exercise 2.8.6

The d orbital splitting diagram for a square planar environment is shown below. Given this diagram, and the axes in the accompanying picture, identify which d orbitals are found at which level.



Answer

The orbitals are shown in order of energy.



Exercise 2.8.7

Predict whether each compound will be high or low spin.

a. $[Fe(py)_6]^{2+}$
b. $[Fe(H_2O)_6]^{2+}$
c. $[FeBr_6]^{3-}$
d. $[Co(NH_3)_6]^{3+}$
e. $[Cu(NH_3)_6]^{2+}$
f. $[Rh(CO)_6]^{3+}$
g. $[Cr(CO)_6]^{3+}$
h. $[PtCl_6]^{2-}$

Answer a

$[Fe(py)_6]^{2+}$ 3d metal, M^{+2}, pi acceptor ligand → low spin

Answer b

$[Fe(H_2O)_6]^{2+}$ 3d metal, M^{+2}, pi donor ligand → high spin

Answer c

$[FeBr_6]^{3-}$ 3d metal, M^{+3}, pi donor ligand → high spin

Answer d

$[Co(NH_3)_6]^{3+}$ 3d metal, M^{+3}, sigma donor ligand → low spin

Answer e

$[Cu(NH_3)_6]^{2+}$ 3d metal, M^{+2}, sigma donor ligand → low spin

Answer f

$[Rh(CO)_6]^{3+}$ 4d metal, M^{+3} → low spin

Answer g

$[Cr(CO)_6]^{3+}$ 3d metal, M^{+3}, pi acceptor ligand → low spin

Answer h

$[PtCl_6]^{2-}$ 5d metal, M^{+4} → low spin

? Exercise 2.8.8

Predict whether each compound will be square planar or tetrahedral.

a. $[Zn(NH_3)_4]^{2+}$
b. $[NiCl_4]^{2+}$
c. $[Ni(CN)_4]^{2-}$
d. $[Ir(CO)(OH)(PCy_3)_2]^{2+}$; Cy = cyclohexyl
e. $[Ag(dppb)_2]^{+}$; dppb = 1,4-bis(diphenylphosphino)butane
f. $PtCl_2(NH_3)_2$
g. $PdCl_2(NH_3)_2$
h. $[CoCl_4]^{2-}$
i. $Rh(PPh_3)_3Cl$

Answer a

$[Zn(NH_3)4]^{2+}$ 3d metal, d^{10}, sigma donor ligand → tetrahedral

Answer b

$[NiCl_4]^{2+}$ 3d metal, d^8, pi donor ligand → tetrahedral

Answer c

$[Ni(CN)_4]^{2-}$ 3d metal, d^8, pi acceptor ligand → square planar

Answer d

$[Ir(CO)(OH)(PCy_3)_2]^{2+}$ 5d metal, d^8 → square planar

Answer e

$[Ag(dppb)_2]^{1+}$ 4d metal, d^{10}, sigma donor ligand → tetrahedral

Answer f

$[PtCl_2(NH_3)_2]$ 5d metal, d^8 → square planar

Answer g

$[PdCl_2(NH_3)_2]$ 4d metal, d^8, M^{+2}, sigma donor ligand → square planar

Answer h

$[CoCl_4]^{2-}$ 3d metal, d^7, sigma donor ligand → tetrahedral

Answer i

$[Rh(PPh_3)_3Cl]$ 5d metal, d^8 → square planar

2.9: Ligand Field Stabilization Energy

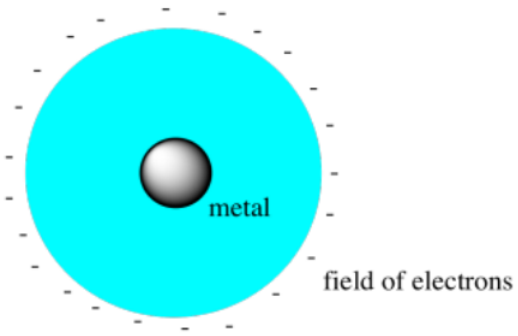
There is a variation on how to think about d orbital splitting diagrams that can be useful in deciding how the d electrons are configured in transition metal complexes. We can use the relative energy levels of the d orbitals in a given complex to calculate whether the overall energy would be higher or lower in a high-spin vs. a low-spin case, for example. The calculation provides us with a value that is called the ligand field stabilisation energy. Although we have been thinking of bonding in transition metal complexes in terms of molecular orbital ideas, ligand field stabilisation energy actually has its roots in a separate approach called crystal field theory.

Origin Story

Crystal field theory was independently developed around 1930 by German physicist Hans Bethe and American physicist John Hasbrouck van Vleck; the two later became professors of physics at Cornell and Harvard, respectively. It actually pre-dates the molecular orbital approach that we have been using so far, but it reaches similar conclusions about transition metal electron configurations.

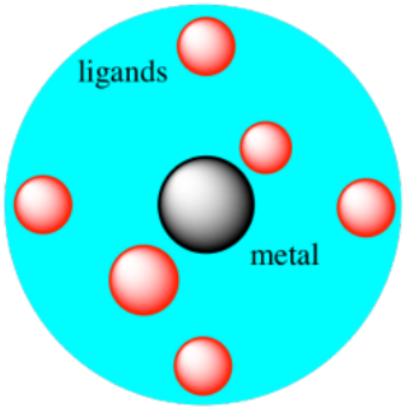
Both scientists were interested in the magnetic properties of metals and metal salts. They knew these properties were related to unpaired electrons. Compounds with unpaired electrons are attracted by magnetic fields, whereas compounds having only paired electrons are not. They were interested in the factors that influenced the d electron configuration of transition metal salts, because how the d electrons filled could result in different numbers of unpaired electrons. Those differences influenced how strongly the compounds interacted with magnetic fields.

Crystal field theory does not consider any bonding interactions in transition metal compounds. It focuses only on the repulsion between the electrons on an anion and the electrons on a metal cation. Of course, all of these electrons have negative charges. As an anion approaches a metal, the physicists reasoned, both sets of electrons would experience repulsive forces that would increase their energy level.

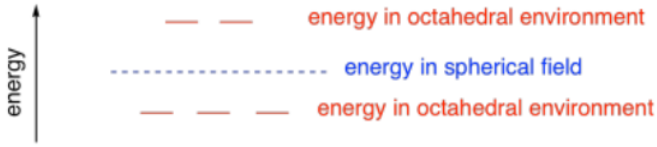


If the metal were surrounded by a spherical field of electrons (physicists like to assume things are spherical because it makes the math easier), then all of the electrons on the metal would be raised equally high in energy by these repulsive forces.

But in a metal salt, electrons are not approaching the metal from all directions. The geometry comes in because of the fact that the cations and anions pack together in specific arrays. For example, if a metal cation is sitting in an octahedral hole, electrons would only approach from six directions: at each end of the x, y, and z axes.



In that case, only the electrons in d orbitals that were aligned along the x, y and z axes would be raised significantly by repulsion with the approaching electrons on the anions. The electrons in the off-axis orbitals would be lower in energy than they would have been in a perfectly spherical field.



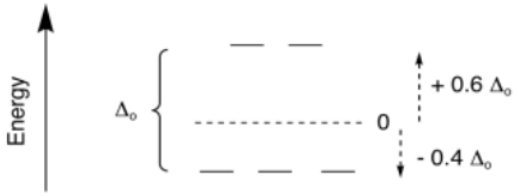
Scientists later adapted this idea to octahedral coordination complexes, in which the metal sits amidst six ligands rather than getting packed among six anions.

That result leads to a picture that is pretty similar to what we get from molecular orbital theory, at least as far as the d orbitals are concerned. In fact, the true mathematical approach to molecular orbital theory does take these electron-electron repulsions into account, but it also factors in attractions between the electrons of the ligands and the nucleus of the metal (and vice versa). The biggest difference is that molecular orbital theory includes what happens to the kinetic energy of the ligand lone pairs as they become shared with the metal (it goes down; that's a big part of why the bonds form).

Application

You don't really have to appreciate where this approach came from to be able to see how it is commonly used. If we take the five d orbitals after they have been placed in an octahedral environment, we see that they are at two different energy levels. The average energy level is not, as it might first appear, halfway between these levels. That's because there are three lower levels and two upper levels. The average is two-fifths of the way up from the bottom three, or three-fifths of the way down from the top two.

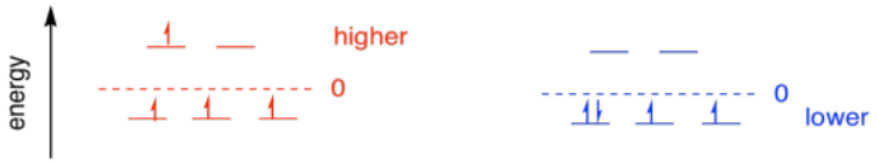
That average energy level of the five d orbitals is called the "barycenter"; it is assigned a relative energy of zero. The difference between the top level and the bottom level is the field splitting; for an octahedral complex, this field splitting is given the symbol Δ_o; here, Δ stands for the energy difference and o stands for octahedral.



If the barycenter is at an energy level of zero, then the lower orbitals are below zero. How far? They are two-fifths of the total Δ_o below the barycenter. Any electrons in those orbitals are $-0.4\Delta_o$ below 0 in energy. Electrons in the upper orbitals are $+0.6\Delta_o$ above zero in energy.

Suppose there are four electrons. The first three electrons sit in each of the three lower orbitals, the ones we sometimes label the t_{2g} orbitals.. The fourth will either go into the upper level, which we sometimes call the e_g level, or else pair up with another electron

at the lower level.



We can now calculate the energy difference between these two possible cases. We can calculate what is called the ligand field stabilisation energy, LFSE (sometimes called crystal field stabilisation energy, or CFSE). It's just the sum of the energies of each of the electrons.

$$LFSE = [(0.6 \times number\ of\ e_g\ electrons) - (0.4 \times number\ of\ t_{2g}\ electrons)]\Delta_o \tag{2.9.1}$$

or if that's too much jargon, $LFSE = [(0.6 \times\ \#upper\ e^-) - (0.4 \times\ \#lower\ e^-)]\Delta_o$

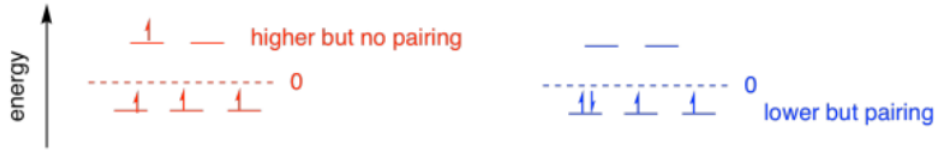
On the left hand side, the high-spin case, that's:

$$LFSE = [(0.6 \times 1) - (0.4 \times 3)]\Delta_o = [0.6 - 1.2]\Delta_o = -0.6\Delta_o \tag{2.9.2}$$

On the right hand side, that's

$$LFSE = [(0.6 \times 0) - (0.4 \times 4)]\Delta_o = -1.6\Delta_o \tag{2.9.3}$$

So far, it certainly seems like the low-spin case is at lower energy. Remember, though, that it requires that we place two electrons together into the same orbital.



Like charges repel. Putting these two electrons so close together is going to cost some energy. But how much?

This repulsion between a pair of electrons in one orbital is called the pairing energy (PE). For each pair of electrons that occupy the same orbital, that energy must be added to take that repulsion into account. As a result, a calculation of the overall stabilization energy includes both the ligand field stabilization energy and the pairing energy.

$$SE = LFSE + PE \tag{2.9.4}$$

If there were two sets of paired electrons, we would add 2PE; if there were three sets of paired electrons, we would add 3PE, and so on.

Overall, deciding quantitatively whether a complex will be high spin or low spin is the most useful application of an LFSE calculation. However, you do have to know the values of the parameters (the field splitting and the pairing energy) for a definitive decision.

? Exercise 2.9.1

Use SE calculations to determine stabilisation in both high spin and low spin cases. Just leave your answer expressed in terms of Δ_o and PE.

a. Fe^{+2}

b. Co^{+2}

c. Co^{+3}

d. Mn^{+2}

e. Ti^{+3}

Answer
Answer a

Fe^{+2}

d^6 low spin

$$SE = [-0.4(6) + 0.6(0)]\Delta_O + 3PE$$

$$= [-2.4]\Delta_O + 3PE$$

d^6 high spin

$SE = [-0.4(4) + 0.6(2)]\Delta_O + 1PE$
$= [-.4]\Delta_O + 1PE$

Answer b

Co^{+2}

d^7 low spin

$$SE = [-0.4(6) + 0.6(1)]\Delta_O + 3PE$$

$$= [-1.8]\Delta_O + 3PE$$

d^7 high spin

$SE = [-0.4(5) + 0.6(2)]\Delta_O + 2PE$
$= [-.8]\Delta_O + 1PE$

Answer c

Co^{+3}
d^6 so this looks the same as Fe^{+2}

Answer d

Mn^{+2}

d^5 low spin

$SE = [-0.4(5) + 0.6(0)]\Delta_O + 2PE$
$= [-2.0]\Delta_O + 2PE$

d^5 high spin

$$SE = [-0.4(3) + 0.6(2)]\Delta_O + 0PE$$

$$= [0]\Delta_O$$

Answer e

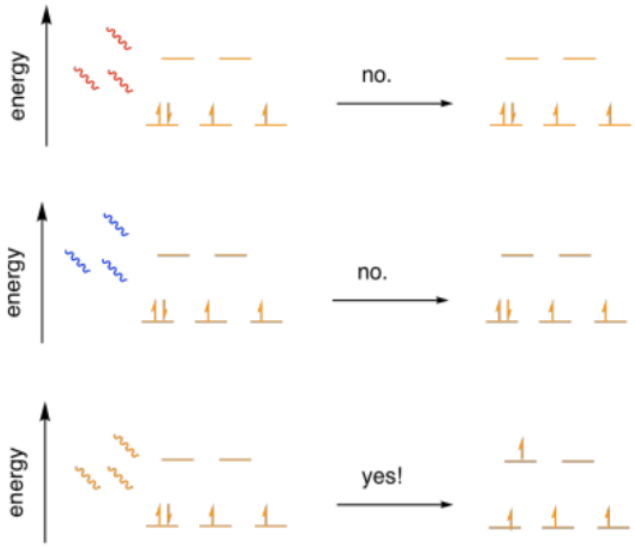
Ti^{+3}
d^1 so there is no possibility of low spin or high spin

The Magnitude of Δ_o and PE

Taking the pairing energy into account in this case suggests that the high-spin case is favored. It cost less energy to jump the gap and put an electron in a high-lying e_g orbital than it did to pair electrons in a low-lying t_{2g} orbital.

Right now, let's think about Δ_o. How much energy is it? How big is the gap between the d orbitals? And how do we know? Well, we can easily measure this gap using a simple spectrophotometer. A spectrophotometer measures how much light is absorbed by a sample. Furthermore, it measures what specific colors of light are absorbed by the sample. As it happens, the absorption of ultraviolet and visible light by a material is associated with electrons in that material becoming promoted to a higher energy level. Shine a light on a transition metal complex, and an electron may jump the gap.

So all we have to do is shine different colors of light on the complex and see whether it absorbs one of the colors.



This experiment is quite reproducible. A specific compound will always absorb the same colors of light. That's why specific materials have specific colors; the color we see represents the light that is *not* absorbed by the material.

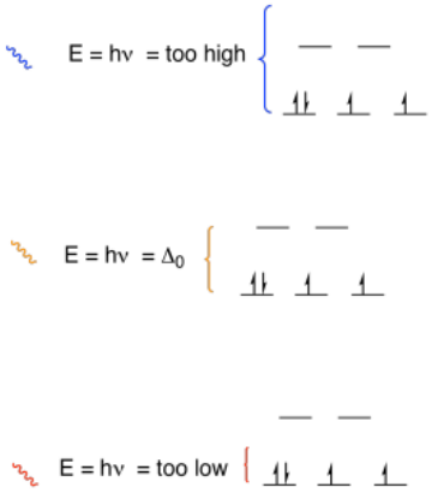
Different colors of light have different amounts of energy. Blue light has higher energy than orange light, which has higher energy than red light. Max Planck and Albert Einstein worked out that the energy of a photon (a "particle" or "packet" of light) is directly proportional to the frequency at which the photon oscillates or vibrates. Blue light has a higher frequency than red light, so it has higher energy.

Planck and Einstein expressed this idea with an equation,

$$E = h\nu$$

in which the Greek letter ν, pronounced "noo", stands for the frequency (some people just use *f* for frequency) and *h* stands for a sort of conversion factor called Planck's constant.

Blue light has too much energy to promote an electron to the next energy level in this case. It would send the electron way past the next level, and quantum mechanics does not allow that sort of thing. Red light does not have enough energy for the electron to get there. Orange light, in this case, is just right. It has exactly the right amount of energy to jump the gap.



So, if we know the frequency of orange light, we know how much energy there is in an orange photon, and we know how big the field splitting is between the d orbitals.

Now, it turns out that historically people have most often described visible light in terms of wavelength rather than frequencies. The wavelength is just the distance from one "peak" to the next as the wave of the photon rolls along. The higher the frequency, the closer these peaks are together, and the shorter the wavelength. Blue light has a shorter wavelength, around 400 nm, than red light, around 700 nm. A nanometer (nm) is 10^{-9} meters (m); a meter is around a yard.

Orange light has a wavelength of around 600 nm, or 600 x 10^{-9} m, or 6 x 10^{-7} m. For reasons we won't get into, spectroscopists in the past (people who measure the interaction of light and matter) sometimes preferred to work in centimeters, cm; there are 100 cm in 1 m, so orange light has a wavelength of 6 x 10^{-5} cm. Now, because they knew there was an inverse relationship between wavelength and energy (the longer the wavelength, the lower the energy; the shorter the wavelength, the higher the energy), they simply took the reciprocal of the wavelength in centimeters to get a number in cm^{-1}, which they called wavenumbers. They used this as a unit of energy. An orange photon has an energy of 1/0.00006 cm = 16,000 cm^{-1}.

So the gap, the field splitting, Δ_o in this complex is 16,000 cm^{-1}.

Let's go back to our comparison between the high-spin and low-spin case. For high spin, that's:

$$LFSE = [(0.6 \times 1) - (0.4 \times 3)]\Delta_o = [0.6 - 1.2]\Delta_o = -0.6\Delta_o = -0.6 \times 16000cm^{-1} = -9600cm^{-1} \quad (2.9.5)$$

For the low-spin case, that's

$$LFSE = [(0.6 \times 0) - (0.4 \times 4)]\Delta_o = -1.6\Delta_o = -1.6 \times 16000cm^{-1} = -25600cm^{-1} \quad (2.9.6)$$

That means that the low-spin case is lower in energy, by 14,000 cm^{-1}. However, we still need to include the pairing energy. Like the field splitting, the pairing energy varies from one complex to another. 20,000 cm^{-1} is a ballpark estimate of a typical pairing energy.

If we use this average value for PE in the example we were discussing above, for the high-spin case:

$$SE = LFSE + PE = -9600 + 0cm^{-1} = -9600cm^{-1} \quad (2.9.7)$$

For the low-spin case,

$$SE = LFSE + PE = -25600 + 20000cm^{-1} = -5600cm^{-1} \quad (2.9.8)$$

Taking the pairing energy into account in this case suggests that the high-spin case is favored. It cost less energy to jump the gap and put an electron in a high-lying e_g orbital than it did to pair electrons in a low-lying t_{2g} orbital.

Let's take a look at some real examples of field splitting values to get an idea of how large they are, and what factors they depend on. For example, we can look at the charge on the metal ion.

Table of Field Splitting Values, Δ_o, in Hexaquo Complexes of Differing Charges[a]

Metal Complex	$[Mn(OH_2)_6]^{2+}$	$[Mn(OH_2)_6]^{3+}$	$[Fe(OH_2)_6]^{2+}$	$[Fe(OH_2)_6]^{3+}$	$[Co(OH_2)_6]^{2+}$	$[Co(OH_2)_6]^{3+}$
Δ_o (cm^{-1})	7,800	21,100	10,400	13,800	9.300	18,300
a) Holleman, A. F.; Wiberg, E.; Wiberg, N. Inorganic Chemistry, 34th Ed. Academic Press: Berlin, 2001.						

In this case, it looks like increased charge on the metal ion results in an increased field splitting. The same thing happens in all three examples: manganese, iron, and cobalt. As the metal ion becomes more charged, attraction of the d electrons toward the nucleus increases. The lower-lying t_{2g} level is more strongly attracted to the nucleus because it is a little closer; consequently, it drops a little further than the e_g level, and the gap gets bigger.

Charge on the metal ion is one of two key factors that influence the size of the field splitting. The other factor is the period or row in the periodic table.

Table of Field Splitting Values, Δ_o, in Hexammine Complexes of Group 9[a,b]

Metal Complex	$[Co(NH_3)_6]^{3+}$	$[Rh(NH_3)_6]^{3+}$	$[Ir(NH_3)_6]^{3+}$
Δ_o (cm^{-1})	21,500	33,100	41,100
a) Holleman, A. F.; Wiberg, E.; Wiberg, N. Inorganic Chemistry, 34th Ed. Academic Press: Berlin, 2001. b) Miessler, G. L.; Tarr, D. A. Inorganic Chemistry, 4th Ed. Pearson, 2010.			

Moving from one row to the next in group 9 of the periodic table, we see that the field splitting increases by about 10,000 cm^{-1} each row.

In general:

- Δ_o increases with charge on the metal
- Δ_o increases with the period in the periodic table

The metal ion is not the only factor that affects the field splitting. The ligands also play an important role, as seen in the table below.

Table of Field Splitting Values, Δ_o, in Assorted Complexes[a]

Metal Complex	$[CrCl_6]^{3-}$	$[CrF_6]^{3-}$	$[Fe(OH_2)_6]^{2+}$	$[Fe(CN)_6]^{4-}$	$[Co(OH_2)_6]^{3+}$	$[Co(NH_3)_6]^{3+}$	$[Co(CN)_6]^{3-}$
Δ_o (cm^{-1})	13,300	15,300	10,400	33,200	18,300	23,000	33,700
a) Holleman, A. F.; Wiberg, E.; Wiberg, N. Inorganic Chemistry, 34th Ed. Academic Press: Berlin, 2001.							

If we sort these ligands into three broad categories, we can form a trend for these effects. It may be easiest to start with the three entries on the right, involving cobalt. The oxygen donor in water has two lone pairs, whereas the nitrogen donor in ammonia has only one. The extra lone pair allows water to act as a π donor; the lone pair can donate to an orbital on the metal to form a pi bond. In this case, it looks like the π donor (water) results in a smaller Δ_o than the normal σ donor (ammonia).

The cyanide ligand has a donor atom that is also participating in a π bond within the ligand; there is a triple bond between the C and N of the cyanide. That means there is also an associated antibonding orbital, π*. That antibinding orbital raises the possibility of back-bonding from the metal. The metal can donate into the π* orbital to make a pi bond. Cyanide is a π-acceptor. Its field splitting is much larger than the sigma donor.

Those conclusions can be confirmed by looking at the entries for iron in the middle of the table. Cyanide is a π-acceptor whereas water is a π-donor. The field splitting in the aquo complex should be much smaller than the field splitting in the cyano complex, and it is.

The two entries for chromium on the left both show halides, which are π-donors. They illustrate a factor that can be used to predict field strength between two ligands from the same group, such as two π-donors or two π-acceptors. In general, the more basic the

ligand, the greater the field splitting. Fluoride ion is more basic than chloride ion (because chloride is a more stable anion than fluoride) so it results in a slightly greater value of Δ_o.

In order to thoroughly estimate the stabilisation energy, we also need reliable values for the pairing energy. Pairing energies can be calculated for free metal ions; correction factors can be applied to arrive at a corresponding value in a complex. In general, the values in coordination complexes are somewhat lower than the values in free metal ions. In the table below, we have made a general estimate that the value in the complex is about 20% lower than in the free metal ion.

Table of Pairing Energies, PE, in Free Ions, with Estimated PE in Complexes

Metal Ion	Mn^{2+}	Mn^{3+}	Fe^{2+}	Fe^{3+}	Co^{3+}	Ru^{3+}
PE, free ion (cm^{-1})	28,000	25,500	17,700	30,100	21,100	~15,000[b]
PE, complex (est., cm^{-1})	20,400	22,900	14,200	24,100	16,900	~12,000[b]
a) Holleman, A. F.; Wiberg, E.; Wiberg, N. Inorganic Chemistry, 34th Ed. Academic Press: Berlin, 2001. b) Estimate.						

If we compare the pairing energies of the 2+ ions to those of the 3+ ions, we see that it is always lower in the more highly charged ion. That's the opposite of the trend in Δ_o. Pairing energy is largely dependent on the size of the ion. The smaller the ion, the smaller the orbital, and the more repulsion between two electrons in the same orbital. Because a Mn^{3+} ion is smaller than a Mn^{2+} ion (Coulomb's Law says there is greater attraction for the electrons in the former case, so the ion shrinks), a pair of electrons on Mn^{3+} is closer together than a pair of electrons on Mn^{2+}.

In general, pairing energies also get smaller upon moving down a column in the periodic table. Second row transition metals are larger than first-row transition metals, so the pairing energy is smaller in the second row than in the first. Third row transition metals are about the same size as first row metals, so ther pairing energies are similar to those of the second row. That's because of a phenomenon called "the lanthanide contraction": third row transition metals contain an extra set of protons in their nuclei because of the f block elements before them; consequently they are a little smaller than might be expected.

? Exercise 2.9.2

Compare pairing energies to field splitting values to determine whether the following complexes would be high-spin or low spin.

a) $Mn(OH_2)_6^{2+}$ b) $Fe(CN)_6^{4-}$ c) $Co(NH_3)_6^{3+}$

Answer

Answer a

Δ_o < PE, so high-spin.

Answer b

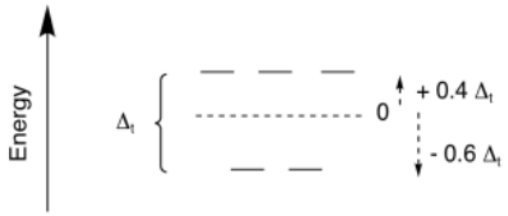
Δ_o > PE, so high-spin.

Answer c

Δ_o > PE, so high-spin.

Other Geometries

Crystal field theory has also been applied to other geometries of coordination compounds. Once again, in terms of the d orbital splitting diagram, the results are similar to what we see from molecular orbital theory. For tetrahedral geometry, which is the most common geometry when the coordination number is four, we again get a set of two high-lying orbitals and three lower ones.



The overall splitting is expressed as Δ_t; the t stands for tetrahedral. However, sometimes it is useful to compare different geometries. In crystal field theory, it can be shown that the amount of splitting in a tetrahedral field is much smaller than in an octahedral field. In general, $\Delta_t = 4/9\ \Delta_o$.

We wouldn't usually use crystal field theory to decide whether a metal is more likely to adopt a tetrahedral or an octahedral geometry. In most cases, the outcome is more strongly dependent on factors other than the d orbital energies. For example, maybe a complex would be too crowded with six ligands, so it only binds four; it becomes tetrahedral rather than octahedral. Or maybe a metal does not have enough electrons in its valence shell, so it binds a couple more ligands; it becomes octahedral rather than tetrahedral.

However, this comparison between Δ_o and Δ_t does help to explain why tetrahedral complexes are much more likely to adopt high-spin configurations than are octahedral complexes. The splitting is smaller in tetrahedral geometry, so pairing energy is more likely to become the deciding factor there than it is in octahedral cases.

? Exercise 2.9.3

Tetrahedral complexes are pretty common for high-spin d6 metals, even though the 18-electron rule suggests octahedral complexes should form. In contrast, low-spin d6 complexes do not usually form tetrahedral complexes. Use calculations of stabilisation energies to explain why.

Answer

high-spin d^6

octahedral

$$SE = [2(0.6) - 4(0.4)]\Delta_O + PE$$

$$SE = -0.4\Delta_O + PE$$

tetrahedral

$$SE = [3(0.4) - 3(0.6)]\frac{4}{9}\Delta_O + PE$$

$$SE = -0.6\Delta_O + PE$$

$$\Delta SE = SE_{oh} - SE_{td} = -0.4\Delta_O + PE - (-0.6\Delta_O + PE) = +0.2\Delta_O$$

This is a slight preference for tetrahedral.

low-spin d^6

octahedral

$$SE = [0(0.6) - 6(0.4)]\Delta_O + 3PE$$

$$SE = -2.4\Delta_O + 3PE$$

tetrahedral

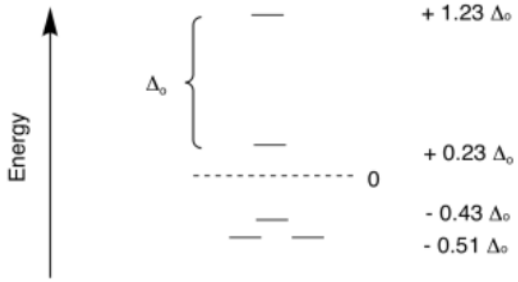
$$SE = [2(0.4) - 4(0.6)]\frac{4}{9}\Delta_O + 2PE$$

$$SE = -1.6\Delta_O + PE$$

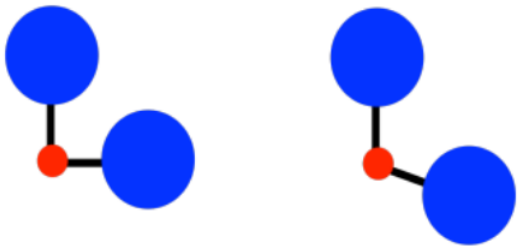
$$\Delta SE = SE_{oh} - SE_{td} = -2.4\Delta_o + 3PE - (-1.6\Delta_o + 2PE) = -0.8\Delta_o + PE$$

This is a preference for octahedral, although it would be offset by the pairing energy.

Crystal field theory has also been used to determine the splittings between the orbitals in a square planar geometry. That is a much more complicated case, because there are four different levels. Once again, the energy levels are often expressed in terms of Δ_o.



We could use a calculation of stabilisation energy to predict whether a particular complex is likely to adopt a tetrahedral or a square planar geometry. Both geometries are possible, so it would be useful to be able to predict which geometry occurs in which case. However, just as in the case of comparing octahedral and tetrahedral geometries, there is another factor that is often more important.



That factor is steric crowding. In a tetrahedron, all the ligands are 109° from each other. In a square planar geometry, the ligands are only 90° away from each other. Tetrahedral geometry is always less crowded than square planar, so that factor always provides a bias toward tetrahedral geometry. As a result, we might expect square planar geometry to occur only when sterics is heavily outweighed by ligand field stabilisation energy.

Exercise 2.9.4

The most common examples of square planar complexes have metals that are d^8. Use calculations of the stabilisation energy to explain why if the complex is:

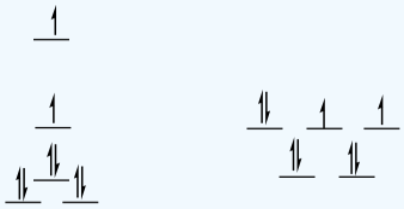
(a) low-spin

(b) high-spin

Answer

Answer a

high-spin d^8



square planar

$$SE = [1.23 + 0.23 - 2(0.43) - 4(0.51)]\Delta_O + 3PE$$

$$SE = -1.44\Delta_O + 3PE$$

tetrahedral

$$SE = [4(0.4) - 4(0.6)]\frac{4}{9}\Delta + 3PE$$

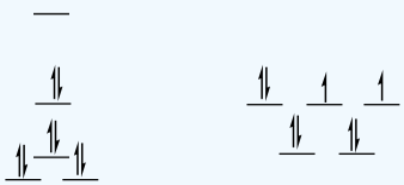
$$SE = -0.36\Delta_O + 3PE$$

$$\Delta = \Delta SE = SE_{sq} - SE_{td} = -1.44\Delta_O + 3PE - (-0.36\Delta_O + 3PE) = -1.08\Delta_O$$

This is an appreciable preference for square planar.

Answer b

low-spin d^8



square planar

$$SE = [0 + 2(0.23) - 2(0.43) - 4(0.51)]\Delta_O + 4PE$$

$$SE = -2.44\Delta_O + 4PE$$

tetrahedral = same as before (ls = hs for d^8 tetrahedral)

$$\Delta SE = SE_{sq} - SE_{td} = -2.44\Delta_O + 3PE - (-0.36\Delta_O + 3PE) = -2.08\Delta_O + PE$$

This is an even more appreciable preference for square planar, although it is offset by pairing energy. Pairing energy would have to be twice as big as Δ_o in order to completely offset the LFSE.

2.10: Spectrochemical Series

Another factor that plays a key role in whether a transition metal complex is high- or low-spin is the nature of the ligands. The d orbital energy splitting is influenced by how strongly the ligand interacts with the metal. Ligands that interact only weakly produce little change in the d orbital energy levels, whereas ligands that interact strongly produce a larger change in d orbital energy levels.

The spectrochemical series is a list of ligands based on the strength of their interaction with metal ions. It is often listed, from weaker to stronger ligands, something like this:

$I^- < Br^- < S^{2-} < \mathbf{S}CN^- < Cl^- < NO_3^- < N_3^- < F^- < OH^- < C_2O_4^{2-} < H_2O < \mathbf{N}CS^- < CH_3CN <$ py $< NH_3 <$ en $<$ bipy $<$ phen $< NO_2^- < PPh_3 < CN^- < CO$

in which py = pyridine; en = ethylenediamine; bipy = 2,2'-bipyridine; phen = 1,10-phenanthroline; **S**CN means the ligand is bound via sulfur and **N**CS via nitrogen.

The list can vary from one metal ion to another, since some ligands bind preferentially to certain metals (as seen in hard and soft acid and base chemistry).

Exercise 2.10.1

What empirical trends can you see within the spectrochemical series? Are there any factors that make something a stronger field ligand?

Answer

The weaker donors include halides and oxygen donors. Nitrogen atom donors are mostly a little stronger than that. The strongest donors include carbon donors, especially with pi bonds.

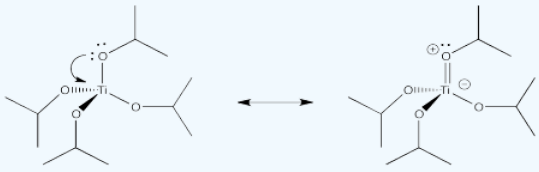
The d orbitals that rise in energy in the presence of a ligand can be thought of as forming an antibonding molecular orbital combination with an orbital on the ligand. In addition, there would also be a bonding combination for this interaction. That bonding orbital would be more like the initial ligand orbital. This premise is based on the idea that a ligand orbital is initially lower in energy than the metal orbital, so a bonding combination between these two orbitals is more like the initial ligand orbital, both in energy and location. The d orbital is initially higher in energy than the ligand orbital, so an antibonding combination between these two orbitals is more like the initial d orbital, both in energy and location.

- When orbitals on two different kinds of atoms combine, the antibonding orbital is considered to be more like the orbital that was initially at higher energy.
- In this case, it is still close to a d orbital in energy, location, and shape.
- When orbitals on two different kinds of atoms combine, the bonding orbital is considered to be more like the orbital that was initially at lower energy.

Exercise 2.10.2

Suppose a ligand has more than one lone pair on the donor atom. The donor atom could share an extra pair of electrons with the metal, to form a double bond. This type of interaction is called pi-donation, because a pi bond is formed (not to be confused with sigma donation *from* a pi bond, as in alkene binding). Show an example using $Ti(O^iPr)_4$.

Answer

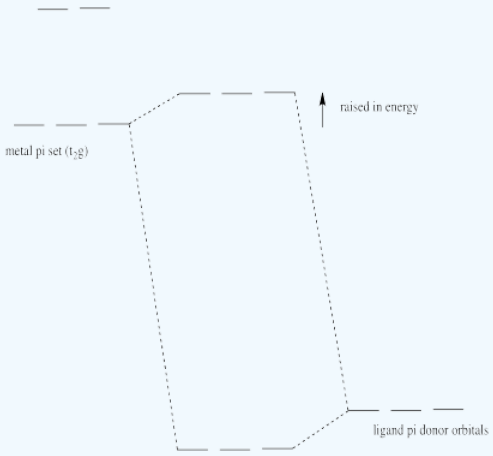


Exercise 2.10.3

In an octahedral environment, three of the d orbitals were not affected by sigma donation from the ligands. Show what happens to the energy level of these d orbitals in the presence of a pi donor.

Answer

Pi donation raises the t_2g electrons (the d electrons of proper symmetry for pi overlap with the ligands in an octahedral geometry).



Exercise 2.10.4

Some ligands can accept a pair of electrons from the metal. An example is a carbonyl complex, which has a C=O pi antibonding orbital that can interact with a d orbital.

a. Show the antibonding orbital on the carbonyl (CO) ligand.
b. Show how a metal d orbital can interact with this orbital.

Exercise 2.10.5

In the previous problem, a lower-energy atomic orbital on the metal interacts with a higher-energy antibonding orbital on the ligand. Show what happens to the energies of these two orbitals when they interact with each other.

Answer

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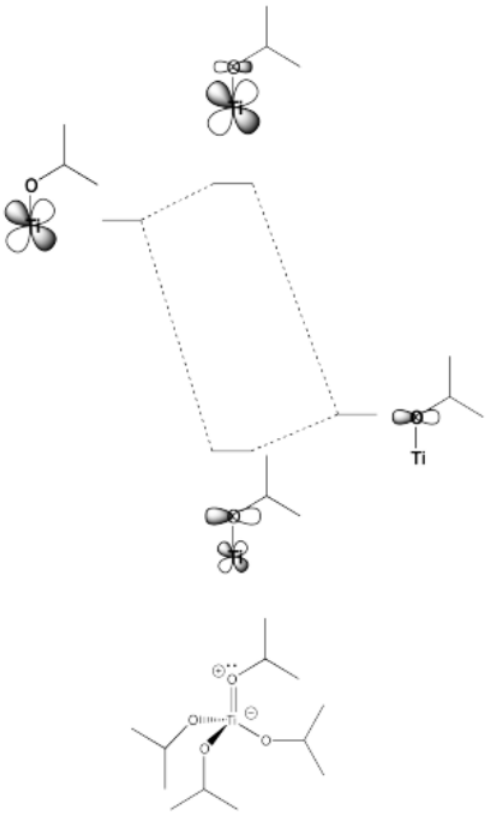
Some of the trends we see in the spectrochemical series arise from pi-donating and pi-accepting effects in the ligand. Ligands that have additional lone pairs (other than the one hat sigma donates) are pi donors. Pi donors raise the otherwise non-bonding t2g orbitals, because the lone pair on the ligand forms a pi bond with the metal. The t2g orbitals and the ligand lone pair orbitals form two new orbitals. The antibonding orbital is closer in energy to the high-energy d orbitals. The bonding orbital is closer in energy to the low-energy ligand orbital.

- Pi donation raises the t2g set of d orbitals in energy.
- As a result, the d orbital splitting gets smaller.
- Also as a result, a complex with pi donation is a little less stable than a complex without pi donation.

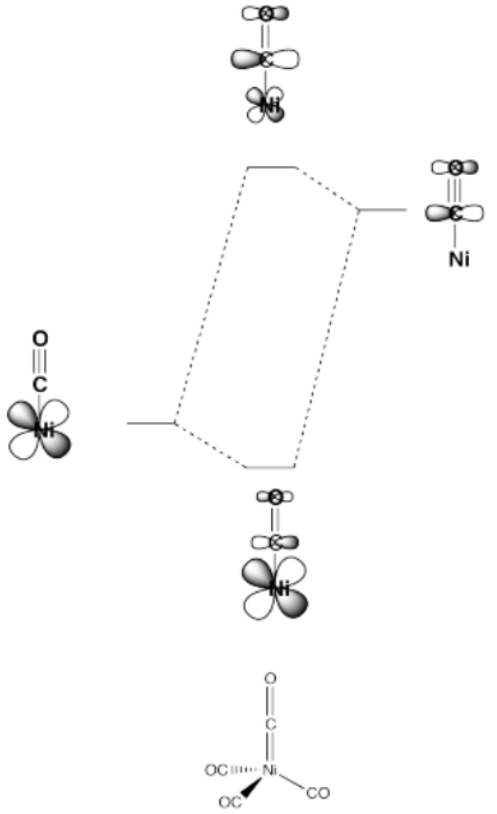
This type of interaction can be seen in the following pictures (a tetrahedral case).



On the other hand, ligands in which the donor atom is already pi bonding to another atom can accept pi donation from the metal. This happens by donating an electron pair from a metal t2g orbital into a pi* orbital on the ligand. In this case, because the pi* is an antibonding orbital, it is higher in energy than the metal d orbital (or the t2g orbital). The resulting bonding orbital is more like the lower energy metal orbital, whereas the resulting antibonding orbital is more like the higher energy pi* orbital on the ligand.

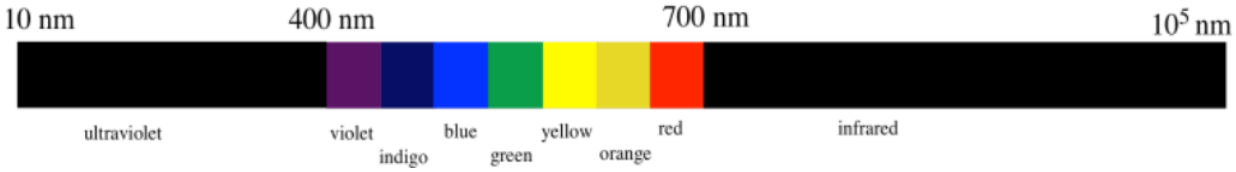
- Pi accepting ligands lower the t2g set of d orbitals in energy.
- As a result, the d orbital splitting gets larger.
- Also as a result, a complex with a pi accepting ligand is a little more stable than a complex without a pi accepting ligand.

This type of interaction can be seen in the following case (a tetrahedral complex).



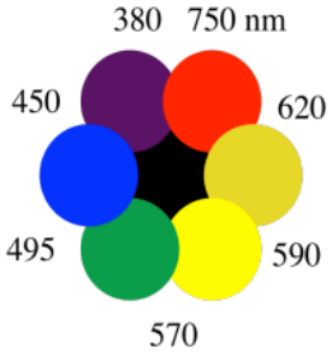
The spectrochemical series gets its name because of a shift in a band of the UV-Vis spectrum when two similar complexes are compared that have two different ligands. The effect of the ligand on the d orbital splitting has an effect on the wavelength of light associated with a d orbital (filled) to d orbital (empty) electronic transition. This transition is actually not associated with a major absorption by the compound; d orbital transitions are actually not that efficient at absorbing light. However, because they often occur in the region of visible light, they often lead to colored transition metal complexes.

The visible region includes photons with wavelengths from approximately 400 to 700 nm (really, a little bit lower and a little bit higher, but we are rounding). Photons with shorter wavelengths are invisible; if they are only a little shorter than visible light they are ultraviolet. Beyond that, photons with very, very short wavelengths are X-rays and gamma rays. Photons with longer wavelengths are also invisible; the infrared region is beyond about 700 nm. Beyond the infrared are microwaves and radio waves.



When we observe an object, what we see is the light that bounces off the object. If all wavelengths of visible light bounces off the object, the object appears white. If all wavelengths of visible light is absorbed by the object, the object appears black. If very specific wavelengths of visible light are absorbed, we see the other wavelengths, but the actual color that we perceive is slightly complicated, because of the way that we sense light.

In simple cases, the color absorbed and the complementary color that we see can be displayed using a color wheel. The color wheel displays the "complementary colors". When we see one of these colors, the light that is getting absorbed is the opposite one in the color wheel.



So, if we see something that looks bright blue, that object is really absorbing mostly orange light. If something absorbs violet light, it appears to us to have a yellow color.

Exercise 2.10.6

Explain what happens to the wavelength of light absorbed for the d-d transition when a chloride ligand on a metal complex is replaced with a hydroxide ligand.

Answer

Because chloride is a weaker ligand than hydroxide, the d orbital splitting gets smaller. A d-d transition would involve less energy, so it would move to longer wavelength (red shift).

Exercise 2.10.7

The $[Cu(OH_2)_6]^{2+}$ ion appears blue-green, whereas the $[Cu(NH_3)_2(OH_2)_4]^{2+}$ ion appears indigo-violet.

a. What colors do each of these complexes absorb?
b. Which complex absorbs the highest-energy photons?
c. If this absorption is due to a d-d transition, which complex has a larger d-d gap?
d. Which compound has stronger field ligands?

Answer

Answer a

The $[Cu(OH_2)_6]^{2+}$ ion appears blue-green, so it absorbs a reddish orange, about 650 nm; whereas the $[Cu(NH_3)_2(OH_2)_4]^{2+}$ ion appears indigo-violet, so it absorbs yellow, about 600 nm.

Answer b

Shorter wavelength is higher energy, according to the Planck-Einstein relation: $E = hc/\lambda$ (in which h = Planck's constant, c = speed of light, λ = wavelength of photon). The $[Cu(NH_3)_2(OH_2)_4]^{2+}$ ion absorbs the shorter wavelength, higher energy photon.

Answer c

The $[Cu(NH_3)_2(OH_2)_4]^{2+}$ ion has the greater d-d gap.

Answer d

The ammonia must be a stronger field ligand than water. In general terms we might think of that as a result of ammonia being only a sigma-donor, whereas water is also a pi-donor.

Exercise 2.10.8

The $[Cr(NH_3)_6]^{3+}$ ion appears yellow, whereas the $[Cr(NH_3)_5Cl]^{2+}$ ion appears pink.

a. What colors do each of these complexes absorb?

b. Which complex absorbs the highest-energy photons?
c. If this absorption is due to a d-d transition, which complex has a larger d-d gap?
d. Which compound has stronger field ligands?

Answer
Answer a

The $[Cu(NH_3)_6]^{3+}$ ion appears yellow, so it absorbs violet, about 400 nm; whereas the $[Cu(NH_3)_5Cl]^{2+}$ ion appears pink, so it absorbs green, about 550 nm.

Answer b

Shorter wavelength is higher energy, according to the Planck-Einstein relation: $E = hc/\lambda$ (in which h = Planck's constant, c = speed of light, λ = wavelength of photon). The $[Cu(NH_3)_6]^{3+}$ ion absorbs the shorter wavelength, higher energy photon.

Answer c

The $[Cu(NH_3)_6]^{3+}$ ion has the greater d-d gap.

Answer d

The ammonia must be a stronger field ligand than chloride. In general terms we might think of that as a result of ammonia being only a sigma-donor, whereas chloride is also a pi-donor.

Exercise 2.10.9

A TA is preparing some cobalt samples for lab: one contains $[Cr(OH_2)_6]^{3+}$, one contains $[Cr(CN)_6]^{3-}$, and one contains $[CrF_6]^{3-}$. Unfortunately, he gets them mixed up. He just has a beaker with green powder, a beaker with yellow powder, and a beaker with violet powder. Can you help him decide which is which?

Answer

The green compound absorbs red; the violet compound absorbs yellow; the yellow compound absorbs violet.

In terms of energy these absorbances can be ranked:

(high energy) violet photon > yellow photon > red photon (low energy)

or in terms of d-d gap:

large gap > middle gap > small gap

In the spectrochemical series, we would expect the order of corresponding ligands to be:

$^-CN > H_2O > F^-$

The cyano compound absorbs violet and appears yellow; the aquo compound absorbs yellow and appears violet; the fluoro compound absords red and appears green.

Exercise 2.10.10

The $[V(OH_2)_6]^{3+}$ ion appears yellow, whereas the $[V(OH_2)_6]^{2+}$ ion appears pink.

a. What colors do each of these complexes absorb?
b. Which complex absorbs the highest-energy photons?
c. If this absorption is due to a d-d transition, which complex has a larger d-d gap?
d. Both compounds contain the same ligands. Why does one have a larger gap?

Answer
Answer a

The $[V(OH_2)_6]^{3+}$ ion appears yellow, so it absorbs violet, about 400 nm; whereas the $[V(OH_2)_6]^{2+}$ ion appears pink, so it absorbs green, about 550 nm.

Answer b

Shorter wavelength is higher energy, according to the Planck-Einstein relation: E = hc/λ (in which h = Planck's constant, c = speed of light, λ = wavelength of photon). The $[V(OH_2)_6]^{3+}$ ion absorbs the shorter wavelength, higher energy photon.

Answer c

The $[V(OH_2)_6]^{3+}$ ion has the greater d-d gap.

Answer d

One ion contains V^{3+}, whereas the other ion contains V^{2+}. As charge increases on an ion, electrons contract toward the nucleus. However, low-lying electrons, which are closer to the nucleus to begin with, are attracted even more than are high-lying electrons. Thus, as charge increases on the ion, the d-d splitting increases.

Exercise 2.10.11

Predict whether each of these coordination complexes is low spin or high spin.

a) $[Co(NH_3)_6]^{+3}$ b) $[Fe(CN)_6]^{-4}$ c) $[CoF_6]^{-4}$

d) $[Rh(CN)_6]^{-3}$ e) $[V(OH_2)_6]^{+3}$ f) $[Fe(py)_6]^{+2}$

g) $[MnCl_6]^{-4}$ h) $[Ru(NH_3)_6]^{+2}$

Answer

Answer a

$[Co(NH_3)_6]^{+3}$

The metal is +3 suggesting a large Δ_0

The ligands are sigma donors, so medium field ligands

The splitting energy is large thus low spin.

Answer b

$[Fe(CN)_6]^{-4}$

The metal is first row, +2 suggesting intermediate Δ_0

The ligands are pi acceptors, so strong field ligands

The splitting energy is large thus low spin.

Answer c

$[CoF_6]^{-4}$

The metal is first row, +2 suggesting a large Δ_0

The ligands are pi donors, so weak field ligands

The splitting energy is small thus high spin.

Answer d

$[Rh(CN)_6]^{-3}$

The metal is 2nd row (4d) and +3 suggesting a large Δ_0

The ligands are pi acceptors, so strong field ligands

The splitting energy is large thus low spin.

Answer e

$[V(OH_2)_6]^{+3}$

The complex is d^2, so there is only one possible spin state.

Answer f

$[Fe(py)_6]^{+2}$

The metal is first row, +2 suggesting intermediate Δ_0

The ligands are pi acceptors, so strong field ligands

The splitting energy is large thus low spin.

Answer g

$[MnCl_6]^{-4}$

The metal is first row, +2 suggesting intermediate Δ_0

The ligands are pi donors, so weak field ligands

The splitting energy is large thus high spin.

Answer h

$[Ru(NH_3)_6]^{+2}$

The metal is 2nd row (4d) and +2 suggesting a large Δ_0

The ligands are sigma donors, so medium field ligands

The splitting energy is large thus low spin.

2.11: Ligand Lability

Lability refers to the ease with which ligands are replaced in coordination complexes. Scandium is referred to as "labile" in the following example.

$[Sc(OH_2)_6]Cl_3$ + 6 NaSCN —> $Na_3[Sc(SCN)_6]$ + 3 NaCl (very fast!)

Lability refers to how easily metal-ligand bonds are broken. A compound in which metal-ligand bonds are easily broken is referred to as "labile". A compound in which metal-ligand bonds are more difficult to break is referred to as "inert".

Henry Taube (Nobel Prize, 1983) tried to understand lability by comparing the factors that govern bond strengths in ionic complexes to observations about the rates of reaction of coordination complexes. He saw some things that were unsurprising. He also drew some new conclusions based on ligand field theory.

? Exercise 2.11.1

In which compound from each pair would you expect the strongest ionic bonds? Why?

a) LiF vs KBr

b) $CaCl_2$ vs. KCl

Answer
Answer a

The ions in LiF are both smaller than in KBr, so the force of attraction between the ions in LiF is greater because of the smaller separation between the charges.

Answer b

Calcium has a 2+ charge in $CaCl_2$, whereas potassium has only a + charge, so the chloride ions are more strongly attracted to the calcium than to the potassium.

Taube observed that many M^{+1} ions (M = metal) are more labile than many M^{+3} ions, in general. That isn't too surprising, since metal ions function as electrophiles or Lewis acids and ligands function as nucleophiles or Lewis bases in forming coordination complexes. In other words, metals with higher charges ought to be stronger Lewis acids, and so they should bind ligands more tightly.

However, there were exceptions to that general rule. For example, Taube also observed that Mo(V) compounds are more labile than Mo(III) compounds. That means there is more going on here than just charge effects.

Another factor that governs ionic bond strengths is the size of the ion. Typically, ions with smaller atomic radii form stronger bonds than ions with larger radii. Taube observed that Al^{3+}, V^{3+}, Fe^{3+} and Ga^{3+} ions are all about the same size. All these ions exchange ligands at about the same rate. That isn't surprising, because they have the same charge and the same radius.

However, Cr^{3+} is also about the same size as those ions and it also has the same charge, but it is much less labile. Once again, there are exceptions to our regular expectations based on simple electrostatic considerations.

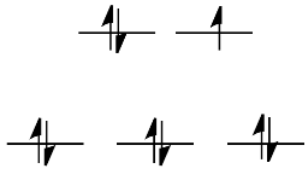
Furthermore, second- and third-row transition metals (Y-Cd and Ac-Hg) are much more inert than first-row transition metals (Sc-Zn). That is a little surprising, since those lower metals are much larger than the first row metals.

However, it gives us a clue about other factors that are playing a role in lability. In ligand field theory, second- and third-row metals have much larger d orbital splitting energies than do first-row metals. That is sometimes explained in terms of diffuse orbitals on these larger atoms forming stronger bonds to ligands, and reminds us that we are not just dealing with electrostatic interactions.

Taube wondered whether d electron configuration influenced whether a compound is labile or inert. That idea forms the basis of Taube's rules about lability.

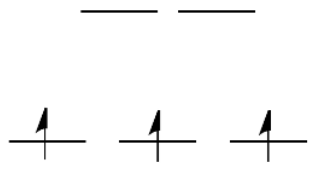
For example, metals like Ni^{2+} and Cu^{2+} are very labile. The d orbital splitting diagrams for those compounds would have d

electrons in the e_g set. Remember, the e_g set arises from interaction with the ligand donor orbitals; this set corresponds to a σ antibonding level.



Cu^{2+}

By comparison, V^{2+} is rather inert. The d orbital splitting diagram in this case has electrons in the t_{2g} set, but none in the e_g set.



V^{2+}

So, having electrons in the higher energy, antibonding e_g level weakens the bond to the ligand, so the ligand can be replaced more easily. In the absence of those higher energy electrons, the bond to the ligand is stronger, and the ligand isn't replaced as easily.

On the other hand, metals like Ca^{2+}, Sc^{3+} and Ti^{4+} are pretty labile. The d orbital splitting diagrams in those cases are pretty simple: there are no d electrons at all in these ions.

That means having no electrons in these mostly non-bonding levels leaves the complex susceptible to ligand replacement. But it's hard to see why population of an orbital that is mostly non-bonding would have an effect on ligand bond strength.

Instead, this factor probably has something to do with the part of ligand substitution that we have ignored so far. Not only does one ligand need to leave, but a second one needs to bond in its place. So, having an empty orbital for the ligand to donate electrons into (or, put another way, not having electrons in the way that may complicate donation from the ligand) makes that part of the reaction easier.

? Exercise 2.11.2

Some metals, like Mn^{2+}, can be either labile or inert, depending on whether they are high spin or low spin. Explain why using d orbital splitting diagrams.

Answer

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? Exercise 2.11.3

Predict whether the following metals, in octahedral complexes, are labile or not.

a) Co^{3+} (high spin)

b) Co^{3+} (low spin)

c) Fe^{2+} (low spin)

d) Fe^{2+} (high spin)

e) Zn^{2+}

Answer

Answer a

labile (electrons in higher energy d orbital set)

Answer b

not labile (all electrons in lower energy d orbitals)

Answer c

not labile (all electrons in lower energy d orbitals)

Answer d

labile (electrons in higher energy d orbital set)

Answer e

labile (electrons in higher energy d orbital set)

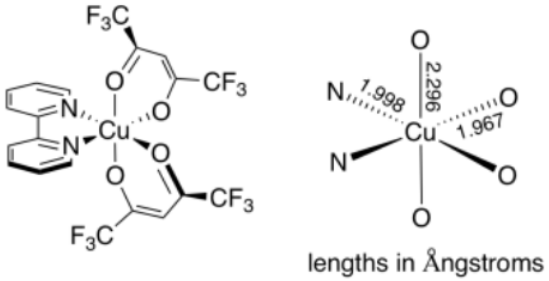
2.12: Jahn-Teller Distortion

Lability can often be understood in terms of the d-electron count on the metal. Sometimes, there is a high-lying electron in a formally σ* orbital that destabilizes the complex and weakens a bond to a ligand. A dissociative substitution pathway may be accelerated as a result. Sometimes, there is a low-lying vacancy in a formally non-bonding level. An associative substitution pathway may be accelerated as a result.

In some cases, the d-electron count can have a subtle influence on the geometry of a complex. For example, an octahedral complex might be distorted, either stretched along one axis or else compressed. In Jahn-Teller Distortion, this effect arises from unequally-distributed electrons in the same level (*degeneracy*). Although this phenomenon is structural, it can sometimes exert an influence on the stability of complexes that translates into accelerated ligand substitutions.

Degeneracy refers to an unequal number of electrons in orbitals at the same energy level; it is sometimes described as a situation in which there are different possible ways to fill in the electrons.

An example of this distortion can be seen in the coordination complex, (bpy)Cu(II)(hfacac)$_2$, shown below. In this complex, one would expect the Cu-N distances to be different from the Cu-O distances. However, the two Cu-O distances should be pretty similar.

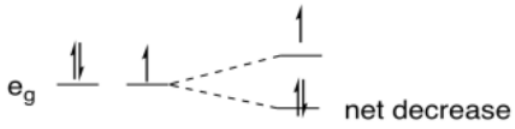


In contrast, it turns out that the two axial Cu-O distances are 17% longer than the two equatorial Cu-O distances.[1] There could be different reasons for this (maybe the neighbouring nitrogen donors influence the Cu-O distances), but the main one turns out to be a Jahn-Teller effect. The same effect can be seen even in complexes such as Cu(II)$(OH_2)_6^{2+}$, in which all of the ligands are the same, but in which two of the Cu-O bonds that are *trans* to each other are significantly longer than the rest.

The origin of the distortion can be seen in the d orbital splitting diagram for an octahedral species. Cu(II) is a d^9 ion. In its d orbital splitting diagram, the upper e_g set of orbitals is unevenly occupied: one orbital contains two electrons, whereas the other contains only one. There does not appear to be anything inherently wrong with that; rather, there is simply an advantage to distortion.

Suppose the two axial ligands in the octahedron back away from the metal. Imagine that they are interacting with the d_z^2 orbital. Their interaction with that orbital resulted in the d_z^2 rising in energy because it is the dominant contributor to the σ* orbital. Consequently, if the ligand backs away, it interacts less strongly with the d_z^2, and the d_z^2 falls slightly in energy. In general, orbital interactions obey conservation of energy, so if the d_z^2 drops in energy, then the $d_{x^2-y^2}$ rises in energy.

So, why does it have anything to do with an uneven distribution of electrons? In the case of Cu(II), which is d^9, there are two electrons in one e_g orbital and one in the other. If one of the orbitals goes down in energy and the other goes up, there may be no overall change in the energy of the orbitals, but there is a net decrease in electronic energy because two electrons are going down and only one is going up.



In comparison, if the metal were d^{10}, two electrons would go down in energy and two would go up. There would be no overall change in energy and no advantage in undergoing a distortion.

Exercise 2.12.1

Would there be an advantage in undergoing a distortion in the following cases?

a. low spin d^7
b. low spin d^8

Answer a

yes; low spin (ls) d^7 is eg^1, so one level has one electron and the other has none - net decrease in energy upon distortion

Answer b

no; d^8 is eg^2, so both levels have one electron - no net change in energy upon distortion

Exercise 2.12.2

In which of the following ions would you expect to see a Jahn-Teller distortion?

a. $Co(OH_2)_6^{2+}$
b. $Ag(OH_2)_6^{2+}$
c. $Ni(OH_2)_6^{2+}$
d. $Mn(OH_2)_6^{2+}$
e. $Ag(OH_2)_6^{+}$

Answer
Answer a

Co^{2+} yes; d^7 so e_g^1

Answer b

Ag^{2+} yes; d^9 so e_g^3

Answer c

Ni^{2+} no; d^8 so e_g^2

Answer d

Mn^{2+} no if hs; d^5 so e_g^2. However, if it were low-spin (unlikely with a first-row metal in a moderately low oxidation state and π-donors), then there would be degeneracy and distortion.

Answer e

Ag^+ no; d^{10} so e_g^4

Similar distortions occur when there is degeneracy in the lower, t_{2g} level. However, the distortions are more subtle because the d orbitals in this level interact much less strongly with the ligands. For example, it has been shown that in the d^1 hexacyano titanium complex, $[Ti(CN)_6]^{3-}$, the equatorial Ti-C bond lengths are 2.168 Å, whereas the axial bond lengths are 2.199 Å, a difference of about 13%.

Exercise 2.12.3

In which of the following ions would you expect to see a Jahn-Teller distortion?

a. $[V(CN)_6]^{3-}$
b. $[Cr(CN)_6]^{3-}$
c. $[Mn(CN)_6]^{3-}$
d. $[Fe(CN)_6]^{3-}$
e. $[Cr(CN)_6]^{4-}$
f. $[Mn(CN)_6]^{4-}$
g. $[Fe(CN)_6]^{4-}$

Answer

Answer a

$[V(CN)_6]^{3-}$ yes d^2 t_{2g}^2

Answer b

$[Cr(CN)_6]^{3-}$ no d^3 t_{2g}^3

Answer c

$[Mn(CN)_6]^{3-}$ yes d^4 t_{2g}^4

Answer d

$[Fe(CN)_6]^{3-}$ yes d^5 t_{2g}^5

Answer e

$[Cr(CN)_6]^{4-}$ yes d^4 t_{2g}^4

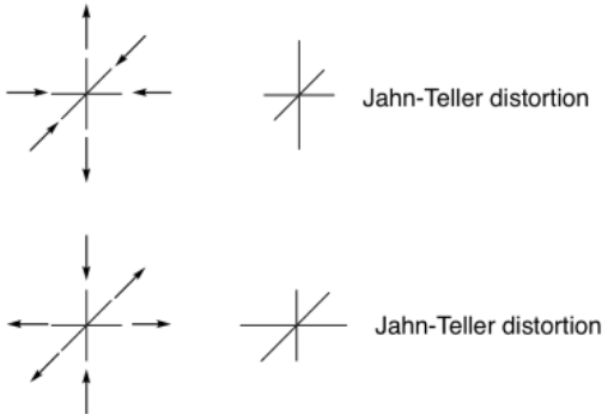
Answer f

$[Mn(CN)_6]^{4-}$ yes d^5 t_{2g}^5

Answer g

$[Fe(CN)_6]^{4-}$ no d^6 t_{2g}^6

Although we have looked at a distortion via elongation of the axial pair of ligands, we could also get a complementary case in which the octahedron is compressed along one axis and stretched along the equatorial plane. However, the reasons for such a distortion are much the same as the one we looked at.



In practice, both distortions are possible, and it's difficult to predict which one will actually occur.

1. Structural data for (bpy)Cu(II)(hfacac)$_2$ from: Veidis, M. V.; Schreiber, G. H.; Gough, T. E.; Palenik, G. J. *J. Am. Chem. Soc.*, **1969**, *91* (7), 1859–1860.
2. Computational data for the $[Ti(CN)_6]^{3-}$ ion from: Atanasov, M.; Comba, P.; Daul, C. A.; Hauser, A. *J. Phys. Chem. A*, **2007**, *111* (37), 9145–9163.

2.13: Multiple Bonds in Coordination Complexes

Metal-Ligand Multiple Bonds

For the most part, we have looked at donor atoms that provide one pair of electrons to a metal. In chelation, two donor atoms on the same ligand can provide a total of four electrons to the metal. In addition, some ligands can form double (or triple) bonds to a metal, providing four or even six electrons from one donor atom.

Oxides may be the most common multiply-bonded ligand. In biology, attention has turned to the role of iron and copper oxides as active intermediates in a variety of enzymes that use molecular oxygen to oxidize substrates. The most notable example is cytochrome P450, a ubiquitous class of oxidizing agents found in most organisms. In humans, cytochrome P450 is found in a variety of tissues, incorporating oxygen atoms into small molecules for a plethora of reasons. One interesting use of cytochrome P450 is as a detoxifying agent in the liver, where it converts C-H bonds in fat-soluble compounds into C-OH groups (alcohols), which can then be excreted via the kidneys and urinary system. The active intermediate involved in breaking the C-H bond appears to be a terminal iron oxide, Fe=O.

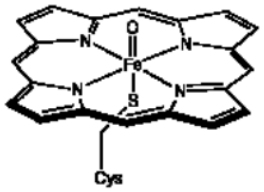


Figure 2.13.1: The proposed activated iron center of Cytochrome P450. The heme ring is simplified.

Oxides are also important industrially. Olefin metathesis catalysts, which are used in refining alkenes in petroleum into more useful isomers, are often metal oxides, which are converted under the reaction conditions into metal carbenes (see below).

? Exercise 2.13.1

Explain, in terms of intermolecular interactions, why oxidation by cytochrome P450 is a necessary step for removal of many compounds from human tissues

? Exercise 2.13.2

Show how a metal orbital and a ligand orbital can combine to form a pi bond. How many different transition metal orbitals could participate in this bond?

Answer

Add texts here. Do not delete this text first.

? Exercise 2.13.3

Often, "terminal" metal-ligand multiple bonds could be in equilibrium with "bridging" ligands between two metal atoms. Show, with drawings, how the oxide ligands on two adjacent Fe=O groups could form a single Fe_2O_2 unit

A second important class of metal-ligand multiple bonds is the carbenes. Carbenes contain metal-carbon double bonds. They are often divided into two classes: Fischer carbenes and Schrock carbenes or alkylidenes. Fischer carbenes were developed by E.O. Fischer, who shared a Nobel Prize with Geoff Wilkinson in 1973 for other work. Fischer carbenes have a heteroatom attached to the double bonded carbon, such as an oxygen or nitrogen. They can be somewhat more stable than alkylidenes, which have only hydrogens or carbons attached to the double bonded carbon.

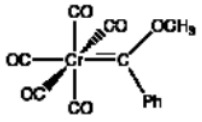


Figure 2.13.2 A Fischer carbene complex.

Exercise 2.13.4

Show, with drawings of molecular orbitals, why Fischer carbenes are stabilized by the presence of adjacent heteroatoms.

Answer

Add texts here. Do not delete this text first.

Alkylidenes were discovered by Dick Schrock, now at MIT, when he was working at DuPont in the early 1970's. While trying to place some bulky alkyl groups on tantalum, he noticed spectroscopic evidence that suggested a double bond. DuPont didn't have him doing this experiment for a particular reason; he was employed as a basic scientist, whose job it was to produce new information for its own sake. However, Schrock quickly realized he had found something with important applications: these kinds of structures had been proposed by Chauvin as intermediates in olefin metathesis, a process used in petroleum refining, but they hadn't been observed before. Years later, Schrock and other workers, including Bob Grubbs at Cal Tech, were able to develop new alkylidene-based catalysts useful in polymer chemistry and organic synthesis. For their contributions in this area, Schrock, along with Bob Grubbs at Caltech and Yves Chauvin at IFP, shared the Nobel Prize in chemistry in 2005.

Exercise 2.13.5

Suggest some examples of spectroscopic evidence that may have tipped Schrock off about the presence of a metal-carbon double bond in his product.

Answer

Add texts here. Do not delete this text first.

Exercise 2.13.6

Determine the electron count at the metal in the following complexes.

Answer

Add texts here. Do not delete this text first.

Metal-Metal Multiple Bonds

Just as additional orbital interactions can lead to metal-ligand multiple bonds, they can also make multiple bonds between metals. Metal-metal bonds in coordination complexes are interesting because they are a sort of halfway state between bulk elemental metals, in which arrays of atoms are bonded together more or less without limit, and molecules, which have discrete shapes and sizes. Non-molecular compounds can sometimes be difficult to study (although they also provide some advantages). Sometimes, researchers are interested in the behavior of compounds having metal-metal bonds because they can provide insight into metals.

It isn't easy to tell how many bonds there are between two metal atoms. Usually, researchers first speculate a multiple bond is present when an x-ray structure shows that the two metal atoms are very close together. Molecular orbital calculations are then performed to get an idea of the electronic structure of the compound. The number of bonds that should be drawn between the two atoms may still be open to debate; most workers draw a bond for every pair of electrons shared between the atoms. However, sometimes there are electrons in antibonding levels as well, so the true bond order between the metals is lower.

Exercise 2.13.7

A sigma bond has maximum electron density along the bond axis. A pi bond has maximum electron density above and below the bond axis (electron density is divided into two lobes along the bond). A delta bond has maximum electron density above and below and in front of and behind the bond axis (electron density is divided into four lobes along the bond). Show how two metal d orbitals can combine to form a delta bond.

Answer

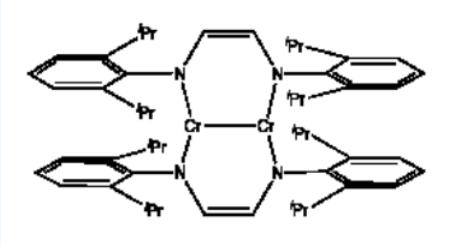
Add texts here. Do not delete this text first.

Exercise 2.13.8

Determine the electron count at each metal in the following complexes.

Exercise 2.13.9

One of the shortest metal-metal bonds on record was reported by Klaus Theopold at the University of Delaware and Clark Landis at the University of Wisconsin-Madison in 2007. The Cr-Cr distance is reported as 1.8028(9) Angstroms (the 9 in parentheses is the error in the last digit, i.e. +/- 0.0009). They believe each chromium atom in the complex has 18 electrons.



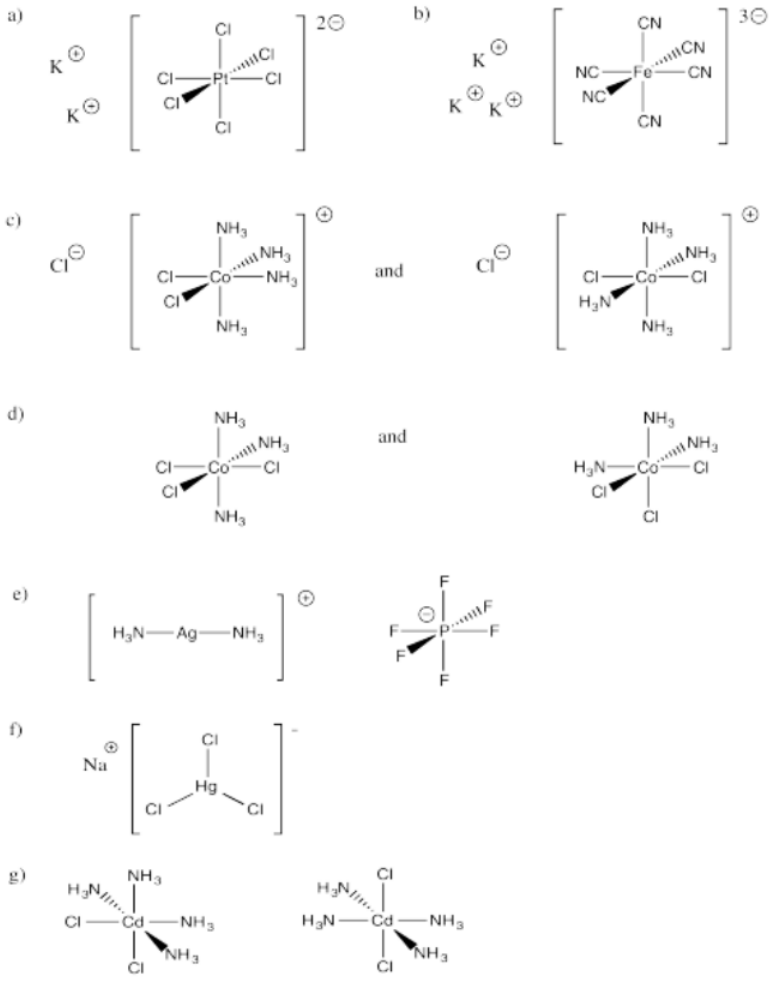
a. How many metal-metal bonds are there between the chromium atoms?
b. Show drawings of the overlap between pairs of orbitals that could be responsible for the metal-metal bond.

Answer

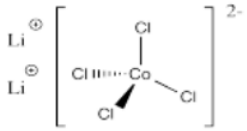
Add texts here. Do not delete this text first

2.14: Solutions to Selected Problems

Exercise 2.1.1:

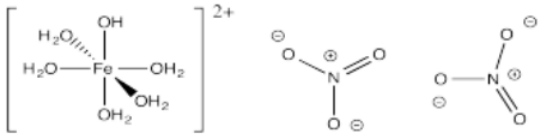


h)

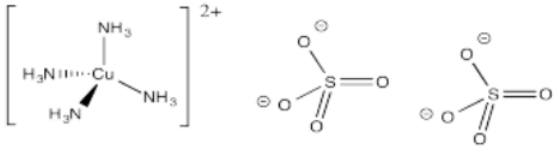


i)

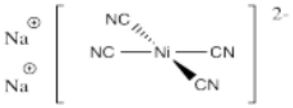
j)



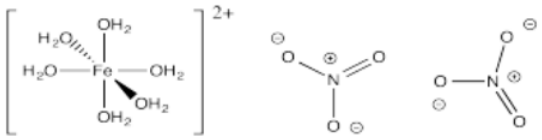
k)



l)

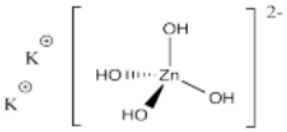


m)



n)

o)



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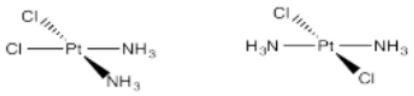
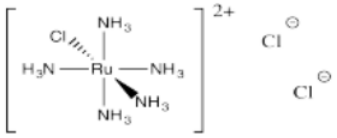


q)



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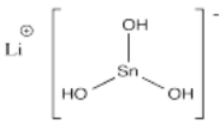

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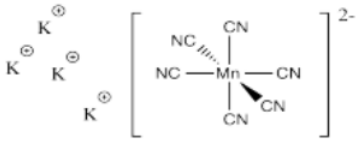
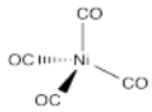


t)

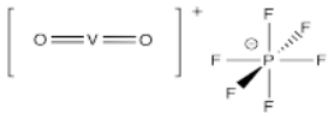


u)

v)

w)

x)



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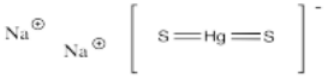
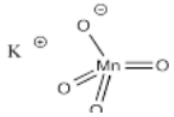


z)



Exercise 2.2.1:

$$K_6 = \frac{[Ni(NH_3)_6^{2+}]}{[Ni(NH_3)_5^{2+}]\,[NH_3]}$$

$$\text{but} \quad K_5 = \frac{[Ni(NH_3)_5^{2+}]}{[Ni(NH_3)_4^{2+}]\,[NH_3]} \quad \text{or} \quad K_5\,[Ni(NH_3)_4^{2+}][NH_3] = [Ni(NH_3)_5^{2+}]$$

$$\text{so} \quad K_6 = \frac{[Ni(NH_3)_6^{2+}]}{K_5\,[Ni(NH_3)_4^{2+}][NH_3][NH_3]} \quad \text{or} \quad K_5 K_6 = \frac{[Ni(NH_3)_6^{2+}]}{[Ni(NH_3)_4^{2+}][NH_3]^2}$$

$$\text{and so on until} \quad K_1K_2K_3K_4K_5K_6 = \frac{[Ni(NH_3)_6^{2+}]}{[Ni^{2+}][NH_3]^6} = K$$

Exercise 2.2.2:

a) $K = K_1 \times K_2 \times K_3 \times K_4 \times K_5 \times K_6$

$= 470 \times 130 \times 41 \times 12 \times 4.2 \times 0.81$

$=1.03 \times 10^8$

b) As the nickel binds ammonia ligands, it becomes more electronically saturated. That means it becomes less Lewis acidic. It does not have as strong an attraction for additional ligands.

Exercise 2.2.3:

a. This is a Zn^{2+} ion binding to either NH_3 or CN^- ligands. The zinc cation is more strongly sttracted to the anionic cyanide ligands than the neutral ammonia ligand, so the binding constant with cyanide is higher than with ammonia.
b. Both cases involve cyanide ions. In one case, the CN^- binds to Fe^{2+}, whereas the other case involves Fe^{3+}. The ligand is more attracted to the more highly charged ion, so the binding constant is higher.

Exercise 2.3.4:

a) Metal valence count: 9

Metal with charge: 6

Donated by ligands: 6 x 2 = 12

Total: 18

b) Metal valence count: 8

Metal with charge: 5

Donated by ligands: 6 x 2 = 12

Total: 17

c) Metal valence count: 9

Metal with charge: 7

Donated by ligands: 6 x 2 = 12

Total: 19

d) Metal valence count: 7

Metal with charge: 0

Donated by ligands: 4 x 4 = 16

Total: 16

e) Metal valence count: 8

Metal with charge: 8

Donated by ligands: 5 x 2 = 10

Total: 18

f) Metal valence count: 10

Metal with charge: 6

Donated by ligands: 6 x 2 = 12

Total: 18

g) Metal valence count: 6

Metal with charge: 6

Donated by ligands: 6 x 2 = 12

Total: 18

h) Metal valence count: 6

Metal with charge: 0

Donated by ligands: 4 x 4 = 16

Total: 16

i) Metal valence count: 9

Metal with charge: 8

Donated by ligands: 4 x 2 = 8

Total: 16

j) Metal valence count: 8

Metal with charge: 4

Donated by ligands: 3 x 4 = 12

Total: 16

k) Metal valence count: 9

Metal with charge: 7

Donated by ligands: 4 x 2 = 8

Total: 15

Exercise 2.3.5:

a) 6 b) 8 c) 5 d) 5 e) 10 f) 1 g) 10 h) 12 i) 2 j) 9 k) 4

a) Metal valence count: 5

Metal with charge: 0

Donated by ligands: 5 x 2 = 10

Total: 10

b) Metal valence count: 8

Metal with charge: 5

Donated by ligands: 3 x 2 = 6

Total: 11

c) Metal valence count: 6

Metal with charge: 0

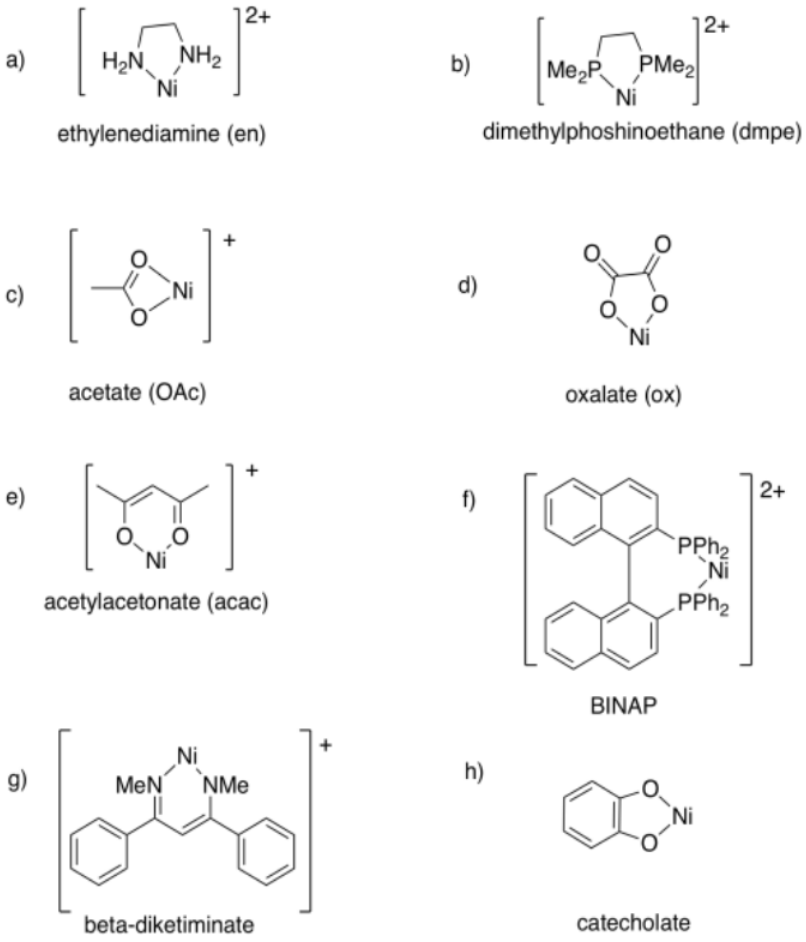
Donated by ligands: 6 x 2 = 12

Total: 12

Exercise 2.3.8:

a. PF_3 (104 vs 87^0)
b. PMe_3 (118 vs 87^0)
c. P^tBu_3 (182 vs 118^0)
d. P^tBu_3 (182 vs 145^0)

Exercise 2.4.1:



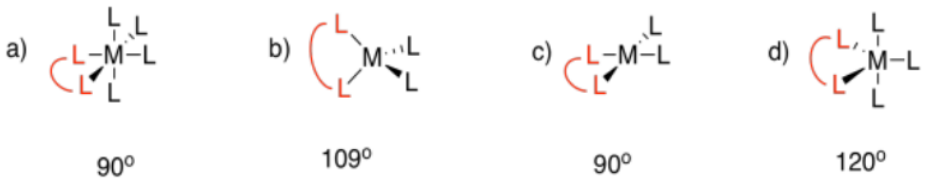
Exercise 2.4.2:

a. tridentate or κ^3; ligand = 0; metal = 1+
b. bidentate or κ^2; ligand = 1-; metal = 0
c. bidentate or κ^2; ligand = 0; metal = 2+
d. tetradentate or κ^4; ligand = 2-; metal = 2+
e. tridentate or κ^3; ligand = 0; metal = 1+
f. bidentate or κ^2; ligand = 0; metal = 1+

Exercise 2.4.3:

a. monodentate or κ^1; maximum bidentate or κ^2; ligand = 0; metal = 2+
b. bidentate or κ^2; maximum tridentate or κ^3; ligand = 1-; metal = 1+
c. bidentate or κ^2; maximum tridentate or κ^3; ligand = 0; metal = 1+
d. bidentate or κ^2; maximum tetradentate or κ^4; ligand = 0; metal = 2+
e. tridentate or κ^3; maximum tetradentate or κ^4; ligand = 1-; metal = 2+
f. tridentate or κ^3; maximum tetradentate or κ^4; ligand = 2-; metal = 2+

Exercise 2.4.4:



Exercise 2.4.5:

a) nitrate vs. oxalate, based on **ring size**

3 x 60° = 180° 4 x 90° = 360° 5 x 108° = 540° 6 x 120° = 720°

The total of the interior angles of a regular polyhedron is given by (n-2)180°, in which n is the number of sides in the polyhedron. Assuming the ring formed by the bidentate ligand and the metal is a regular polyhedron (it won't be, but we are simplifying), then nitrate gives a triangle with 60° angles, including a 60° O-M-O bite angle. Oxalate gives a square with a larger, 90° bite angle.

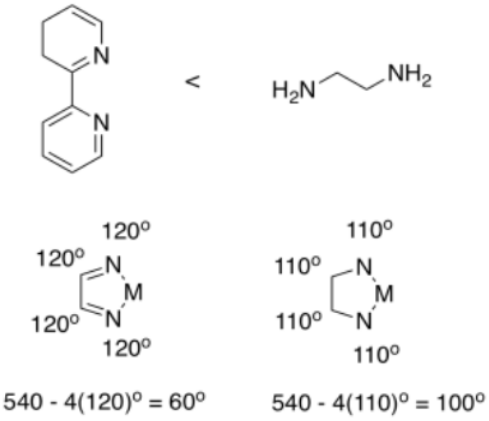
In reality, the bite angle for nitrate varies with the complex that is formed, but it is usually somewhere around sixty degrees, whereas oxalate usually gives somewhere around eighty five degrees (see, for example, Alvarez, *Chem. Rev.* **2015**, *115*, 13447-13483). The smaller ring size gives a smaller bite angle.

b) dithiocarbamatre vs. acetate, based on **bond lengths**

Sulfur is larger than oxygen, so its bonds will be a little longer. As a result, you can imagine those two sides of the square being a little longer with sulfur than with oxygen. From the perspective of the metal, the gap between the two donor atoms widens out a little.

Acetate forms bite angles of around sixty degrees, but dithiocarbamate forms larger bite angles of seventy or seventy five degrees.

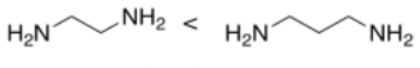
c) bipyridyl vs. ethylenediamine, based on **hybridization / bond angles**



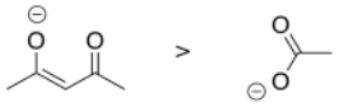
There are lots of differences between these two ligands, but if we simplify and only consider bond angle, we can make a prediction. If the atoms in bipridyl can be considered sp^2 hybridised, then they form 120° bond angles. The atoms in ethylenediamine could be considered sp^3 hybridised, forming approximately 110° angles. The angle N-M-N still has to complete the shape of the regular pentagon, so if all of the other angles are bigger in the bipyridyl complex, we would expect the bite angle to be smaller.

Really, the bite angles are much closer than this rough estimate suggests. Bipyridyl forms average bite angles of around eighty degrees, whereas ethylenediamine forms average bite angles of around eighty-five degrees. Keep in mind that those are just averages, though. These two values are close enough that their ranges overlap; lots of bipyridyl complexes would have bite angles smaller than ethylenediamine complexes.

Exercise 2.4.6:

a) 

ring size

b) 

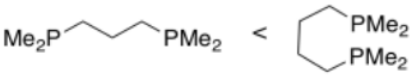
ring size

c) 

ring size

d) 

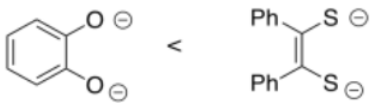
bond length / atom size

e) 

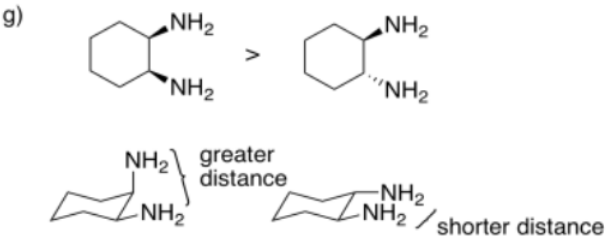
ring size

f) 

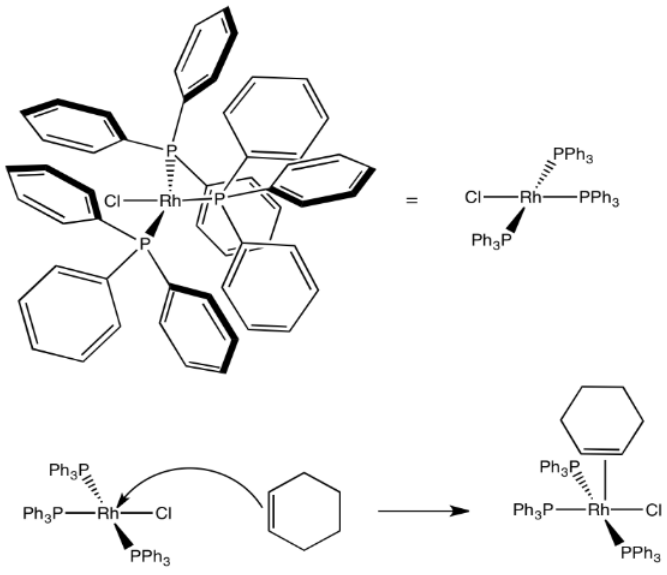
bond length / atom size

f) 

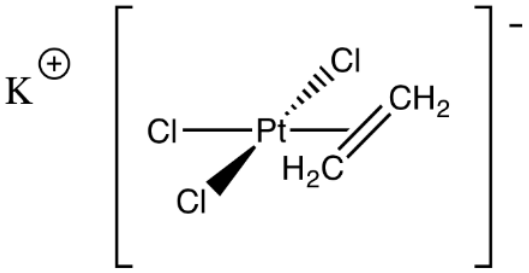
bond length / atom size

g) 

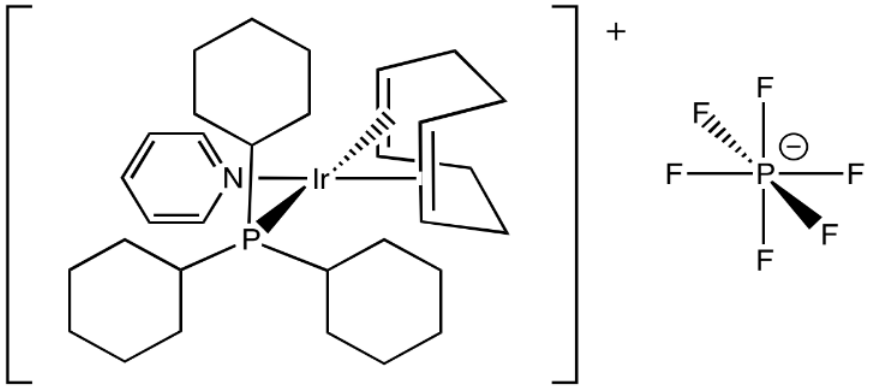
Exercise 2.5.1:



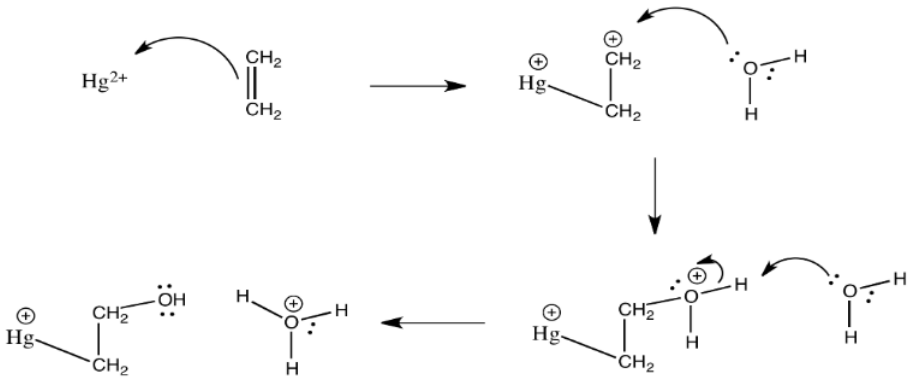
Exercise 2.5.2:



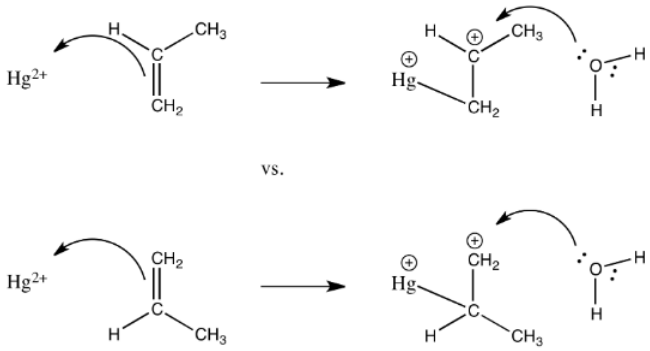
Exercise 2.5.3:



Exercise 2.5.4:



Exercise 2.5.5:



Exercise 2.5.6:

Zr(IV) or Zr^{4+} has no valence d electrons. That means that, although an alkene could certainly donate its pi bond to the zirconium atom, the zirconium has no electrons with which it can stabilize the alkene complex via "back-donation" to the pi antibonding orbital on the alkene.

Nevertheless, d^0 metals such as Zr(IV) and Ti(IV) can be used as alkene polymerization catalysts to make common plastics such as HDPE, LDPE and polypropylene. That means that, although an alkene complex isn't directly observed with these metal ions, these metals can evidently bind alkenes briefly and get them to react with other alkenes to form long chains. Even so, most industrial olefin polymerization catalysts use Ti(III).

Exercise 2.5.8:

We will use (a), the binding constant between Ag(I) and ethylene or ethene (CH_2=CH_2), as our baseline value. Other constants will be compared with this one in order to look for a trend.

In (b), the binding constant is much smaller, so the silver ion binds *cis*-2-hexene much less tightly than it does ethene. This is just another alkene, like ethene, but instead of having just hydrogen atoms attached to the C=C unit, *cis*-2-hexene has some other stuff. Maybe this other stuff causes some problem for alkene binding. The obvious difference between hydrogen atoms and this other stuff is that this *other stuff is bigger*. Maybe the complex gets *too crowded* when the *cis*-2-hexene binds to the silver ion.

Very often when we see metal ions on paper, we are not dealing with bare metal ions in reality. The ion often has other ligands already attached to it at the beginning, such as water molecules, and what we are sometimes looking at is replacement of an old ligand with a new ligand. Other ligands attached to the silver could make crowding problems even worse.

There is an alternative explanation as well. If you compare two alkenes that differ only in the number of hydrogens attached to the double bond, such as 1-butene, CH_2=$CHCH_2CH_3$, and 2-butene, CH_3CH=$CHCH_3$, you invariably find that the alkene with fewer hydrogens attached to the double bond (and more other stuff) is more stable. "Terminal alkenes", with double bonds at the ends of the chain, are always less stable than "internal alkenes", with double bonds somewhere along the middle of the chain. This difference can be explained by looking at some quantum mechanical calculations, but we're not going to do that right now.

The point is, the difference in this reaction might be caused, not by the alkene complexes, but by the alkenes themselves, on the other side of the reaction profile. It's important to remember that equilibrium constants always compare two sides of a reaction. Ethene, having fewer substituents on the double bond than *cis*-2-hexene ("substituents" is a four syllable word for "other stuff"), may simply be less stable and more reactive.

Do either of these ideas hold up in the other examples?

In (c), *trans*-2-hexene is bound even less tightly than *cis*-2-hexene. We could argue that in a *cis*-2-hexene complex, the substituents, which are on the same side of the double bond, might both be held away from other ligands on the metal that may exacerbate crowding problems. That would be more difficult to do with *trans*-2-hexene, since one substituent is on either side of the double bond. Getting one substituent away from the crowding may be possible, but probably not both.

Once again, the alternative explanation holds up here, too. *cis*-2-Hexene is less stable than *trans*-2-hexene, because the substituents on the double bond crowd each other in *cis*-2-hexene, but are held away from each other in *trans*-2-hexene. So maybe *cis*-2-hexene binds to silver ion more easily because it is more reactive.

Exercise 2.6.1:

a. There are two double bonds here, and they are conjugated: CH_2=CH-CH=CH_2. The conjugated double bond would allow the ligand to bind η^4.
b. There are two double bonds here, but they are not conjugated: CH_2=CH-CH_2-CH=CH_2. Each double bond would bind η^2, and the ligand would be able to bind in a bidentate fashion, but since the double bonds are not conjugated and binding all in a row, we would not describe binding as η^4. It would most commonly be described as η^2,η^2; that simply means each double bond is an η^2-donor, and there are two of them. It could also be considered a κ^2 donor because of its denticity.
c. This is another non-conjugated case: CH_2=CH-CH_2-CH_2-CH=CH_2. In terms of hapticity, it could be described as η^2,η^2.
d. There are three double bonds here, and they are conjugated: CH_2=CH-CH=CH-CH=CH_2. The conjugated double bond would allow the ligand to bind η^6.

Exercise 2.6.2:

a. The ligand is bound η^5; it donates 6 electrons, from two double bonds and one lone pair; the ligand has a charge of -1.
b. The ligand is bound η^4; it donates 4 electrons, from two double bonds; the ligand has no charge.

c. The ligand is bound η^7; it donates 8 electrons, from three double bonds and one lone pair; the ligand has a charge of -1.
d. The ligand is bound η^6; it donates 6 electrons, from three double bonds; the ligand has no charge.

Exercise 2.6.3

a. The ligand is bound η^1; it donates one lone pair; however, it could donate an additional pi bond and then it would bind η^3.
b. The ligand is bound η^2; it donates one pi bond; however, it could donate two more pi bonds and then it would bind η^6.
c. The ligand is bound η^4; it donates two pi bonds; however, it could donate one more pi bond and then it would bind η^6.
d. The ligand is bound η^3; it donates one lone pair and one pi bond; however, it could donate an additional pi bond and then it would bind η^5.
e. The ligand is bound η^4; it donates two pi bonds; however, it could donate one more pi bond and then it would bind η^6.
f. The ligand is bound η^2; it donates one pi bond; however, it could donate one more pi bond and then it would bind η^4.

Exercise 2.6.4:

a. The resulting anion has aromatic stability. It is cyclic, fully conjugated, flat and has an odd number of electron pairs.
b. Cp anion could bind to a metal through just one pair or through two pairs, but in most cases it will bind via three pairs of electrons.

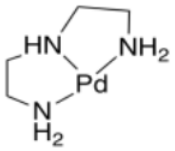
d) Valence count on metal: 8

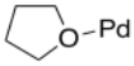
Count on metal, correcting for +2 charge: 6

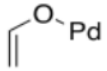
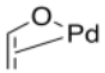
Donated from ligands: 2 x 6 = 12

Total: 18

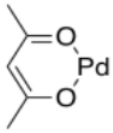
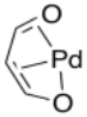
Exercise 2.6.5:

a)  tridentate, κ^3

b)  monodentate, κ^1

c)  monodentate, κ^1 OR  η^3

d)  η^2

e)  bidentate, κ^2 OR  η^5

f)  η^6

Exercise 2.6.6:

This problem deals with the "bite angle" of the ligand. Remember, a chain of atoms becomes more flexible the longer it gets, because of the possibility for rotation around each bond along the chain. As the two double bonds move further apart from each other (one bond apart in (a), two bonds apart in (b) and three bonds apart in (c)), the chain can "open up" and bind with a more optimal overlap with the metal.

2.15: More Solutions to Selected Problems

Exercise 2.7.1:

a) Zn(II), because it is smaller and less polarizable.

b) K^+, because it is less electronegative.

c) Fe(III), because of the higher charge.

Exercise 2.7.2:

a) Me_3P, because phosphorus is larger and more polarizable than nitrogen.

b) Iodide, which is larger and more polarizable than chloride.

c) Azide, which has a more polarizable, delocalized pi bonding system.

Exercise 2.7.3:

a) ZrO_2

b) CdS

c) WO_3

d) ZnS

e) Cu_2S

Exercise 2.7.4:

a) Hg(I) and Hg(II) are both large, polarizable ions. They are soft cations and should bind well to soft donors.

b) The most common soft donor is a sulfur atom or sulfide ion; in amino acids, that suggests cysteine or methionine.

Exercise 2.7.5:

Fe(III) is a hard cation and should bind well to oxygen donors. Enterobactin has several oxygen donors it could provide to the iron. In fact, there is a pair of OH groups on each of the benzene rings in enterobactin. These benzene rings with two OH groups next to each other are called "catechols". Because there are three of these groups in enterobactin, and there is enough space in between for the groups to fold around a central atom, enterobactin is a chelating (hexadentate) donor with a high binding constant.

Exercise 2.8.1:

a)

low spin high spin

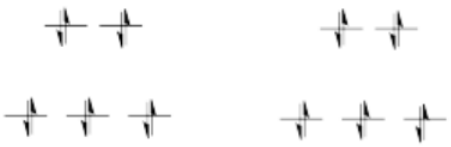
b)

low spin high spin

c)

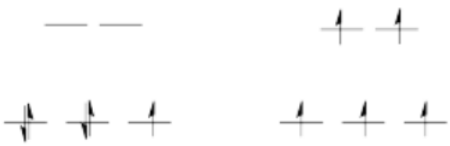
low spin high spin

d)



low spin high spin

e)

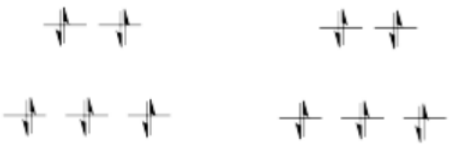


low spin high spin

f)

low spin high spin

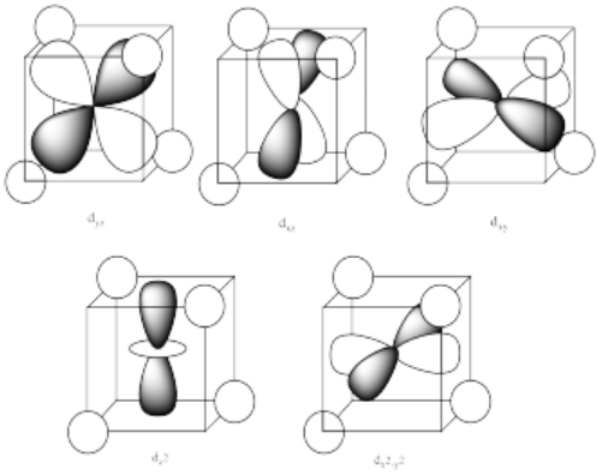
g)



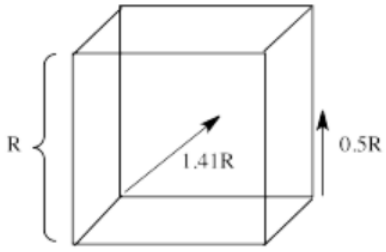
low spin high spin

Exercise 2.8.2:

The three orbitals shown above interact a little more strongly with the ligands. The three orbitals shown below interact a little more weakly.



The reason for the difference in the interaction has to do with how close the nearest lobe of a d orbital comes to a ligand. There are really two possible positions: the face of a cube or the edge of a cube. If the ligands are at alternating corners of the cube, then the orbitals pointing at the edges are a little closer than those pointing at the faces of the cube.



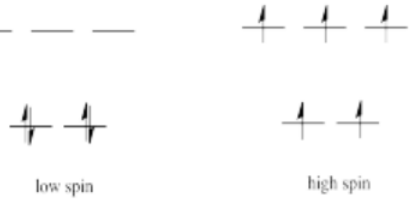
$$\sqrt{R^2 + R^2} = 0.5\sqrt{2R^2} = 0.705R$$

Exercise 2.8.3:

The ligands do not overlap with the d orbitals as well in tetrahedral complexes as they do in octahedral complexes. Thus, there is a weaker bonding interaction in the tetrahedral case. That means the antibonding orbital involving the d electrons is not raised as high in energy, so the splitting between the two d levels is smaller.

Exercise 2.8.4:

a)

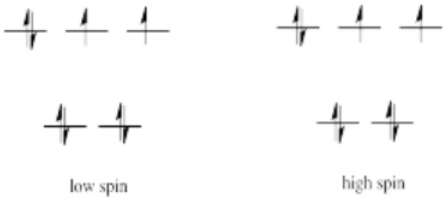


low spin high spin

b)

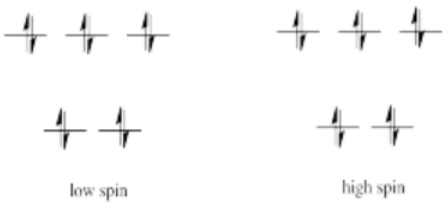
low spin high spin

c)

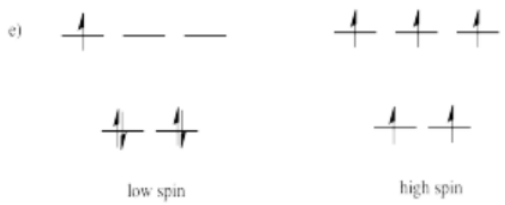


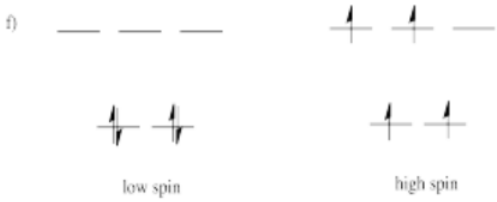
low spin high spin

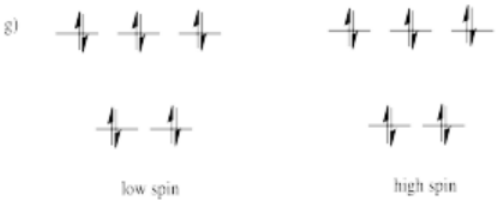
d)



low spin high spin





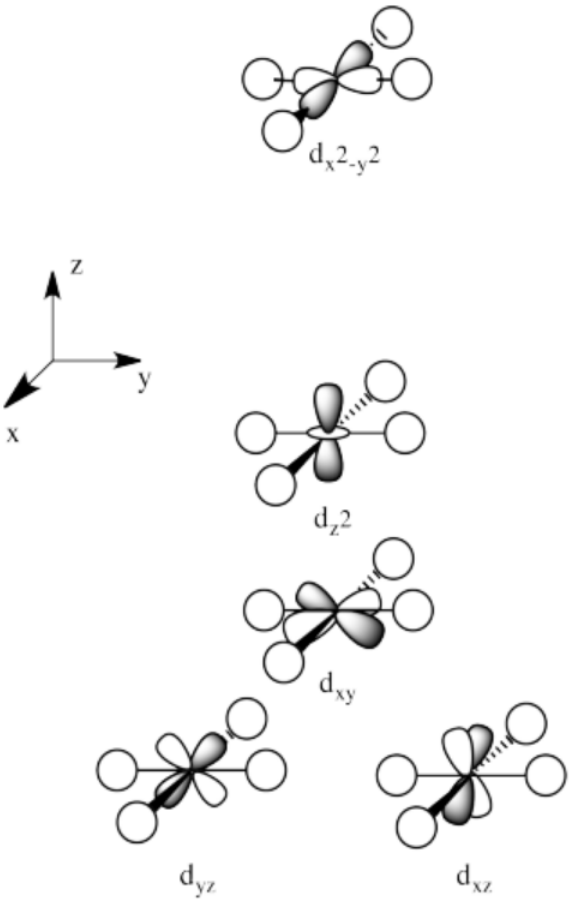


Exercise 2.8.5:

Because the d orbital splitting is much smaller in the tetrahedral case, it is likely that the energy required to pair two electrons in the same orbital will be greater than the energy required to promote an electron to the next energy level. In most cases, the complex will be high spin.

Exercise 2.8.6:

The orbitals are shown in order of energy.



Exercise 2.8.7:

a. $[Fe(py)_6]^{2+}$ 3d metal, M^{+2}, pi acceptor ligand → low spin

b. $[Fe(H_2O)_6]^{2+}$ 3d metal, M^{+2}, pi donor ligand → high spin

c. $[FeBr_6]^{3-}$ 3d metal, M^{+3}, pi donor ligand → high spin

d. $[Co(NH_3)_6]^{3+}$ 3d metal, M^{+3}, sigma donor ligand → low spin

e. $[Cu(NH_3)_6]^{2+}$ 3d metal, M^{+2}, sigma donor ligand → low spin

f. $[Rh(CO)_6]^{3+}$ 4d metal, M^{+3} → low spin

g. $[Cr(CO)_6]^{3+}$ 3d metal, M^{+3}, pi acceptor ligand → low spin

f. $[PtCl_6]^{2-}$ 5d metal, M^{+4} → low spin

Exercise 2.8.8:

a. $[Zn(NH_3)4]^{2+}$ 3d metal, d^{10}, sigma donor ligand → tetrahedral

b. $[NiCl_4]^{2+}$ 3d metal, d^8, pi donor ligand → tetrahedral

c. $[Ni(CN)_4]^{2-}$ 3d metal, d^8, pi acceptor ligand → square planar

d. $[Ir(CO)(OH)(PCy_3)_2]^{2+}$ 5d metal, d^8 → square planar

e. $[Ag(dppb)_2]^{1+}$ 4d metal, d^{10}, sigma donor ligand → tetrahedral

f. $[PtCl_2(NH_3)_2]$ 5d metal, d^8 → square planar

g. $[PdCl_2(NH_3)_2]$ 4d metal, d^8, M^{+2}, sigma donor ligand → square planar

i. $[CoCl_4]^{2-}$ 3d metal, d^7, sigma donor ligand → tetrahedral

f. $[Rh(PPh_3)_3Cl]$ 5d metal, d^8 → square planar

Exercise 2.9.1:

a. Fe^{+2}

d^6 low spin

$$SE = [-0.4(6) + 0.6(0)]\Delta_o + 3PE$$

$$= [-2.4]\Delta_o + 3PE$$

d^6 high spin

$SE = [-0.4(4) + 0.6(2)]\Delta_o + 1PE$
$[-.4]\Delta_o + 1PE$

b. Co^{+2}

d^7 low spin

$$SE = [-0.4(6) + 0.6(1)]\Delta_o + 3PE$$

$$= [-1.8]\Delta_o + 3PE$$

d^7 high spin

$$SE = [-0.4(5) + (0.6)2]\Delta_o + 2PE$$

$$= [-.8]\Delta_o + 1PE$$

c. Co^{+3}
d6 so this looks the same as Fe+2

d. Mn^{+2}

d^5 low spin

$$SE = [-0.4(5) + 0.6(0)]\Delta_o + 2PE$$

[-2.0] \Delta_o} + 2PE

d^5 high spin

$SE = [-0.4(3) + 0.6(2)]\Delta_o + 0PE$
$= [0]\Delta_o$

e. Ti^{+3}
d^1 so there is no possibility of low spin or high spin

Exercise 2.9.2:

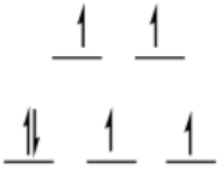
a) Δ_o < PE, so high-spin.

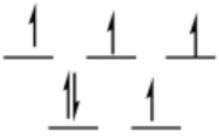
b) Δ_o > PE, so high-spin.

c) Δ_o > PE, so high-spin.

Exercise 2.9.3:

high-spin d^6





octahedral

$$SE = [2(0.6) - 4(0.4)]\Delta_o + PE$$

$$SE = -0.4\Delta_o + PE$$

tetrahedral

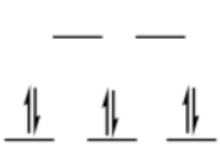
$$SE = [3(0.4) - 3(0.6)]\frac{4}{9}\Delta_o + PE$$

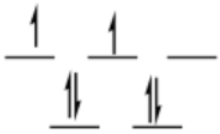
$$SE = -0.6\Delta_o + PE$$

$$\Delta SE = SE_{oh} - SE_{td} = -0.4\Delta_o + PE - (-0.6\Delta_o + PE\backslash) = +0.2\Delta_o$$

This is a slight preference for tetrahedral.

low-spin d^6





octahedral

$$SE = [0(0.6) - 6(0.4)]\Delta_o + 3PE$$

$$SE = -2.4\Delta_o + 3PE$$

tetrahedral

$$SE = [2(0.4) - 4(0.6)]\frac{4}{9}\Delta_o + 2PE$$

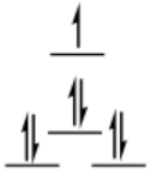
$$SE = -1.6\Delta_o + PE$$

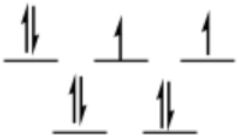
$$\Delta SE = SE_{oh} - SE_{td} = -2.4\Delta_o + 3PE - (-1.6\Delta_o + 2PE) = -0.8\Delta_o + PE$$

This is a preference for octahedral, although it would be offset by the pairing energy

Exercise 2.9.4:

high-spin d^8





square planar

$$SE = [1.23 + 0.23 - 2(0.43) - 4(0.51)]\Delta_o + 3PE$$

$$SE = -1.44\Delta_o + 3PE$$

tetrahedral

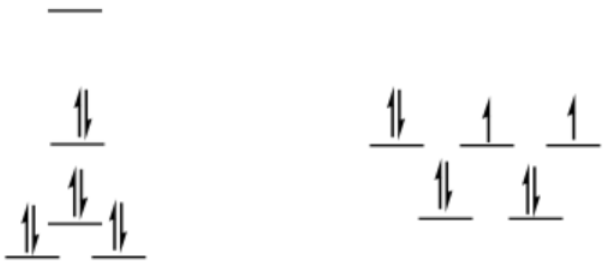
$$SE = [4(0.4) - 4(0.6)]\frac{4}{9}\Delta_o + 3PE$$

$$SE = -0.36\Delta_o + 3PE$$

$$\Delta SE = SE_{sq} - SE_{td} = -1.44\Delta_o + 3PE - (-0.36\Delta_o + 3PE) = -1.08\Delta_o$$

This is an appreciable preference for square planar.

low-spin d^8



square planar

$$SE = [0 + 2(0.23) - 2(0.43) - 4(0.51)]\Delta_o + 4PE$$

$$SE = -2.44\Delta_O + 4PE$$

tetrahedral = same as before (ls = hs for d^8 tetrahedral)

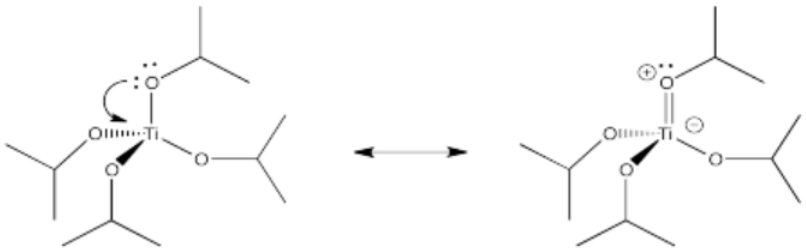
$$\Delta SE = SE_{sq} - SE_{td} = -2.44\Delta_O + 3PE - (-0.36\Delta_O + 3PE) = -2.08\Delta_O + PE$$

This is an even more appreciable preference for square planar, although it is offset by pairing energy. Pairing energy would have to be twice as big as Δ_o in order to completely offet the LFSE.

Exercise 2.10.1:

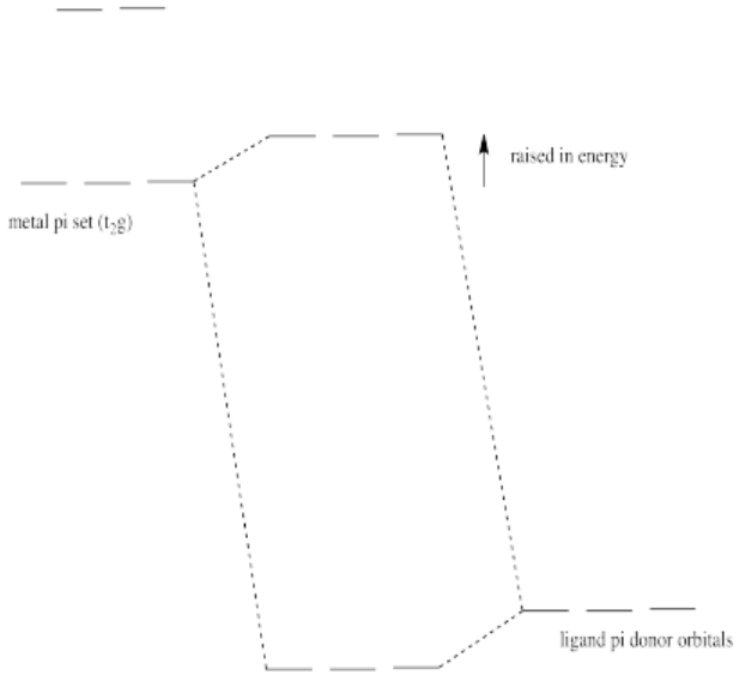
The weaker donors include halides and oxygen donors. Nitrogen atom donors are mostly a little stronger than that. The strongest donors include carbon donors, especially with pi bonds.

Exercise 2.10.2:



Exercise 2.10.3:

Pi donation raises the t_2g electrons (the d electrons of proper symmetry for pi overlap with the ligands in an octahedral geometry).



Exercise 2.10.6:

Because chloride is a weaker ligand than hydroxide, the d orbital splitting gets smaller. A d-d transition would involve less energy, so it would move to longer wavelength (red shift).

Exercise 2.10.7:

a) The $[Cu(OH_2)_6]^{2+}$ ion appears blue-green, so it absorbs a reddish orange, about 650 nm; whereas the $[Cu(NH_3)_2(OH_2)_4]^{2+}$ ion appears indigo-violet, so it absorbs yellow, about 600 nm.

b) Shorter wavelength is higher energy, according to the Planck-Einstein relation: $E = hc/\lambda$ (in which h = Planck's constant, c = speed of light, λ = wavelength of photon). The $[Cu(NH_3)_2(OH_2)_4]^{2+}$ ion absorbs the shorter wavelength, higher energy photon.

c) The $[Cu(NH_3)_2(OH_2)_4]^{2+}$ ion has the greater d-d gap.

d) The ammonia must be a stronger field ligand than water. In general terms we might think of that as a result of ammonia being only a sigma-donor, whereas water is also a pi-donor.

Exercise 2.10.8:

a) The $[Cu(NH_3)_6]^{3+}$ ion appears yellow, so it absorbs violet, about 400 nm; whereas the $[Cu(NH_3)_5Cl]^{2+}$ ion appears pink, so it absorbs green, about 550 nm.

b) Shorter wavelength is higher energy, according to the Planck-Einstein relation: $E = hc/\lambda$ (in which h = Planck's constant, c = speed of light, λ = wavelength of photon). The $[Cu(NH_3)_6]^{3+}$ ion absorbs the shorter wavelength, higher energy photon.

c) The $[Cu(NH_3)_6]^{3+}$ ion has the greater d-d gap.

d) The ammonia must be a stronger field ligand than chloride. In general terms we might think of that as a result of ammonia being only a sigma-donor, whereas chloride is also a pi-donor.

Exercise 2.10.9:

The green compound absorbs red; the violet compound absorbs yellow; the yellow compound absorbs violet.

In terms of energy these absorbances can be ranked:

(high energy) violet photon > yellow photon > red photon (low energy)

or in terms of d-d gap:

large gap > middle gap > small gap

In the spectrochemical series, we would expect the order of corresponding ligands to be:

$^{-}CN > H_2O > F^{-}$

The cyano compound absorbs violet and appears yellow; the aquo compound absorbs yellow and appears violet; the fluoro compound absords red and appears green.

Exercise 2.10.10:

a) The $[V(OH_2)_6]^{3+}$ ion appears yellow, so it absorbs violet, about 400 nm; whereas the $[V(OH_2)_6]^{2+}$ ion appears pink, so it absorbs green, about 550 nm.

b) Shorter wavelength is higher energy, according to the Planck-Einstein relation: $E = hc/\lambda$ (in which h = Planck's constant, c = speed of light, λ = wavelength of photon). The $[V(OH_2)_6]^{3+}$ ion absorbs the shorter wavelength, higher energy photon.

c) The $[V(OH_2)_6]^{3+}$ ion has the greater d-d gap.

d) One ion contains V^{3+}, whereas the other ion contains V^{2+}. As charge increases on an ion, electrons contract toward the nucleus. However, low-lying electrons, which are closer to the nucleus to begin with, are attracted even more than are high-lying electrons. thus, as charge increases on the ion, the d-d splitting increases.

Exercise 2.10.11:

a) $[Co(NH_3)_6]^{+3}$

The metal is +3 suggesting a large Δ_0

The ligands are sigma donors, so medium field ligands

The splitting energy is large thus low spin.

b) $[Fe(CN)_6]^{-4}$

The metal is first row, +2 suggesting intermediate Δ_0

The ligands are pi acceptors, so strong field ligands

The splitting energy is large thus low spin.

c) $[CoF_6]^{-4}$

The metal is first row, +2 suggesting a large Δ_0

The ligands are pi donors, so weak field ligands

The splitting energy is small thus high spin.

d) $[Rh(CN)_6]^{-3}$

The metal is 2nd row (4d) and +3 suggesting a large Δ_0

The ligands are pi acceptors, so strong field ligands

The splitting energy is large thus low spin.

e) $[V(OH_2)_6]^{+3}$

The complex is d^2, so there is only one possible spin state.

f) $[Fe(py)_6]^{+2}$

The metal is first row, +2 suggesting intermediate Δ_0

The ligands are pi acceptors, so strong field ligands

The splitting energy is large thus low spin.

g) $[MnCl_6]^{-4}$

The metal is first row, +2 suggesting intermediate Δ_0

The ligands are pi donors, so weak field ligands

The splitting energy is large thus high spin.

h) $[Ru(NH_3)_6]^{+2}$

The metal is 2nd row (4d) and +2 suggesting a large Δ_0

The ligands are sigma donors, so medium field ligands

The splitting energy is large thus low spin.

Exercise 2.11.1:

a) The ions in LiF are both smaller than in KBr, so the force of attraction between the ions in LiF is greater because of the smaller separation between the charges.

b) Calcium has a 2+ charge in $CaCl_2$, whereas potassium has only a + charge, so the chloride ions are more strongly attracted to the calcium than to the potassium.

Problem CC11.3.

a) labile (electrons in higher energy d orbital set)

b) not labile (all electrons in lower energy d orbitals)

c) not labile (all electrons in lower energy d orbitals)

d) labile (electrons in higher energy d orbital set)

e) labile (electrons in higher energy d orbital set)

Exercise 2.12.1:

a) yes; ls d^7 is eg^1, so one level has one electron and the other has none - net decrease in energy upon distortion

b) no; d^8 is eg^2, so both levels have one electron -- no net change in energy upon distortion

Exercise 2.12.2:

a) Co^{2+} yes; d^7 so e_g^1

b) Ag^{2+} yes; d^9 so e_g^3

c) Ni^{2+} no; d^8 so e_g^2

d) Mn^{2+} no if hs; d^5 so e_g^2. However, if it were low-spin (unlikely with a first-row metal in a moderately low oxidation state and π-donors), then there would be degeneracy and distortion.

e) Ag^+ no; d^{10} so e_g^4

Exercise 2.12.3:

a) $[V(CN)_6]^{3-}$ yes d^2 t_{2g}^2 b) $[Cr(CN)_6]^{3-}$ no d^3 t_{2g}^3

c) $[Mn(CN)_6]^{3-}$ yes d^4 t_{2g}^4 d) $[Fe(CN)_6]^{3-}$ yes d^5 t_{2g}^5

e) $[Cr(CN)_6]^{4-}$ yes d^4 t_{2g}^4 f) $[Mn(CN)_6]^{4-}$ yes d^5 t_{2g}^5

g) $[Fe(CN)_6]^{4-}$ no d^6 t_{2g}^6

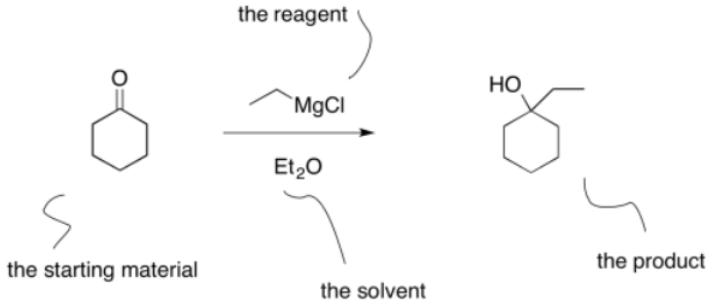
CHAPTER OVERVIEW

3: Addition to Carbonyls

3.1: What is a Solvent?

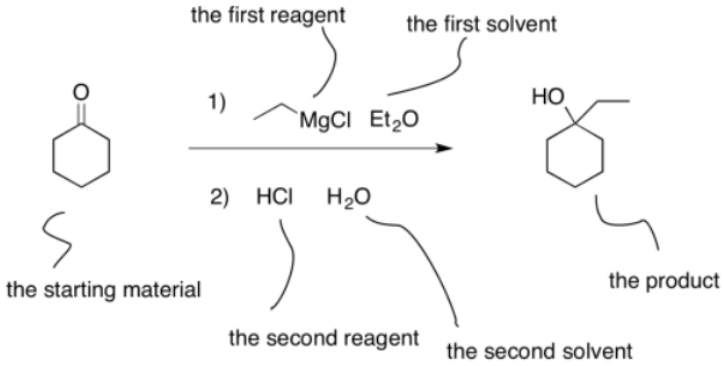
From the student's point of view, the information presented in an equation of a reaction can be confusing. The starting material and the product are linked by a straight reaction arrow. The starting material is the compound at the beginning of the reaction; the product is the compound at the end. The reagent is usually shown above the arrow. The reagent is the compound needed to turn the starting material into the product.

However, something else is often listed along with the reagent: the solvent. That can make students wonder: what does this thing do? Is it a second reaction I should be worrying about?



Students sometimes make the assumption that the reagent is written above the arrow and the solvent written below the arrow. That's a good observation, because reactions are often written that way, although there is no rule that says they have to be. However, there are exceptions in which that typical way of writing things is abandoned. Some reactions require lots of different reagents, additives, and promoters, or else there is a need to report the temperature or the pressure. In these cases, additional items are written below the arrow, just because there isn't enough room on top.

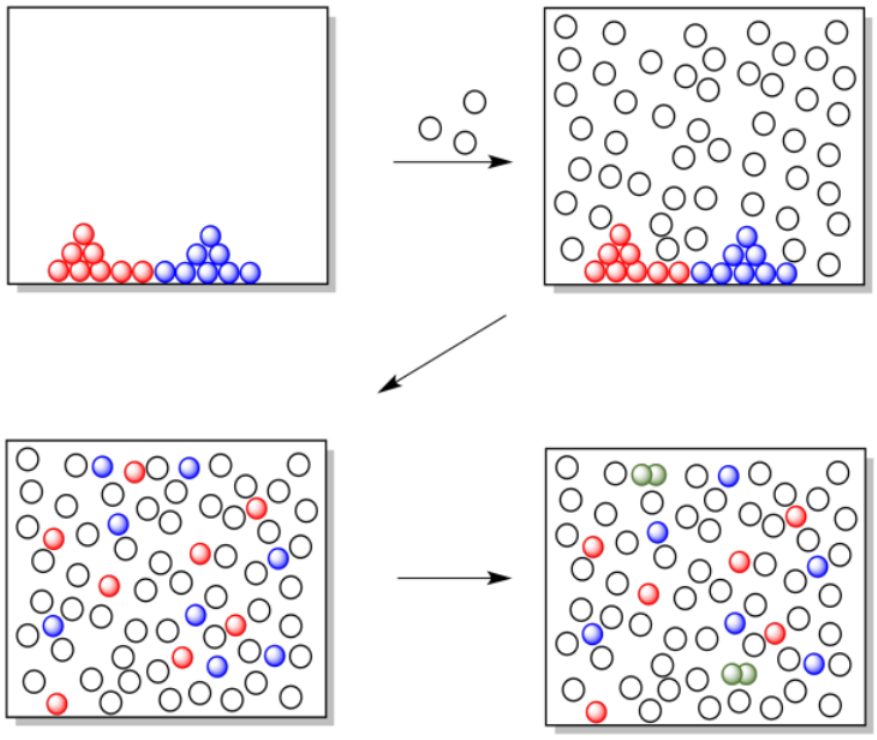
In other cases, a series of reactions are run. For example, in the above reaction it is assumed that there was an aqueous workup to neutralise the product. We might write that reaction out explicitly. In that case, the two different steps are numbered, so that we know that they were done one step at a time, rather than throwing everything in all at once.



Chemists often list the solvent in the reaction because the solvent is, practically speaking, tremendously important. Performing a reaction without solvent is a little like washing your hands without water. You could take a bar of soap and run it between your fingers, but not much will happen without the power of the water. The water dissolves up the soap (or at least suspends it in micelles), moves it around, gets it into contact with the dirt and carries it away.

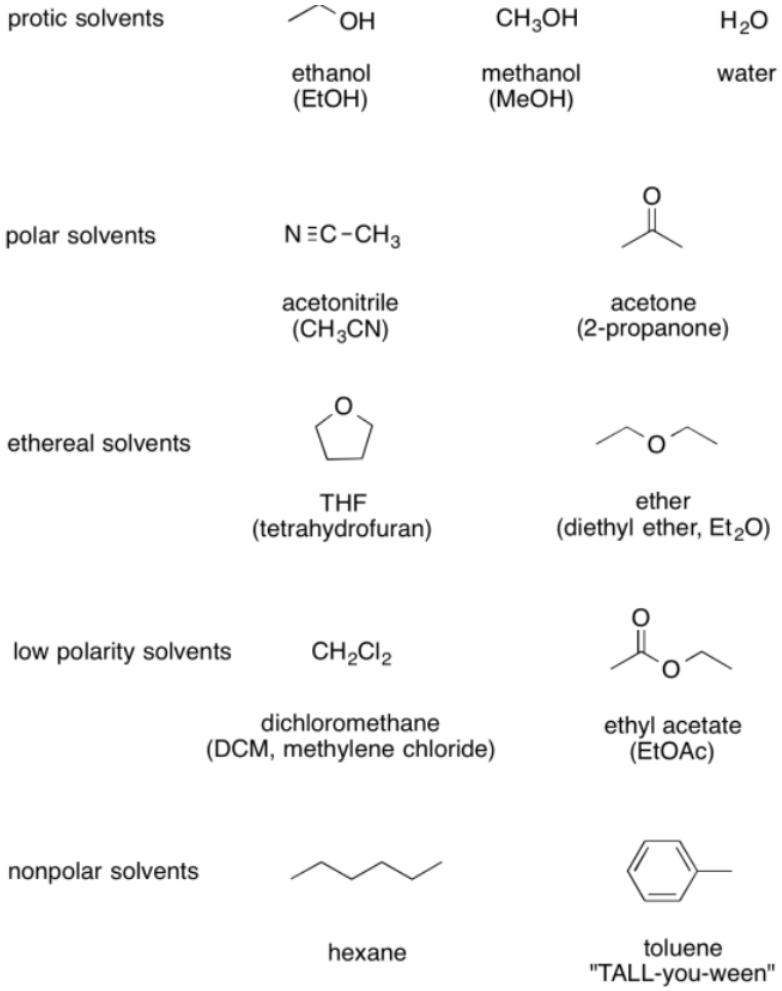
In fact, water is literally the solvent in the physical process of washing. It can be a solvent in many chemical reactions as well. The solvent has many roles to play in a reaction. Foremost, it dissolves the reactants. In that state, the reactants are very mobile. Without the solvent, the reactants may be solids, or if liquids, they may be too thick for molecules to move around very quickly; they may be more like oils. Depending on the nature of the solvent, intermediates may be stabilised, allowing them to form more easily and aiding the course of the reaction. Solvents also act like baths, moderating heat flow into or out of the reaction as needed.

In the cartoon below, nothing happens when the two reagents are dumped together. When a solvent is added, the two reagents start to dissolve, and as they move around in the solution the two reagents encounter each other and start to react.



At the beginning, you may not want to worry too much about the role of the solvent. However, you may still want to know what sorts of things are likely to be solvents, if only so that you can safely ignore them when trying to sort out how the reactant gets to the product.

The following table sums up a number of the most common solvents, displayed from most polar at the top to least polar at the bottom.



Note that, just because something acts as a solvent in one reaction does not mean it must be one in another. For example, acetone is a pretty common solvent, but it also happens to be a ketone. It's likely to undergo carbonyl addition reactions if presented with good nucleophiles. For that reason, carbonyl addition reactions wouldn't be carried out with acetone, because the nucleophile would just react with the solvent instead of the intended electrophile.

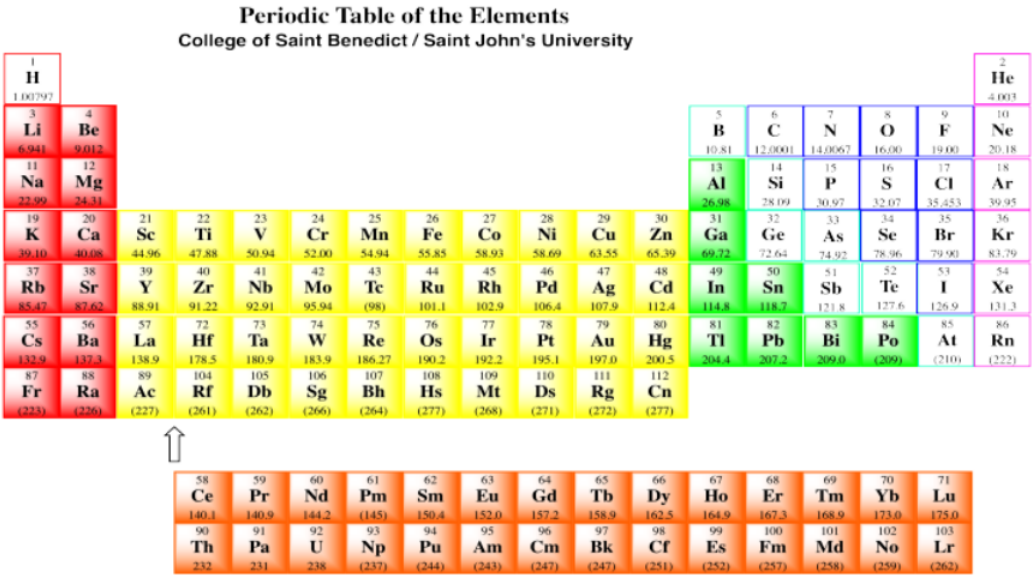
3.2: Semi-Anionic Nucleophiles

Some nucleophiles are added to carbonyls in the form of salts, such as sodium cyanide. In a salt, there is an anion and a cation. The anion can act as a nucleophile, donating a lone pair to the carbonyl. The cation is just a counterion; it is there to balance the charge but does not usually play an active role.

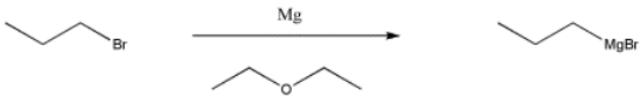
Some anions are too unstable and reactive to be used as salts. This is especially true with a number of carbon nucleophiles. C-H bonds are not usually acidic enough to deprotonate with a strong base. That makes it hard to make a simple salt containing such nucleophiles. There are exceptions, such as acetylide or alkynyl protons like $CH_3CC\mathbf{H}$. In that case, the resulting anion is relatively stable because the lone pair is in a lower-energy orbital with more s character, so it is held more tightly to the nucleus.

Less stable carbon anions can be be stabilized through a covalent bond. If the carbon is covalently attached to a less electronegative atom, the carbon has a partially negative charge. It can still act as though it were an anion. However, the covalent bond stabilizes the would-be "lone pair". Compounds like this can be considered to be "semi-anionic". Frequently, they are described as polar covalent compounds, although that is really a much more general term.

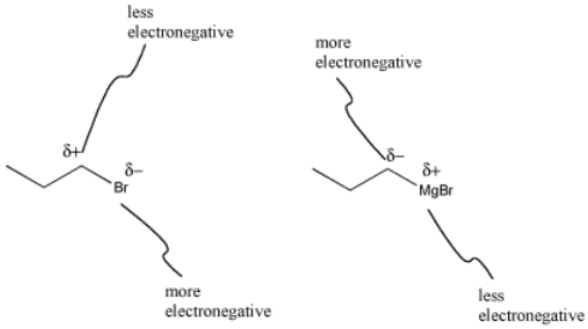
These polar covalent bonds can be found any time a carbon atom is bound to a metal. Remember, the metals are the aroms in the colored boxes in the periodic table below.



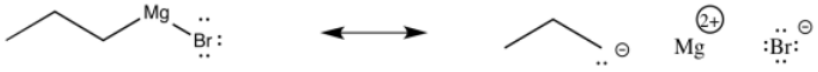
One of the most common classes of this type of compounds is the family of organomagnesium halides or Grignard reagents (Green-yard reagents). Victor Grignard was awarded the Nobel Prize in Chemistry for his development of these reagents. These compounds are made by reacting an alkyl halide (such as chloropropane, $CH_3CH_2CH_2Cl$, or bromopropane, $CH_3CH_2CH_2Br$) with magnesium metal. With bromopropane, the metal undergoes an insertion into the C-Br bond, forming $CH_3CH_2CH_2MgBr$. (You don't need to worry about how this happens.) Because magnesium is less electronegative than carbon, the C-Mg bond acts as though it were a lone pair on the carbon and the magnesium acts as though it were a cation.



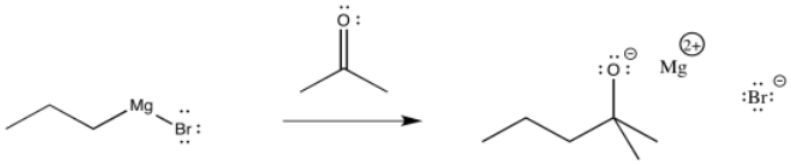
What's striking about Grignard formation is that polarity is reversed in this reaction. In the alkyl halide, the carbon attached to the halogen has a partially positive charge, because carbon is further to the left than halogens in the periodic table. After magnesium insertion, this same carbon has a partial negative charge, because carbon is farther to the right in the periodic table than magnesium. This sort of reversal in reactivity is sometimes called "umpolung chemistry".



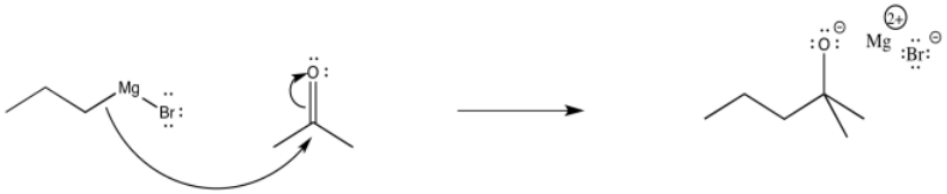
At the extreme, we could think of propylmagnesium bromide as a propyl anion with a magnesium counterion. That picture really isn't very accurate; there really is a covalent bond between the carbon and the magnesium, which is what makes the compound more stable than if it were purely ionic. However, thinking of it as a propyl anion might help you understand its role as a nucleophile.



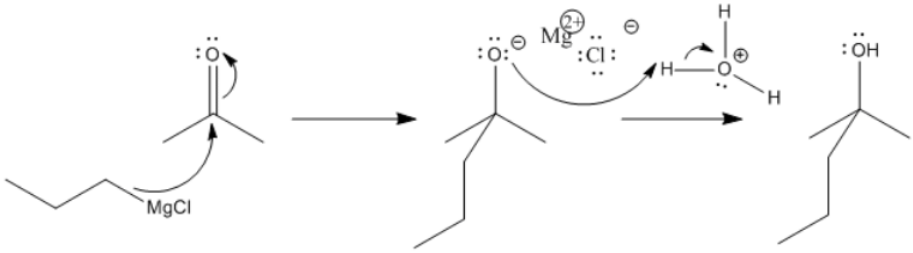
Propylmagnesium chloride and other Grignard reagents can deliver alkyl nucleophiles to carbonyls. Just like with simple anionic nucleophiles, an alkoxide ion results.



The relatively simple mechanism is shown below. The nucleophilic bond donates to the carbon of the carbonyl, breaking the π-bond, releasing a pair of electrons to the electronegative oxygen atom. Alternatively, you could still draw the bromine attached to a Mg+ at this point.

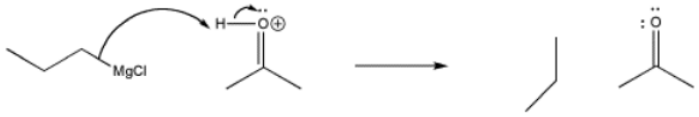


Of course, subsequent treatment of the alkoxide with acid provides a proton, resulting in an alcohol. We can see the two consecutive reactions in the following mechanism.

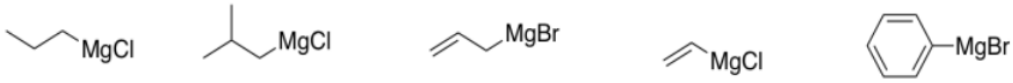


In that first step, there is no apparent lone pair involved. Instead, the polar magnesium carbon bond behaves just as if it were a lone pair on carbon.

Remember, the order of these two steps is very important. Adding the acid before the Grignard reagent would not work, because the Grignard reagent would become protonated at the carbon. Although the Mg-C bond is covalent, it is still polar enough so that the carbon can act as a nucleophile or as a base. Once propylmagnesium has become protonated, it forms propane, which isn't likely to act as a nucleophile.

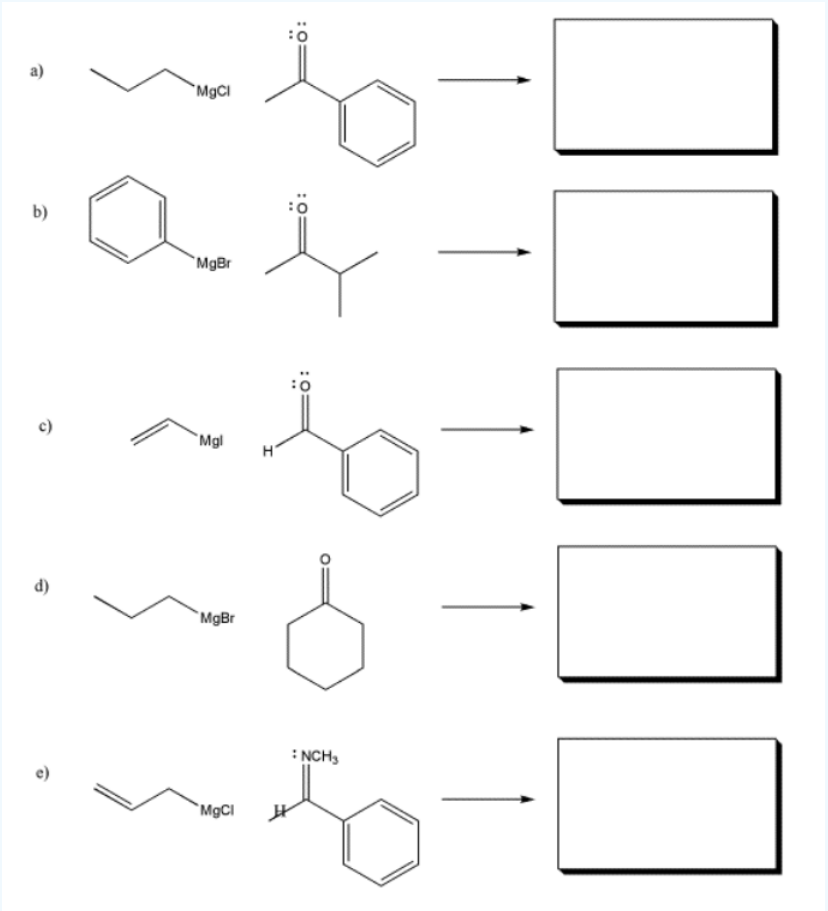


Grignards can have a variety of structures, but they are almost always hydrocarbons, with no other functional groups in the structure. Other functional groups are frequently incompatible with the reactive metal-carbon bond. The same is true for the closely-related alkyllithium compounds, such a methyllithium,CH_3Li. Other than that, Grignards and alkyllithiums can be saturated (containing only sp^3 carbons) or they can contain double bonds.

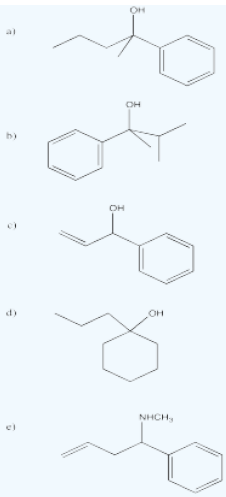


Exercise 3.2.1

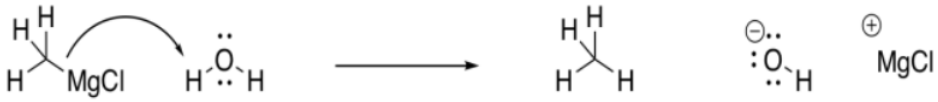
Show the products of the following reactions. Assume workup with aqueous acid after each reaction.



Answer



Grignard reagents are very delicate. Solvents must be chosen very carefully for Grignard reactions. Grignard reagents are basic enough that they can't tolerate protic solvents. Protic solvents are solvents that are capable of hydrogen-bonding. Although they don't seem very acidic, they can still give up a proton to a strong enough base. A Grignard reagent is a strong enough base to take that proton from an O-H bond.

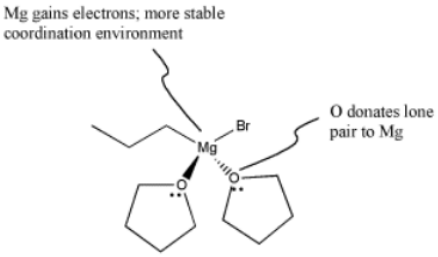


Exercise 3.2.2

Show why Grignard reagents cannot be used with ethanol as a solvent.

Answer

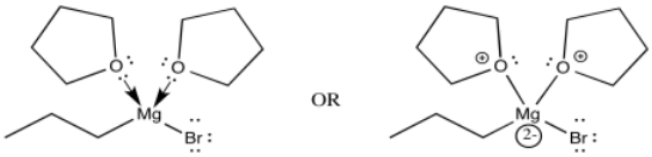
In fact, Grignard reagents are even fussier than that. Not only do they not get along well with acidic or even semi-acidic protons, but they tend to need coordinating solvents to help support the magnesium atom and keep the complex stable. The most common solvents for this use are (diethyl) ether and tetrahydrofuran (THF). When two ethers bind to the magnesium, the magnesium has a full octet. Because coordination of magnesium by these weakly donating solvents is crucial, Grignard reagents can't generally be isolated. Instead, they are sold and used as solutions in ethereal solvents.



THF complex

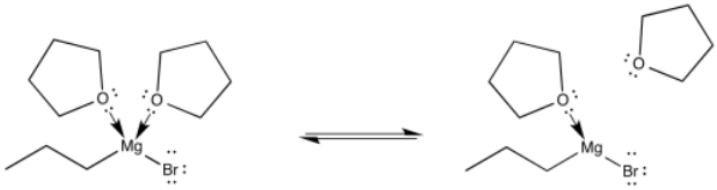
The THF complex, like other coordination complexes, can be drawn in a number of additional ways. The drawing above is probably the most common type, but a couple of other drawings are shown below. In the drawing on the left, we are distinguishing between two slightly different types of bonds on the magnesium. One bond, which we have already discussed, is a polar covalent

bond. It is shown with a straight line. However, we know the carbon behaves as if it were an anion with a lone pair. The other is a dative bond from a neutral donor. The oxygen is simply sharing one of its lone pairs with the magnesium. If the oxygen took its lone pair back, it would be a neutral atom. If the bromine left, it would be an anion. A convention widely adopted in coordination chemistry shows bonds from anionic donors to metals as lines, whereas bonds from neutral donors to metals are shown as short, straight arrows. On the other hand, if we know anything about formal charge, we would look at the picture above and correct it, giving the version below, right.

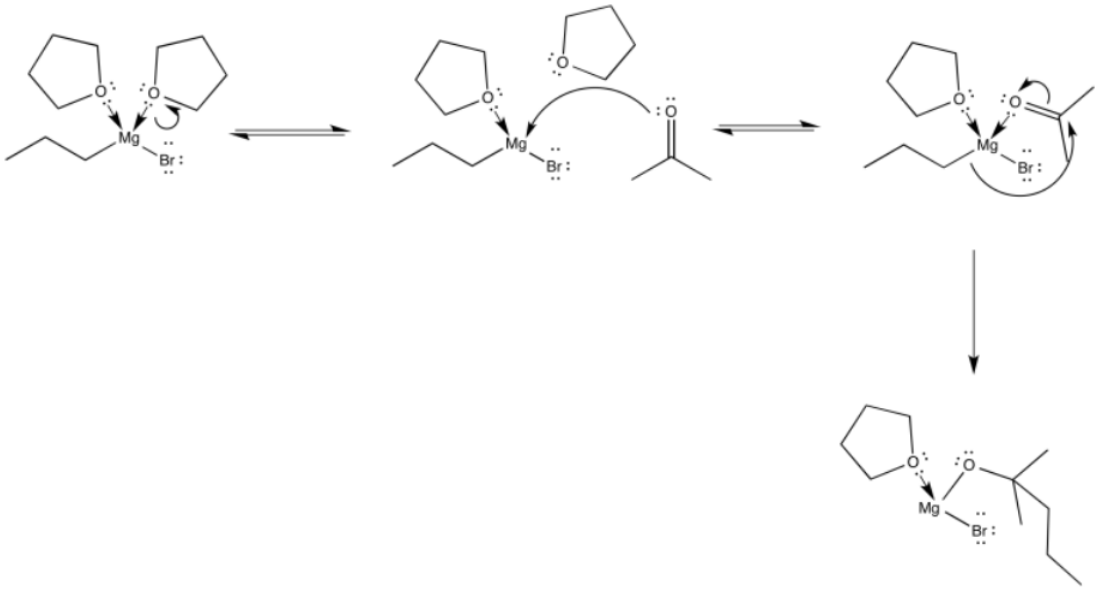


Each drawing has its merits. The first one is probably the simplest; in this case, we could even afford the luxury of drawing in a wedge and a dash to show stereochemistry without getting too complicated. The second quickly conveys the idea of the charges on the ligands and the metal in the coordination complex; there are two neutral ligands and two anionic ones, and therefore the metal has a +2 charge. The third tells us something about how charge has been transferred in bonding. Because the oxygen has shared its electrons with magnesium, magnesium gets a little more electron density and oxygen's goes down a little bit. Despite being notably electronegative, oxygen frequently donates to other atoms if needed. (A generous act may not always be good for the donor, but it is frequently good for the universe.)

Eventually, it will be useful to know that coordination complexes (or Lewis acid-base adducts) frequently form reversibly. There is actually an equilibrium in which donors come on and off the metal, especially if the donors are pretty stable by themselves.

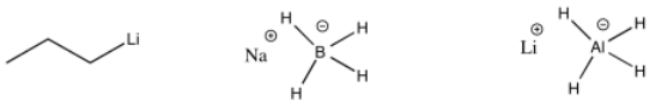


We can picture the propylmagnesium bromide swimming through the THF, swinging from one THF molecule to another. Of course, it is always possible that it bumps into another oxygen donor: an aldehyde or ketone. It would certainly coordinate to that oxygen as well, but the situation wouldn't last long as the nucleophilic addition would immediately ensue.

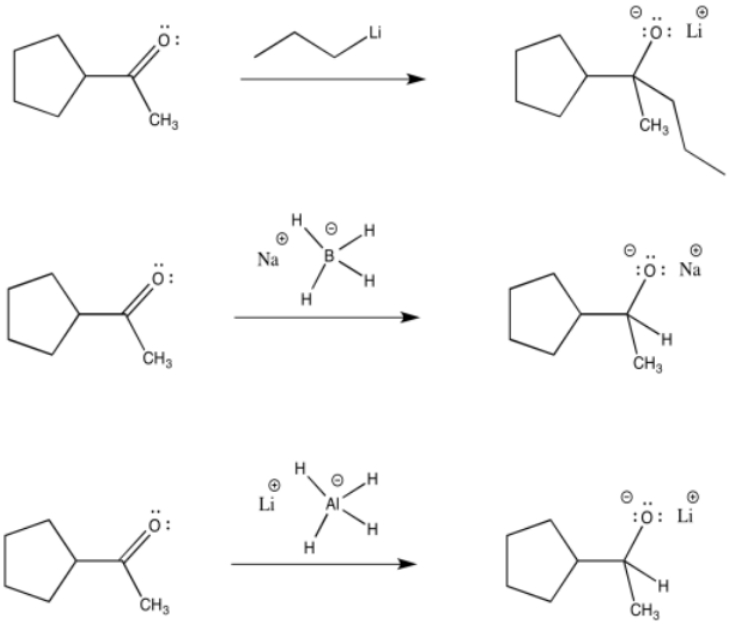


The carbon-magnesium bond is polar, and it allows carbon to act as a nucleophile, donating its bonding pair to an electrophile. Other polar bonds behave in a similar way. Common examples include carbon-lithium bonds (which you will see in a question below), as well as aluminum-hydrogen and boron-hydrogen bonds (in complexes such as Na^+ BH_4^- and Li^+ AlH_4^-, also in a

question below). Perhaps surprisingly, because both aluminum and boron are less electronegative than hydrogen, these bonds are polarized toward the hydrogen (carbon, just to the right of boron, is slightly more electronegative than hydrogen, although not enough to make us think of a C-H bond as polar). That means that these compounds act as sources of nucleophilic hydride ion, H^-.



Just like Grignard reagents, alkyllithium reagents and complex hydride anions are good nucleophiles for aldehydes and ketones. The nucleophilic part is donated to the carboonyl to make an alkoxide anion.



Like Grignard reactions, these reactions are usually followed by treatment with aqueous acid (such as HCl or H2SO4 in water). The alkoxide ion picks up a proton to make an alcohol. The salts (including sodium or lithium ions) are washed away in the water.

Exercise 3.2.3

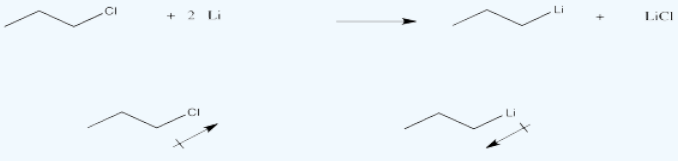
There are plenty of other semi-anionic nucleophiles. For example, alkyl lithium reagents are also very common, and they are prepared by treatment of alkyl halides with finely divided lithium metal. The reaction produces lithium chloride as a side product.

a) Show an equation, with structures, for the preparation of butyllithium from 1-bromobutane.

b) Explain what happens to polarity at carbon number one before and after this reaction.

c) Why would the amount of charge on carbon number one be somewhat similar in butyllithium and butylmagnesium bromide?

Answer

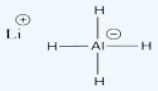


Exercise 3.2.4

Another class of semi-anionic nucleophiles is the family of complex metal hydrides. Examples include sodium borohydride, $NaBH_4$, and lithium aluminum hydride (LAH), $LiAlH_4$. There are many other variations.

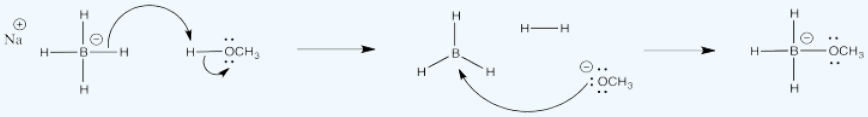
a. Draw a Lewis structure for lithium aluminum hydride.
b. Explain why LAH functions as a source of the hydride nucleophile, H^-.
c. LAH is much more reactive that sodium borohydride; it can reduce compounds that sodium borohydride will not. For example, it can reduce a nitrile such as CH_3CN to an amine such as $CH_3CH_2NH_2$ (after an aqueous workup). Explain why LAH is so much more reactive than $NaBH_4$.
d. Sodium borohydride is sometimes used in methanol, but care must be taken in dissolving the $NaBH_4$. It does not just dissolve; it quickly reacts with the methanol to produce a flammable gas and $NaBH_3OCH_3$. Provide a mechanism for this reaction with arrows.
e. Although $NaBH_3OCH_3$ also reacts with methanol, it does so much more slowly than $NaBH_4$, and so it is still able to reduce aldehydes and ketones in methanol. Explain the difference between sodium borohydride and sodium methoxyborohydride in terms of reactivity with methanol.
f. LAH cannot be used in protic solvents such as methanol. Explain why.

Answer a



Answer b & c

Answer d



Exercise 3.2.5

Barbier reactions are a general class of reactions involving metal alkyls and carbonyls. Treatment of a halide such as propargyl bromide ($HCCCH_2Br$) with zinc metal in the presence of an aldehyde such as benzaldehyde (C_6H_5CHO) results in nucleophilic addition of the propargyl group to the aldehyde.

a. Zinc can insert into a carbon-halogen bond, just like magnesium. Show the product of the insertion described above.
b. This reaction is usually performed in water with some ammonium chloride, NH_4Cl, in solution. Show a mechanism, with curved arrows, for the reaction of the alkylzinc species with the aldehyde to yield an alcohol.
c. Explain why this alkylzinc reaction can be conducted in the presence of water, but a Grignard reaction cannot.
d. "Green chemistry" refers to the intentional use of processes that are better for the environment, by minimizing the use of toxic reagents and solvents. Compare the zinc-mediated Barbier reaction with the Grignard reaction in terms of "greenness".

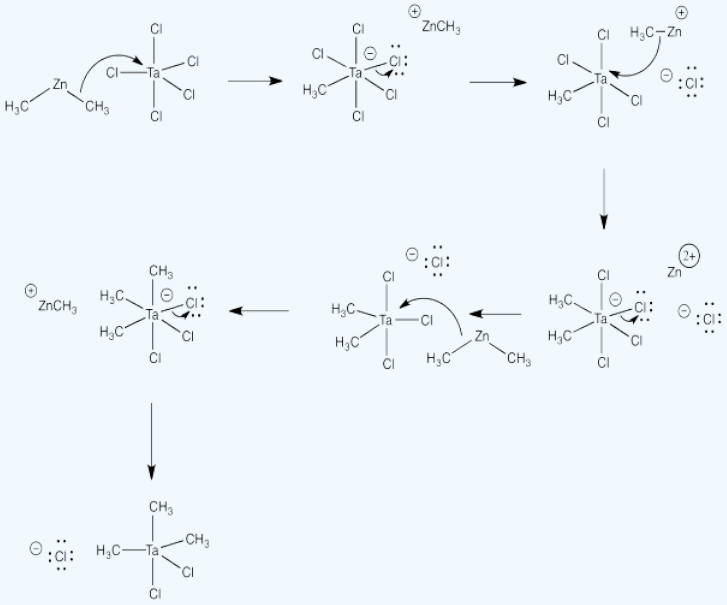
Answer
Answer a

Exercise 3.2.6

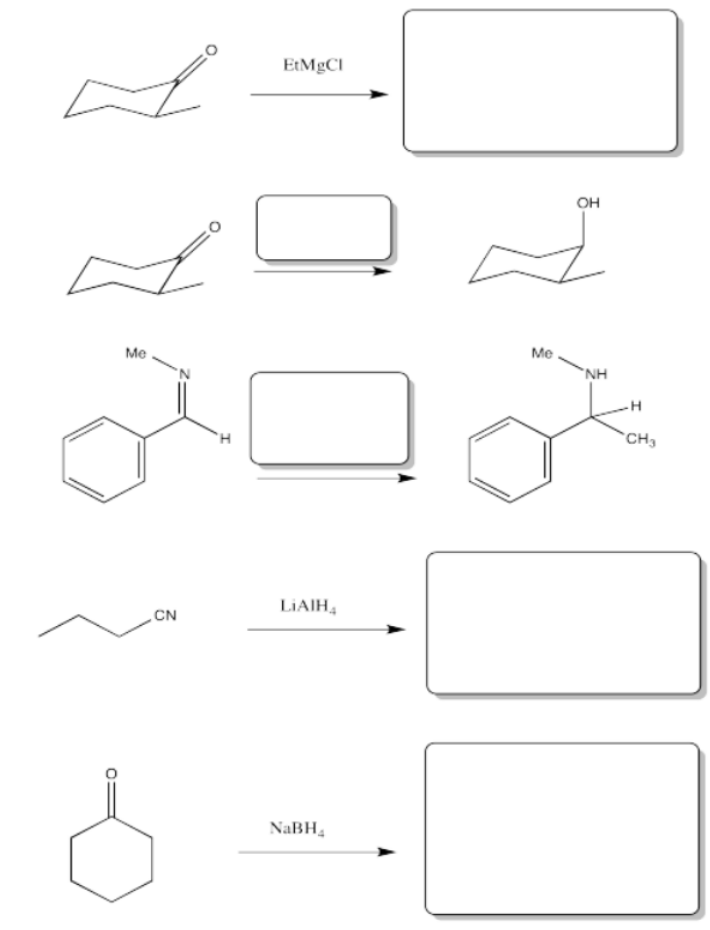
Semi-anionic nucleophiles do not just react with carbonyls. They are also frequently used to prepare organometallic compounds via "transmetallation". For example, treatment of tantalum pentachloride, $TaCl_5$, with dimethylzinc, $(CH_3)_2Zn$, affords trimethyltantalum dichloride, $(CH_3)_3TaCl_2$.

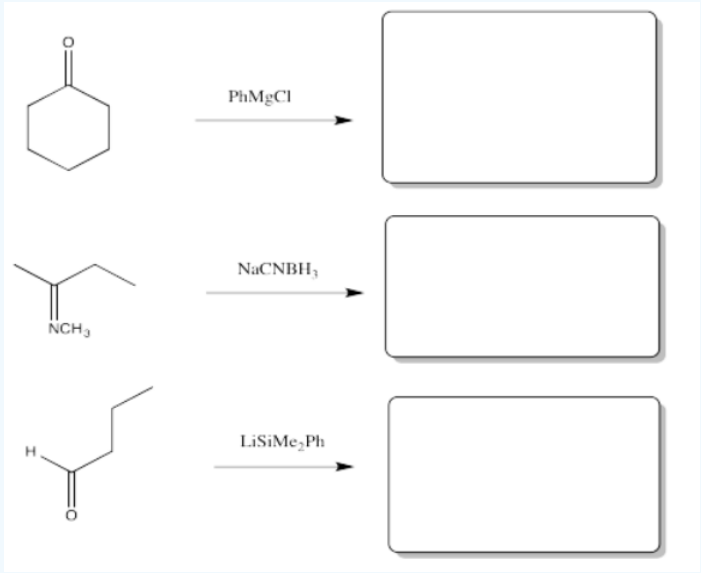
a. Assume for the moment that tantalum pentachloride and dimethylzinc are both covalently-bonded molecules. What would you say about bond polarity in each case?
b. What is the side-product of the reaction (i.e. what else must be produced given the production of trimethyltantalum dichloride from these reactants?)
c. In what ratio would you mix the two reactants to get these products?
d. Show a mechanism, with curved arrows, for the formation of trimethyltantalum dichloride.
e. Like some of the other compounds on this page, trimethyltantalum dichloride is remarkably pyrophoric: it catches fire upon contact with air. This behavior often depends on weather and humidity. Show a mechanism, with curved arrows, for what happens when this compound is exposed to air.

Answer
Answer

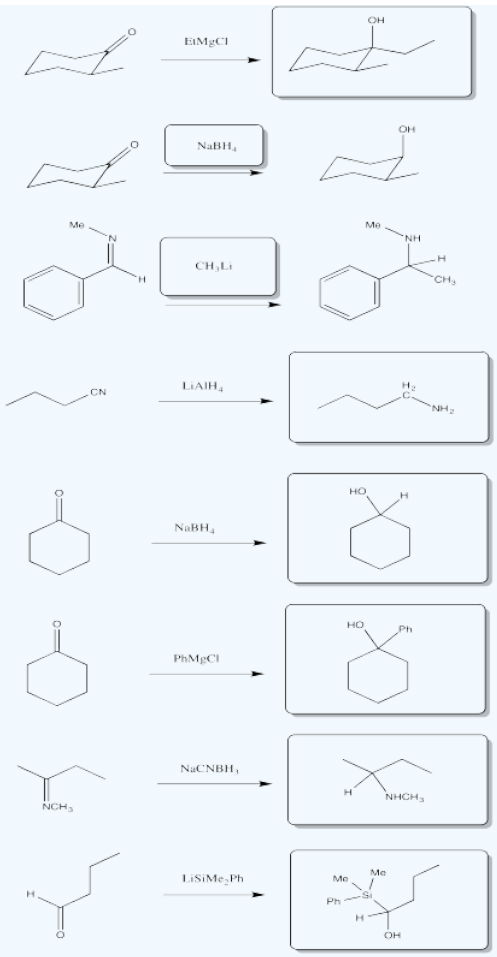


Exercise 3.2.7


EtMgCl
OH
Me
N
H
Me
NH
H
CH3
CN
LiAlH4
NaBH4

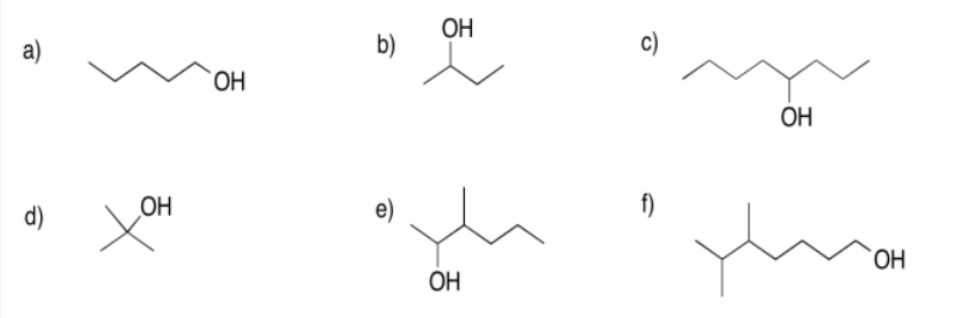

PhMgCl
NaCNBH3
NCH3
H
LiSiMe2Ph

Answer



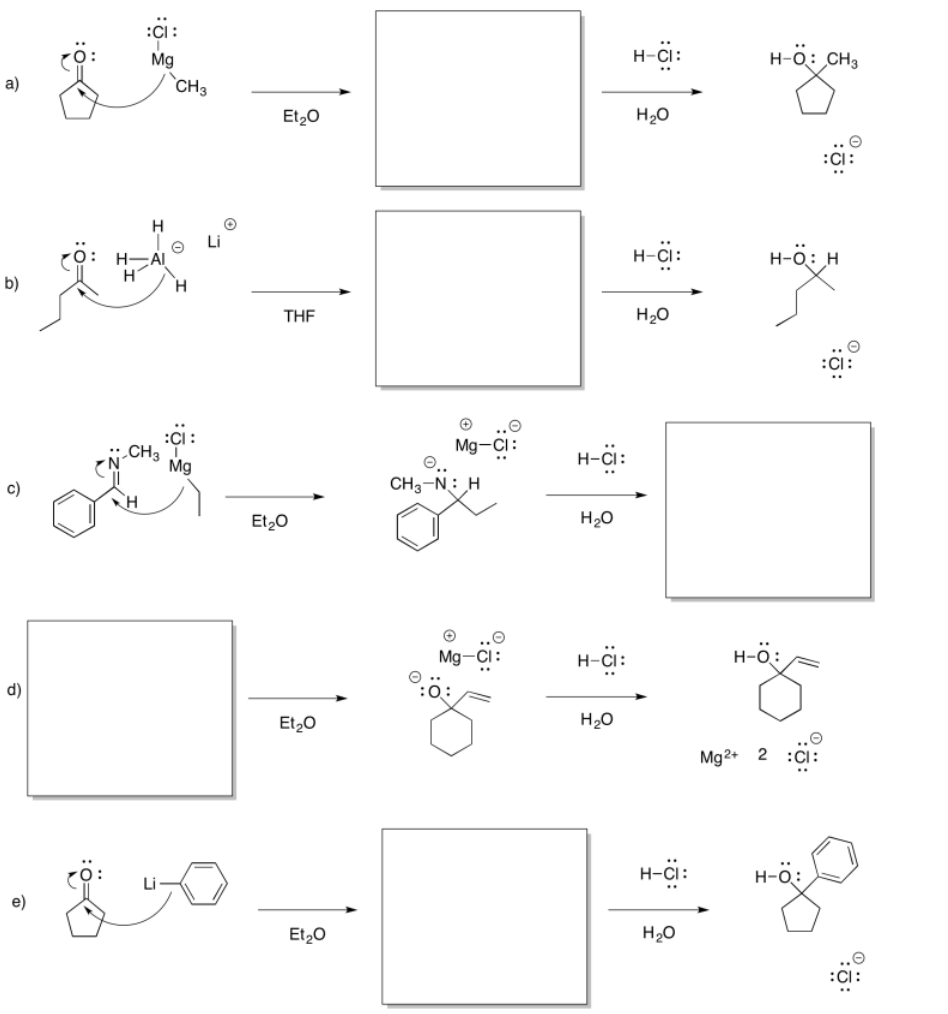
Exercise 3.2.8

Provide IUPAC names for the following alcohols. For help, see the functional group section, simple heteroatomics.

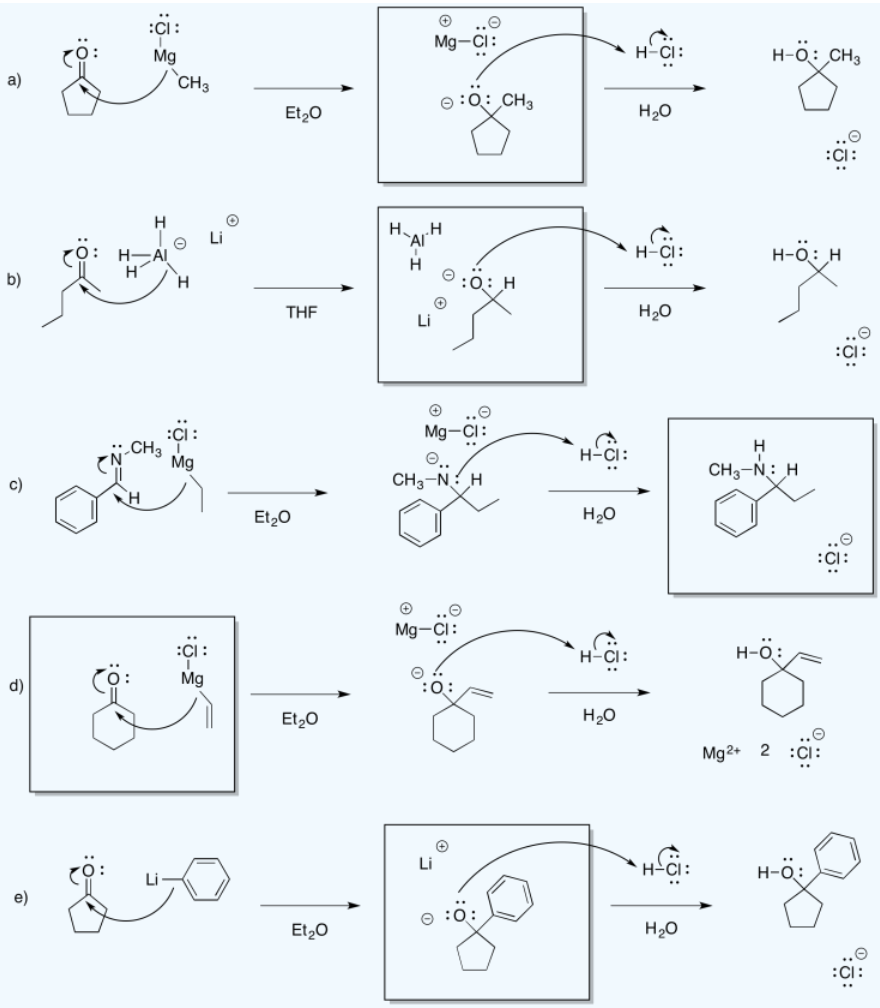


Exercise 3.2.9

Fill in the missing intermediates and add curved arrows to show electron movement.



Answer



3.3: Enolate Addition- Aldol reactions

Enolate ions are just another example of anionic carbon nucleophiles. The reason they get a page to themselves is that they are especially important, especially in biological chemistry. They are also important in the synthesis of organic compounds, such as in the pharmaceutical industry.

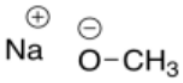
Forming Enolate Ions

An enolate ion is the anion that forms when a proton is removed next to a carbonyl. The carbon next to the carbonyl is called the α-position (alpha position). The alpha position is acidic both because of the amount of positive charge on a proton in that position and because of the stability of the anion that results if that proton is removed.

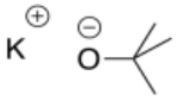
You might have learned about metal hydroxides such as sodium hydroxide and lithium hydroxide. The metal-oxygen bond is ionic because of the large electronegativity difference between the metal and the oxygen. These compounds give rise to hydroxide ions. Those hydroxide ions are basic because they can easily pick up protons to become neutral water molecules. Metal hydroxides are commonly seen in chemistry, and they are thought of as strong bases.

Other oxygen anions are also able to act as strong bases, unless there is some resonance factor that delocalises the anion and makes it less reactive. Methoxide ion and butoxide ion are also common strong bases.

lithium hydroxide



sodium methoxide

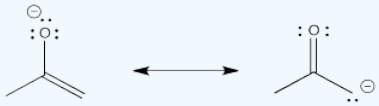


potassium *tert*-butoxide

Exercise 3.3.1

Show why an enolate ion, such as the one formed from 2-propanone, above, is particularly stable.

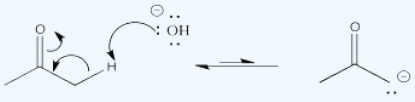
Answer



Exercise 3.3.2

Show a mechanism, with curved arrows, for the formation of the enolate ion from 2-propanone, above.

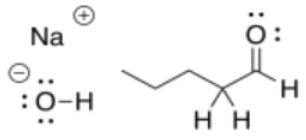
Answer

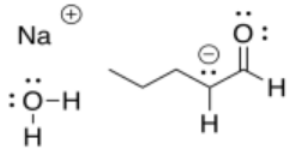


In the example above, 2-propanone is deprotonated at the α position to form the corresponding enolate ion. Note that sodium hydroxide is not a strong enough base to convert all of the 2-propanone to its enolate. The resulting enolate is basic enough to pull a proton from a water molecule, so an equilibrium results.

That would be the case any time a strong base such as a hydroxide or an alkoxide was used to deprotonate a ketone or aldehyde. In the following example with pentanal, the reaction would also result in an equilibrium between the reactants and the products.

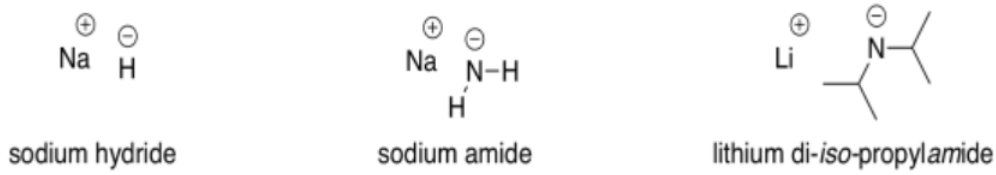
That means that all of those compounds on both the left hand and right hand side of the arrow would all be present as a mixture.





Negative charges are fairly stable on oxygen atoms. That allows this particular reaction to shift back to the left again, to form that hydroxide ion again. To make the reaction go all the way to the right, we would need a less stable anion on the left. That would make that anion more basic. Can you think of atoms that would be less stable as anions than oxygen?

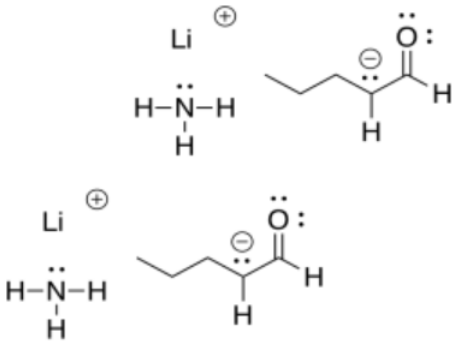
The most commonly used very strong bases in synthetic chemistry involve anions of carbon, nitrogen or hydrogen. Some examples of compounds used as very strong bases are sodium hydride (NaH), sodium amide ($NaNH_2$), lithium diisopropylamide ($LiN[CH(CH_3)_2]_2$, also called LDA for short), and butyllithium ($CH_3CH_2CH_2CH_2Li$, abbreviated BuLi).



In all of these compounds, the negative charge is on a less electronegative element than the oxygen of the hydroxide ion. That means that they are less stable and more reaction than hydroxide.

If one of these bases were to react with an aldehyde or ketone, the proton would be removed irreversibly. The delocalised enolate ion is actually more stable than the original amide ion in sodium amide, for example.

As a consequence, adding a very strong base to an aldehyde or ketone results in complete conversion into products. At the end of the reaction, there are no reactants left.



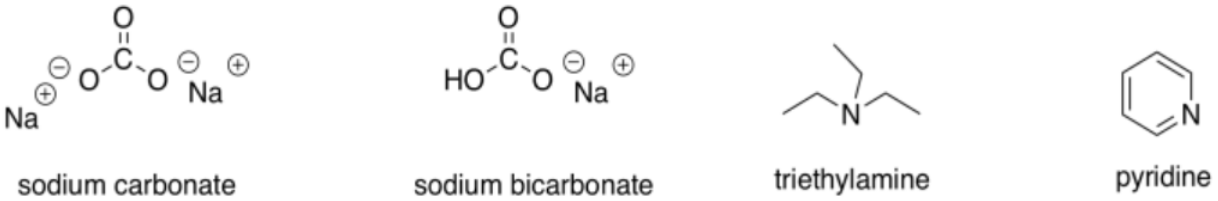
In contrast, a "strong base" such as sodium hydroxide won't really do the job. If it did, we would be trading in an anion on a more electronegative atom (oxygen) for an anion on a less electronegative atom (carbon) in the same row of the periodic table. That's not possible. The enolate anion that forms would be more basic than the hydroxide we began with, and most of the time it would just snatch the proton back from the water again, making ketone and hydroxide again.

- Enolate ions form in equilibrium with their parent carbonyl compounds if a moderately strong base like sodium hydroxide is used.
- A very strong base, like sodium amide ($NaNH_2$), butyllithium ($CH_3CH_2CH_2CH_2Li$, or BuLi) or sodium hydride (NaH), would result in complete enolate formation.

However, it is sometimes really useful to have an equilibrium between a carbonyl compound and its enolate. That situation allows both a ketone (the 2-propanone, left) and its enolate (right) to be present at the same time. That means there is both a nucleophile and an electrophile (the ketone and the enolate). They will be able to react together.

- Simple carbonyls are electrophiles.
- The enolate ions that form from simple carbonyls are nucleophiles.
- Carbonyls react with enolate ions.

While we are on the subject of bases, there is a third category of compounds that we would consider weak bases. The most common examples are amines (but not amides) and resonance-stabilised oxygen anions.

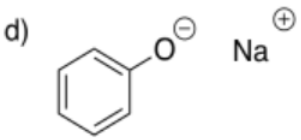


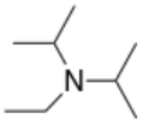
These compounds would be good at picking up excess protons that were floating around. However, in most cases they wouldn't be strong enough bases to provide an appreciable amount of enolate ion.

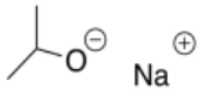
Exercise 3.3.3

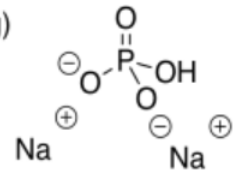
Identify the following compounds as weak, strong, or very strong bases.

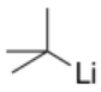
a) KOH b) KNH_2 c) Me_3N

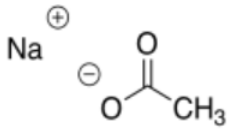












Answer
Answer a

very strong

Answer b

very strong

Answer c

weak

Answer d

weak

Answer e

weak

Answer f

strong

Answer g

weak

Answer h

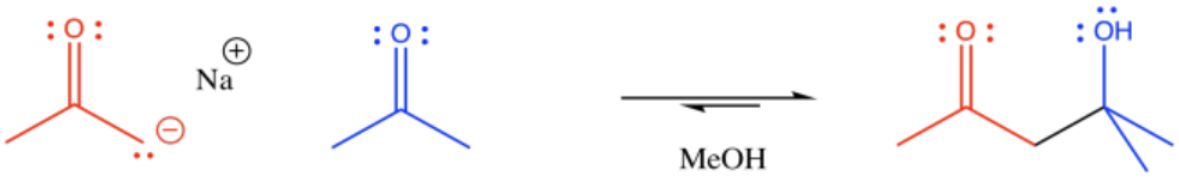
very strong

Answer i

weak

Aldol Reactions: Adding Enolates to Carbonyl Electrophiles

The reaction of an enolate nucleophile with another carbonyl compound is called an aldol reaction. A simple example of this reaction is shown here. This example involves the reaction of 2-propanone with its enolate.

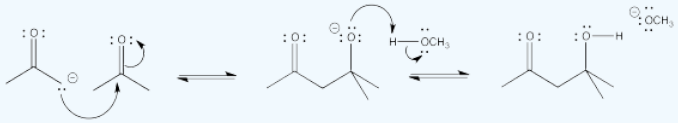


Note the pattern in the product. The carbonyl of the enolate is connected to the enolate carbon which is connected to the alcohol carbon.

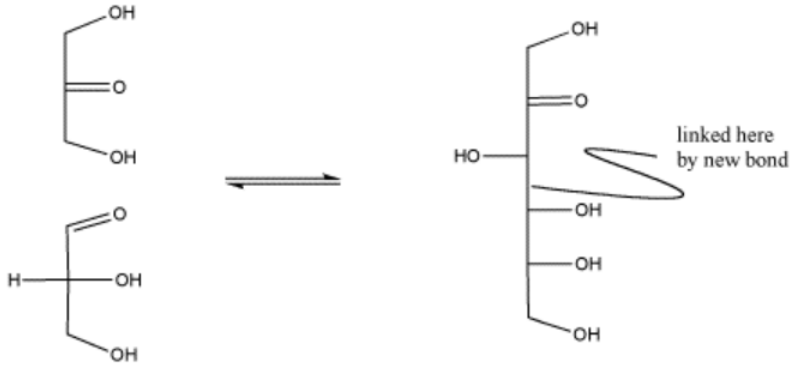
Exercise 3.3.4

Provide a mechanism, with curved arrows, for the aldol reaction of 2-propanone, above.

Answer



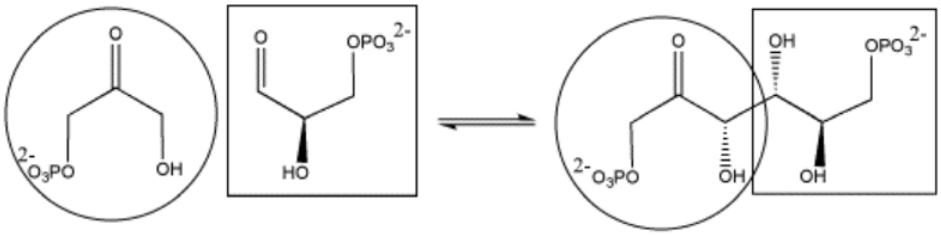
The biosynthesis of sugars, such as fructose, involves coupling smaller sugars together. If one sugar is converted into a nucleophile, it can donate electrons to the carbonyl on the other sugar, forming a new C-C bond. The carbonyl on the second sugar becomes a hydroxyl group in the new, larger sugar.



two 3-carbon sugars

fructose, a 6-carbon sugar

In the cell, sugars are typically in a phosphorylated form when they react in this way. Phosphorylation is often an important step in activating molecules for biochemical reactions.



Exercise 3.3.5

Show the mechanism for the formation of the phosphorylated fructose shown above.

Answer

Add texts here. Do not delete this text first.

A Variation: Aldol Condensation

Sometimes, aldol reactions are followed by a subsequent reaction, called an elimination reaction. That reaction formally produces a molecule of water. Early studies of this reaction would result in droplets of condensation on the glassware in which the reaction occured; hence, it is sometimes called a condensation reaction.

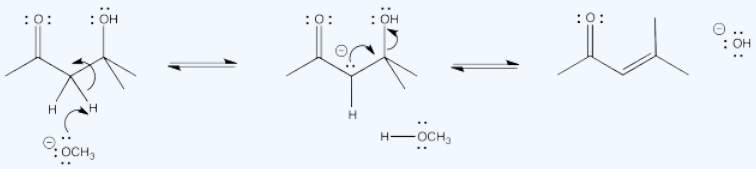
The term "condensation" comes from the fact that the reaction formally results in loss of a water molecule from the alpha and beta positions (H from alpha and OH from beta). Early reactions that were observed to result in loss of water were frequently described as condensations because of the water droplets that would appear on the glassware (literally, condensation) as the reaction proceeded. The term "dehydration" is also used to describe this loss of water.

However, don't get too tied to the descriptions of the reactions (condensation vs. addition). The terms are used loosely and sometimes interchanged. On this page, we try to use addition to describe the initial product and condensation to describe the product after loss of water, but sources elsewhere might not describe it that way.

Exercise 3.3.6

Provide a mechanism for the dehydration step in the aldol condensation shown above.

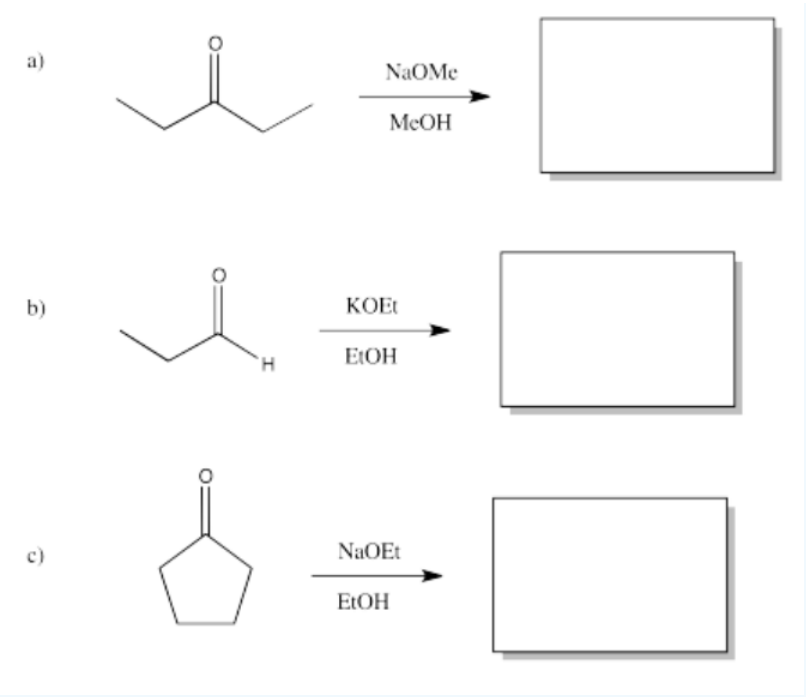
Answer



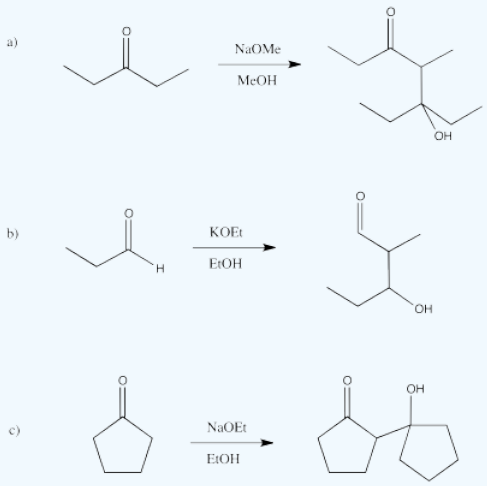
It can be hard to predict the outcome of an aldol reaction because of the fact that there are two possible products from an aldol reaction (one with a new hydroxyl and one with a new double bond). A chemist might try to make one product in the laboratory, and end up with the other. This process can be difficult to control. However, in general, the elimination reaction is encouraged by heating the reaction. The reaction sometimes occurs without elimination if the reaction is kept cool. However, there are also other factors that may come into play.

Exercise 3.3.7

Predict the products of the following aldol reactions.

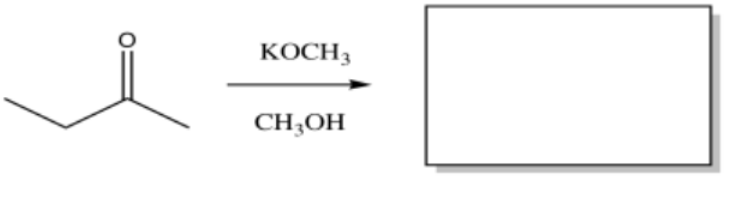


Answer

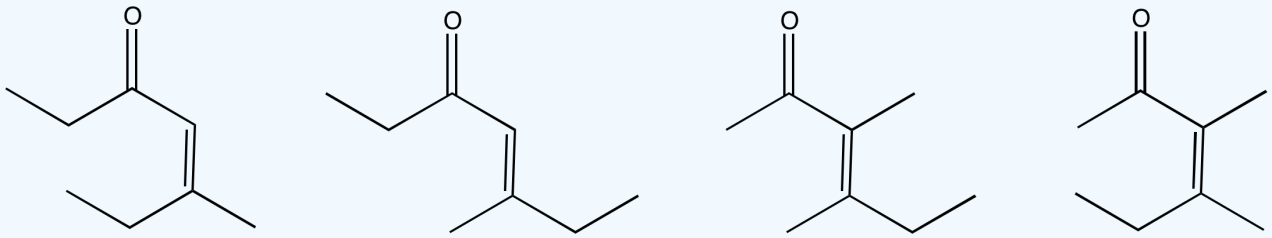


Exercise 3.3.8

The following compound would give multiple products through different aldol condensation reactions. Show the products.



Answer

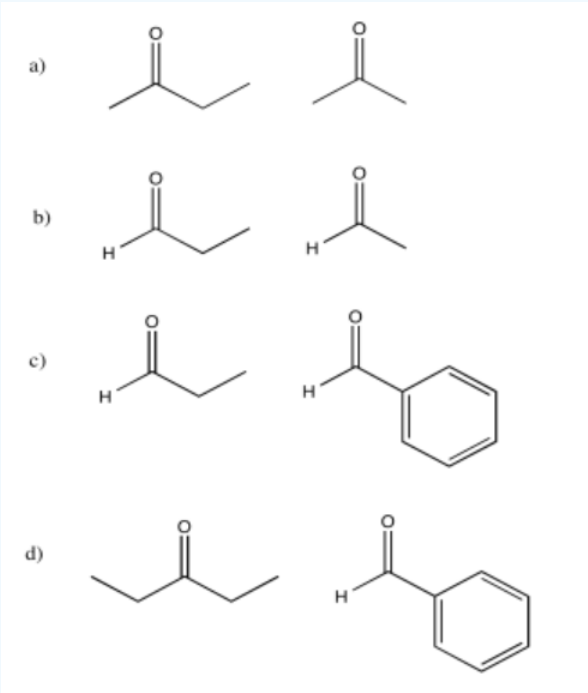


Sometimes, two different compounds may react together in an aldol reaction. One compound acts as the nucleophile, and the other one acts as the electrophile. However, the reaction is really not much different that the aldol reactions we have already seen.

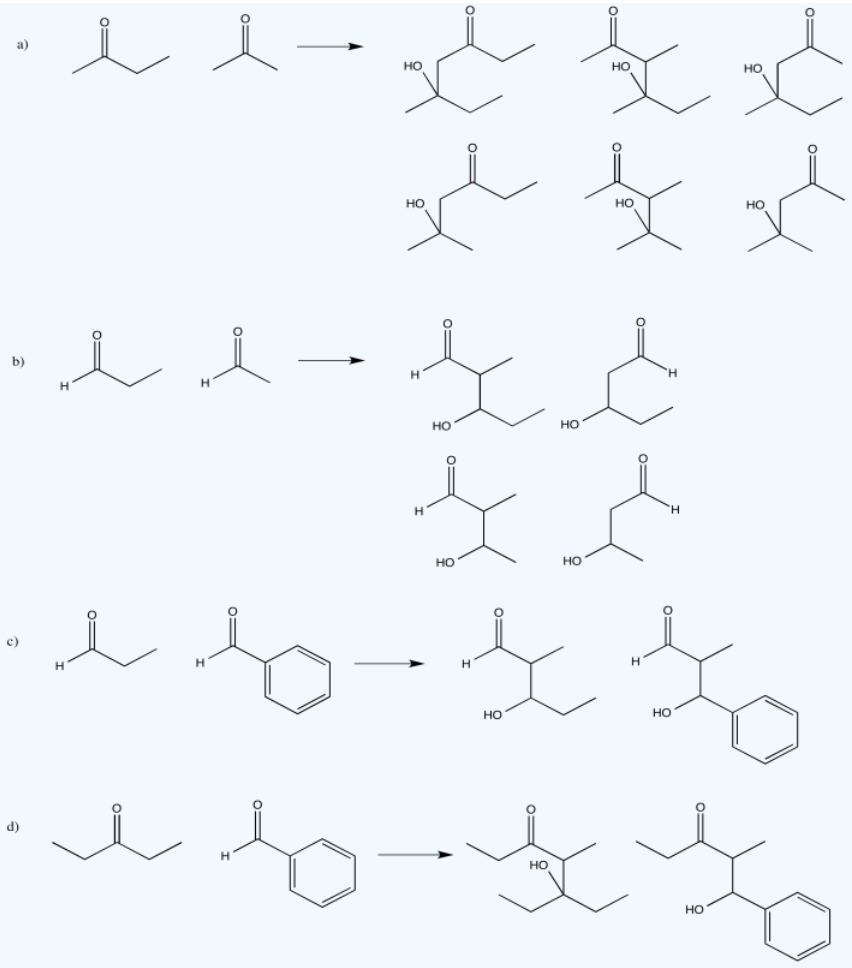
The only complication is that now there are two different compounds that could potentially be nucleophiles and two different compounds that could potentially be electrophiles. That makes predicting the outcome of the reaction a little more difficult.

Exercise 3.3.9

The following compounds would give multiple products through different aldol condensation reactions. Show the products.

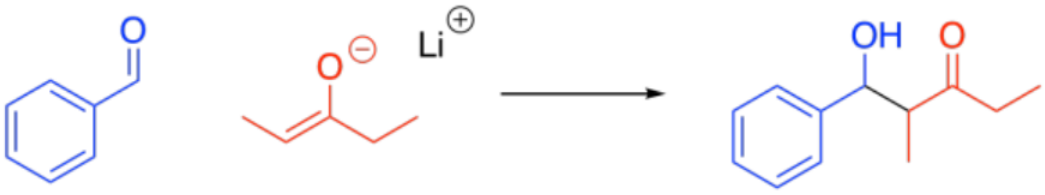


Answer



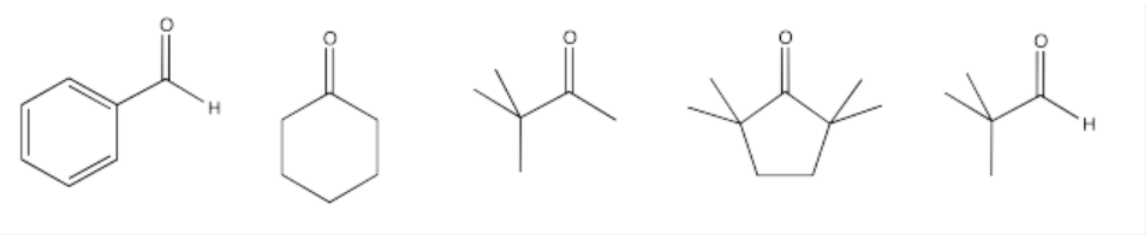
There are cases where it becomes a lot more obvious which compound would be the electrophile and which one would be the nucleophile. Maybe one of the compounds has a carbonyl that is much less crowded than the other. For example, maybe one compound is an aldehyde and the other one is a ketone. The less crowded carbonyl is much more likely to act as a good electrophile.

Maybe one of the compounds does not even have any alpha-protons. In that case, it can't be deprotonated and it can't form an enolate anion. It won't be able to act as the nucleophile.



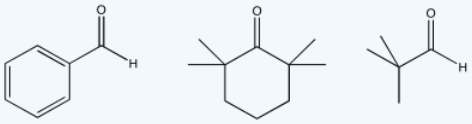
Exercise 3.3.10

Only some of the following compounds may undergo aldol reactions. Select which ones may not undergo the reaction, and explain what factor prevents them from reacting.



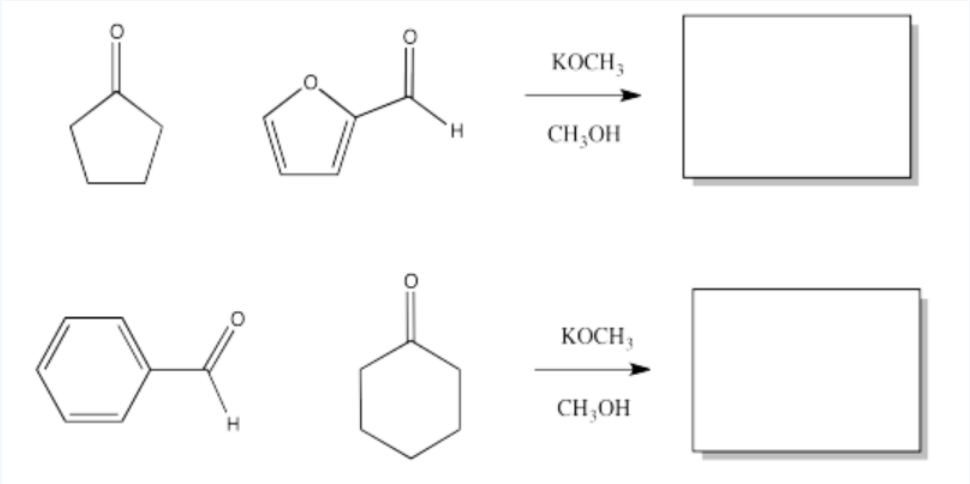
Answer

Some of these compounds do not have alpha-protons, so they cannot form enolate ions.

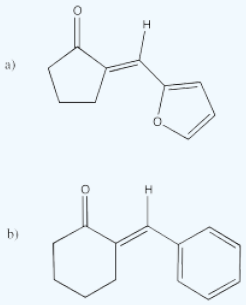


Exercise 3.3.11

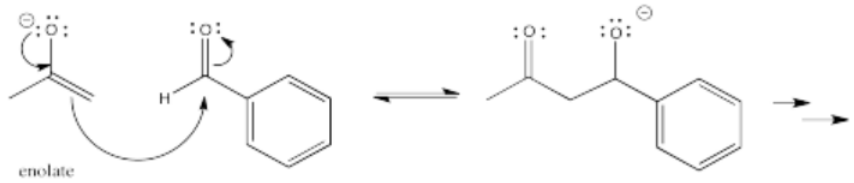
Fill in the products of the following aldol condensations.

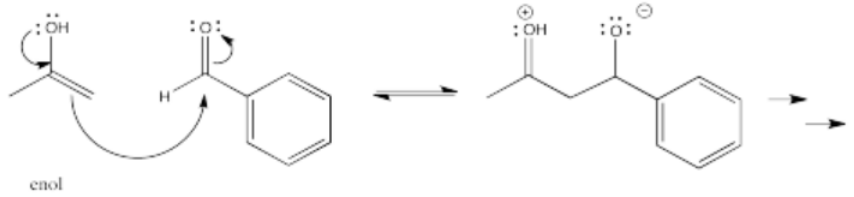


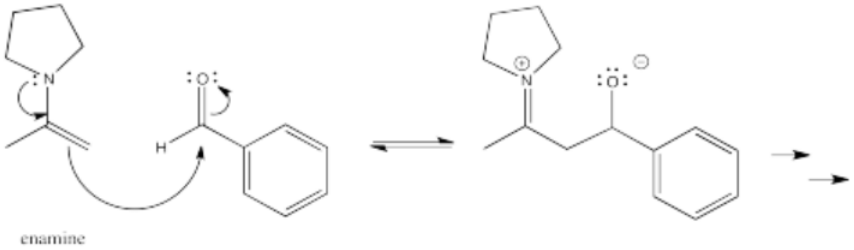
Answer



Aldol reactions do not just occur with enolate anions, however. Enols are the neutral form of enolates, protonated on the oxygen instead of the alpha carbon. Enols are also good nucleophiles. In an enol nucleophile, the pi bond acts as the electron source, rather than the lone pair. However, the pi bond gets a boost from the lone pair on the oxygen.







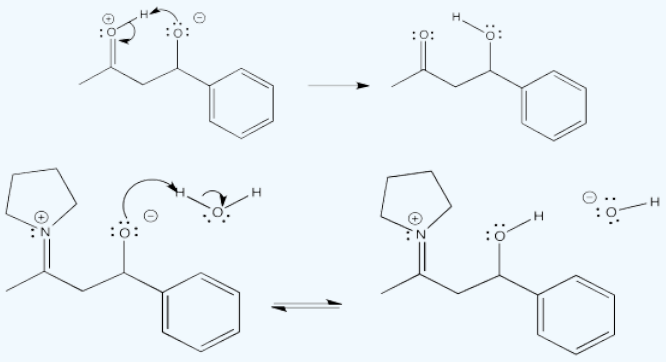
Enols are always present in equilibrium with aldehydes and ketones. An enol is a simple tautomer of a carbonyl compound. To get from one to the other, a proton is simply transferred from one position to the other.

- Enamines and enols are also good nucleophiles for aldol reactions.
- Because either acid or base can catalyse keto-enol tautomerism, aldol reactions can be catalysed by either acid or base.

Exercise 3.3.12

Show the subsequent protonation step in the reactions involving the enol and the enamine above.

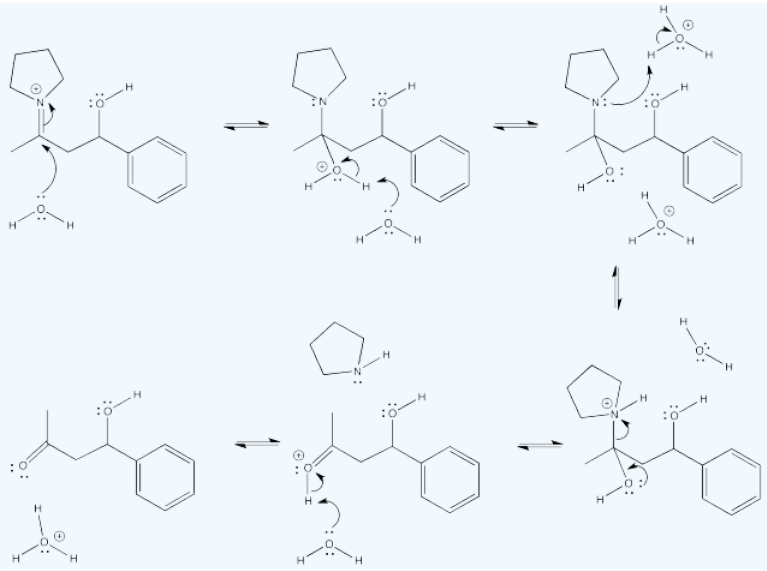
Answer



Exercise 3.3.13

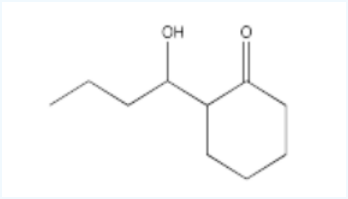
An enamine reaction is usually followed by hydrolysis of the C=N bond in the iminium ion. Show the mechanism for conversion of the iminium ion to the carbonyl via addition of aqueous acid.

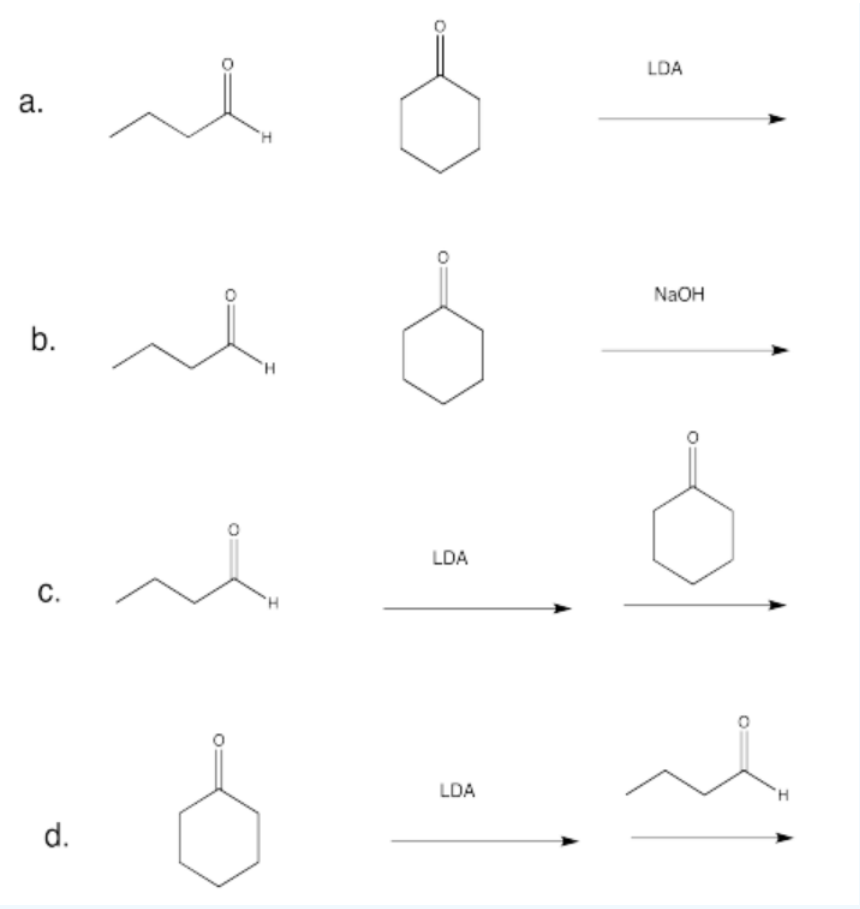
Answer



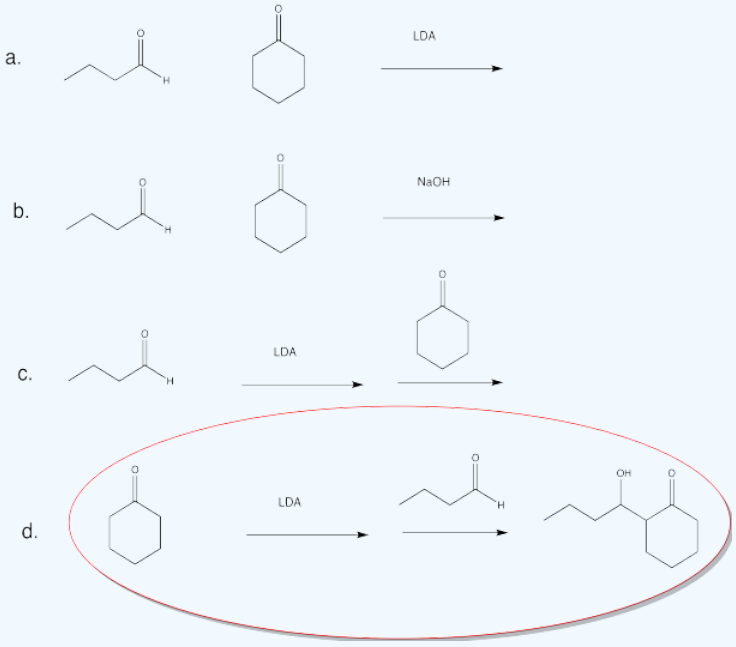
Exercise 3.3.14

Which conditions would be most likely to form this aldol product (select a, b, c or d below)?



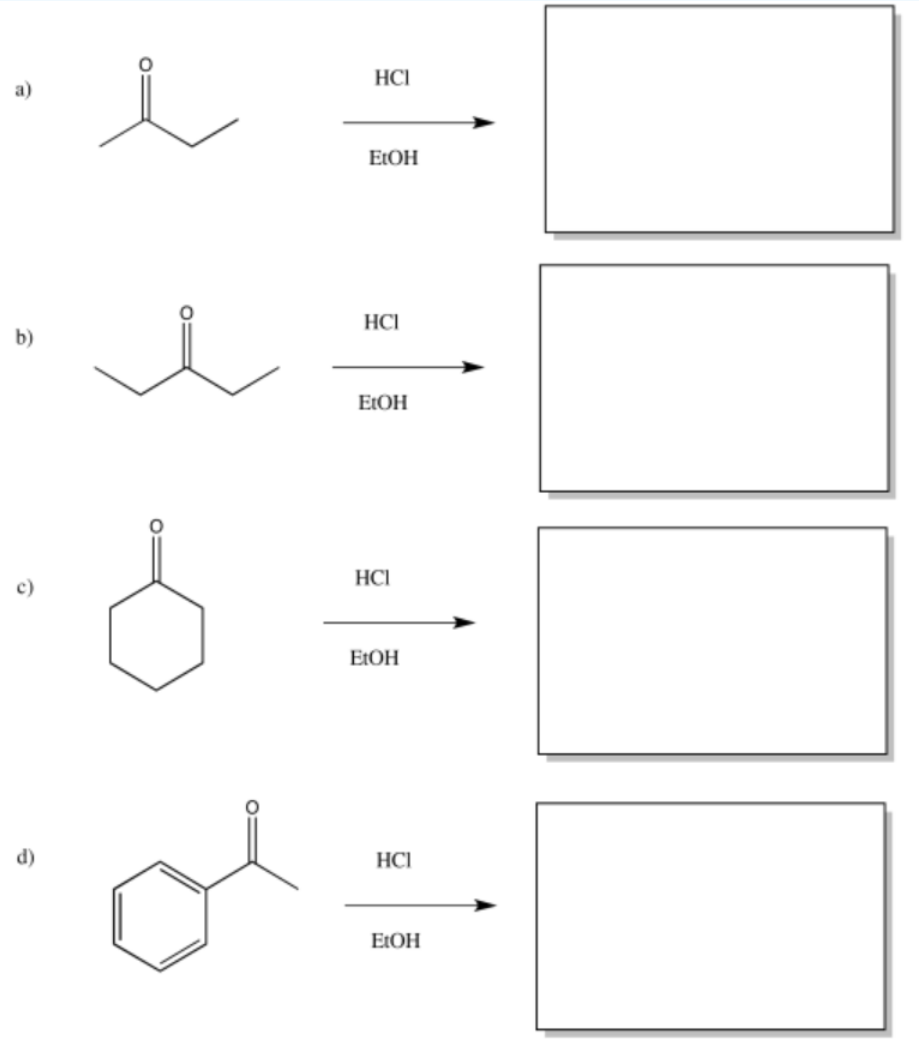


Answer

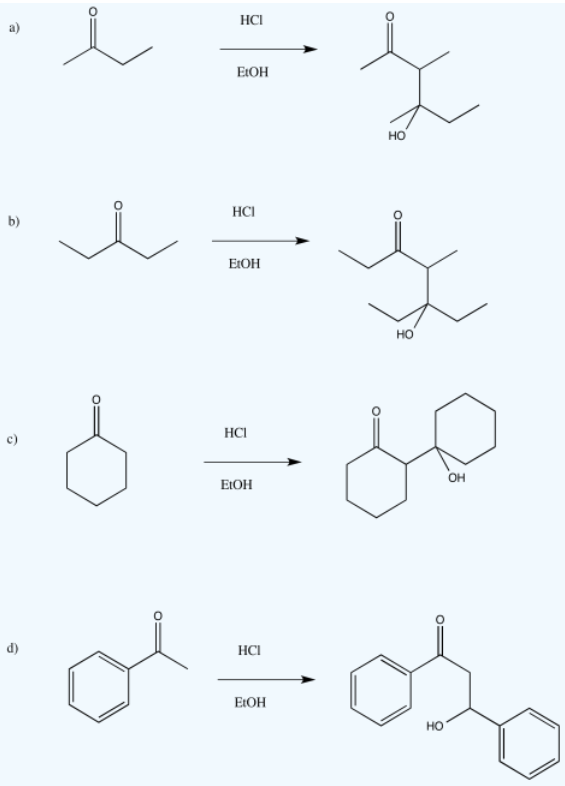


Exercise 3.3.15

Provide products of the following acid-catalysed aldol reactions.



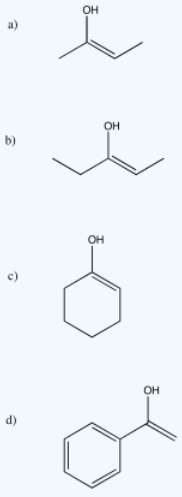
Answer



Exercise 3.3.16

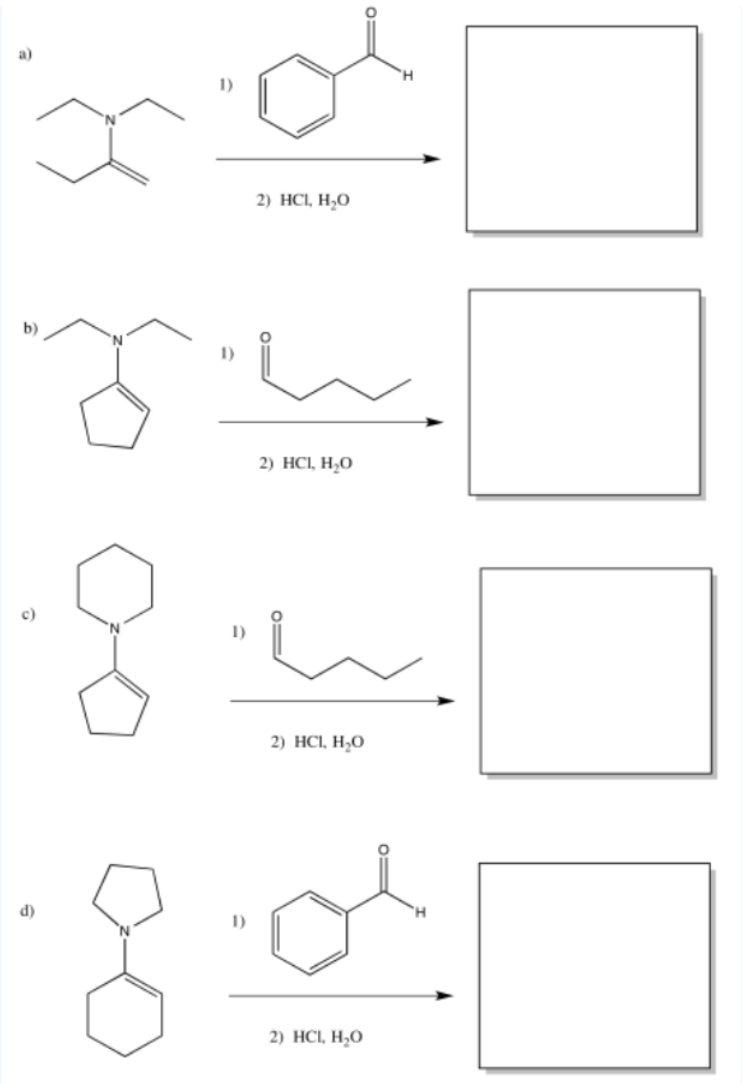
Draw the enol nucleophiles for the above question.

Answer

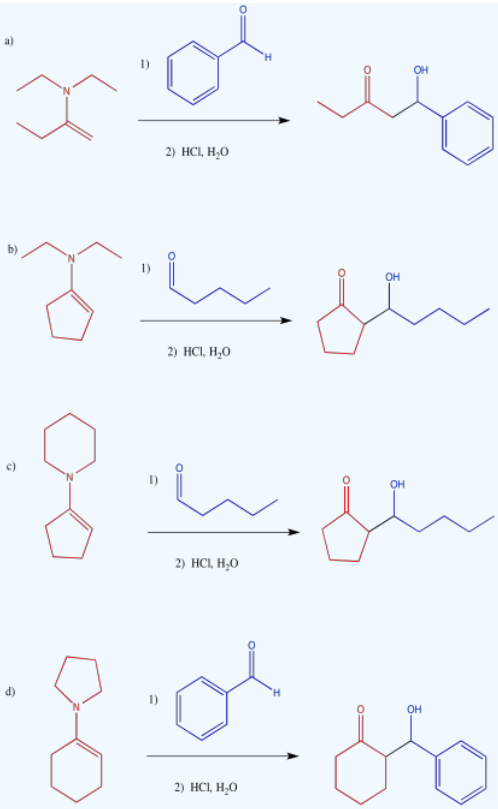


Exercise 3.3.17

Provide the products of the following enamine additions, after hydrolysis.



Answer



3.4: Activation of Carbonyls

A secondary theme in carbonyl chemistry centers on the role played by the oxygen lone pairs. A compound with lone pairs can act as a Lewis base. Can carbonyl compounds also act as Lewis bases? The answer is yes, although it is most important to think about carbonyls primarily as Lewis acids.

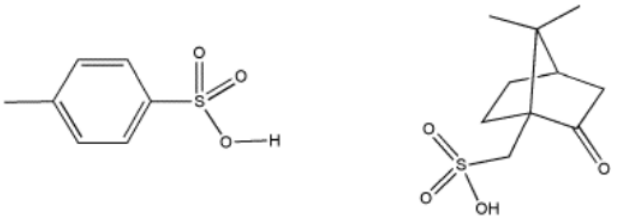
One of the reasons the basicity of the lone pair matters is because of carbonyl activation. If a carbonyl donates a lone pair to a Lewis acid, forming a bond, the carbonyl gets a formal positive charge. If the carbonyl has a formal positive charge, it attracts electrons more strongly. In that case, nucleophiles react more easily with the carbonyl. The carbonyl is said to be activated.

Figure 3.4.1: Activation of a carbonyl via donation to a proton.

A carbonyl can be activated by the addition of a proton donor, such as HCl or other common acids.

- An activated carbonyl has a positive charge.
- Carbonyls become activated by donating a lone pair to a Lewis acid (also called an electrophile).
- Once activated, carbonyls become more reactive.
- Activated carbonyls attract nucleophiles more strongly.

Most common mineral acids are used as aqueous solutions (the familiar HCl, H_2SO_4, HNO_3, H_3PO_4 and so on). The acid is only found in the presence of water. Many of them are actually hydrates; if you take sulfuric acid,H_2SO_4, and set it to boil on a hotplate, eventually it reverts back to sulfur trioxide, SO_3, as the water boils away, and a fog appears above the beaker. Sometimes, in a laboratory reaction, it isn't helpful to have all that water around (the reasons will become clear later). Other, organic acids are sometimes used instead, such as camphorsulfonic acid or toluenesulfonic acid; these are both solids that are easy to weight out and add to a reaction, and they don't add a bunch of water to the reaction.



toluenesulfonic acid (TsOH) camphorsulfonic acid (CSA)

Figure 3.4.2: Some protic acids useful in activating carbonyls.

Carbonyls are also activated by more general Lewis acids. Often, metal chloride salts are used. These may include main group metals, such as aluminum, bismuth or indium, or transition metals such as scandium, titanium or iron.

Figure 3.4.3: Activation of a carbonyl by a metal ion.

Once the carbonyl is activated, nucleophiles are more strongly attracted to the carbon. The carbon was already partially positive, but with a full positive charge on the molecule, electrons are attracted much more strongly.

It is tempting to donate electrons from a nucleophile to the positive oxygen. However, the oxygen already has three bonds and an octet. Remember, donating a lone pair from a nucleophile means the lone pair is becoming a bond between the nucleophile and the electrophile. Giving a pair of electrons directly to the oxygen would give it four bonds and more than an octet-- it would have 10

electrons. Instead, donation to the neighbouring carbon allows the C=O pi bond to move to the oxygen and become a lone pair. The positive charge on the oxygen disappears.

- The nucleophile donates to the activated carbonyl carbon
- That event lets the pi bond become a lone pair on oxygen

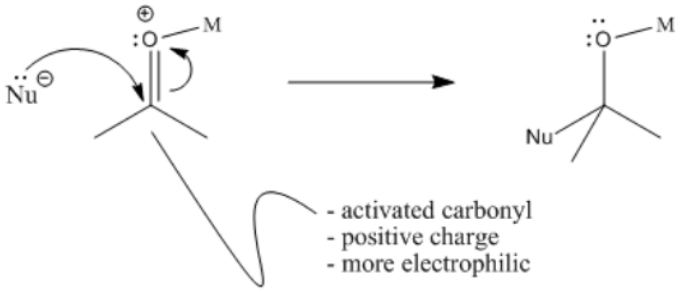
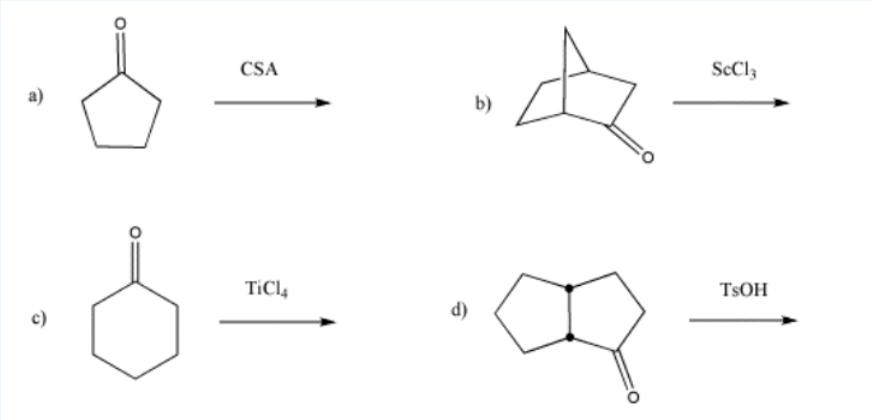


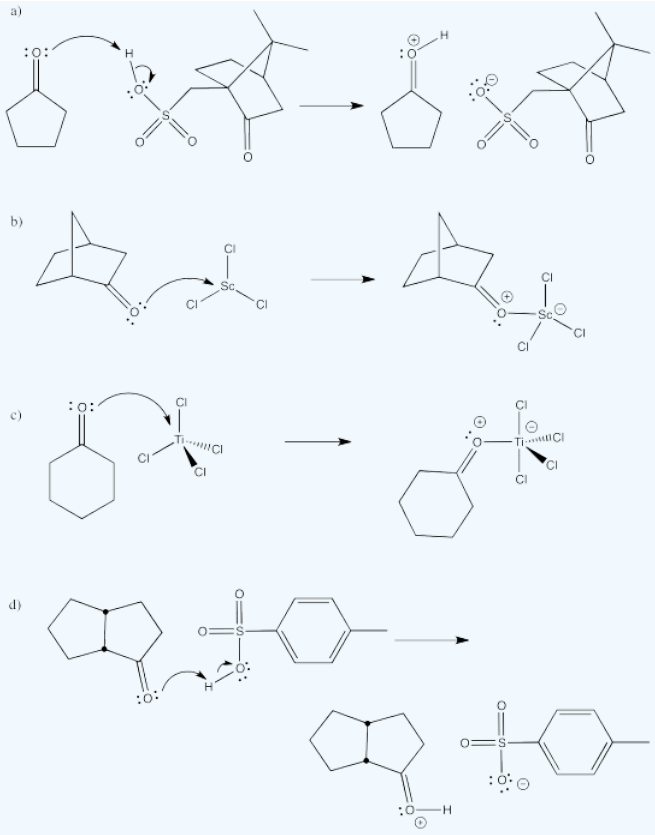
Figure 3.4.4: Donation of nucleophile to an activated carbonyl.

Exercise 3.4.1

Show, with arrows, the activation of the following carbonyls.



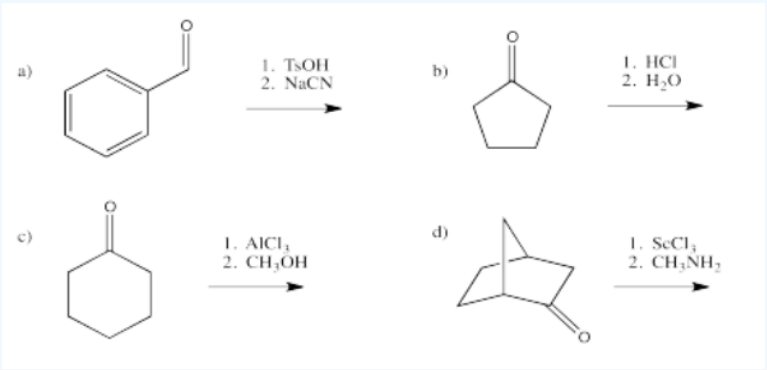
Answer



Exercise 3.4.2

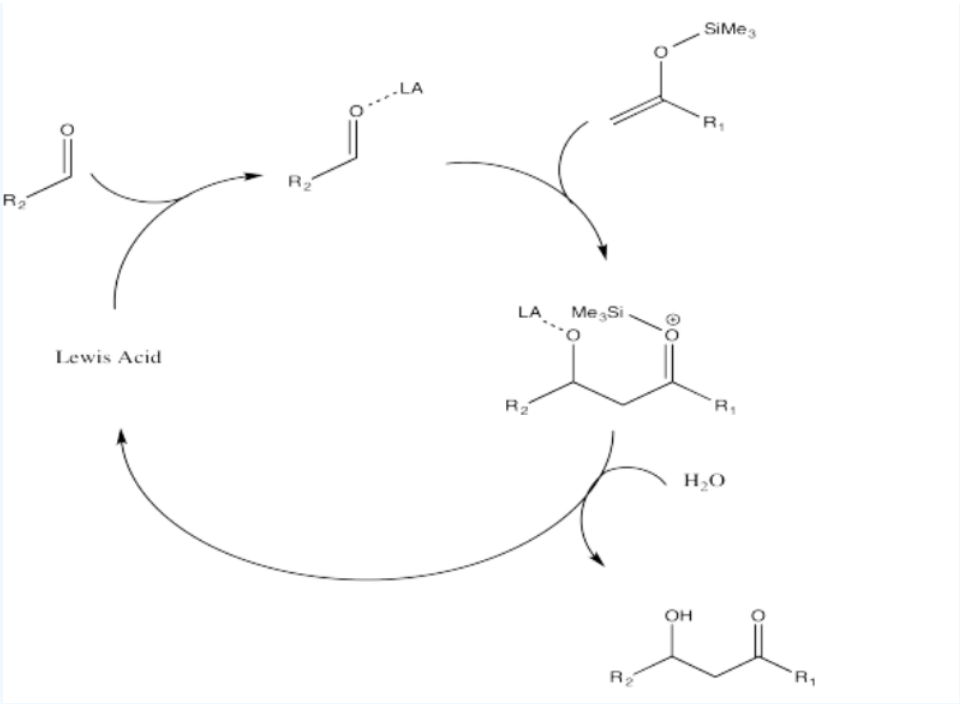
Show, with arrows, the activation of the following carbonyls, followed by donation from the nucleophile.

Answer

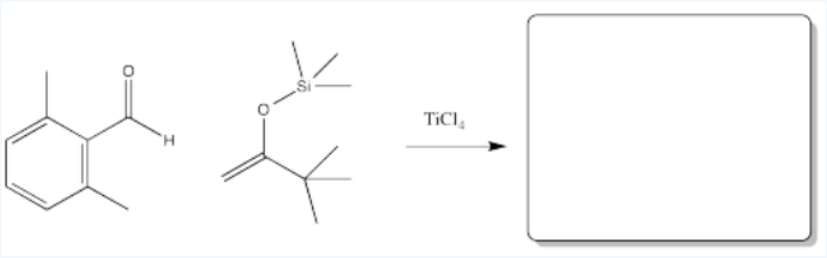


Exercise 3.4.3

Part a. Use curved arrows to denote electron flow in the following mechanism for the Mukaiyama Aldol Addition.



Part b. Using these starting molecules in Mukaiyama Aldol Addition, predict the product formed.



Answer

Add texts here. Do not delete this text first.

Exercise 3.4.4

Provide Lewis-Kekule structures for the following commonly used acids.

a) hydrochloric acid, HCl b) hydrofluoric acid, HF c) hydrobromic acid, HBr

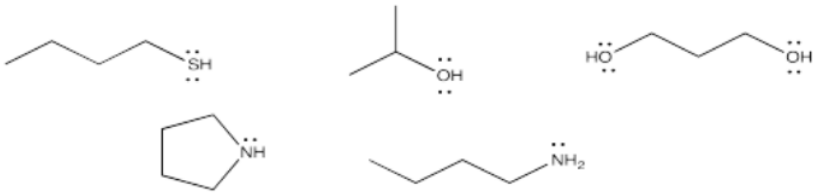
d) nitric acid, HNO_3 e) perchloric acid, $HClO_4$ f) phosphoric acid, H_3PO_4

g) formic acid, HCO_2H h) acetic acid, CH_3CO_2H i) benzoic acid, $C_6H_5CO_2H$

j) sulfuric acid, H_2SO_4 k) toluenesulfonic acid, $CH_3C_6H_4SO_3H$ l) methanesulfonic acid, CH_3SO_3H

3.5: Addition of Neutral Nucleophiles

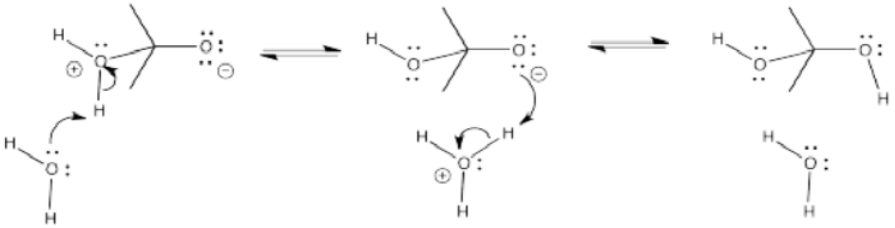
Nucleophiles do not have to be ionic, or even "semi-anionic". The basic requirement for a nucleophile is a lone pair. If a nucleophile has a lone pair, it can donate the lone pair to an electrophile such as a carbonyl. By donating a lone pair to a carbonyl, it can form a bond.



However, donation of a lone pair to a carbonyl is reversible. If there is something about the nucleophile/electrophile adduct that isn't very stable, the reaction may revert to reactants again. In the case of neutral nucleophiles, charge separation may destabilize the first-formed products of the reaction. Let's think about addition of water to propanone. Two neutral molecules, water and propanone, come together. The water donates a lone pair to the carbonyl carbon in propanone. That leaves the oxygen atom from the water with a positive charge, and the oxygen atom from the propanone with a negative charge.

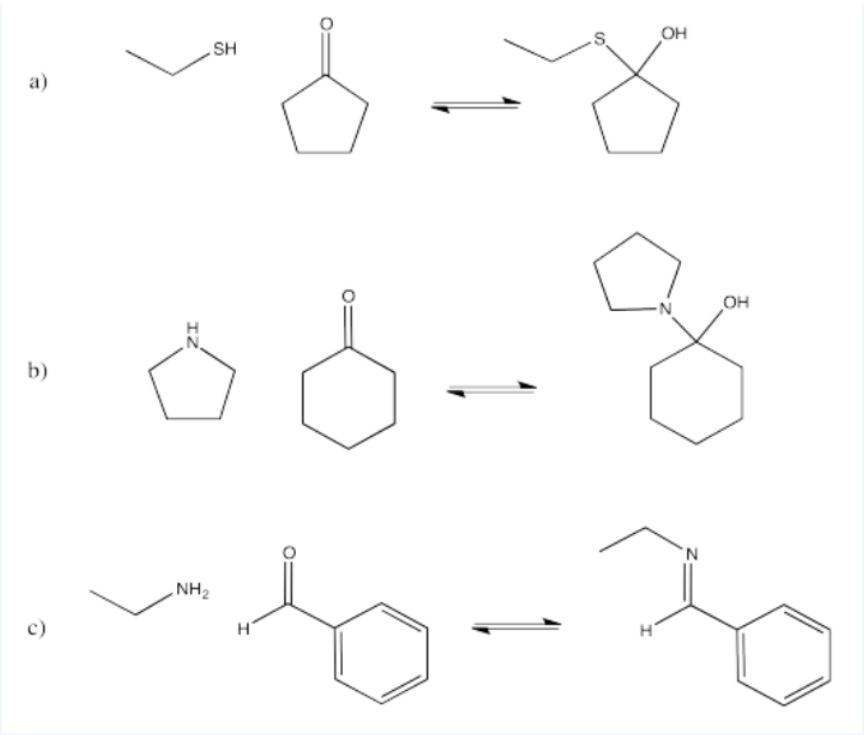
One easy way to get rid of the charge separation is for the water to leave again. That step would just be the reverse of the first one.

On the other hand, another way to solve the charge problem is to move a proton (H^+) from the positively charged oxygen to the negatively charged one. That turns out to be pretty easy to do. If that happens, a "hydrate" or a "geminal diol" forms. A geminal diol, or twin diol, has two hydroxy groups on one carbon.



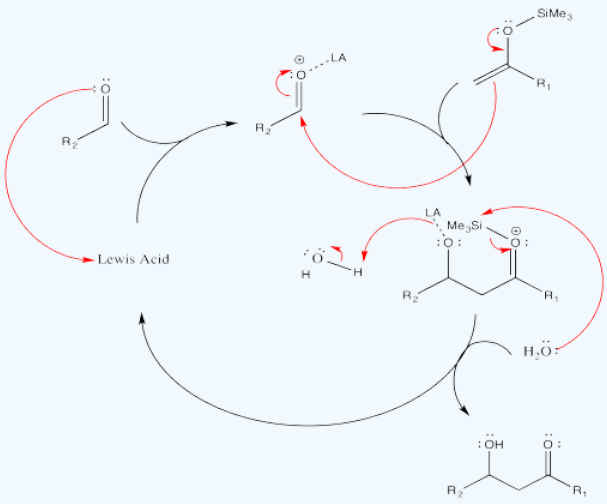
Exercise 3.5.1

In the following cases, a nucleophile donates to the carbonyl, followed by a proton transfer. Show mechanisms, with curved arrows, for each of the following reactions.

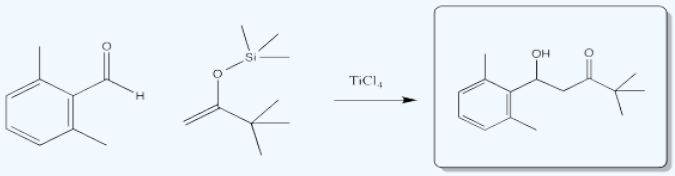


Answer

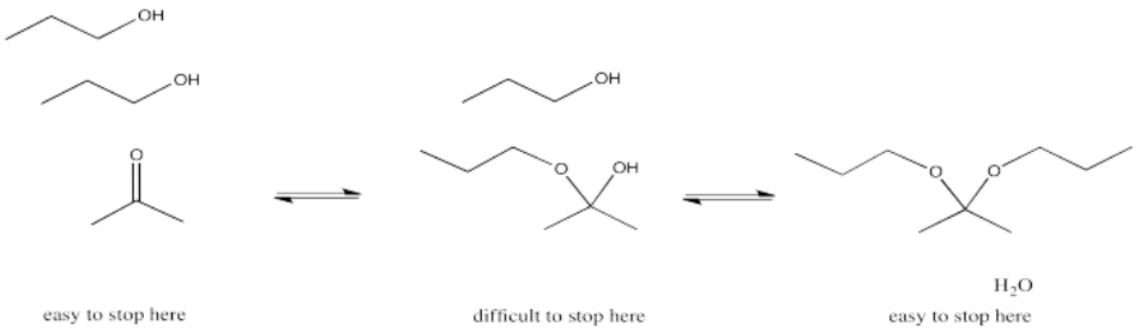
Answer a



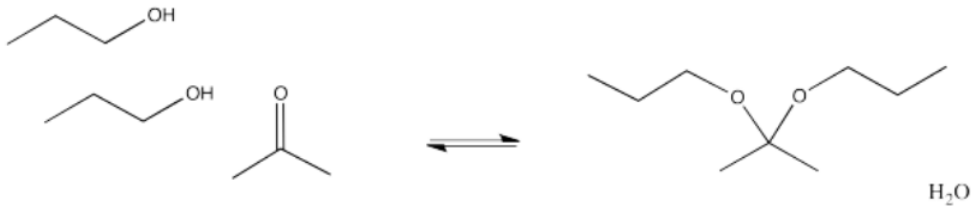
Answer b



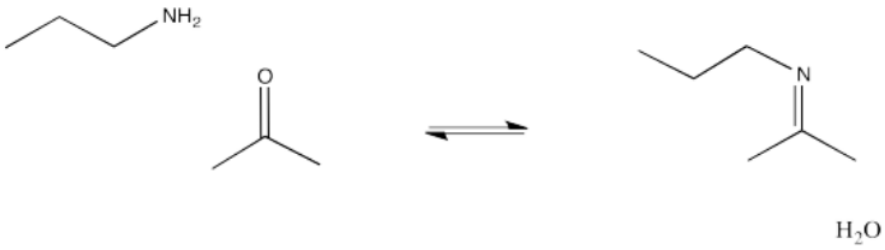
The immediate products that form from the addition of neutral nucleophiles to carbonyls turn out to be a little unstable. That's partly because they can easily revert back to reactants. It's also because there are other processes that carry the reaction away from the first-formed products and turn them into other things. For example, in most cases the reaction does not involve the simple addition of one nucleophile, but involves a second molecule of the nucleophile as well.



We will keep looking at these other processes and see where these reactions lead. In the meantime, it can be useful to know the patterns that different types of nucleophiles will usually follow. For example, addition of alcohols to aldehydes or ketones leads to the formation of ketals or acetals. Ketals or acetals have the specific chain of atoms C-O-C-O-C, in which each carbon is tetrahedral or sp^3.



On the other hand, the addition of amines leads to a very different kind of structure. Instead of adding two amine molecules into the final structure, only one amine is incorporated, and a double bond appears again. The C=O of the aldehyde or ketone is replaced with the C=N of an imine. Imines form important linkages in biological chemistry, especially in connecting small molecules to lysine side chains in proteins.



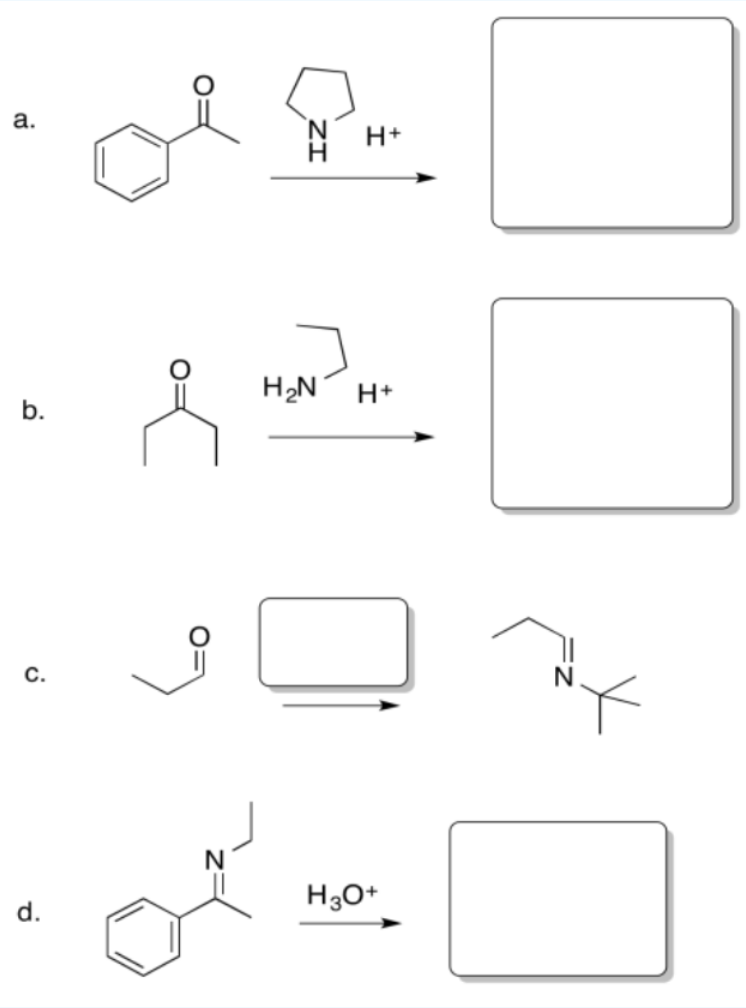
If the amine is "secondary", meaning the nitrogen is connected to two carbons instead of just one, the double bond ends up one position over. It is between the former carbonyl carbon and the one next to it, which is called the alpha position.

Note that all three of these reactions involve ultimate loss of water from the original carbonyl compound. That's a very important feature of reactions with neutral nucleophiles.

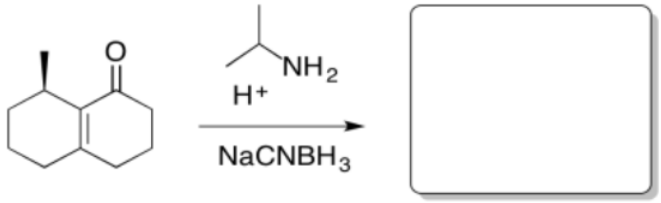
- Addition of a neutral nucleophile to a carbonyl almost always leads to loss of the original carbonyl oxygen in a water molecule.

Exercise 3.5.2

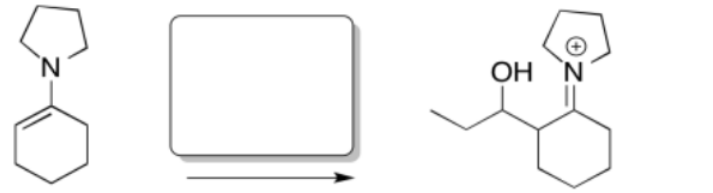
Fill in the missing reagents or products in the following reaction equations.



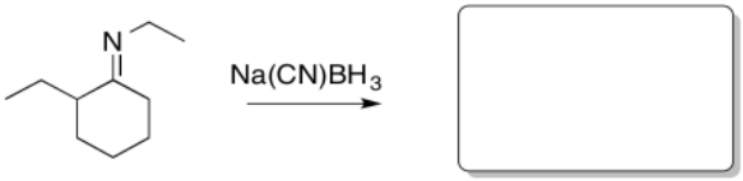
e.



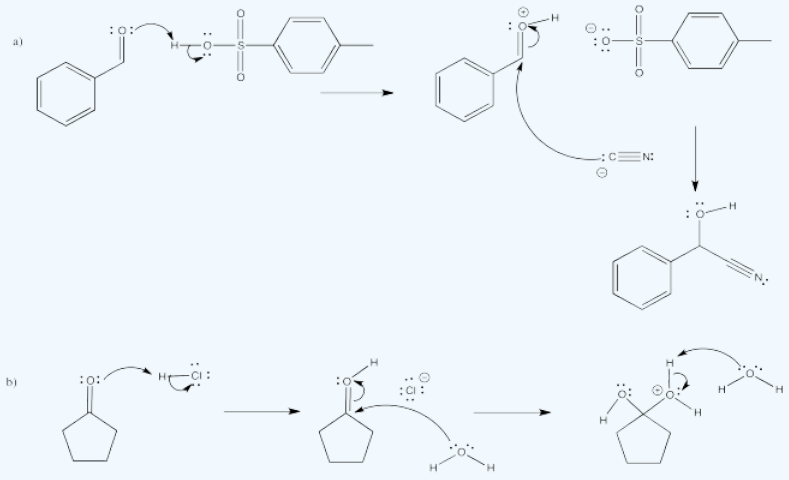
f.



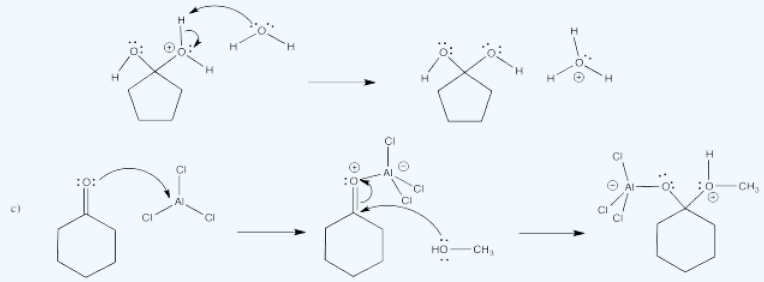
g.



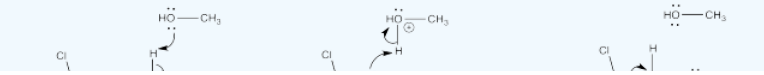
Answer

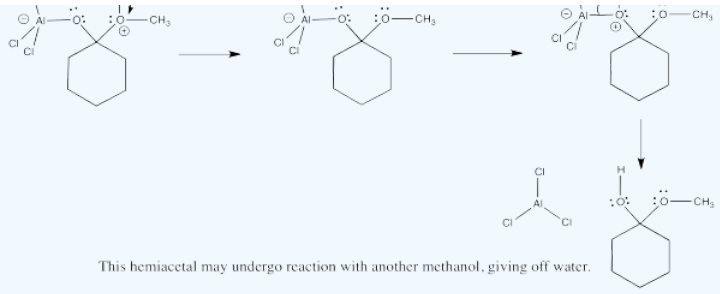


Nucleophilic donation would probably be followed by a proton transfer step (below)

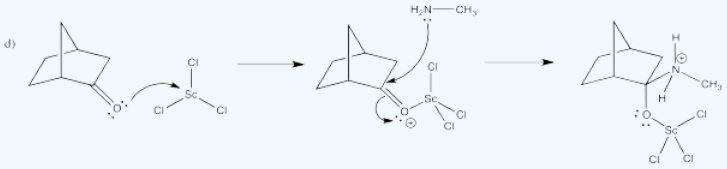


Nucleophilic donation would probably be followed by a series of other steps (below)

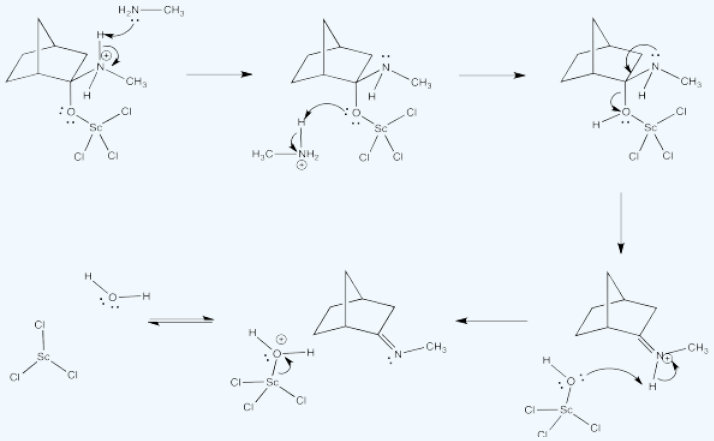




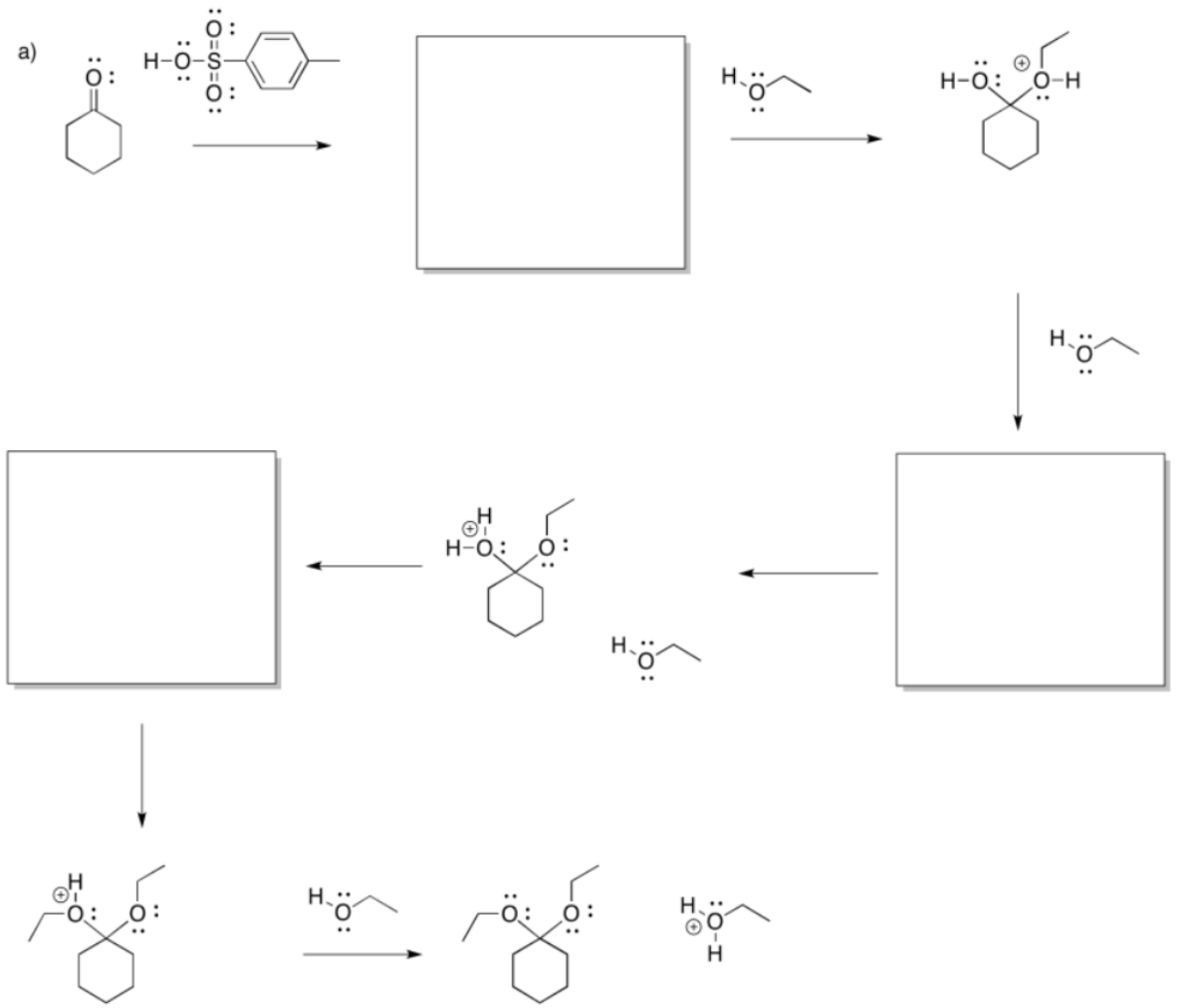
This hemiacetal may undergo reaction with another methanol, giving off water.

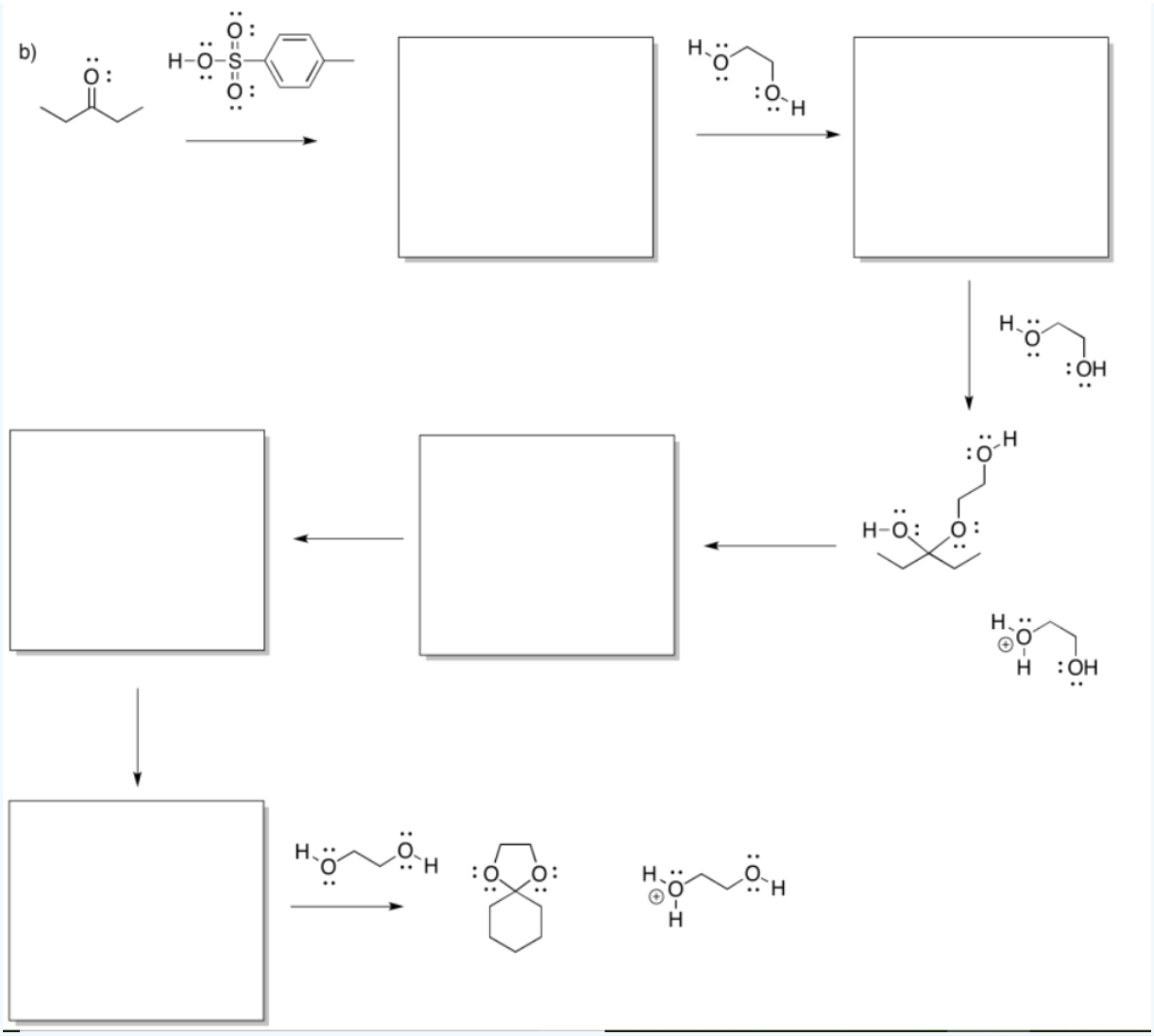


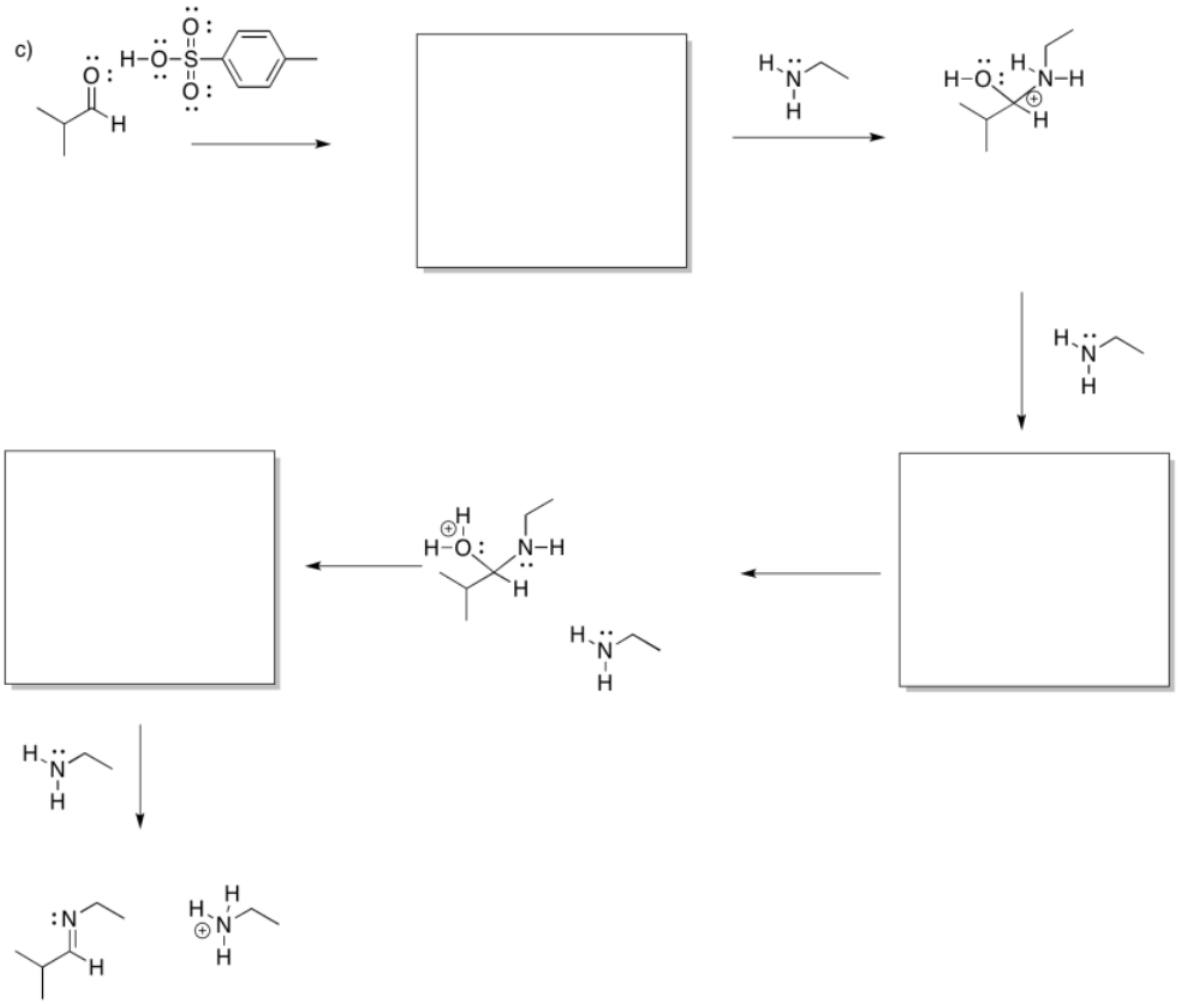
Nucleophilic donation would probably be followed by a series of other steps (below)

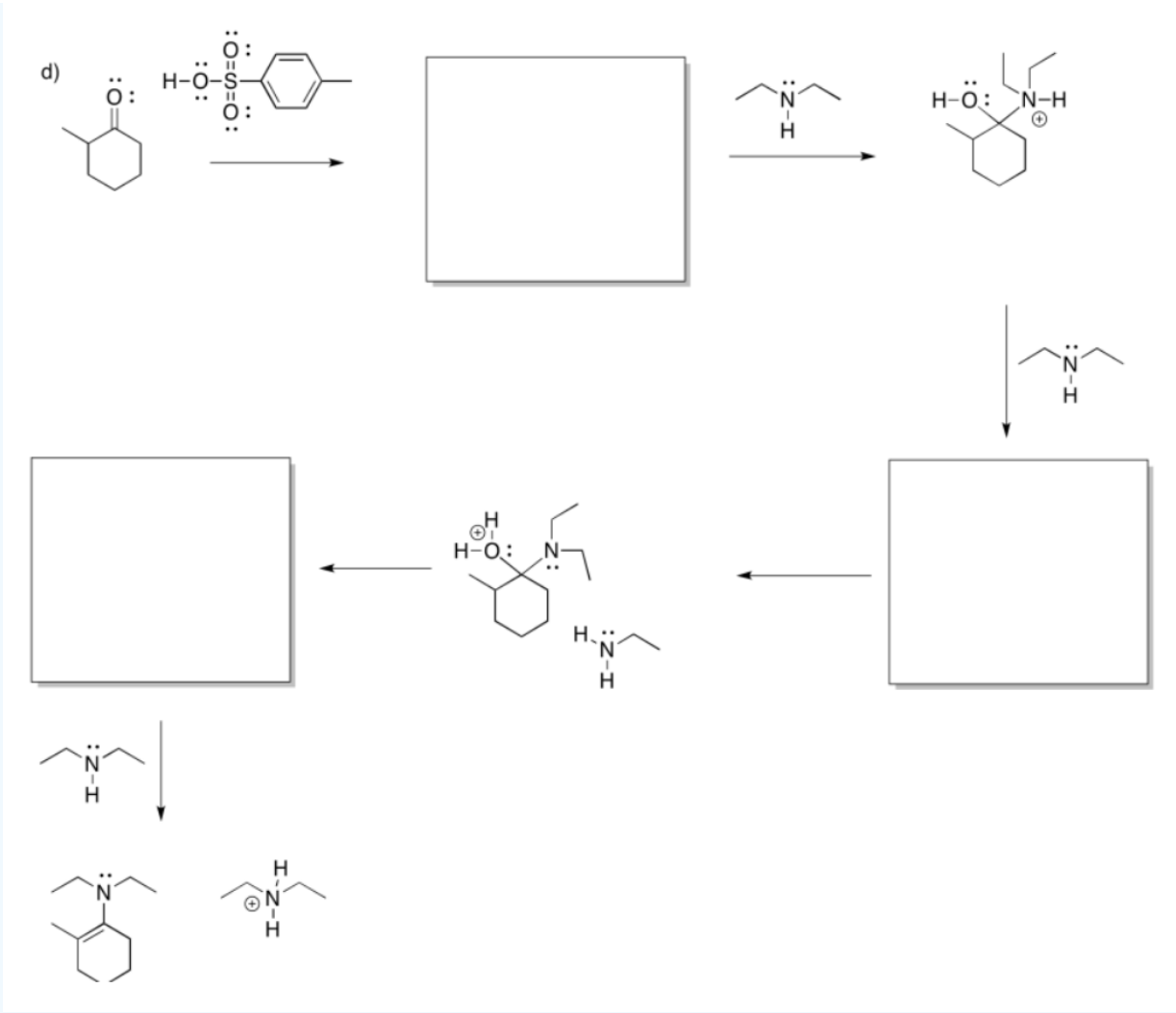


Exercise 3.5.3

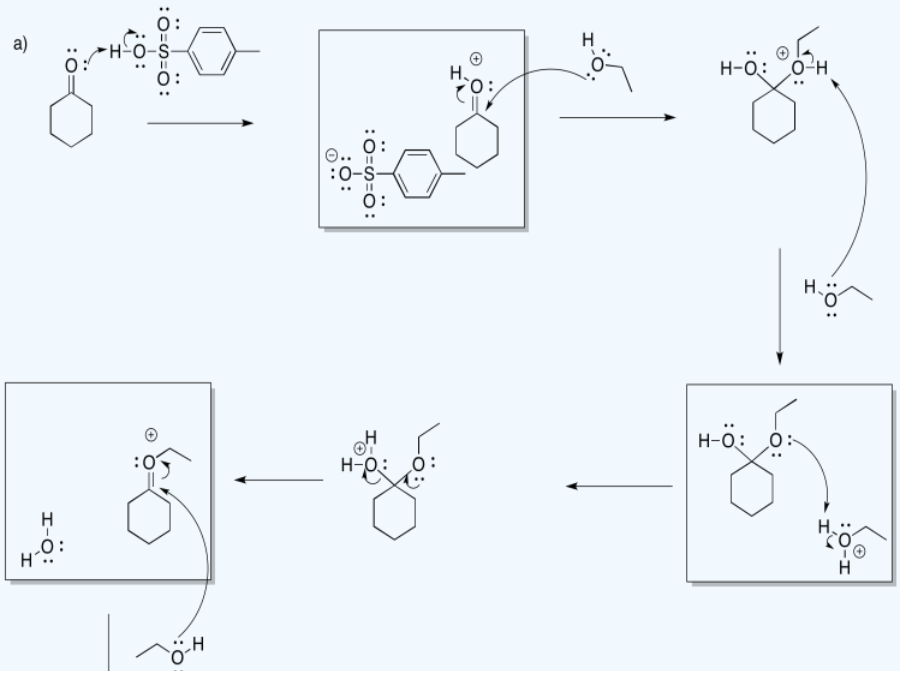


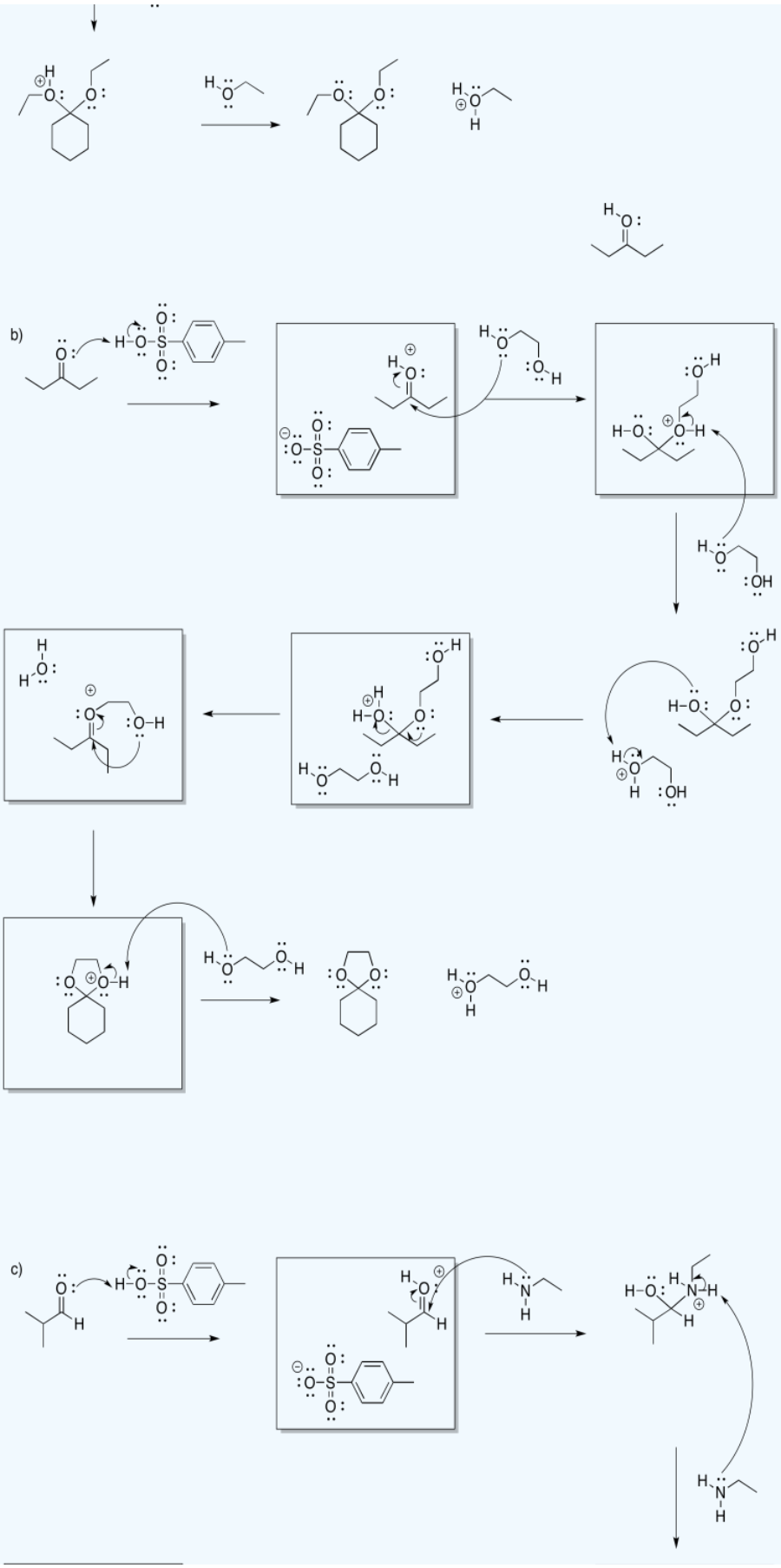


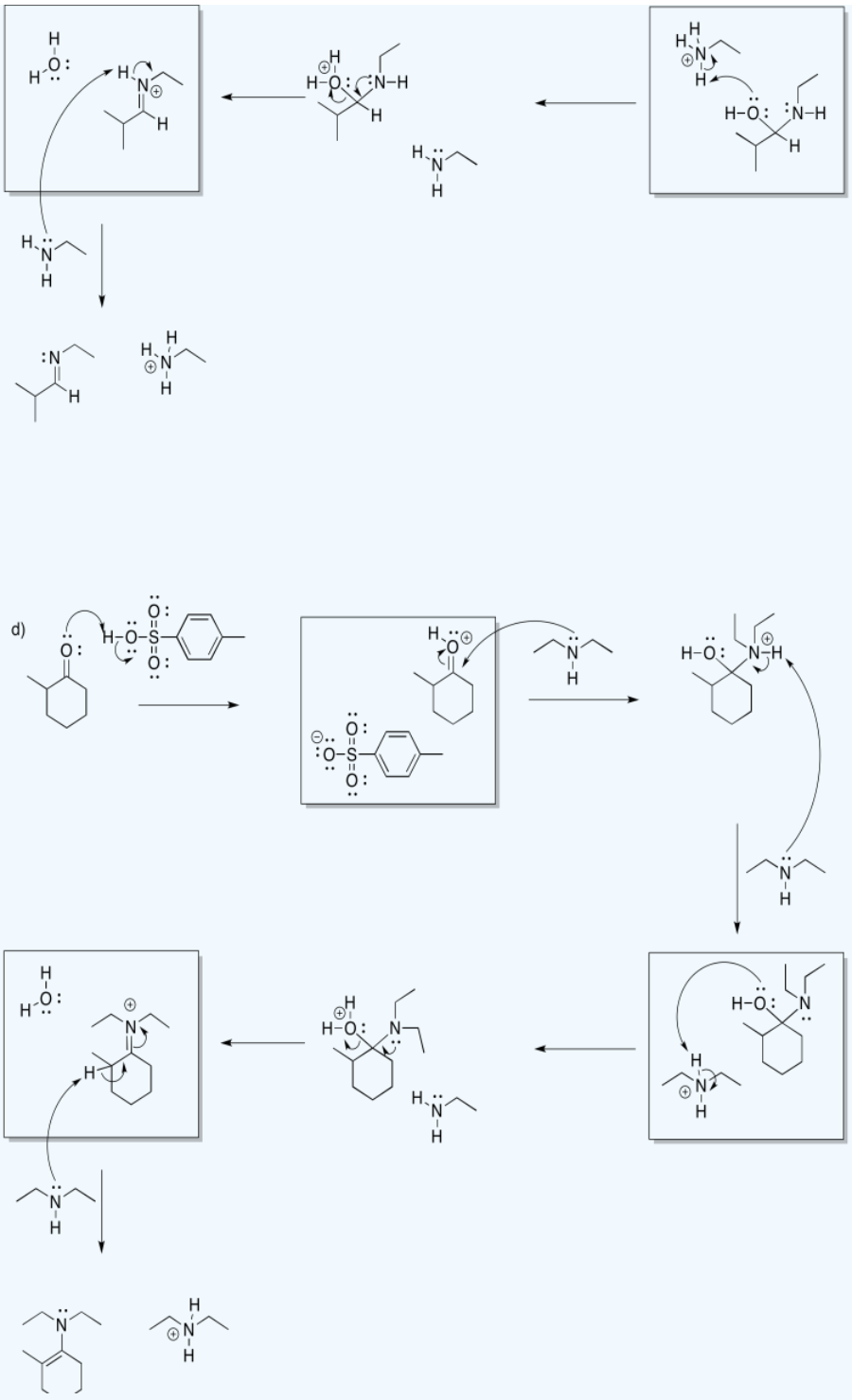




Answer





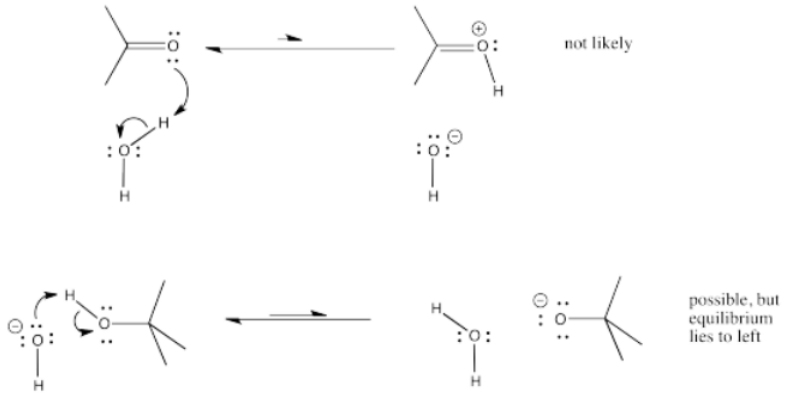


3.6: Proton Transfer in Carbonyl Addition

Proton transfer is rapid, especially if it is transferred from a very acidic position. For example, a proton can easily be transferred from a positively charged oxygen atom to a neutral oxygen (resulting in a new, neutral oxygen and a new, positive oxygen). These species would be in equilibrium with each other.

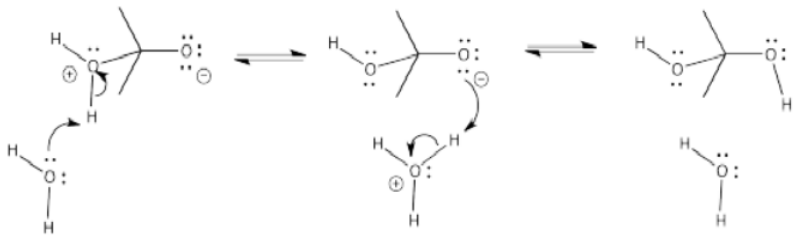
- Proton transfer is rapid.
- Protons can be transferred from more acidic to less acidic position.
- Protons can be transferred from one acidic position to another of similar acidity, although the equilibrium may not be favored.

It would not be as easy to transfer a proton from a neutral oxygen to another neutral oxygen. Sometimes, a neutral oxygen can transfer a proton to a negatively charged one, but the equilibrium will depend on the relative pKa values of the two species. In the case below, the *tert*-butoxide is a less stable anion than the hydroxide because the *tert*-butoxide is larger and requires more organization of solvent molecules around it.



It is tempting to think that a proton could be transferred directly from a cationic position to an anionic position in the same molecule. That might not occur, however. In terms of conformational analysis, the two positions might not be able to twist around and reach each other. The usual rule applies: two atoms may need to be greater than five atoms away from each other along a chain before they can reach around and make contact.

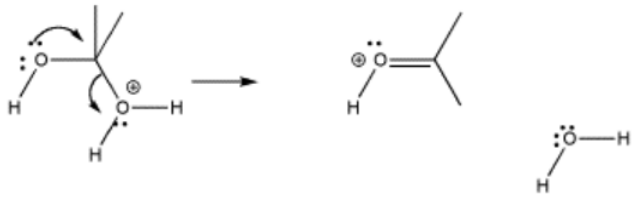
If the solvent has a lone pair, it may pick up the proton from the acidic position and drop it off on the basic position. These events are made easy by the fact that the reacting molecules are usually surrounded by many solvent molecules.



- Solvent can often act as a proton shuttle.

3.7: Pi Donation

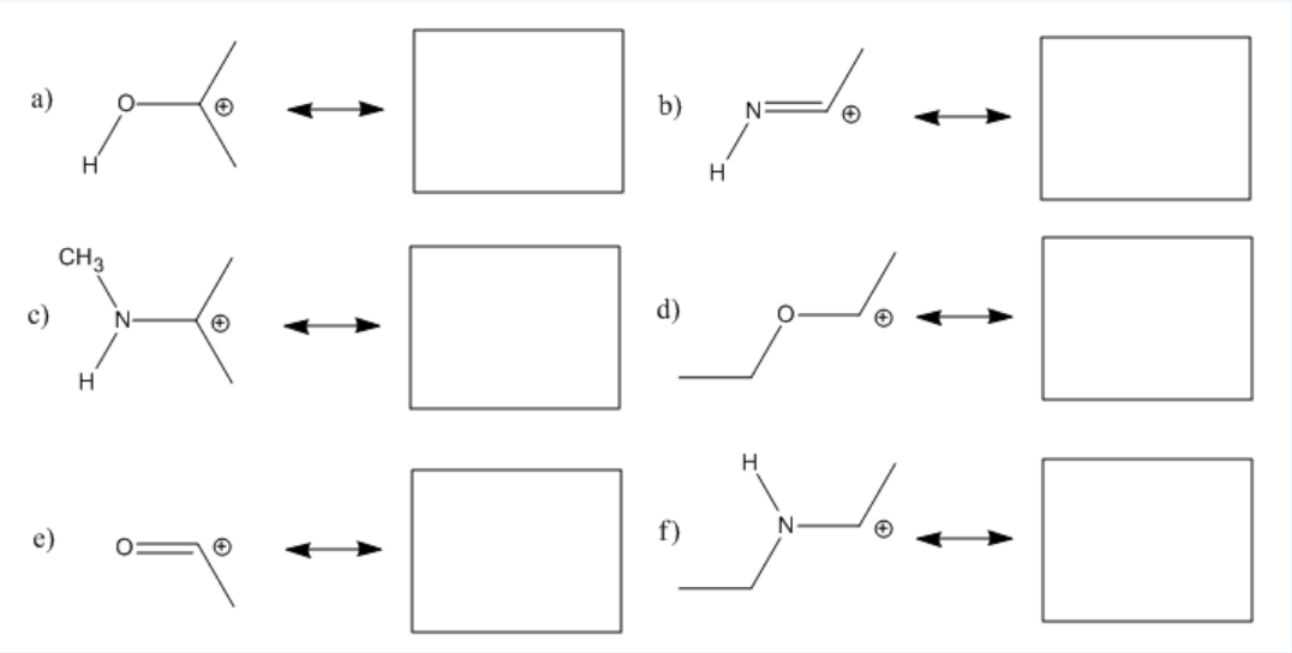
Some nucleophiles are added to carbonyls, lose a proton to drop a positive charge, and have a lone pair again. If the (former) carbonyl oxygen also has a lone pair, a potential lone-pair/lonepair repulsion problem exists. Partly for this reason, two heteroatoms bonded to one carbon often present an inherently unstable situation. These kinds of species often decompose readily via pi donation.



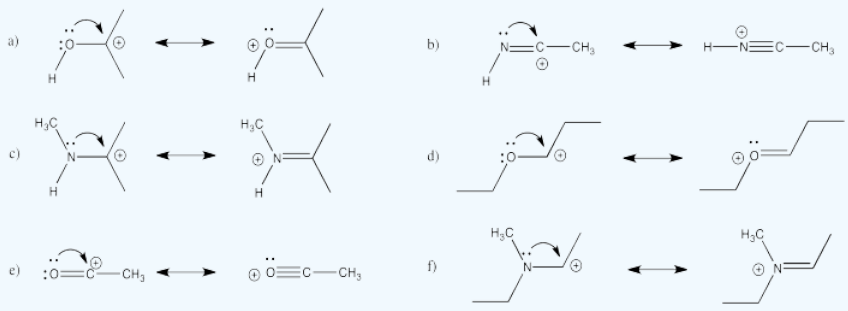
In pi donation, a lone pair on one heteroatom is donated to the carbon shared by both heteroatoms. As a result, the other heteroatom is pushed off the carbon. This event is helped if one of the heteroatoms is already protonated, so that it comes off as a neutral species.

Exercise 3.7.1

Fill in any missing lone pairs, provide curved arrows to show pi donation, and show the resonance structures that result.

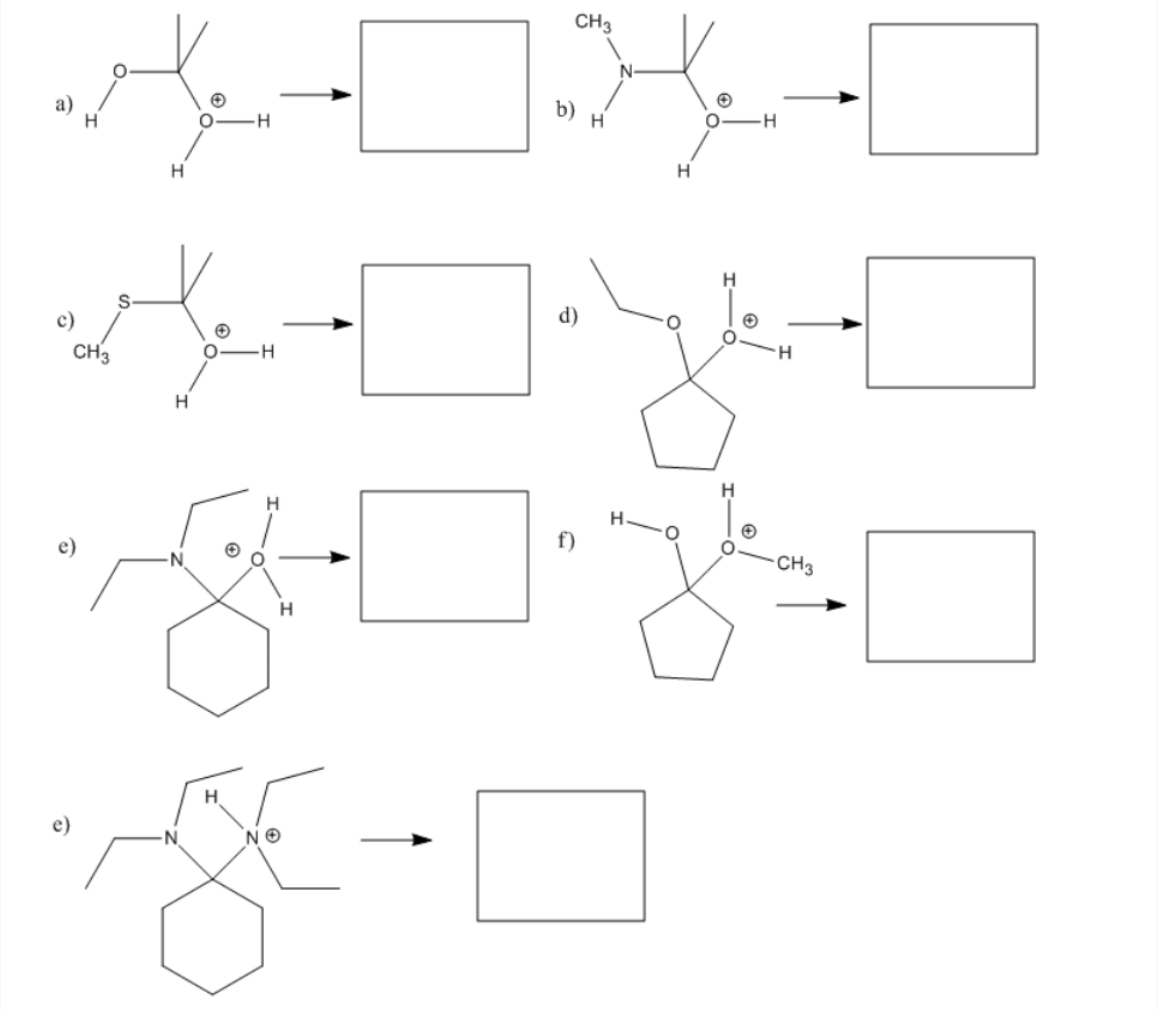


Answer

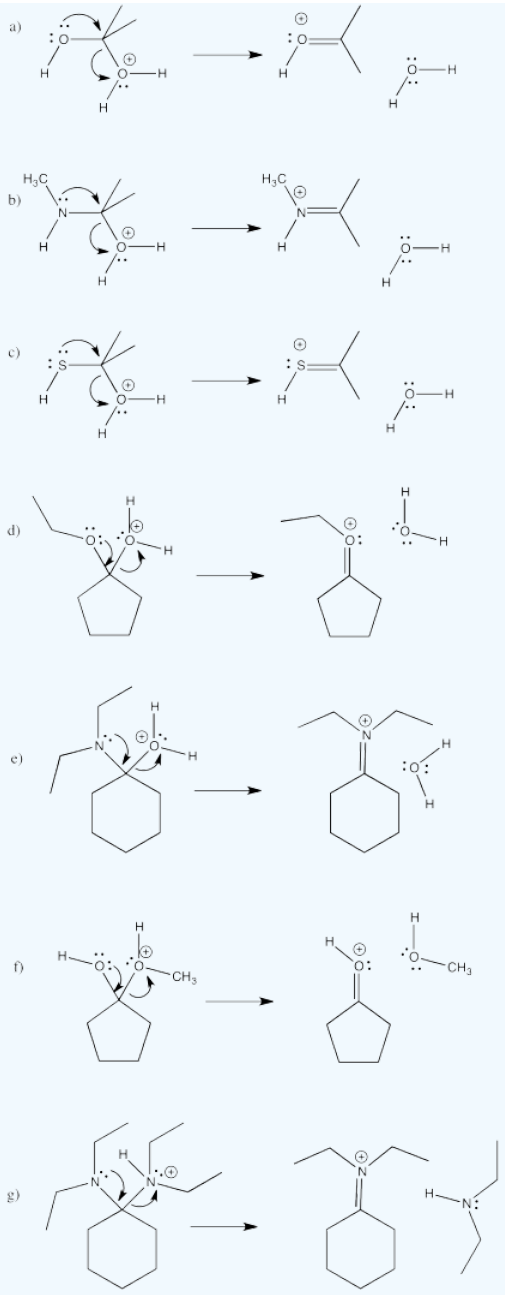


Exercise 3.7.2

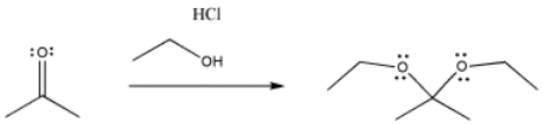
Show how each of the following species might break down into two molecules via pi donation.



Answer

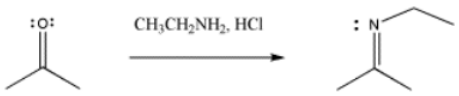


As a result of pi donation, neutral, protic nucleophiles often replace the carbonyl oxygen entirely. In effect, the nucleophile adds twice. The lone pair that is revealed after a deprotonation step adds again to the same carbon, pushing that carbonyl oxygen out of the molecule entirely. In the case of alcohol nucleophiles, a ketal or acetal results. This kind of molecule looks like two ethers that meet at one carbon. A ketal is a "masked" carbonyl; it still contains a carbon with two bonds to oxygen. However, a ketone is no longer an electrophile like a carbonyl compound.



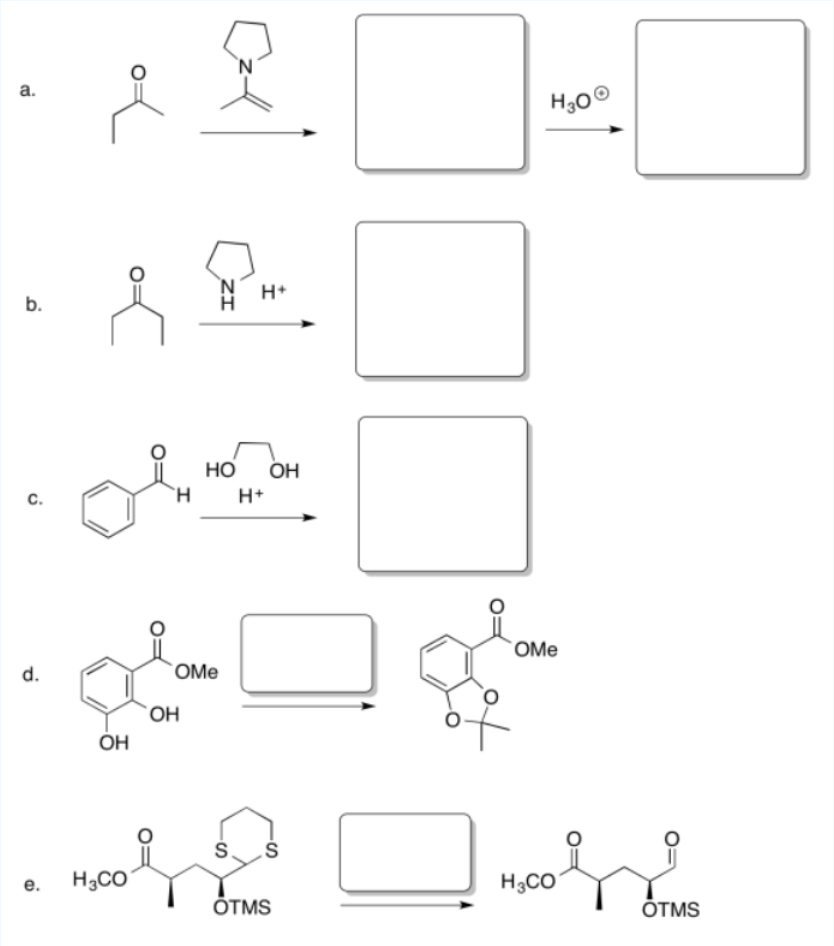
Imines also result from pi donation. If an primary amine donates to a carbonyl, it can lose its first proton to reveal a lone pair. Once that lone pair donates, pushing off the carbonyl oxygen, a second proton can be dropped to allow the nitrogen to lose its positive

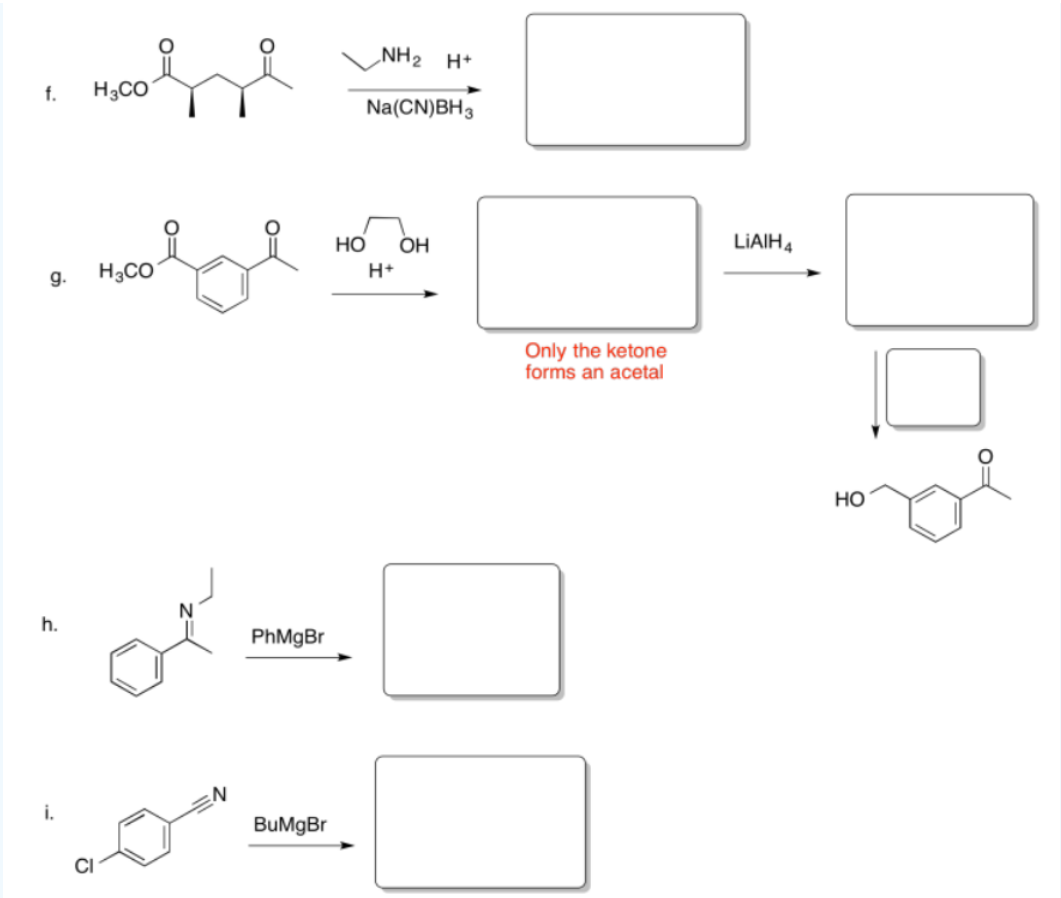
charge. Imines are similar to carbonyls in that they contain a carbon-heteroatom double bond and so they are still good electrophiles.



Exercise 3.7.3

Fill in the missing reagents and products in the following reaction schemes.





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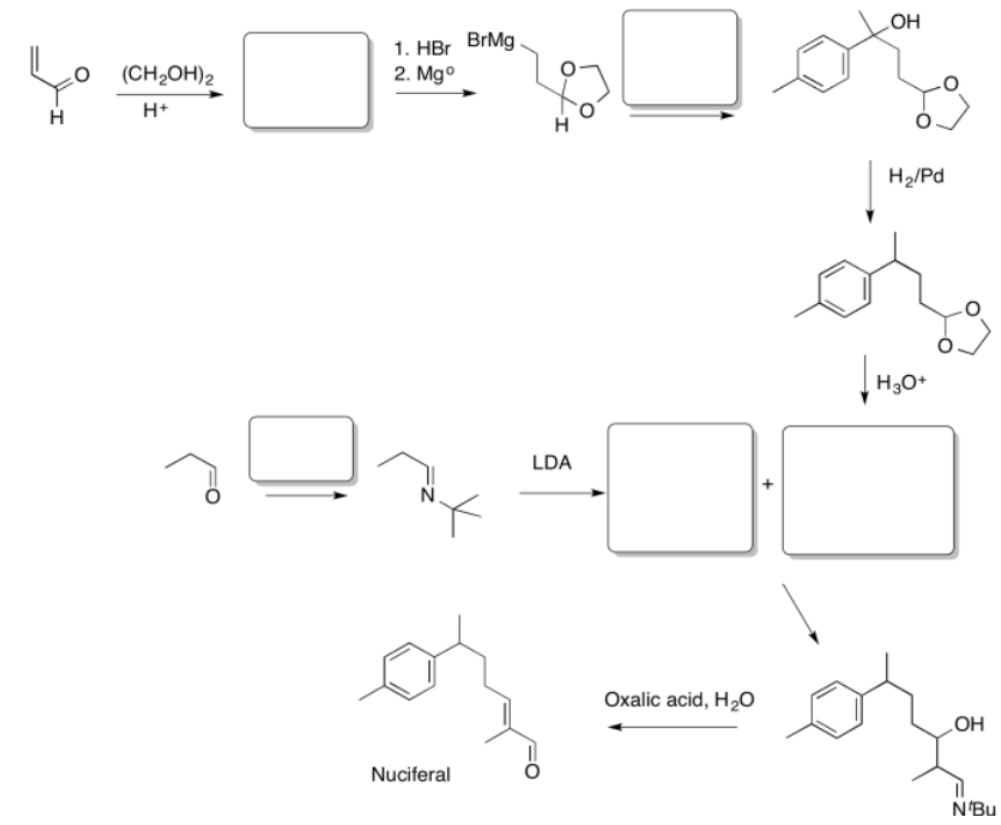

Answer

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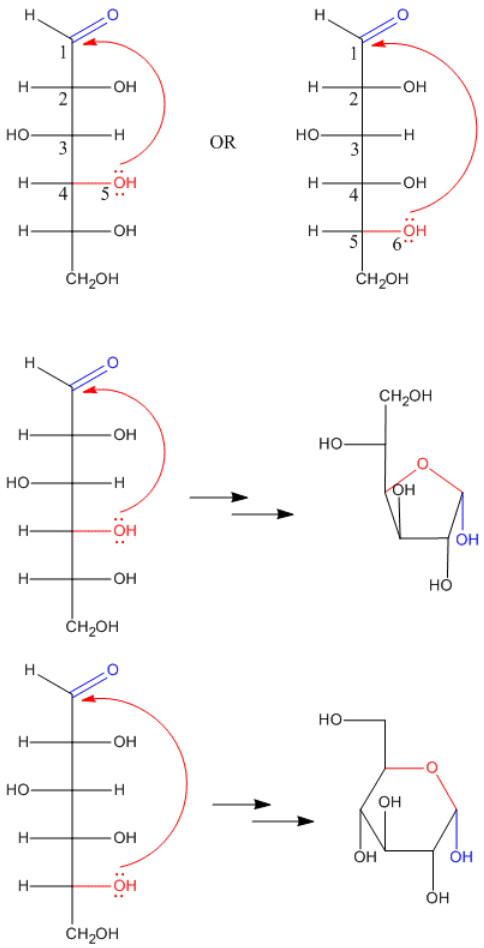
3.8: Sugars- Pyranose and Furanose Forms

Carbohydrates are an important class of biological molecules. Although their best-known role is in energy storage in the form of glucose and starch, carbohydrates play a number of other roles. For example, they lend structural support in the backbone of DNA. They aid in homebody security and defense operations by forming molecular codes on the surfaces of cells that identify whether the cell is one of our own or an intruder. They carry specialized chemical reagents into enzymes where reactions essential to life are carried out. Some of them are sweet.

The term "sugar" is often applied to any simple carbohydrate. One strict definition of a carbohydrate is a polyhydroxylated aldehyde or ketone. In general, a sugar is a molecule that contains an aldehyde or a ketone, and every carbon other than the carbonyl carbon has a hydroxyl group attached to it.

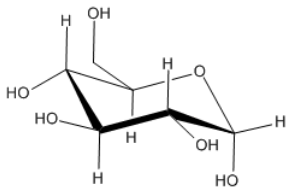
This sort of structure presents lots of possibilities for reactions. In just one molecule, we have both an electrophile (the carbonyl) and a number of nucleophiles (the hydroxyls). Can sugars react with each other? Yes. Can a sugar react with itself? Of course.

In fact, if you have seen drawings of sugars before, you might not have noticed the carbonyl. That's because the carbonyl is usually "masked" as a hemiacetal. The hemiacetal forms when a hydroxyl group along the carbon chain reaches back and bonds to the electrophilic carbonyl carbon. As a result, five- and six-membered rings are very common in sugars. Five-membered rings are called "furanoses" and six-membered rings are called "pyranoses".

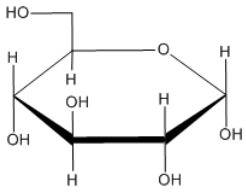


The most common way of drawing these rings are in "Haworth projections". Haworth projections don't reflect the real shape of the ring. For example, in a six-membered ring, the atoms in the ring adopt a zig-zag, up-and-down pattern in order to optimize bond angles. The chair drawing shows that relationship, but in a Haworth projection, the ring is drawn as though it were flat. Also, substituents on the atoms in the ring can be found above the ring, below the ring, or sticking out around the edge of the ring. The chair drawing or "diamond lattice projection" shows these relationships pretty well. A Haworth projection does not try to do that. Instead, it tries to depict stereochemical relationships: whether two substituents are on the same face of the ring or opposite faces of

the ring. In a diamond lattice projection, we have to keep track of whether a given substituent is in the upper or lower position at its particular site on the ring, and that requires careful attention. In a Haworth projection, substituents are simply drawn straight up or straight down. Because there are many chiral canters in sugars, and becuase two sugars can differ by just one chiral center, Haworth projections make it easier to tell different sugars apart.



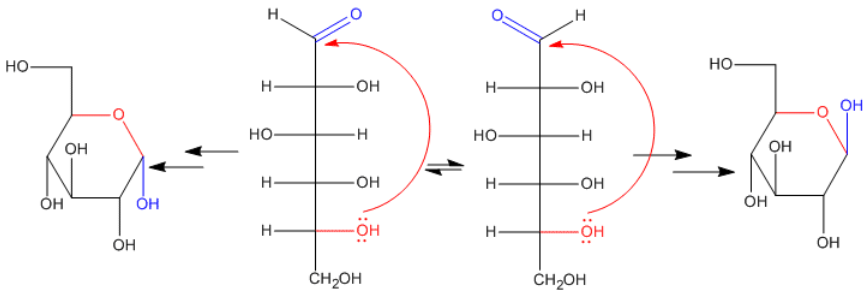
chair projection



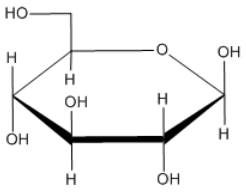
Haworth projection

When an open-chain sugar cyclizes by forming a hemiacetal, it forms a new stereocenter. Because the carbonyl carbon is trigonal planar, the hydroxyl group can approach it from either face. There is nothing to distinguish one face from the other, and so approach from either face is equally likely. That means that two different stereochemical configurations can form at the hemiacetal carbon: *R* and *S*.

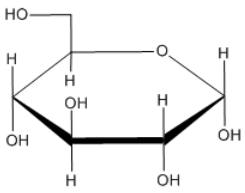
In sugar chemistry, these two isomers are named a different way: alpha and beta. To distinguish these two designations, you need to look at the Haworth projection. In a Haworth projection, the lower edge of the ring is read as being nearer to you. The upper edge is read as being farther away. Remember, that's how we usually read a chair structure, too. However, in a Haworth projection, we have to orient the ring in a specific way. The hemiacetal carbon is always placed at the right edge of the drawing. In addition, we always keep the oxygen atom on the back edge of the ring (i.e. the upper edge of the drawing). That means the ring oxygen in a Haworth projection is always found in the upper or upper right part of the drawing, with the hemiacetal carbon directly beside it to the right.



If we have the Haworth projection, we can designate whether we have the alpha or beta from by seeing whether the hydroxy part of the hemiacetal points up or down. If it is down like the ants, we have an alpha isomer. If it is up like the butterflies, we have a beta isomer.



β isomer



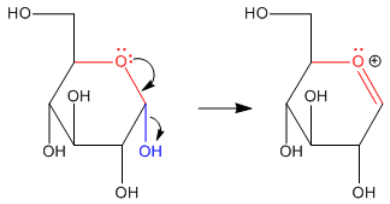
α isomer

Because the hemiacetal carbon can adopt either of two configurations in a ring, it is given a special name. It is called the anomeric position.

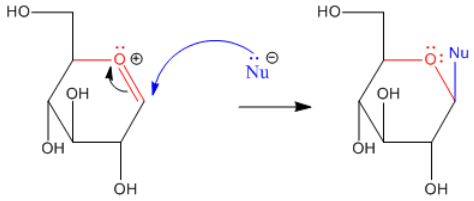
3.9: The Anomeric Center

When a sugar cyclizes via donation of a hydroxy lone pair to the carbonyl, it forms a "hemiacetal". We have already seen that hemiacetals are unstable with respect to further substitution. Pi donation from an oxygen in the hemiacetal can displace the other oxygen. A second nucleophile can then donate to the pseudo-carbonyl that results.

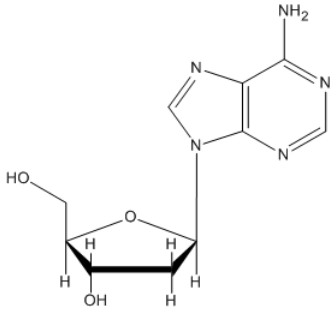
The hemiacetal position in the sugar is called the anomeric center. The anomeric center is special for two reasons. First, as you have already seen, the anomeric center is a chiral center. This new center can form with either of two configurations. The sugar, which is already chiral, can become either of two diastereomers when it cyclizes. Second, the anomeric center is a site of enhanced reactivity in the sugar, in terms of substitution of the carbonyl.



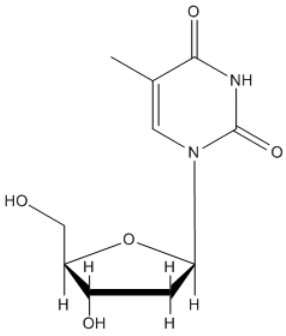
Anomeric reactivity involves pi donation from one oxygen to push off the other oxygen. This mode of reaction should be familiar. The C=O+ unit that forms resembles a carbonyl. Furthermore, the positive charge on the oxygen brings to mind an activated carbonyl. This position is especially attractive for nucleophiles.



It isn't an accident that in many sugar-containing biomolecules, substituents are found at the anomeric center. For example, nucleosides sub-units found in DNA and RNA are all substituted at this position. A number of other biological agents contain this motif as well.



adenosine

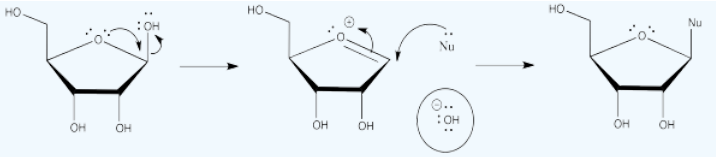


thymosine

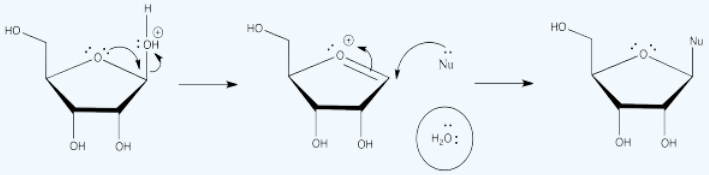
Exercise 3.9.1

Substitution at the anomeric position can be accelerated if a proton source is available. Show why.

Answer



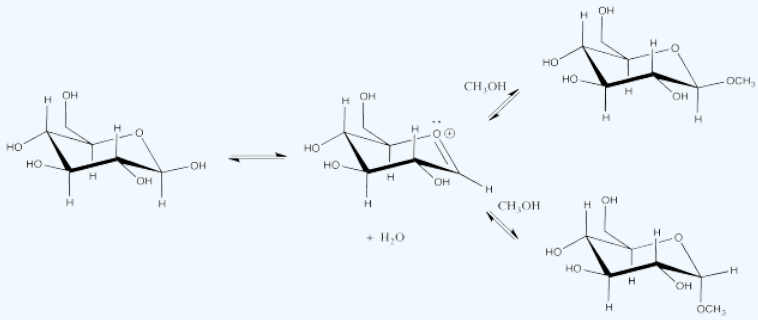
The leaving group in the above reaction is a reactive hydroxide ion, but if the oxygen is protonated, the leaving group is a stable water molecule.



Exercise 3.9.2

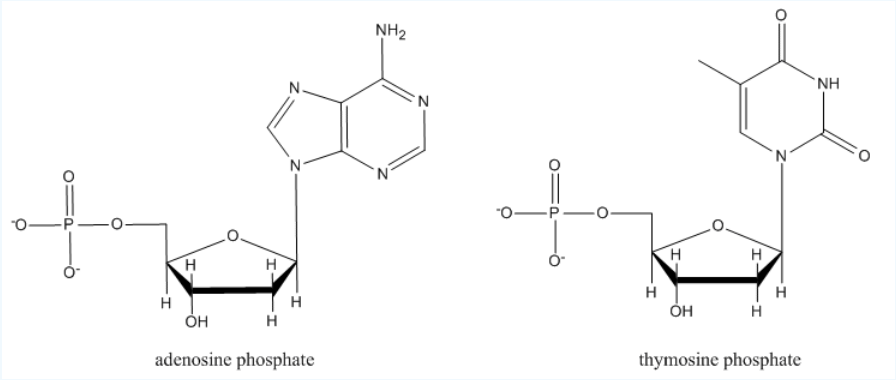
Show the stereochemical results of substitution at the anomeric center of glucose with methanol.

Answer



Exercise 3.9.3

Nucleotides, which form DNA and RNA chains, are just like nucleosides, but they all have a phosphate at a specific position. Explain what is special about this position that could make it form a phosphate more easily than the other hydroxyl sites.



adenosine phosphate

thymosine phosphate

Answer

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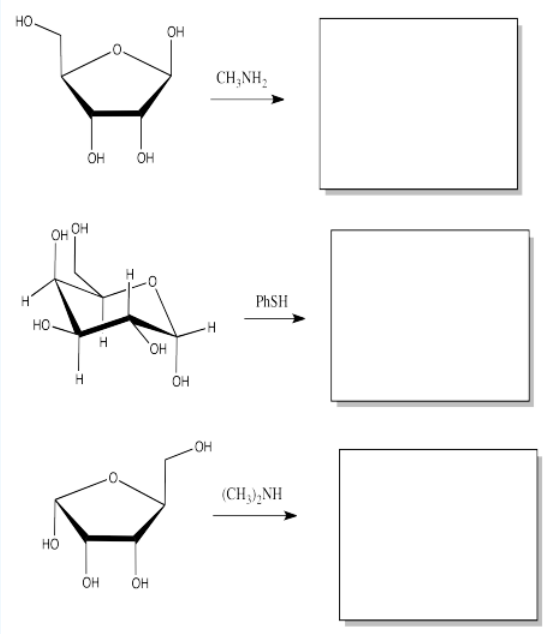
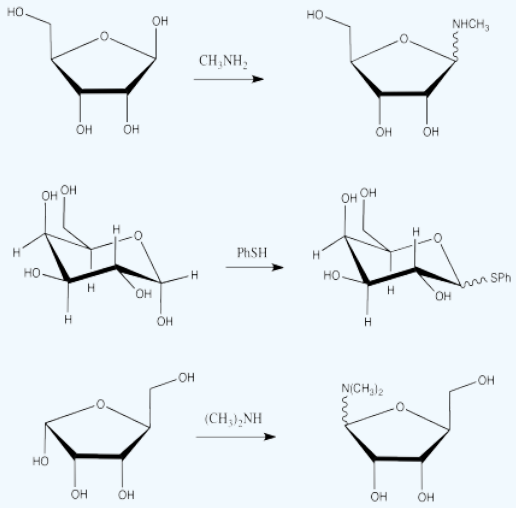
Exercise 3.9.4

Show the products of the following substitution reactions.



Answer

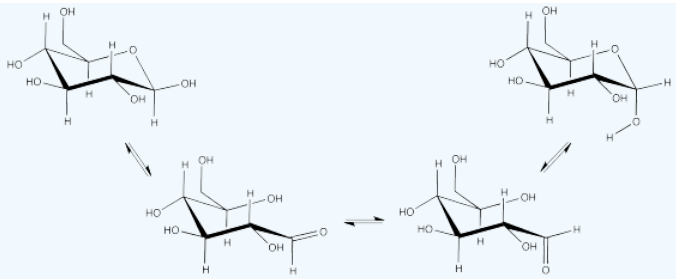


Although sugars contain a number of chiral centers, characterizing them by polarimetry is complicated. Optical rotation measurements are done in solution, in a polarimetry cell. Polarimetry is always a little bit complicated, because the optical rotation varies with the concentration of the solution and the length of the polarimetry cell. When a pure enantiomer of a sugar such as alpha-D-glucose is dissolved, usually in water, its optical rotation also varies with time. In other words, the reading keeps changing, eventually settling out far from the initial value. That means care must be taken in measuring this information, and in interpreting the data.

Exercise 3.9.5

Show why alpha-D-glucose would exhibit a changing optical rotation value after being dissolved.

Answer



Exercise 3.9.6

Suppose a one gram sample of alpha-D-glucopyranose is dissolved in 1 mL of water and its optical rotation is measured in a a 1 dm cell. Initially, a value of 100 degrees is recorded. After several hours, the value has stopped changing, and is 48 degrees.

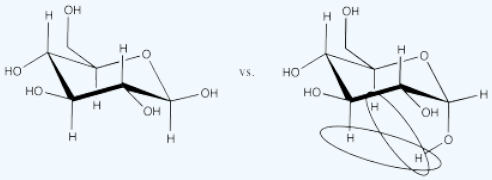
The experiment is repeated with beta-D-glucopyranose.

a. What can you predict about the initial value with beta-D-glucopyranose?
b. What can you predict after several hours?

Exercise 3.9.7

In water, alpha-D-glucopyranose predominates over the beta form in solution. Explain why.

Answer

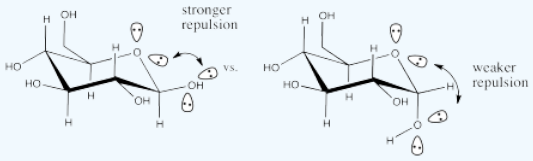


Exercise 3.9.8

In less polar solvents (compared to water) such as dichloromethane, beta-D-glucopyranose predominates over the alpha form. This phenomenon is thought to result from the influence of lone pair-lone pair repulsion.

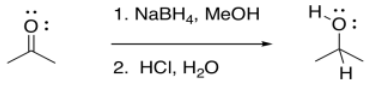
a. Show why this factor might favor one isomer over the other.
b. Show why this factor is less important in water.

Answer



3.10: Biological Reduction

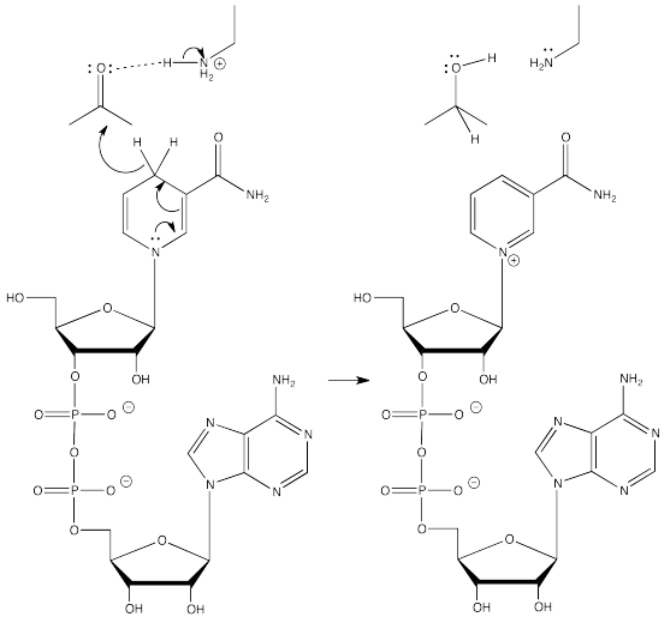
Addition to a carbonyl by a semi-anionic hydride, such as $NaBH_4$, results in conversion of the carbonyl compound to an alcohol. The hydride from the BH_4^- anion acts as a nucleophile, adding H^- to the carbonyl carbon. A proton source can then protonate the oxygen of the resulting alkoxide ion, forming an alcohol.



Formally, that process is referred to as a reduction. Reduction generally means a reaction in which electrons are added to a compound; the compound that gains electrons is said to be reduced. Because hydride can be thought of as a proton plus two electrons, we can think of conversion of a ketone or an aldehyde to an alcohol as a two-electron reduction. An aldehyde plus two electrons and two protons becomes an alcohol.

Aldehydes, ketones and alcohols are very common features in biological molecules. Converting between these compounds is a frequent event in many biological pathways. However, semi-anionic compounds like sodium borohydride don't exist in the cell. Instead, a number of biological hydride donors play a similar role.

NADH is a common biological reducing agent. NADH is an acronym for nicotinamide adenine dinucleotide hydride. Insetad of an anionic donor that provides a hydride to a carbonyl, NADH is actually a neutral donor. It supplies a hydride to the carbonyl under very specific circumstances. In doing so, it forms a cation, NAD^+. However, NAD^+ is stabilized by the fact that its nicotinamide ring is aromatic; it was not aromatic in NADH.



3.11: Carbonyls in Biology

Organic compounds are a broad class of compounds that got their name because they were originally found in living, or organic, matter. Physicians during the Renaissance and afterward strove to develop new medicines by extracting "active principles" from plants that were known to have medicinal properties. The same practice remains the most common method by which pharmaceutical companies develop medicines today.

Carbonyls are organic compounds that contain C=O bonds; that is, they contain double bonds between carbon and oxygen. (The word is pronounced car-bow-KNEEL.) This group of compounds is probably the most important single class of organic molecules. They can be divided into two classes. There are simple carbonyls, in which the carbon of the C=O bond is attached to other carbons, or possibly to hydrogens. There are also carboxylic acid derivatives, or carboxyloids, in which the carbony carbon is attached to a "heteroatom": an atom other than carbon or hydrogen, such as oxygen, nitrogen, sulfur, or a halogen.

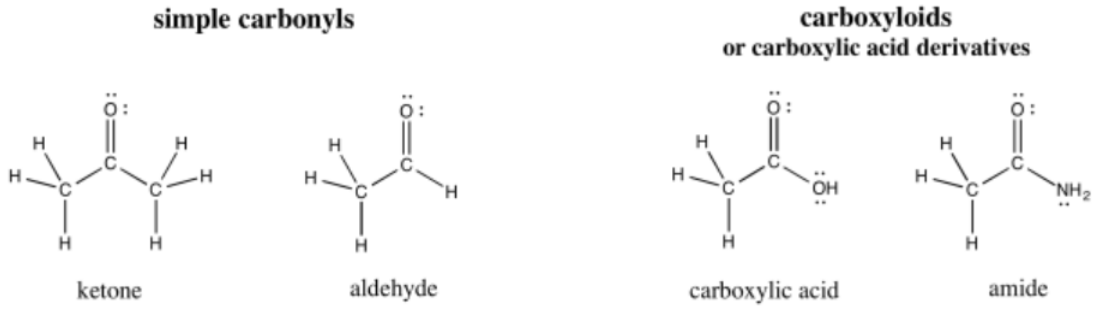


Figure 3.11.1: Some carbonyl compounds

Carbonyl compounds are very common in biological chemistry. Classes of compounds that contain the C=O bond include amides (found in proteins & peptides, used as signaling molecules and to help catalyze and guide reactions), aldehydes and ketones (found in carbohydrates, which play structural roles in cellulose, starch and DNA, for example) and esters (found in fats that form cell membranes, among other things). Understanding the reactivity of these bonds will help you to learn about many biological processes, as well as other transformations that are important in human society.

Common clusters of atoms, such as the H-C=O group in an aldehyde or the HO-C=O group in a carboxylic acid, are called "functional groups".

The amino acids are some of the fundamental building blocks of life. Fundamentally, they are carbonyl compounds.

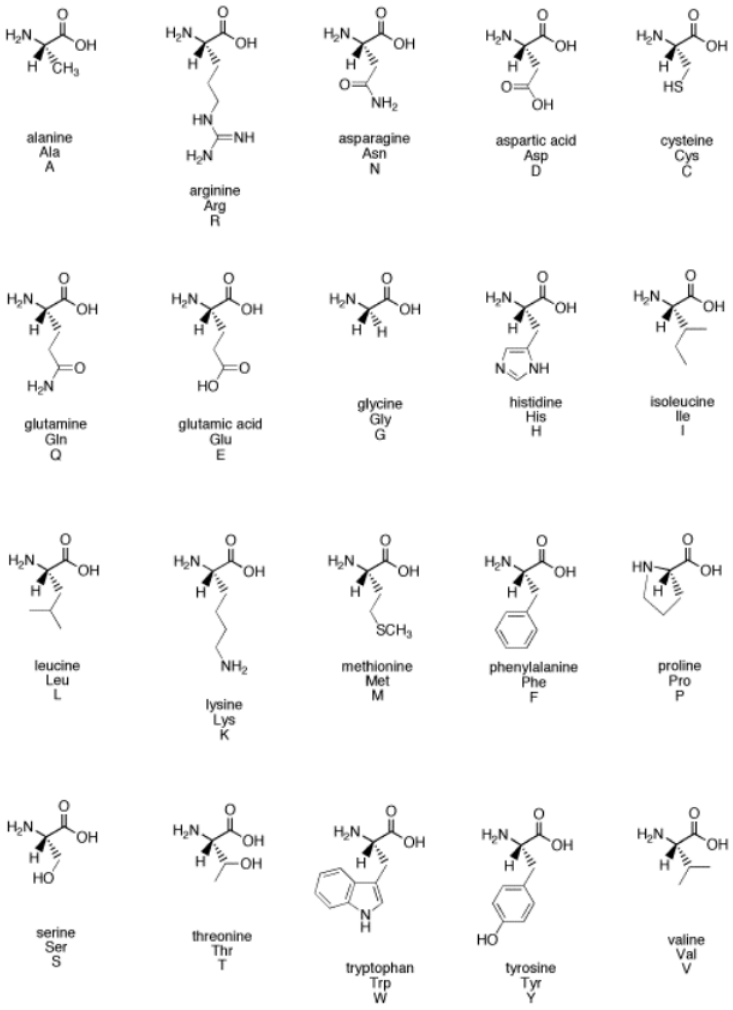


Figure 3.11.2 An alphabet of amino acids illustrates how common carbonyls are in biological chemistry.

Exercise 3.11.1

What functional groups contain carbonyls in the family of amino acids illustrated above?

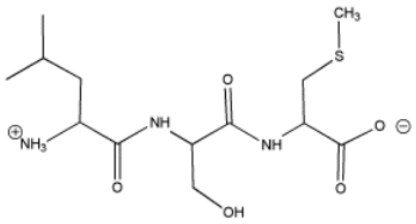
Answer

The HO-C=O or CO_2H group present in all of the amino acids is called a carboxylic acid.

An additional carboxylic acid is present in aspartic acid and glutamic acid.

The H_2N-C=O or $CONH_2$ group present in asparagine and glutamine is called an amide.

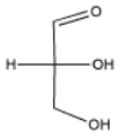
Amino acids are connected together to form peptides. Peptides are "polymers", which means they are very large molecules made up of small, repeating units.



a tripeptide

Figure 3.11.3: A tripeptide, composed of three amino acids. See if you can identify the three separate sub-units.

Carbohydrates are another important class of biomolecules. They also contain carbonyl groups. Like amino acids, there are many variations of carbohydrates, and they are sometimes found bound together to form polymers. Of course, carbohydrates are important in energy storage. In plants, they also provide structural strength, helping to form cell walls.

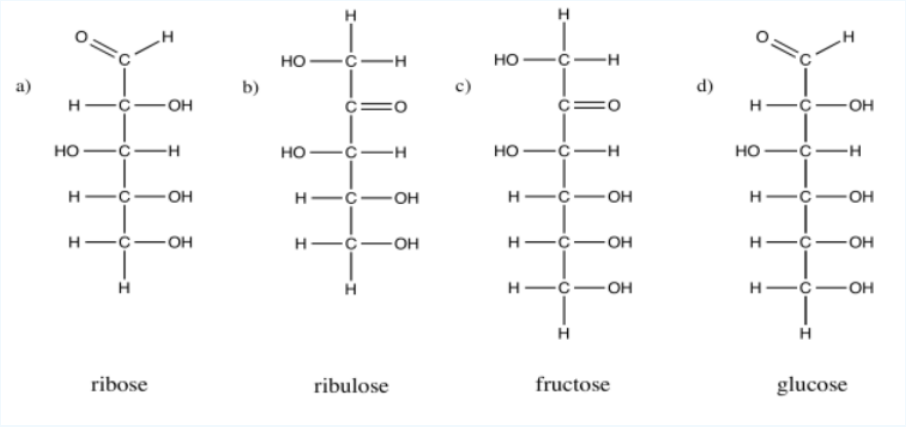


glyceraldehyde

Figure 3.11.4: A simple carbohydrate, glyceraldehyde.

Exercise 3.11.2

Identify which group is contained in each of the following carbohydrates: an aldehyde or a ketone?



Answer

Answer a

aldehyde

Answer b

ketone

Answer c

ketone

Answer d

aldehyde

Fatty acids, triglycerides and phospholipids are a third class of biomolecules that contain carbonyls. These compounds are also used in energy storage. In addition, phopholipids form a major part of cell membranes, so these compounds also play an important

structural role in biology.

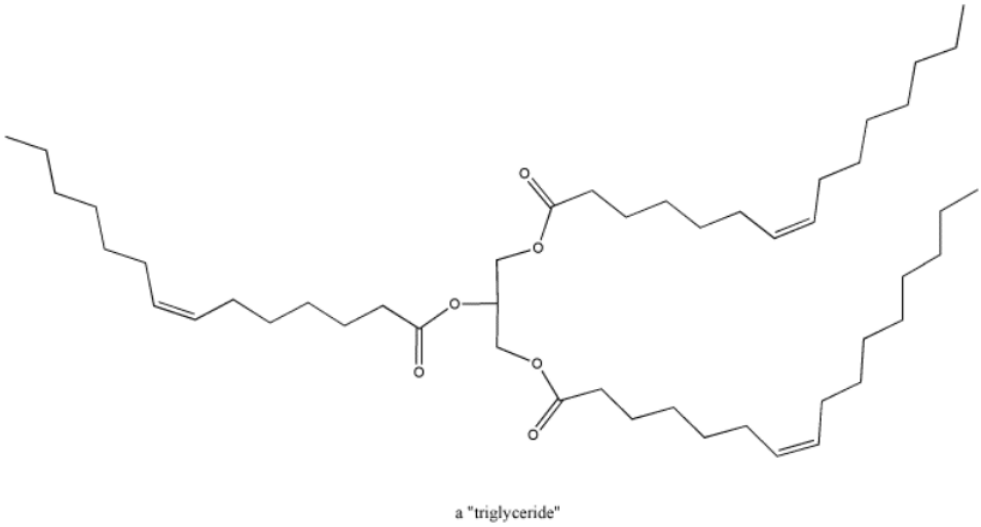
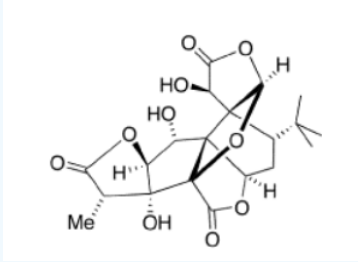


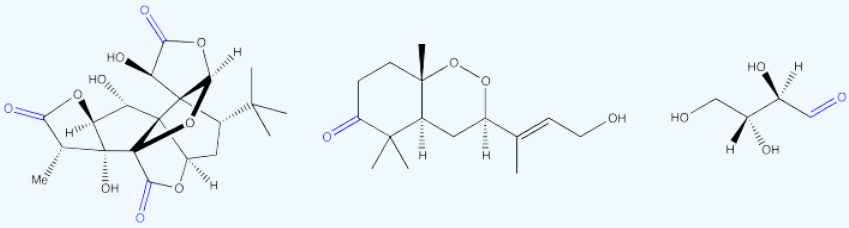
Figure 3.11.5: A triglyceride.

Exercise 3.11.3

Locate the carbonyls in the following biological molecules and the functional groups that contain carbonyls in each case.



Answer



Ginkgolides are biologically active terpenoids from Ginkgo trees. They are thought to have medicinal properties.

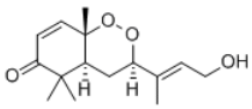


Figure 3.11.6:

Okundoperoxide is isolated from a type of sedge in Cameroon. It has modest anti-malarial properties.

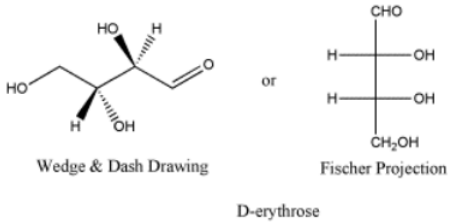
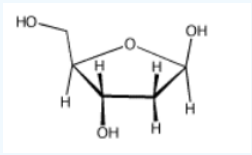


Figure 3.11.7:

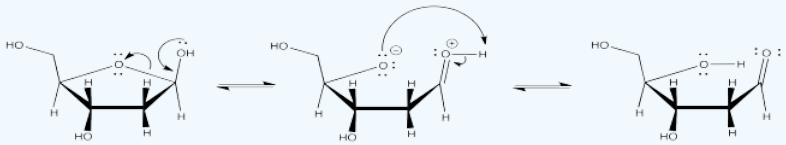
D-erythrose is a typical carbohydrate.

Exercise 3.11.4

Frequently, the carbonyls in carbohydrates are "masked", as in deoxyribose (below).



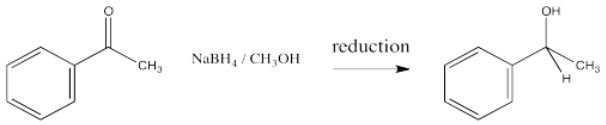
Answer



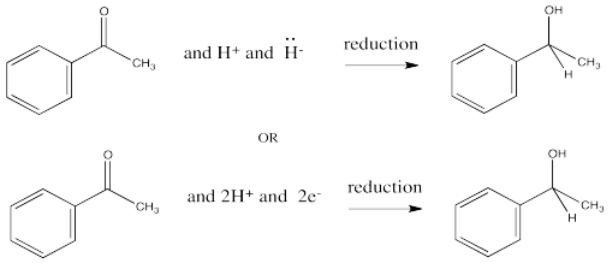
By moving one proton from one position to another, and then breaking a single C-O bond, discover where the carbonyl is hiding.

3.12: Organic Oxidation

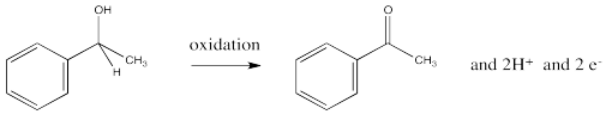
You may recall that conversion of an aldehyde or ketone to an alcohol is referred to as a reduction. The hydride from an NADH molecule or a BH_4^- anion acts as a nucleophile, adding H^- to the carbonyl carbon. A proton source can then protonate the oxygen of the resulting alkoxide ion, forming an alcohol.



In this reduction, two electrons and two protons are donated to the carbonyl compound to produce an alcohol.



The opposite process, the loss of two protons and two electrons from an alcohol to form a ketone or aldehyde, is an oxidation.



In biological pathways, oxidation is often the microscopic reverse of reduction. That means that the products of a reduction, NAD^+ and an alcohol, could react together under the right circumstances to form NADH and a carbonyl. The reduction of NAD+ by a hydride donor is possible because, although the NAD^+ loses the aromaticity of its nicotinamide ring upon becoming NADH, it also loses its positive charge. Charge stabilization is frequently an energetic problem for molecules.

This general type of reaction, hydride transfer reduction, has been adapted by Ryoji Noyori, of Nagoya University in Japan, to produce a single enantiomer of a chiral alcohol product. Noyori's work on this reaction, and others, led to him being awarded the Nobel Prize in Chemistry in 2001.

Exercise 3.12.1

Show the two enantiomers that could be produced from reduction of acetophenone, $CH_3(CO)C_6H_5$

Exercise 3.12.2

Provide a mechanism with arrows for the Oppenauer oxidation of benzyl alcohol, $C_6H_5CH_2OH$.

Exercise 3.12.3

Explain why acetone is used as the solvent in an Oppenauer oxidation.

Answer

Add texts here. Do not delete this text first.

Exercise 3.12.4

Meerwein-Ponndorf-Verley reduction of a ketone is carried out with aluminum tris(isopropoxide) in isopropanol as solvent. Provide a mechanism for the reduction of acetophenone, $CH_3(CO)C_6H_5$, via this reaction.

Exercise 3.12.5

Explain why isopropanol is used as the solvent in a Meerwein-Pondorf-Verley reduction

A second general method for alcohol oxidation employs a "redox-active" transition metal to accept a pair of electrons from from an alcohol during the oxidation. Because oxidation of an alcohol formally involves the loss of two electrons and two protons, a proton acceptor is also involved in this oxidation. There are many redox-active metals, but one of the most commonly used is Cr(VI). When Cr(VI) accepts a pair of electrons, it becomes Cr(IV).

In order to look at how chromium oxidation works, we'll use chromium oxide, CrO_3, as an oxidant and water as a solvent. Note that water could also act as a proton acceptor or proton shuttle, moving protons from one place to another as needed. To carry out an oxidation, a number of events need to happen.

- The alcohol needs to bind to the chromium.
- A proton needs to be removed. This event is helped by the formal positive charge on the alcohol after it donates a lone pair to the chromium.
- A second proton must be removed and a pair of electrons given to the chromium for good.

In reality, CrO_3 isn't used that often as an oxidant. It tends to catch fire when mixed with organic compounds. Instead, a variety of other chromium compounds are used.

Exercise 3.12.6

In determining an oxidation state, we imagine giving both electrons in a bond to the more electronegative atom and looking at the resulting charges on the ions that result. Assuming all of the oxygens in chromium oxide can be thought of as dianions, confirm that the chromium can be thought of as a Cr^{6+} cation (in other words, in oxidation state Cr(VI)).

Answer

Exercise 3.12.7

By the reasoning used in the previous question, determine the oxidation state of the transition metal in the following compounds. Note that in some cases, there is an anion and cation in the compound.

a) $KMnO_4$ b) $NaIO_4$ c) Ag_2O d) OsO_4 e) $(CH_3CH_2CH_2)_4N\ RuO_4$

Answer

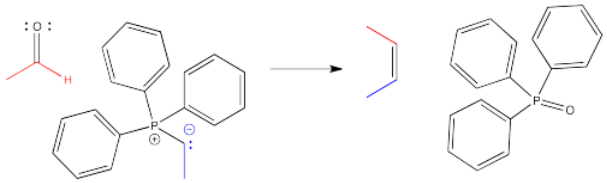
Add texts here. Do not delete this text first.

3.13: Addition of Ylides

Sometimes, nucleophiles adding to a carbonyl do not follow the normal reactivity patterns that have been common so far. This is often the case with the addition of ylides.

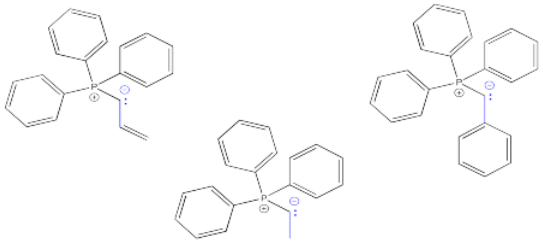
Ylides are compounds that are often depicted with a positive charge one one atom and a negative charge on the next atom. They are examples of zwitterions, compounds that contain both positive and negative charges within the same molecule. What distinguishes them from other zwitterions is the proximity of the opposite charges.

The classic example of an ylide addition to a carbonyl is the Wittig reaction. The Wittig reaction involves the addition of a phosphorus ylide to an aldehyde or ketone. Rather than producing an alcohol, the reaction produces and alkene. The reaction is driven by formation of a phosphorus oxide "side product".

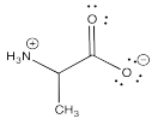


This is a special case. The phosphorus-oxygen bond is strong enough to change the course of this reaction away from the normal pattern, and it isn't something you would have been able to predict based on related reactions.

An ylide is an example of a molecular compound that contains both a positive and a negative formal charge on two adjacent atoms. The charges are right beside each other: in this case, there is a positive charge on the phosphorus and a negative charge on the carbon.



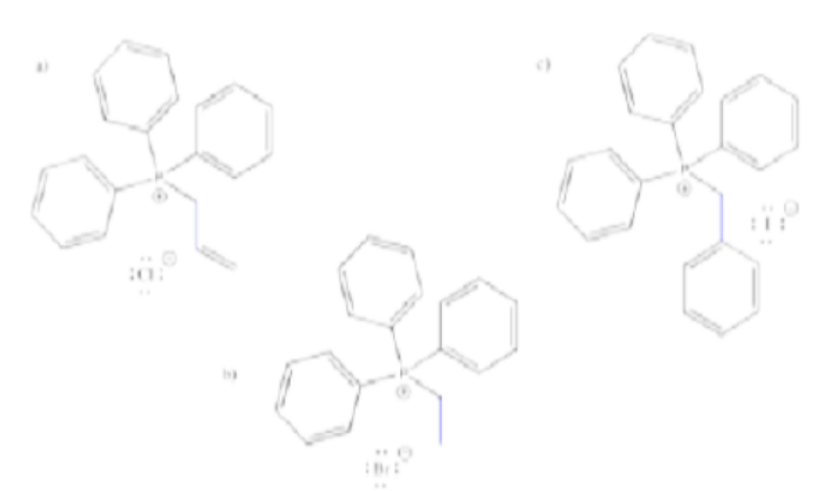
Ylides are specific examples of zwitterions, which are molecules that contain positive and negative charges. The most common example of a zwitterion is probably an amino acid, which contains a positive ammonium ion and a negative carboxylate ion, within the same molecule.



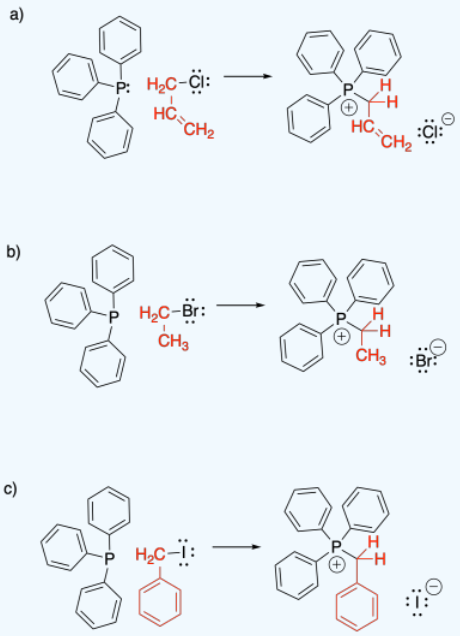
Phosphorus ylides are made one charge at a time. A phosphonium ion must first be assembled, containing the positive charge on phosphorus. This event occurs via a nucleophilic substitution reaction, in which a phosphorus nucleophile displaces a halogen from an alkyl halide.

Exercise 3.13.1

Show, with reaction arrows, formation of the three alkyltriphenyl phosphonium bromide salts shown below.

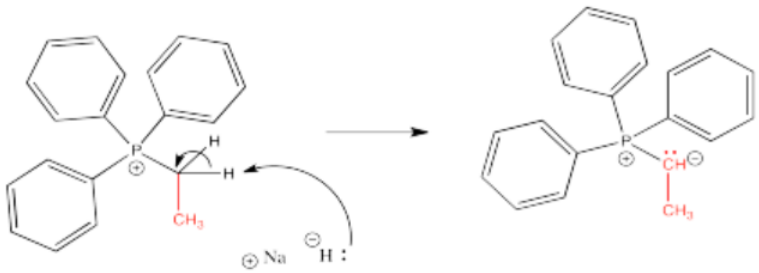


Answer



In most cases, the source of the phosphorus is triphenylphosphine. Triphenylphosphine is used for several practical reasons. First of all, it is a solid, so it is easy to weigh out the right amount of it and add it to a reaction. Secondly, organophosphorus compounds are often very toxic and smelly, but triphenylphosphine is less offensive. Thirdly, in the Wittig reaction, the original phosphorus compound is eventually discarded as waste, and the more useful alkene is kept. Since the phosphorus part does not matter that much, the most convenient possible phosphine is generally used. However, there are other variations of this reaction that use other phosphorus compounds.

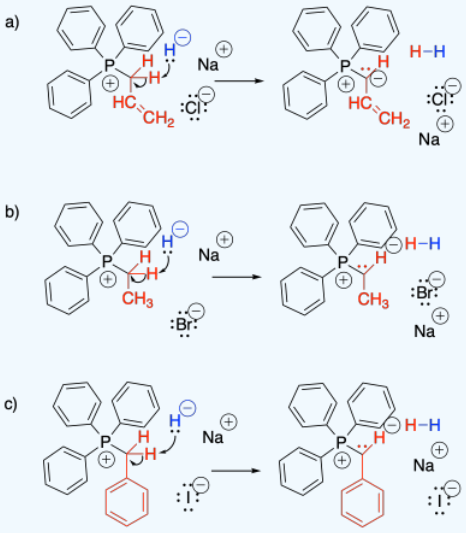
Once the phosphonium salt has been made, the phosphorus ylide can then be obtained via deprotonation of a phosphonium ion. The hydrogens on a carbon next to a phosphorus cation are a little bit acidic because of the positive charge on the phosphorus. One of these hydrogens is easily removed via adddition of a very strong base such as sodium hydride.



Exercise 3.13.2

Show, with reaction arrows, formation of ylides from the three alkyltriphenyl phosphonium bromide salts shown above in Exercise 3.13.1

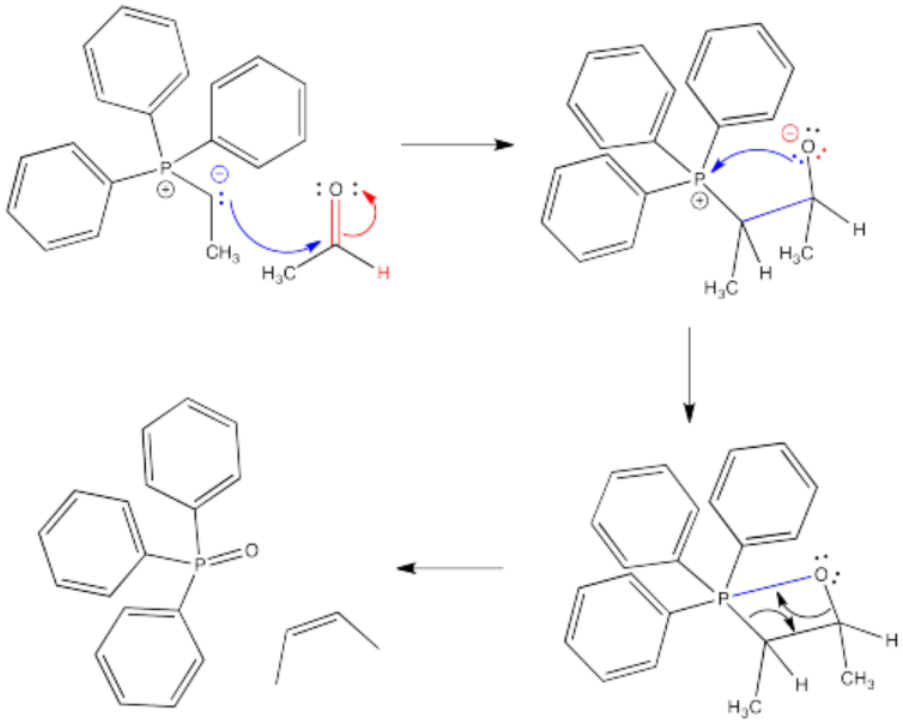
Answer



The reaction of a phosphorus ylide with a carbonyl compound does begin like other nucleophilic additions. The ylide donates its nucleophilic lone pair to the carbonyl and the carbonyl pi bond breaks. However, the strong P-O bond then takes over the reaction. To begin, a lone pair on the resulting alkoxide ion is donated to the positively charged phosphonium ion.

Wait! That violates one of our mechanistic rules. Usually, we don't have an atom donate to a positively charged atom that already has an octet; if we do so, the atom will have too many electrons. However, the octet rule does not strictly apply to sulfur and phosphorus. These atoms are larger than second-row atoms like nitrogen and oxygen, and they are often observed to "exceed the octet rule". Sulfur and phosphorus are frequently observed with trigonal bipyramidal or octahedral molecular geometries, meaning they may have up to 12 electrons in their valence shells.

So go ahead! Donate a pair of electrons to the phosphorus. It can't help itself, because of the strength of the P-O bond that forms.

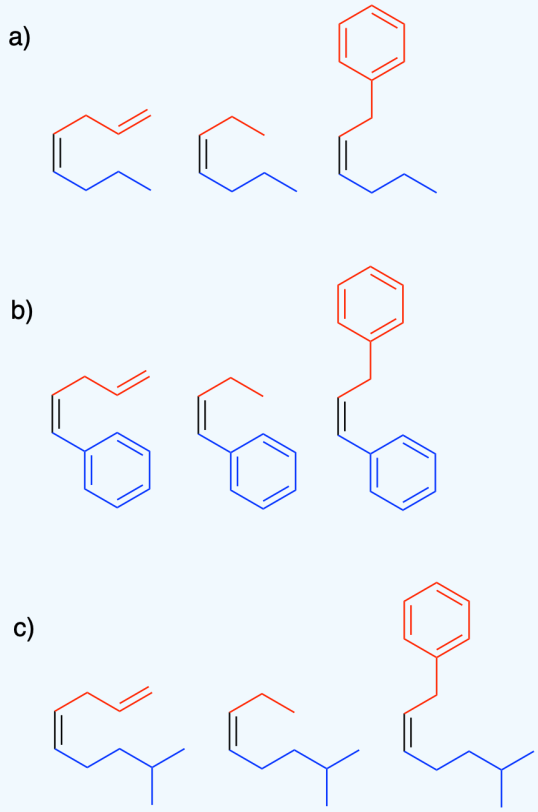


Exercise 3.13.3

Show the products of the reactions of each of the ylides you made in Exercise 3.13.2 (Problem CO18.2.) with the following electrophiles:

a) butanal b) benzaldehyde c) 4-methylpentanal

Answer



This is when things really get interesting. It turns out that one P-O bond just isn't enough. The phosphorus is so oxophilic that it takes the oxygen atom all to itself, pulling it right out of the molecule. It probably does not hurt that the four-membered ring is pretty strained, so it is motivated to decompose (but be careful: there are plenty of stable four- and even three-membered rings in nature).

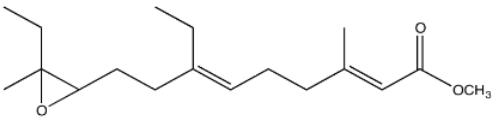
The arrows shown in the decomposition of the four-membered ring (called a betaine) are just meant to keep track of electrons; there isn't a true nucleophile and electrophile in this step. Instead this step may resemble a pericyclic reaction, which is covered in another section.

Exactly how to draw the P=O bond is debatable. There isn't much doubt that it is a double bond; it is stronger and shorter than a P-O single bond. However, quantum mechanical calculations indicate that the phosphorus can't form a pi bond. This double bond is different than other double bonds you have seen. For that reason, some people prefer to draw this compound as an ylide, too, with a positive charge on the phosphorus, a single bond, and a negative charge on the oxygen.

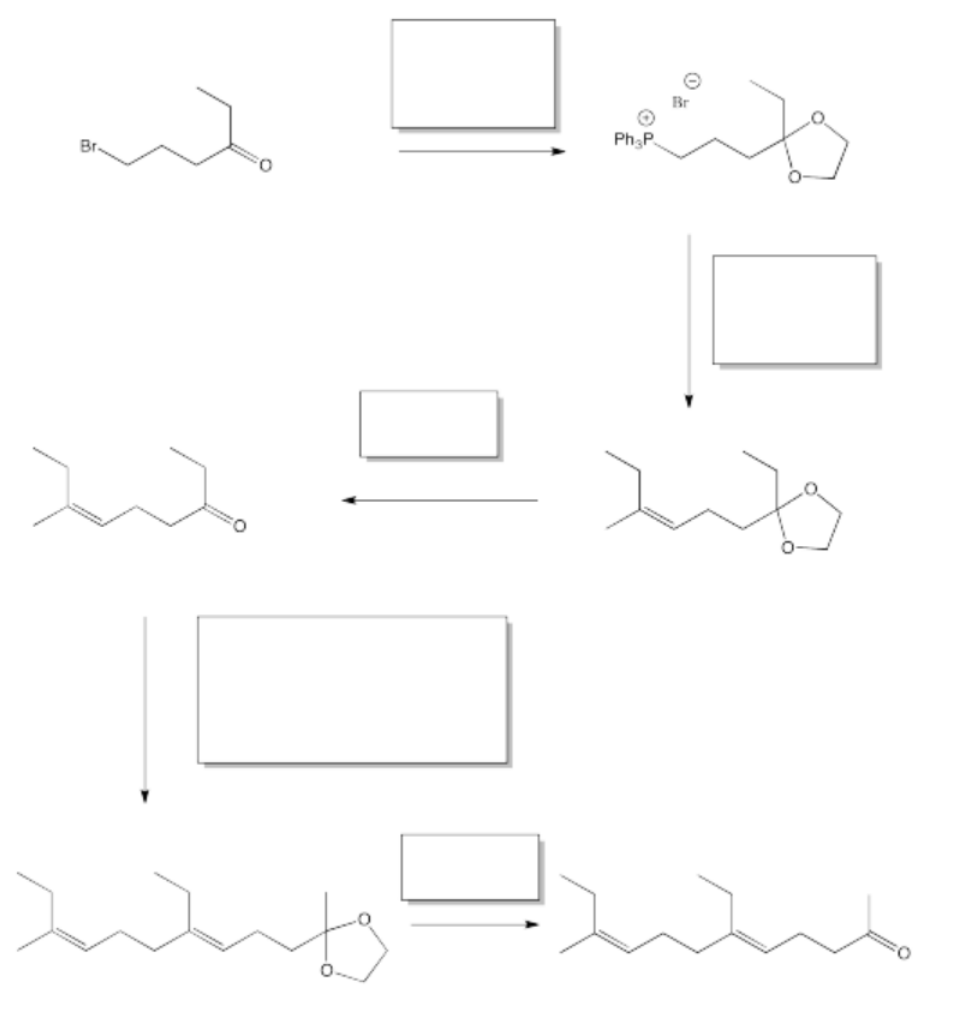
The phosphorus oxide compound forms, leaving behind an alkene. Alkenes are very common in nature, and this reaction has frequently been used to make interesting alkene-containing compounds for further use or study.

Exercise 3.13.4

The juvenile hormone of the cecropia moth caterpillar (JH-1, below) is a regulatory hormone used to control the organism's development by preventing it from pupating until conditions are right.



Synthesis of insect hormones is often undertaken in order to control insect populations. The following synthesis of JH-1 was developed by Barry Trost (Stanford) in the 1960's. Fill in the missing reagents and reaction products.

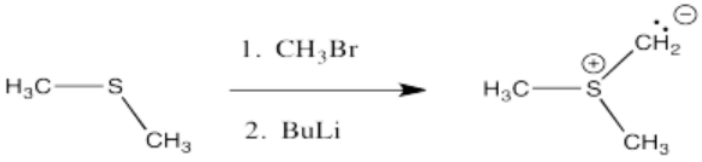


Answer

One of the keys in this problem is recognizing that in some steps, two different reactions are involved. For example, in the first box, there is an addition of a diol to a carbonyl followed by an ylide addition.

Sulfur ylides are also good nucleophiles for aldehydes and ketones. However, the unusual stability of the phosphorus-oxygen bond does not have a similar analogue in sulfur chemistry.

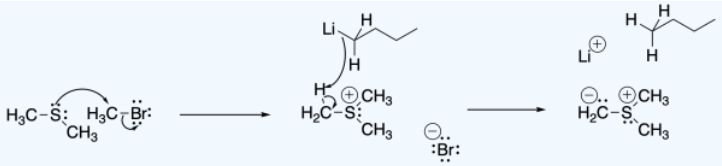
Sulfur ylides are formed in a manner very similar to phosphorus ylides.



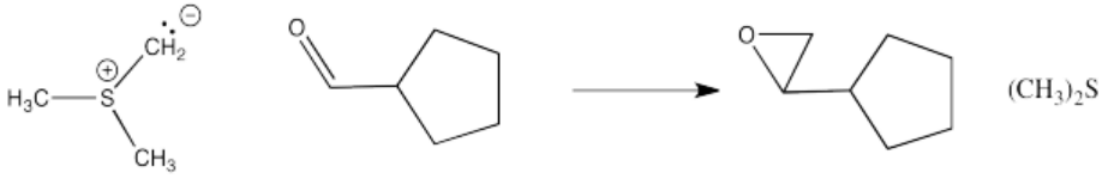
Exercise 3.13.5

Show, with arrows, the mechanism for formation of the sulfur ylide above.

Answer



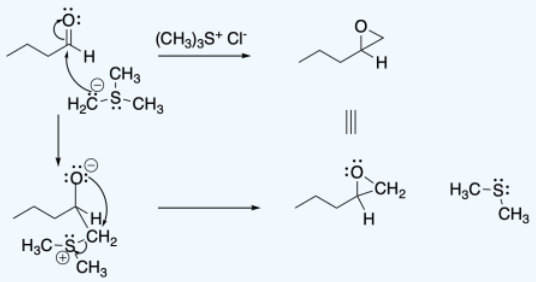
Once formed, sulfur ylides react with aldehydes or ketones. Like phosphorus ylides, the reaction starts out just like any other nucleophile, but a second step takes a very different direction. Epoxides are formed in these reactions, and the original sulfur compound (a thioether) is regenerated.



Exercise 3.13.6

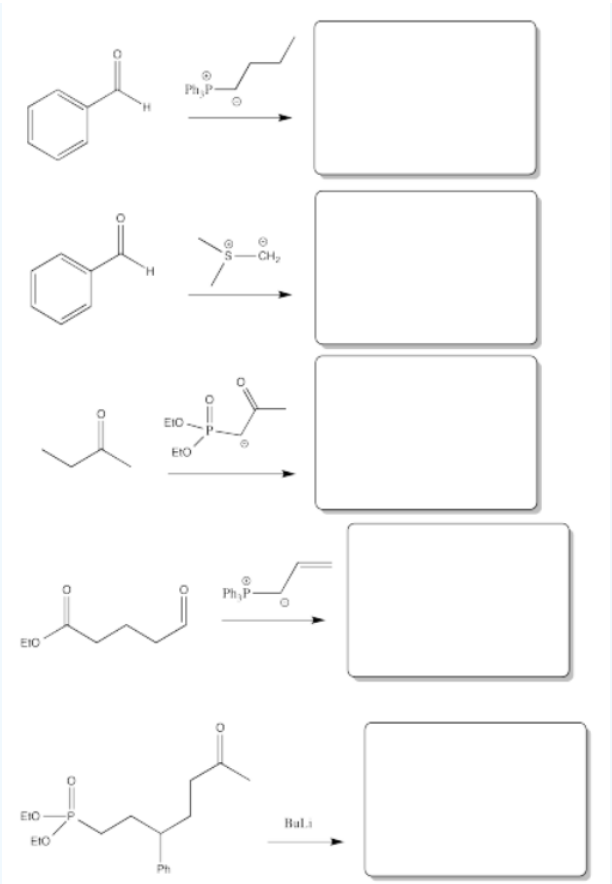
Show, with arrows, the mechanism for the epoxide-forming reaction above.

Answer

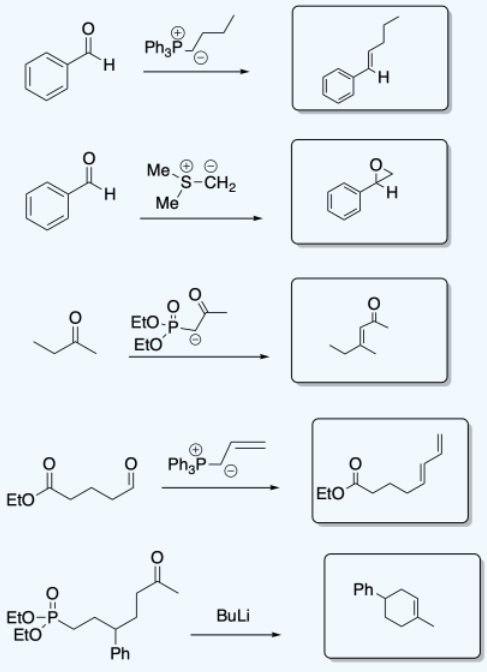


Exercise 3.13.7

Fill in the product or reagent for each of the following transformations. Remember there is always an acidic workup assumed.



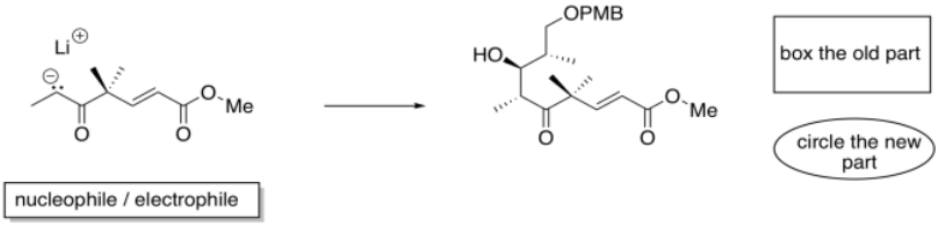
Answer



Exercise 3.13.8

Identify the starting material as nucleophile or electrophile in the following reactions (from the synthesis of an epothilone analogue by K.H. Altmann at ETH). In the product, box the part of the structure that came from the compound on the left; circle the new part.

a)



nucleophile / electrophile

b)

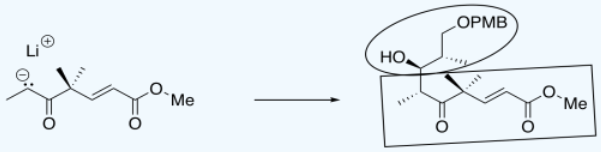
nucleophile / electrophile

c)

nucleophile / electrophile

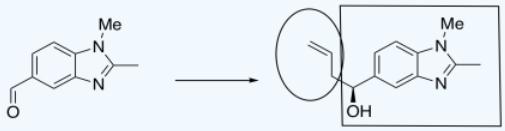
Answer

a)



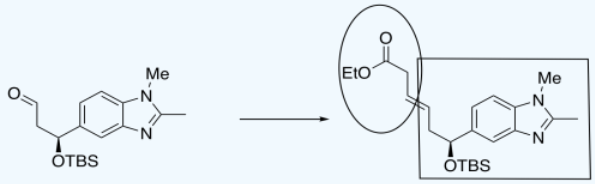
nucleophile

b)



electrophile

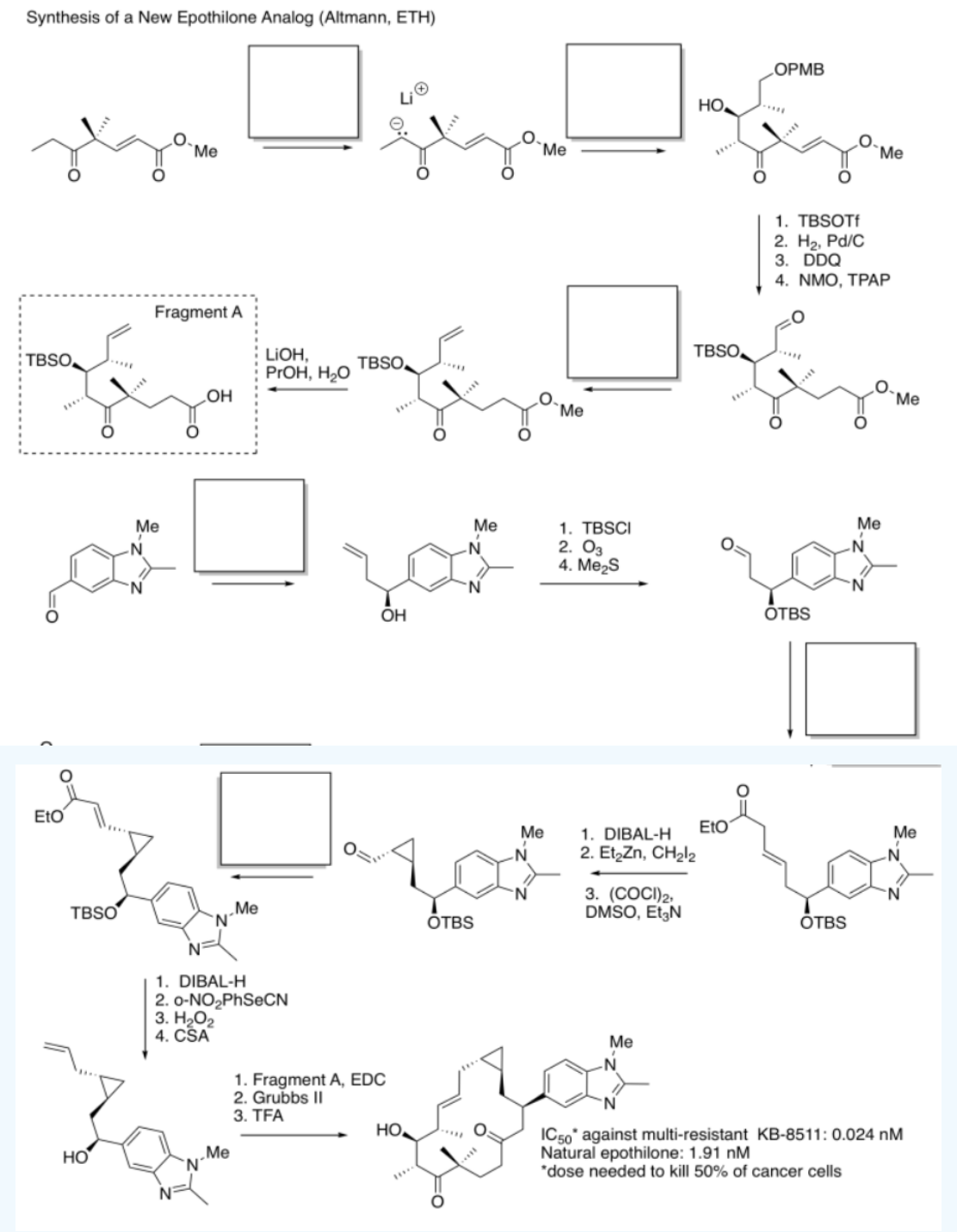
c)



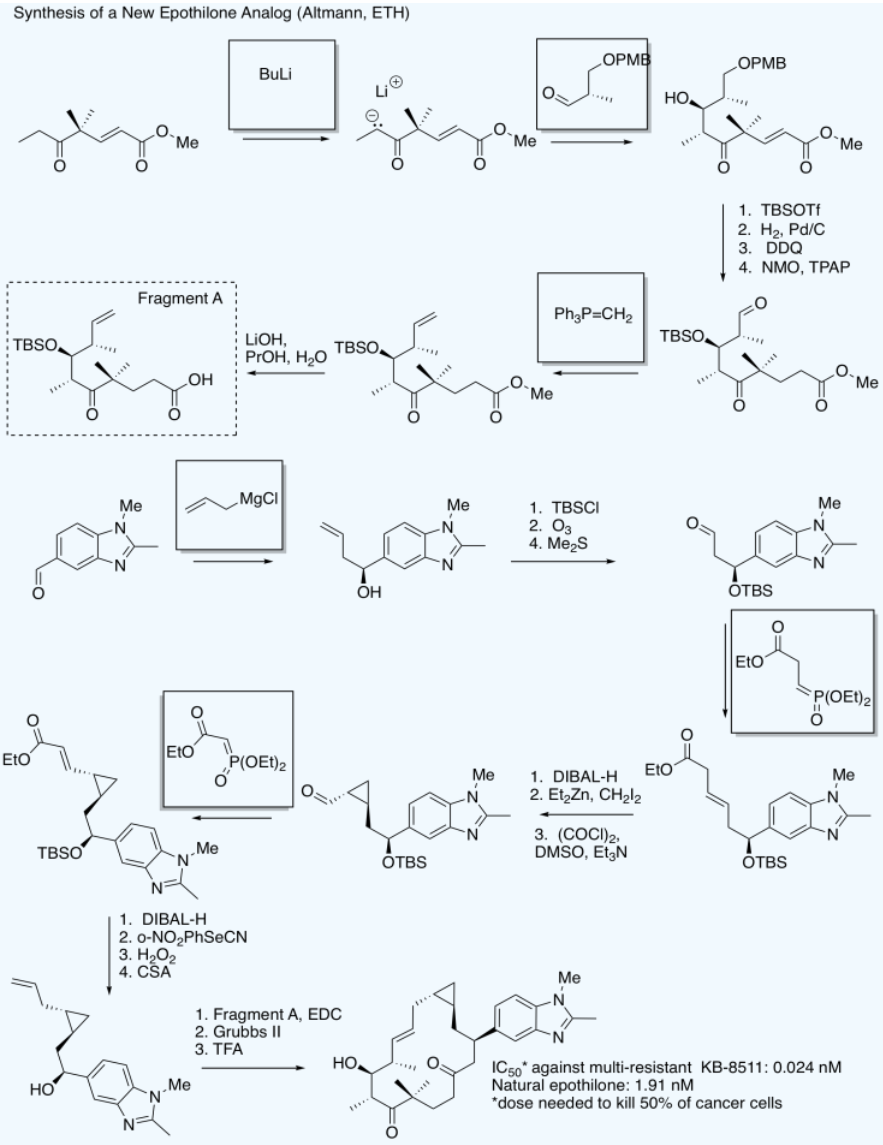
electrophile

Exercise 3.13.9

Fill in the blanks in the following synthesis. Requires knowledge of aldol addition, Grignard additions, and Wittig / Horner-Wadsworth-Emmons reactions.

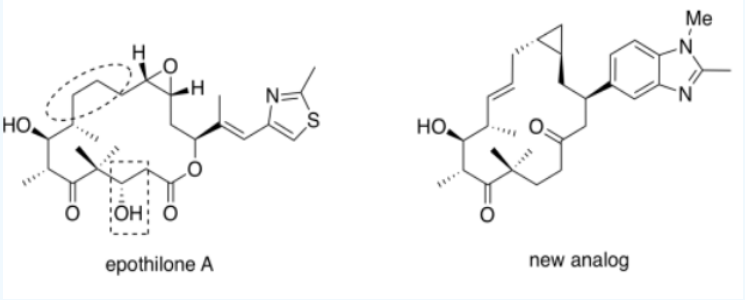


Answer



Exercise 3.13.10

Altmann's epothilone analogue synthesized above (shown on the right, below) clearly bears some resemblance to natural epothilone A (below, left). However, the analogue is effective at much lower concentrations than the natural product. That information may actually reveal something about how the natural product interacts with its target.

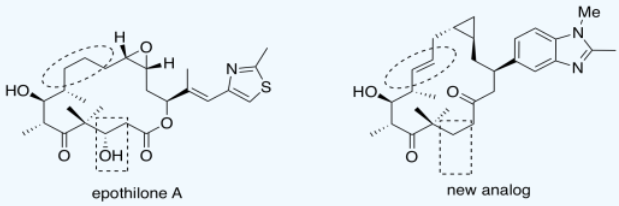


a. Parts of the epothilone A are highlighted. Circle and box the corresponding parts of the analog.
b. Describe the differences between the highlighted portions of the natural and synthetic versions.

c. One could imagine the boxed alcohol group forming part of a pharmacophore -- the part of the compound that binds with its target. What intermolecular attractions seem likely with this group?
d. Comment on the apparent importance of this group in binding to the target, based on the evidence.
e. One could imagine the circled part of the natural compound adopting different conformations via changes in the dihedral angle. What dihedral angle appears to be shown in the natural epothilone?
f. What dihedral angle appears to be shown in the analogue?
g. Based on the evidence, which dihedral angle is preferred in order to bind to the target?

Answer

Answer a



Answer b

The circled part changed from a single bond to a double bond. The boxed part changed from an alcohol to unadorned hydrocarbon chain.

Answer c

Hydrogen bonding is the most obvious.

Answer d

However, the analog works better without this group; this particular alcohol group is probably not an important part of the pharmacophore. It is probably not needed in order to bind to the target.

Answer e

In epothilone A, as drawn, the dihedral angle appears to be 0 degrees.

Answer f

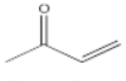
In the new analog, the dihedral angle is 180 degrees.

Answer g

Based on the superior activity of the analog, the active conformation of the ring is probably more like the one on the right than the one on the left. The circled bond probably adopts a dihedral angle closer to 180 degrees, with the rest of the ring twisting into a shape more like the one shown on the right, in order to bind to the target.

3.14: Conjugate Addition

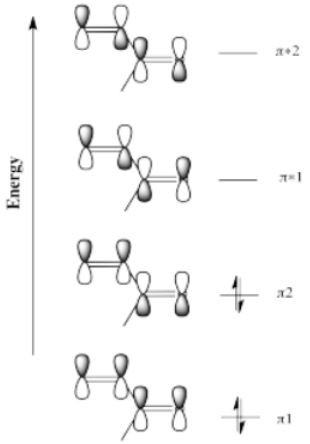
Conjugated systems are structures that contain alternating double and single bonds (or, in some cases, a double bond that is next to an atom with either a lone pair or a vacant orbital). Conjugated systems are usually at lower energy than regular double bonds because the electrons involved in bonding are delocalized; they are spread out over a greater area and thus can have a longer wavelength.



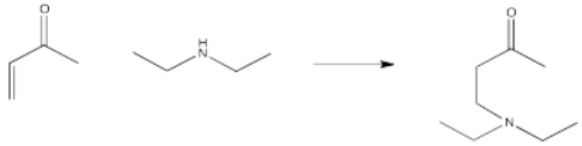
3-butene-2-one

(or methyl vinyl ketone)

For example, the -bonding system for 3-butene-2-one (or methyl vinyl ketone) is described by orbitals involving both the carbonyl group and the alkene group. These two groups become linked together so that there is not longer an independent carbonyl nor an independent alkene, but one "enone" (a term taken from the words alk*ene* and ket*one*).



Because of that extra stability, it might not be surprising that conjugated carbonyls are often a little slower to react than regular carbonyls. The surprise is that conjugated carbonyls can sometimes give additional products in which addition does not take place at the carbonyl.



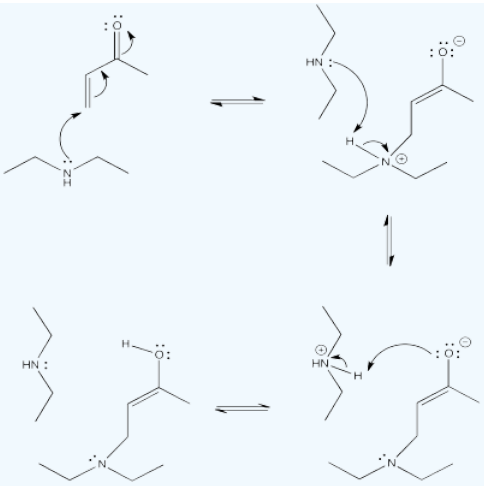
The product shown above is called a conjugate addition product, or a 1,4-addition product. In conjugate addition, the nucleophile does not donate to the carbonyl, but instead donates to an atom that is involved in conjugation with the carbonyl. This additional electrophilic position is sometimes called a "vinylogous" position (from the word *vinyl*, which refers to that $CH=CH_2$ unit next to the carbonyl).

- Conjugate additions (or 1,4-additions) can occur when a carbonyl is attached to a C=C bond.

Exercise 3.14.1

Draw a mechanism with curved arrows for the conjugate addition shown above.

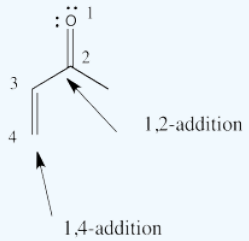
Answer



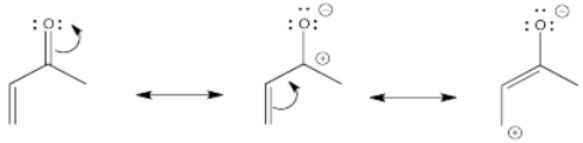
Exercise 3.14.2

Regular additions to carbonyls are sometimes called 1,2-additions, whereas conjugate additions are called 1,4-additions. Show why.

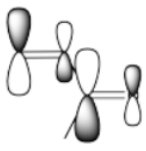
Answer



Remember that we can look at another resonance structure of a carbonyl, one that emphasizes the electron-poverty of the carbonyl carbon. It's not a good Lewis structure because of the lack of an octet on carbon, but it does reinforce the idea that there is at least some positive charge at that carbon because it is less electronegative than oxygen. Extending that idea, we can draw an additional resonance structure in a conjugated system. That third structure suggests there may be some positive charge two carbons away from the carbonyl, on the β position on the double bond.



The idea that there are two electrophilic positions in an enone is reinforced by the picture of the LUMO (the lowest-energy "empty" frontier orbital, the virtual place where an additional electron would probably go). When a lone pair is donated to an electrophile, the electrons are most likely to be donated into the LUMO.



Although it isn't obvious from the cartoons we often draw for molecular orbitals, quantum mechanical calculations suggest that the LUMO is "larger" at the carbonyl position as well as the β-position on the vinyl group.

How can it be larger on some atoms than others? A molecular orbital is an algebraic combination of atomic orbitals. In this case,

$$LUMO = ap_{C1} + bp_{C2} + cp_{C3} + d_{pO}$$

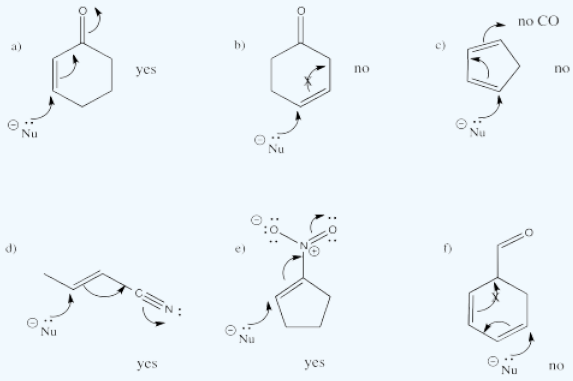
in which p_{C1} is the p orbital on the carbon on the left, p_O is the p orbital on the oxygen, and so on. The letters a, b, c and d are just numbers; they are the coefficients in the equation. The result of the molecular orbital calculation in this case suggests that the numbers a and c are a little bigger than b and d. Incidentally, it also suggests that a and d have opposite sign from b and c (maybe a and d are positive numbers whereas b and c are negative numbers), meaning that a and d are out of phase with b and c.

In any case, we sometimes think of the large LUMO on particular atoms as being an easier "target", an easier place to throw the incoming electrons. These mathematical results really just reflect what we would expect from the resonance structures.

Exercise 3.14.3

Indicate whether the following systems are capable of undergoing conjugate addition, and show why or why not.

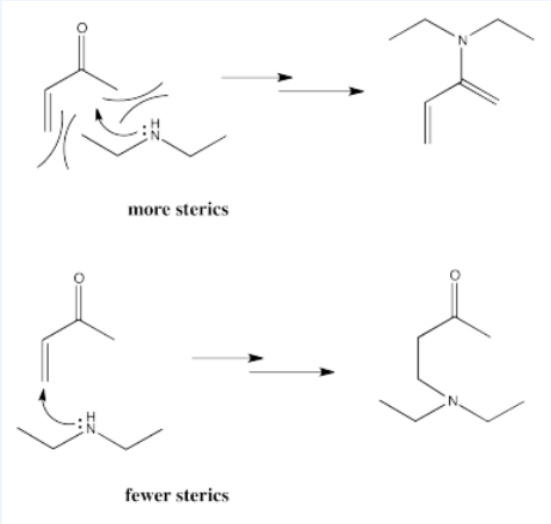
Answer



Having two possible products of a reaction can be confusing. How do you know which one will result? Often, you don't know. Frequently, both products result, so there is a mixture of compounds. However, one product often predominates. In conjugate addition, there are a few different factors that may tilt the reaction in one direction or another.

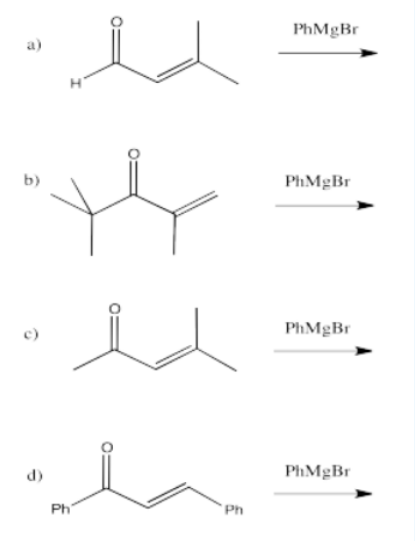
Possibly the simplest reason is steric effects. Maybe one of the electrophilic positions is more crowded than the other, and the nucleophile can access that position more easily.

- Addition of a nucleophile often occurs at the least crowed electrophile.
-

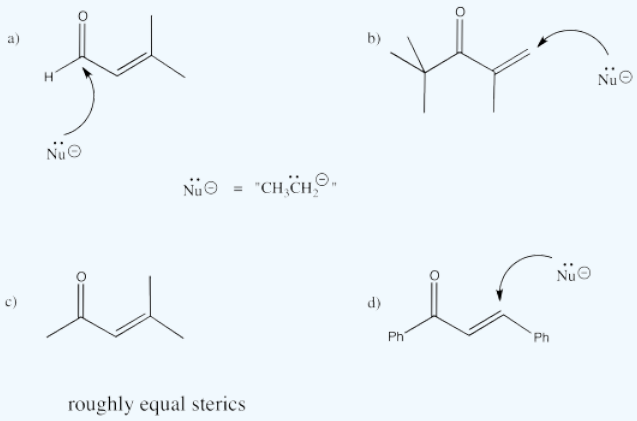


Exercise 3.14.4

In each of the following cases, indicate whether the addition of a nucleophile will be via 1,2-addition, via 1,4-addition, or an equal mixture.



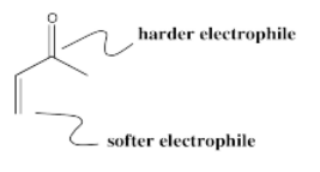
Answer



roughly equal sterics

The hard/soft acid characteristics of the two electrophilic positions also influence the reaction. The carbonyl position is closer to the oxygen, of course, and it makes sense that the oxygen would have a greater influence on this carbon. The carbonyl position, with its more concentrated positive charge, is a harder electrophile. The vinylogous position, with less positive charge, is a softer electrophile.

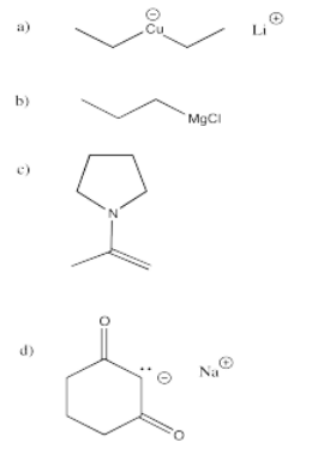
- Carbonyls are hard electrophiles.
- Vinylogous positions are soft electrophiles.



Soft nucleophiles are more likely to react with soft electrophiles, and hard nucleophiles are more likely to react with hard electrophiles. The amount of negative charge concentrated at the nucleophilic atom is the biggest factor determining hardness. The lower the charge, or the more spread out the charge, the softer the nucleophile.

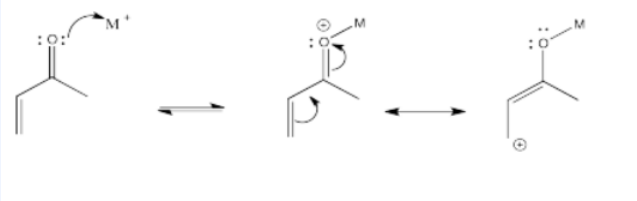
Exercise 3.14.5

Indicate whether the following nucleophiles are more likely to undergo 1,2-addition or 1,4-addition.



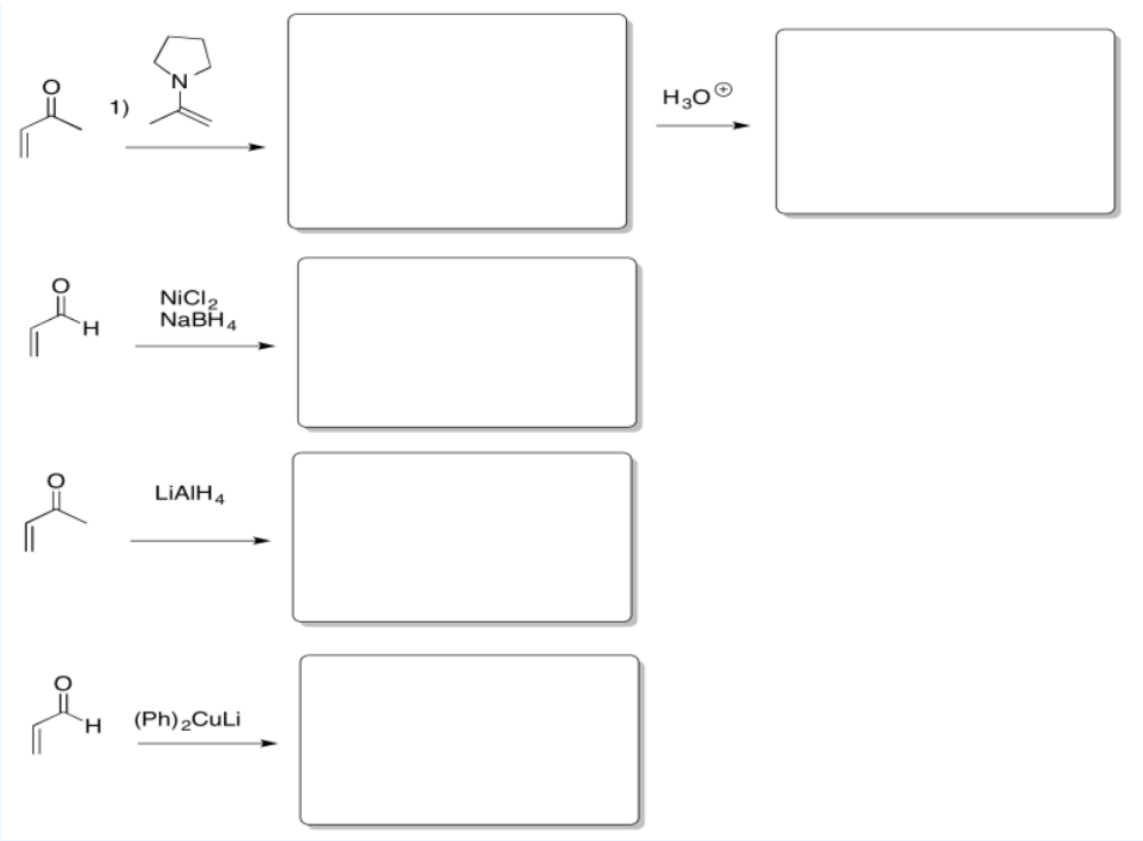
There are other factors that play roles in influencing the course of these reactions. Sometimes the mechanism of reaction is slightly different under different circumstances. The presence of Lewis acid catalysts can also influence reactivity in these systems, but not always in a predictable way.

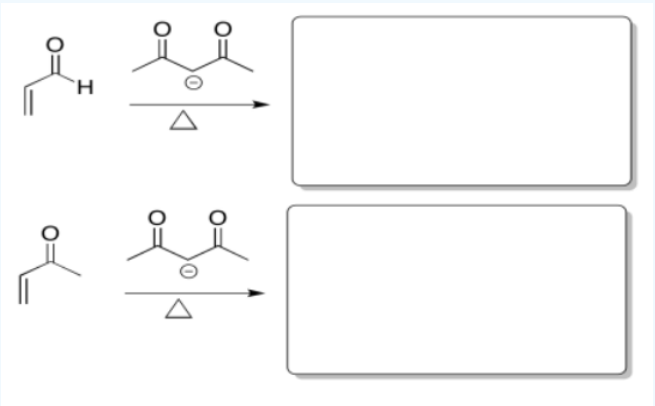
Lewis acid catalysts can influence whether a reaction proceeds via 1,4-addition.



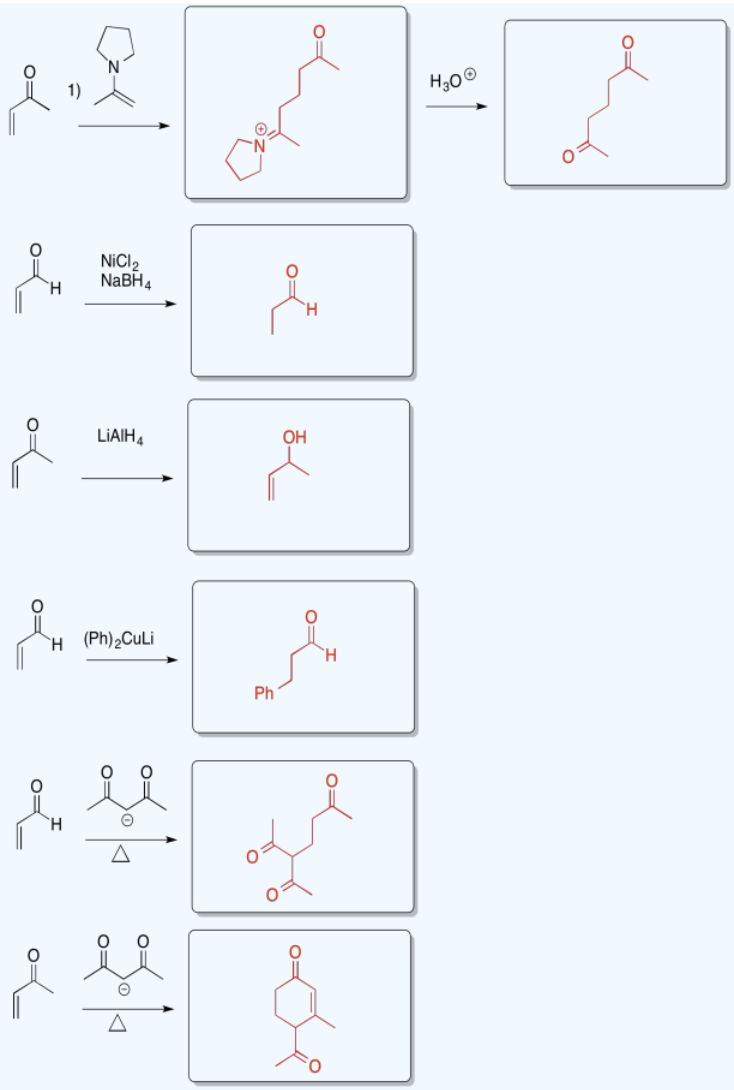
Exercise 3.14.6

Fill in the products of the following reactions.

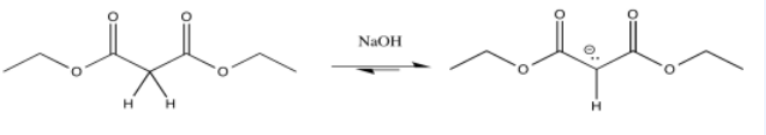




Answer

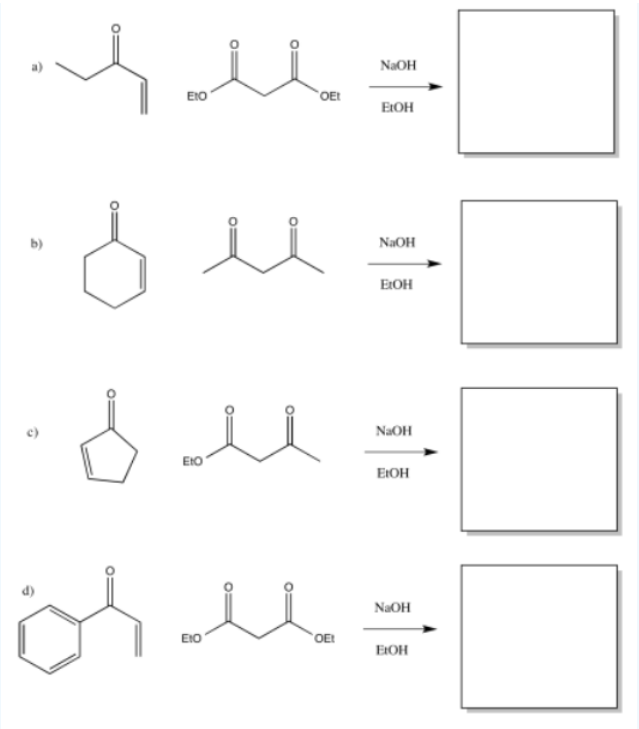


The Michael addition is one of the most important examples of conjugate addition. In a Michael addition, an enolate nucleophile undergoes 1.4-addition to an enone. Typically, the nucleophile is diactivated; that is, there is a carbonyl on either side of the alpha position.

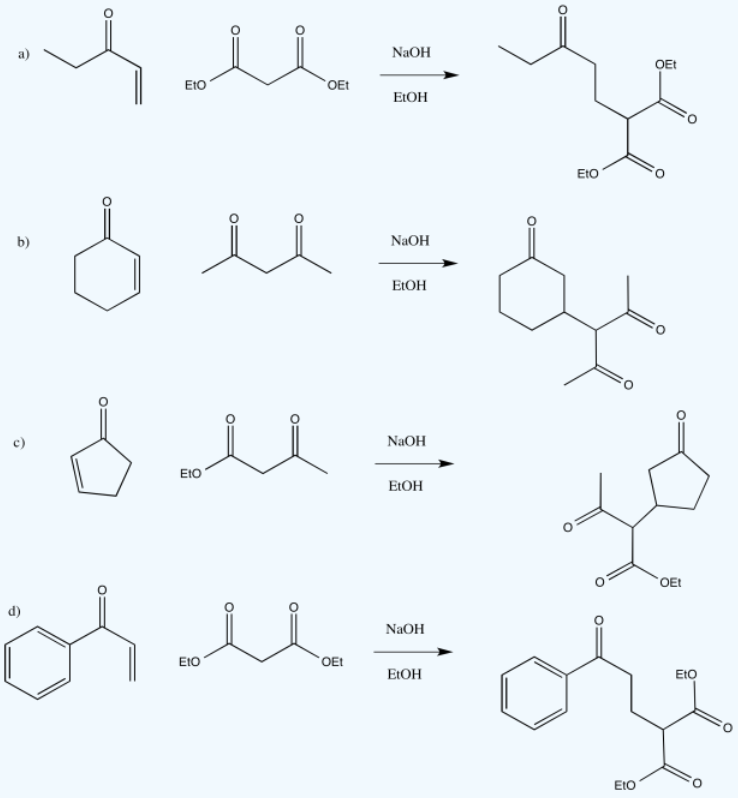


Exercise 3.14.7

Provide the product of the following Michael additions.

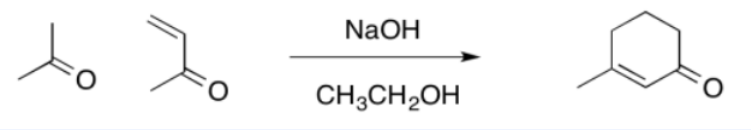


Answer

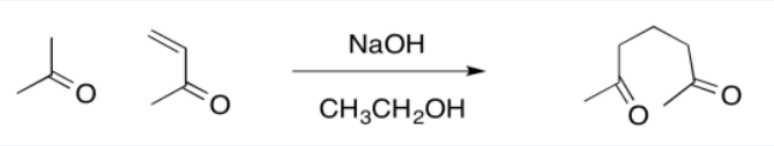


Robinson Annulation

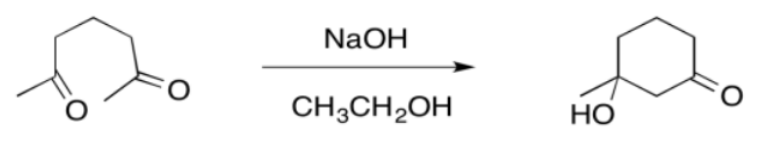
Robinson annnulation allows for formation of a six-membered ring via a Michael addition and subsequent aldol condensation.



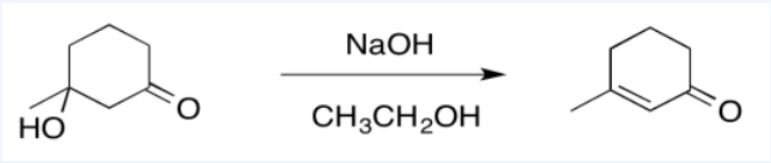
The first reaction, a Michael addition, links two molecules together via a 1,4-addition of an enolate to an enone.



After that, a regular aldol reaction ensues, closing the ring.



Typically, the aldol reaction continues through a condensation. That's the variation of the aldol reaction in which a water molecule is lost, forming a double bond in conjugation with the carbonyl.

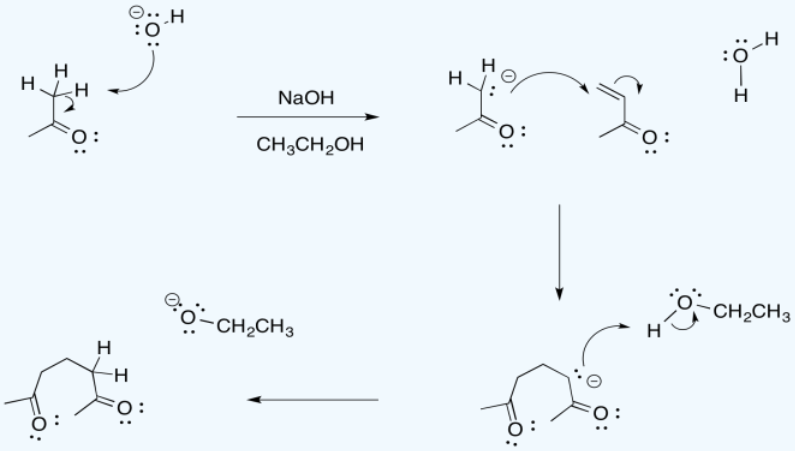


Exercise 3.14.8

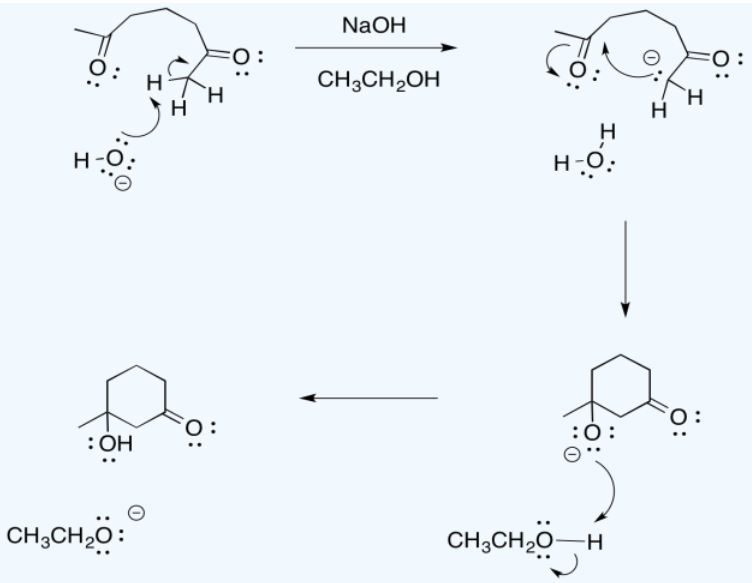
Provide mechanism for the following steps in the Robinson annulation above:

a. the Michael addition
b. the aldol reaction to form the six membered ring
c. the dehydration of the aldol product to form the enone product

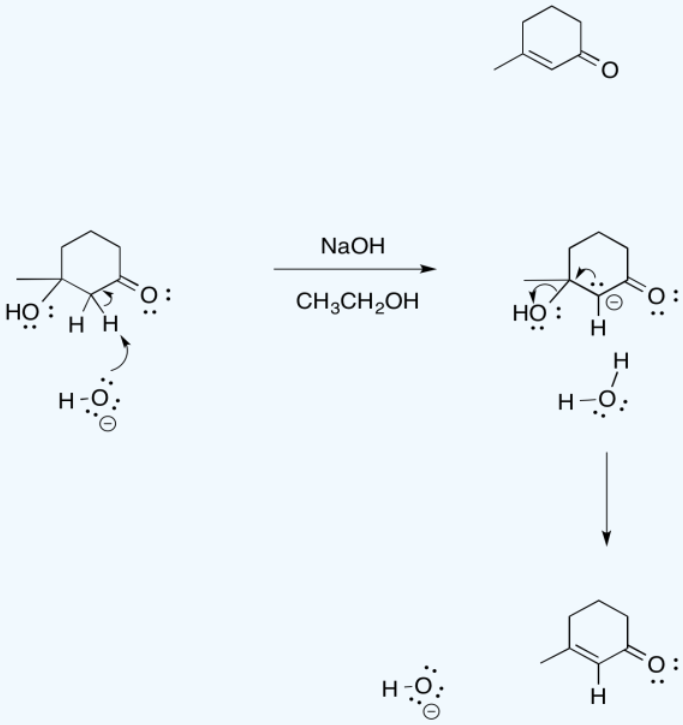
Answer
Answer a



Answer b

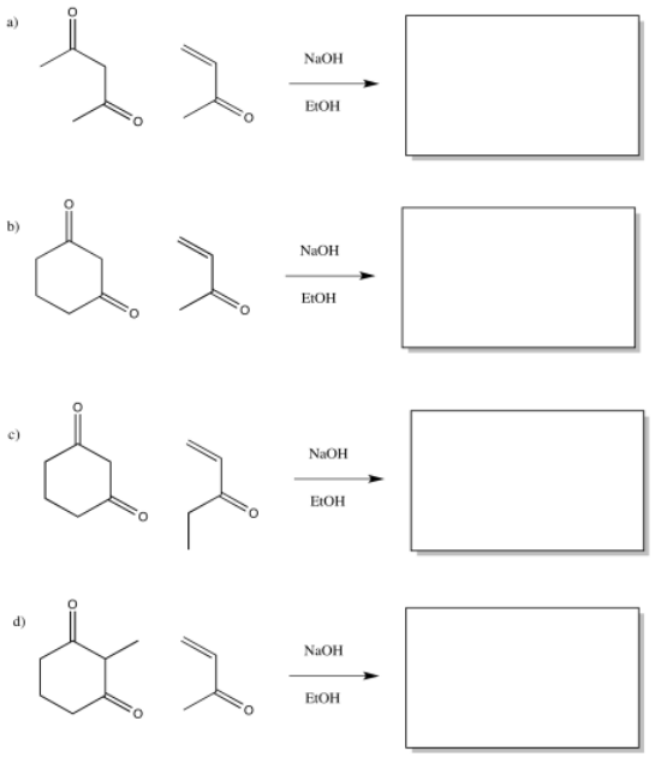


Answer c

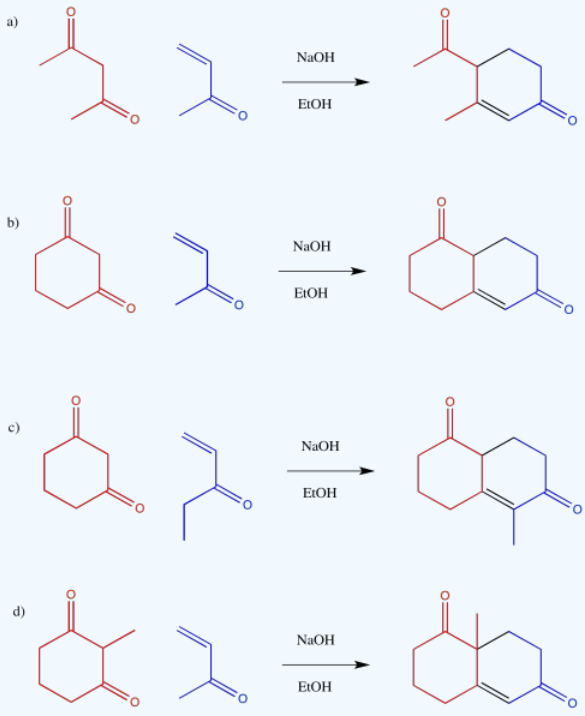


Exercise 3.14.9

Provide products of the following Robinson annulations.



Answer



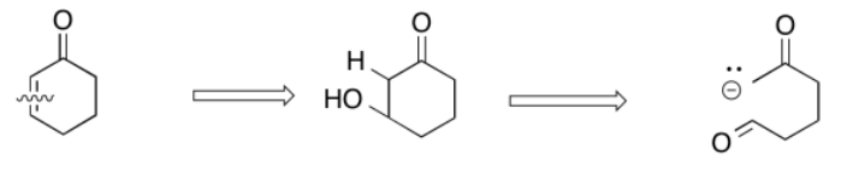
Sometimes, it is useful to think "backwards" about a reaction. Given a particular structure, can we picture the reaction that may have taken place to form that structure? This type of analysis is very useful to bio-organic chemists, who often seek to find out how different compounds formed in nature. By imagining different ways

in which a natural product may have formed, they can design different experiments that may shed light on how the process really happened.

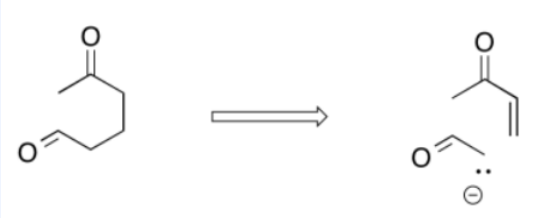
Of course, synthetic chemists find this way of thinking about things is very helpful, too. Given the task of making a particular compound, they must imagine the most efficient ways in which the compound could be made.

Let's take a look at how that approach to thinking about reactions would work with a Robinson Annulation. There are two reactions in a Robinson Annulation. One is a Michael addition and another is an aldol condensation. They always happen in that order. To analyse the product, we need to work backward from the product and “disconnect” the molecule. That means we need to find where the aldol reaction happened, then where the Michael reaction happened.

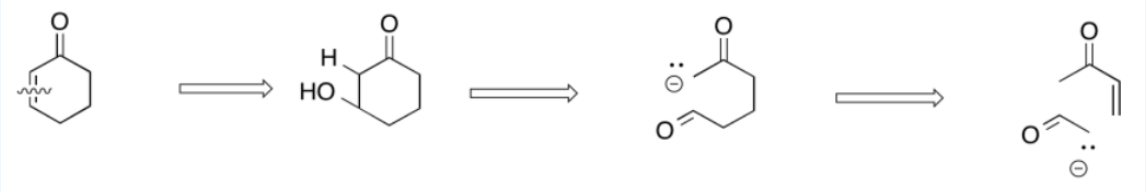
A diagnostic aldol fragment can look either like R-CO-CH_2-CHOH-R (carbonyl-carbon-alcohol) or, if there is a condensation/dehydration step, RCO-CH=CHR (carbonyl-alkene). That’s the first part of the molecule you need to find. It forms when the enolate fragment RCO-CH_2^- adds to the carbonyl RCHO. We must break the product at the double bond to uncover the aldol reactant.



A Michael fragment looks like R-CO-CH_2-CH_2-CH_2-CO-R. There are two carbonyls, with three carbons in between them. That’s the part of the molecule we need to find next, but we won’t see it until we have stepped back to the situation we had before the aldol step. The Michael fragment forms from the electrophile RCO-CH=CH_2 and the enolate nucleophile $^-CH_2$–CO-R.

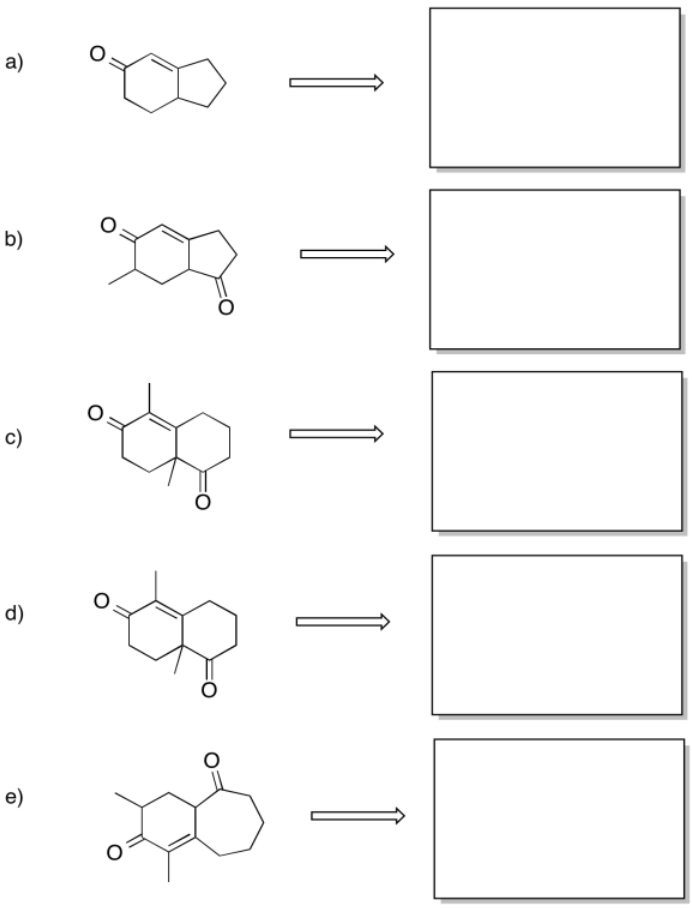


Overall, the Robinson annulation is the sum of these two steps.

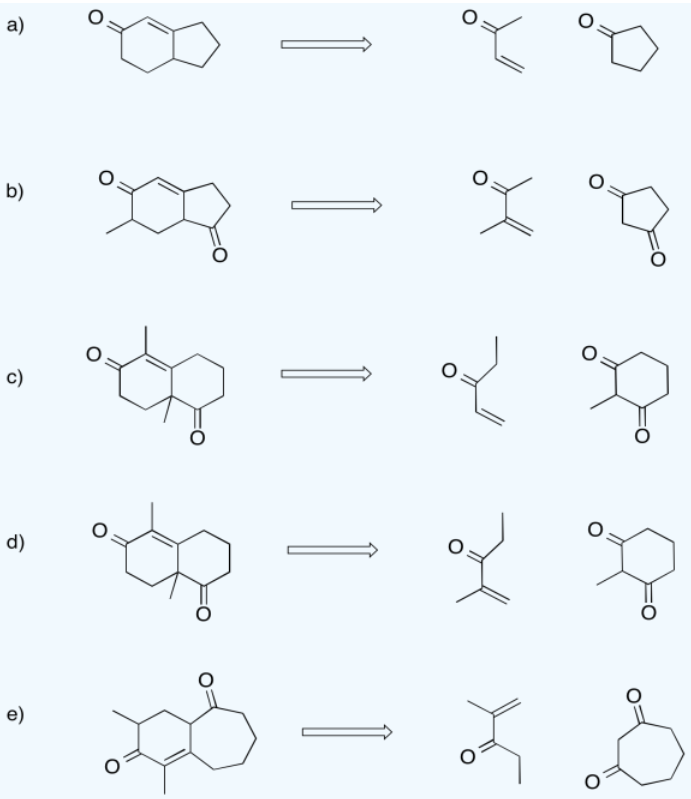


Exercise 3.14.10

Provide the starting materials needed to make the following compounds via Robinson annulation.

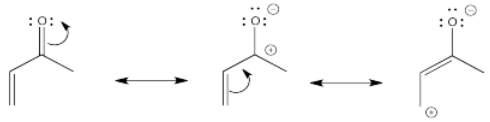


Answer

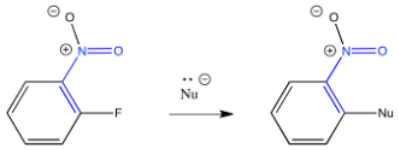


3.15: Conjugate Addition and Elimination in Aromatics

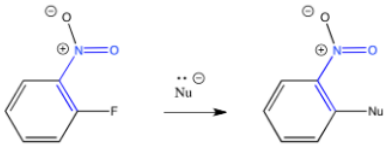
In conjugate addition, a carbonyl group turns a neighbouring alkene into an electrophilic site. An enone, such as the one below, has two electrophilic positions.



A similar situation happens when pi-acceptors such as nitro groups are attached to aromatic rings.

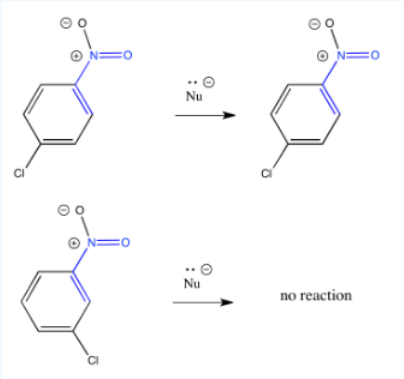


The key step in the mechanism is the loss of the halide ion, which allows the aromaticity to be restored.



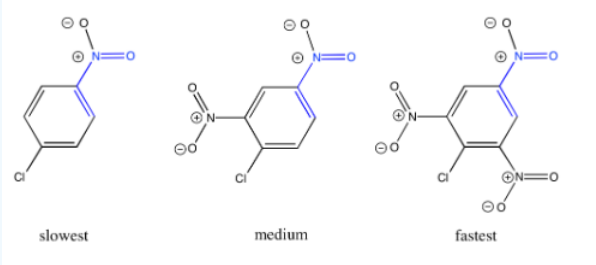
Exercise 3.15.1

The location of the halogen and the electron-withdrawing group matters. Explain why the reaction occurs if the groups are in the 1 and 2 positions (ortho to each other) or the 1 and 4 positions (para to each other), but not if they are in the 1 and 3 positions (meta to each other).



Exercise 3.15.2

Explain why the reaction is faster if additional electron-withdrawing groups are present.



Answer

Add texts here. Do not delete this text first.

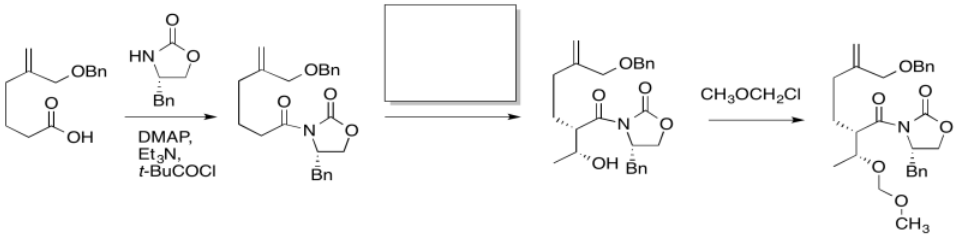
3.16: Carbonyl Addition in Synthesis

As you are probably aware, most of our medicines ultimately come from natural sources. They are derived from natural products, although they have often been modified in some way in order to limit side effects or maximise their effectiveness. You probably also know that the contents of a pill you get from the pharmacy does not come directly from nature. More likely, it is a synthetic product. Pharmaceutical companies make these compounds from smaller, more readily available starting materials.

The total synthesis of natural products provides an interesting context for reactions of organic molecules. We can see where familar reactions have been used to make something important. Whether or not the natural product is ever developed as a commercial drug is beside the point. Often, the exercise of making one compound provides answers that allow researchers to find a better way to make another compound.

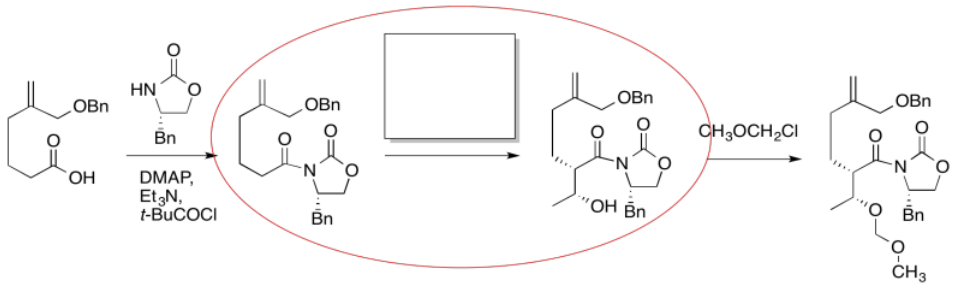
Looking at reactions within an actual synthesis also forces us to develop some spatial reasoning skills. We need to be able to recognise familiar reactions in unfamiliar contexts.

For example, in the following sequence of steps, a set of reagents has been left out. How would we get from one compound to the other?

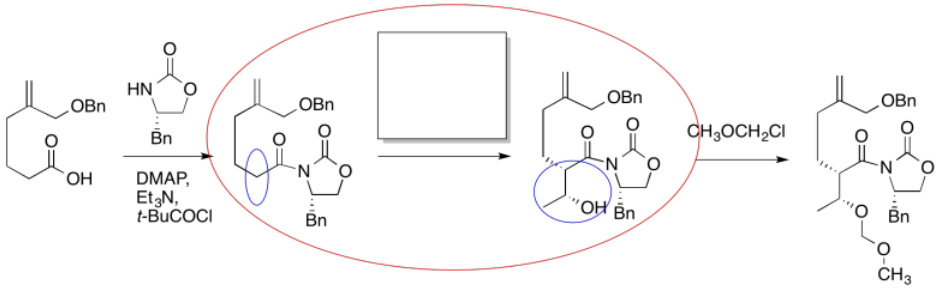


precursor for pseudolaric acids
Pauline Chiu *et al*, *Org. Lett.* **2001**, 1721

The first thing we need to do is block out the infromation we don't need to worry about right now. We'll circle the one reaction that is missing information, and focus only on that one.

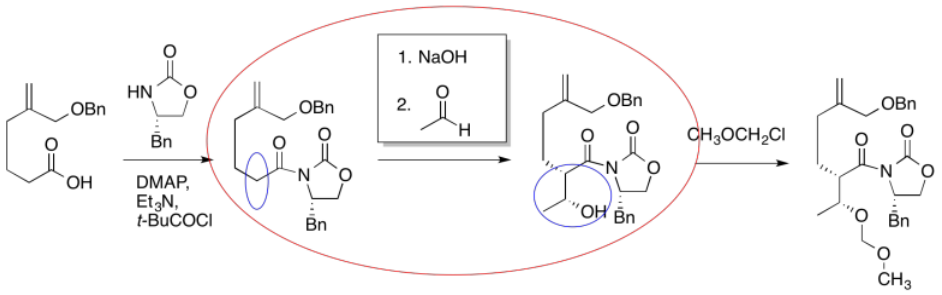


The compound on the right still looks pretty similar to the one on the right. We might try circling the part of the molecule where we can see a difference. That way, we can focus on what reagents would make that difference. What kind of reaction is happening here?



It looks like an aldol reaction. We'll put some typical reagents in the box. First, we'll add a base, to remove a proton from the alpha-position (the acidic hydrogen next to the carbonyl, in the blue ellipse on the left). Second, we'll add the electrophile that would lead

to the product on the right.

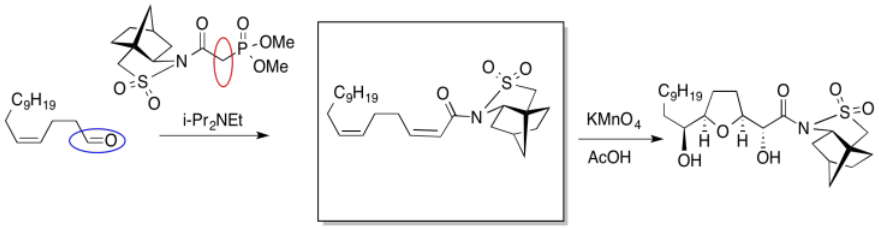


Those might not be exactly the same conditions used by the researchers in this synthesis, but it is a reasonable idea of what needs to be added.

In the following example, an intermediate product has been left out. It is the product of the first reaction, but the starting material for the second reaction.

Once again, we might do an exercise to focus on the important part of the question. What is the electrophile? What is the nucleophile?

On the left, there is an aldehyde. It's a carbonyl compound, so maybe it is an electrophile. We'll circle it in blue. Above the arrow, there is a phosphorus compound. It does not have a positive charge as shown, but there is a very positive phosphorus atom because of the attached oxygens. There is also a base present, although it's a relatively weak one. Maybe we will remove a proton next to the phosphorus to make an ylide. Ylides are good nucleophiles.

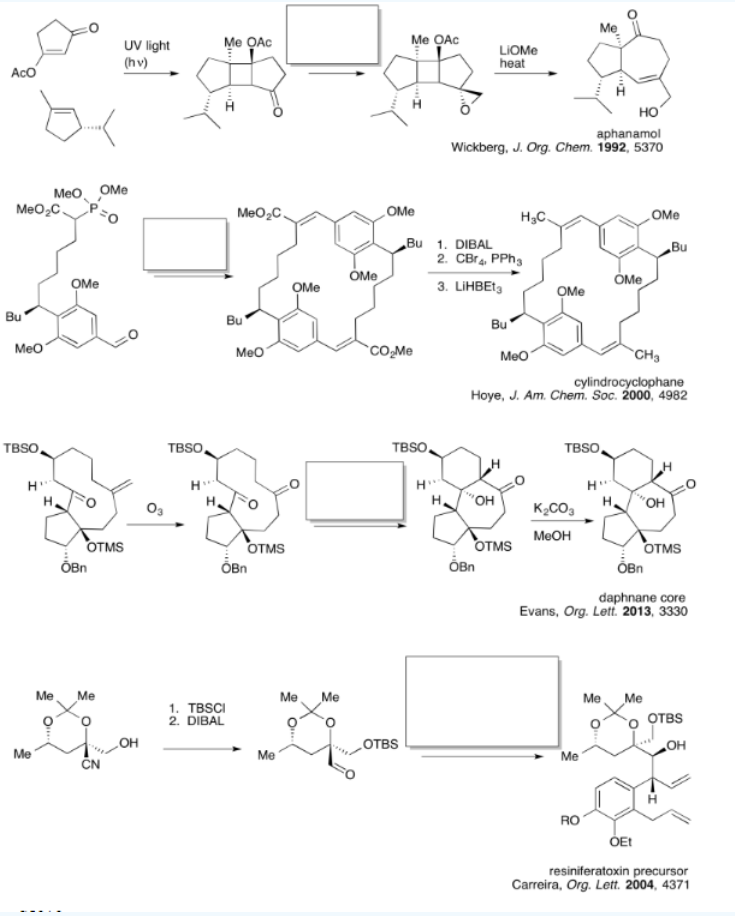


If we are correct, the ylide would combine with the aldehyde to make a C=C double bond. The phosphorus would remove the oxygen atom from the aldehyde. The resulting compound is shown in the box.

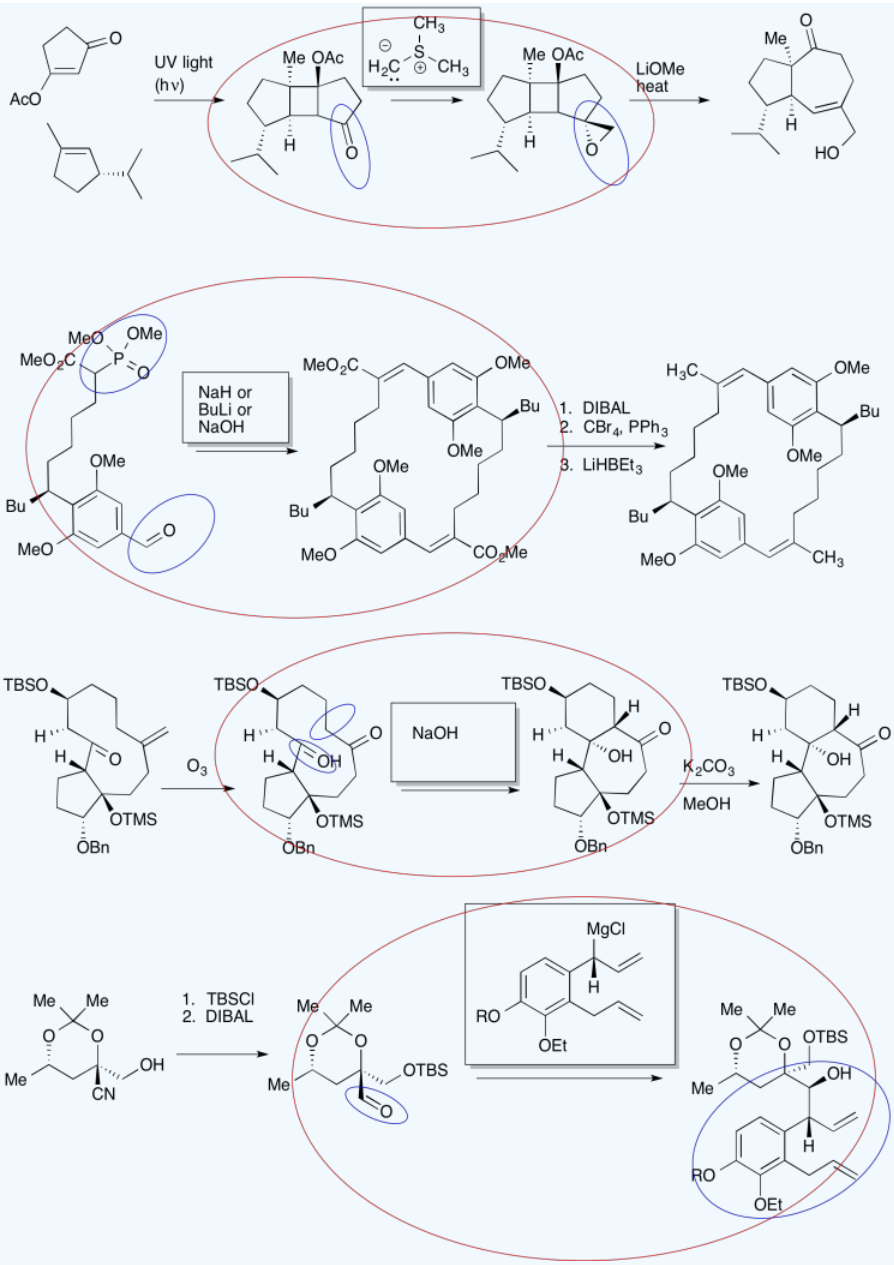
Sometimes, our guesses can be confirmed by looking further ahead in the synthesis to see evidence for the compound we think has formed. In this case, the product of the second reaction may be complicated enough to make that process difficult (even if we already know something about alkene oxidations).

Exercise 3.16.1

Practice the methods described above to fill in the missing reagents.

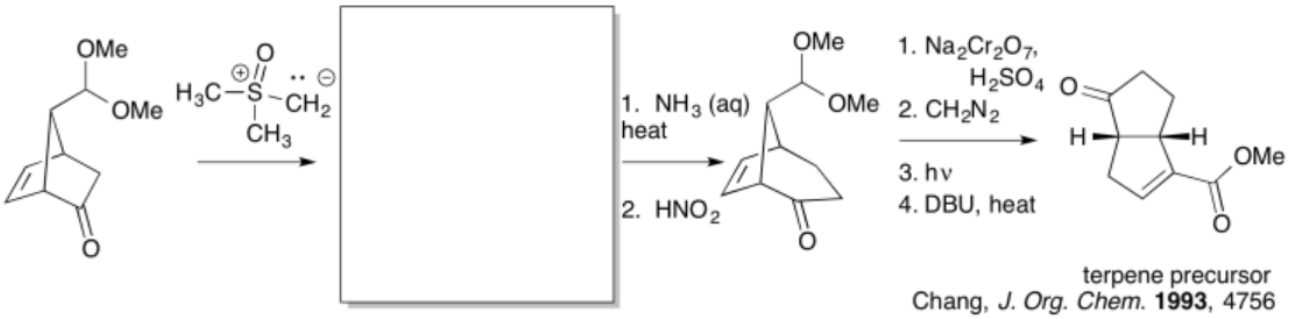


Answer



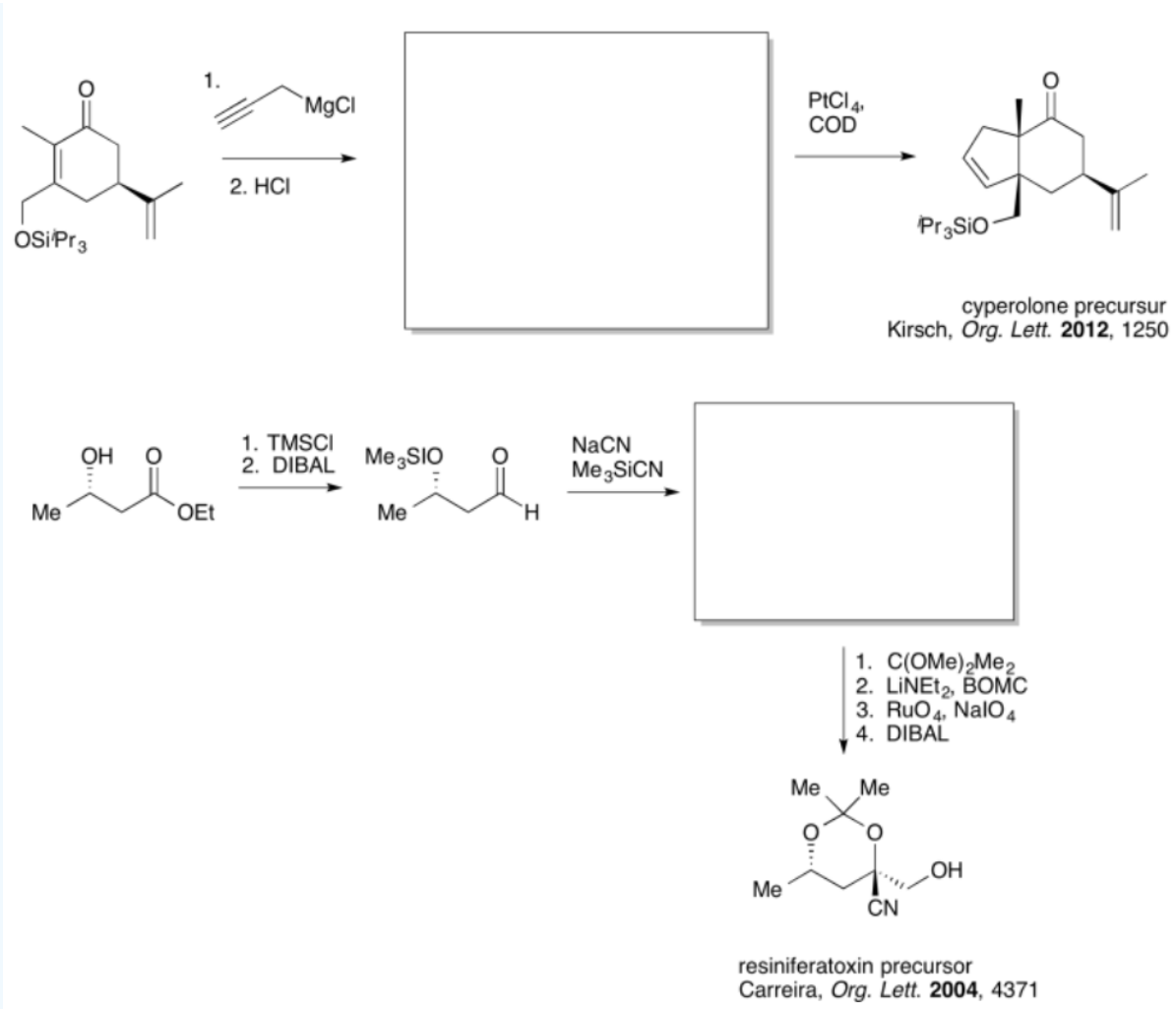
Exercise 3.16.2

Practice the methods described above to fill in the missing products.

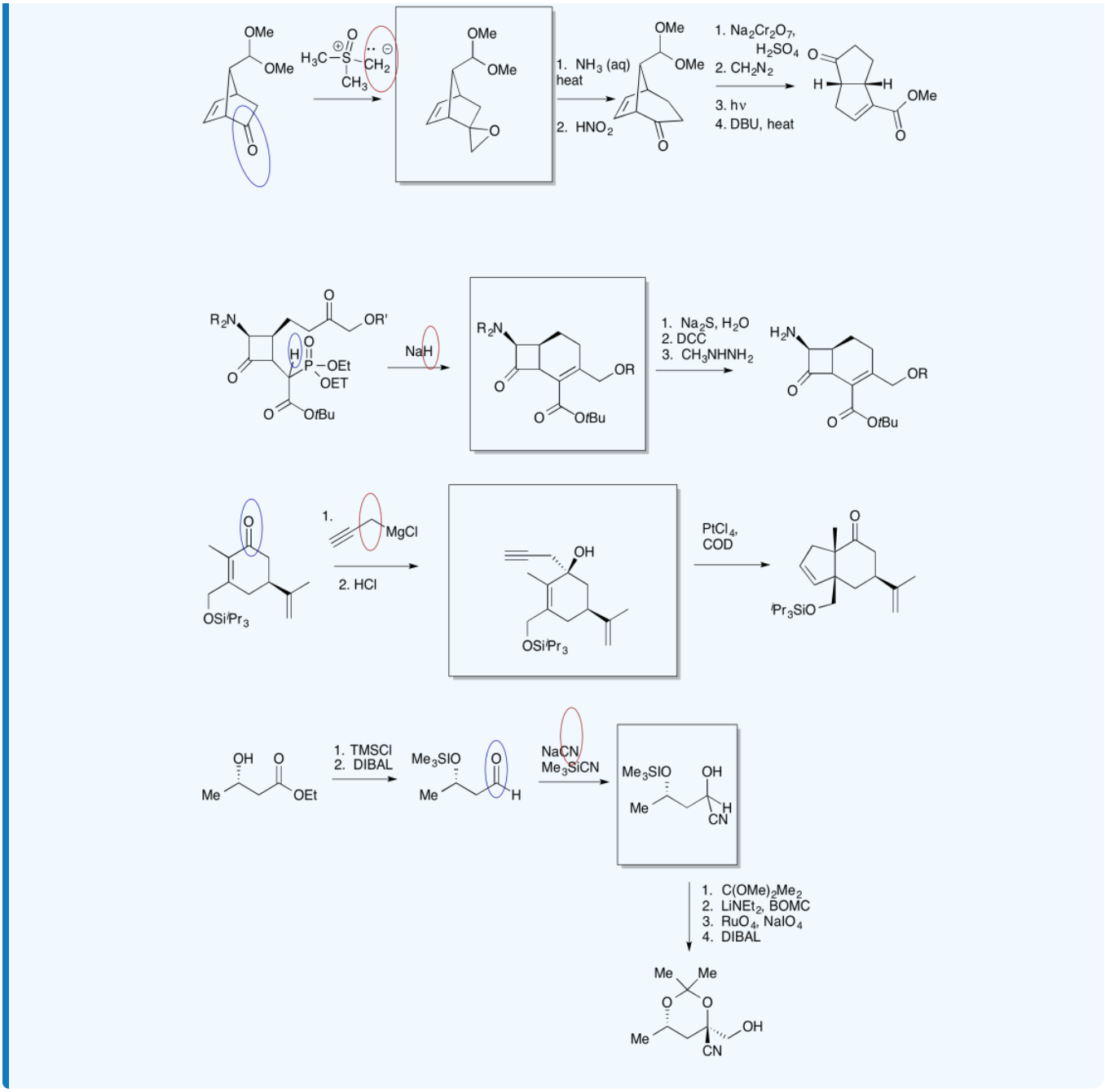


terpene precursor
Chang, *J. Org. Chem.* **1993**, 4756

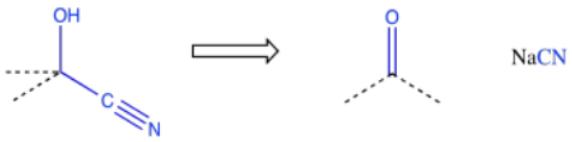
cephalosporin precursor
Miller, *J. Org. Chem.* **1998**, 1221



Answer



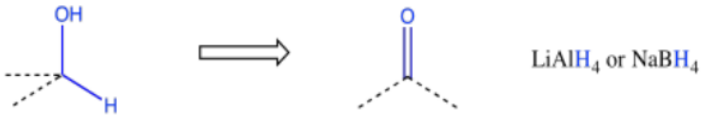
Because chemists are generally working toward a specific synthetic target, they frequently need to work backwards to plan out a series of reactions that will produce the desired compound. A good memory of specific patterns that occur in reaction products can help to identify what reaction is needed to get there. For example, if the product contains a cyanohydrin, a CN attached to the same carbon as an OH, then it may be possible to construct that part of the compound using addition of cyanide to a carbonyl.



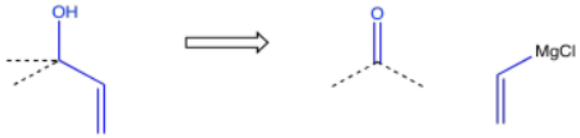
This type of thinking is called "retrosynthetic analysis". The open arrow shown above is called a retrosynthetic arrow, and it roughly translates as "can be made from". That is, the cyanohydrin on the left can be made from the carbonyl compound on the right. By working backwards through a series of such reactions, we could eventually arrive at simple starting materials that could

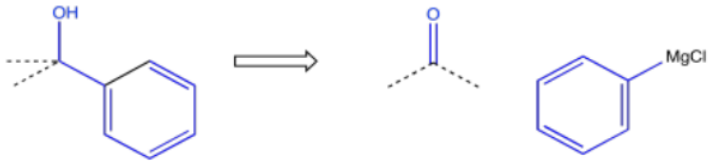
be used to make a very complicated molecule. This approach to thinking about how to make organic molecules is generally attributed to E. J. Corey of Harvard University. Corey was awarded the Nobel Prize in chemistry for his transformative work in organic synthesis.

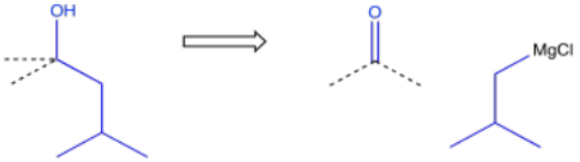
Other retrosynthetic patterns may be familiar to you at this point. For example, an alcohol could always be made from reduction of a carbonyl.



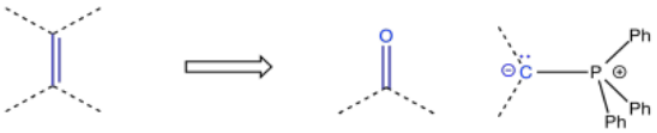
On the other hand, it may be more convenient to make the alcohol via addition of a Grignard reagent (or something similar) to a carbonyl. That approach may be especially appealing if the alcohol carbon is attached to a common hydrocarbon fragment such as a vinyl, a phenyl or an alkyl group.



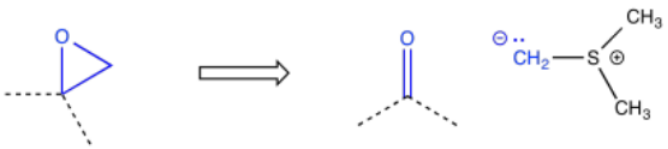




So, there are a number of ways in which an alcohol could be incorporated into a molecule. Other functional groups are also commonly targeted in this approach. For example, alkenes are very frequently added via Wittig or Horner-Wadsworth-Emmonds reactions, which make use of phosphorus ylides.

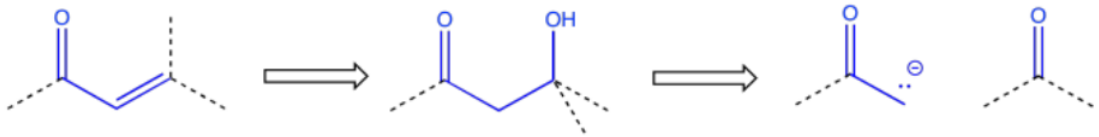


Epoxides are often added via the Corey-Chaykovsky epoxidation, just one of many reactions named after E. J. Corey. This reaction uses a sulfur ylide.



Sometimes a wider collection of atoms indicates a particular route to the target. For example, the pattern carbonyl-carbon-alcohol -- or C=O-C-COH -- would result from an aldol reaction.

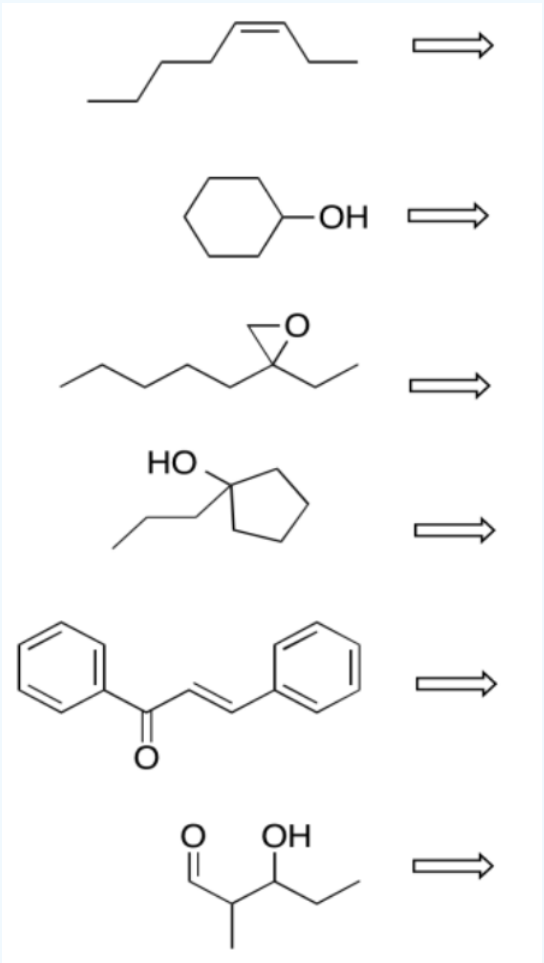
An enone -- that is, a C=O-C=C pair in conjugation -- also suggests origins in an aldol reaction, although the aldol in this case resulted in a condensation or dehydration.



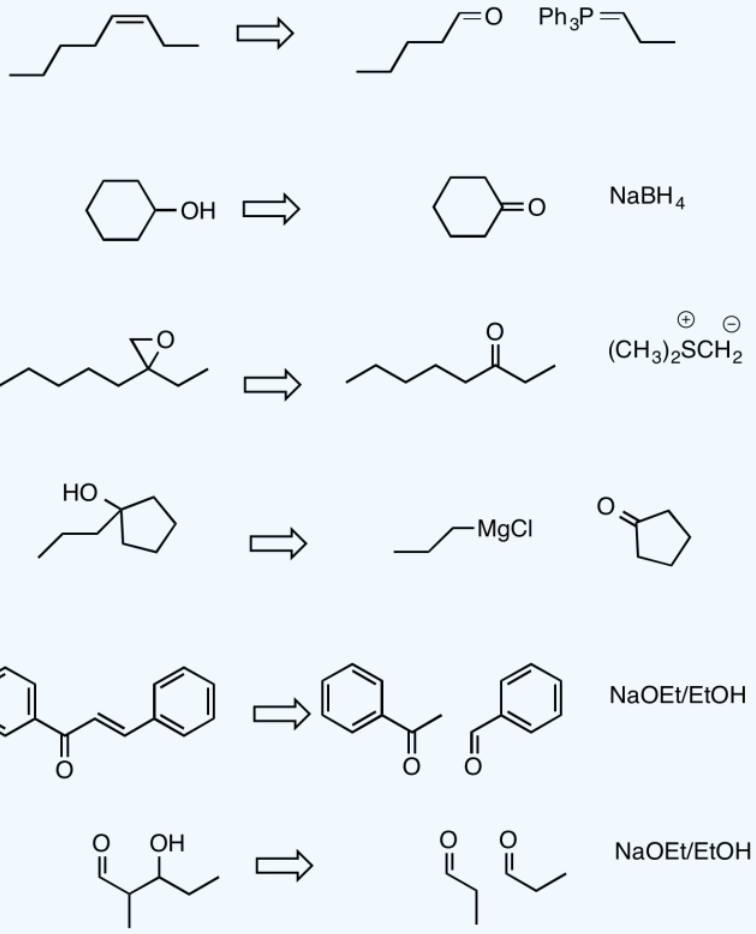
These relationships between products and the starting materials that they can be made from are useful in planning out syntheses. The ones we have looked at here involve only the addition to carbonyls of anionic and semianionic nucleophiles, as well as ylides. There are plenty of other such relationships in other areas of organic reactivity.

Exercise 3.16.3

Perform retrosynthetic analysis in each of the following cases, proposing something that the compound could be made from.

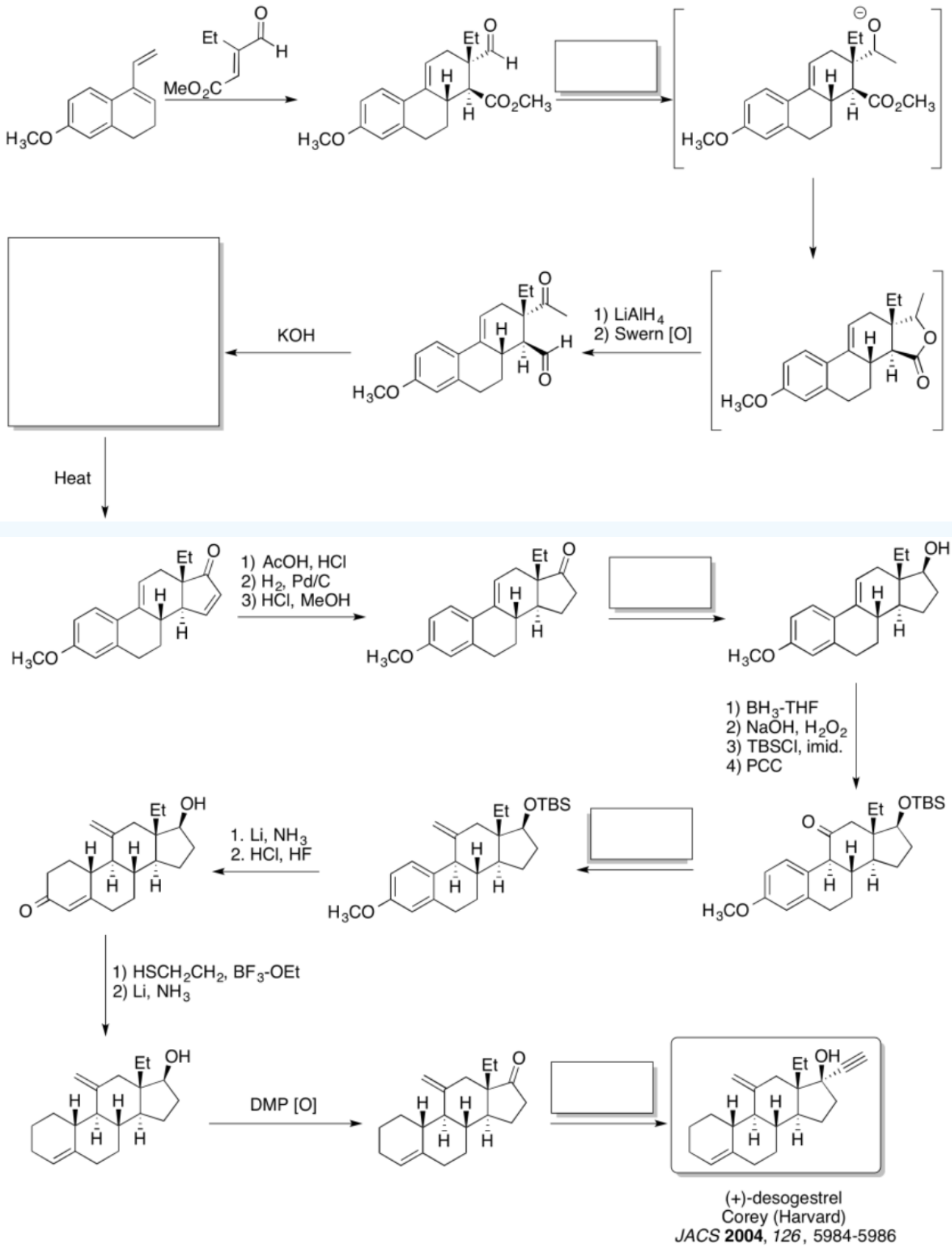


Answer

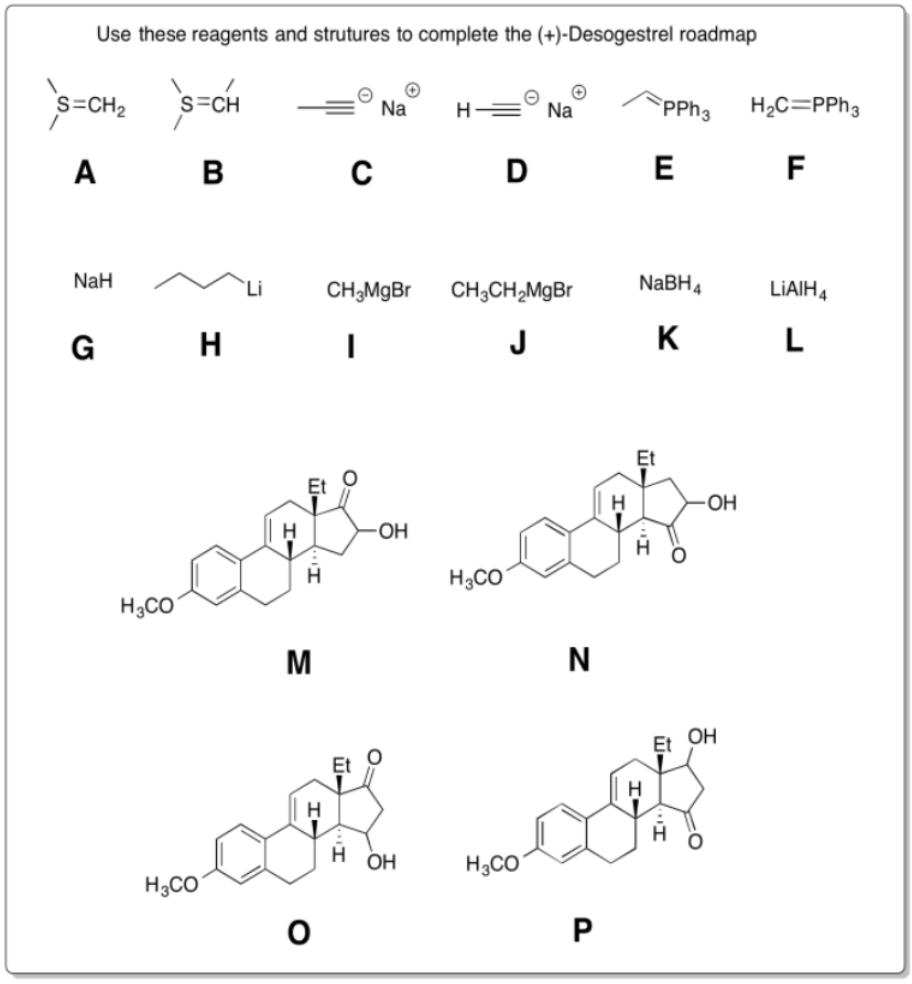


Exercise 3.16.4

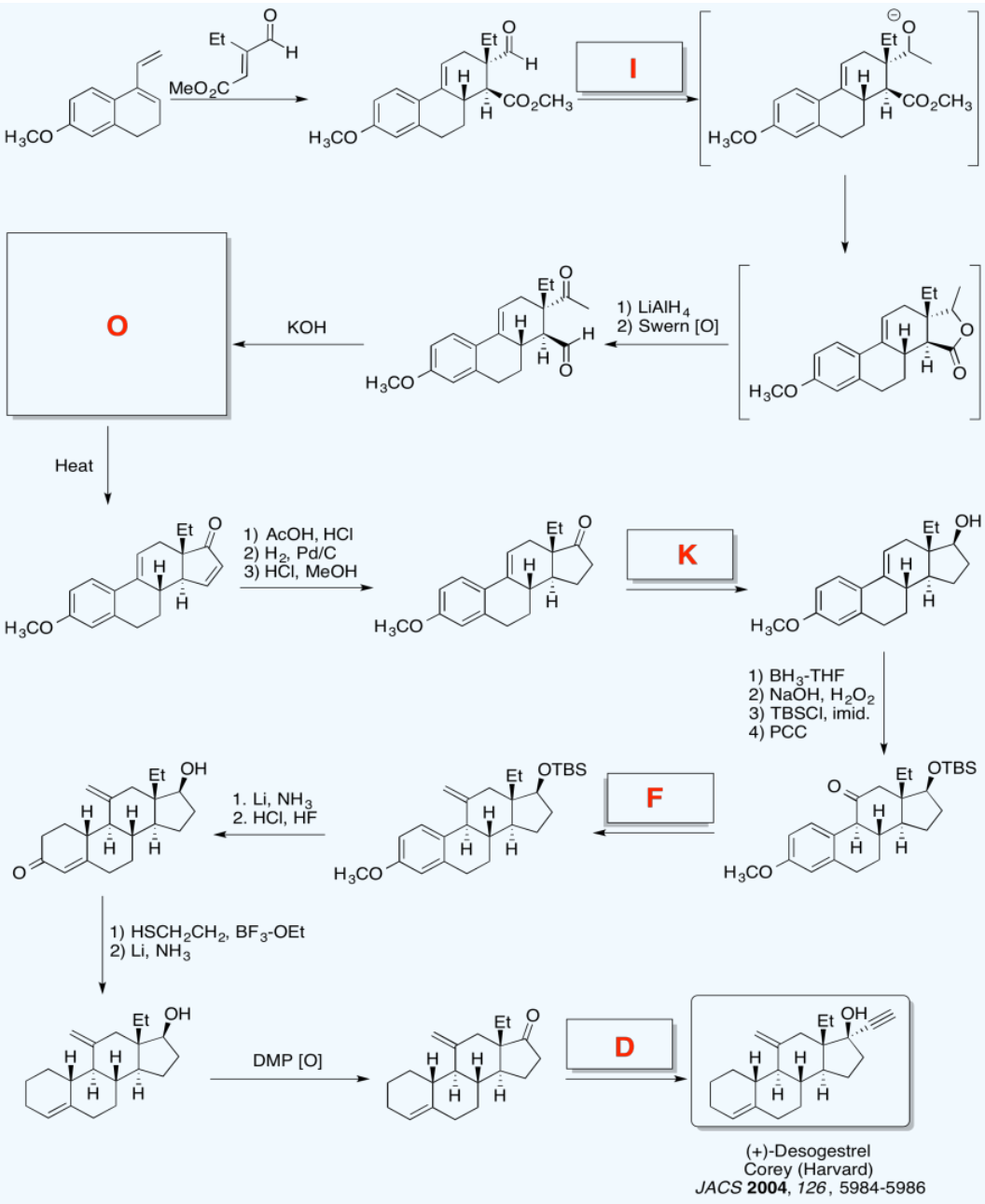
Practice the methods described above to fill in the missing reagents and products in the following synthesis. Requires knowledge of anionic and semi-anionic nucleophiles, aldols and ylides. A list of possible reagents is provided below the roadmap.



(+)-desogestrel
Corey (Harvard)
JACS **2004**, *126*, 5984-5986


Use these reagents and strutures to complete the (+)-Desogestrel roadmap
S=CH2
S=CH
Na
H
Na
PPh3
H2C=PPh3
A
B
C
D
E
F
NaH
Li
CH3MgBr
CH3CH2MgBr
NaBH4
LiAlH4
G
H
I
J
K
L
Et
O
OH
H
H
H3CO
M
Et
H
OH
H
O
H3CO
N
Et
O
H
H
OH
H3CO
O
Et
OH
H
H
O
H3CO
P

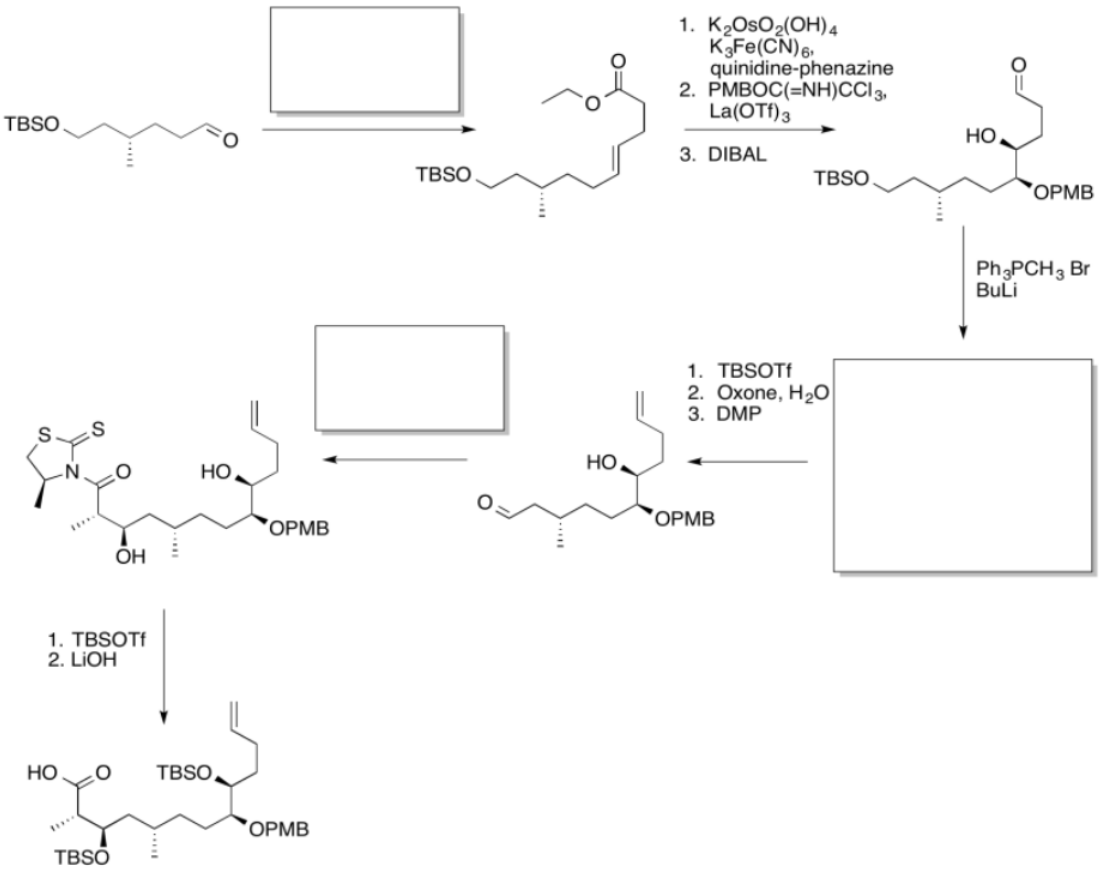
Answer

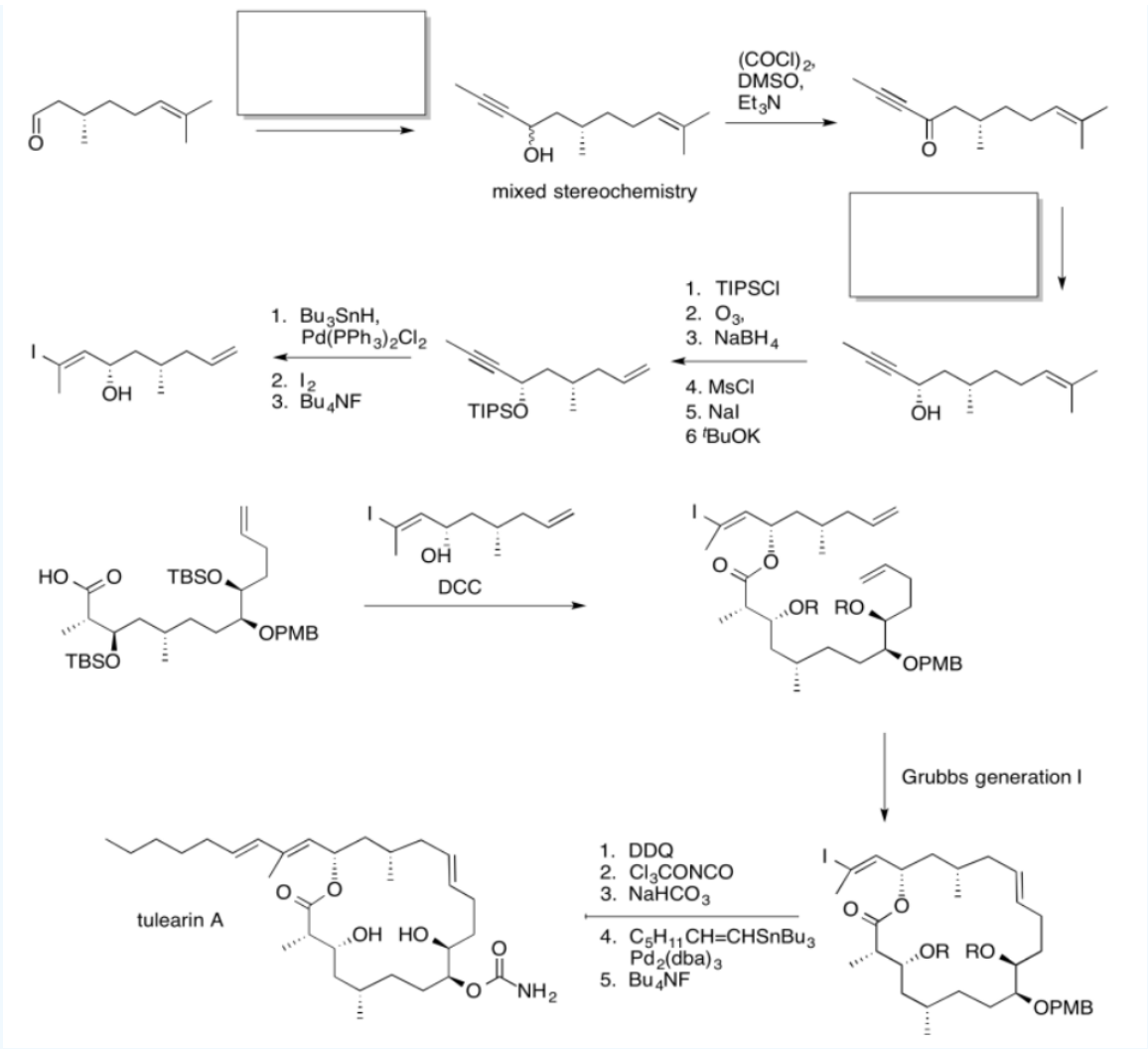


Exercise 3.16.5

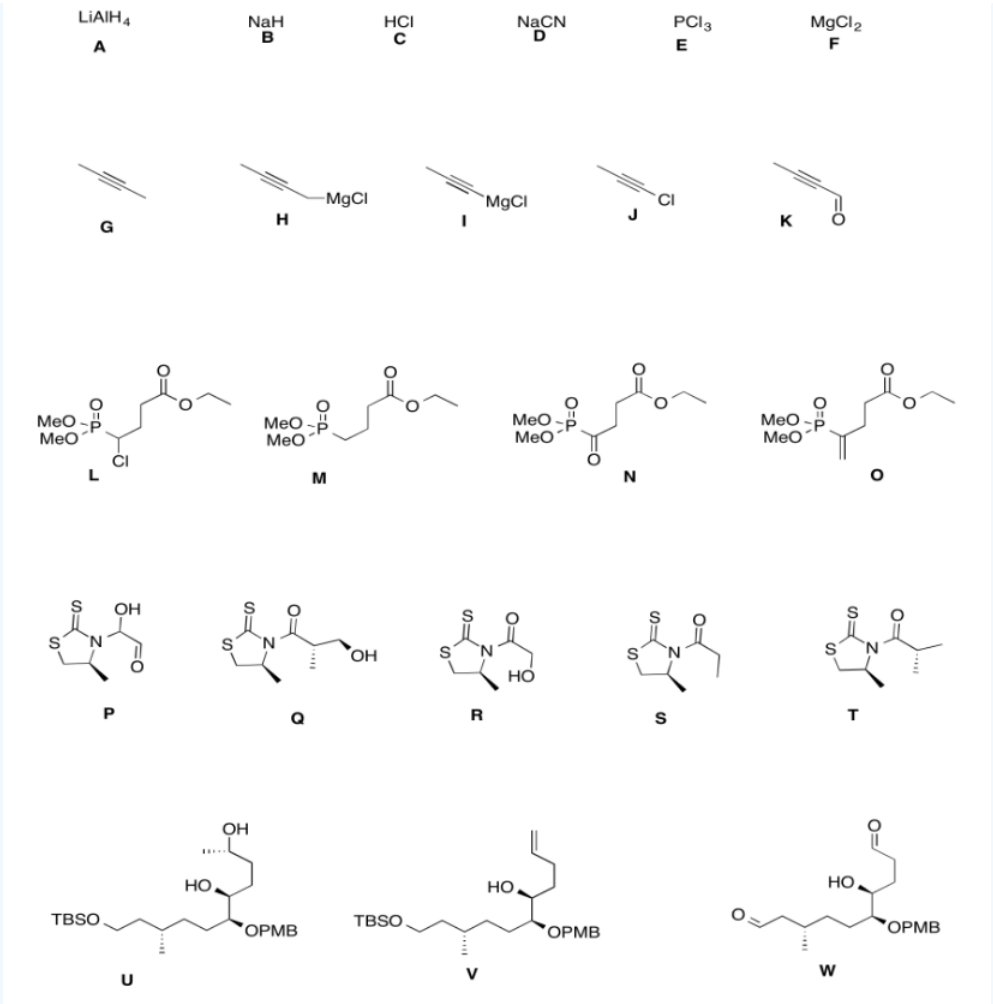
Practice the methods described above to fill in the missing reagents and products in the following synthesis. Requires knowledge of anionic and semi-anionic nucleophiles, aldols and ylides. A list of possible reagents is provided below the roadmap.

Synthesis of tulearin A, Janine Cossy, ESPCI ParisTech, 2009
Isolated from a Madagascar marine sponge; potent activity against leukemia cell lines.



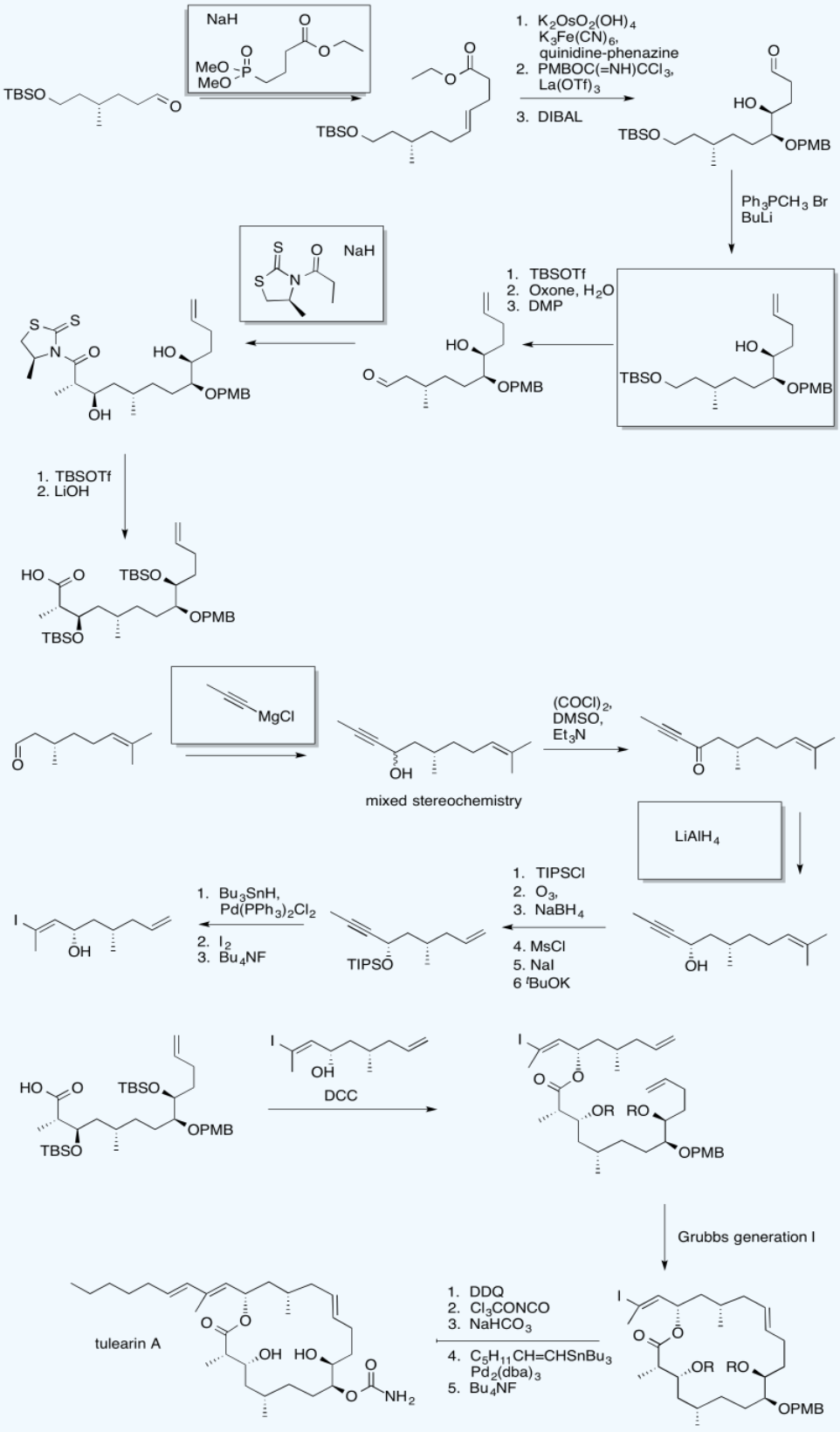


Use the reagents below to finish the tulearin A roadmap.


LiAlH4
A
NaH
B
HCl
C
NaCN
D
PCl3
E
MgCl2
F
G
H
MgCl
I
MgCl
J
Cl
K
O
MeO
MeO
P
O
Cl
L
M
N
O
S
OH
N
O
P
Q
R
HO
S
T
TBSO
OPMB
U
V
W

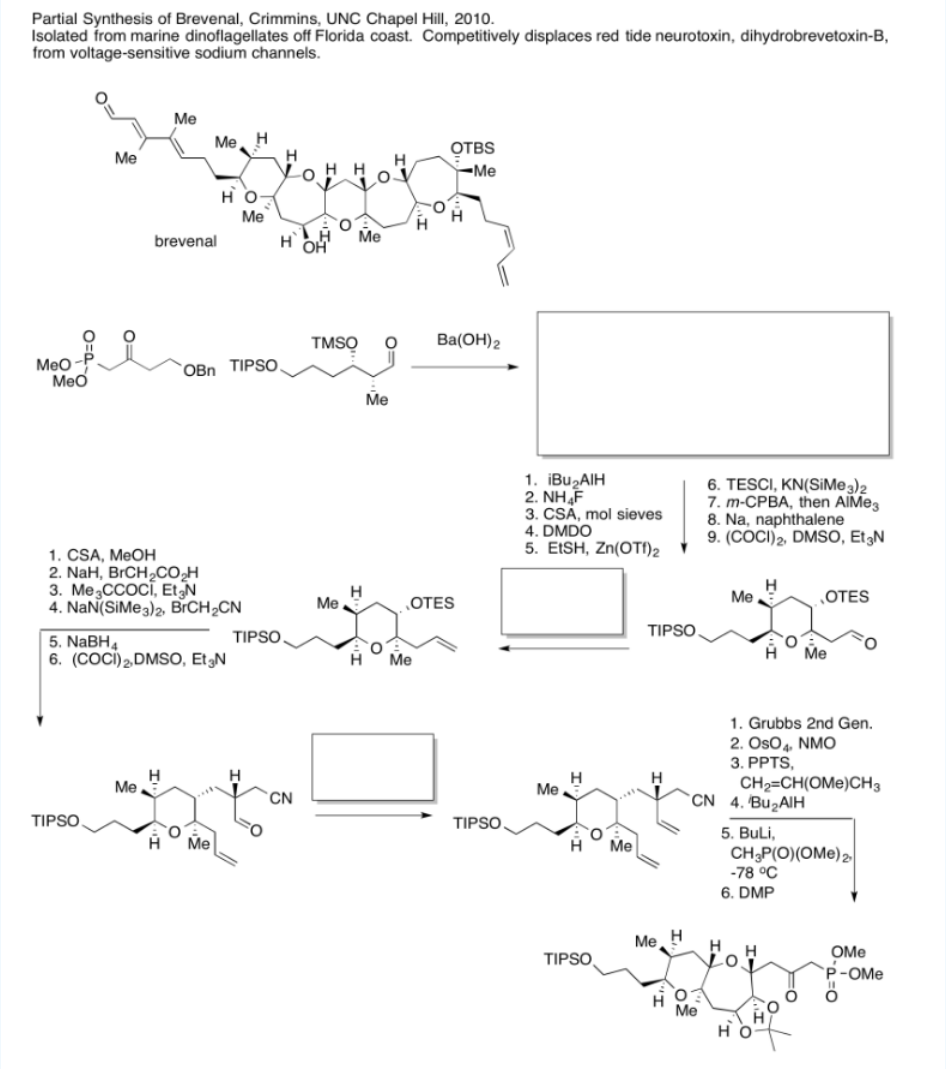
Answer

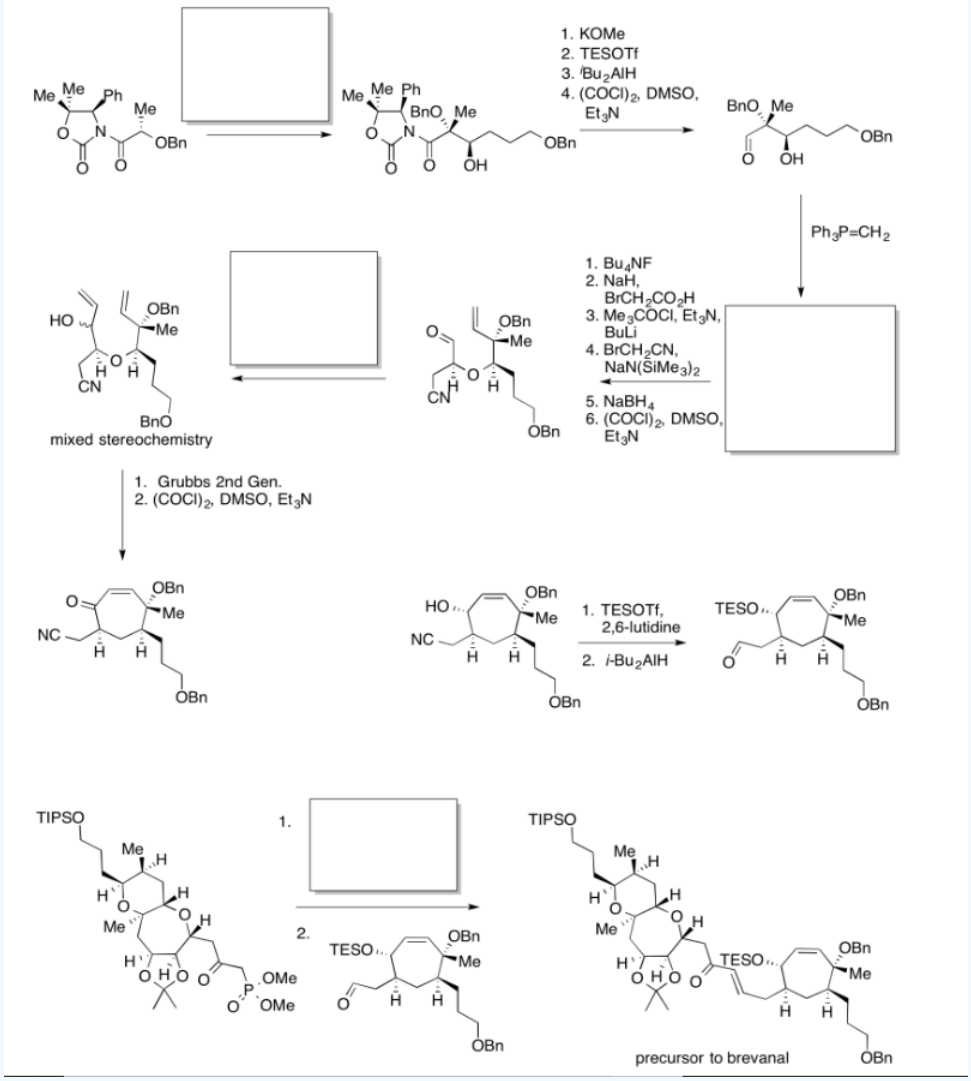
Synthesis of tulearin A, Janine Cossy, ESPCI ParisTech, 2009
Isolated from a Madagascar marine sponge; potent activity against leukemia cell lines.



Exercise 3.16.6

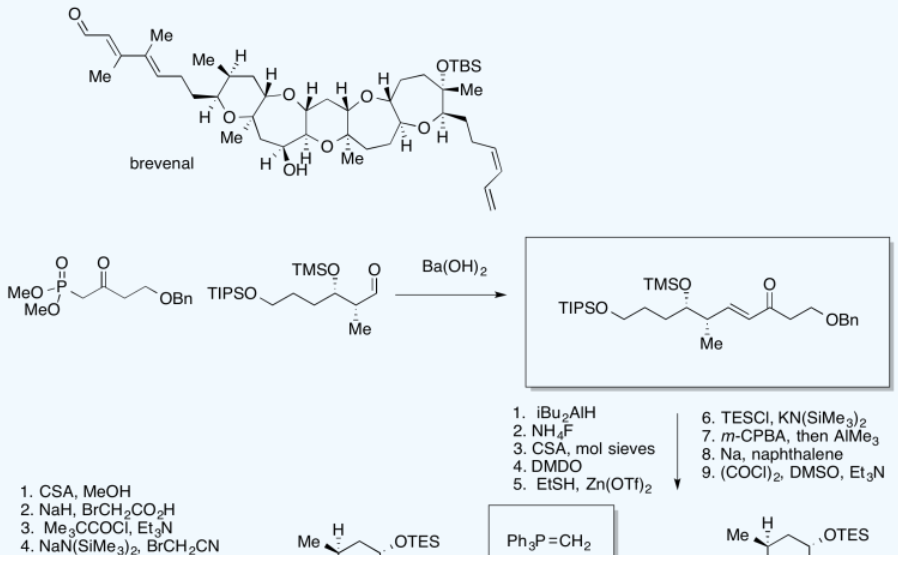
Practice the methods described above to fill in the missing reagents and products in the following synthesis. Requires knowledge of anionic and semi-anionic nucleophiles, aldols and ylides.

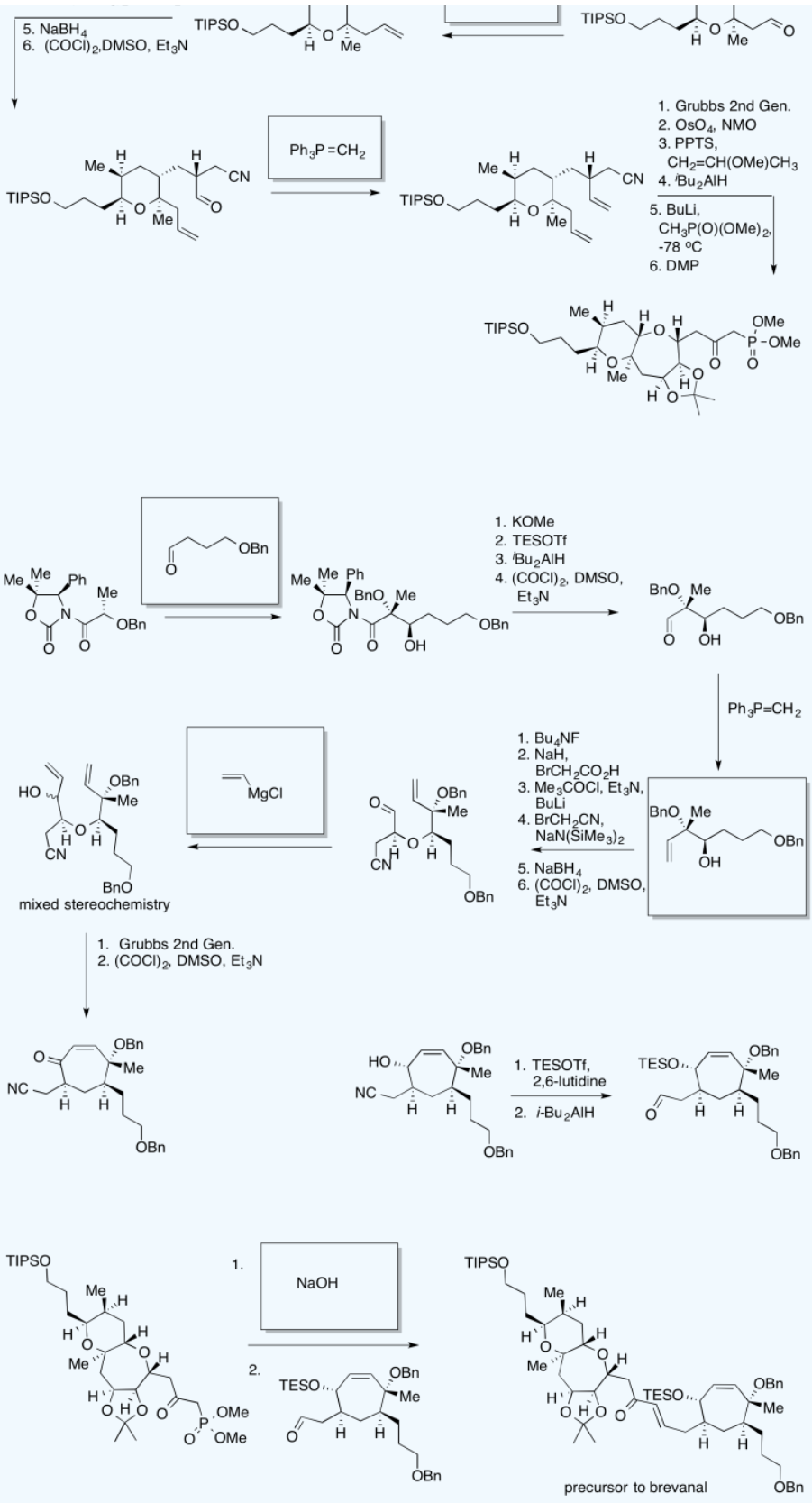




Answer

Partial Synthesis of Brevenal, Crimmins, UNC Chapel Hill, 2010.
Isolated from marine dinoflagellates off Florida coast. Competitively displaces red tide neurotoxin, dihydrobrevetoxin-B, from voltage-sensitive sodium channels.

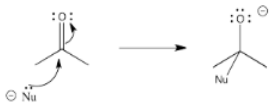




3.17: Summary of Elementary Steps

The reactions of carbonyls can become very complicated, involving many steps. In essence, though, the steps involve only a few, different elementary reactions.

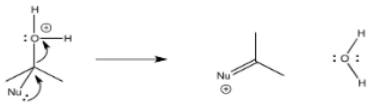
- Donation to the carbonyl.
- A lone pair is donated from a nucleophile to the carbonyl carbon, forming a bond.



- Proton transfer.
- Protons are most often transferred from a positively charged atom to a neutral atom with a lone pair.
- Protons are also easily transferred from a positively charged atom to a negatively charged atom.
- Sometimes, a proton might be transfered from a neutral atom to a negatively charged one.

In many of the reactions of anionic and semi-anionic nucleophiles, these two steps complete the entire reaction mechanism. However, if an additional lone pair can be revealed at the nucleophilic atom (often by transferring a proron away from this site), additional steps occur.

- Pi donation.
- In pi donation, two heteroatoms, both with lone pairs, are attached to the same carbon. A lone pair is donated to the carbon, and one of the heteroatoms is pushed off.



Many mechanisms involve a number of proton transfers and pi donations. These steps occur over and over, inching the molecule along step by step towards the product. Usually, each proton transfer helps to prepare an atom for eventual removal via pi donation.

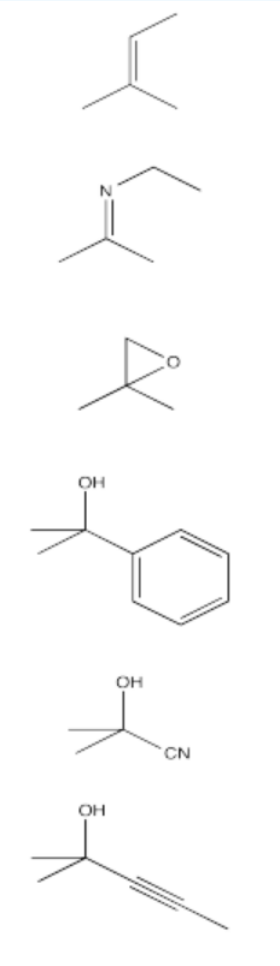
Occasionally, if the nucleophile is neutral, these steps are preceded by an initial activation step.

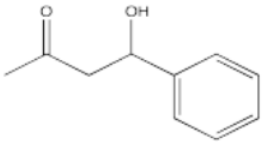
- Carbonyl activation.
- Usually makes the reaction faster.
- Is especially helpful when the nucleophile is uncharged, and hence less reactive.
- The carbonyl is often activated by a proton (from a protic acid) but it can also be activated by a Lewis acid (such as a metal ion).

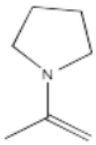
3.18: Additional Problems

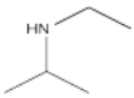
Exercise 3.18.1

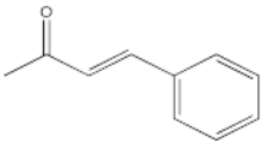
Synthesize the following compounds starting from acetone.





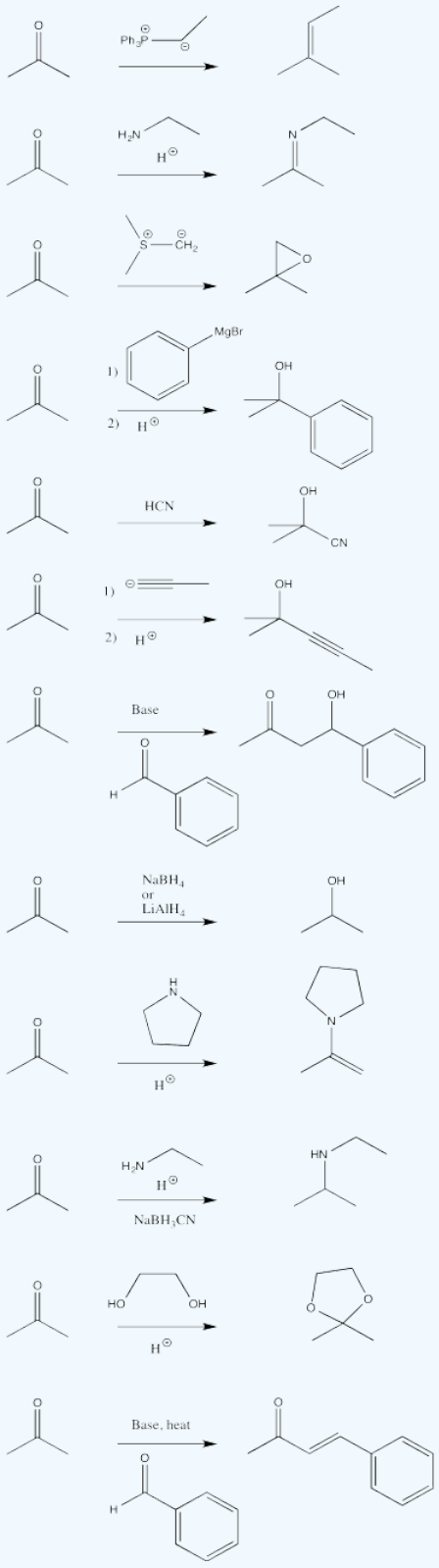






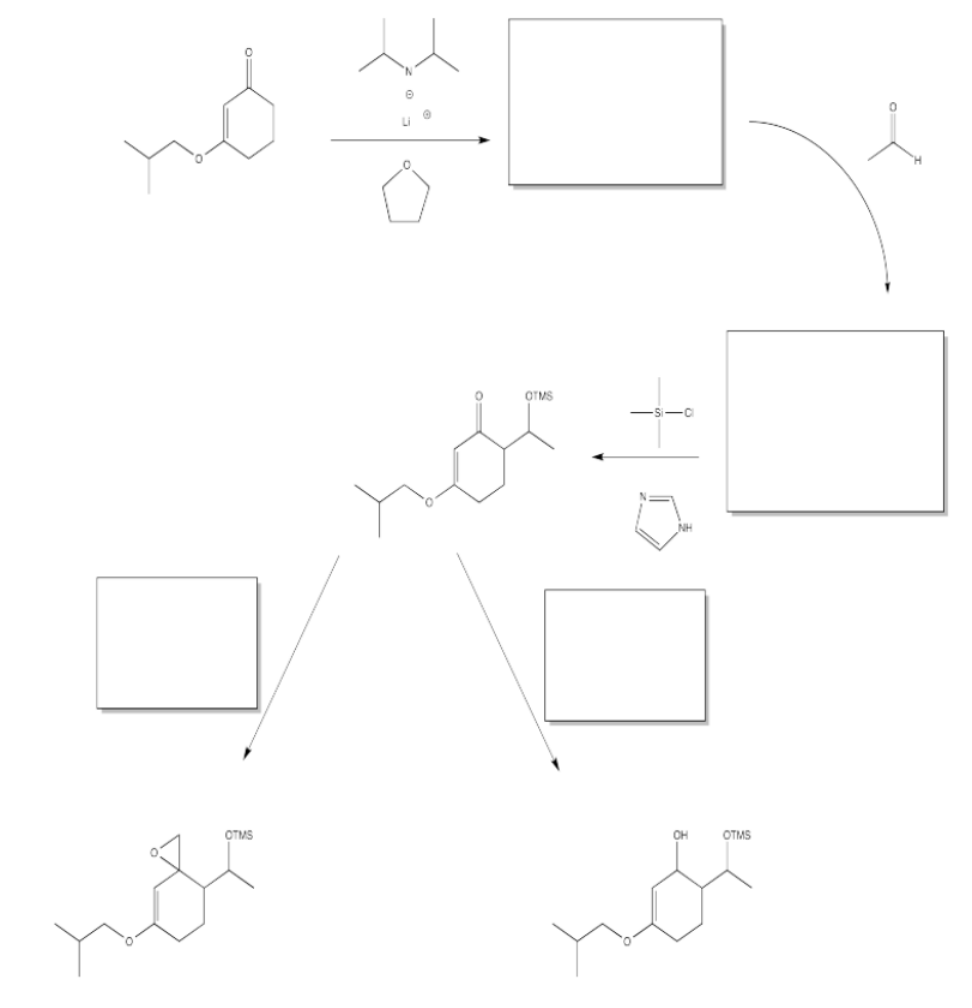
Answer

Synthesize the following stating from acetone.

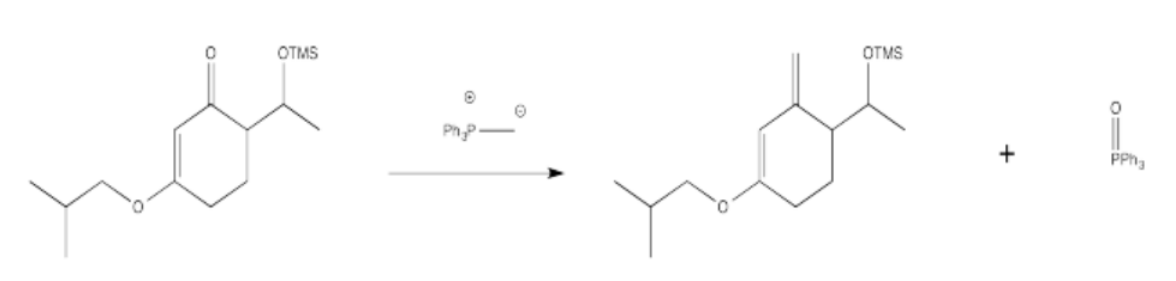


Exercise 3.18.2

Researchers are investigating cyclohexenone derivatives as potential inhibitors for esterases. Below is a scheme for the synthesis of several of these derivatives. Fill in the boxes with the appropriate intermediates or reagents.

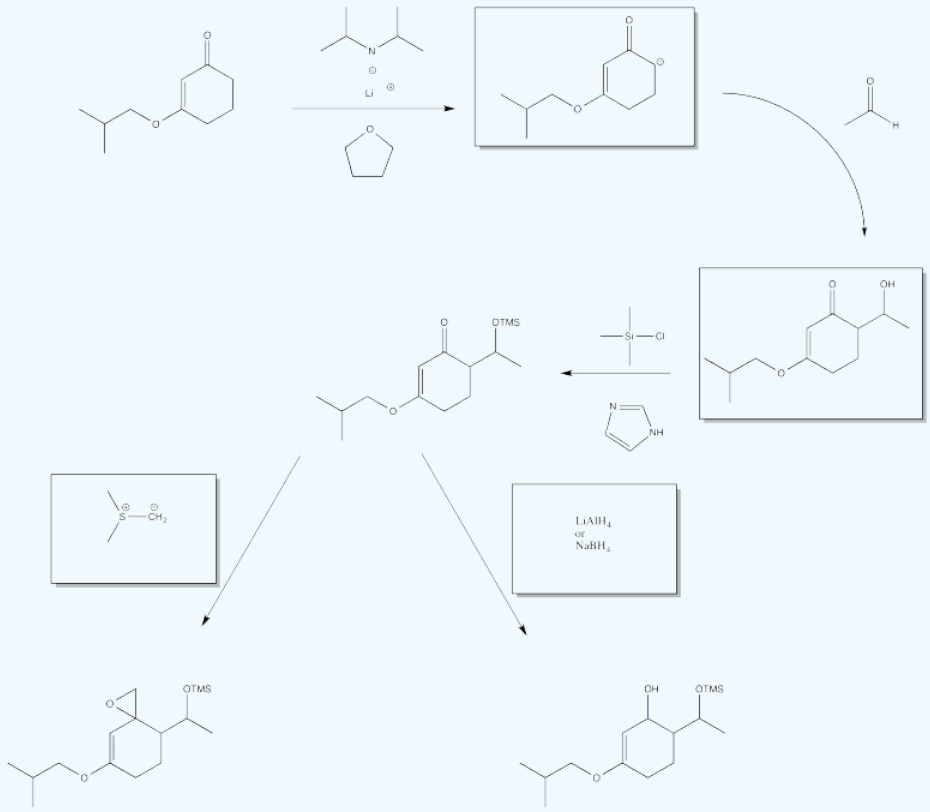


Below is another derivative that they made. Provide a mechanism (make sure to draw arrows) for the following reaction:

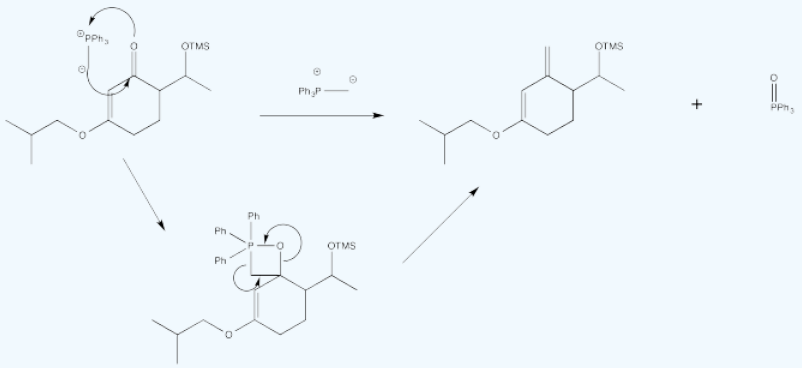


Answer

Researchers are investigating cyclohexenone derivatives as potential inhibitors for esterases. Below is a scheme for the synthesis of several of these derivatives.
Fill in the boxes with the appropriate intermediates or reagents.

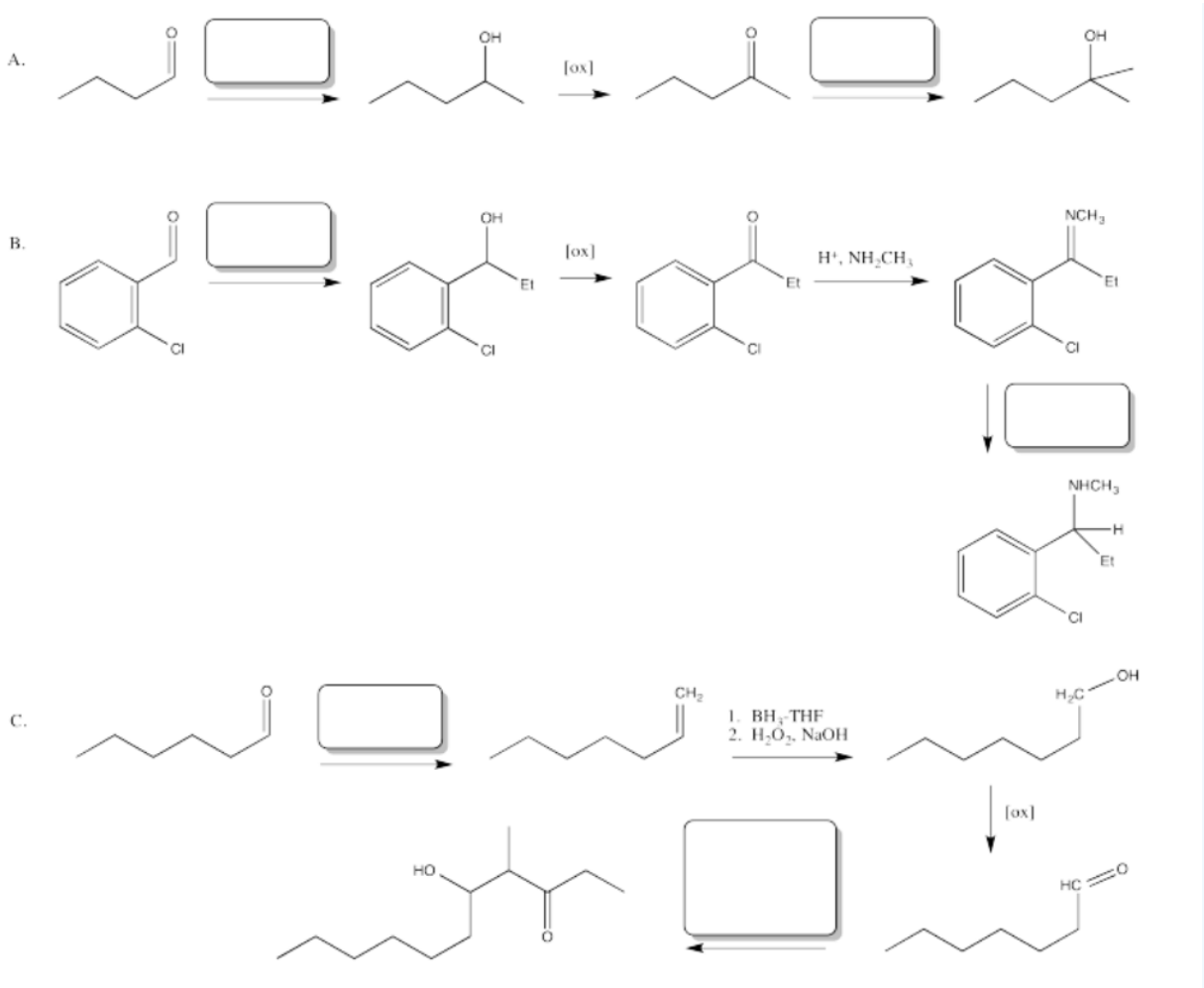


Below is another derivative that they made. Provide a mechanism (make sure to draw arrows) for the following reaction:

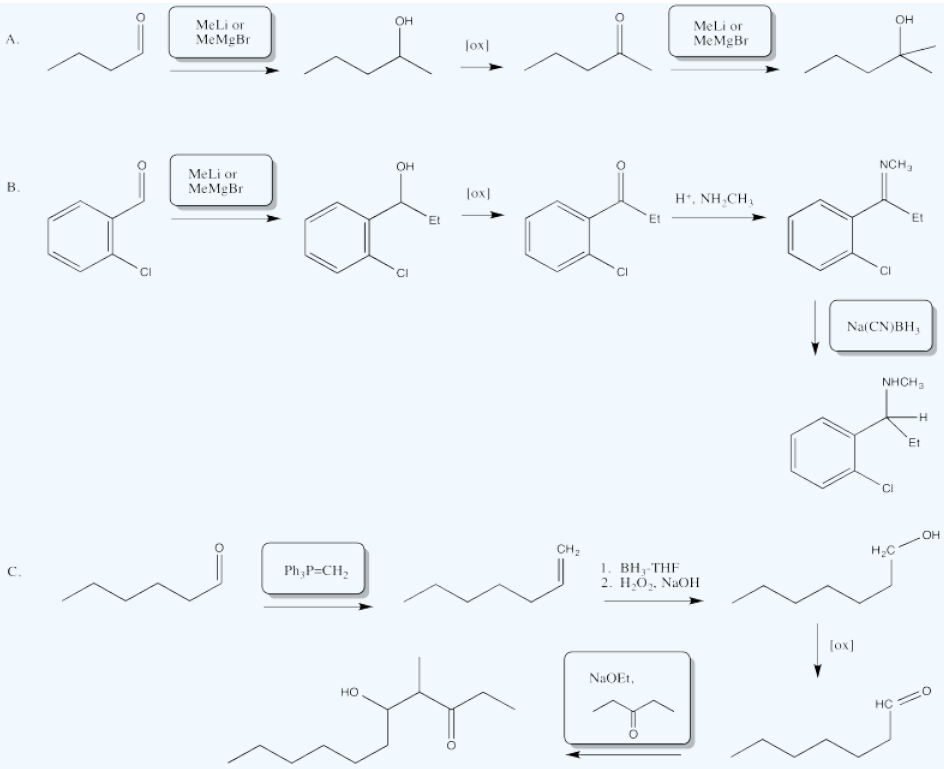


Exercise 3.18.3

Fill in the product or reagent for each of the following transformations. Remember there is always an acidic workup assumed.

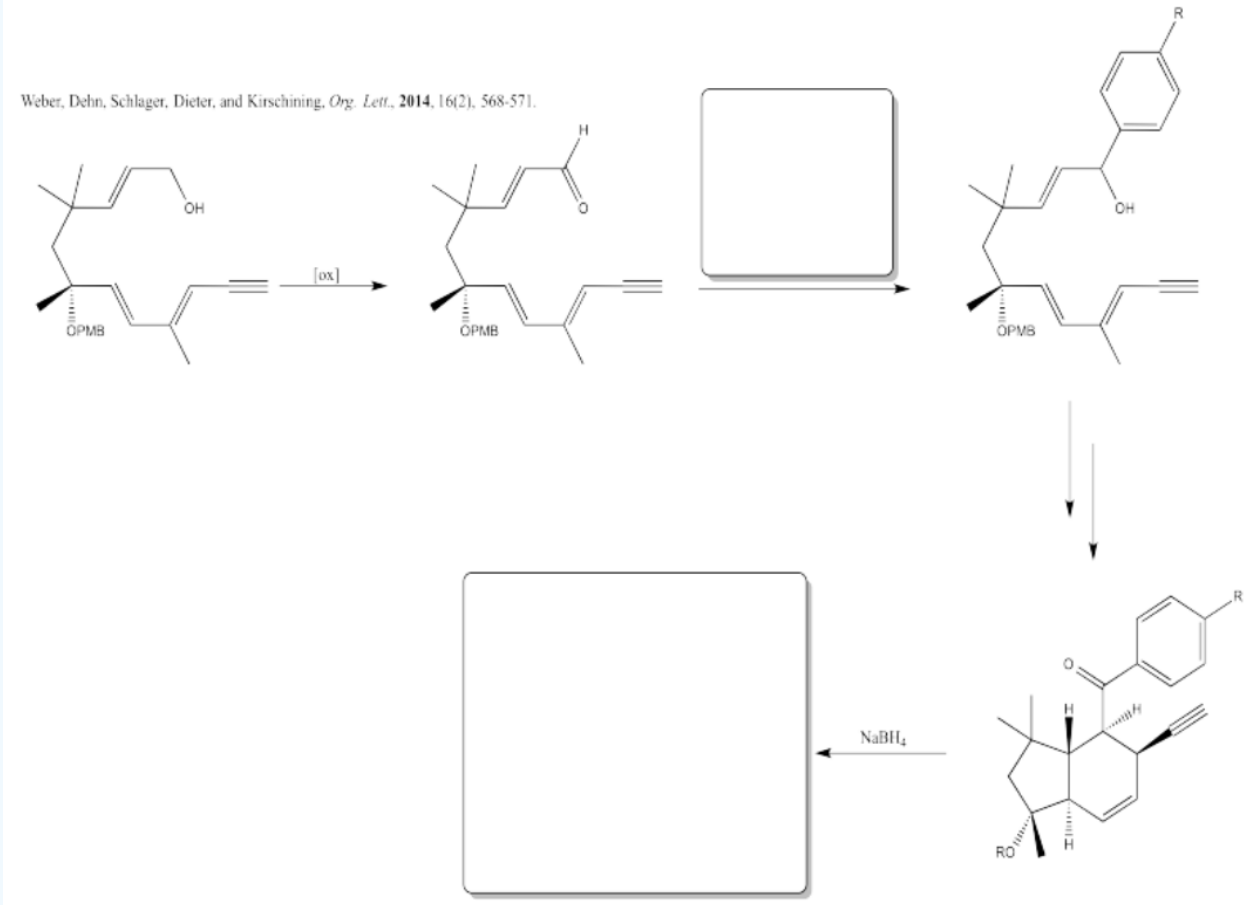


Answer

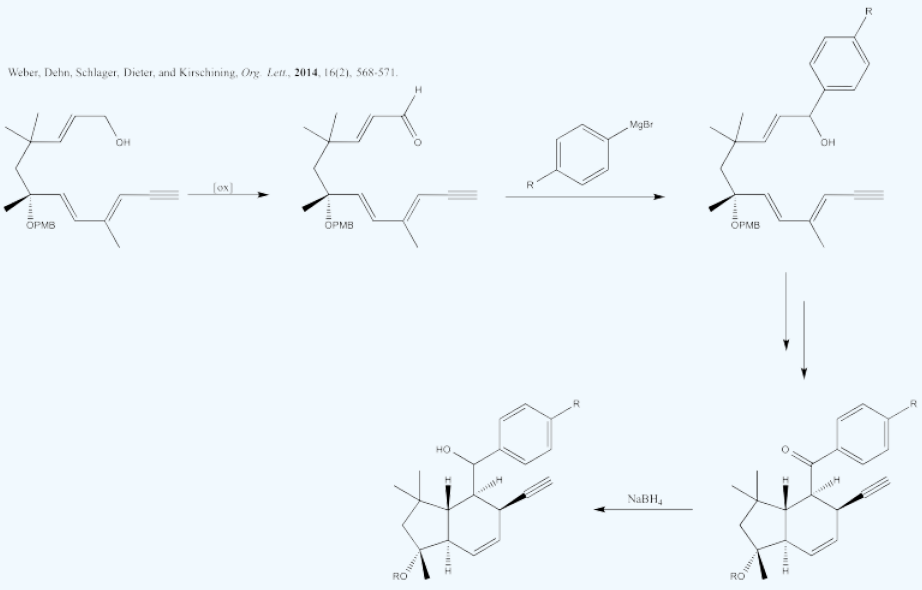


Exercise 3.18.4

Fill in the blanks in the following synthesis. Includes addition to carbonyls (anionic nucleophiles).

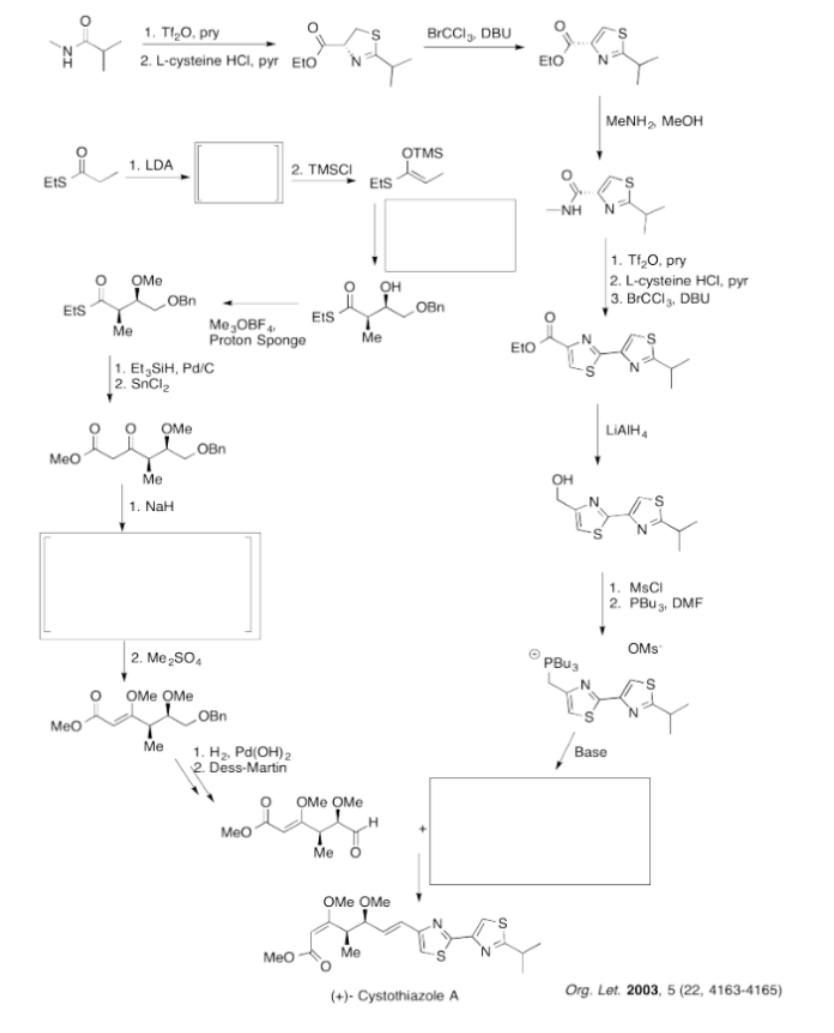


Answer

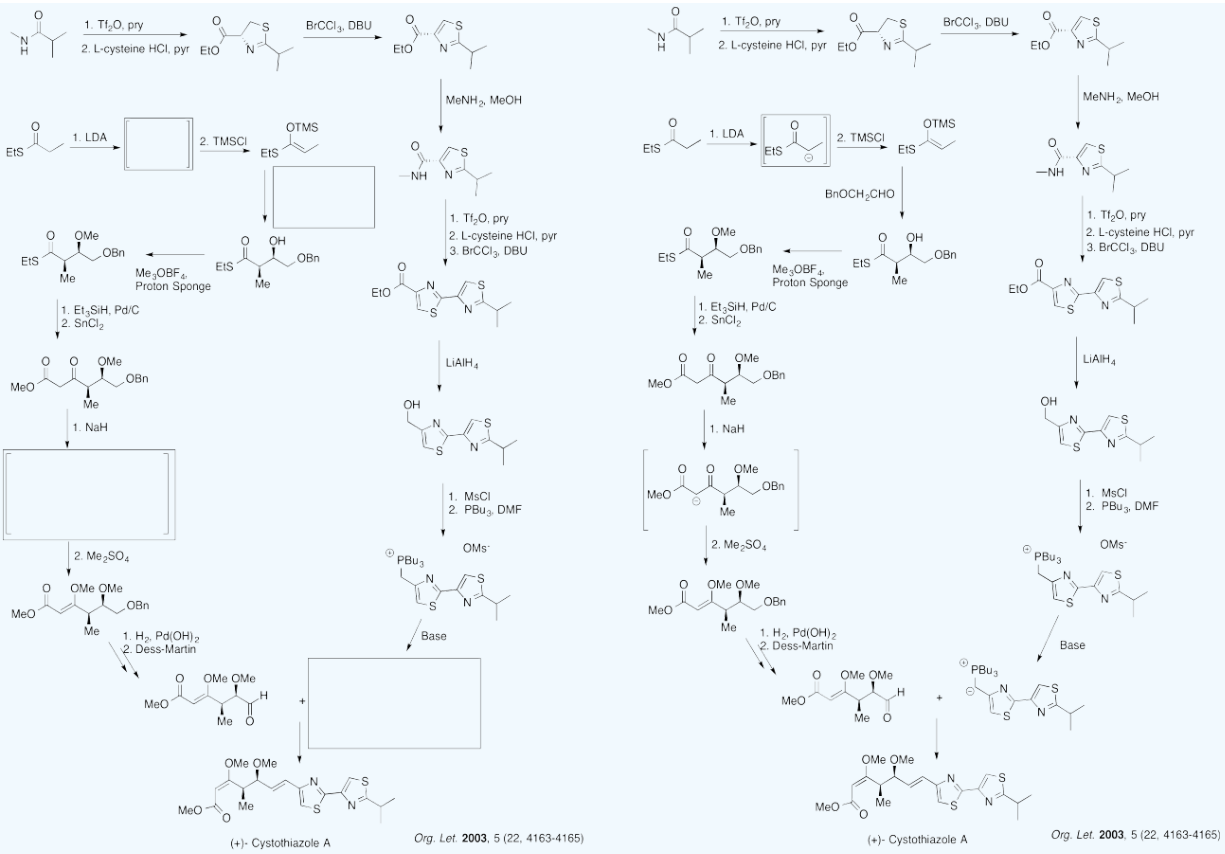


Exercise 3.18.5

Fill in the blanks in the following synthesis. Includes addition of nucleophiles to carbonyls (anionic nucleophiles, enolates, ylides).



Answer

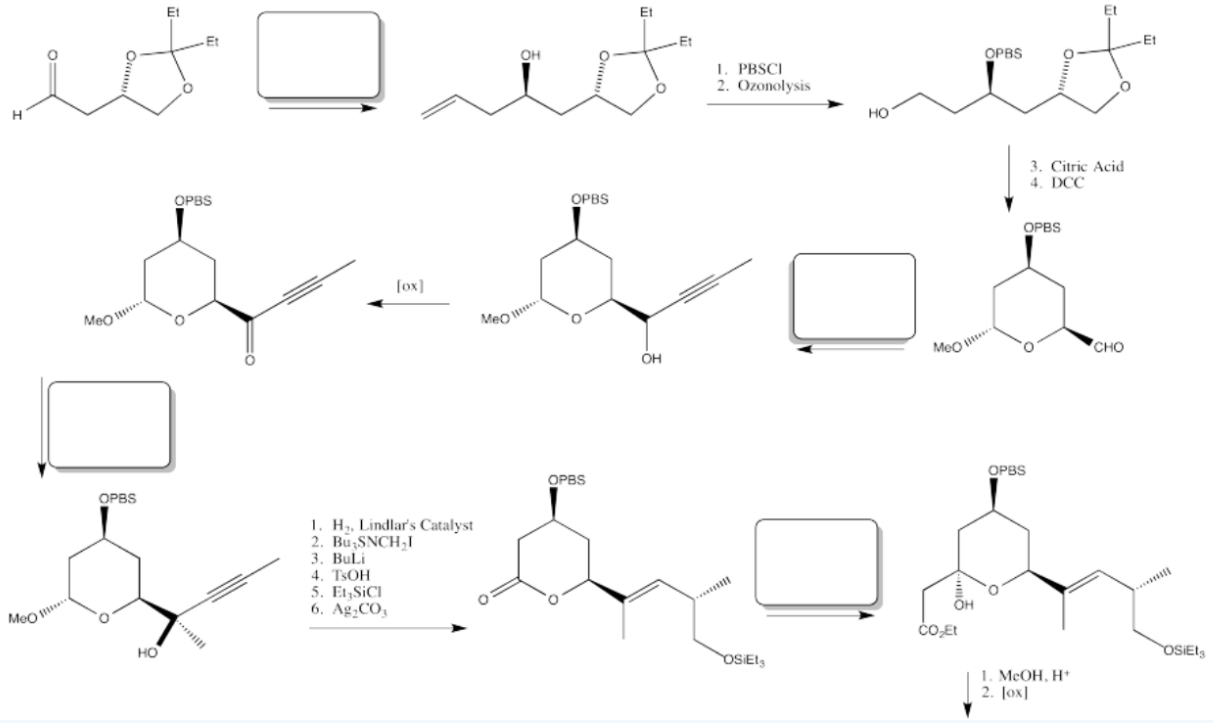


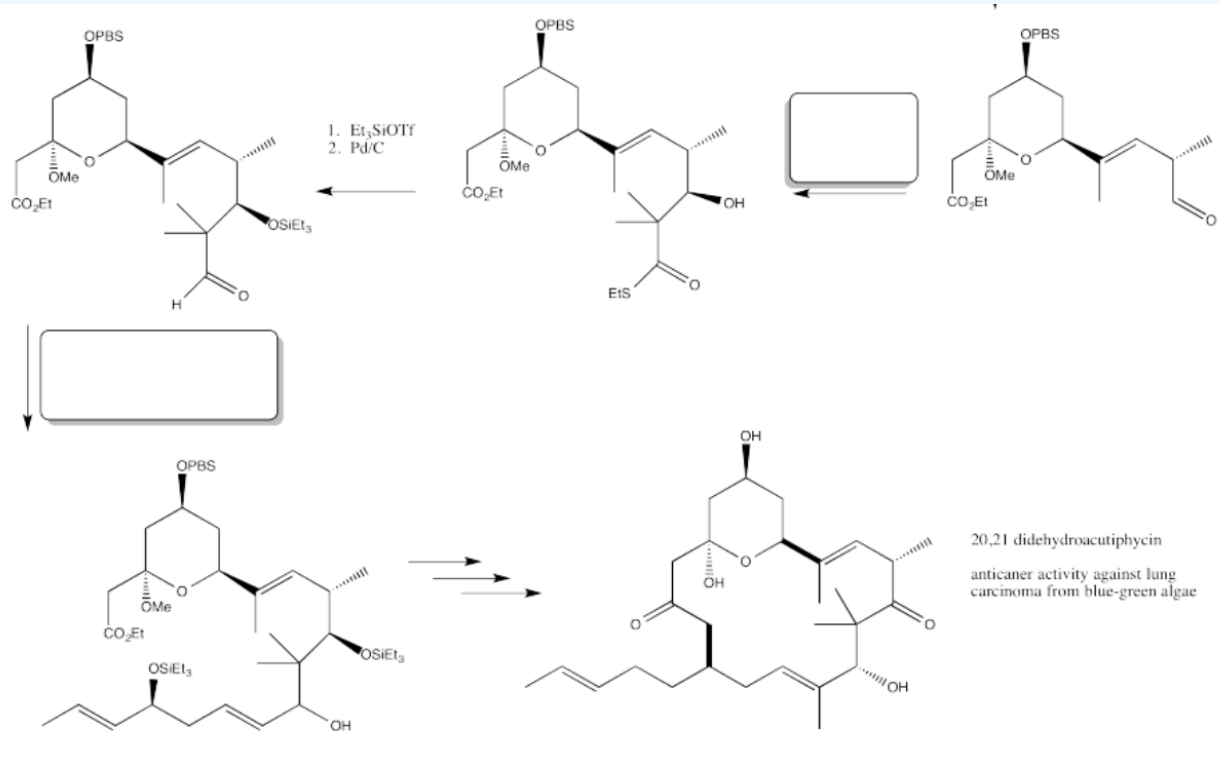
Exercise 3.18.6

Fill in the blanks in the following synthesis. Includes addition of nucleophiles to carbonyls (anionic nucleophiles, enolates).

Acutiphycin

Smith, Chen, Nelsom, Reichert, Salvatore, *J. Am. Chem. Soc.* **1997**, *119*, 10935.

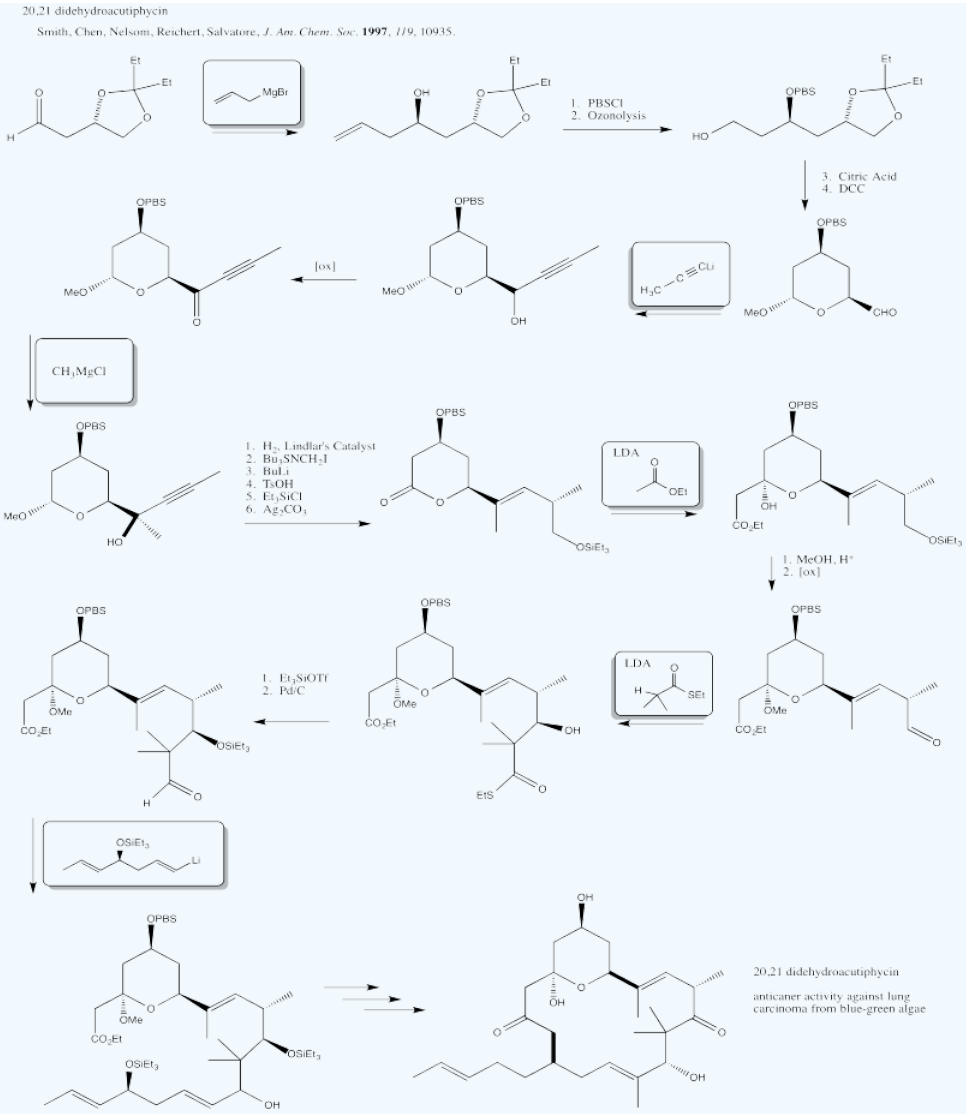




20,21 didehydroacutiphycin

anticaner activity against lung carcinoma from blue-green algae

Answer

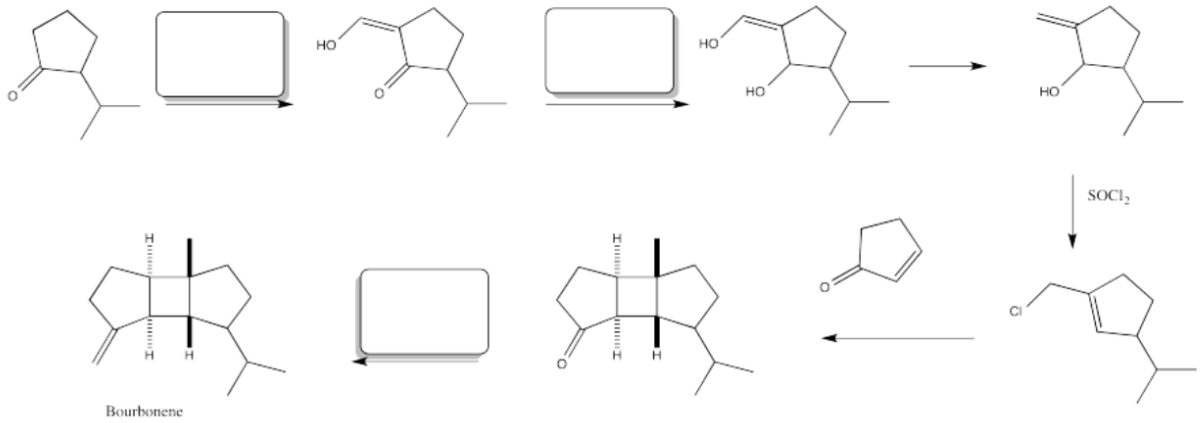


Exercise 3.18.7

Fill in the blanks in the following synthesis. Includes addition of nucleophiles to carbonyls (anionic nucleophiles, enolates, ylides).

Bourbonene

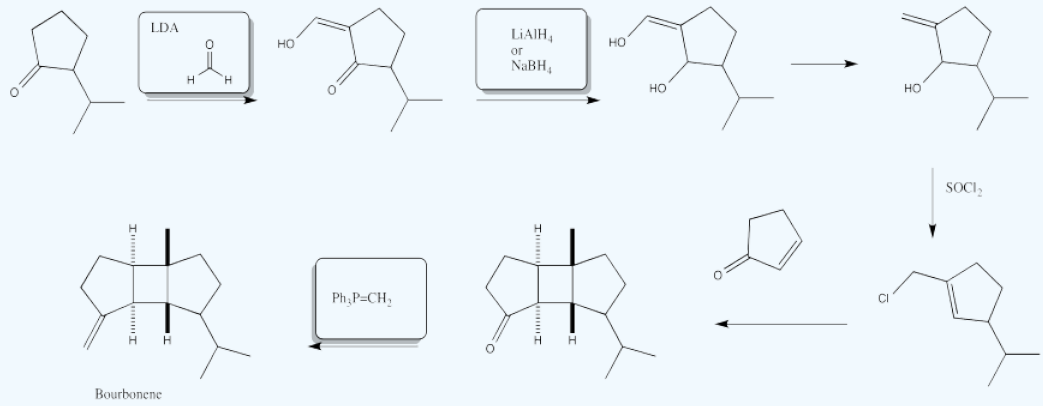
White and Gupta, *J. Am. Chem. Soc.* **1966**, *88*, 5364-5365.



Answer

Bourbonene

White and Gupta, *J. Am. Chem. Soc.* **1966**, *88*, 5364-5365.

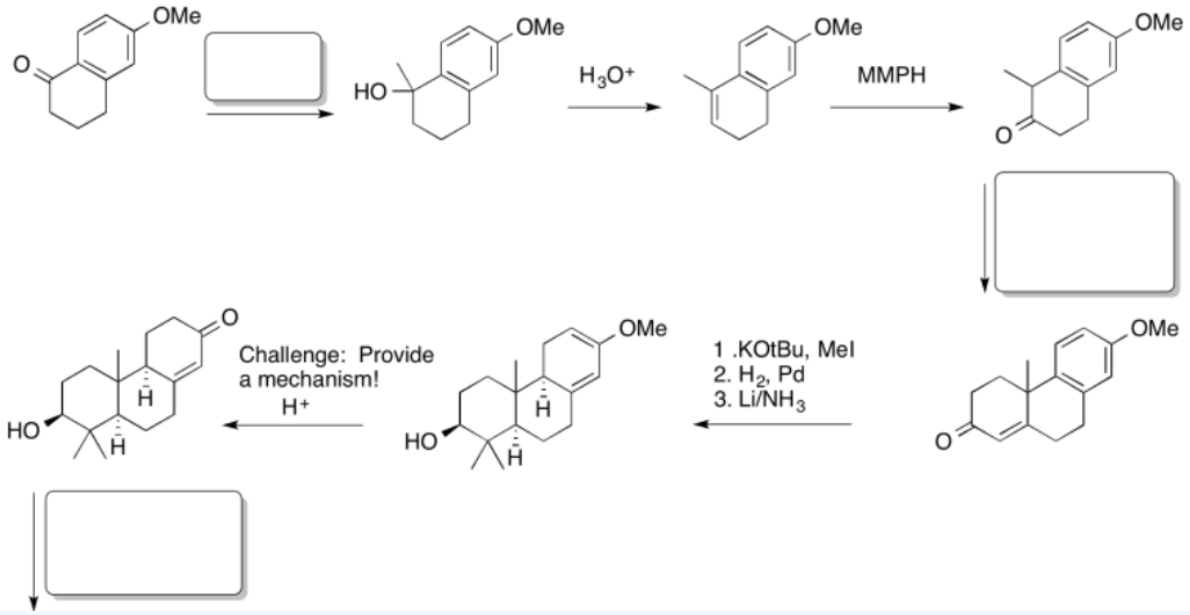


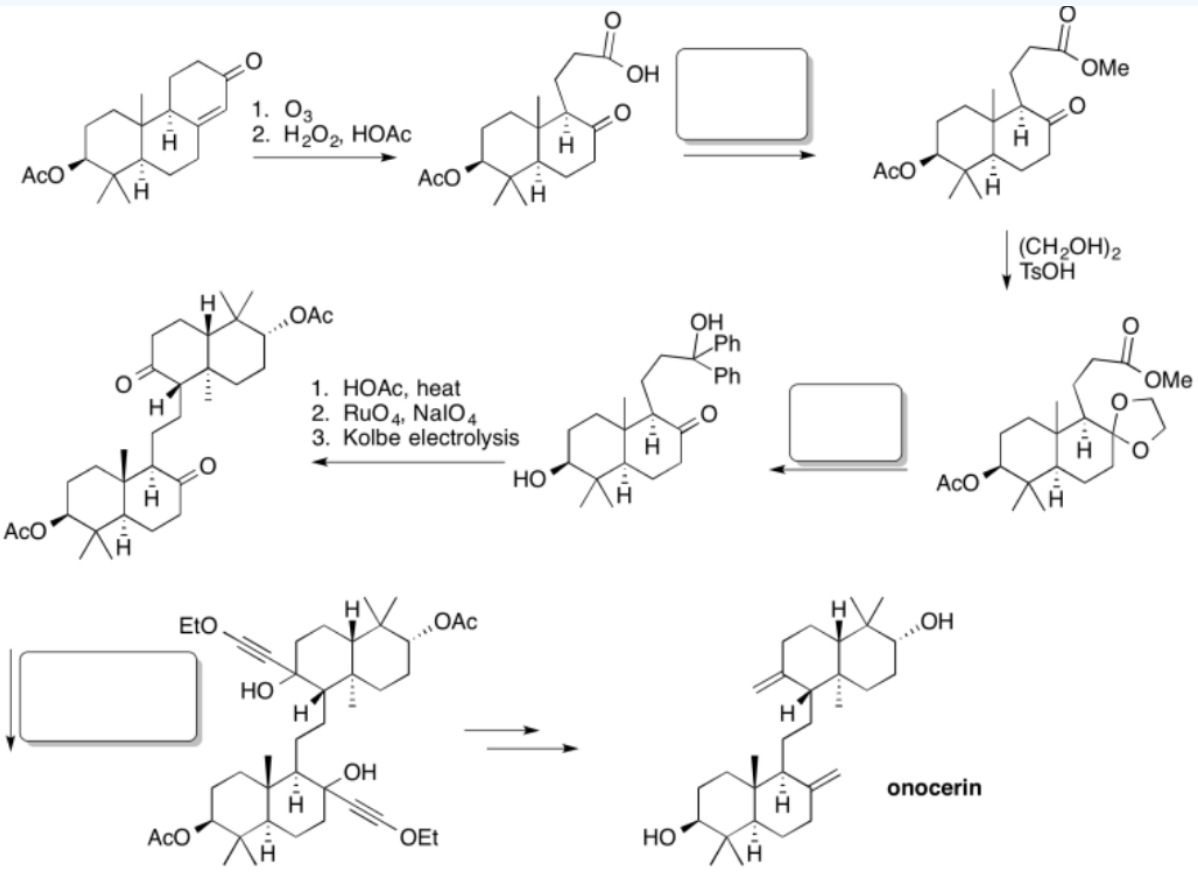
Exercise 3.18.8

Fill in the blanks in the following synthesis. Includes addition of nucleophiles to carbonyls (anionic nucleophiles, enolates, conjugate additions, carboxyloid substitutions).

Onocerin

Stork, et. al., *J. Am. Chem. Soc.*, **1963**, *85*, 3419-3425.

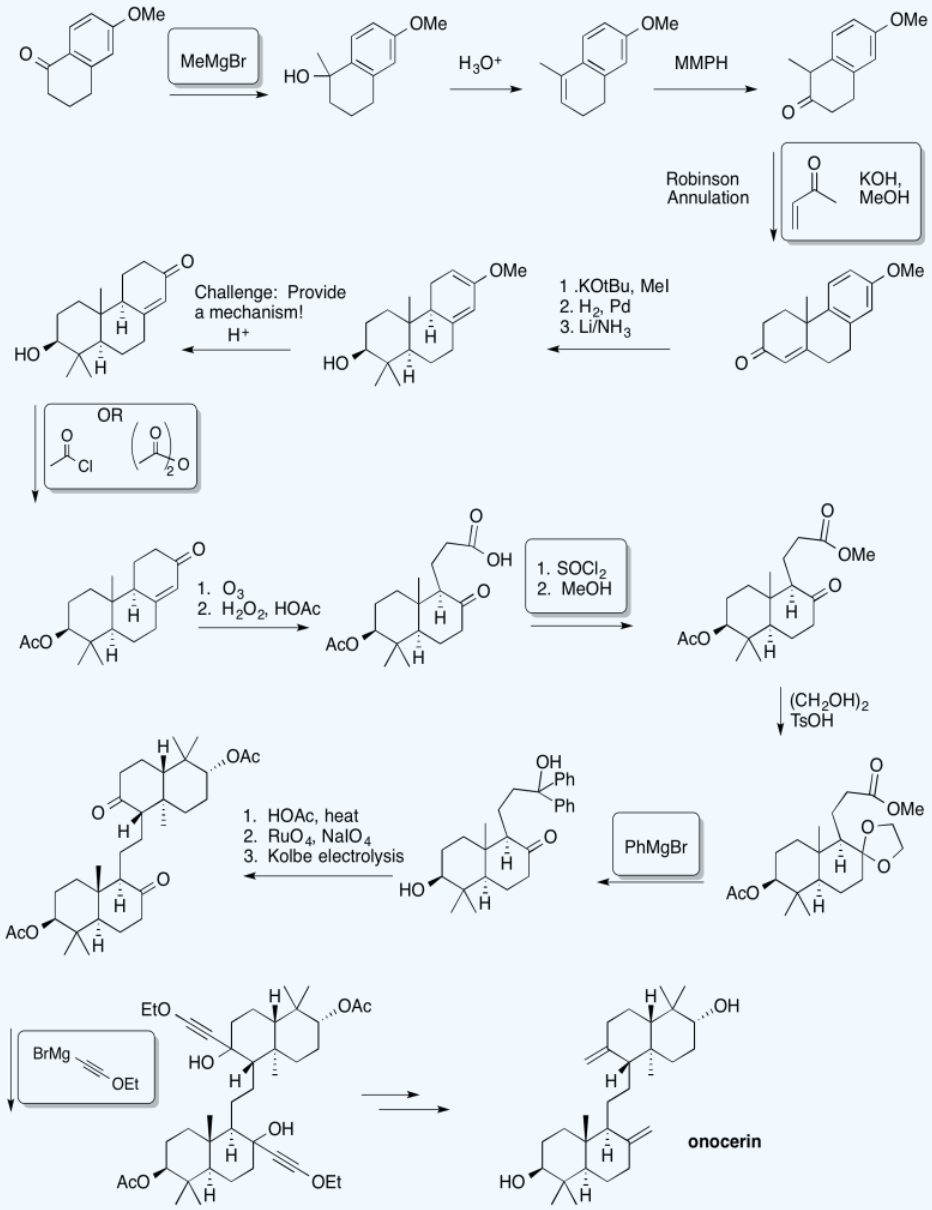




Answer

Onocerin

Stork, et. al., *J. Am. Chem. Soc.*, **1963**, *85*, 3419-3425.

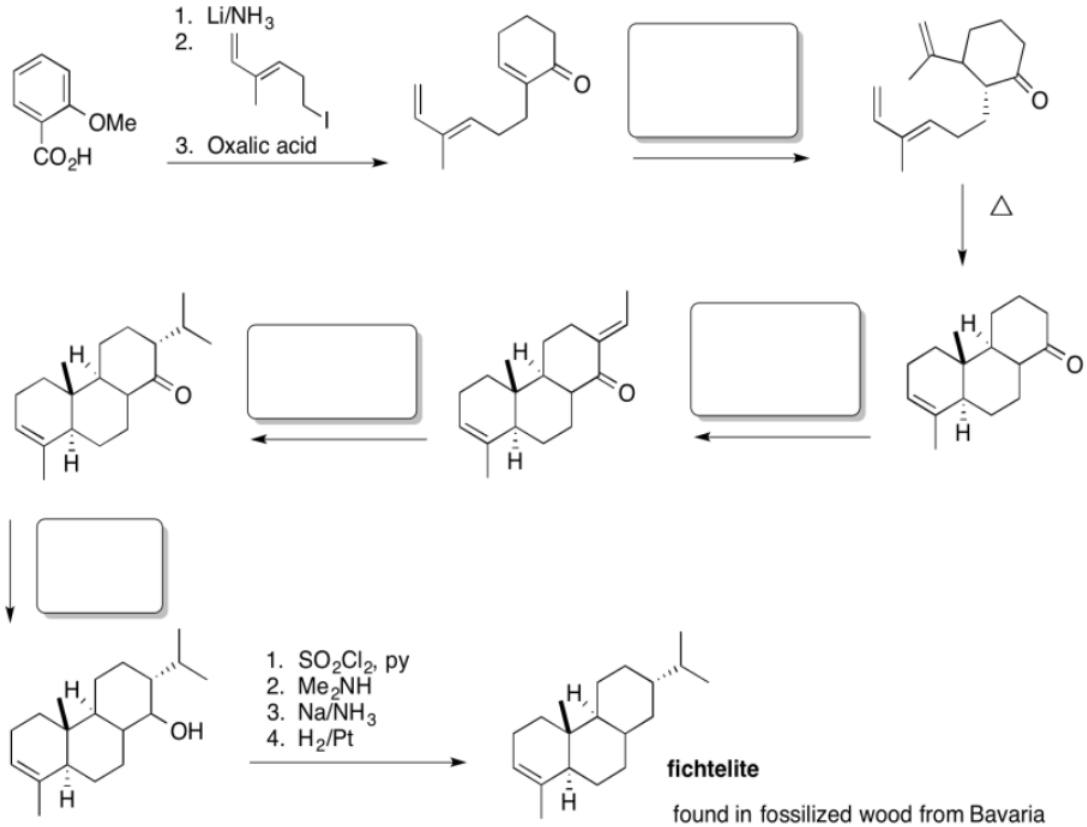


Exercise 3.18.9

Fill in the blanks in the following synthesis. Includes addition of nucleophiles to carbonyls (anionic nucleophiles, enolates, conjugate addition).

Fichtelite

Taber and Saleh, *J. Am. Chem. Soc.*, **1980**, *102*, 5085-5088.



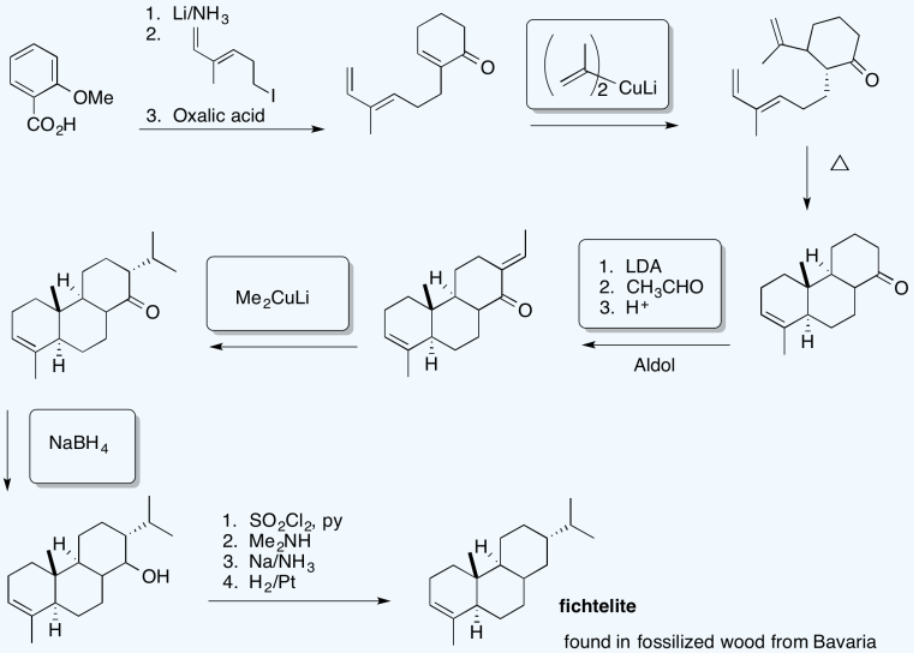
fichtelite

found in fossilized wood from Bavaria

Answer

Fichtelite

Taber and Saleh, *J. Am. Chem. Soc.*, **1980**, *102*, 5085-5088.



fichtelite

found in fossilized wood from Bavaria

3.19: Solutions to Selected Problems, Part A

Problem CO1.1.

The HO-C=O or CO_2H group present in all of the amino acids is called a carboxylic acid.

An additional carboxylic acid is present in aspartic acid and glutamic acid.

The H_2N-C=O or $CONH_2$ group present in asparagine and glutamine is called an amide.

Problem CO1.2.

a) aldehyde b) ketone c) ketone d) aldehyde

Problem CO1.3.

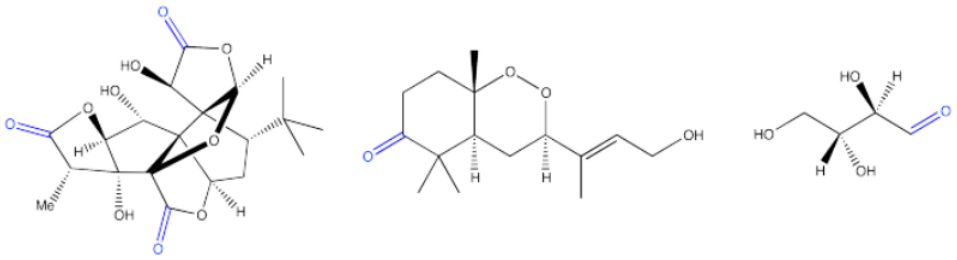


Figure 3.19.1:

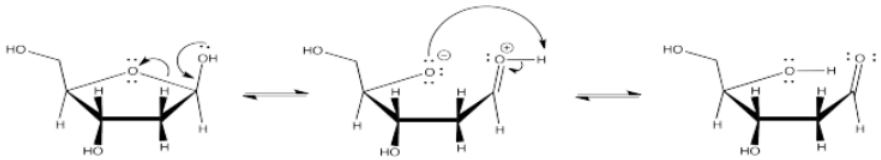


Figure 3.19.2:

a) The double bond means two pairs of electrons are shared between the carbon and oxygen, instead of just one. As a result, the oxygen is able to pull more electron density away from the carbon. The carbon becomes much more positive in this case than in the case of a double bond.

Not only that, but the second bond between the carbon and the oxygen is a pi bond. Those electrons are farther from the nucleus than a sigma bond, in which the electrons are tightly held between the atoms. That means the pi electrons are more easily drawn toward the oxygen, so the bond becomes even more polarized.

b) A C=N bond would be very similar to a C=O bond, because nitrogen is the third most electronegative element after oxygen and fluorine (ignoring noble gases).

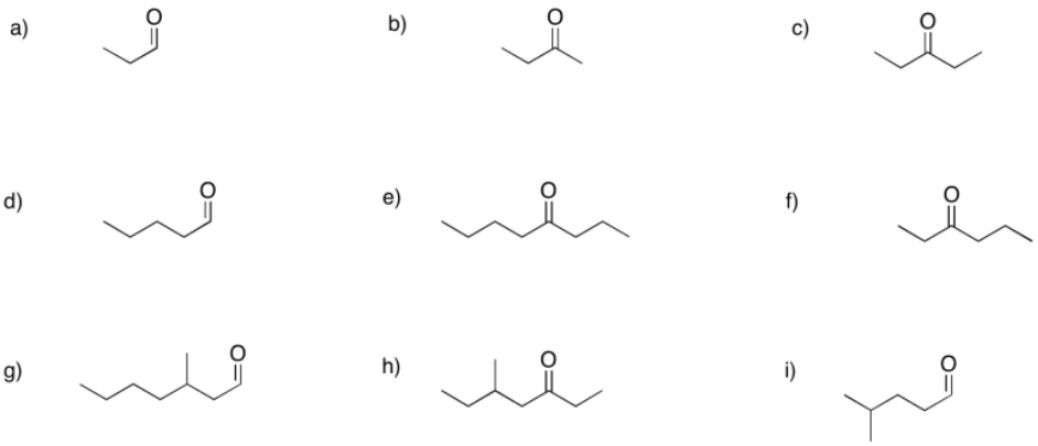


Figure 3.19.3:

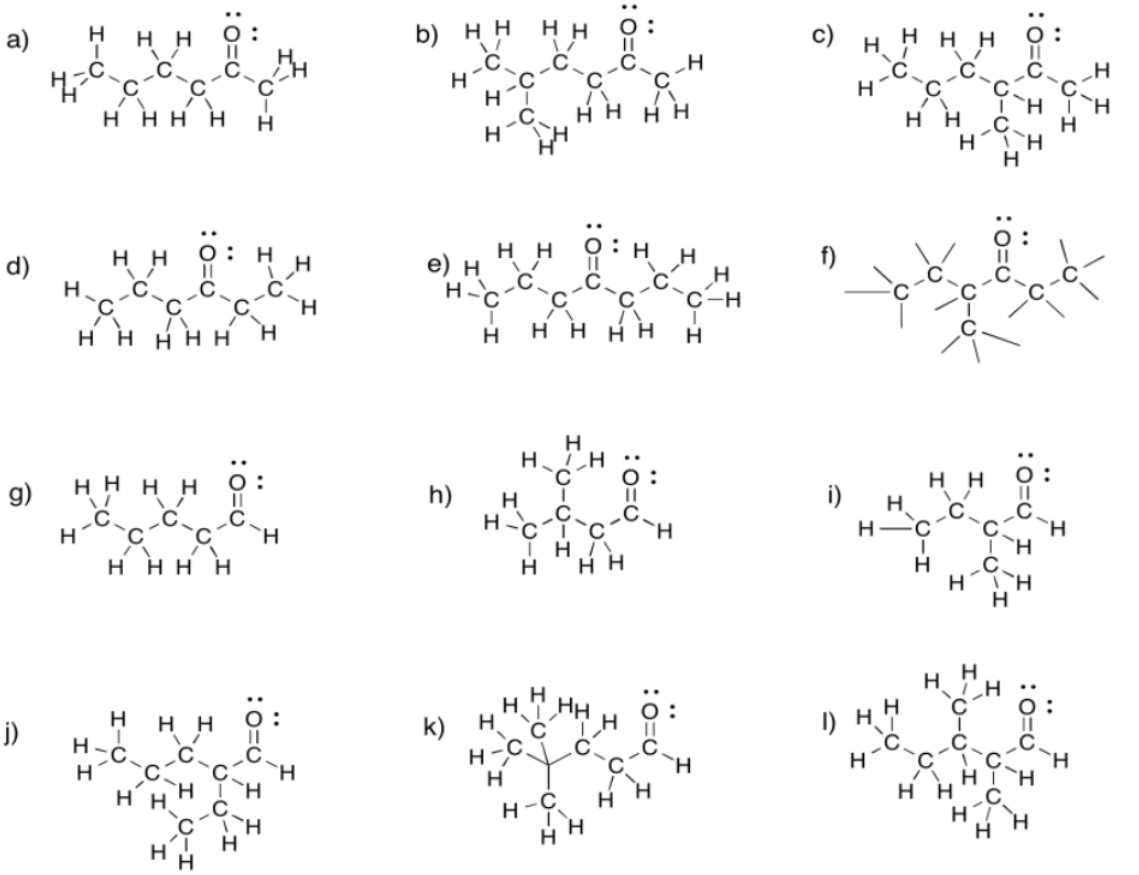


Figure 3.19.4:

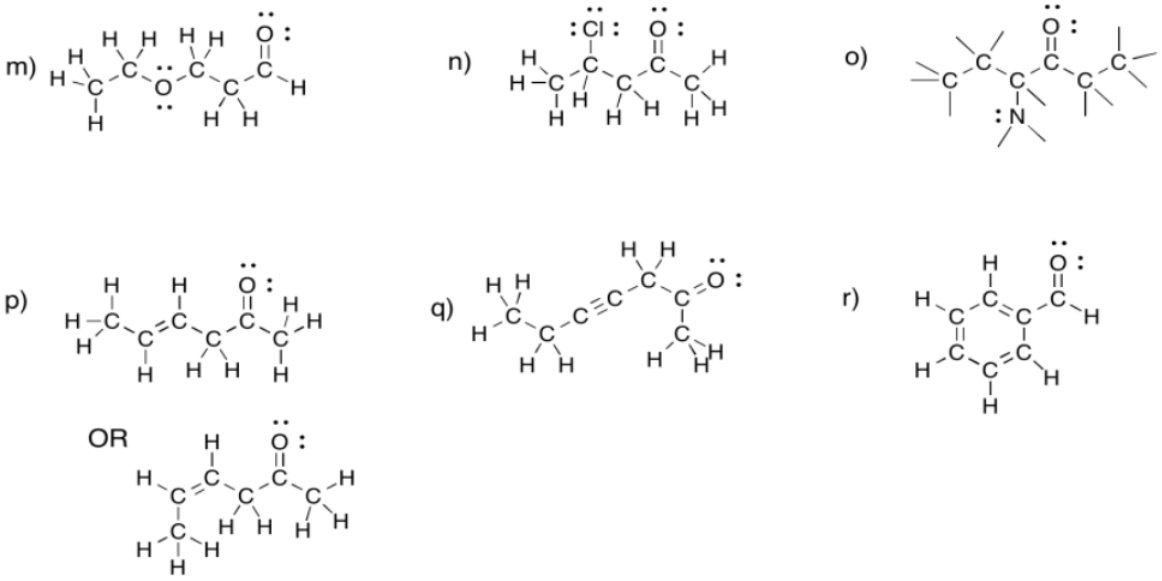


Figure 3.19.5:

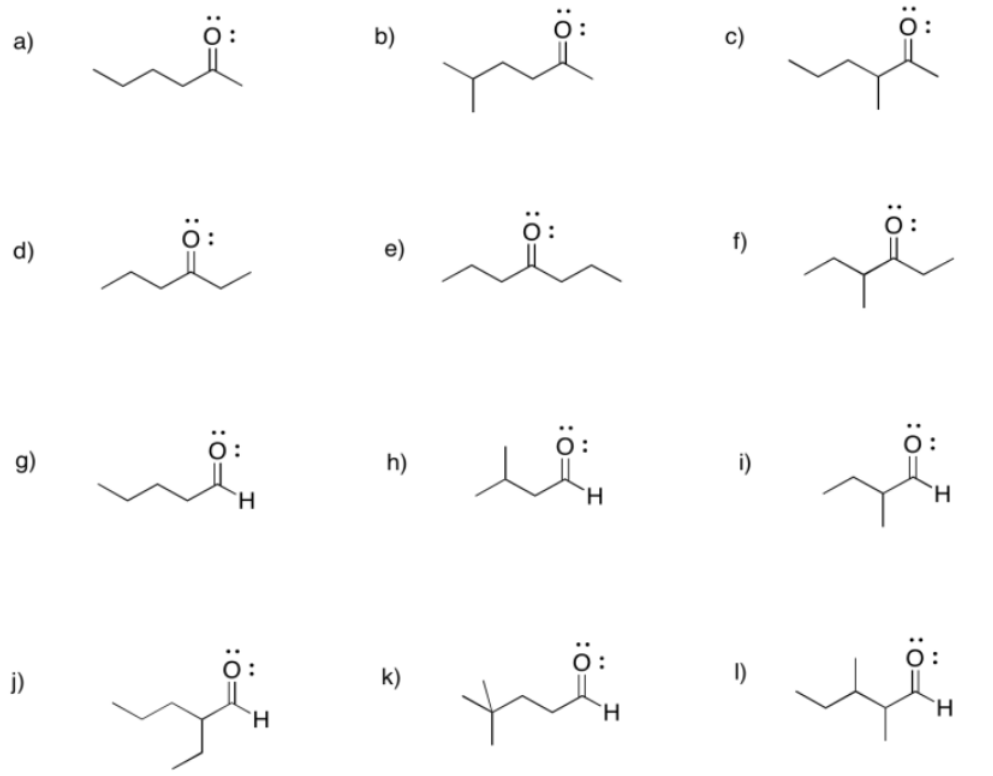


Figure 3.19.6:

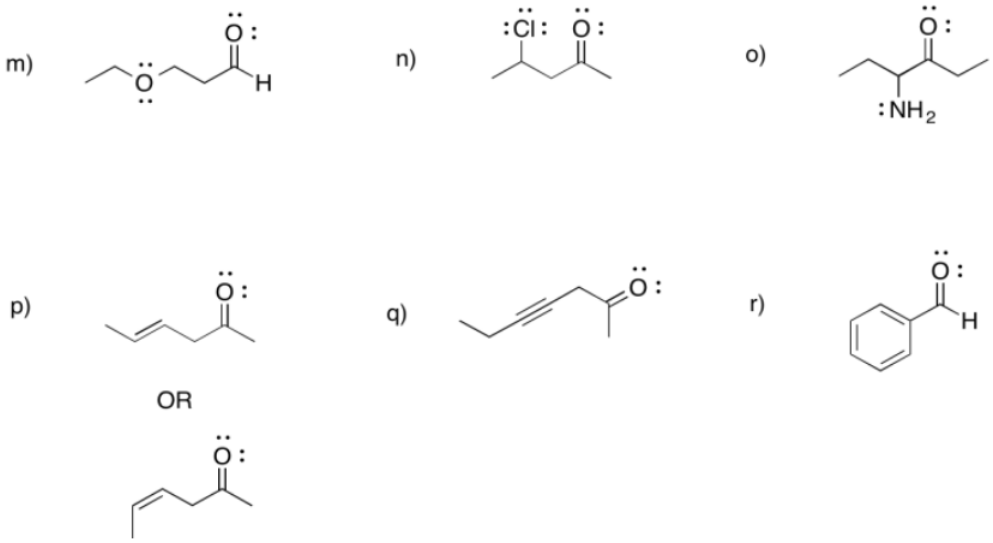


Figure 3.19.7:

a) 2-hexanone or hexan-2-one b) 5-methylhexan-2-one c) 3-methylhexan-2-one

d) hexan-3-one e) heptan-4-one f) 4-methylhexan-3-one

g) hexanal h) 3-methylbutanal i) 2-methylbutanal

j) 2-ethylpentanal k) 4,4-dimethylpentanal l) 2,3-dimethylpentanal

m) 3-ethoxypropanal n) 4-chloropentan-2-one o) 4-aminohexan-3-one

p) hex-4-en-2-one (in the solution above, (*E*)-hex-4-en-2-one is shown first and (*Z*)-hex-4-en-2-one is shown second).

q) hept-4-yn-2-one r) benzaldehyde (this is a common name adopted for formal naming. Benz means a carbon attached to a benzene ring.)

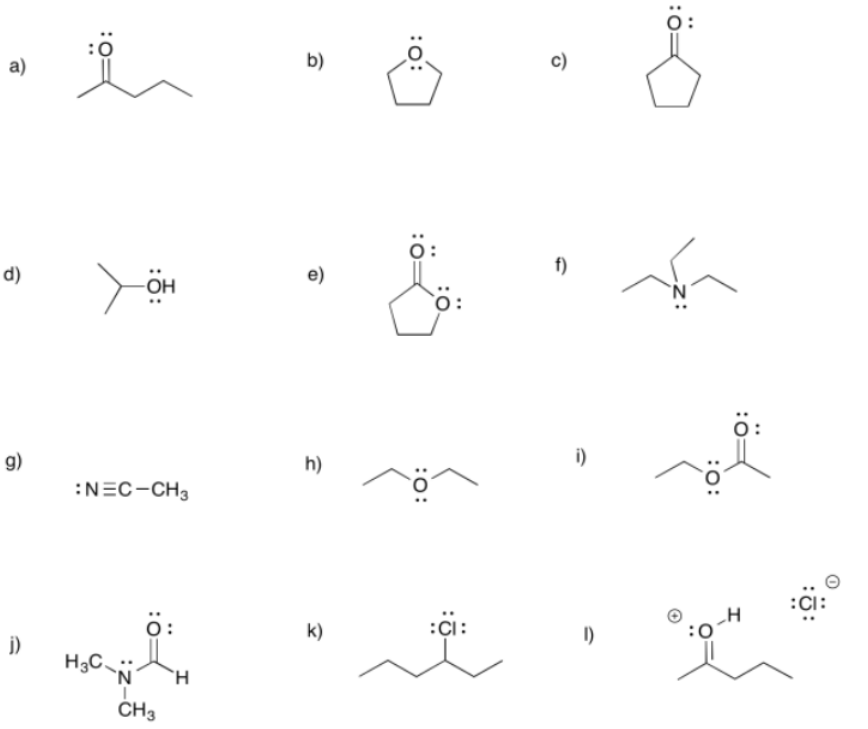


Figure 3.19.8:

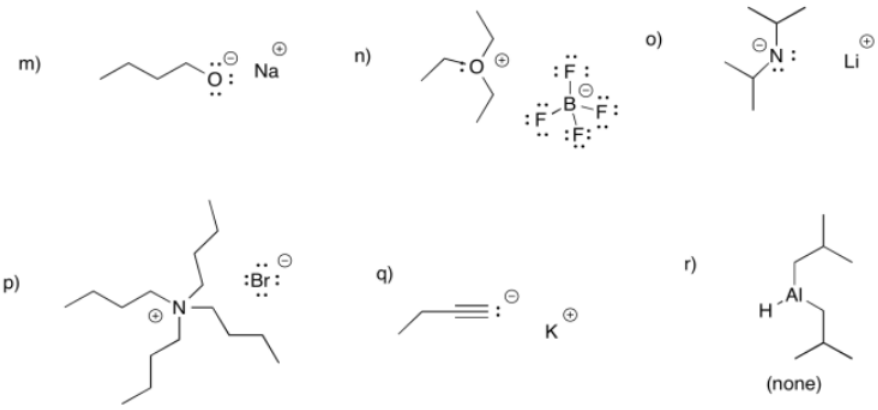


Figure 3.19.9:

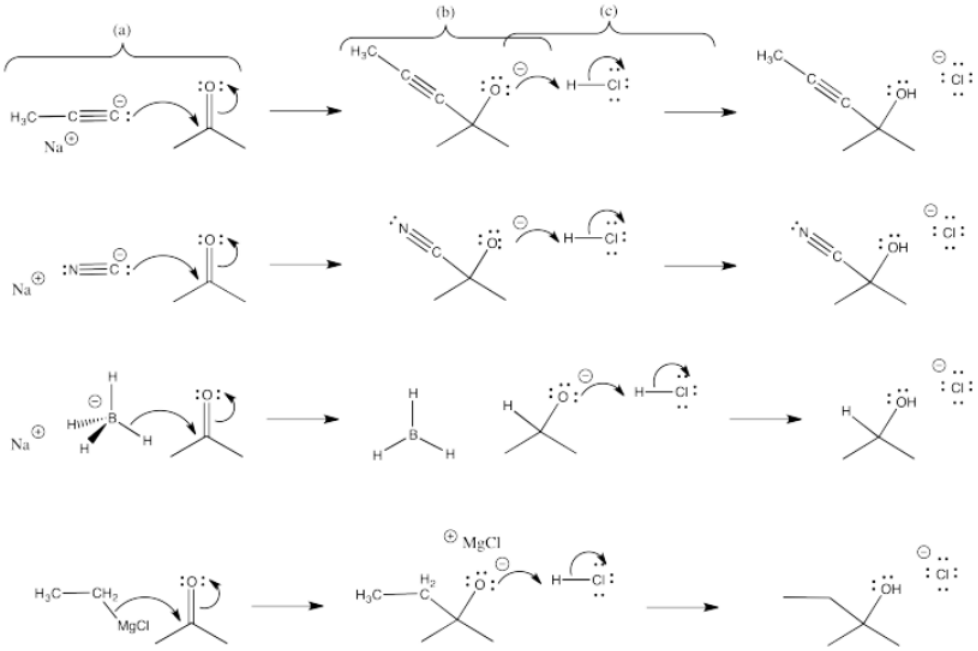


Figure 3.19.10:

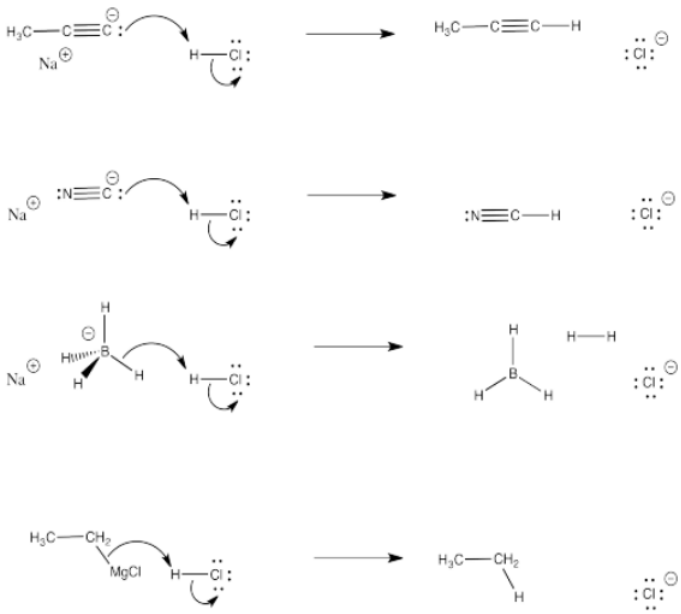
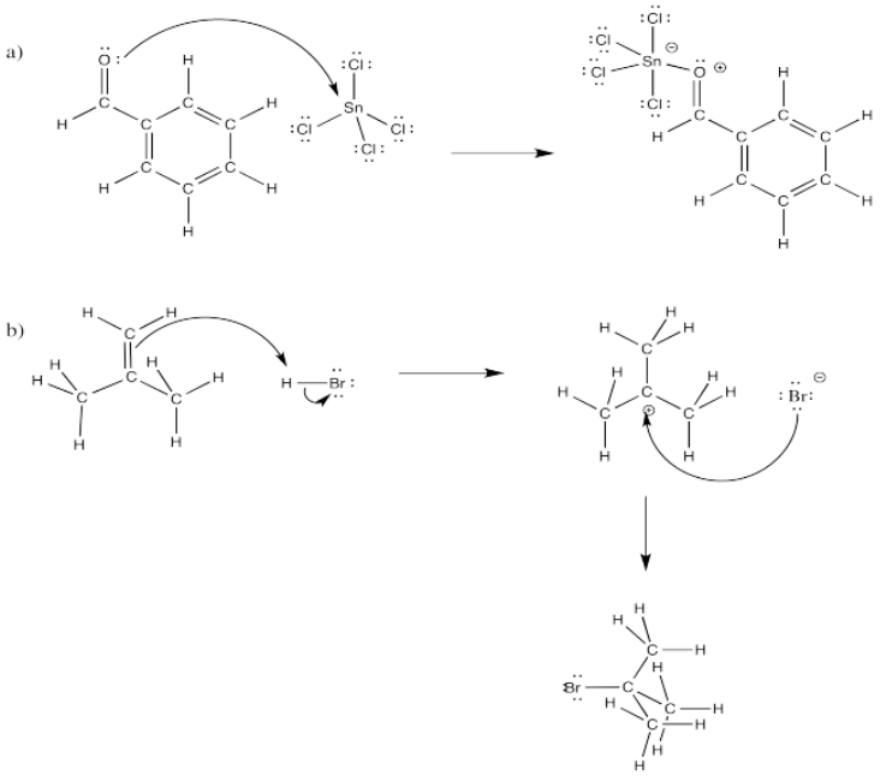


Figure 3.19.11:

Figure 3.19.12:



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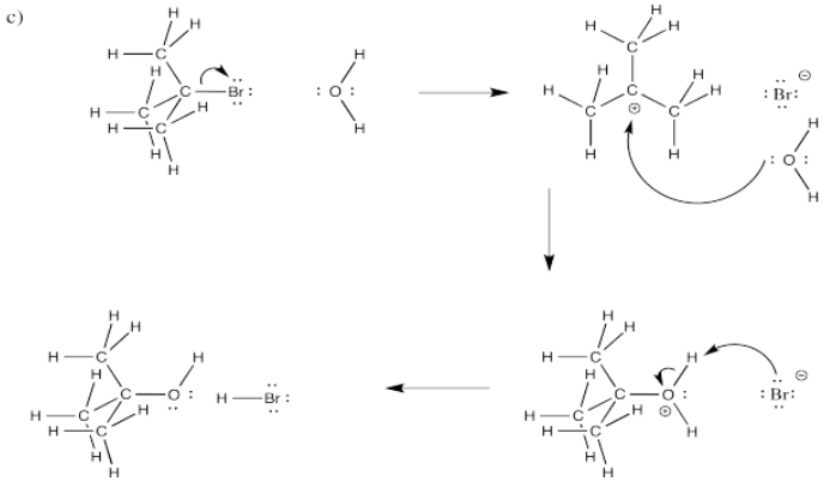

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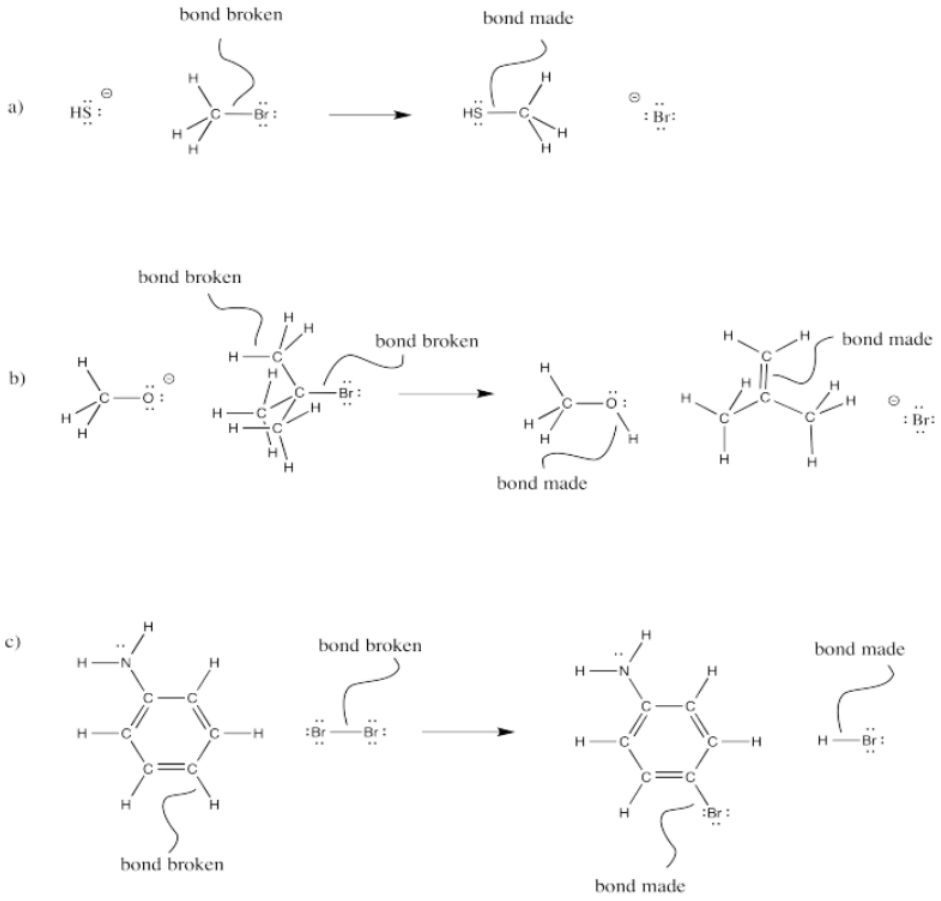


Figure 3.19.15:

The LUMO in this case is the π*, an antibonding level. If electrons populate this level, the π bond will break.

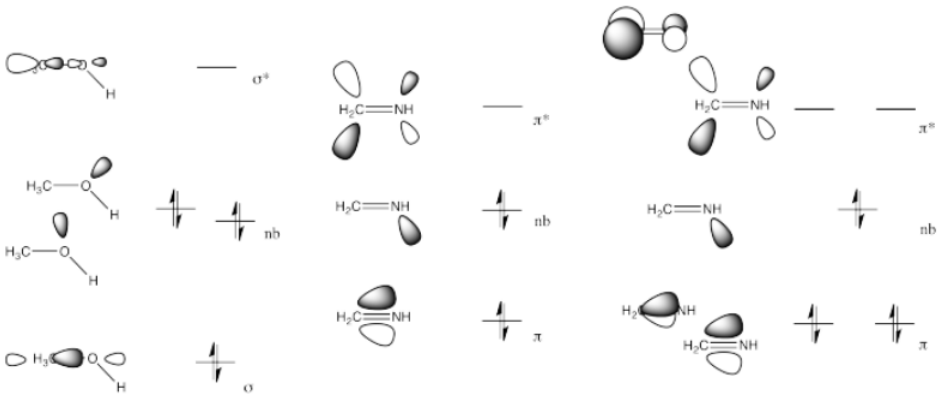


Figure 3.19.16:

Both the imine (b) and nitrile (c) have a low-lying pi antibonding level (π*), similar to a carbonyl.

a. On the basis of steric crowding, the first one is most reactive, then the last one, then the middle.
b. On the basis of steric crowding, the last one is most reactive, then the first one, and then the middle.

Although there is a large group on the nitrogen in that last compound, the site of reactivity is the carbon, which is less crowded.

c) On the basis of electronics, the middle one is most reactive, then the last, and then the first. The fluorine atom is very electronegative and pulls electron density towards itself. That leaves more positive charge on the nearby carbonyl carbon. The more fluorines on that nearby carbon, the more positive the carbon. The more positive the carbon, the more it attracts electrons from a nucleophile.

a) propanal b) butanal c) propanal, again!

d) pentanal e) hexanal f) heptanal

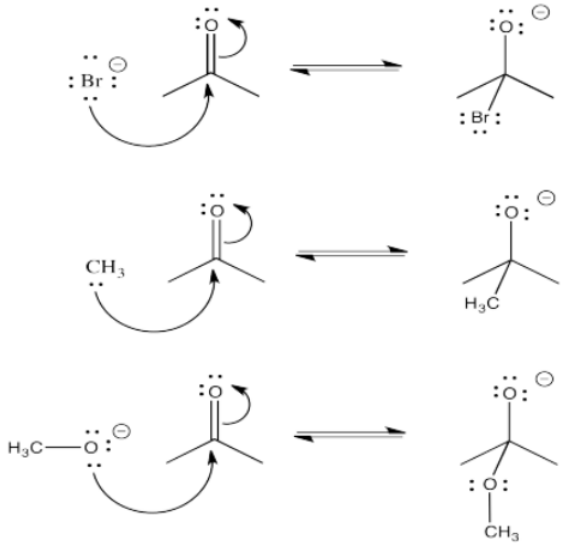
a) 3-pentanone b) 3-hexanone c) 4-heptanone

d) 2-butanone e) 3-octanone f) 5-decanone

a) 2-methyl-3-pentanone or 2-methylpentan-3-one b) 4-ethyl-3-hexanone or 4-ethylhexan-3-one

c) 3,3-dimethyl-2-butanone or 3,3-dimethylbutan-2-one d) 2,5,5-trimethyl-4-heptanone or 2,5,5-trimethylheptan-4-one

e) 6-ethyl-4-methyl-3-octanone or 6-ethyl-4-methyloctan-3-one f) 6-ethyl-4,5-dimethyl-3-octanone or 6-ethyl-4,5-dimethyloctan-3-one



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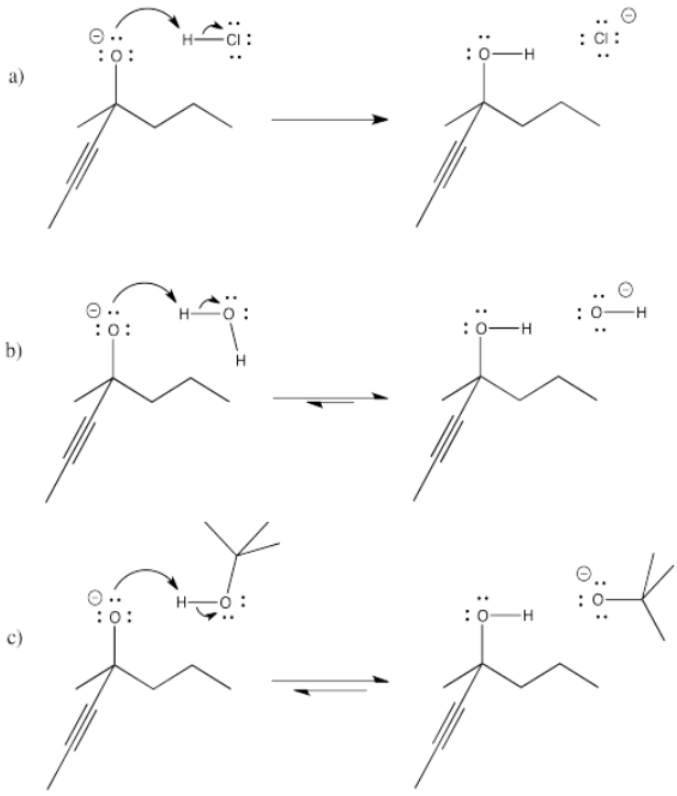

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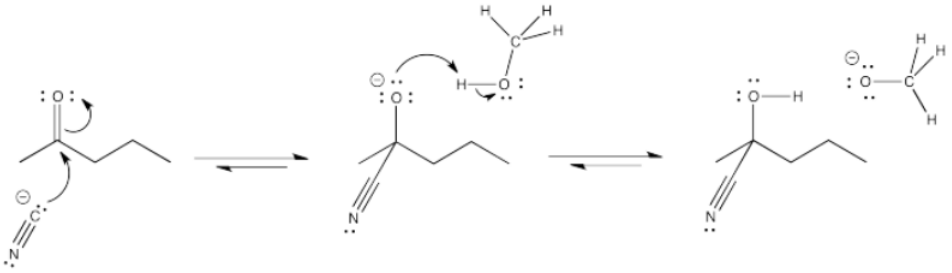


Figure 3.19.19:

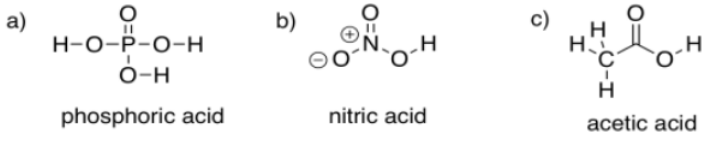
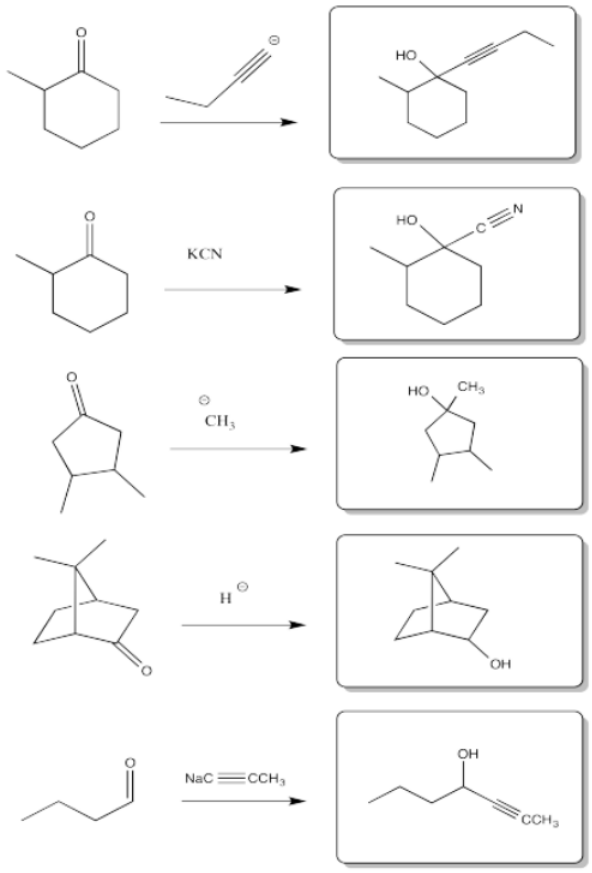


Figure 3.19.20:

Ammonium chloride has an N-H bond, normally less polar than the O-H bond of water. However, the positive charge makes this compound give up a proton more easily, because it results in a neutral (uncharged) ammonia molecule.

Sodium carbonate has a polar O-H bond, just like water. However, the anion that results from loss of a proton is resonance-stabilised. That makes this compound more acidic than water.

Figure 3.19.21:



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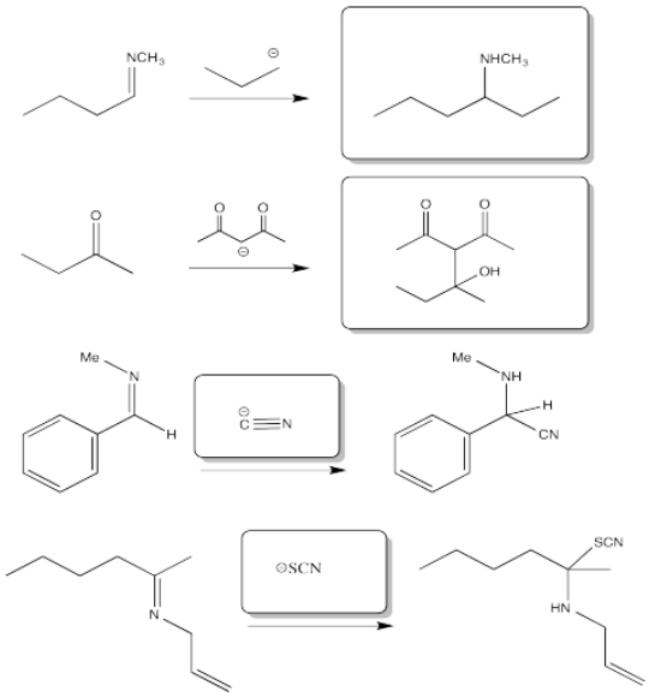

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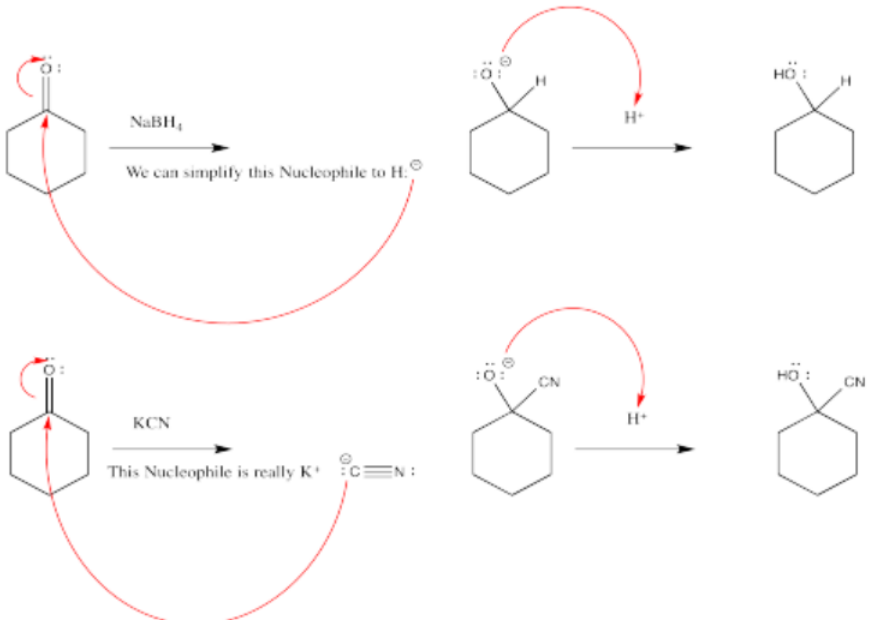

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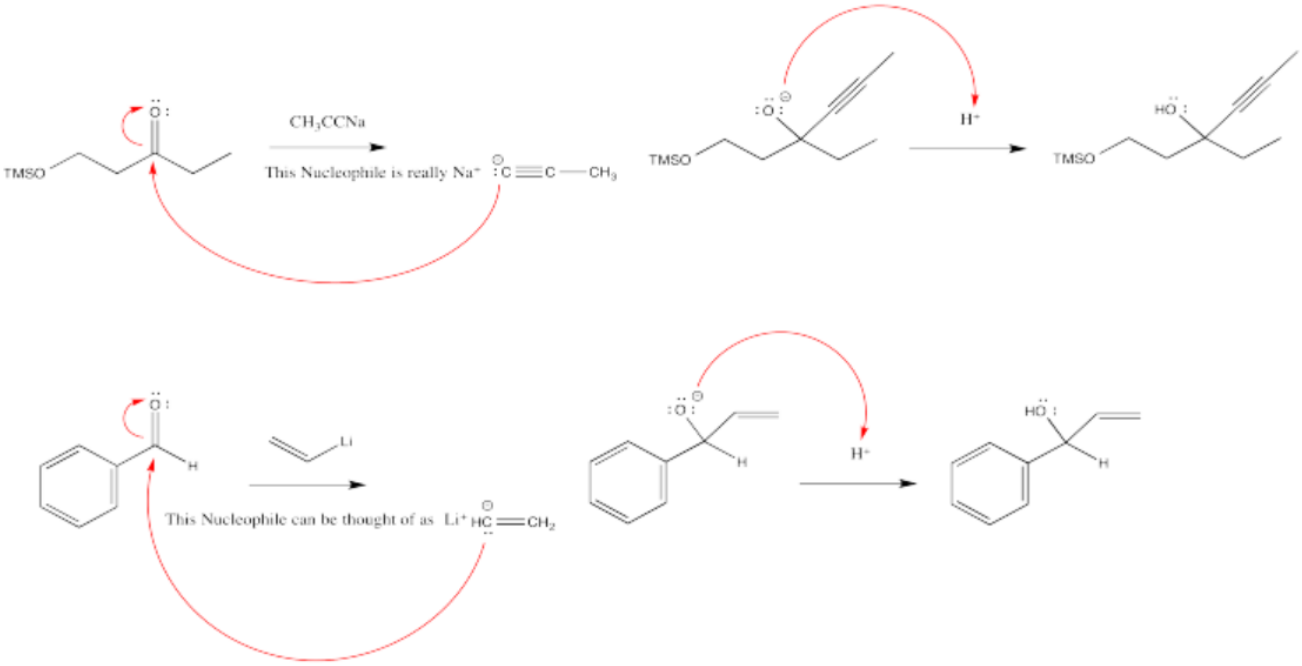


Figure 3.19.25:

a) In acetylide, the lone pair is on a linear carbon or sp carbon. In methyl anion, the lone pair is on a tetrahedral carbon or sp^3 carbon. The description "sp" indicates that sigma bonding to neighbors involves a 2s orbital and a 2p orbital on carbon; there is a 50% contribution from the s orbital.

The description "sp^3", on the other hand, indicates that sigma bonding to neighbors involves a 2s orbital and three 2p orbitals; there is a 25% contribution from the s orbital.

The 2s orbital is lower in energy than the 2p orbital. The greater the s orbital contribution to the bond (or in this case to the lone pair), the lower it is in energy. Thus, a lone pair on an sp carbon is lower in enrgy than a lone pair on an sp^3 carbon.

b) In cyanide, the same argument outlined in pary (a) hold true. In addition, the nearby electronegative nitrogen stabilizes the charge by drawing electron density toward itself.

a. CH_3OK, because of the ionic O-K bond. This is an anionic nucleophile. It is more reactive and nucleophilic than the corresponding neutral nucleophile.
b. CH_3NH_2, because nitrogen is less electronegative than oxygen. Its lone pair is held less tightly and is more easily donated to the electrophile.
c. NaCCH, because the neighbouring carbon in this case does not have the inductive electron-withdrawing effect that the nitrogen does in the case of NaCN. In that case, the lone pair is stabilized and made less reactive.
d. c-$C_6H_{11}ONa$, because the negative charge is localized on one atom. In c-C_6H_5ONa, the negative charge is delocalized over four different positions in the molecule. Delocalization of charge stabilizes the anion and makes it less reactive.

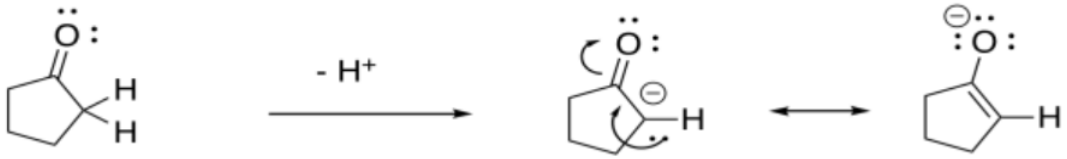
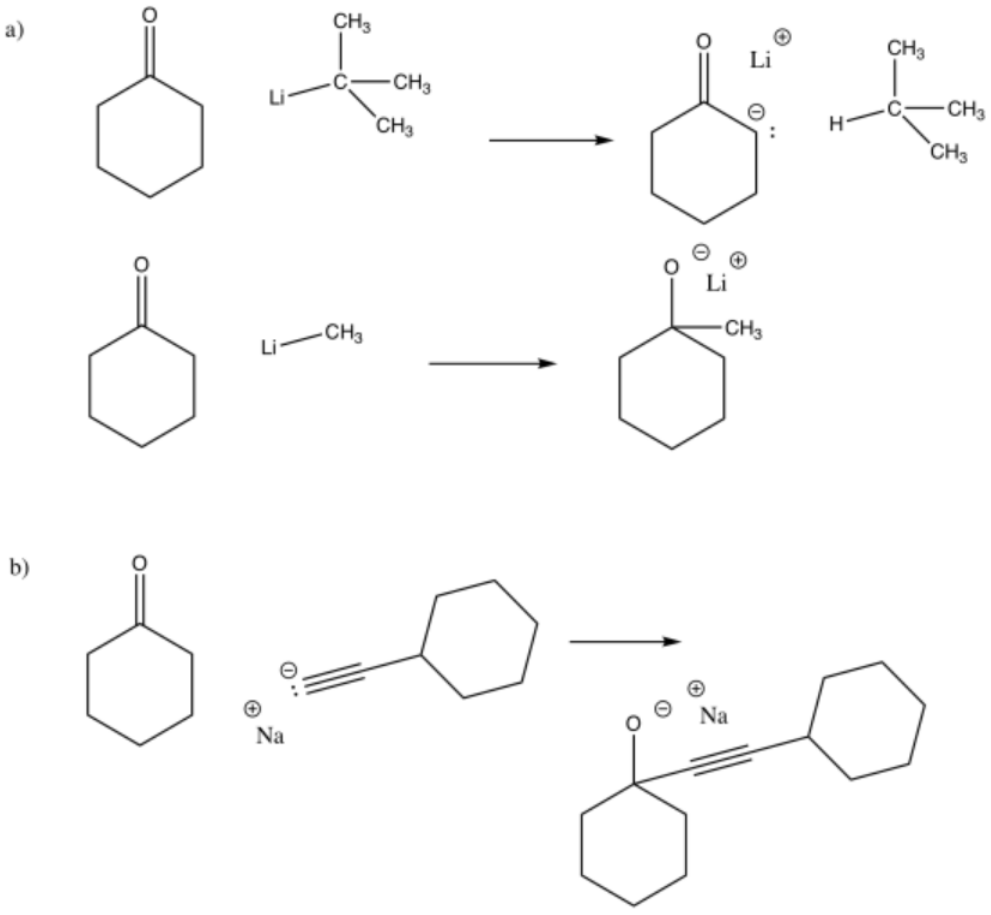


Figure 3.19.26:

The resulting anion is stabilised by resonance.

The case with more steric crowding is more likely to result in deprotonation.



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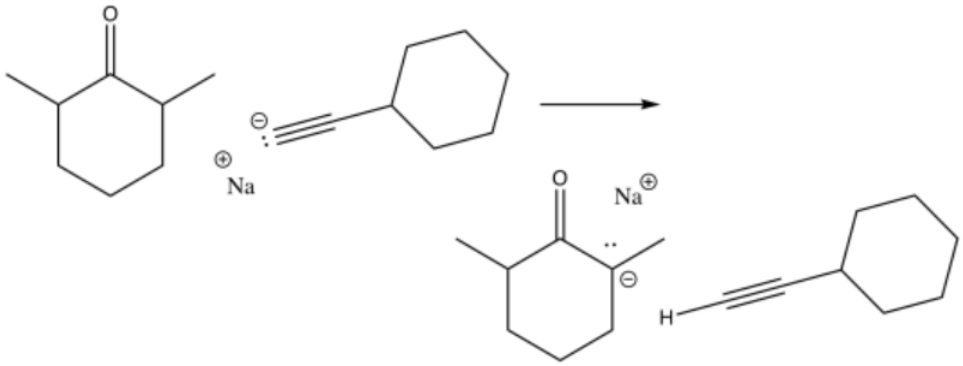

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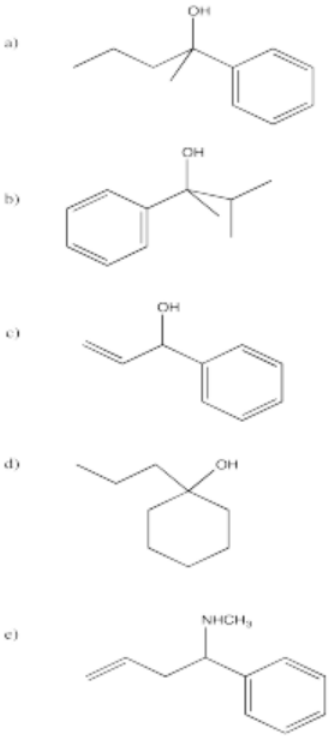


Figure 3.19.29:

Figure 3.19.30:

Figure 3.19.31:

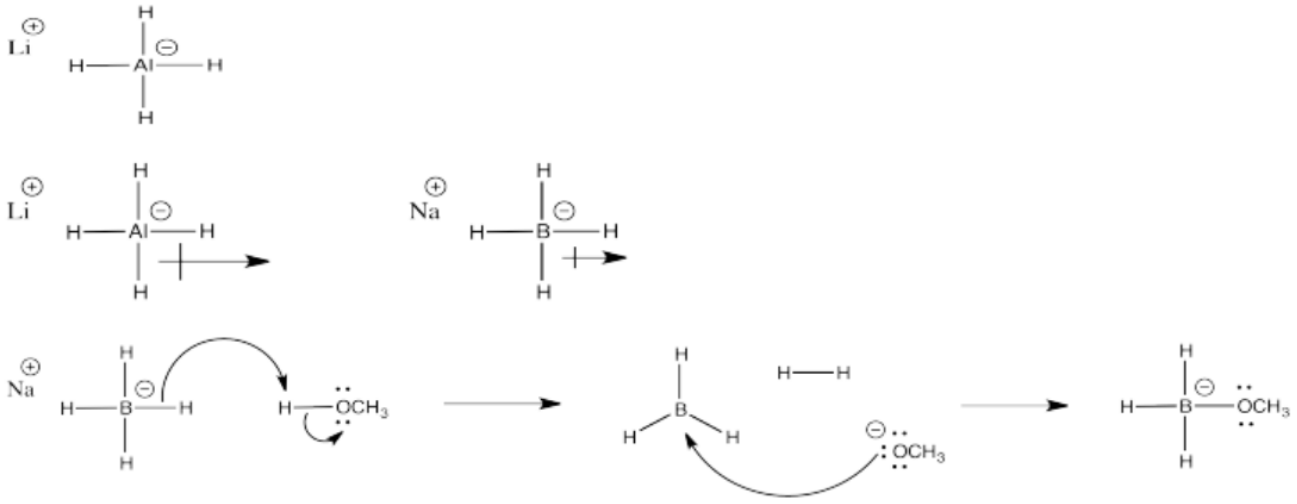
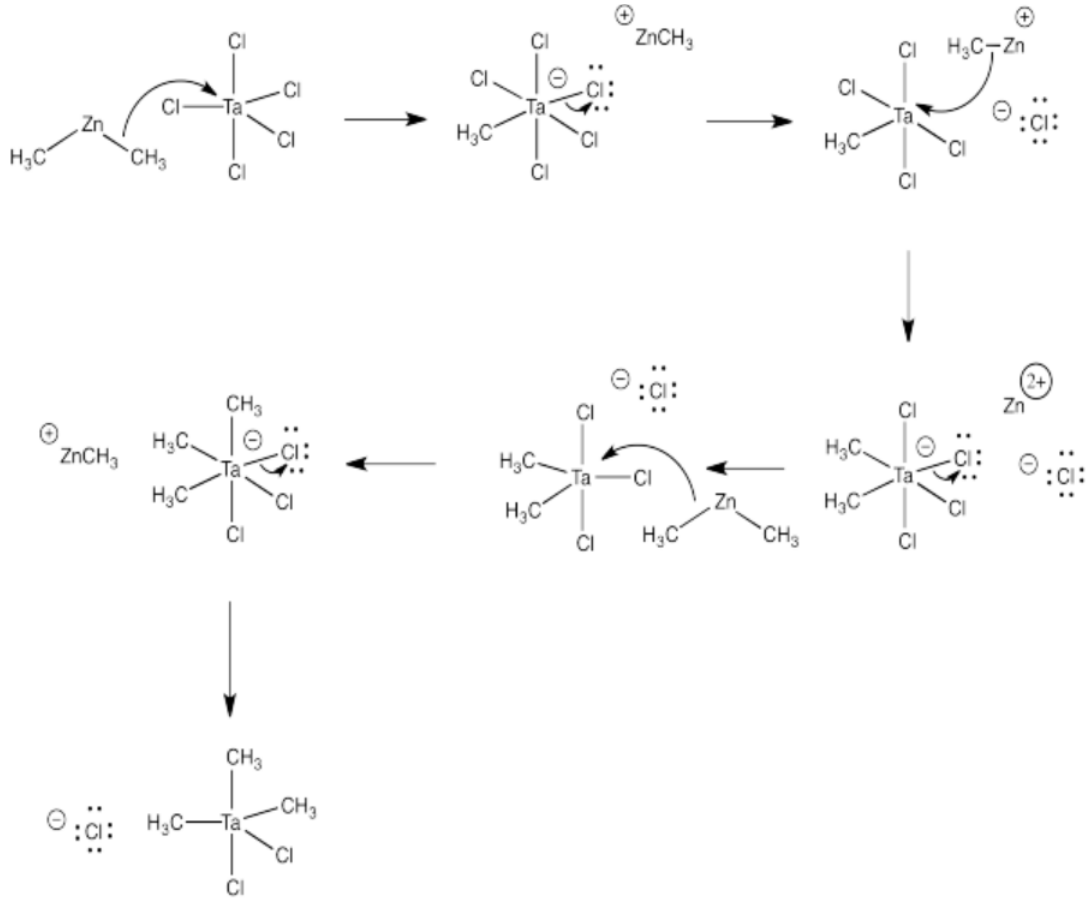


Figure 3.19.32:

Problem CO11.5.

Figure 3.19.33:



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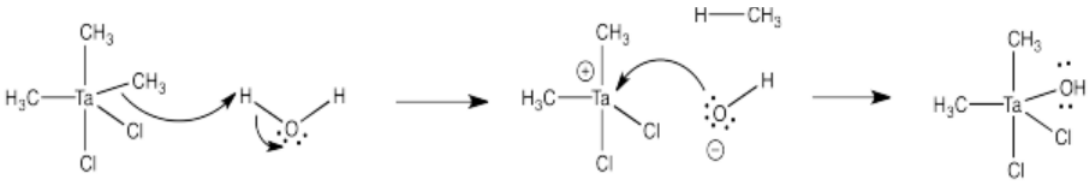

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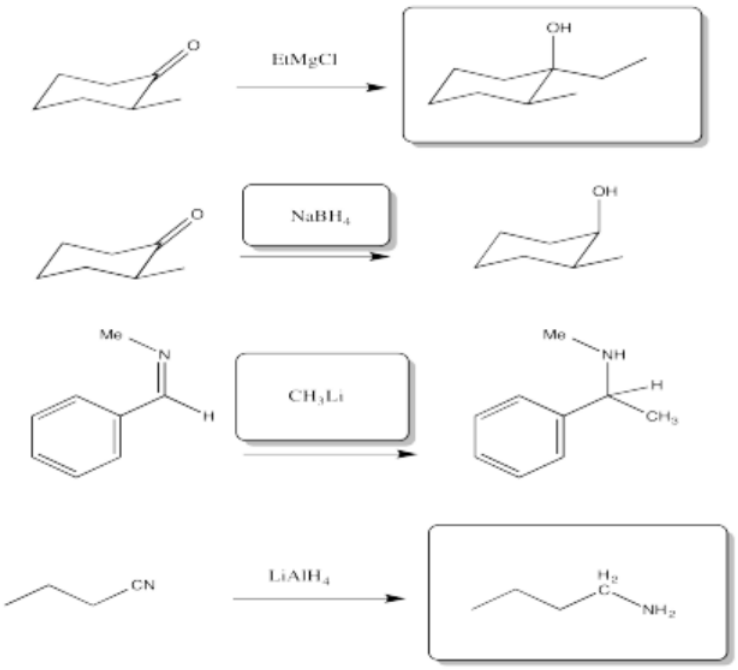

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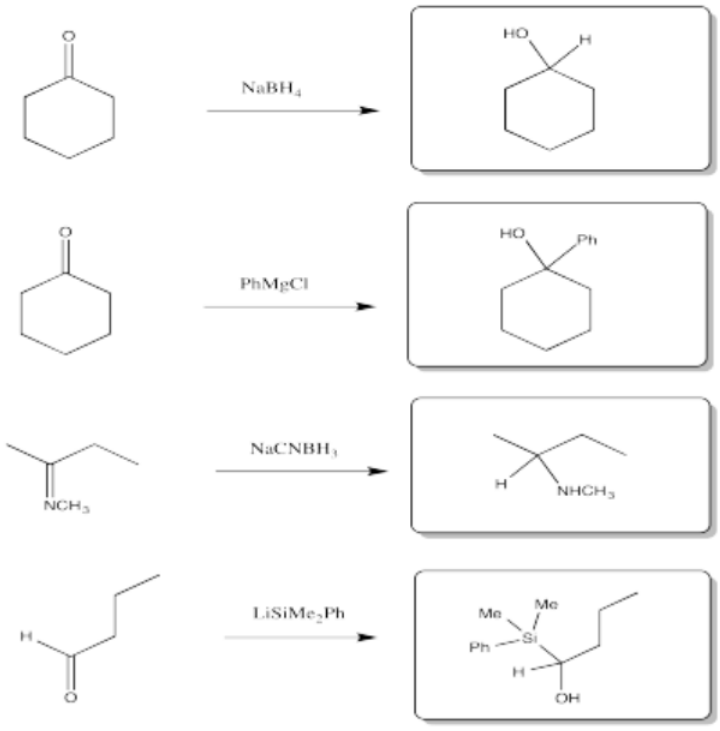

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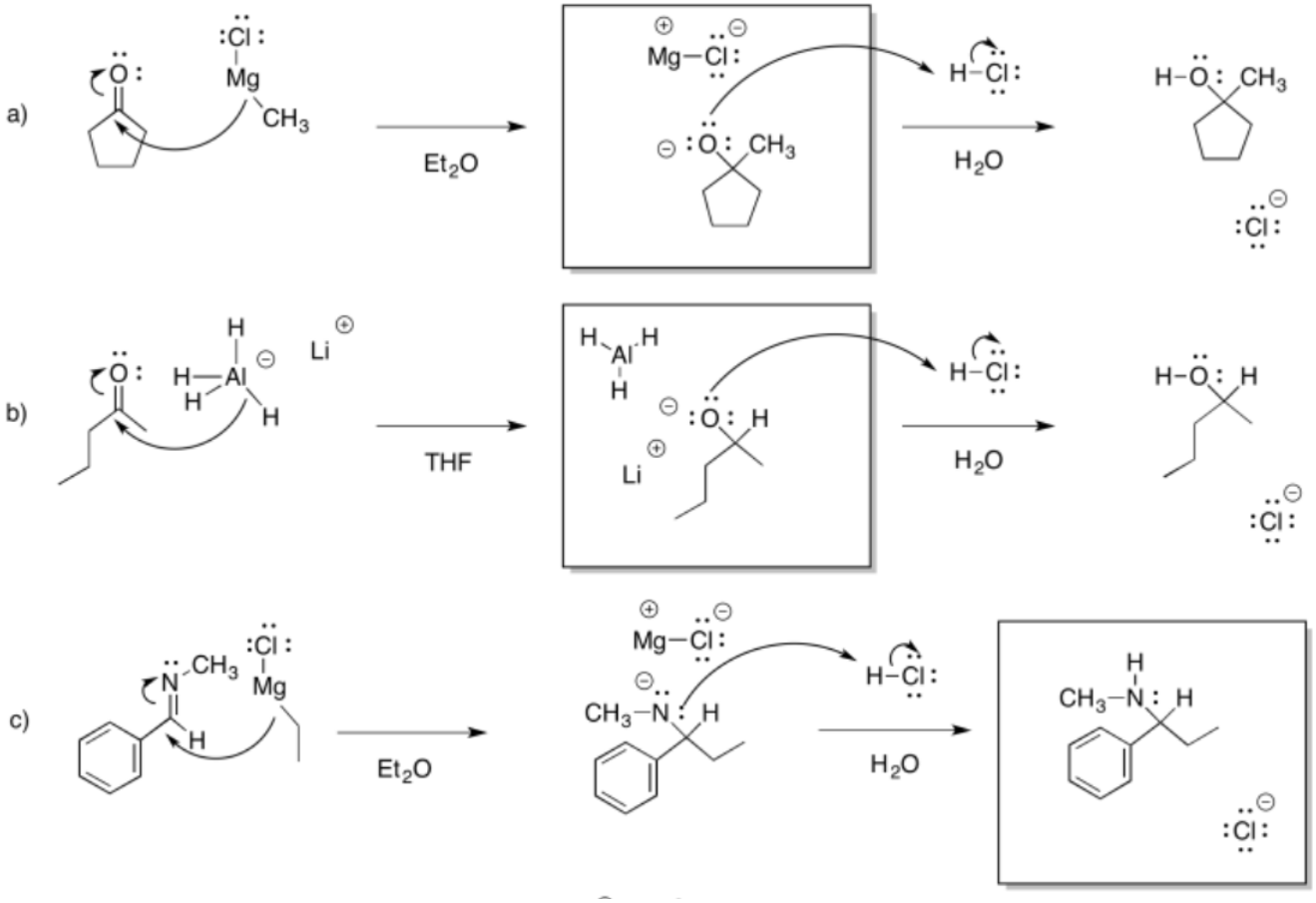

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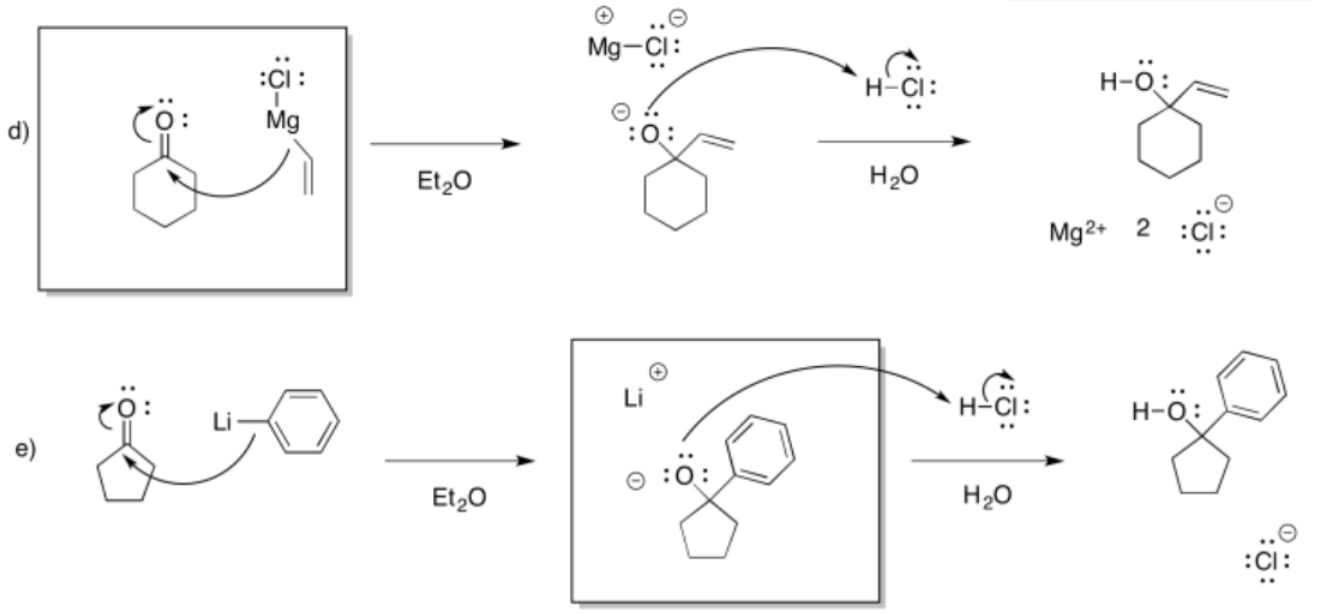
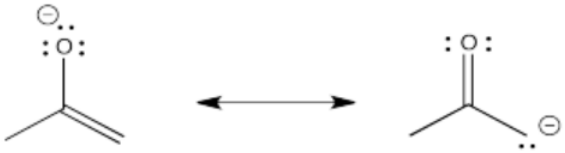


Figure 3.19.39:

a) pentanol b) 2-butanol c) 4-octanol

d) 2-methylpropan-2-ol or 2-methyl-2-pronanol e) 3-methylhexan-2-ol or 3-methyl-3-hexanol

f) 5,6-dimethylheptan-1-ol or 5,6-dimethyl-1-heptanol



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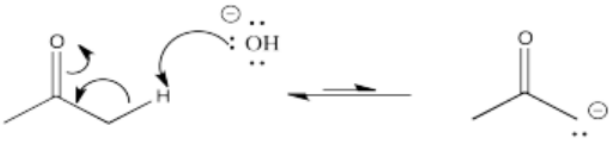


Figure 3.19.41:

a) KOH

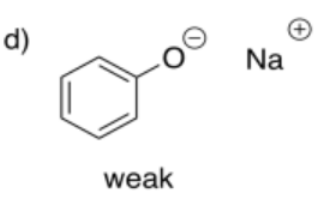
strong

b) KNH_2

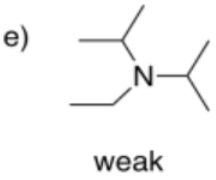
very strong

c) Me_3N

weak



weak



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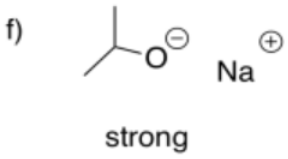
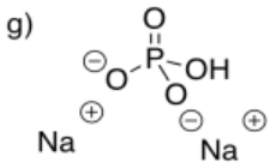
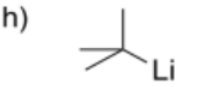


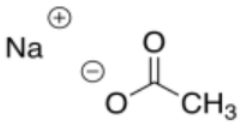
strong



weak

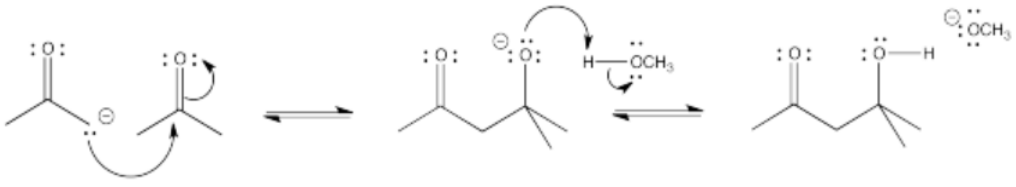


very strong



weak

Figure 3.19.42:



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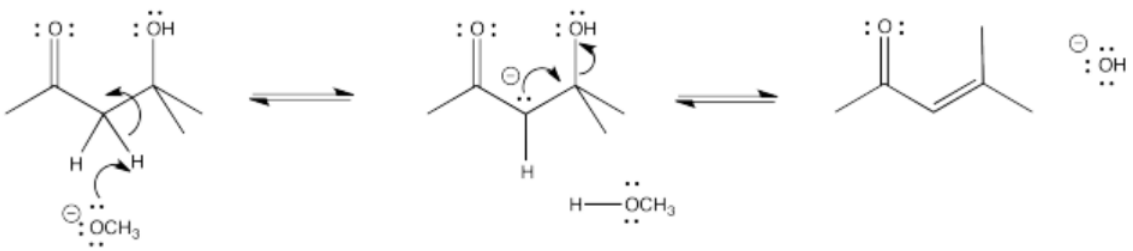

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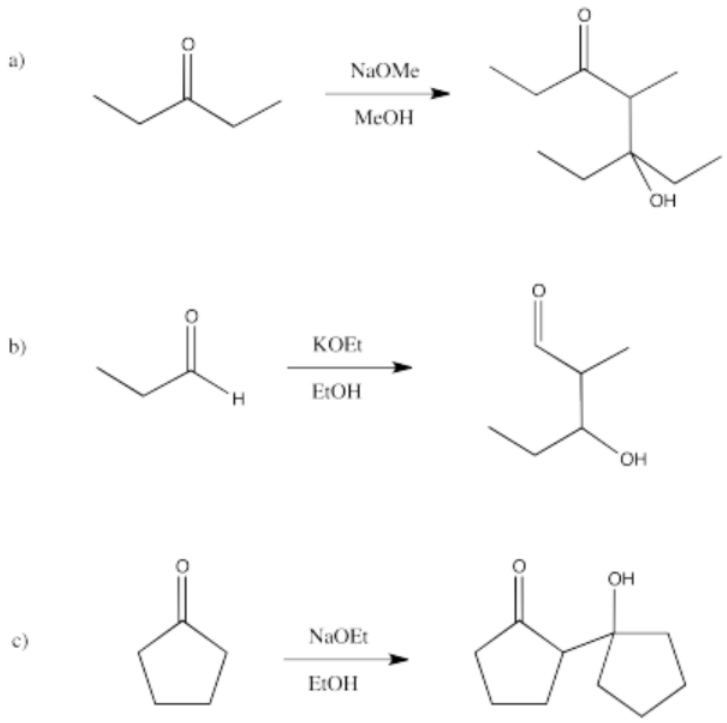

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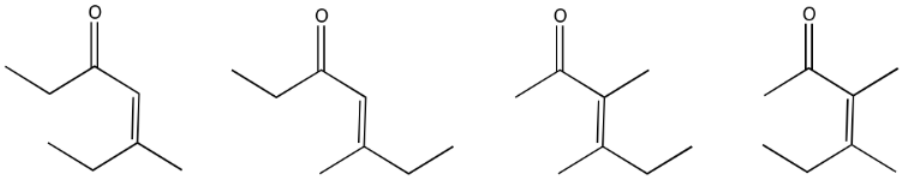

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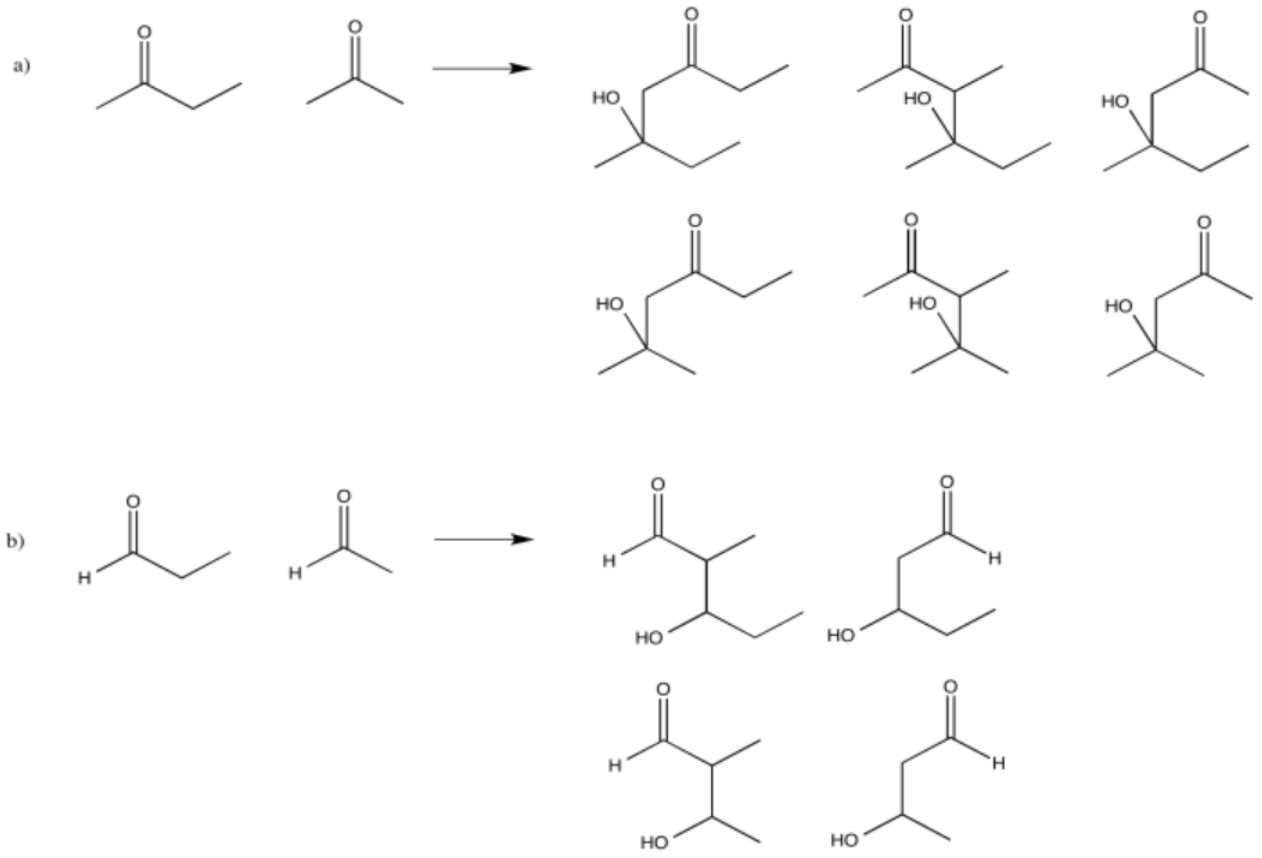

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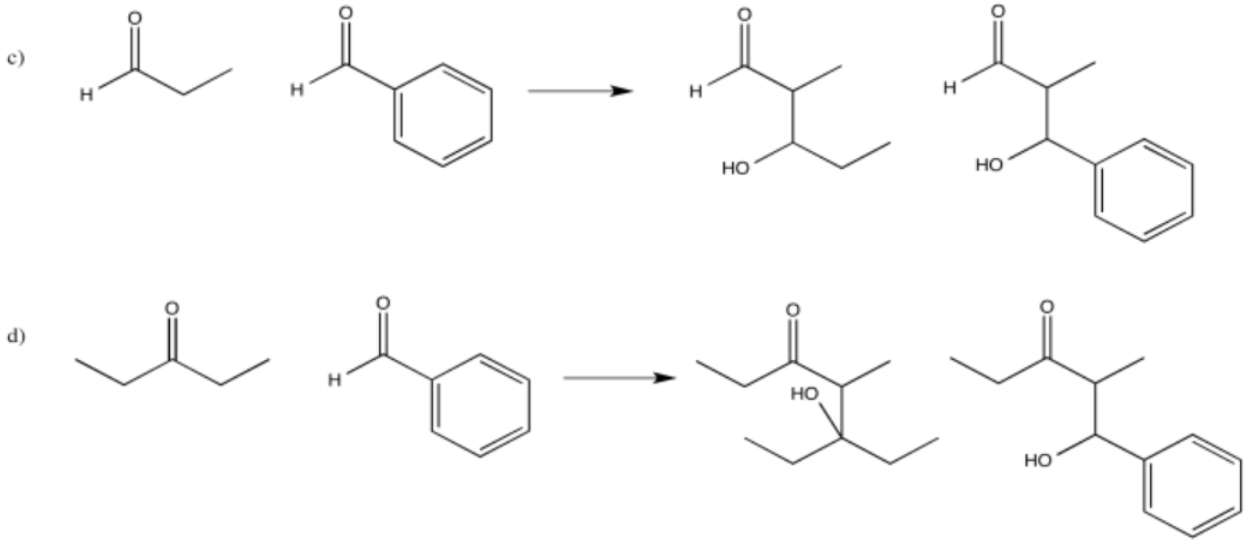


Figure 3.19.48:

Some of these compounds do not have alpha-protons, so they cannot form enolate ions.

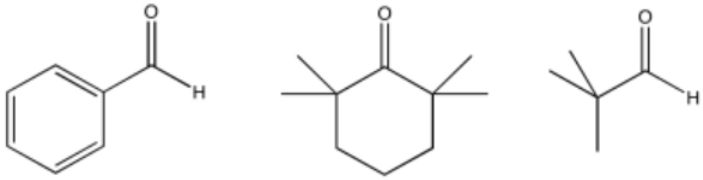
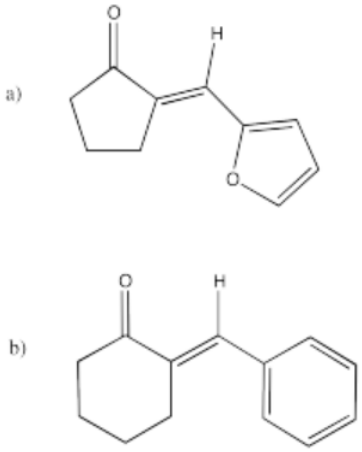


Figure 3.19.49:

Problem CO12.11.



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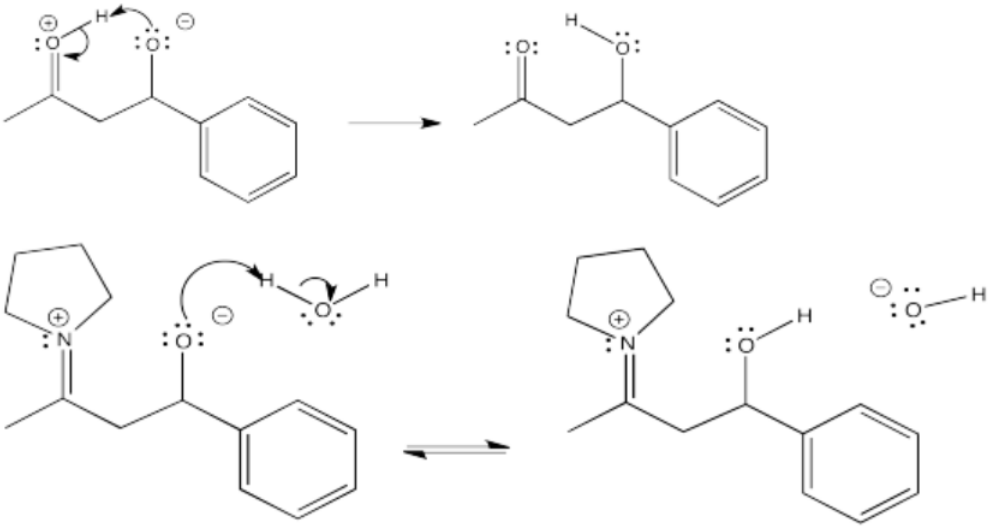
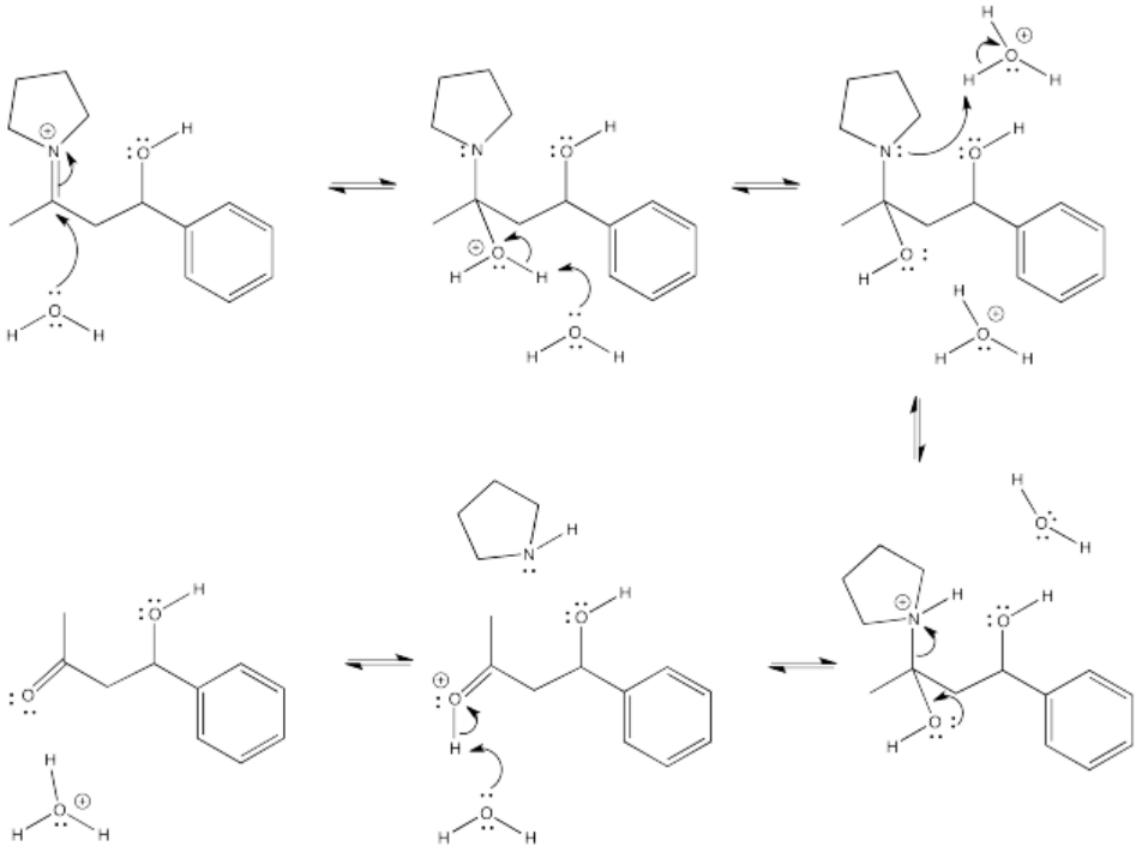


Figure 3.19.51:



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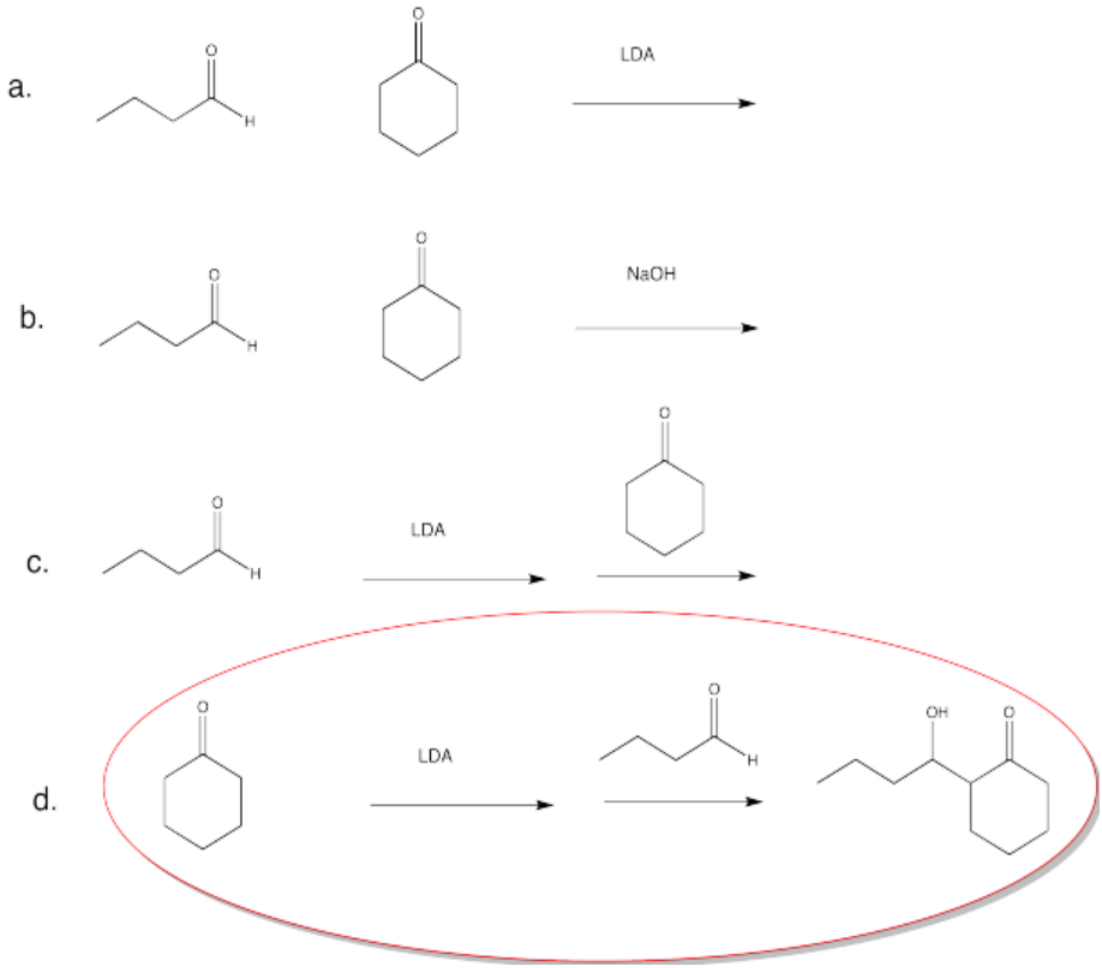

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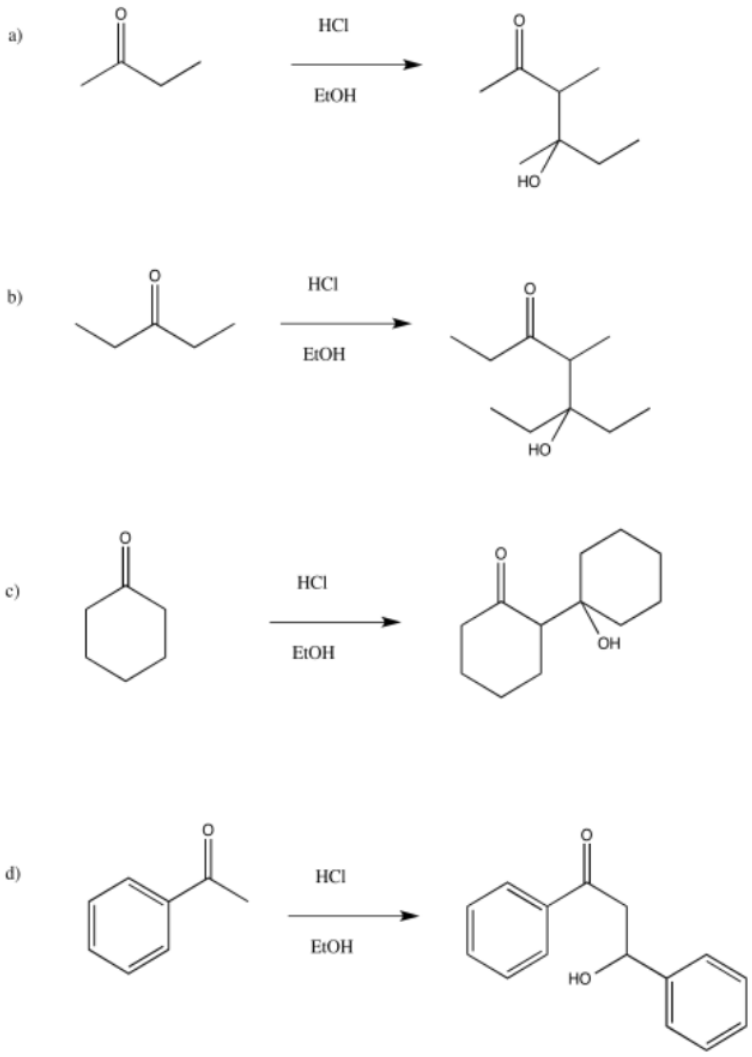

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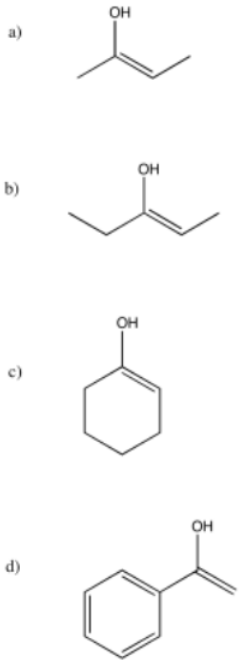

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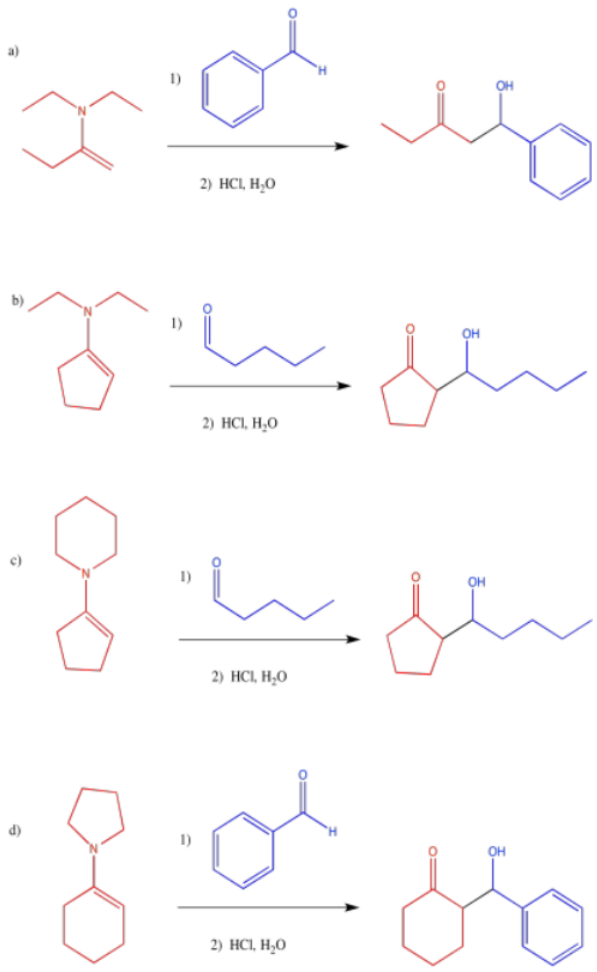


Figure 3.19.56:

3.20: Solutions to Selected Problems, Part B

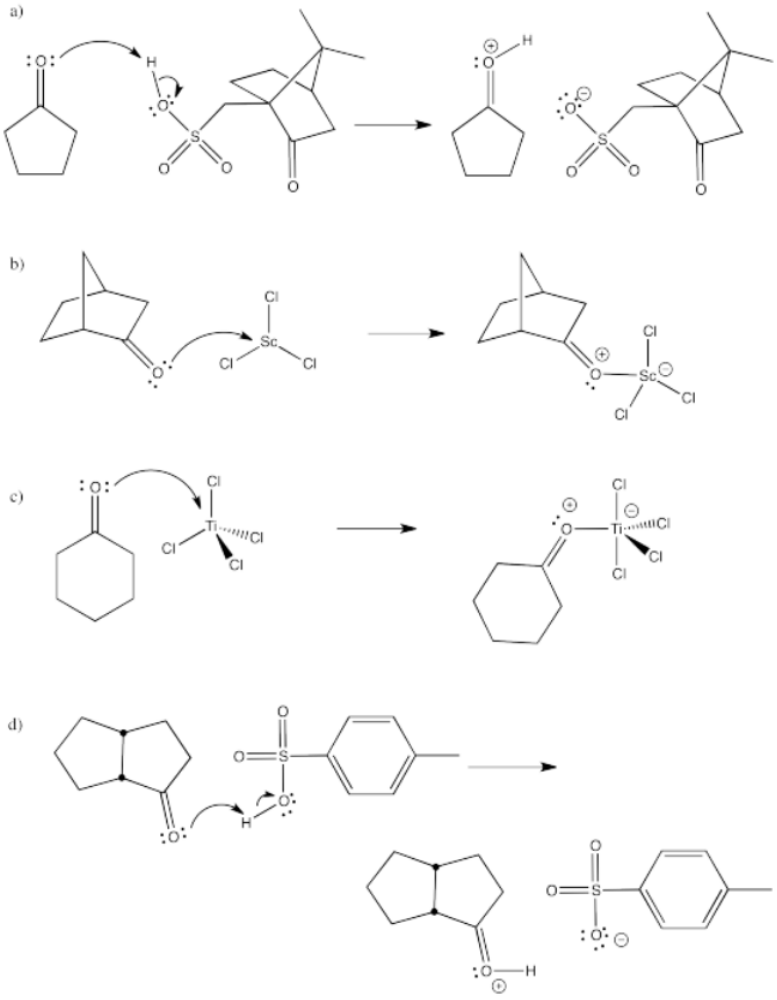
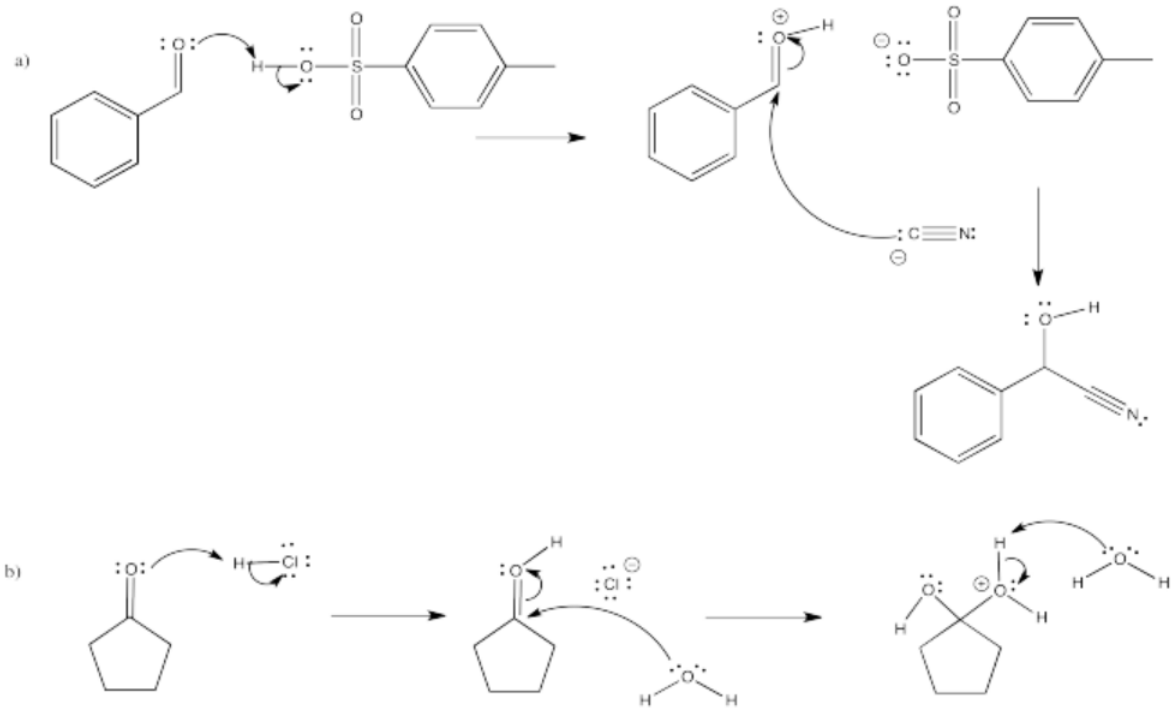
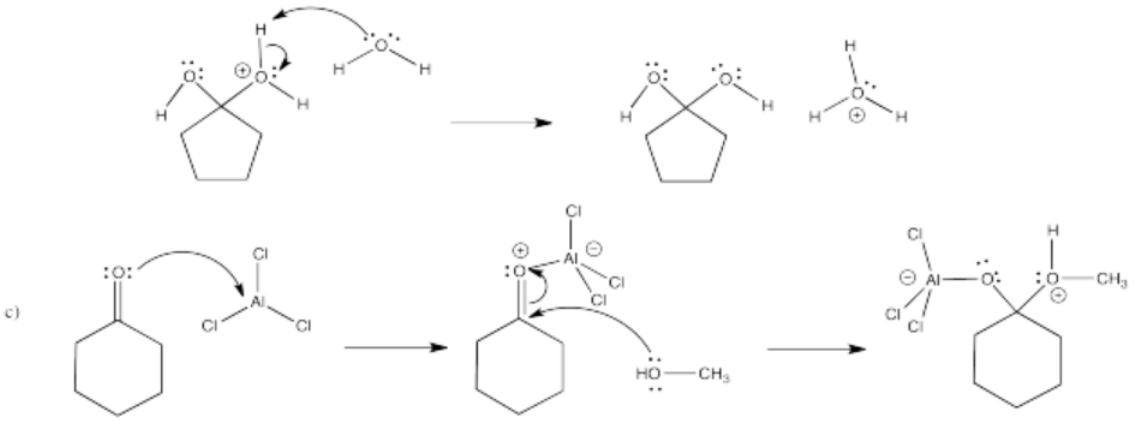


Figure 3.20.1:

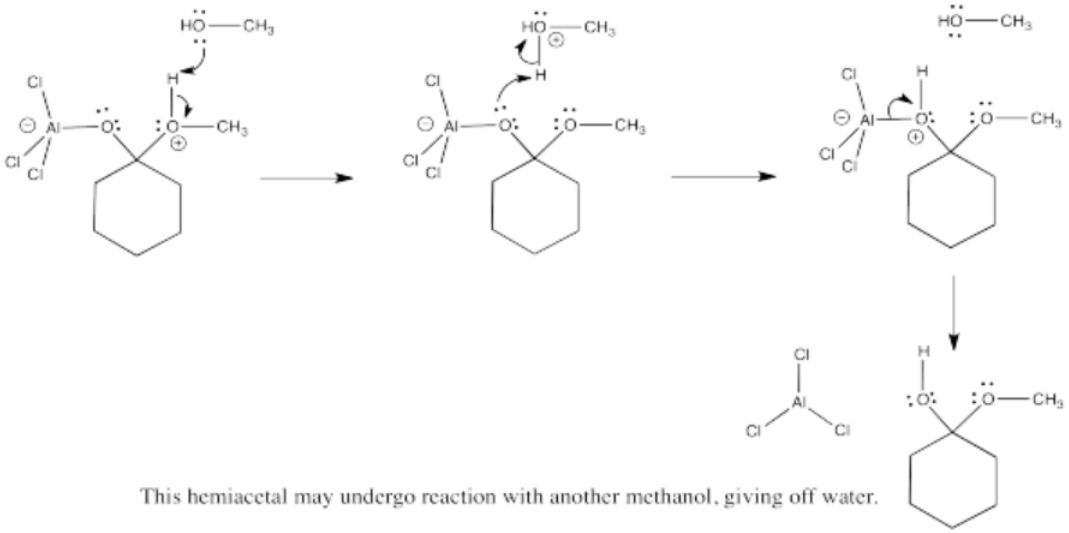


Nucleophilic donation would probably be followed by a proton transfer step (below)

Figure 3.20.2:

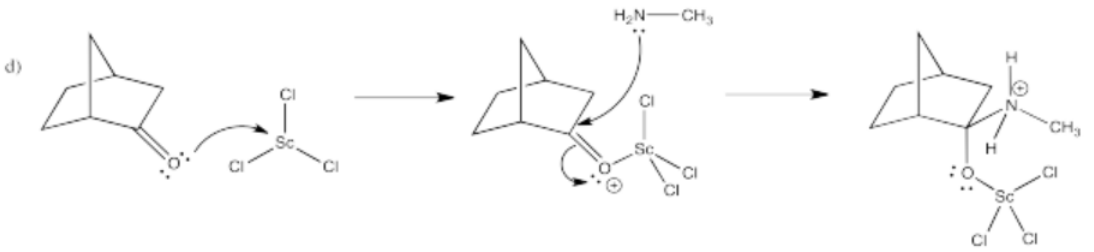


Nucleophilic donation would probably be followed by a series of other steps (below)



This hemiacetal may undergo reaction with another methanol, giving off water.

Figure 3.20.3:



Nucleophilic donation would probably be followed by a series of other steps (below)

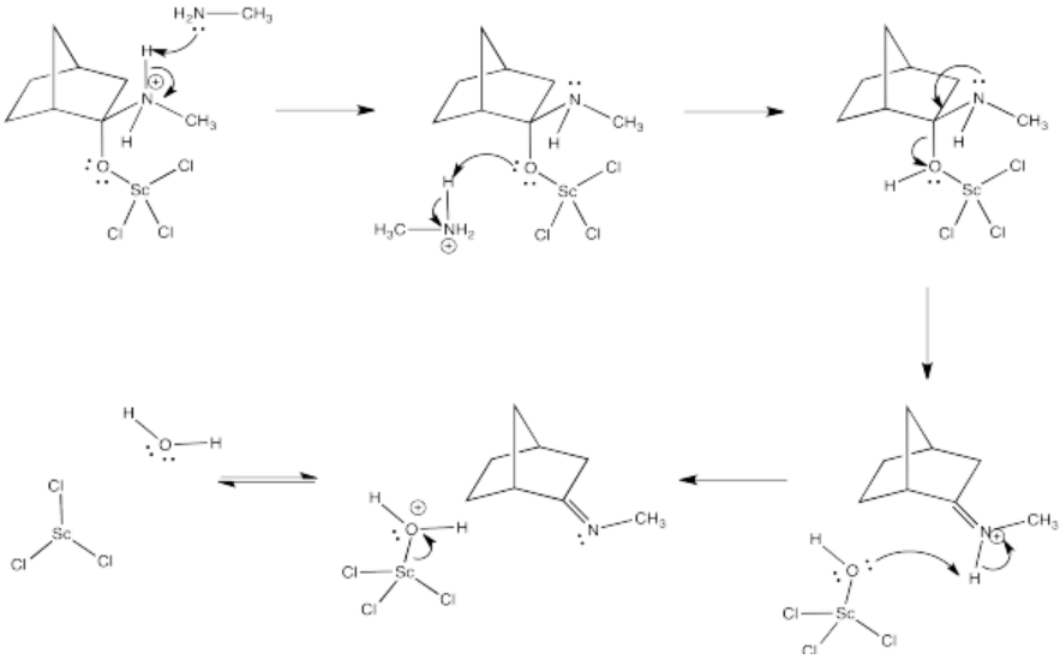


Figure 3.20.4:

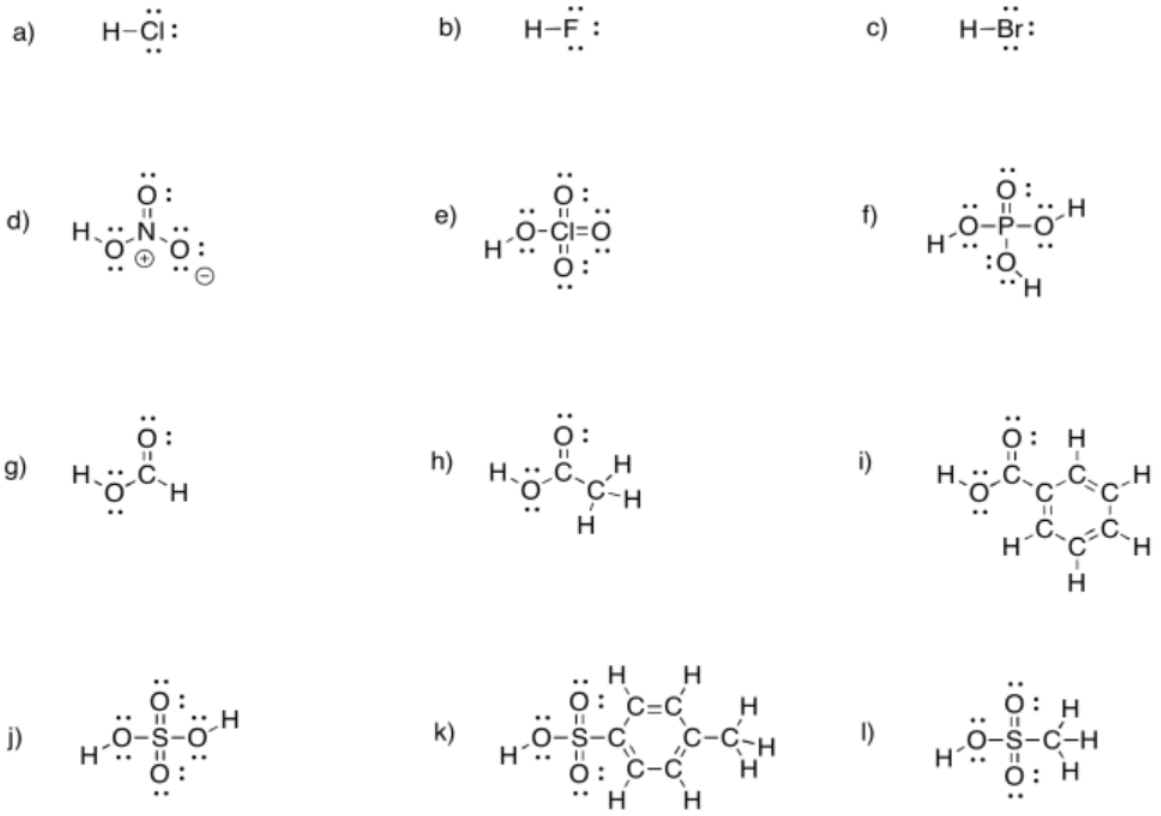


Figure 3.20.5:

Part a.

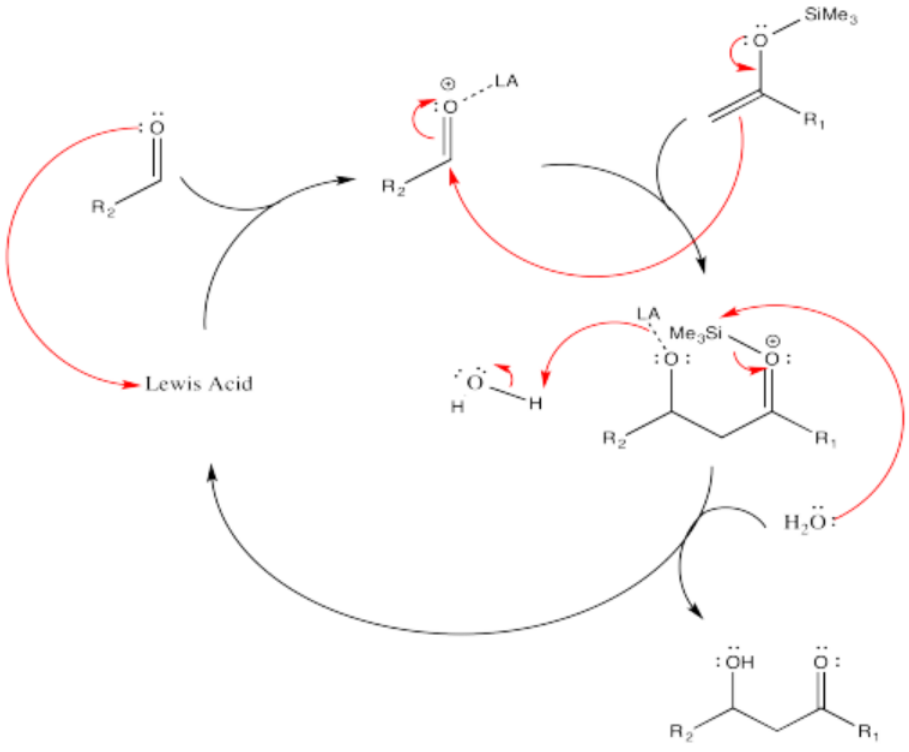


Figure 3.20.6:

Part b.

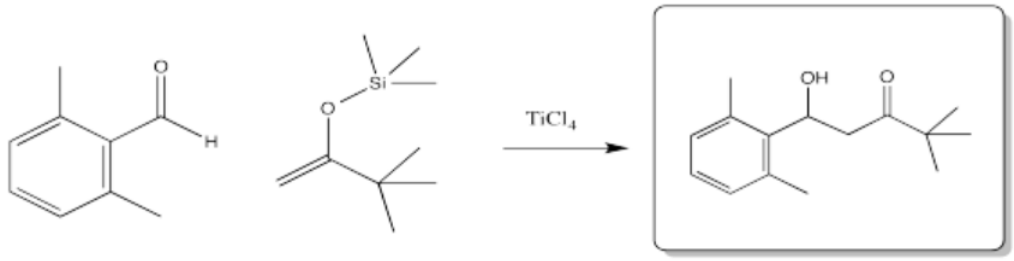


Figure 3.20.7:

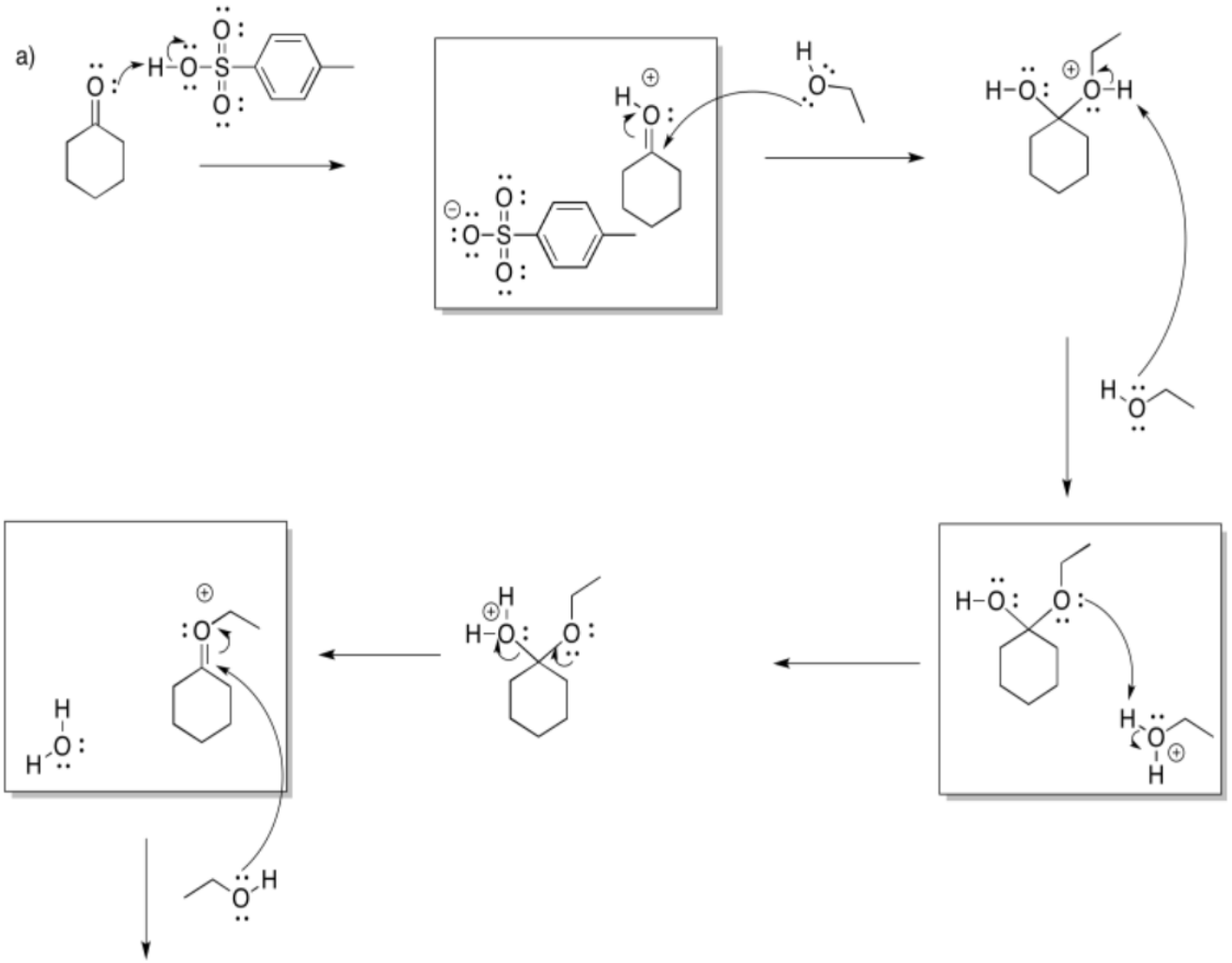
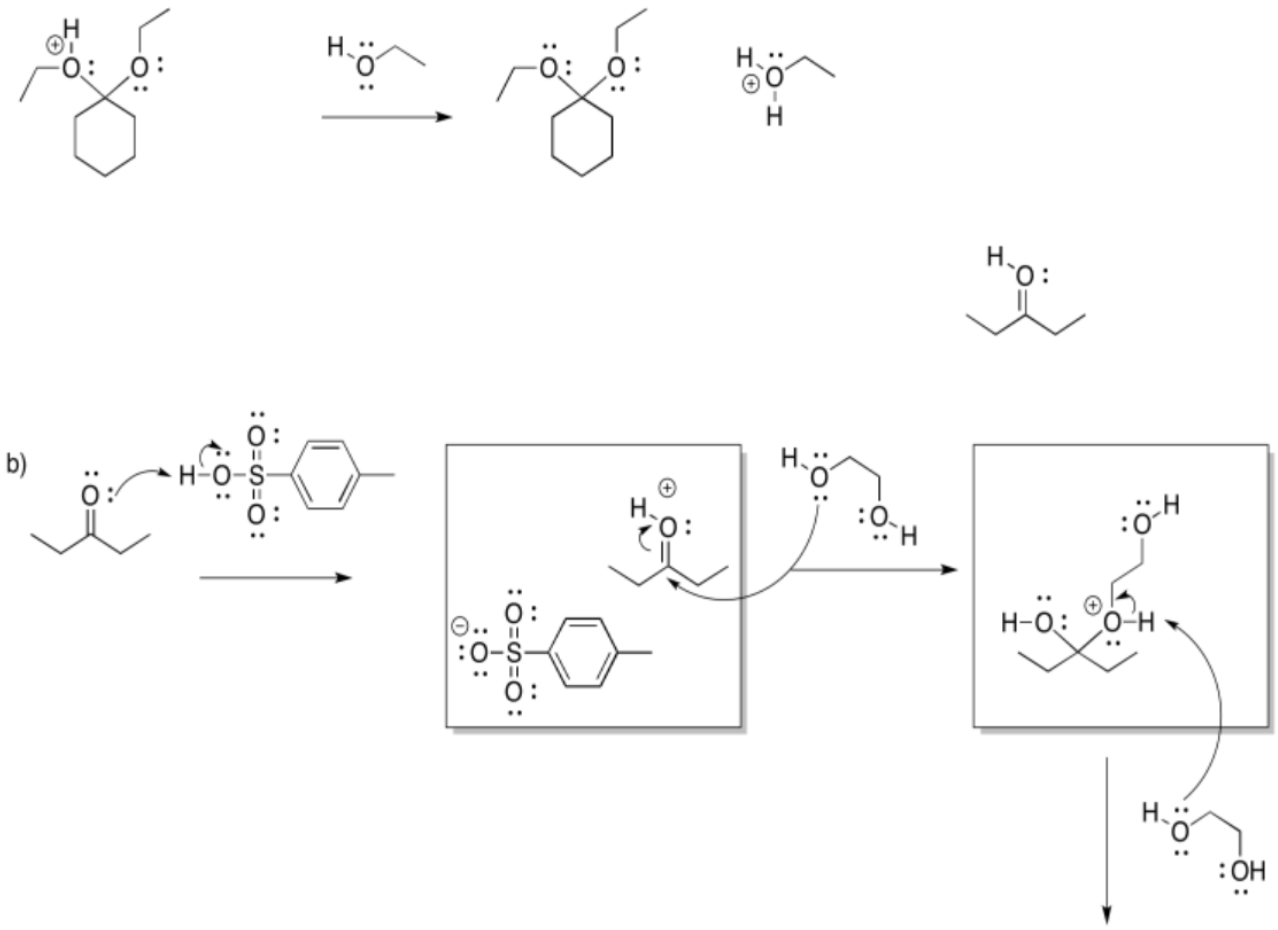


Figure 3.20.8:



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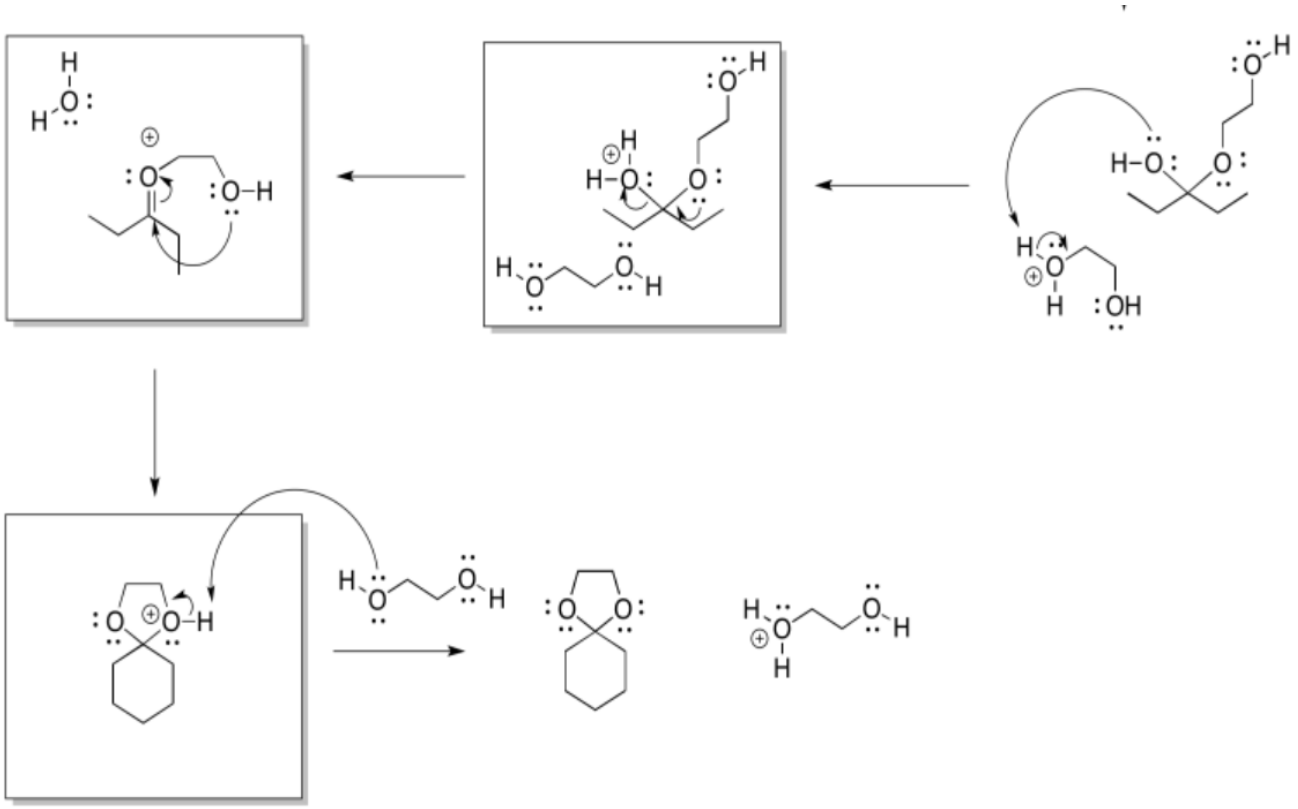

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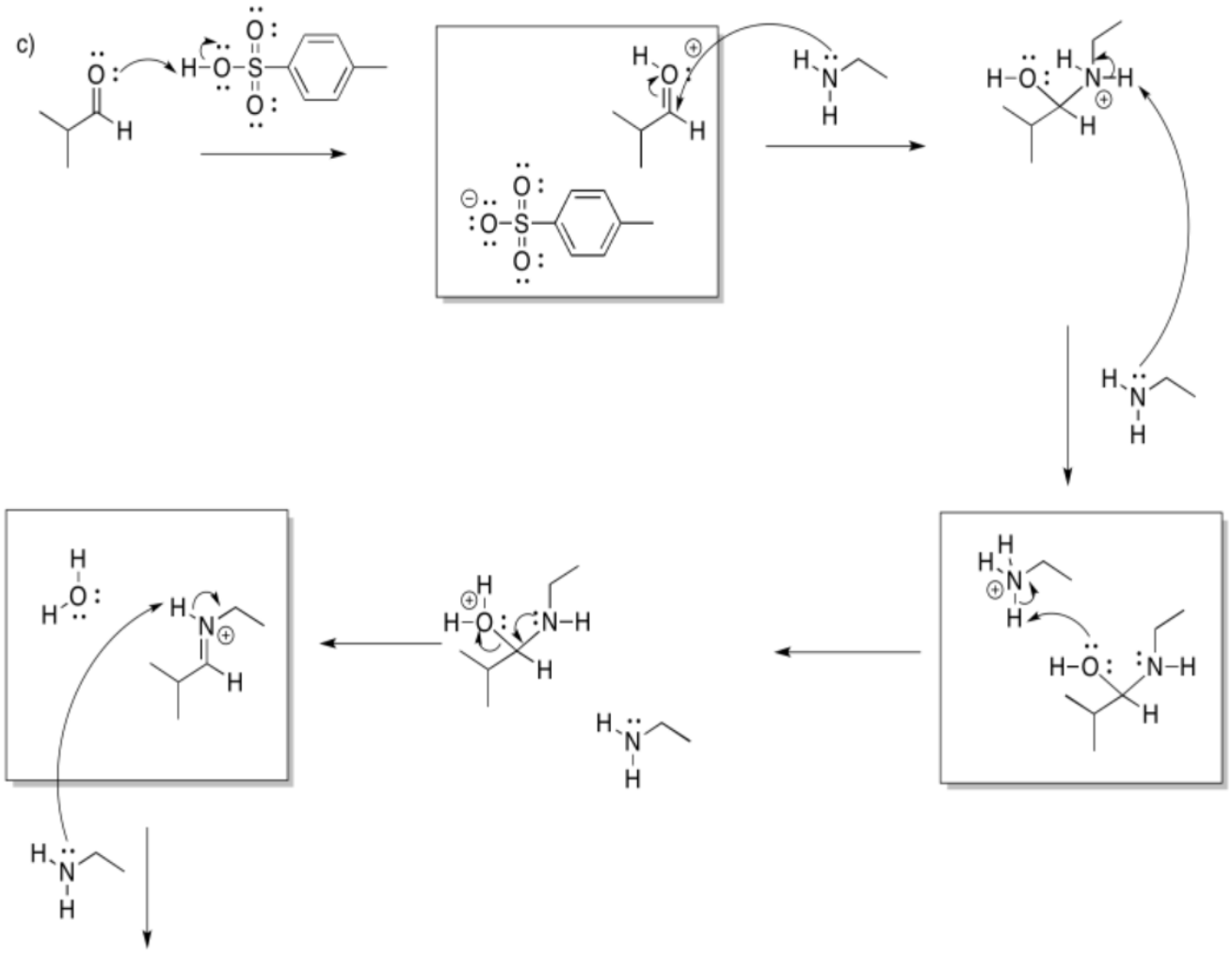
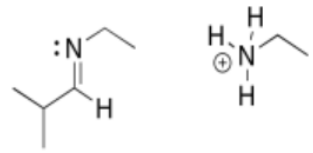
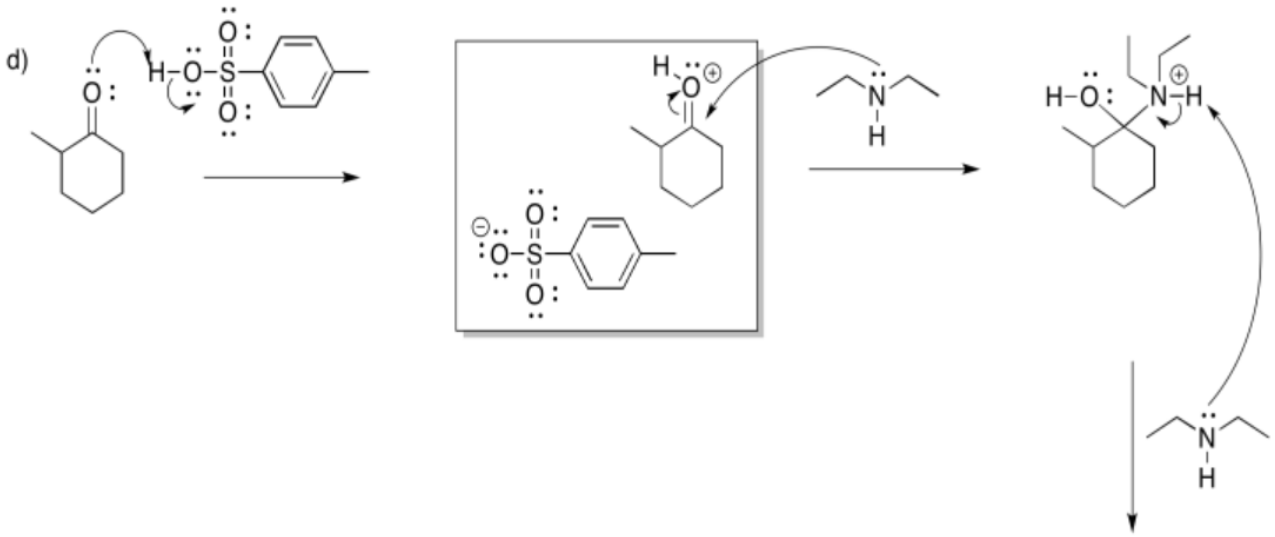


Figure 3.20.11:





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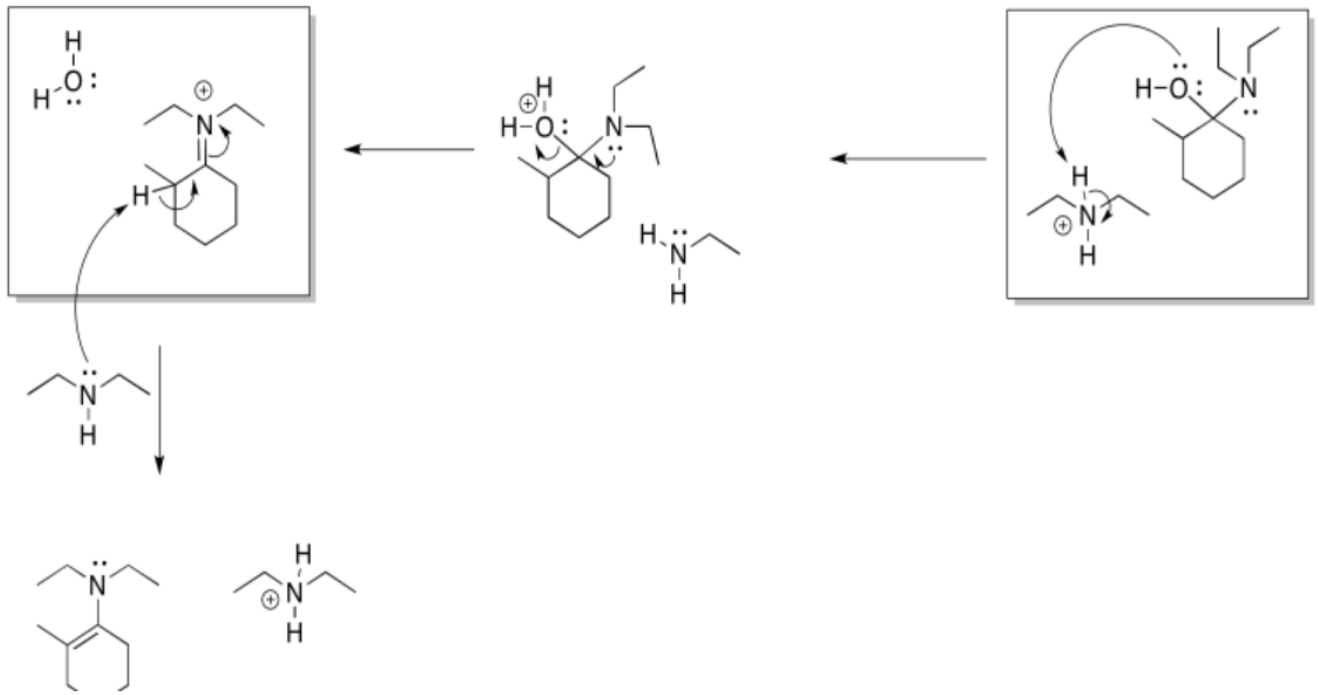

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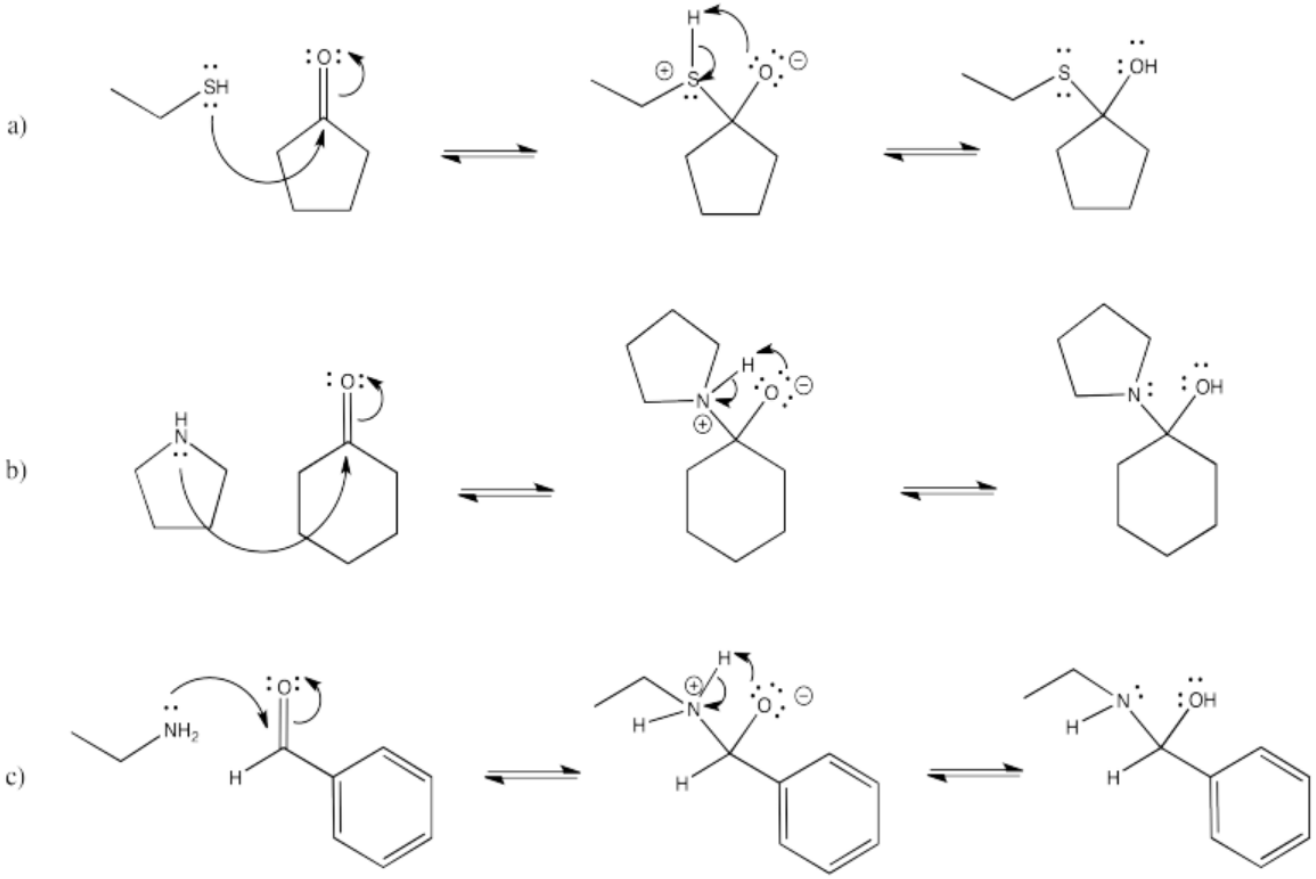

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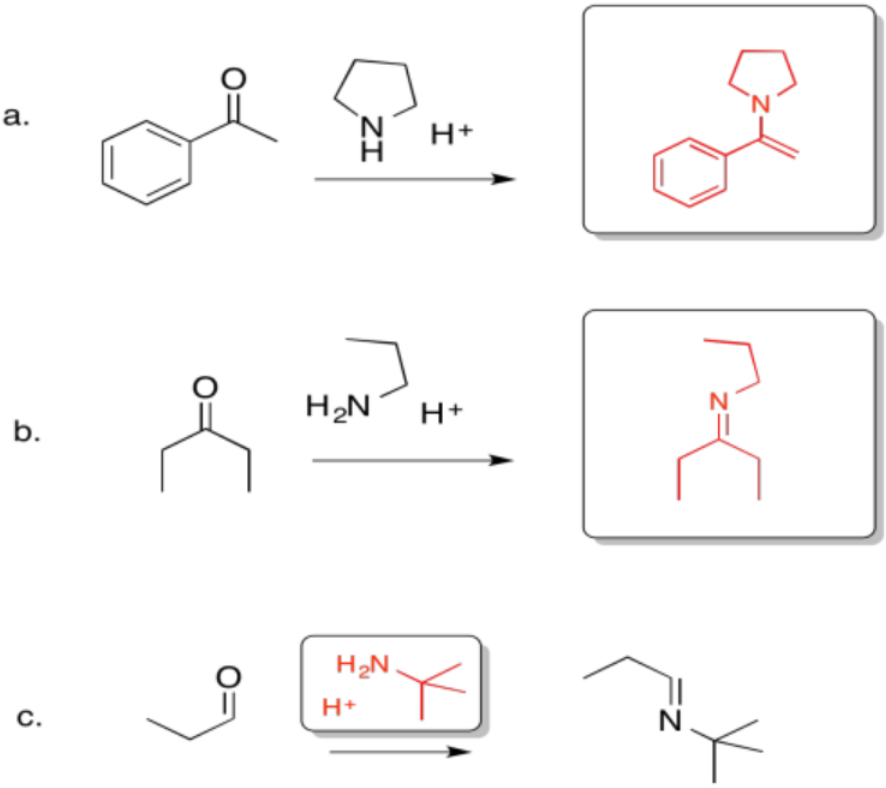

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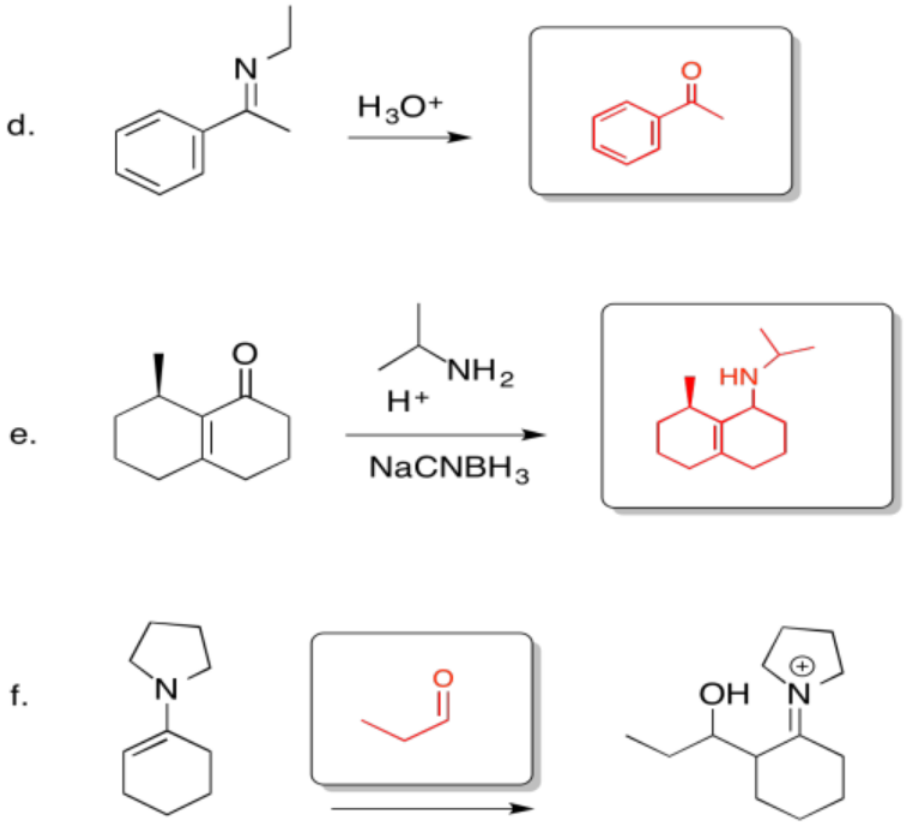

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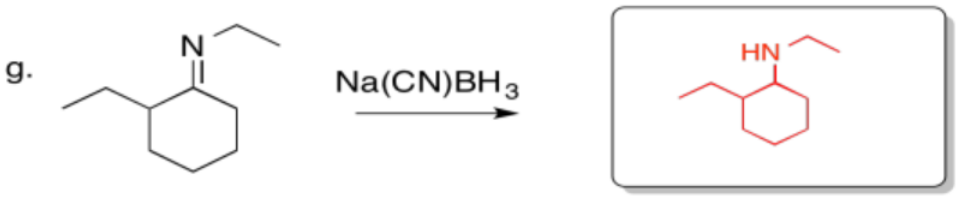

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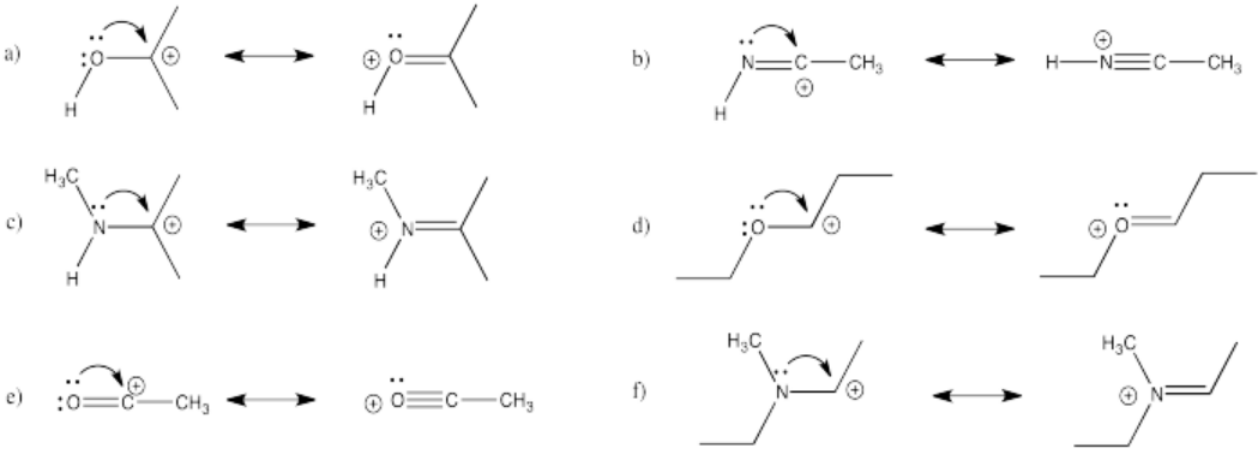

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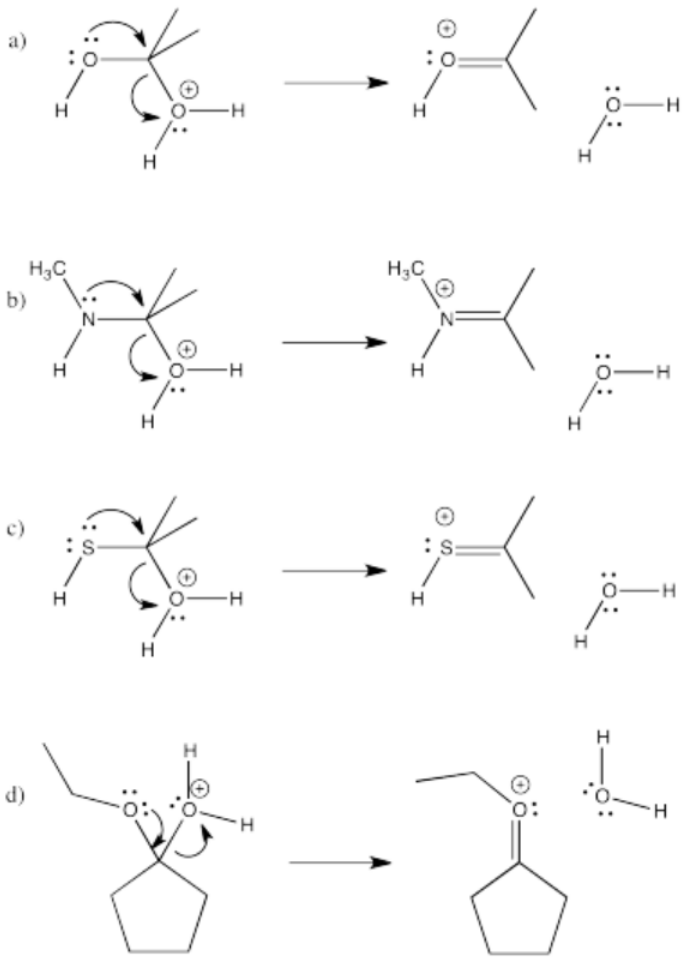
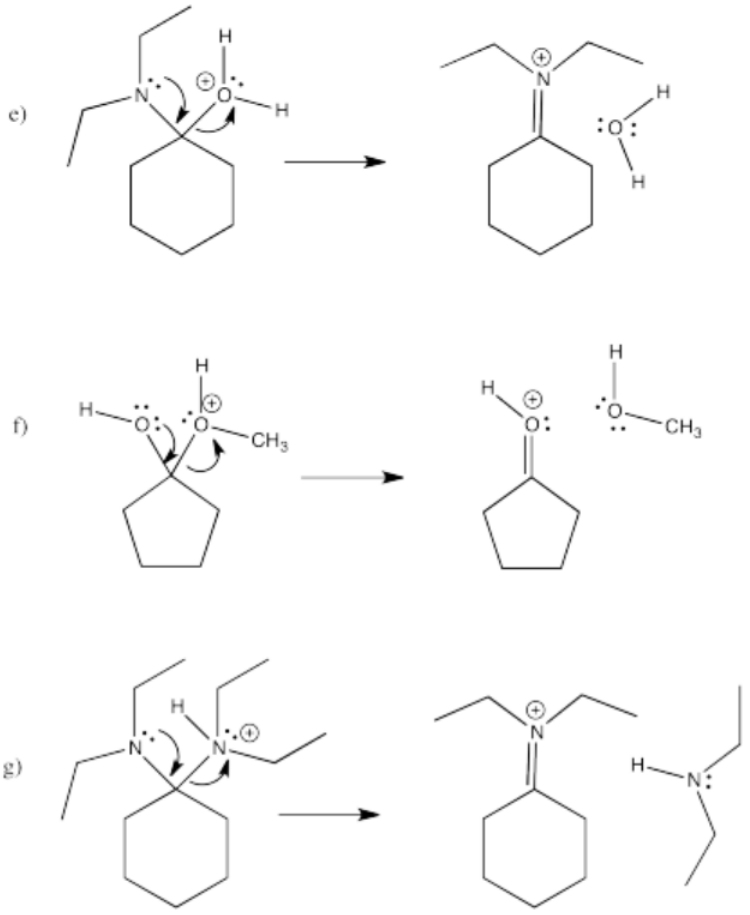


Figure 3.20.19:



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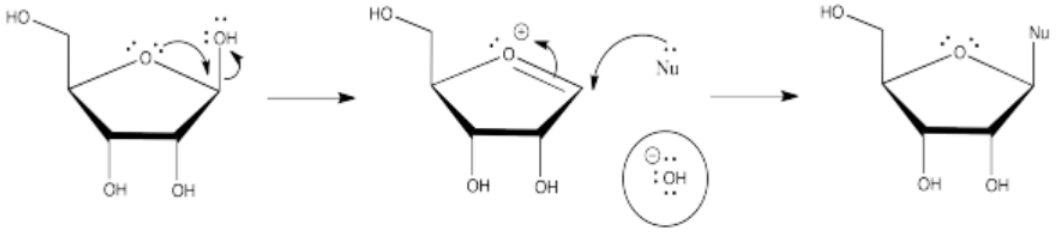
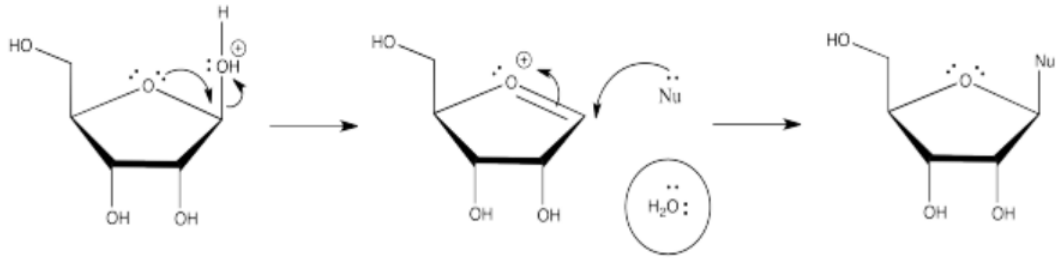


The leaving group in the above reaction is a reactive hydroxide ion, but if the oxygen is protonated, the leaving group is a stable water molecule.



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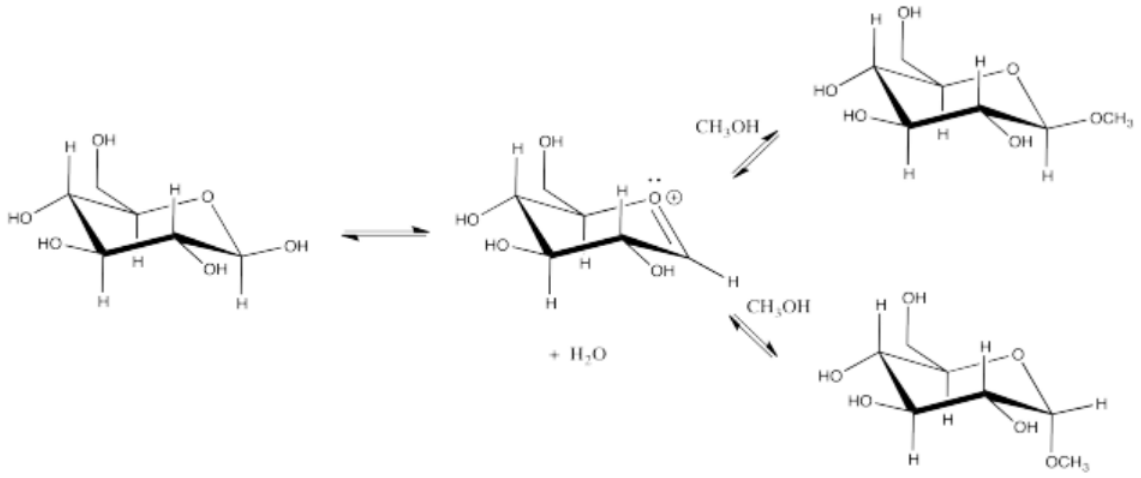

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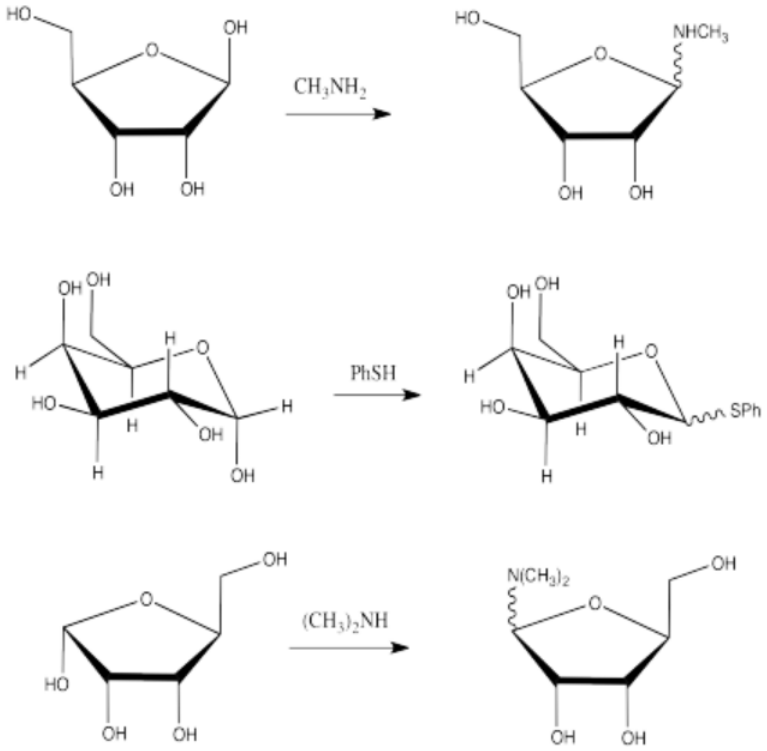

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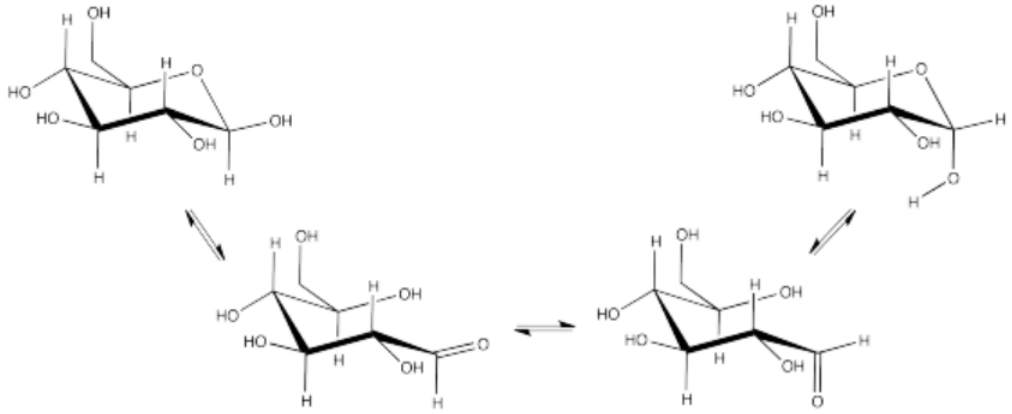

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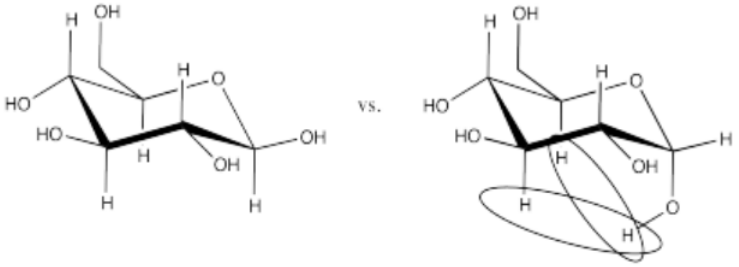

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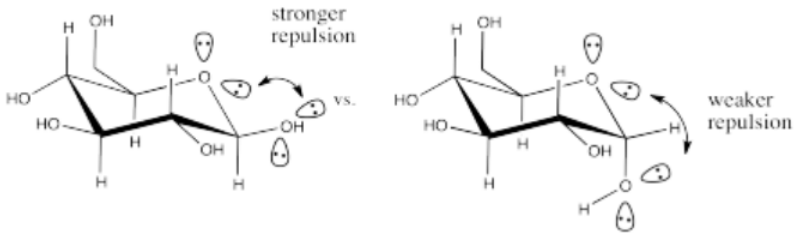

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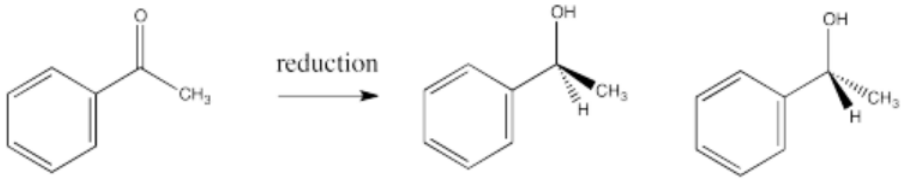
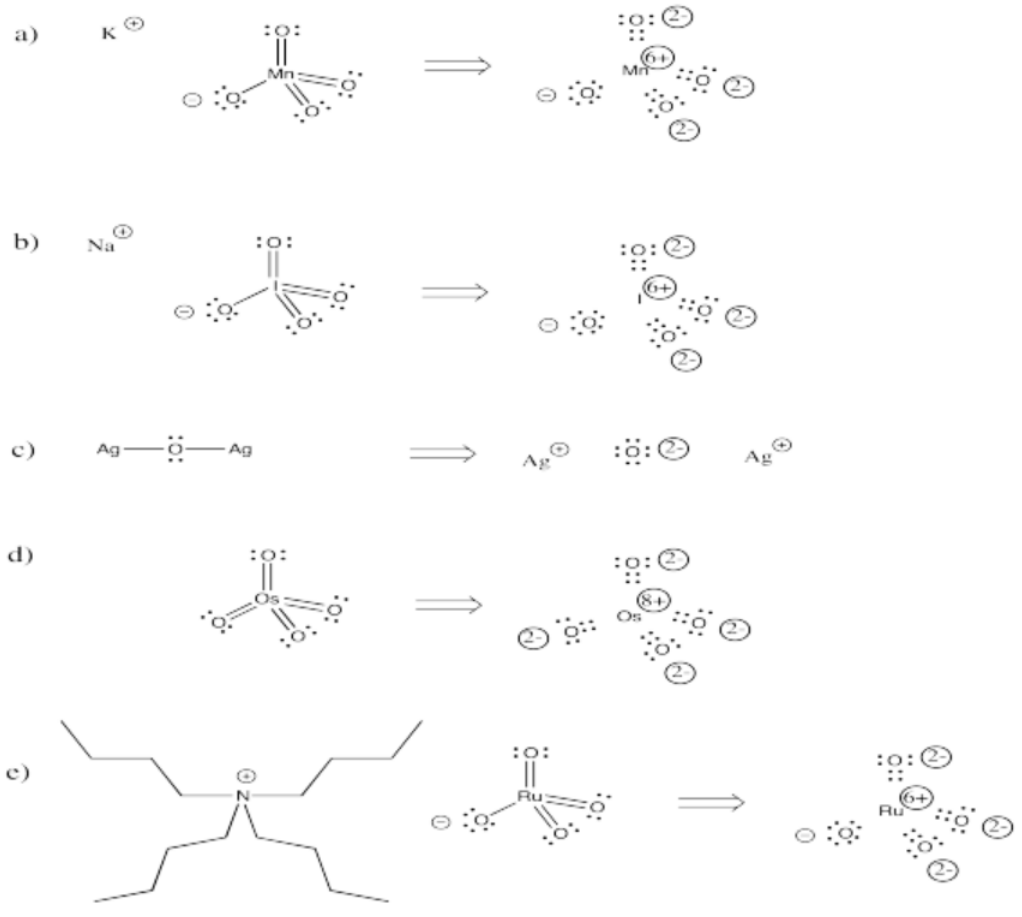


Figure 3.20.27:

Figure 3.20.28:



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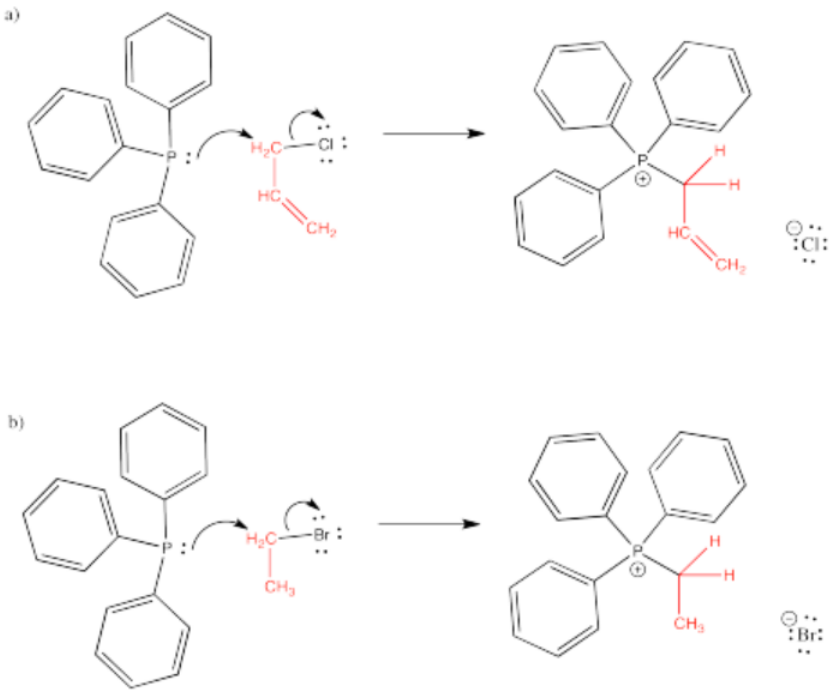

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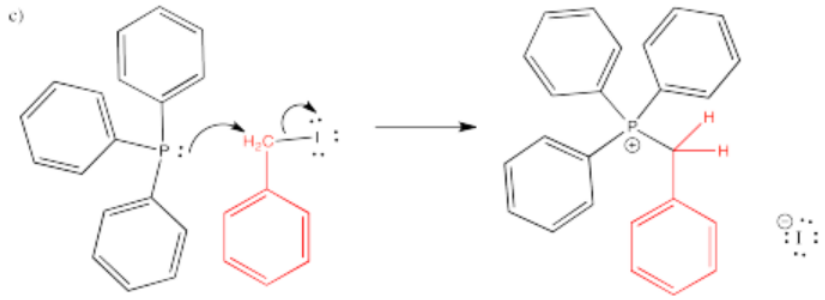

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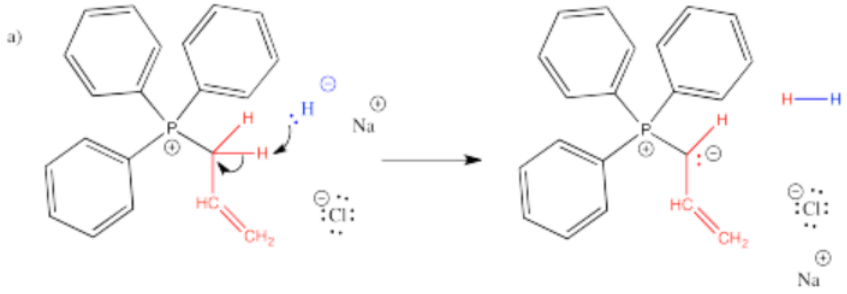

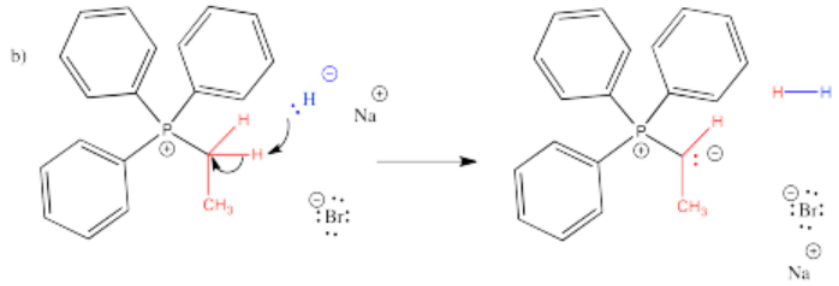

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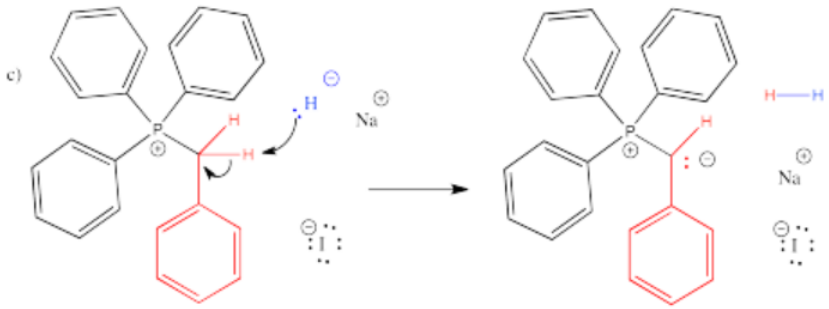
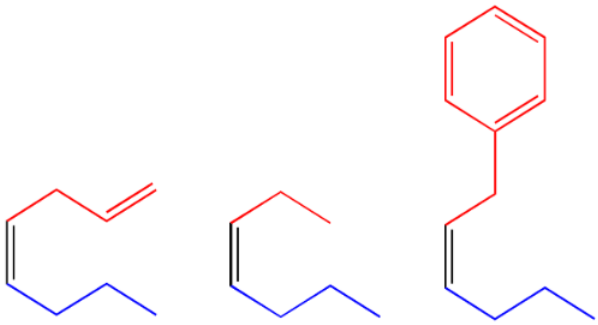


Figure 3.20.33:

a)



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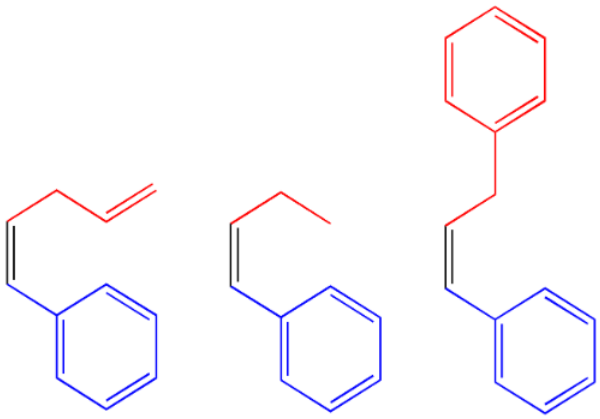


Figure 3.20.34:

c)

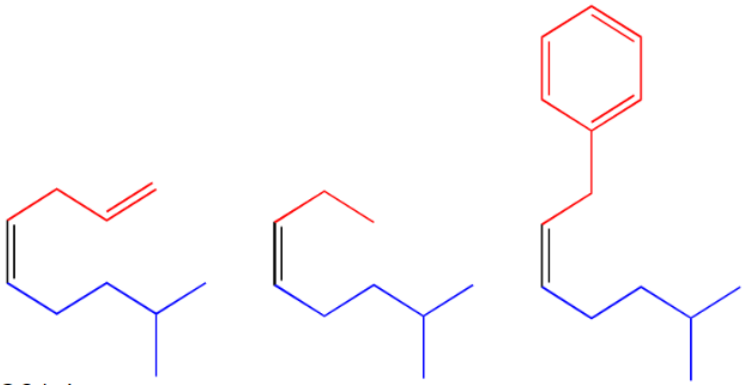
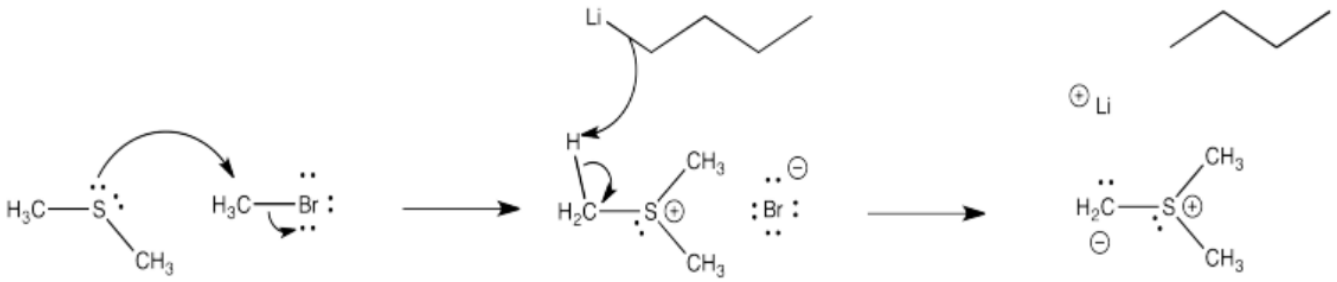


Figure 3.20.35:

One of the keys in this problem is recognizing that in some steps, two different reactions are involved. For example, in the first box, there is an addition of a diol to a carbonyl followed by an ylide addition.



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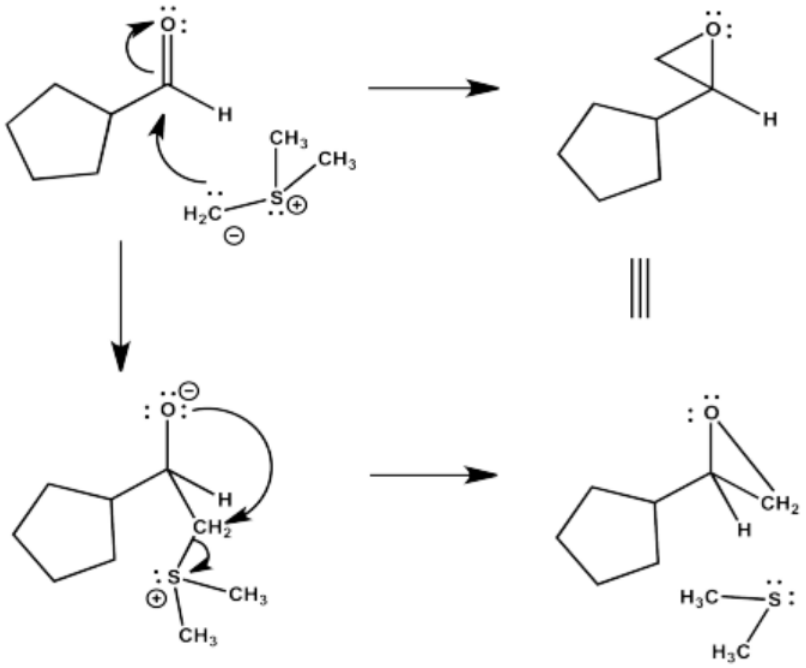
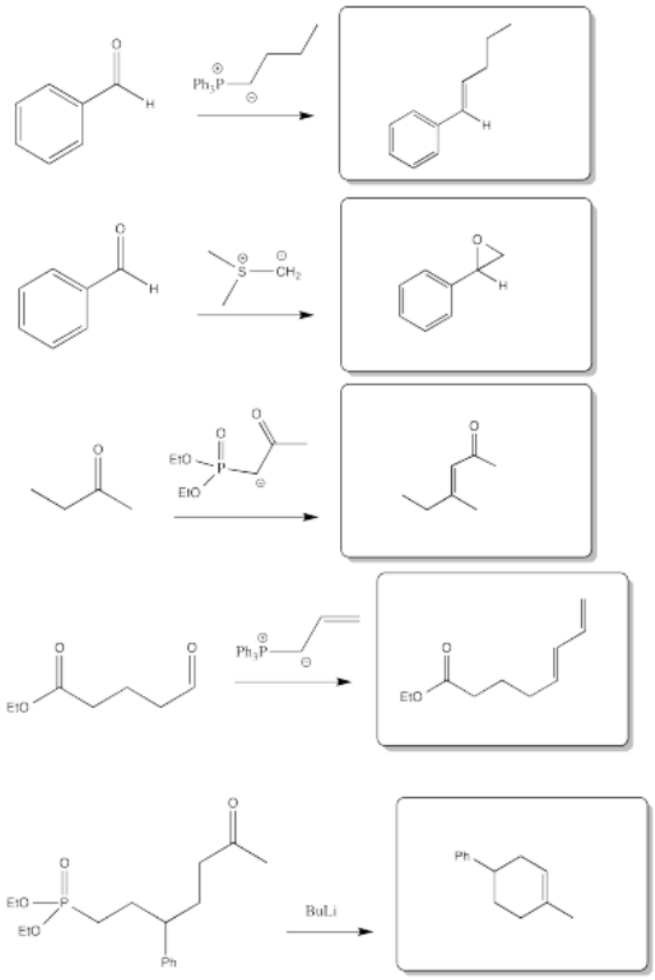


Figure 3.20.37:



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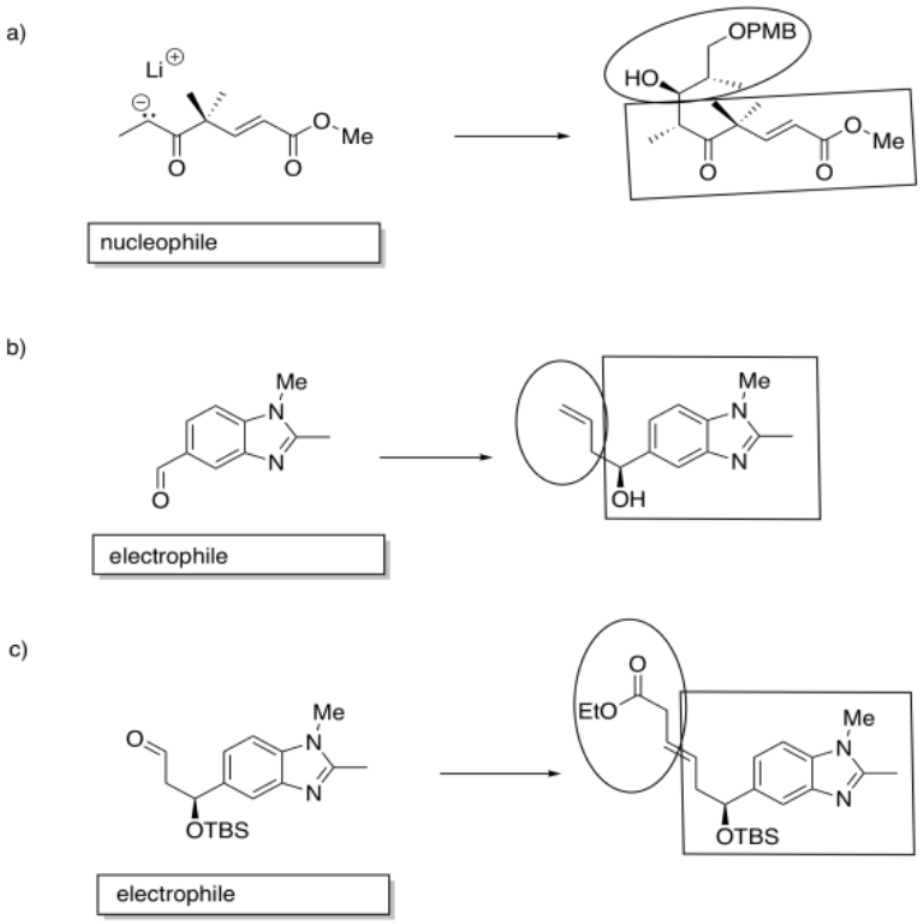
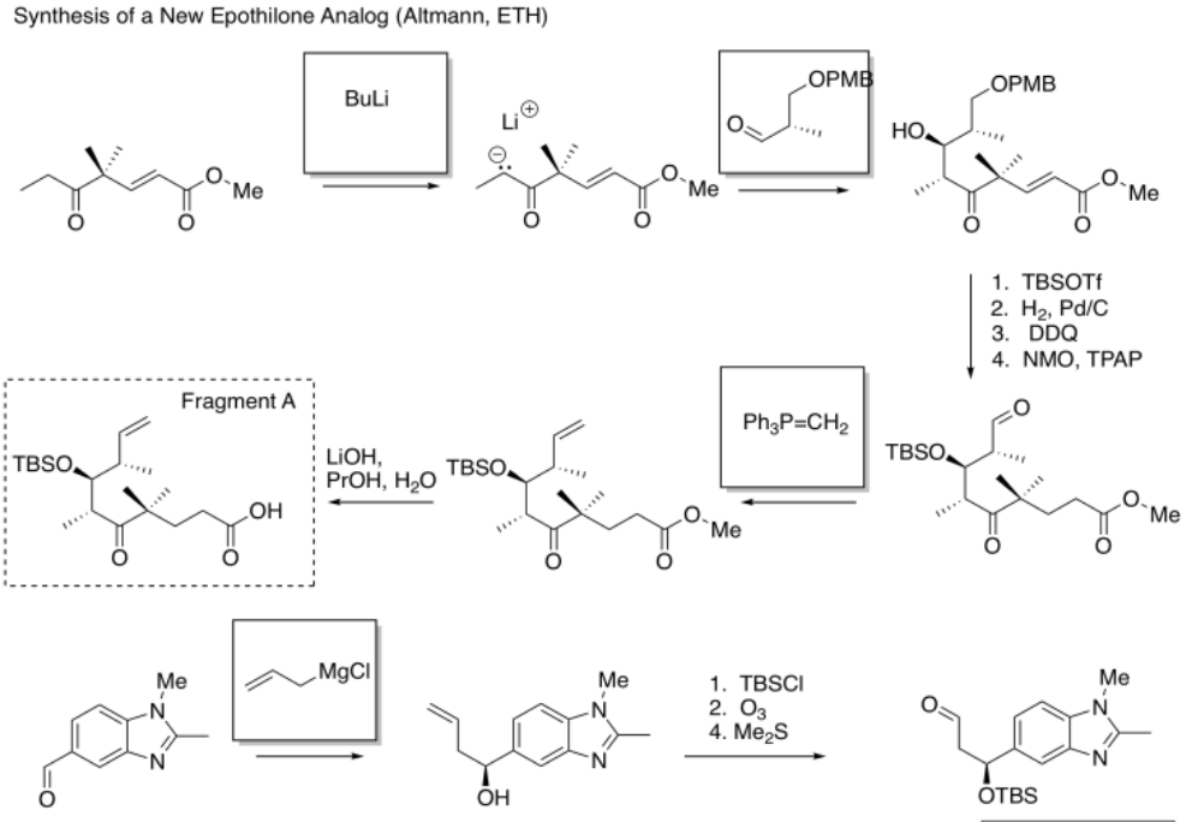


Figure 3.20.39:



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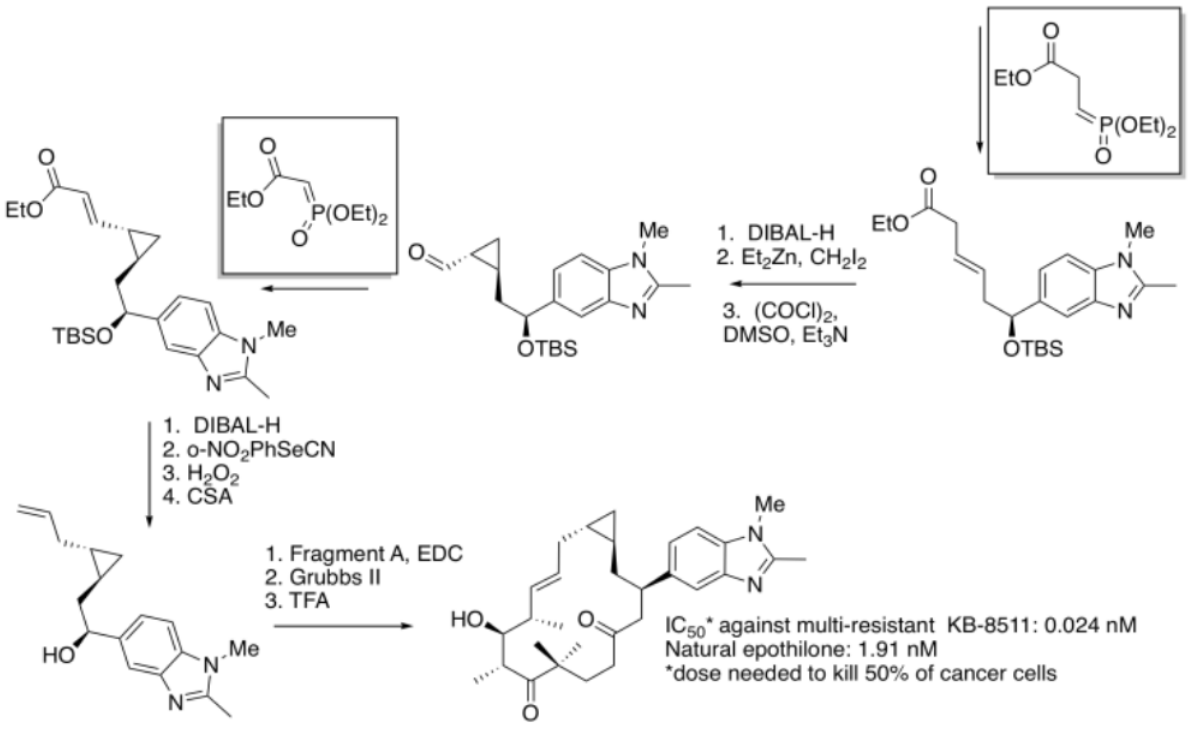


Figure 3.20.41:

a)

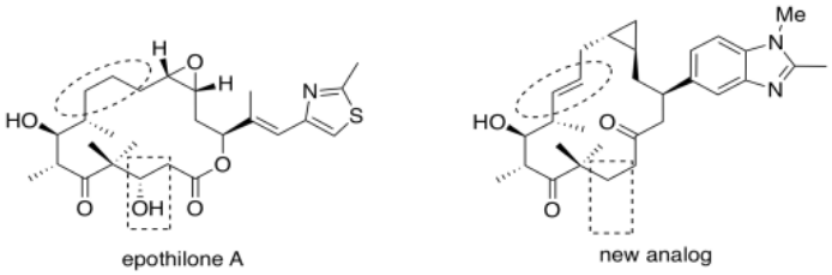


Figure 3.20.42:

b) The circled part changed from a single bond to a doube bond. The boxed part changed from an alcohol to unadorned hydrocarbon chain.

c) Hydrogen bonding is the most obvious.

d) However, the analog works better without this group; this particular alcohol group is probably not an important part of the pharmacophore. It is probably not needed in order to bind to the target.

e) In epothilone A, as drawn, the dihedral angle appears to be 0 degrees.

f) In the new analog, the dihedral angle is 180 degrees.

g) Based on the superior activity of the analog, the active conformation of the ring is probably more like the one on the right than the one on the left. The circled bond probably adopts a dihedral angle closer to 180 degrees, with the rest of the ring twisting into a shape more like the one shown on the right, in order to bind to the target.

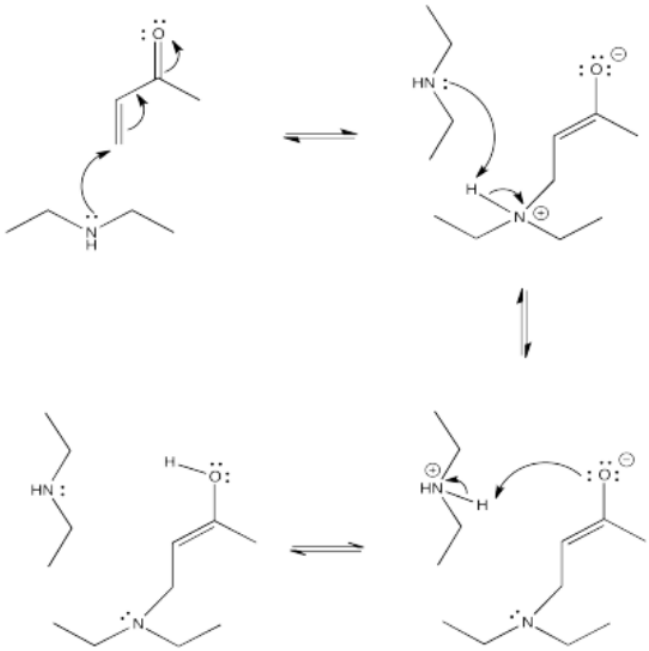


Figure 3.20.43:

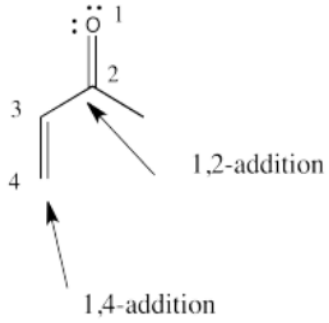


Figure 3.20.44:

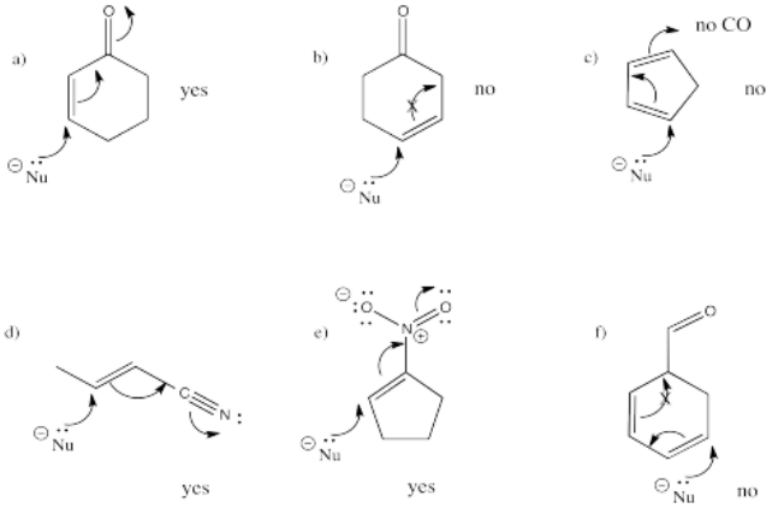


Figure 3.20.45:

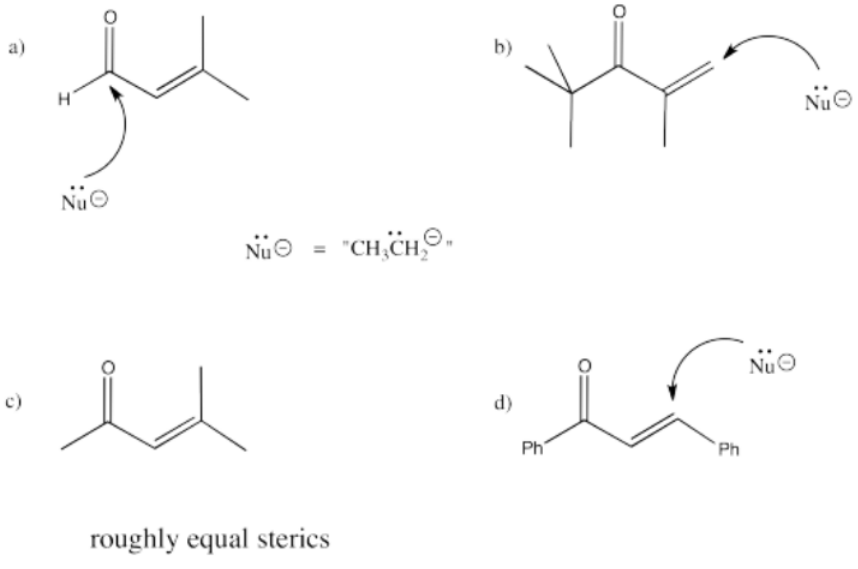
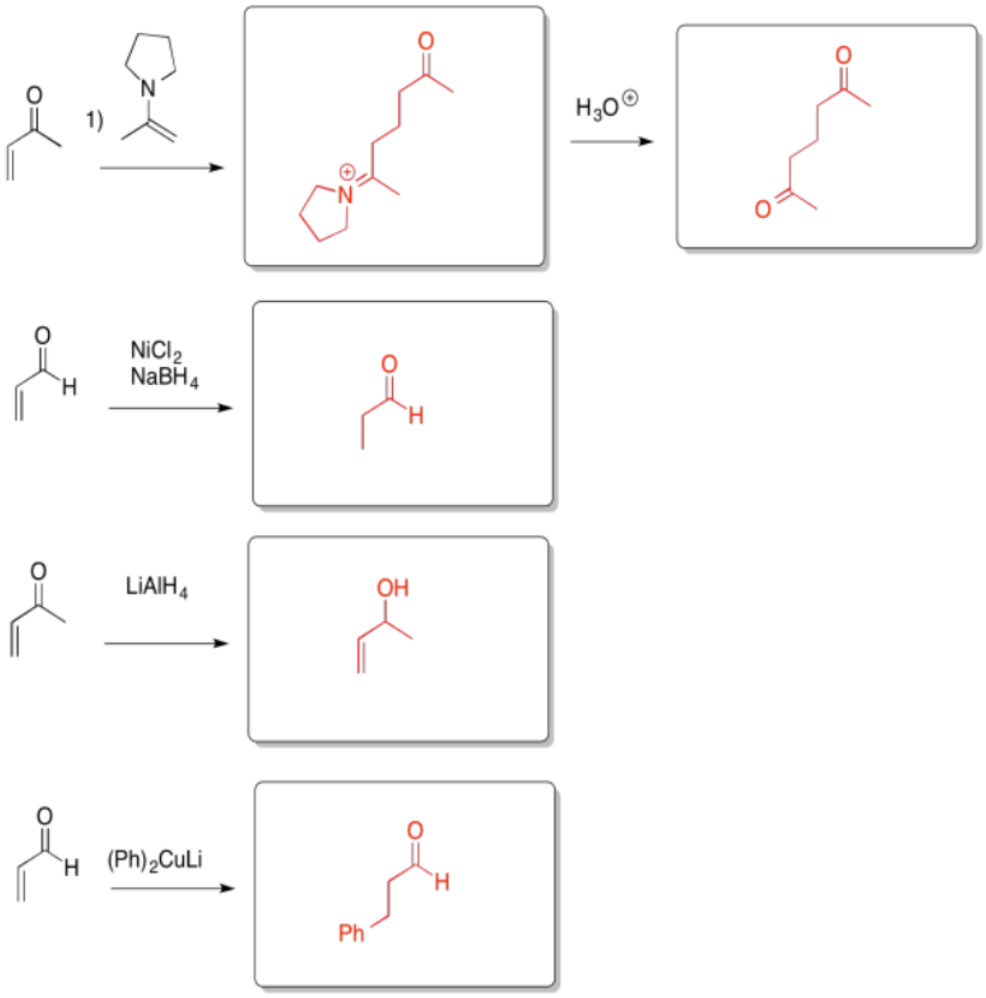


Figure 3.20.46:



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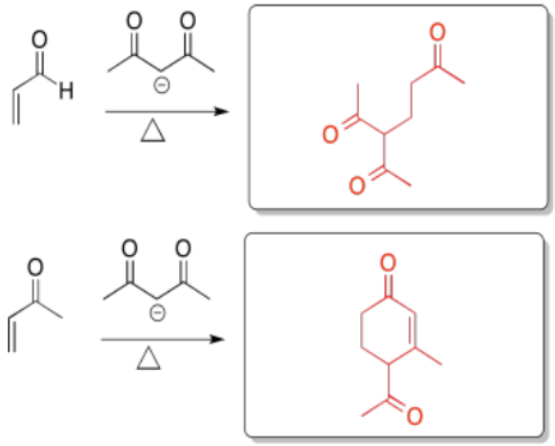


Figure 3.20.48:

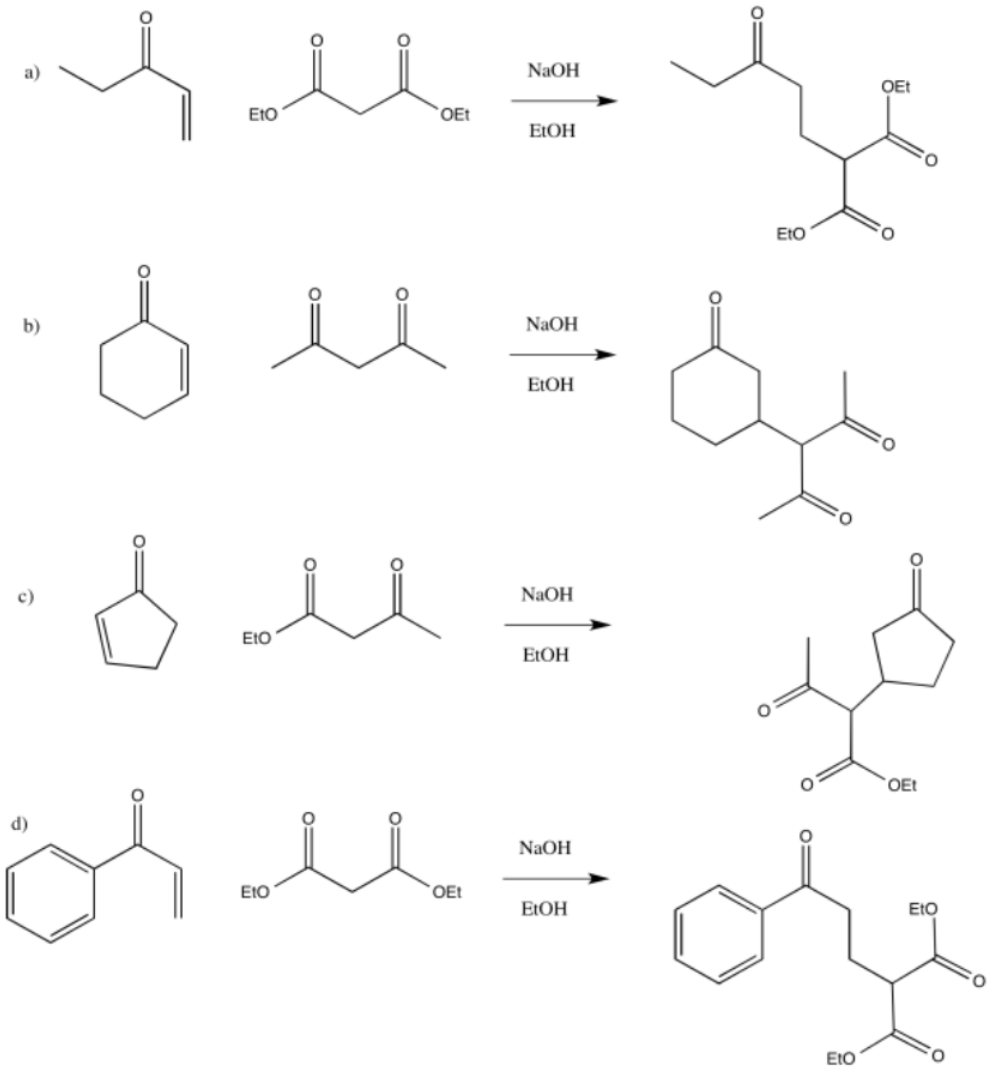
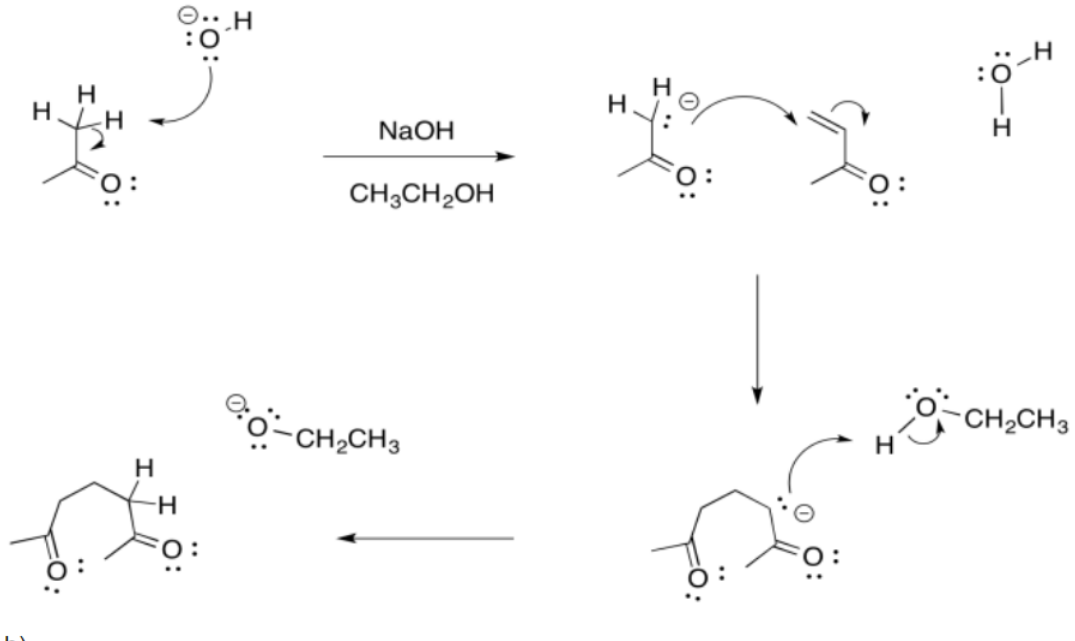
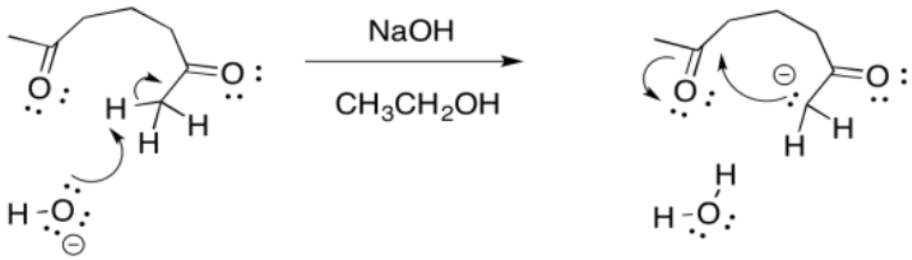


Figure 3.20.49:

a)



b)



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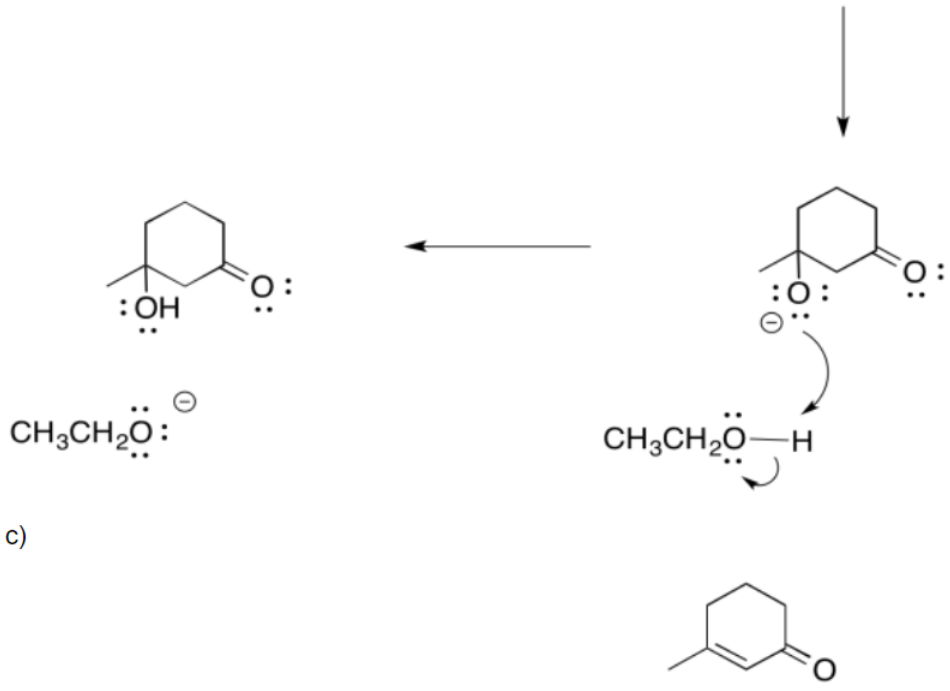


c)

Figure 3.20.51:

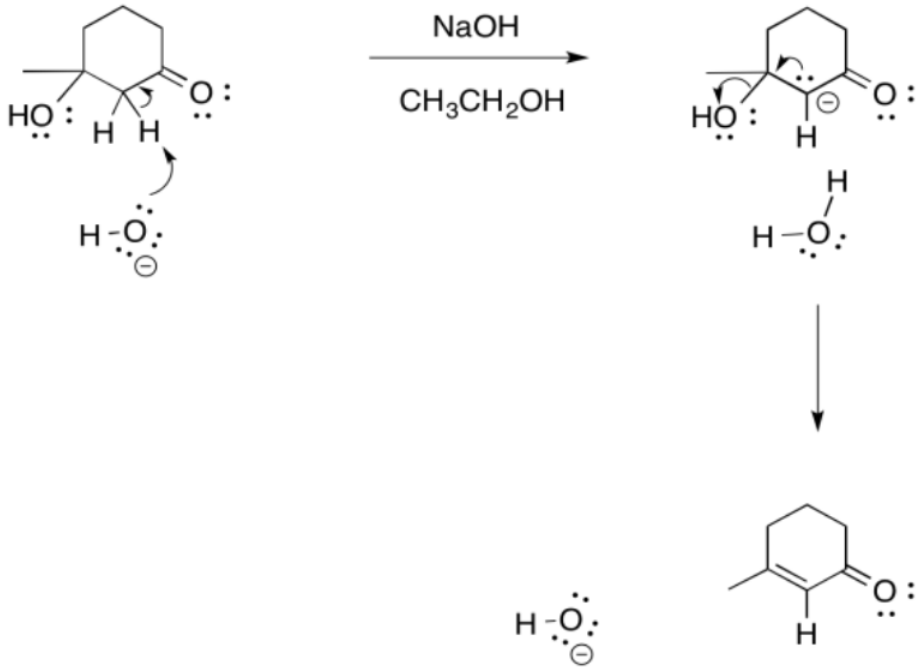
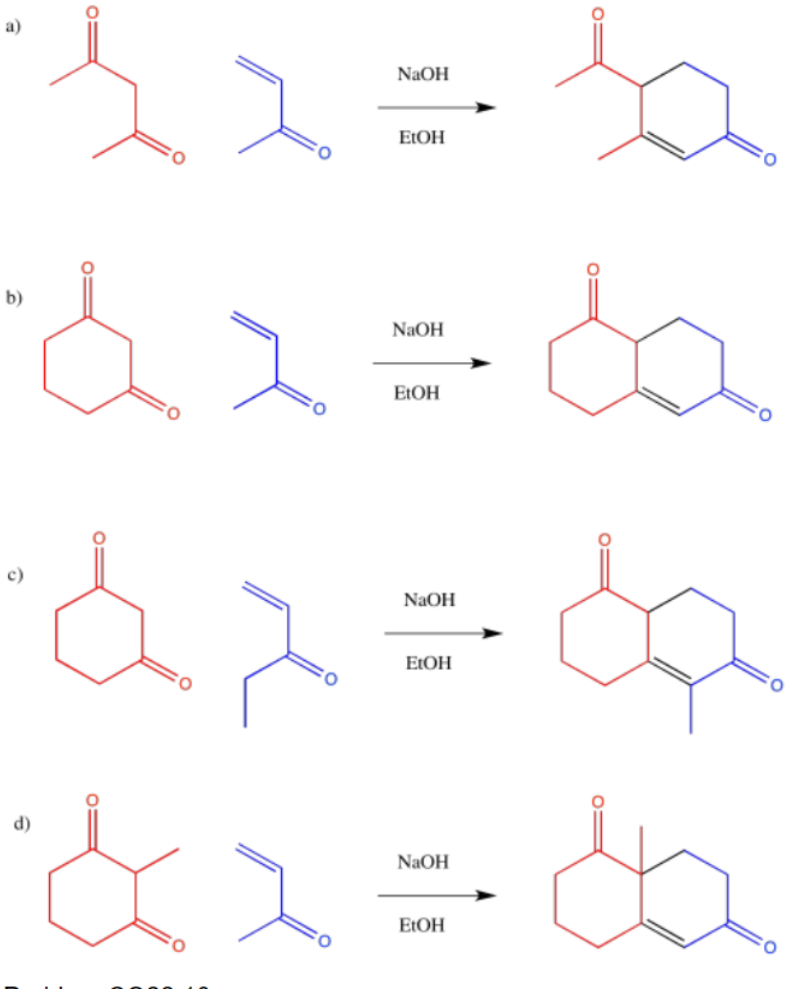


Figure 3.20.52:



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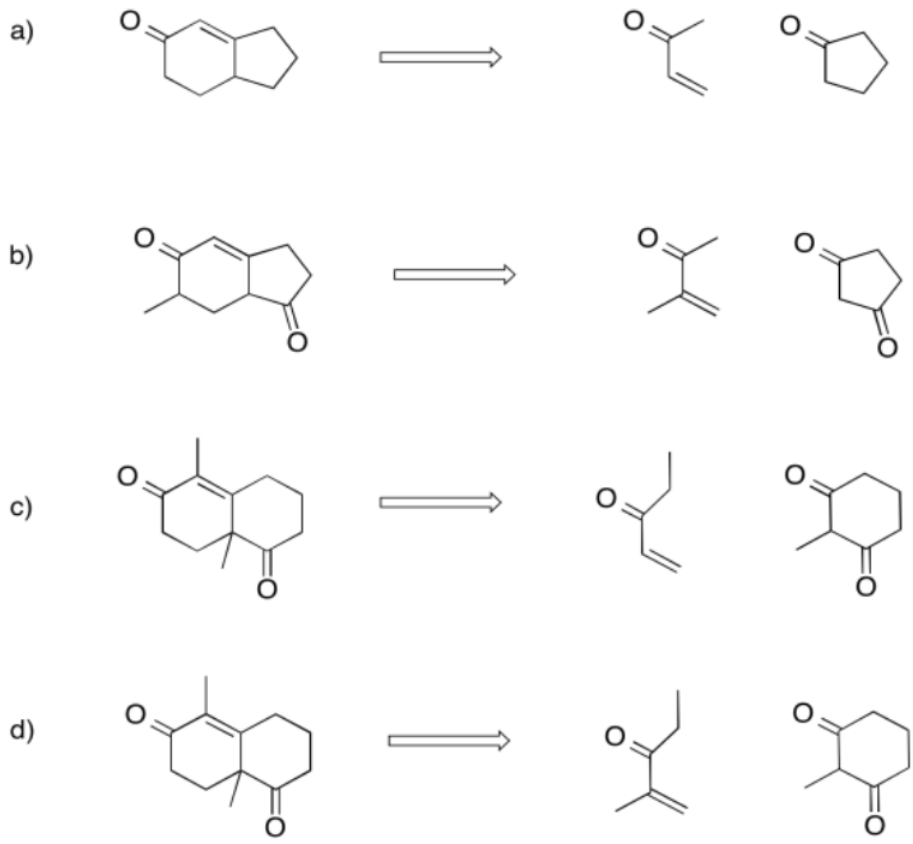


Figure 3.20.54:

Figure 3.20.55:

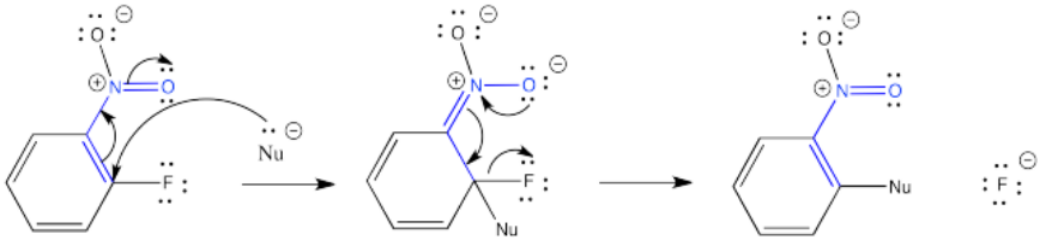
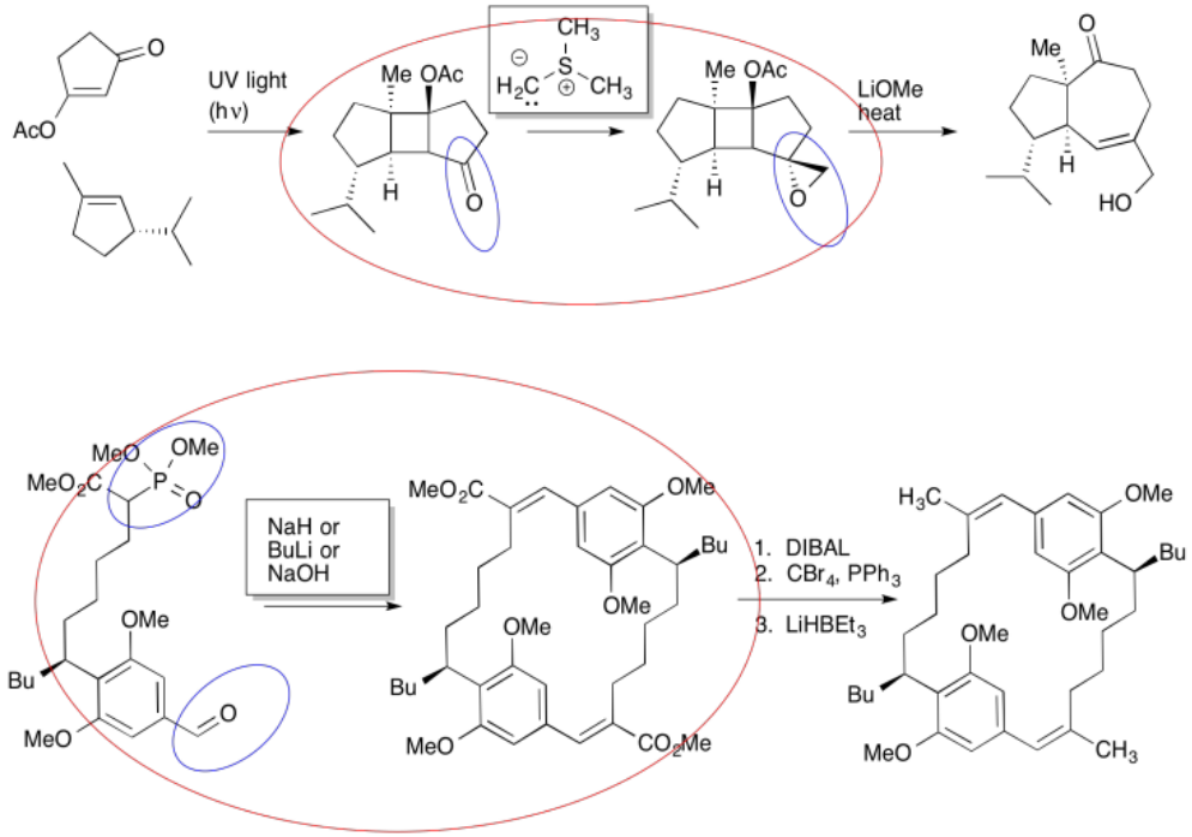


Figure 3.20.56:



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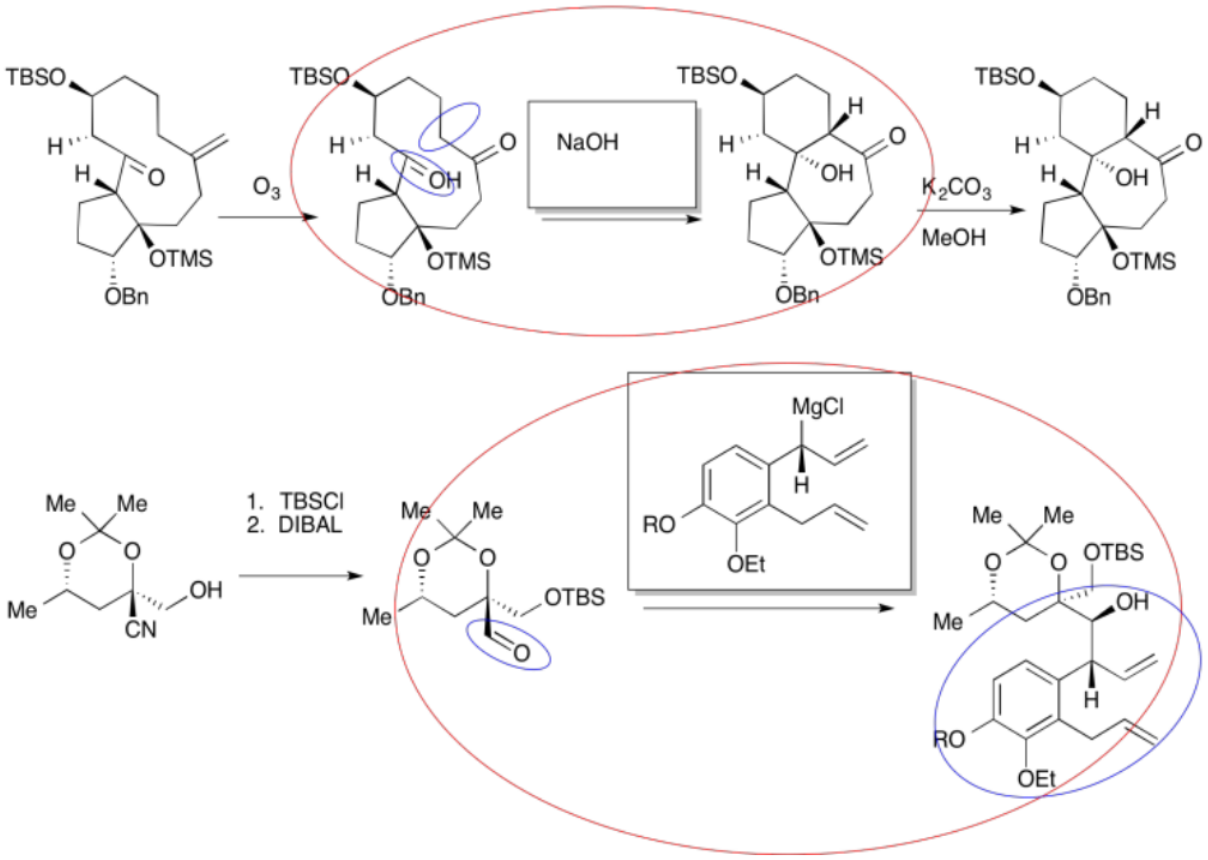
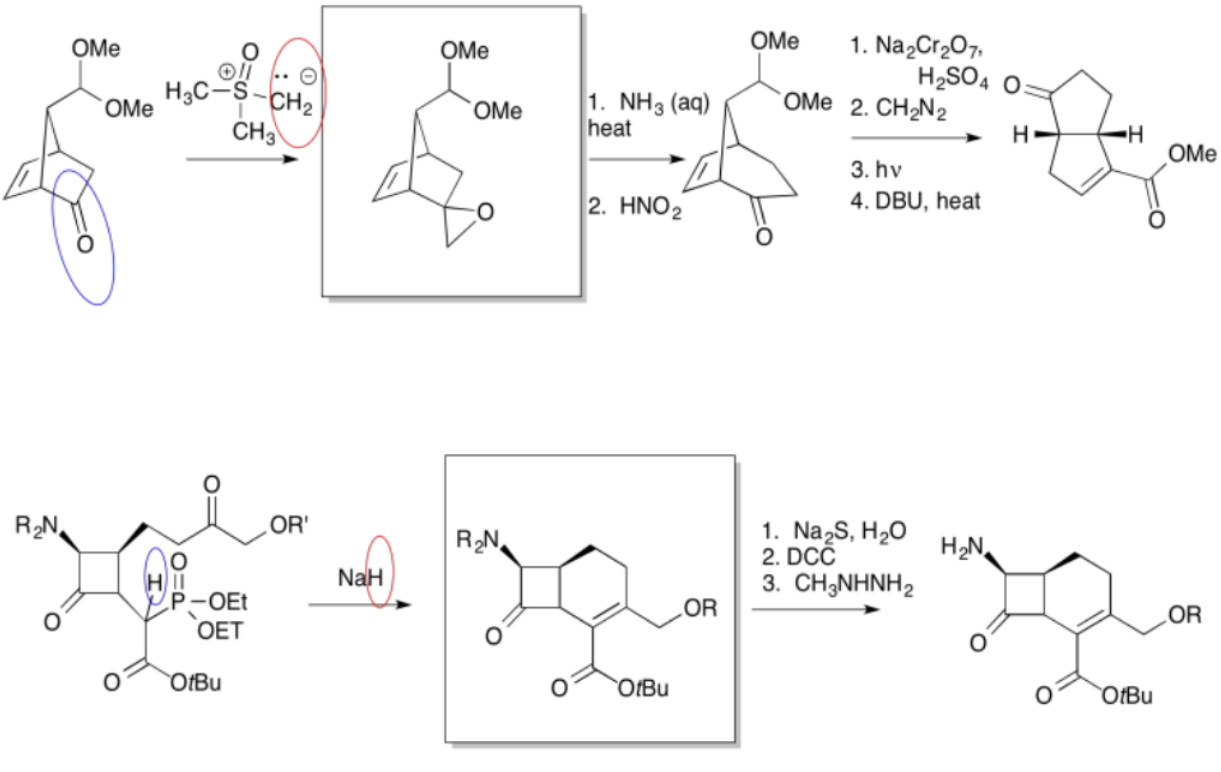


Figure 3.20.58:



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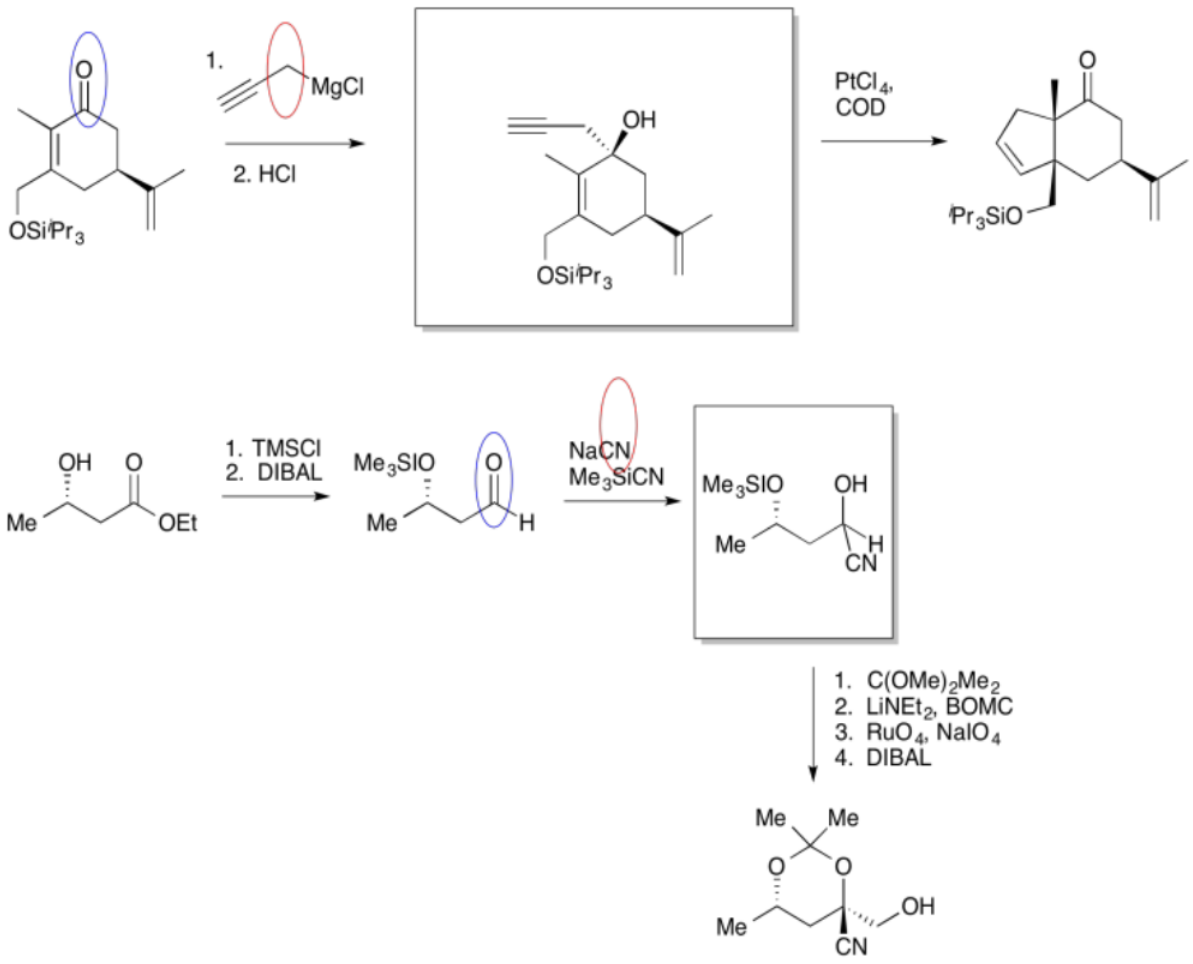

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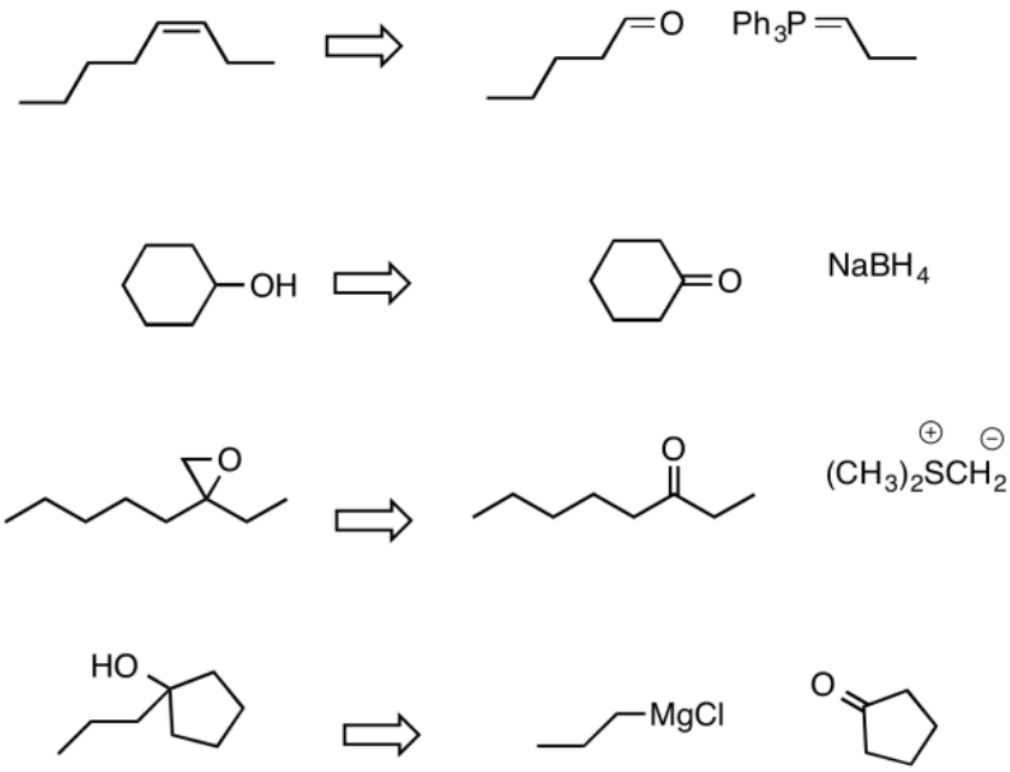

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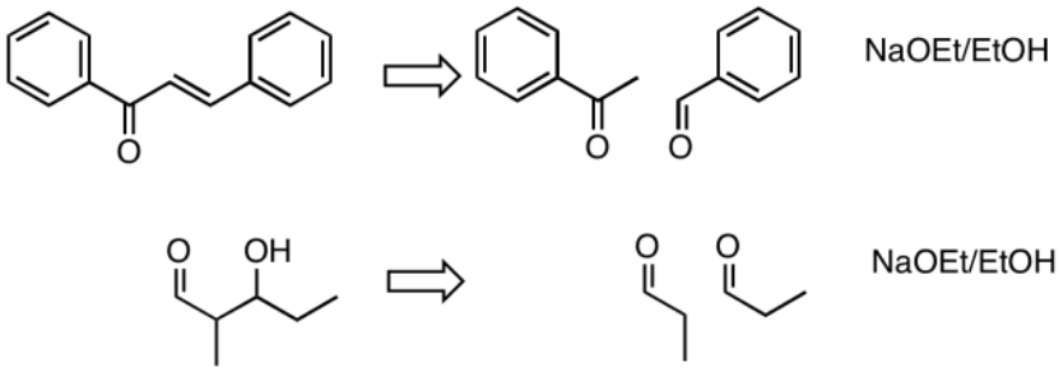

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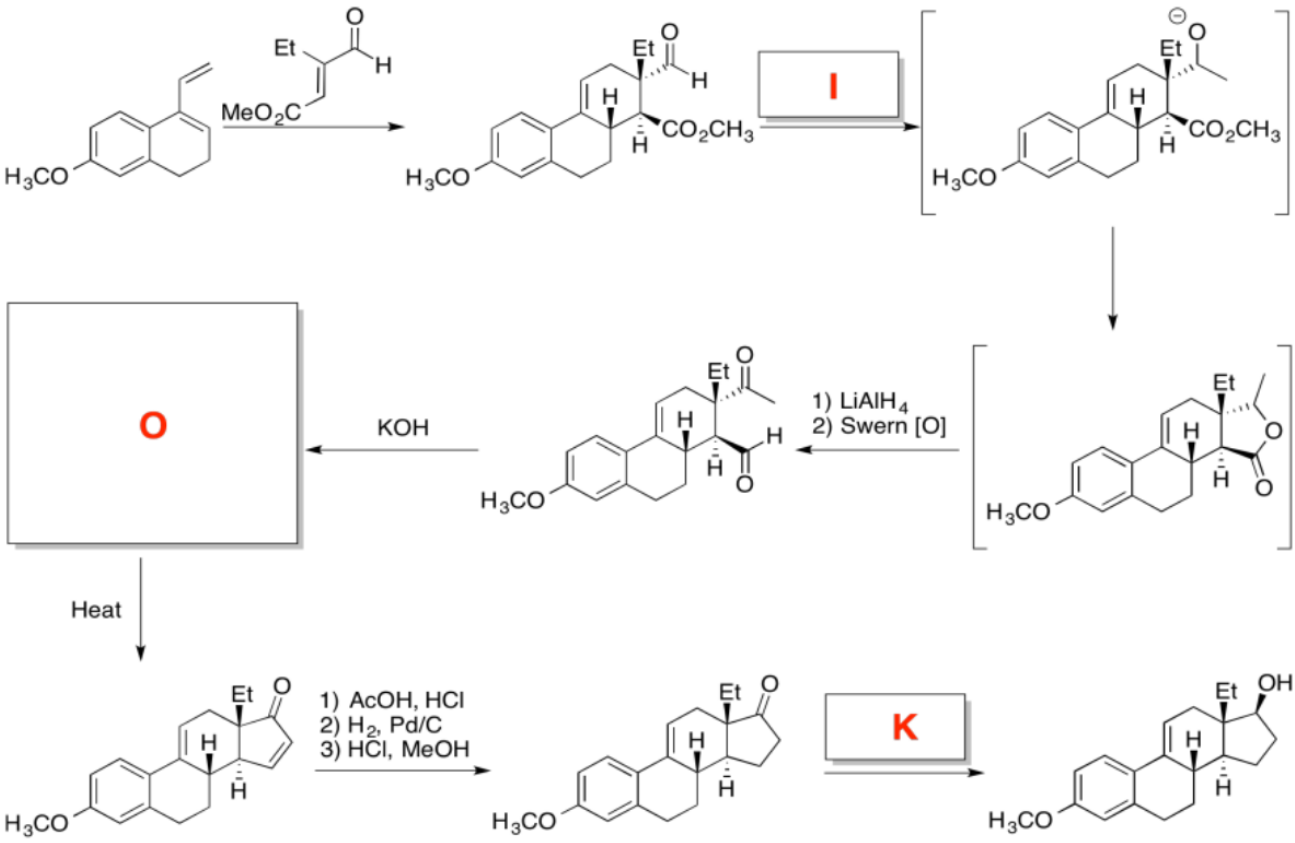

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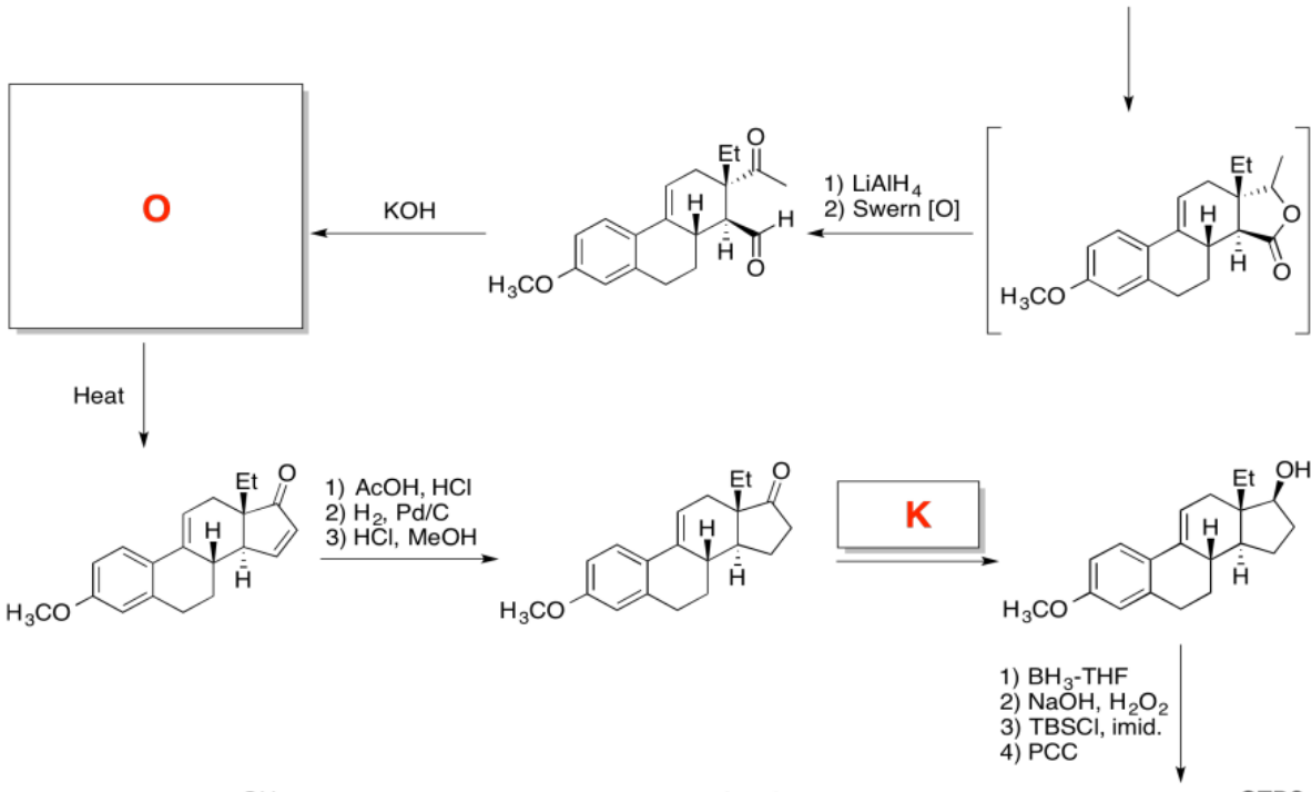


Figure 3.20.64:

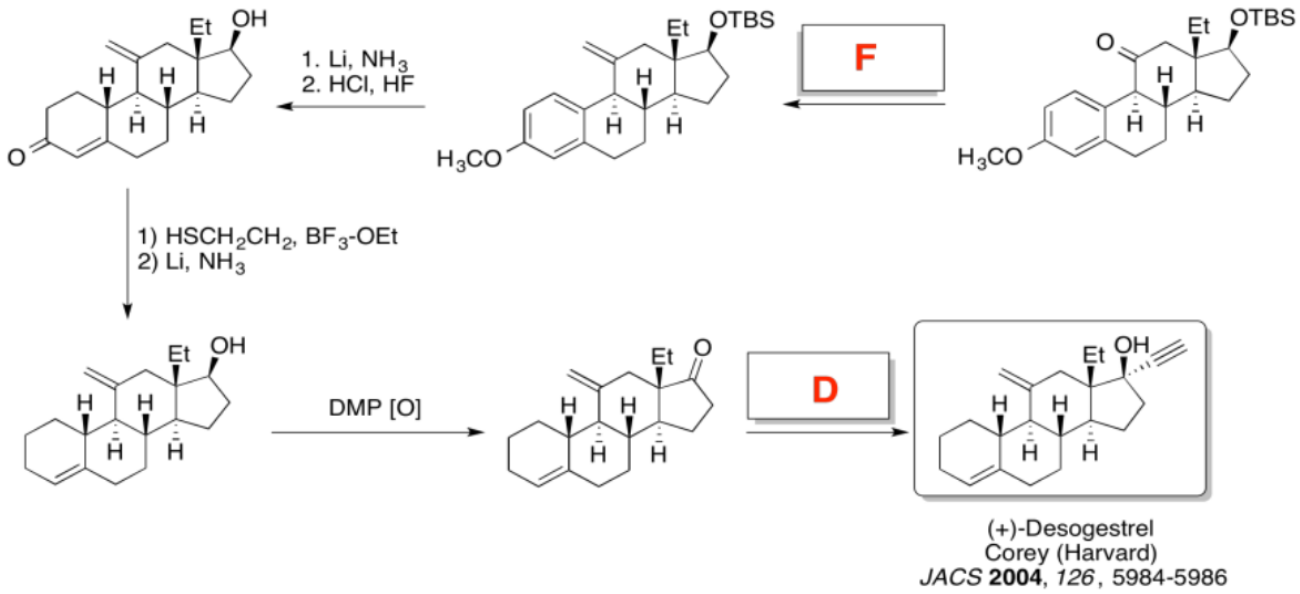


Figure 3.20.65:

Synthesis of tulearin A, Janine Cossy, ESPCI ParisTech, 2009
Isolated from a Madagascar marine sponge; potent activity against leukemia cell lines.

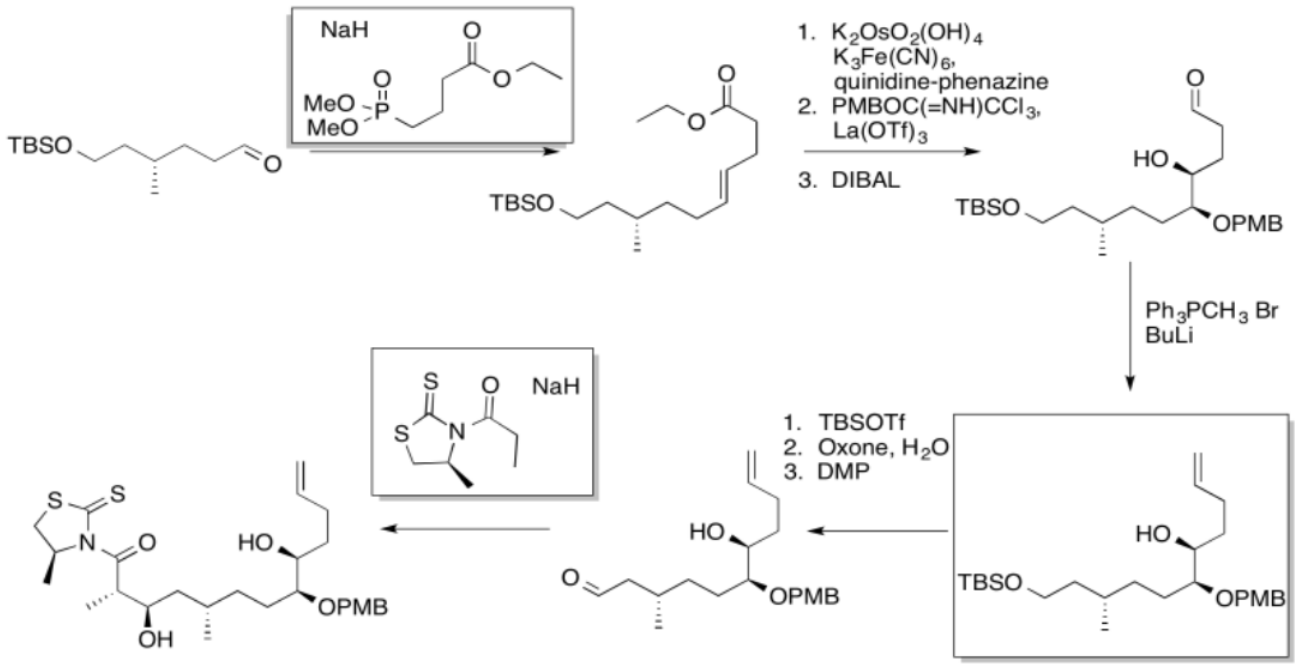


Figure 3.20.66:

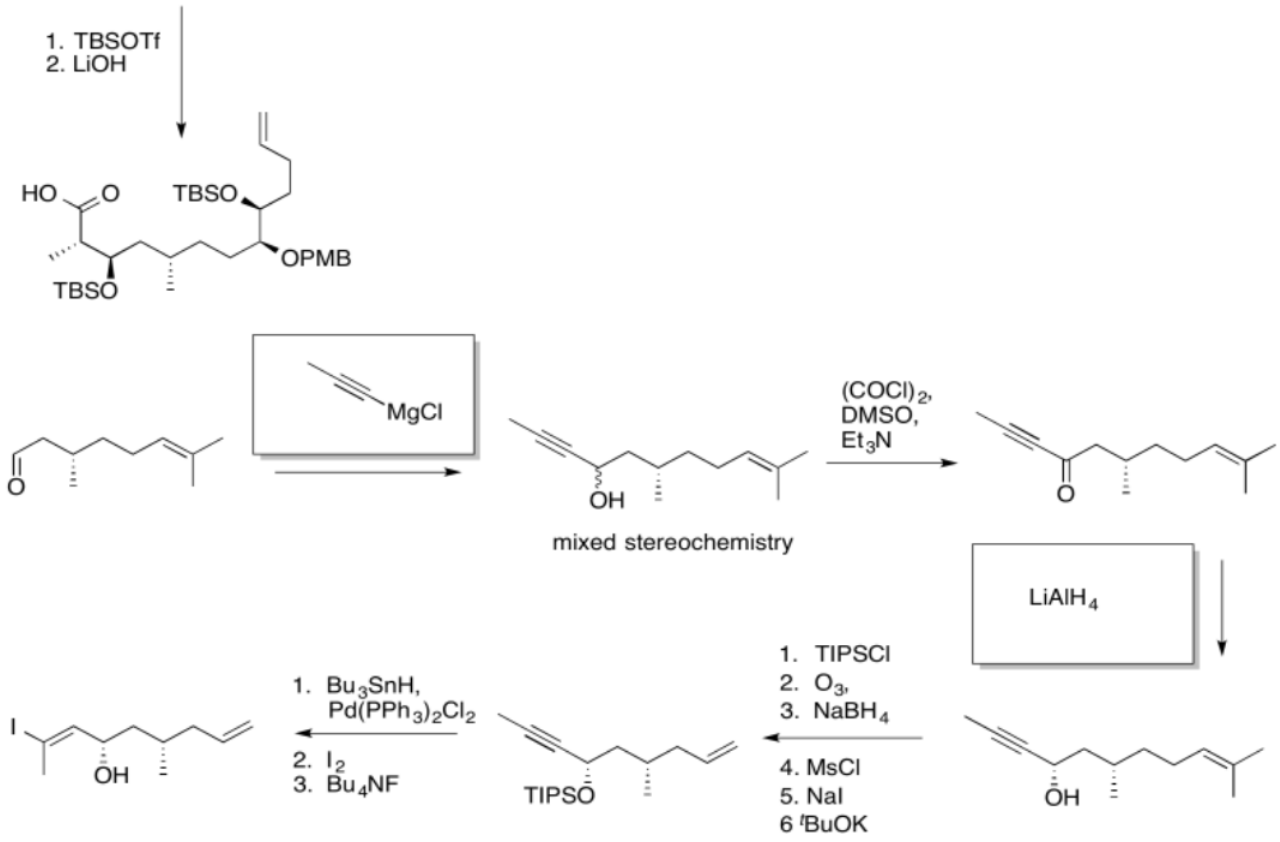


Figure 3.20.67:

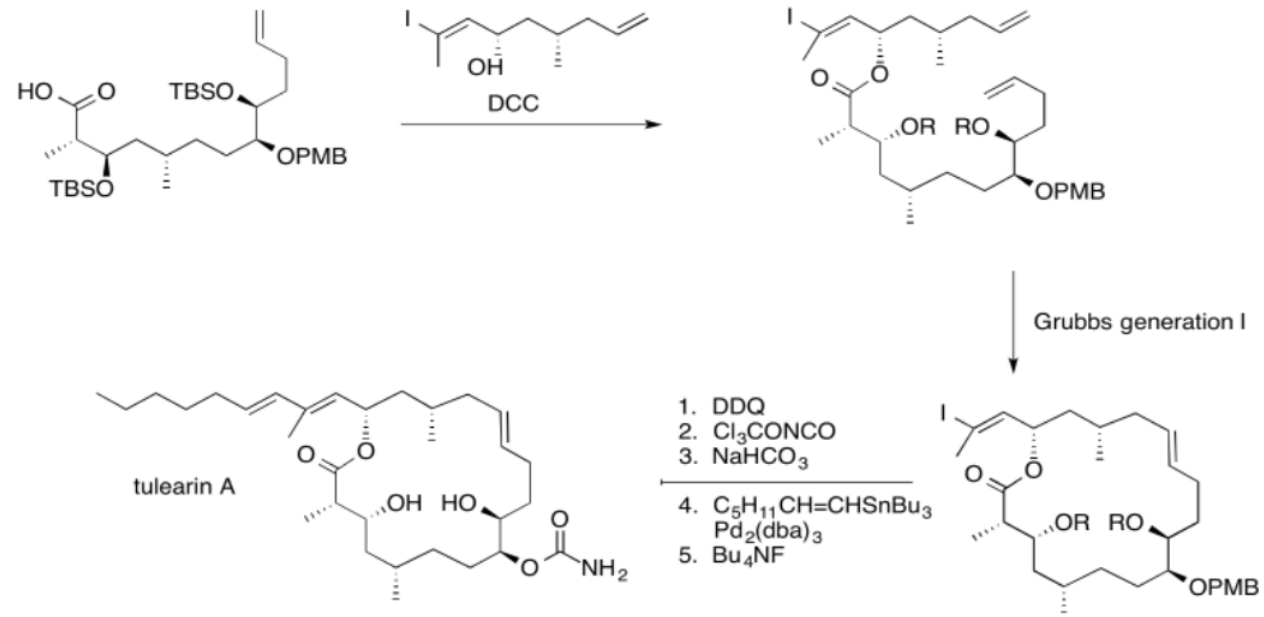


Figure 3.20.68:

Partial Synthesis of Brevenal, Crimmins, UNC Chapel Hill, 2010.
Isolated from marine dinoflagellates off Florida coast. Competitively displaces red tide neurotoxin, dihydrobrevetoxin-B, from voltage-sensitive sodium channels.

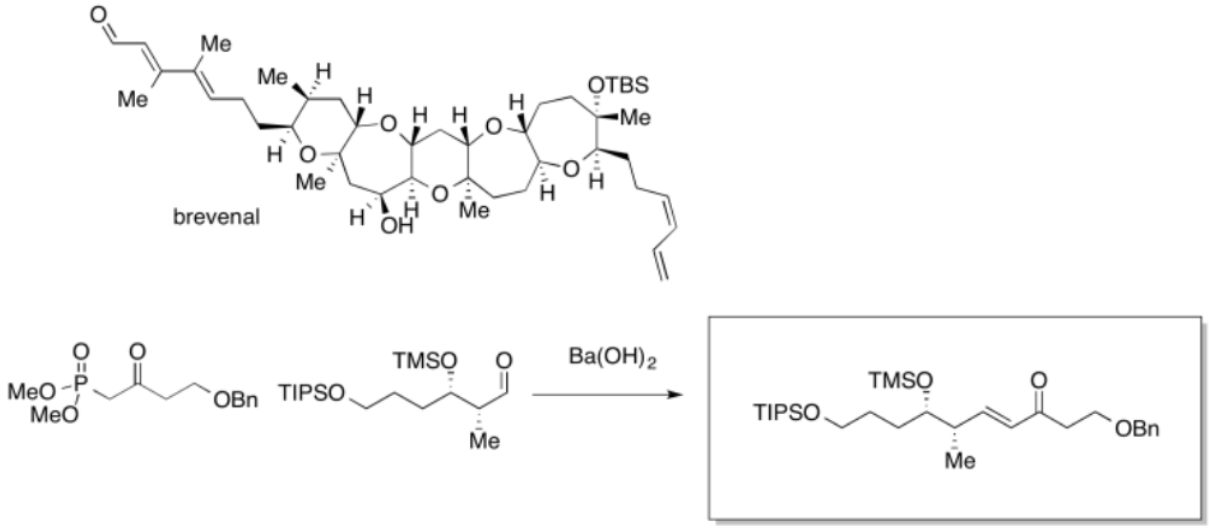


Figure 3.20.69:

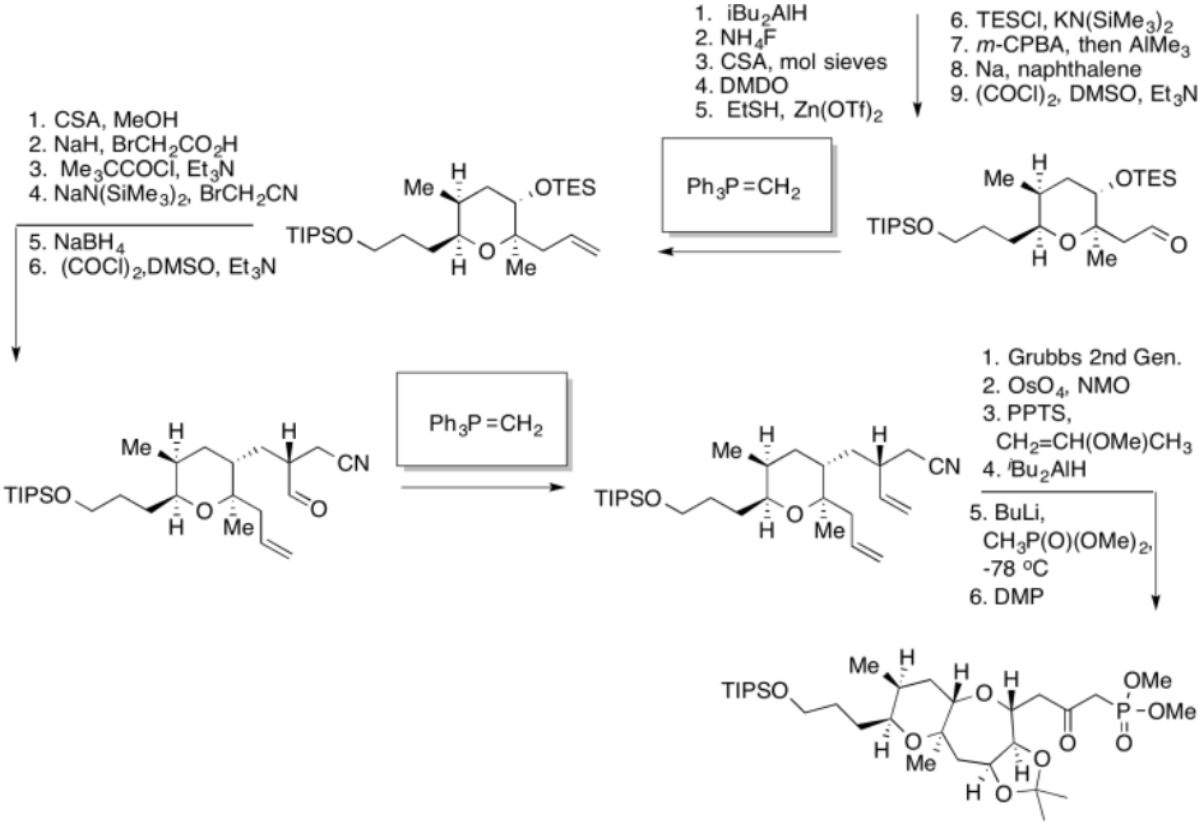


Figure 3.20.70:

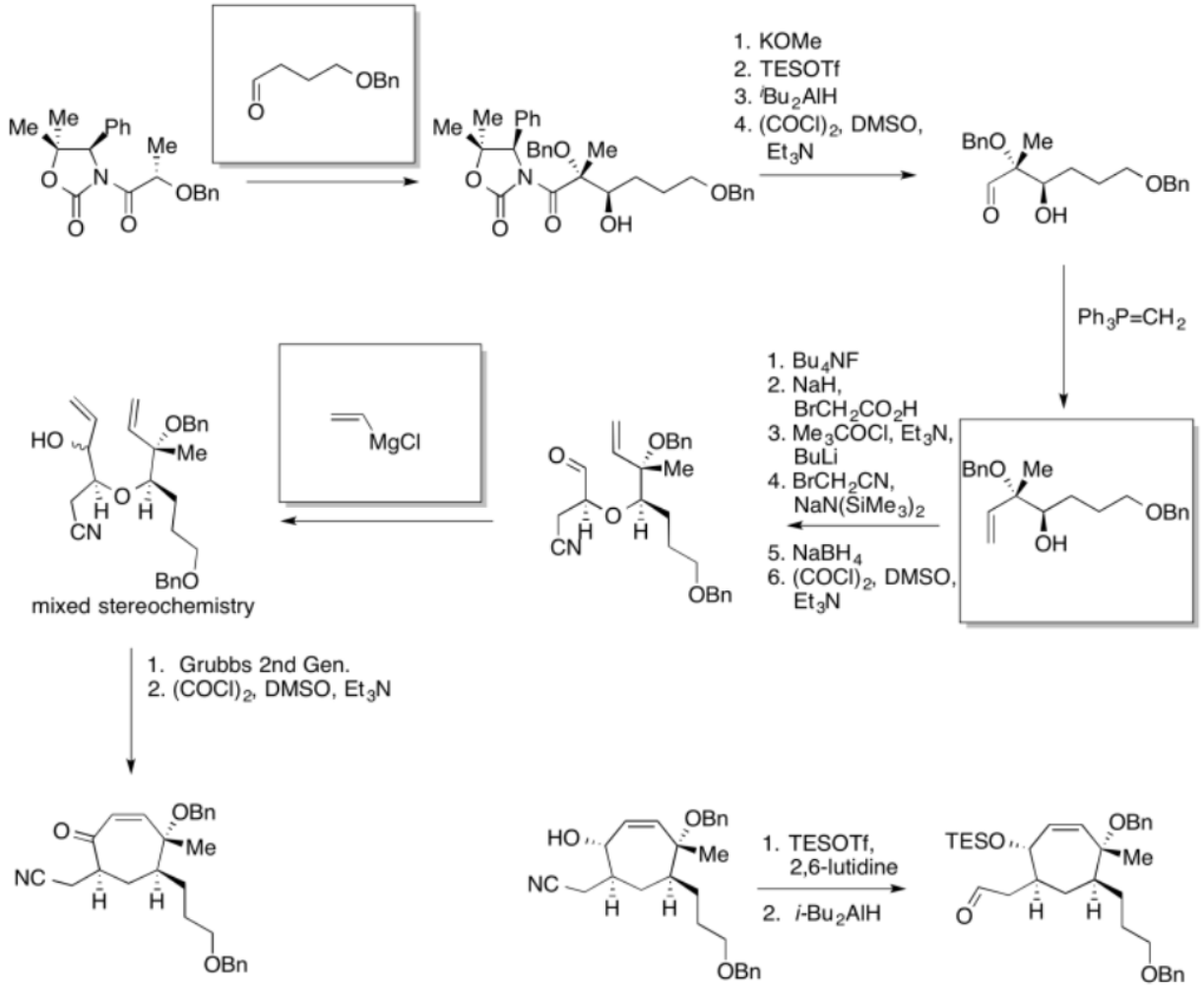


Figure 3.20.71:

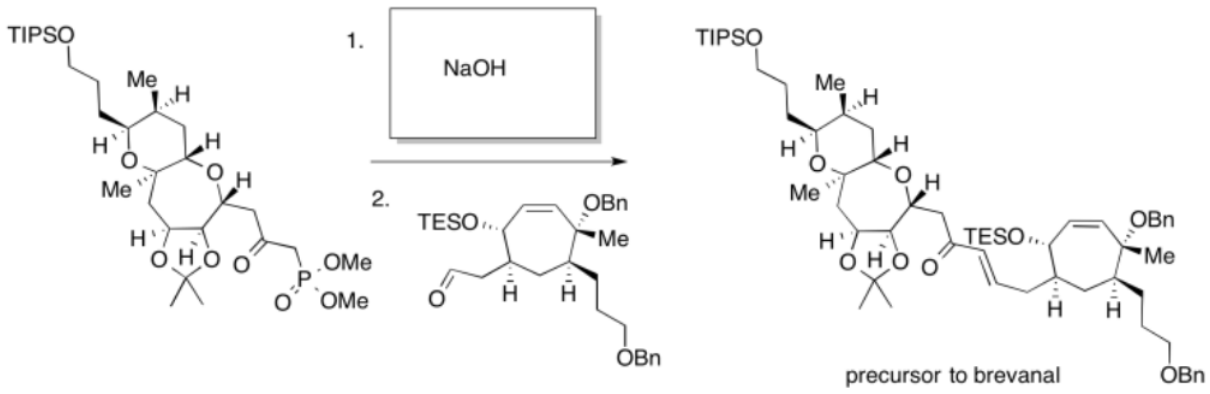


Figure 3.20.72:

Synthesize the following stating from acetone.

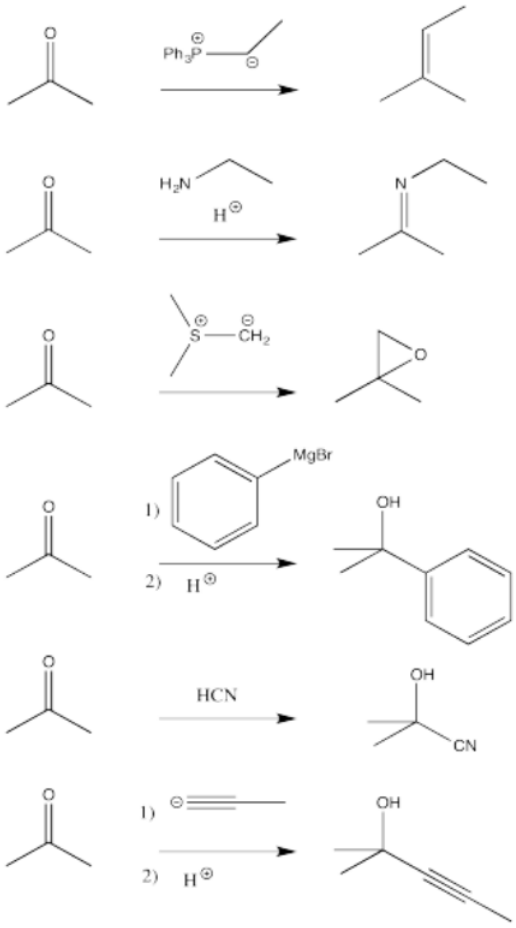


Figure 3.20.73:

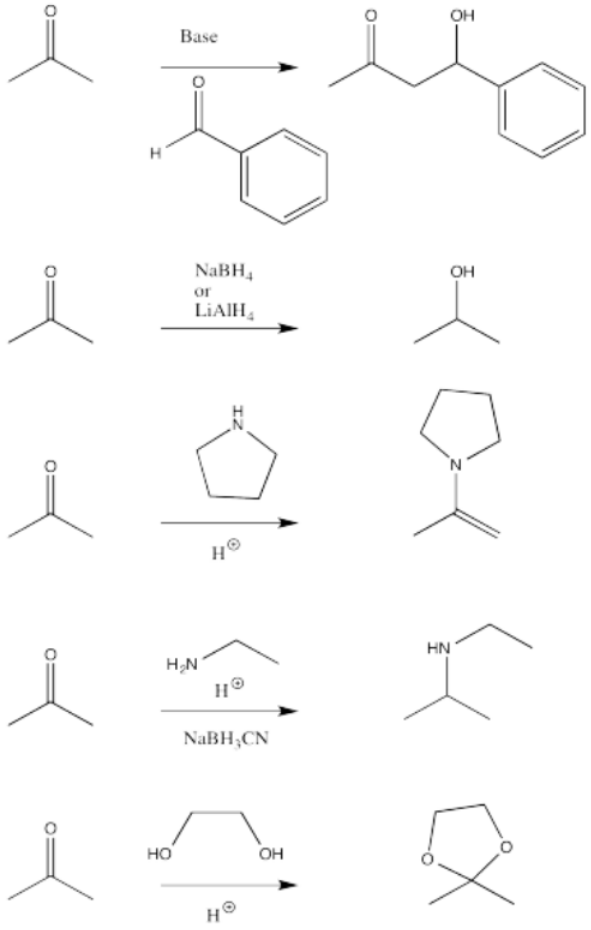


Figure 3.20.74:

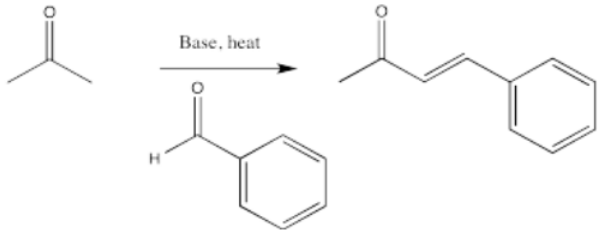


Figure 3.20.75:

Researchers are investigating cyclohexenone derivatives as potential inhibitors for esterases. Below is a scheme for the synthesis of several of these derivatives. Fill in the boxes with the appropriate intermediates or reagents.

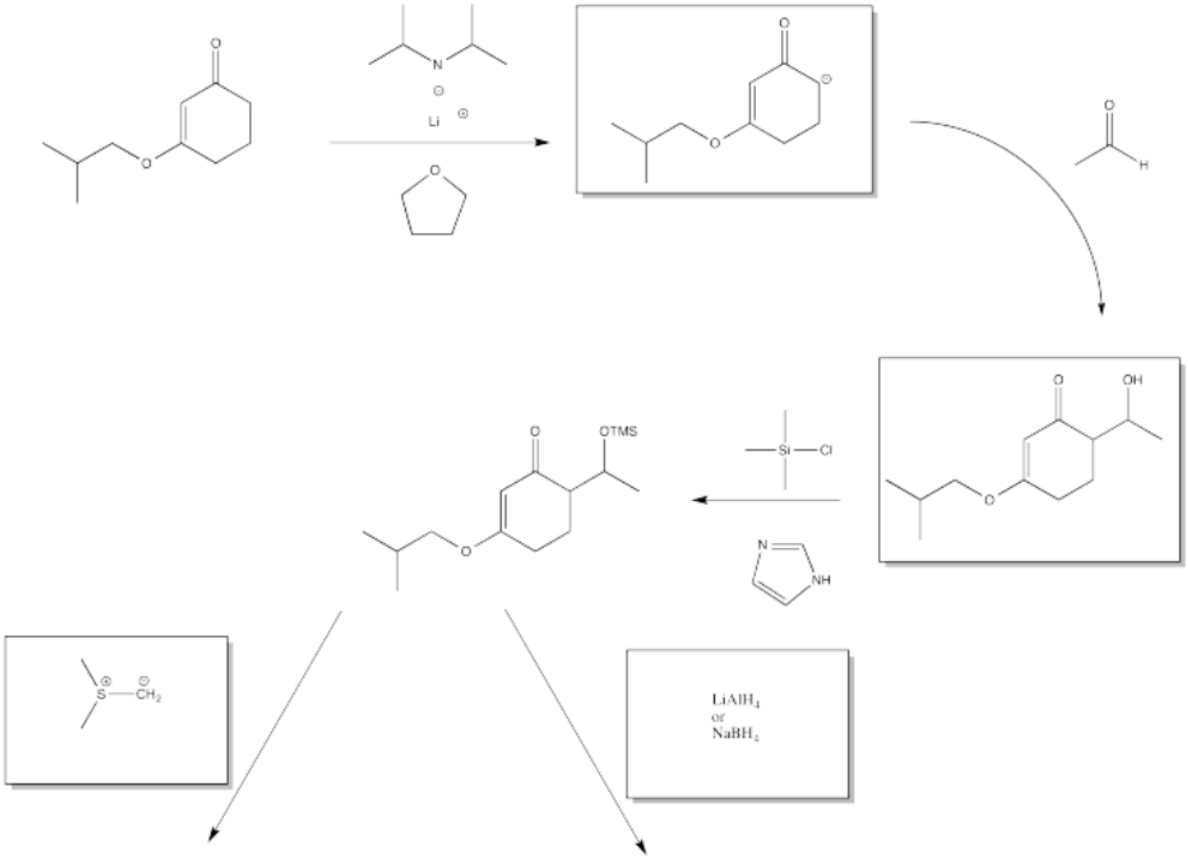
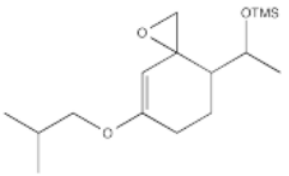
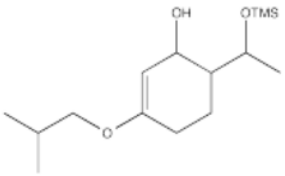


Figure 3.20.76:





Below is another derivative that they made. Provide a mechanism (make sure to draw arrows) for the following reaction:

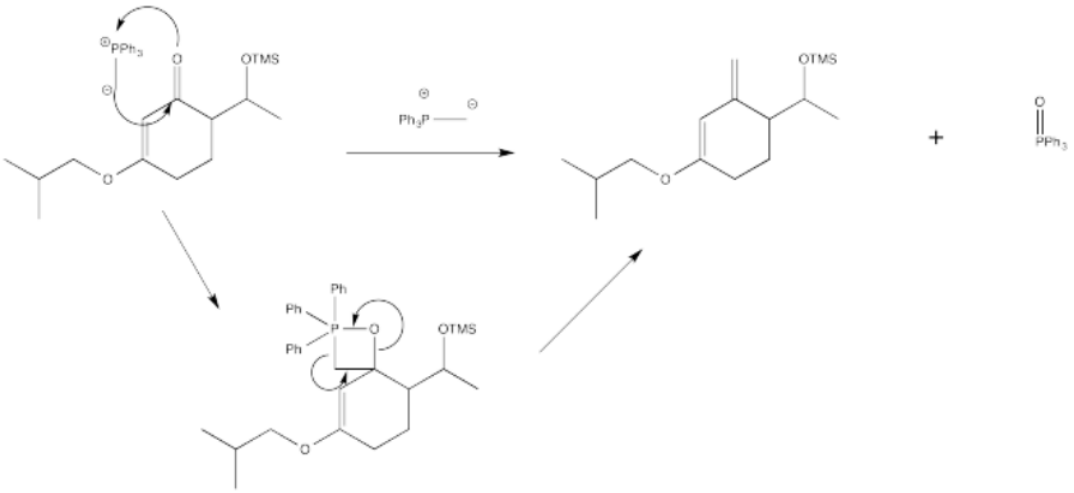


Figure 3.20.77:

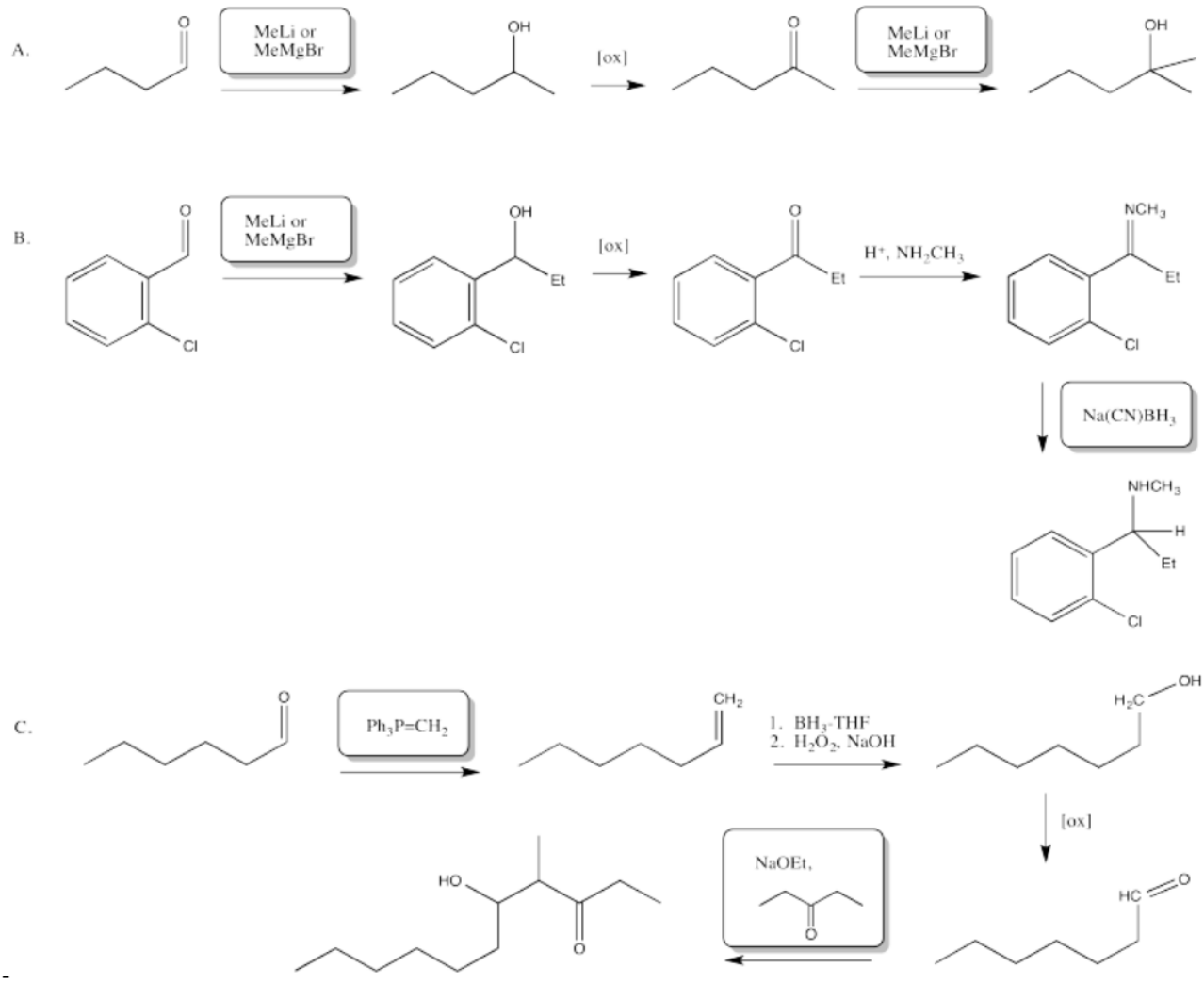


Figure 3.20.78:

Weber, Dehn, Schlager, Dieter, and Kirschning, *Org. Lett.*, **2014**, 16(2), 568-571.

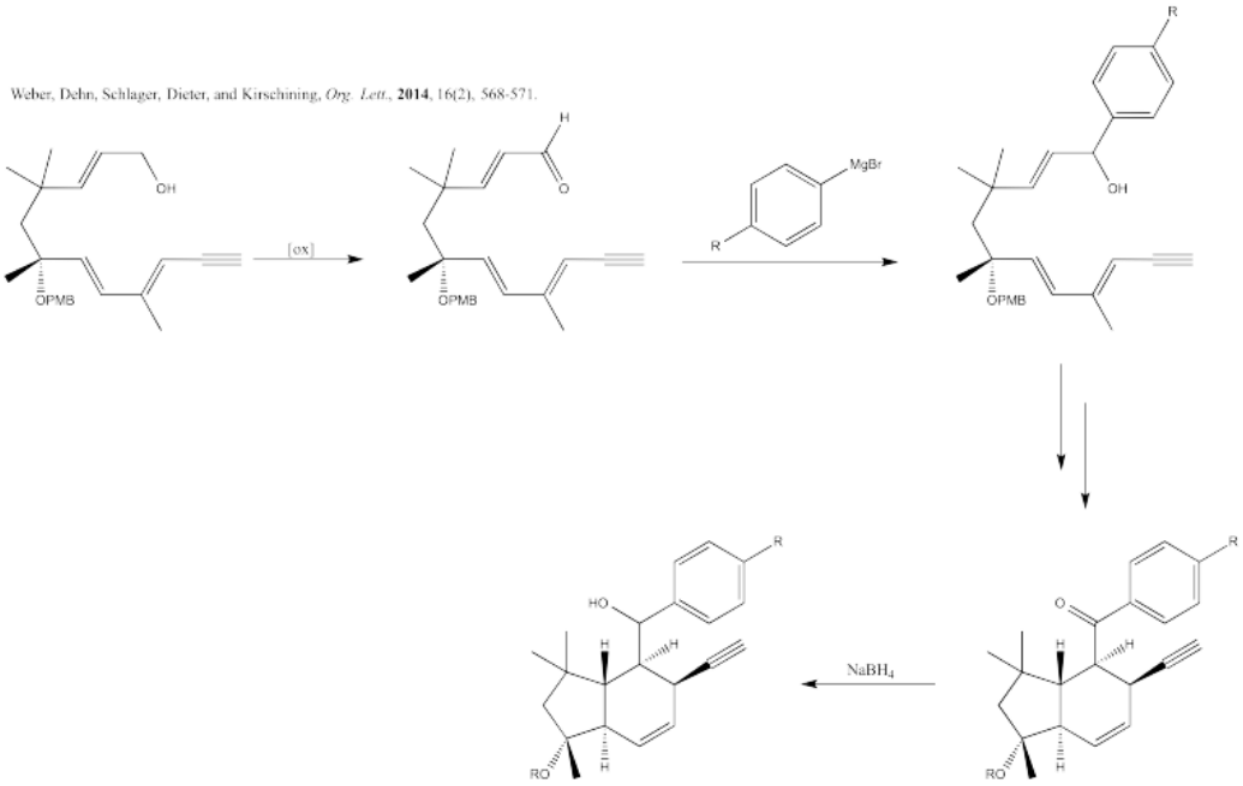


Figure 3.20.79:

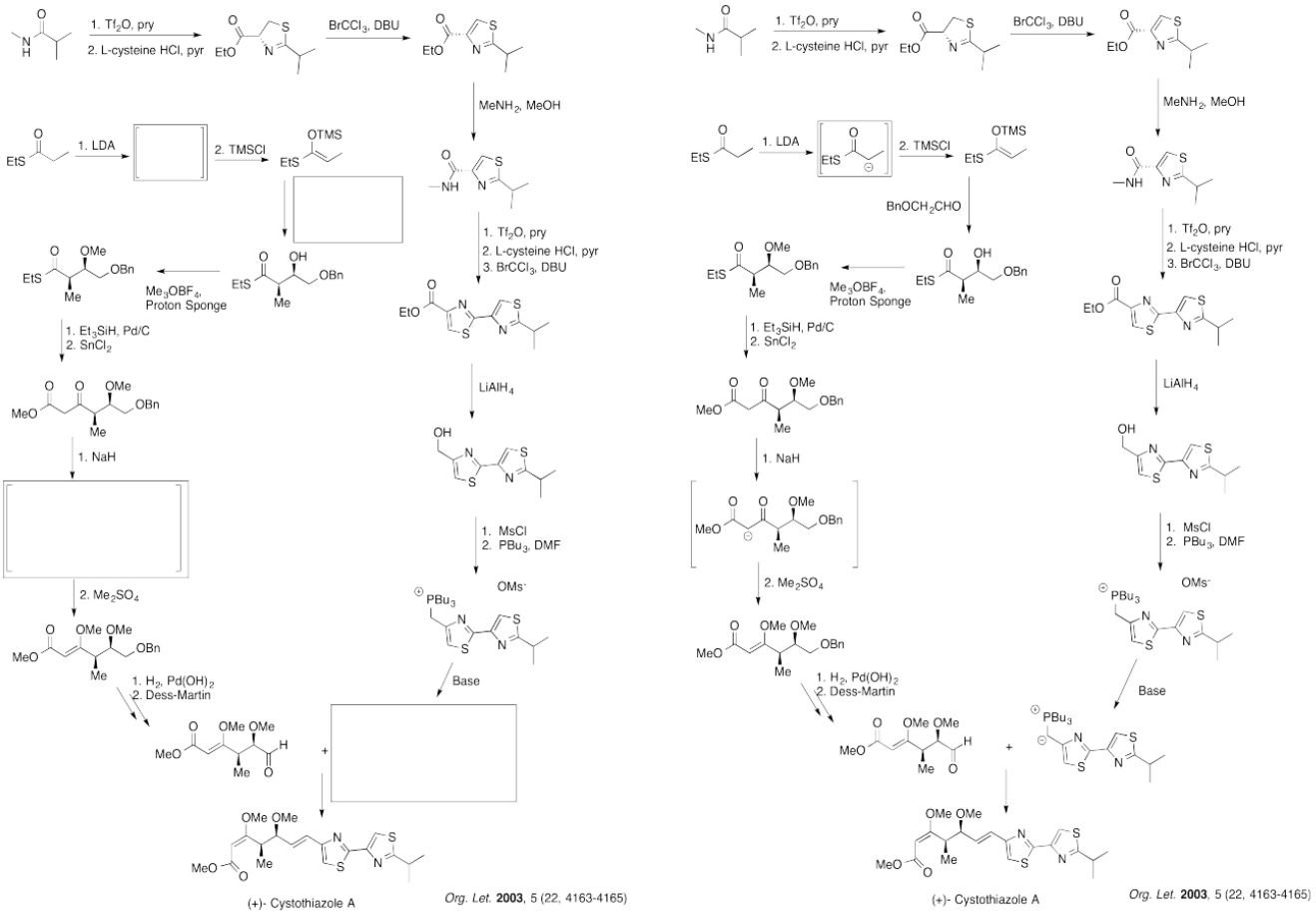
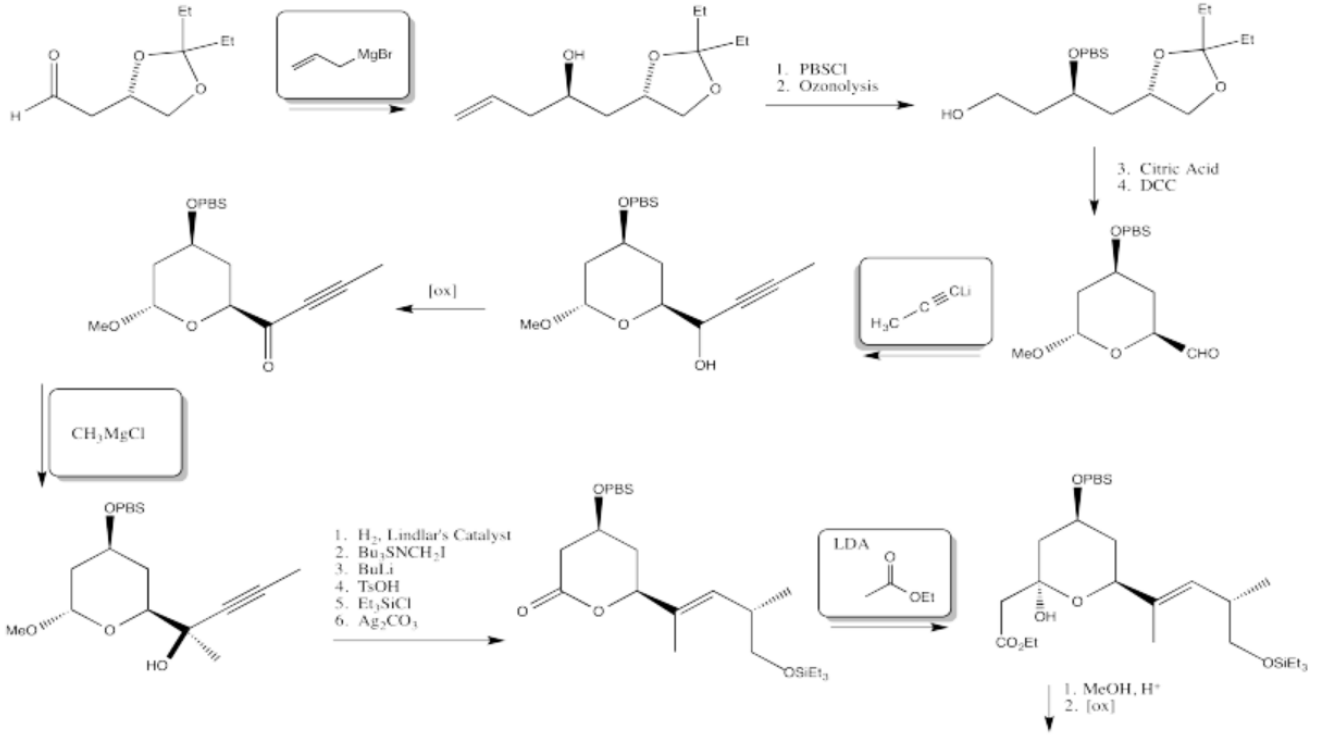


Figure 3.20.80:

20,21 didehydroacutiphycin

Smith, Chen, Nelsom, Reichert, Salvatore, *J. Am. Chem. Soc.* **1997**, *119*, 10935.



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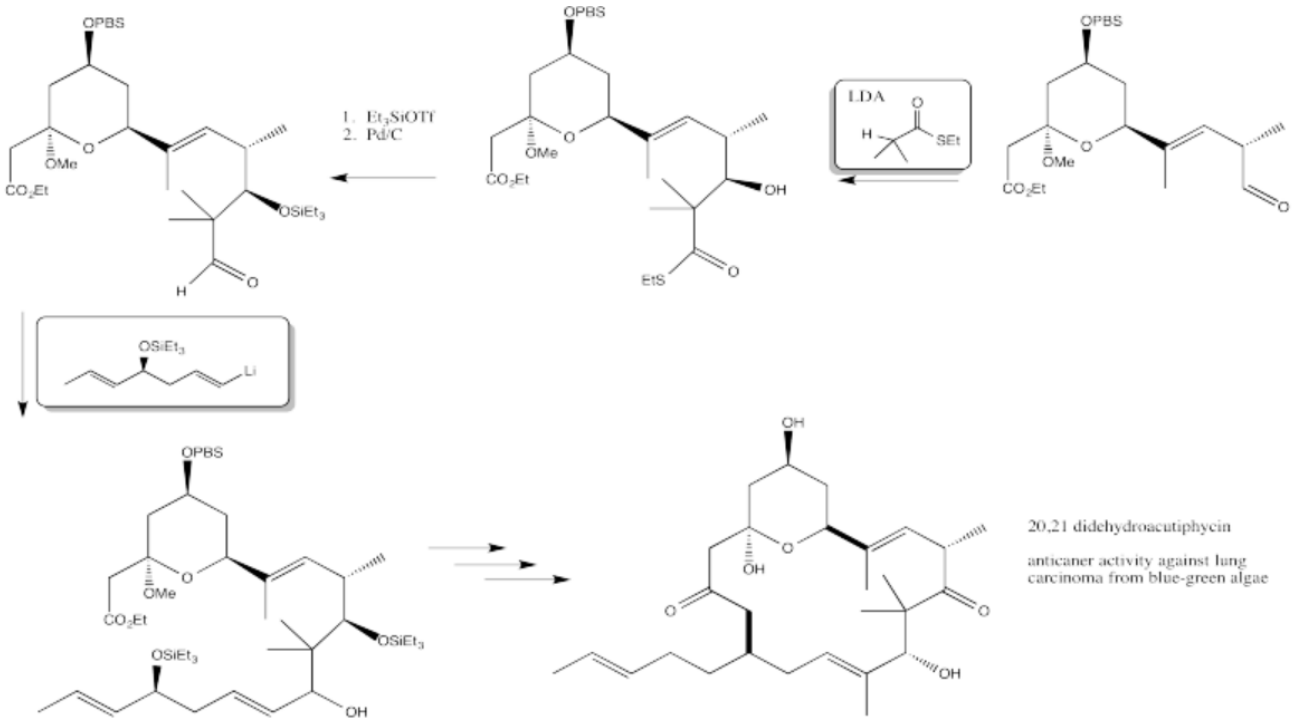


Figure 3.20.82:

Bourbonene

White and Gupta, *J. Am. Chem. Soc.* **1966**, *88*, 5364-5365.

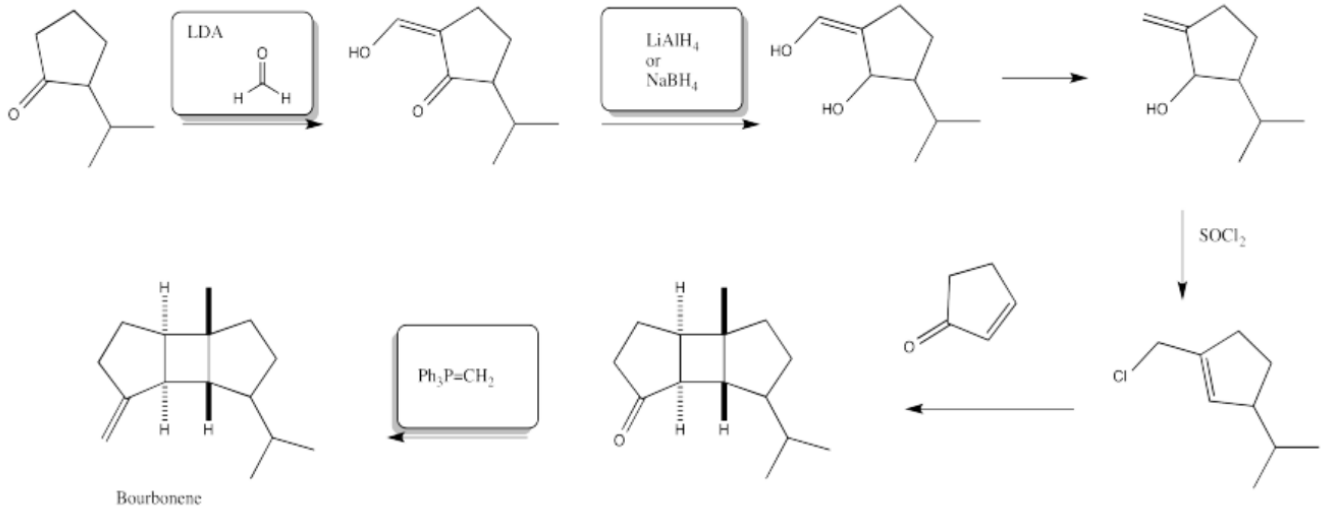
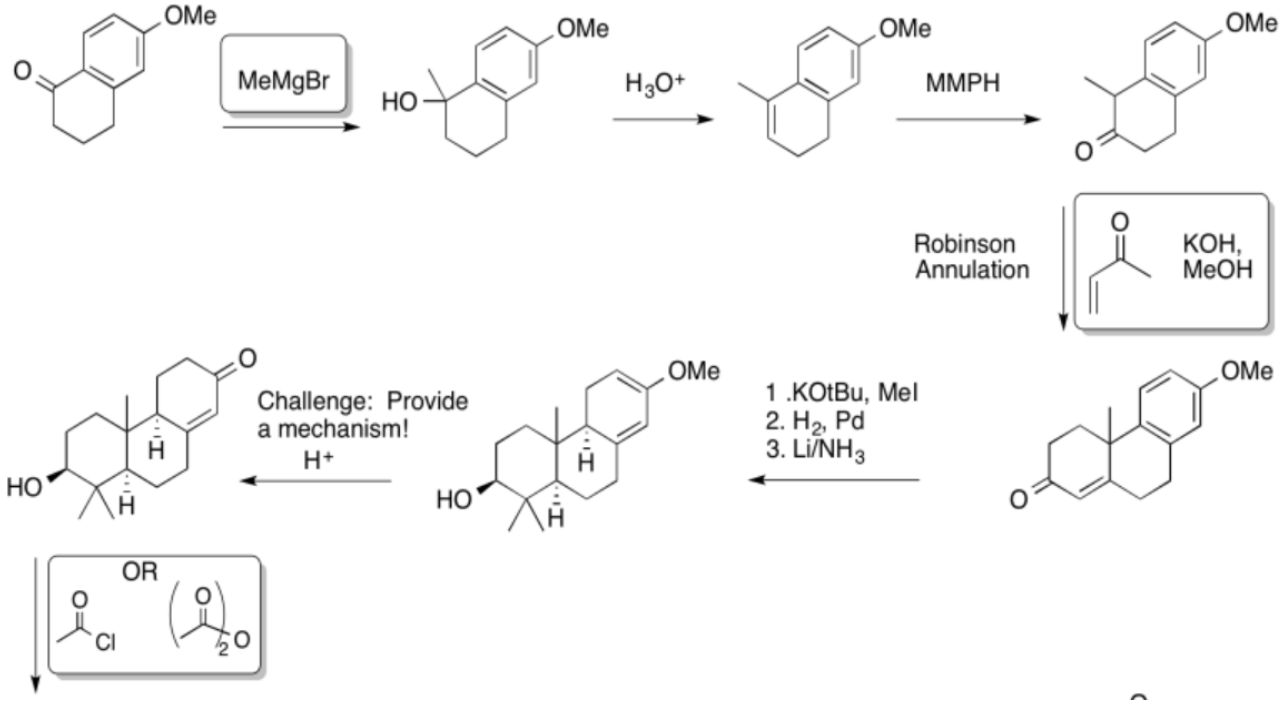


Figure 3.20.83:

Problem CO26.8.

Onocerin

Stork, et. al., *J. Am. Chem. Soc.*, **1963**, *85*, 3419-3425.



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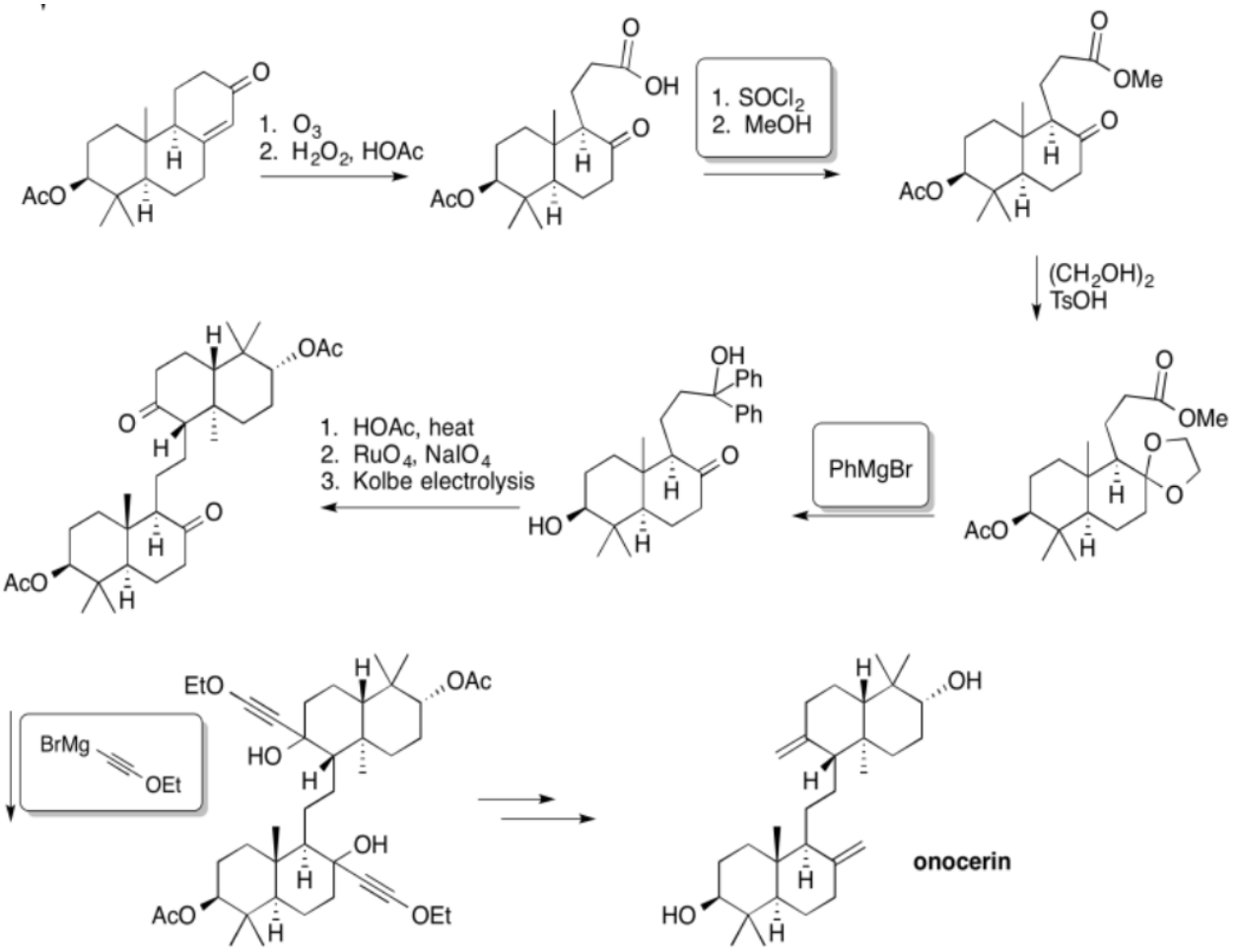


Figure 3.20.85:

Taber and Saleh, *J. Am. Chem. Soc.*, **1980**, *102*, 5085-5088.

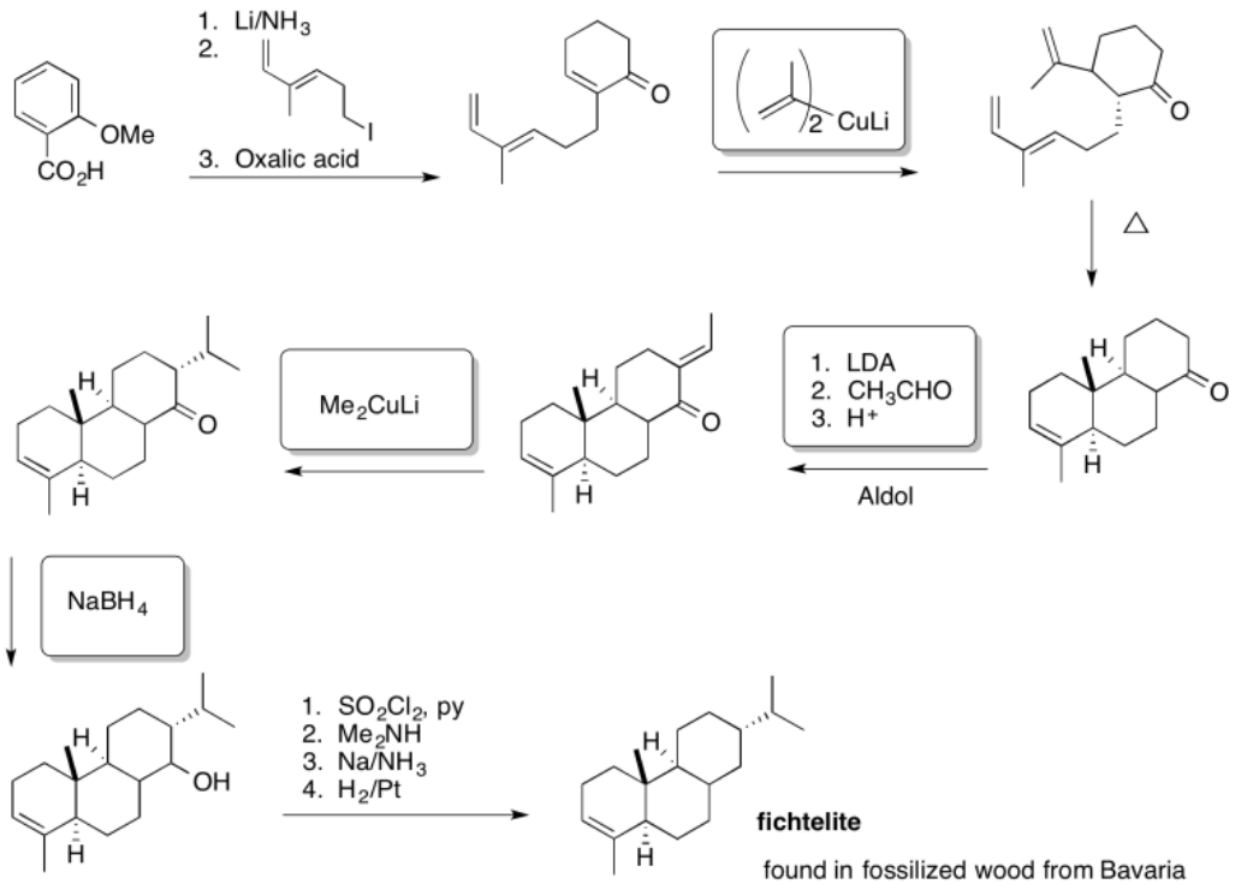


Figure 3.20.86:

3.21: Carbonyls are Electrophiles

The carbonyl bond is very polar. There is a partial positive charge on the carbon and a partial negative charge on the oxygen, because oxygen is more electronegative than carbon. This charge separation is intensified because of the double bond between the carbon and oxygen. Rather than just pulling one pair of bonding electrons towards itself, the oxygen pulls two pairs of electrons towards itself.

- The C=O bond is very polar.
- The carbonyl carbon is very positive.

Sometimes, a resonance structure is drawn to emphasize the charge separation in the carbonyl. The structure has only one bond between the carbon and oxygen. In this structure, oxygen has an octet but carbon does not. This is not really a good Lewis structure, because the other resonance structure satisfies octets on all the atoms. However, this Lewis structure emphasizes the polarity of the bond and is sometimes drawn to reinforce that idea.

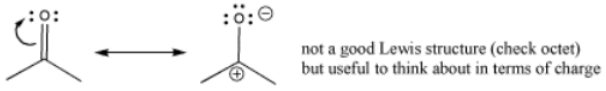


Figure 3.21.1: Thinking about charge distribution in a carbonyl group

Because of the positive charge on the carbonyl carbon, the most important theme in carbonyl chemistry is reaction of the carbonyl as a Lewis acid. Reactions of carbonyls almost always involve addition of an electron donor to the carbonyl carbon.

- Electrophile is another term for Lewis acid.
- Lewis acids attract electrons.
- Lewis acids have a positive charge on an atom, a partial positive charge on an atom, or an atom lacking an octet.
- Carbonyl compounds are good electrophiles.

The electrophilicity of carbonyls is very important in their reactivity. The goal of this chapter is to develop an understanding of how carbonyls react. We will learn about a few key factors that will be used in different combinations under different circumstances. Eventually, you will build an understanding that will allow you to follow both biological reactions and modern synthetic reactions.

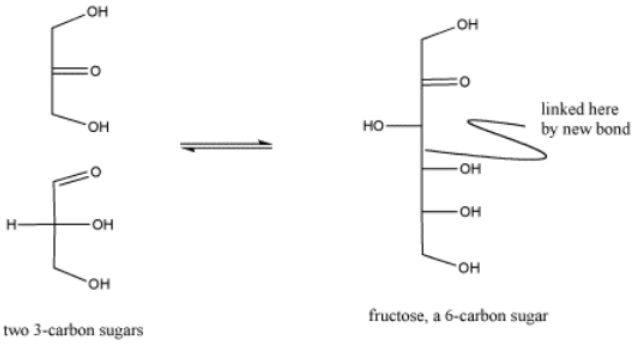


Figure 3.21.2: Reactivity in carbonyl compounds. The carbonyl in the lower sugar on the left has reacted with the neighbouring molecule.

It is important to realize that biological reactions, such as carbohydrate synthesis, are very complex and can involve many, many steps. For example, the carbohydrate synthesis shown above involves additional acid-base steps as well as a reaction of a carbonyl. The additional acid base steps may involve proton donors and acceptors as well as more general Lewis acids.

Exercise 3.21.1

Problem CO2.1.

a) Explain why the carbon in a C=O unit is very electrophilic, but the carbon in a C-O unit is much less so.

b) Propose other carbon-heteroatom bonds that may make the carbon electrophilic (heteroatom means not carbon or hydrogen).

Answer a

The double bond means two pairs of electrons are shared between the carbon and oxygen, instead of just one. As a result, the oxygen is able to pull more electron density away from the carbon. The carbon becomes much more positive in this case than in the case of a double bond.

Not only that, but the second bond between the carbon and the oxygen is a pi bond. Those electrons are farther from the nucleus than a sigma bond, in which the electrons are tightly held between the atoms. That means the pi electrons are more easily drawn toward the oxygen, so the bond becomes even more polarized.

Answer b

A C=N bond would be very similar to a C=O bond, because nitrogen is the third most electronegative element after oxygen and fluorine (ignoring noble gases).

Exercise 3.21.2

Problem CO2.2.

Provide line structures for the following compounds.

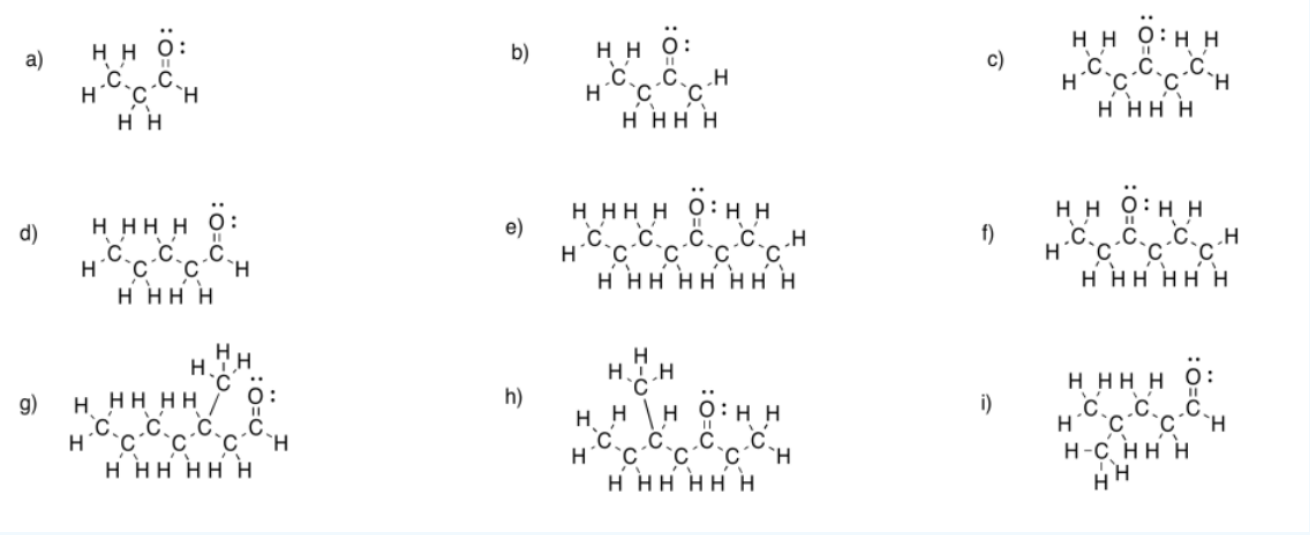
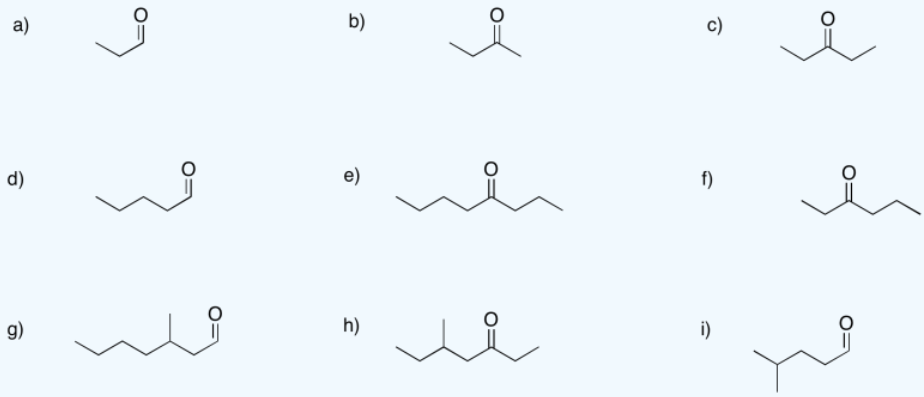


Figure 3.21.3:

Answer



Exercise 3.21.3

Problem CO2.3.

Translate the following condensed formulae into Lewis-Kekule structures (i.e. like Lewis structures, but use lines for bonds). All of the compounds are adehydes or ketones.

a) $CH_3CH_2CH_2CH_2COCH_3$ b) $((CH_3)_2CH_2CH_2COCH_3$ c) $CH_3CH_2CH_2CH(CH_3)COCH_3$

d) $CH_3CH_2CH_2COCH_2CH_3$ e) $CH_3CH_2CH_2COCH_2CH_2CH_3$ f) $CH_3CH_2CC(CH_3)COCH_2CH_3$

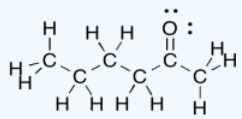
g) $CH_3CH_2CH_2CH_2CHO$ h) $((CH_3)_2CH_2CHO$ i) $CH_3CH_2CH(CH_3)CHO$

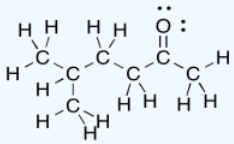
j) $CH_3CH_2CH_2CH(CH_2CH_3)CHO$ k) $((CH_3)_3CH_2CH_2CHO$ l) $CH_3CH_2CH(CH_3)CH(CH_3)CHO$

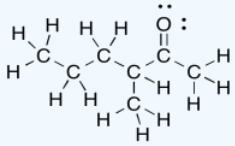
m) $CH_3CH_2OCH_2CH_2CHO$ n) $CH_3CHClCH_2COCH_3$ o) $CH_3CH_2CH(NH_2)COCH_2CH_3$

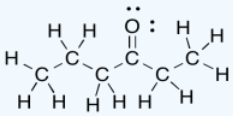
p) $CH_3CHCHCH_2COCH_3$ q) $CH_3CH_2CCCH_2COCH_3$ r) C_6H_5CHO

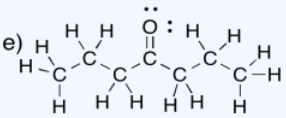
Answer

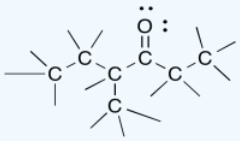
a) 

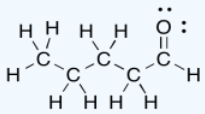
b) 

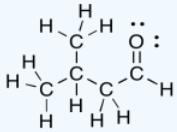
c) 

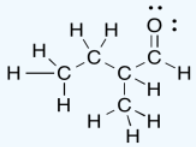
d) 

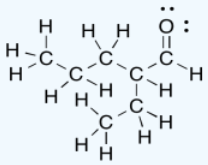
e) 

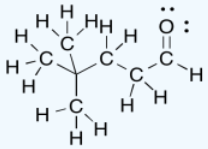
f) 

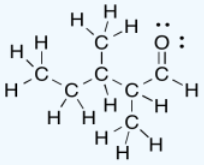
g) 

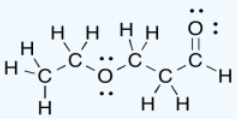
h) 

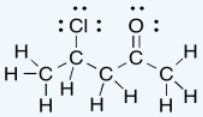
i) 

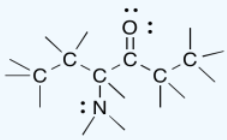
j) 

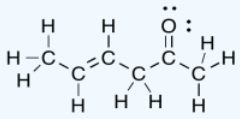
k) 

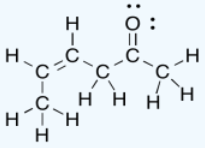
l) 

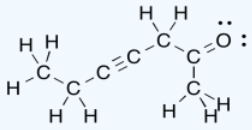
m) 

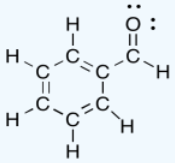
n) 

o) 

p) 

OR 

q) 

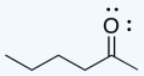
r) 

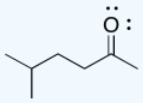
Exercise 3.21.4

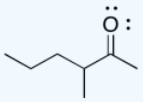
Problem CO2.4.

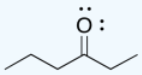
Translate the condensed formulae in the previous problem into line structures.

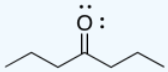
Answer

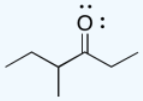
a) 

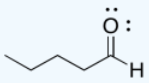
b) 

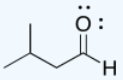
c) 

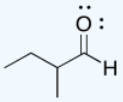
d) 

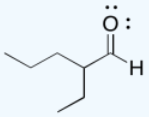
e) 

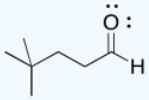
f) 

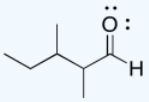
g) 

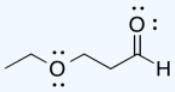
h) 

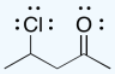
i) 

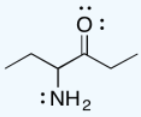
j) 

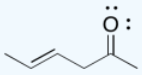
k) 

l) 

m) 

n) 

o) 

p) 

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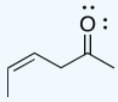
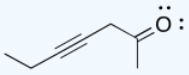
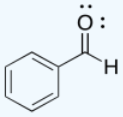


q) 

r) 

Exercise 3.21.5

Provide IUPAC names for the compounds in the previous problem. For help, see the functional group section, simple carbonyls.

Answer a

2-hexanone or hexan-2-one

Answer b

5-methylhexan-2-one

Answer c

3-methylhexan-2-one

Answer d

hexan-3-one

Answer e

heptan-4-one

Answer f

4-methylhexan-3-one

Answer g

hexanal

Answer h

3-methylbutanal

Answer i

2-methylbutanal

Answer j

2-ethylpentanal

Answer k

4,4-dimethylpentanal

Answer l

2,3-dimethylpentanal

Answer m

3-ethoxypropanal

Answer n

4-chloropentan-2-one

Answer o

4-aminohexan-3-one

Answer p

hex-4-en-2-one (in the solution above, (*E*)-hex-4-en-2-one is shown first and (*Z*)-hex-4-en-2-one is shown second).

Answer q

hept-4-yn-2-one

Answer r

benzaldehyde (this is a common name adopted for formal naming. Benz means a carbon attached to a benzene ring.)

Exercise 3.21.6

Fill in any missing lone pairs in the following structures.

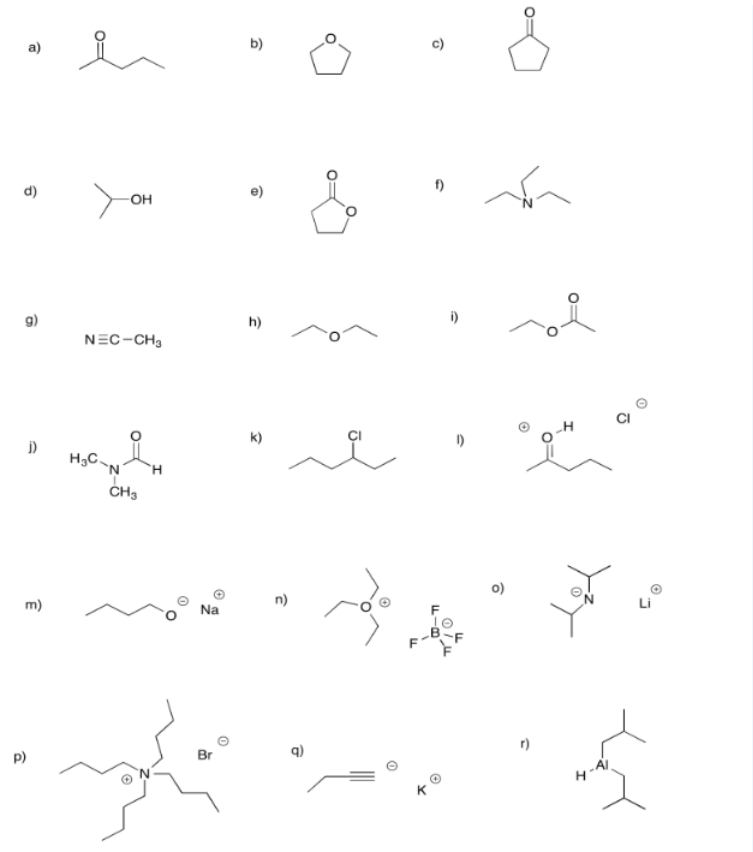
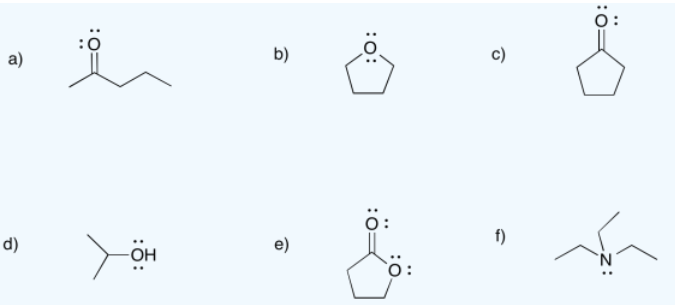
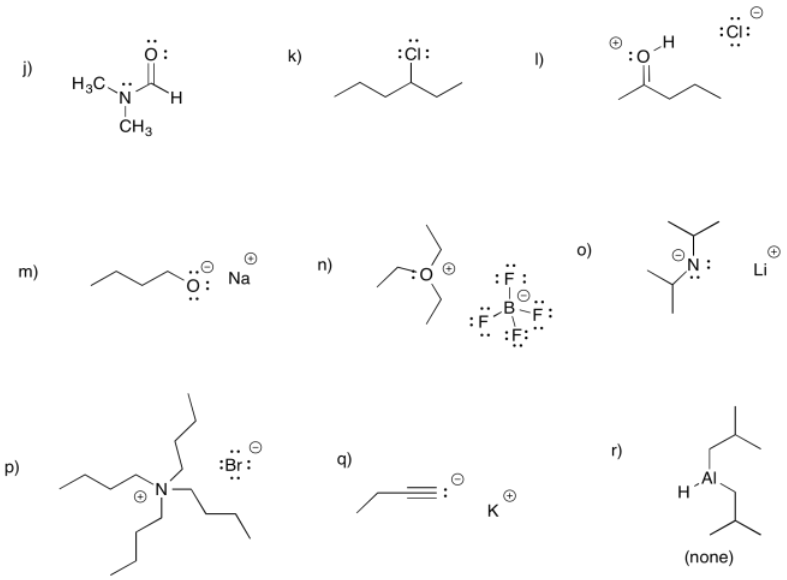


Figure 3.21.4:

Answer





3.22: General Reactivity Patterns

In the following pictures, a number of anions are added to a simple carbonyl compound, a ketone (2-propanone, or acetone). In each case, addition of the nucleophile is followed by addition of a proton source. Note that, overall, the reaction involves addition of the nucleophile to the carbonyl carbon and addition of the proton to the carbonyl oxygen.

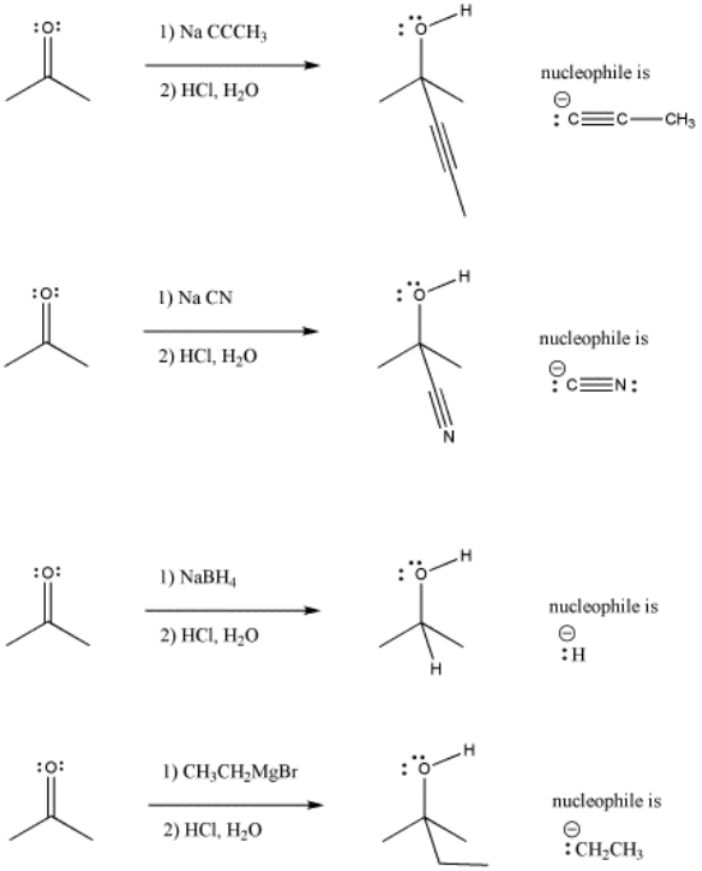


Figure 3.22.1: Addition of some anionic (and "semi-anionic") nucleophiles to a ketone.

- Addition of anionic nucleophiles to ketones or aldehydes transforms the carbonyl into an alcohol.

Look at the way the reaction is presented in each case. The organic (carbon-based) starting material is presented on the left hand side of the reaction arrow. The reagent added to this starting material is often shown over the arrow. This reagent transforms the starting material into something else. That something else, the product, is shown to the right of the arrow.

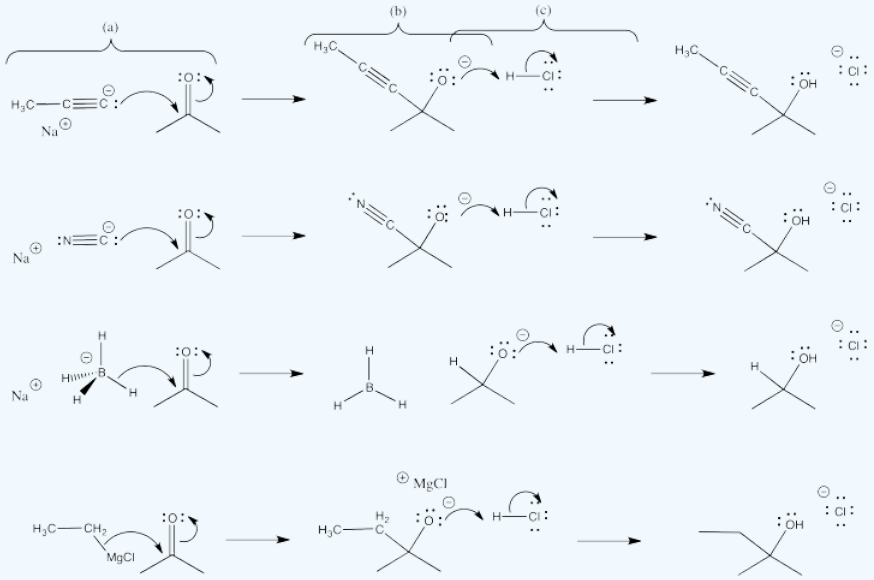
Very often, the solvent for the reaction is shown underneath the arrow. The solvent is the liquid that is used to dissolve the starting material and reagents. This is done for a number of reasons. First, reactions generally happen much more quickly in solution than they do without a solvent. When dissolved, the reactants can move around more easily and bump into each other, as if they are swimming. Also, most useful reactions generate heat, and the solvent acts as a heat sink, carrying the excess heat away. (People who have not thought about the importance of solvent sometimes accidentally start fires as a result.) However, there are exceptions, and not all reactions need solvent.

These reactions shown above do need solvent, but the solvent is not shown for other reasons. There is something else to focus on, and the solvent would have just cluttered up the picture. Instead, the focus of the picture is that these reagents must be added in a particular order: first the nucleophile and then the acid. The nucleophile and acid cannot be allowed to mix before the nucleophile has a chance to react with the carbonyl. If they did, they would just react with each other, and leave the carbonyl electrophile alone.

Exercise 3.22.1

a. For each of the cases shown above, use curved arrows to show the movement of electrons in the reaction between the anion and the carbonyl.
b. Show the intermediate that results.
c. Use curved arrows to show the movement of electrons in the reaction of the intermediate with acid to form the product.

Answer



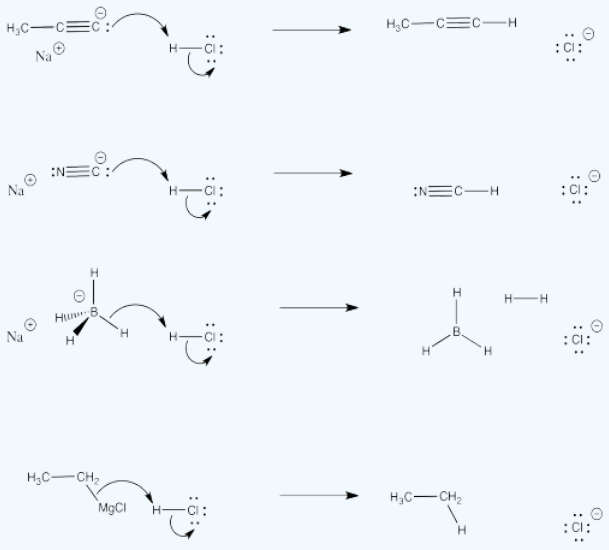
Exercise 3.22.2

Problem CO3.2.

a) For each of the cases shown above, used curved arrows to show what would happen if acid were mixed with the nucleophile.

b) Why would the nucleophile no longer be able to react with the carbonyl?

Answer



Previously, we saw that nucleophiles add to carbonyl electrophiles, breaking the pi bond of the carbonyl and converting it into an OH group.

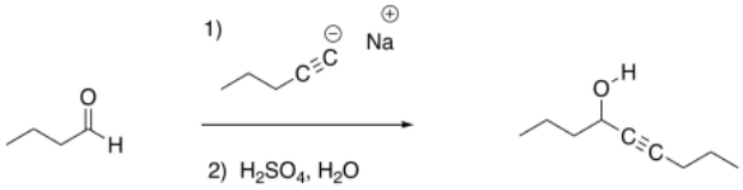


Figure 3.22.2:

The pattern of reactivity is very different with another class of nucleophile. These could be called neutral nucleophiles (as opposed to anionic ones). Neutral nucleophiles do not have a negative charge like the previous ones. However, they still have a lone pair, and that fact still makes them nucleophiles.

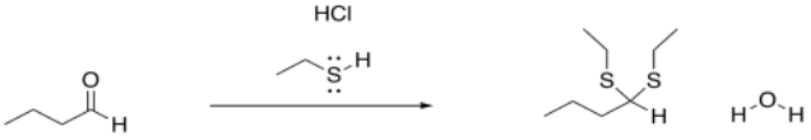


Figure 3.22.3:

However, the outcome of the reaction looks a little different from what we saw with the earlier anionic nucleophiles. In this case, the carbonyl is not converted into an OH group. (At some point we will see that it can be under some circumstances, but that is the exception rather than the rule.) Instead, the osygen is completely displaced from the carbonyl. It is lost as water. It is replaced by two nucleophiles, instead.

The same thing happens in the following case, involving an oxygen nucleophile instead of a sulfur. Oxygen is in the same column of the periodic table as sulfur, so similar behavior is not really a surprise.

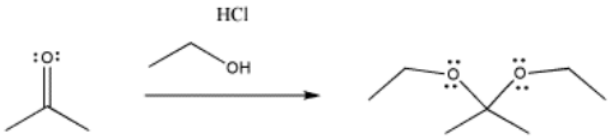


Figure 3.22.4:

With nitrogen nucleophiles, the oxygen of the carbonyl is still displaced as water, but the nucleophile does not appear to add twice. Instead, the C=O is replaced with a C=N.

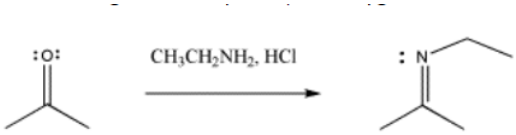


Figure 3.22.5:

Other nitrogen compounds give a similar product, with the double bond in a slightly different place. We will see that the difference has to do with how many hydrogens there are on the original nitrogen atom. If there are two, it is an even trade: the nitrogen replaces the carbonyl oxygen, and the oxygen takes the two hydrogens to form water. If there is only one NH, the oxygen needs to pick up a second hydrogen from elsewhere, and it takes it from the alpha position, next to the former carbonyl.

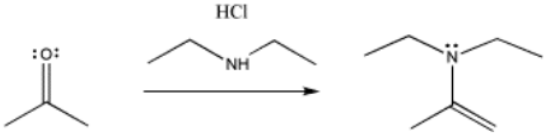


Figure 3.22.6:

These nucleophiles are a little less likely to react with the acid, so we have not taken care to add them in a particular order. They are less likely to react with the acid because they are not anions. They are neutral, so they will not attract the proton as strongly as anions would. In reality, you have to be a little bit careful about conducting reactions like these. With the amine nucleophiles in particular, if you add *too much* acid, the nucleophiles will react with the acid after all.

Take another look at the general pattern of reactivity for the anionic nucleophiles and the neutral nucleophiles. In the case of the anionic nucleophiles, the pattern is relatively easy to discover. The product has incorporated the nucleophile into its structure (or at least the anionic part of the nucleophile, which you will soon learn about). The nucleophile has attached at the carbonyl carbon. The carbonyl oxygen has become part of a hydroxyl group. These are very common patterns in the addition of nucleophiles to carbonyls.

In the case of the neutral nucleophiles, there are some similarities and some differences. The nucleophile is still incorporated into the product structure. It has added at the carbonyl position in the electrophile. However, the fate of the carbonyl oxygen is a little bit different with neutral nucleophiles. Generally, this atom is lost as a water molecule in these cases. If you look closely, you will be able to tell where the two protons come from in each case in order to form the water molecule. It's not really the HCl, which is only added in very tiny amounts and acts catalytically. The protons come from other positions in the nucleophile, and sometimes from the electrophile, too.

This chapter will help you to develop skills so that you can recognize where nucleophilic additions have taken place in reactions. You will also be able to predict what products may result from a nucleophilic addition.

3.23: Reaction Mechanism

Much of the chapter will focus on mechanisms of reaction. A reaction mechanism is, at the very least, the series of elementary steps needed to accomplish an overall reaction, and all of the intermediate structures that would be formed on the way from the reactants to the products.

- A reaction mechanism shows the structures of intermediates that occur after each elementary step.

Consider the following reaction. It's called a keto-enol tautomerism. A tautomerism is just a reaction in which, overall, a proton or hydrogen atom has changed positions. The structure on the left is a ketone. The structure on the right is called an enol, because it has a hydroxyl group (OH) attached directly to an alkene carbon (C=C). Just by moving one hydrogen atom, we go from one structure to the other.

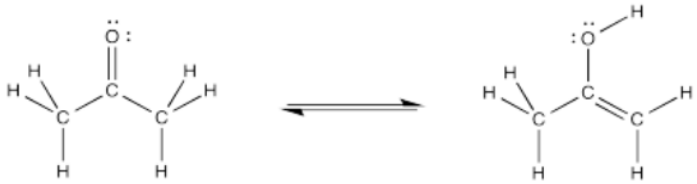


Figure 3.23.1:

Exercise 3.23.1

Try drawing the reaction above using skeletal drawings instead of full Lewis structures.

Answer

An elementary reaction is typically a bond-forming or a bond-breaking step. In a bond-forming step, a pair of electrons are donated from one atom to another. In a bond-breaking step, a pair of electrons that were shared between two atoms are drawn to one end of the bond or the other, so that the bond breaks and the electrons end up on one atom only.

What are the elementary steps in a keto-enol tautomerism? What sorts of stops do we make along the way?

These reactions can actually occur in a couple of different ways, depending on whether the compounds are in acidic conditions or basic conditions. In acidic conditions, there are extra protons floating around. They aren't all by themselves; remember, protons tend to stick to things that have lone pairs to share.

Under basic conditions, there aren't a significant amount of extra protons around. There might be hydroxide ions or other nucleophilic species around. Nucleophile species are electron-donating compounds that are attracted to positive charges or electrophiles.

We're going to look at this reaction under acidic conditions. If there are protons around, maybe some mineral acid has been added, such as hydrochloric acid or sulfuric acid. Those things are typically used in water, so we'll assume there is some water around. We have hydronium ions $(H_3O)^+$ in solution. There must be some counterion, too, but we'll ignore it.

Under those conditions, what will the first step look like? Maybe a proton is transferred from the hydronium ion to the oxygen atom on the ketone. That would get us halfway there. Remember, the keto-enol tautomerism involves addition of a proton to that oxygen.

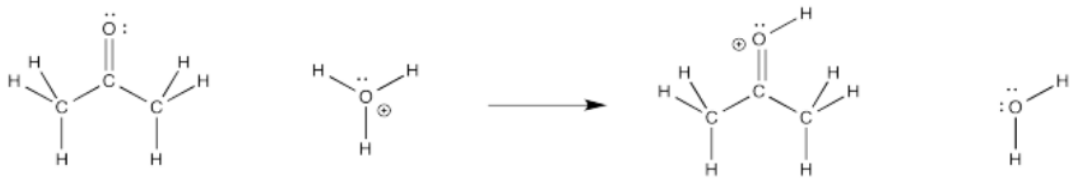


Figure 3.23.2:

The bond-making event involves the carbonyl oxygen. What differences do you see at that atom before and after the transfer? Certainly a proton has appeared, and a positive charge, but there is also a lone pair missing. Where did it go?

On the hydronium ion, meanwhile, a lone pair has appeared along with the departure of the proton. Where did that come from?

Of course, a covalent bond is a pair of electrons shared between two atoms. If we are making and breaking bonds, electrons are playing a prominent role. It may be useful to illustrate the role they are playing.

Very often, curved arrows are used to show the path that electrons take in these elementary steps. These arrows are always drawn from the source of the electrons to the place to which the electrons are attracted. These arrows help to illustrate bond-making and bond-breaking steps and also serve a book-keeping function, helping us to keep track of electrons over the course of the reaction.

Figure 3.23.3:

Notice that, in the elementary step shown above, a bond forms between the carbonyl oxygen and one of the protons on the hydronium ion (H_3O^+). A covalent bond is a pair of electrons shared by two atoms. Where do the electrons come from to form that bond? They used to be a lone pair on the carboyl oxygen. A curved arrow is used to show that.

At the same time, the bond breaks between that hydrogen and the oxygen in the hydronium ion. Where do those electrons go? They become a lone pair on the oxygen. Another curved arrow shows that event.

We're not finished, yet. What happens after that initial transfer? It seems reasonable that we might just take a proton off the carbon next to the carbonyl. That position, right next to the carbonyl carbon, is called the alpha position. We are taking a proton that was attached to an alpha carbon.

Is it OK to take protons away and break C-H bonds? Only sometimes, but this is one of those cases. Removal of a proton from an alpha position happens all the time in organic and biochemical reactions (those involving carbon-based molecules, and those involved in living systems).

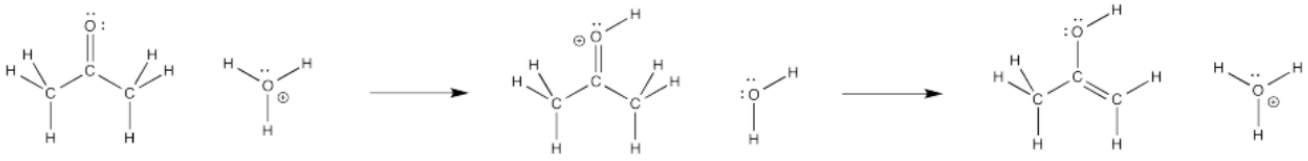


Figure 3.23.4:

Filling in curved arrows shows the bonds have been made or broken.

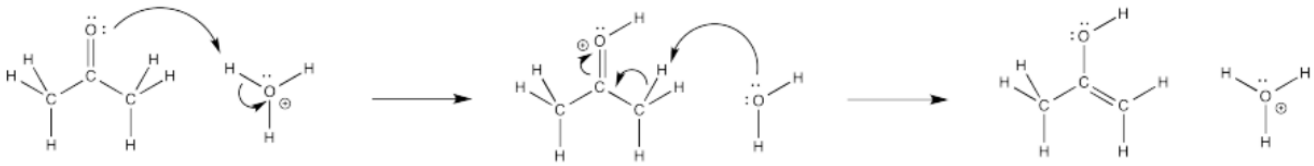


Figure 3.23.5:

- Curved arrows from the nucleophile to the electrophile show the path of electrons in the reaction.

- Curved arrows illustrate bond-making and bond-breaking events.

Sometimes, only one arrow is required in showing an elementary step, but not always. Often, a bond-making step can happen at the same time as a bond-breaking step. This usually happens when an atom isn't large enough to accommodate the electrons from the new bond and sill keep the electrons from an old bond. In this case, two pairs of electrons move in the same elementary step, so two curved arrows are shown. Very rareley, more than two curved arrows are needed to show the events in one elementary step.

This is how chemists have thought about reactions, on paper, for about a hundred years. Always they try to draw a sequence of reasonable intermediates along the course of a reaction. Reactions rarely happen in one step, especially if multiple bonds are formed and broken, although you will eventually learn about some that happen that way. Usually, especially in organic and biochemical reactions, curved arrows are used in an attempt to map out the movement of electrons.

Exercise 3.23.2

Draw the entire keto-enol tauomerism mechanism shown above using skeletal drawings rather than full Lewis structures. Remember, it is important that you still show the lone pairs, for electron accounting purposes.

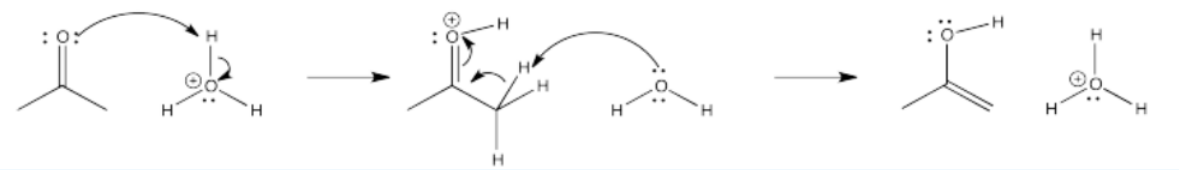


Figure 3.23.6:

Sometimes other information is displayed in a reaction mechanism. Computational chemists will often leave out the curved arrow notation but will instead indicate the relative energy differences between all the intermediate structures along the reaction pathway. These energies may be experimentally determined (i.e. they may be based on the measurement of real reactions) or they may be calculated using an appropriate level of quantum theory. The energies may be displayed numerically, possibly in a table, or they may be illustrated using a picture, such as a reaction profile.

Exercise 3.23.3

Fill in curved arrows on the following mechanisms.

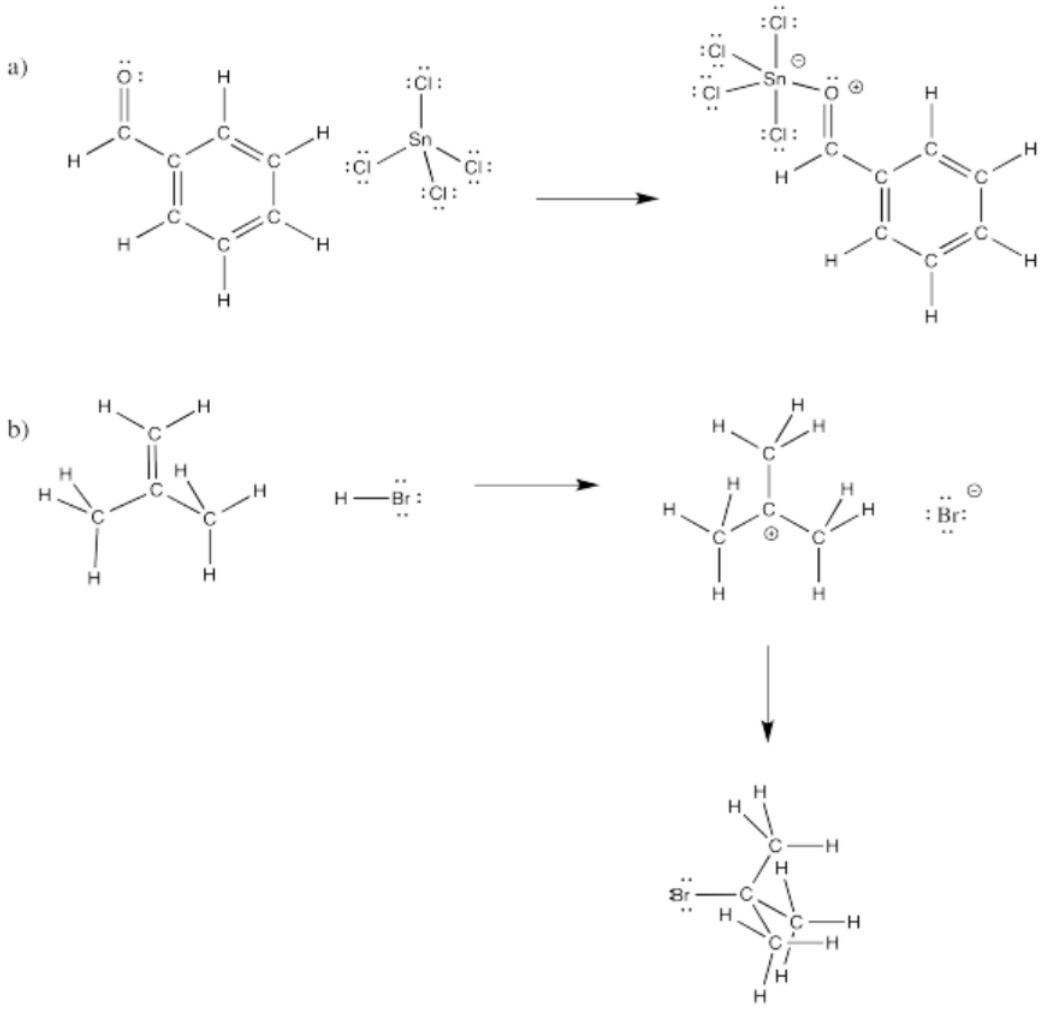


Figure 3.23.7:

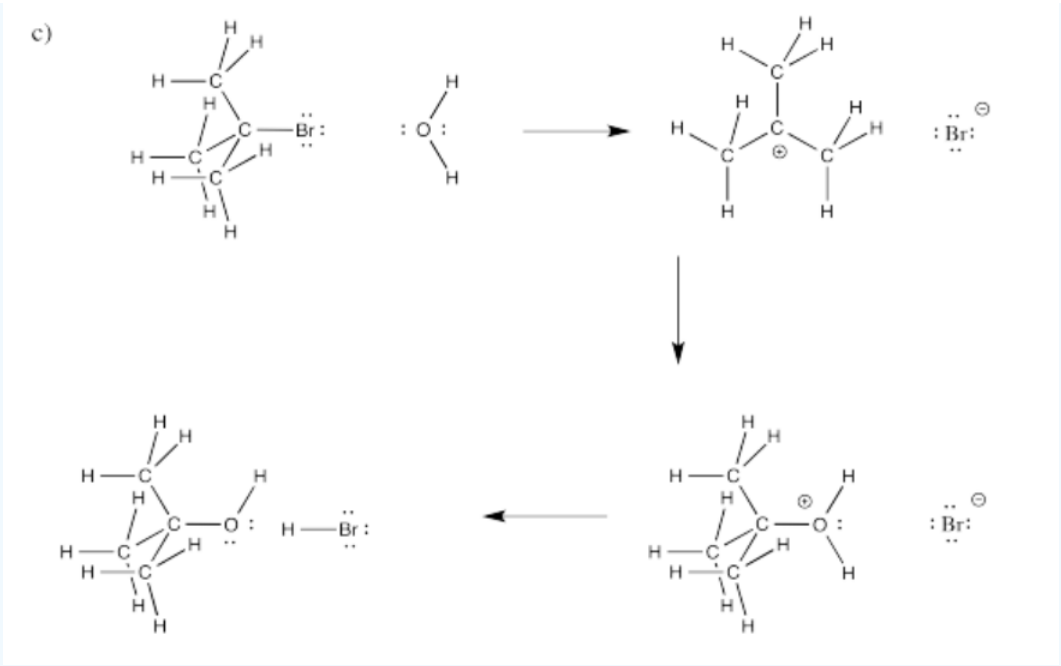
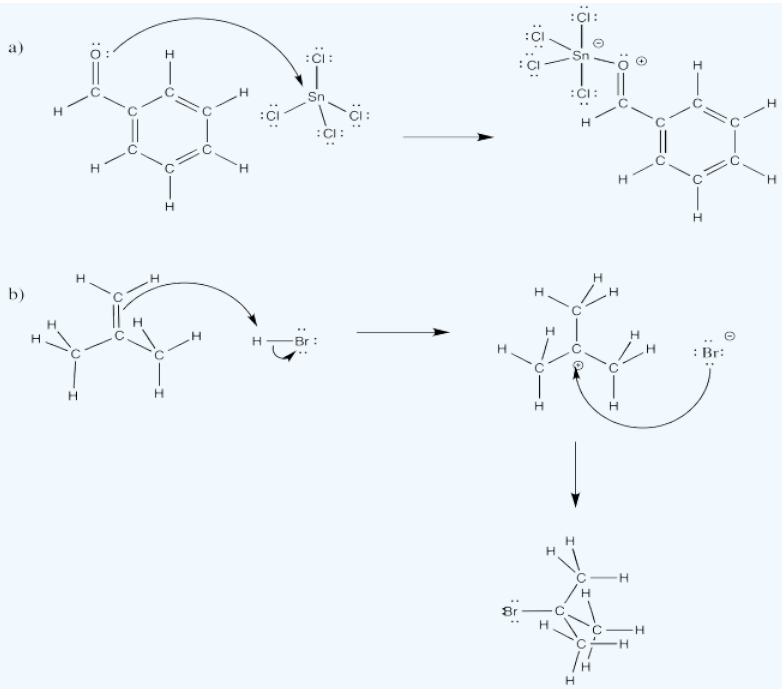


Figure 3.23.8:

Answer



Exercise 3.23.4

In the following overall reactions, identify where bonds have been broken and where bonds have been made.

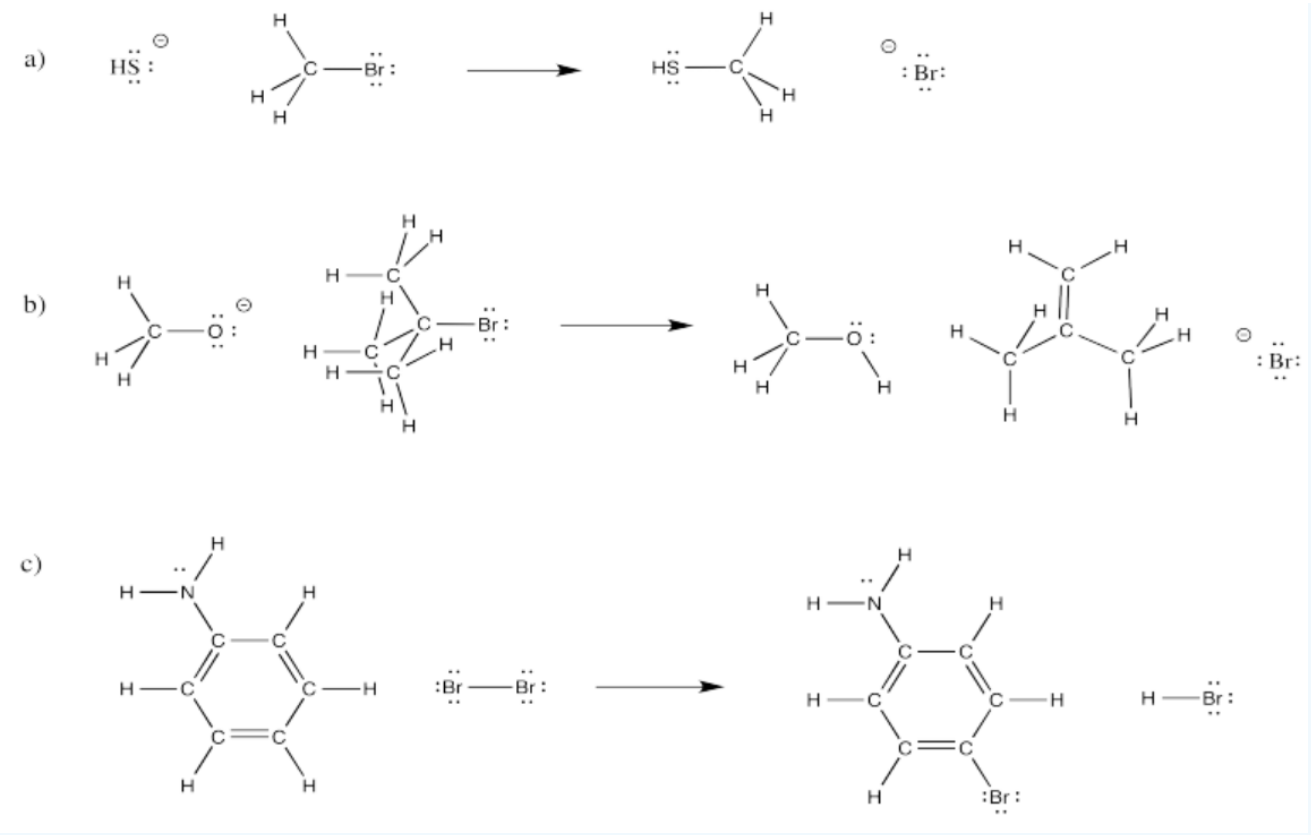
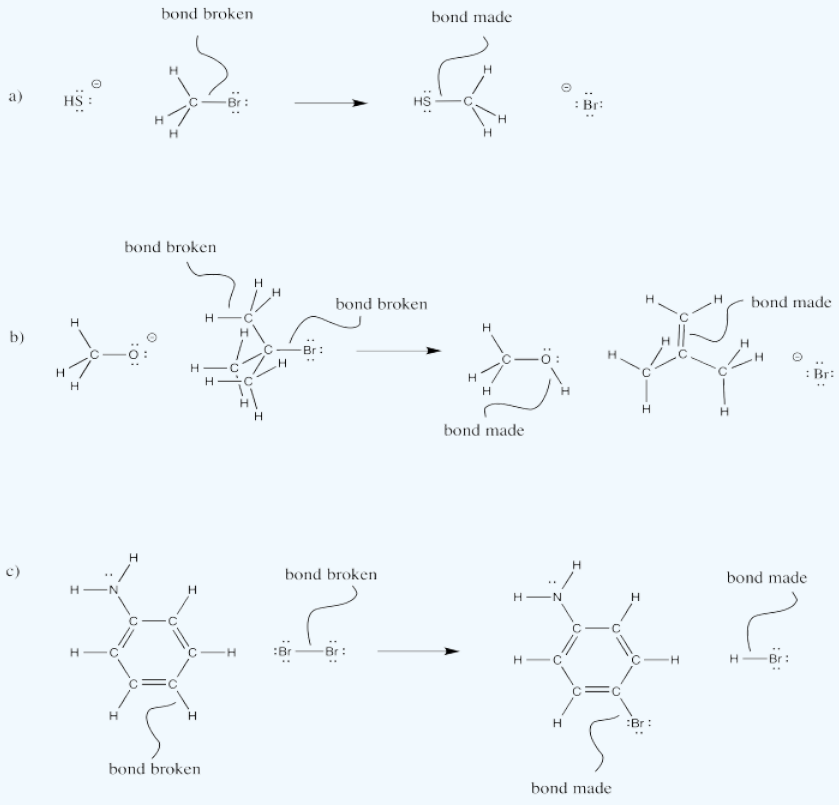


Figure 3.23.9:

Answer



Exercise 3.23.5

In the following reactions, specific atoms have moved to specific places. Propose elementary mechanisms for these transformations.

Exercise 3.23.6

Propose a mechanism, with arrows, for the keto-enol tautomerism above, but this time under basic conditions. Assume there is some sodium hydroxide dissolved in aqueous solution.

3.24: Molecular Orbital Picture of Carbonyls

Often it is useful to look at the molecular orbital picture of a molecule to learn something about its reactivity.

In the case of carbonyls, frontier orbital ideas tell us to look at the lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO).

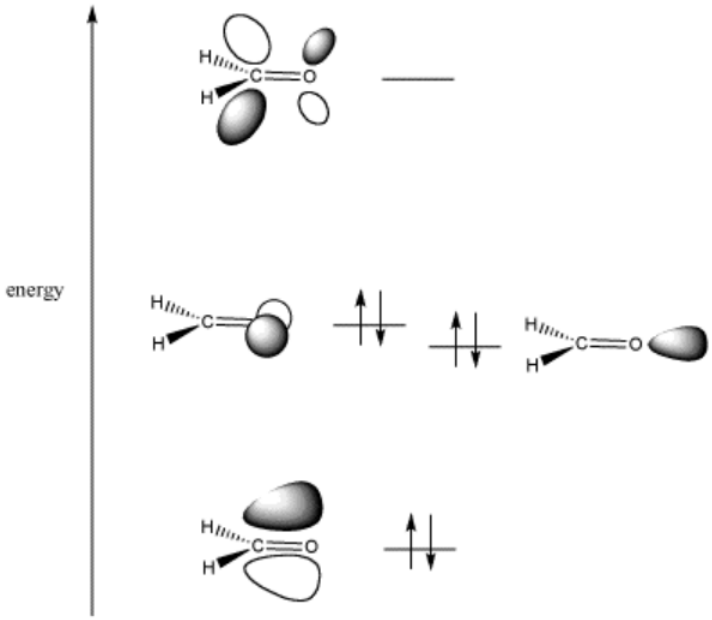


Figure 3.24.1: Frontier orbitals in a carbonyl compound.

When two different atoms bond together, the molecular orbitals that they form are not evenly distributed between the atoms. Instead, the new molecular orbital is closest in space to the atom to which it is closest in energy.

In the case of carbon and oxygen, oxygen is more electronegative than carbon. That means its electrons are more tightly held than carbon's. That means its electrons are lower in energy than carbon's.

When carbon and oxygen combine, a bonding orbital and an antibonding orbital result. The bonding orbital is lower in energy than the orbitals on either carbon or oxygen. However, it is closer in energy to oxygen. Thus, the orbital itself is more centered on oxygen. In other words, the electrons in the bond are closer to oxygen than to carbon.

The antibonding orbital, on the other hand, is closer to carbon in energy, although it is higher in energy than either carbon or oxygen. It is more centered on the carbon than the oxygen. That means the "target" for the electron donation is mostly found on the carbon. The carbonyl carbon is the electrophilic position.

If electrons are going to be donated to the molecule, the lowest energy position available for electrons in the molecule is described by the LUMO. The LUMO in this case is the C=O pi* or pi antibonding orbital.

If the carbonyl is going to donate electrons, the electrons will come from the HOMO. In this case, that refers to the non-bonding electrons. These electrons are found on the oxygen, and are equivalent to the lone pairs in the Lewis structure.

Exercise 3.24.1

Explain what happens to bonding in the molecule if an electron pair is donated to the LUMO of $H_2C{=}O$.

Answer

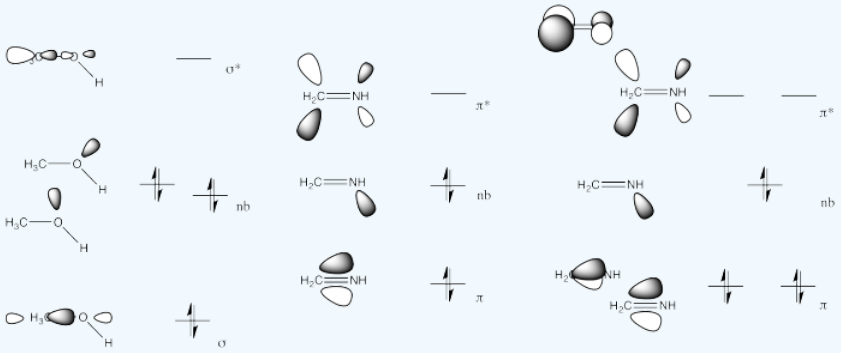
The LUMO in this case is the π*, an antibonding level. If electrons populate this level, the π bond will break.

Exercise 3.24.2

Draw the frontier-orbital diagram (including orbital pictures) for the following compounds.

a) CH_3OH b) $H_2C{=}NH$ c) CH_3CN

Answer



Exercise 3.24.3

Problem CO5.3.

In the previous problem, which MO pictures most closely resemble the one shown for $H_2C{=}O$? Which compounds will behave most like a carbonyl compound? Explain.

Answer

Both the imine (b) and nitrile (c) have a low-lying pi antibonding level (π*), similar to a carbonyl.

3.25: Relative Reactivity of Carbonyls

Sterics

Steric hindrance, or crowdedness around the electrophile, is an important factor that influences reactivity.

- The less crowded the electrophile, the more easily it will react.
- Aldehydes are more reactive than ketones.

Crowdedness affects reactivity simply by preventing nucleophiles from easily approaching the electrophilic site in the carbonyl. If the nucleophile hits something other than the carbonyl carbon, it will probably just bounce off. It needs to collide with the carbonyl carbon in order to deliver its electrons to the right place.

Charge

Amount of positive charge on the electrophile is an important factor that influences reactivity.

- The more positive the electrophile, the more easily it will react.

Factors that place more positive charge on the carbonyl (electron withdrawing groups nearby) make the carbonyl more positive and more reactive. Factors that place additional electron density on the carbonyl (electron donors nearby) make the carbonyl less reactive.

There is another resonance structure that we can think about that illustrates the electrophilicity of a carbonyl. That structure places a full negative charge on the oxygen and a full positive charge on the carbon. This isn't a good Lewis structure because the carbon does not have an octet. Nevertheless, when taken together with the regular Lewis structure, it suggests something real about the nature of the carbonyl: there is partial positive charge on the carbon and partial negative charge on the oxygen.

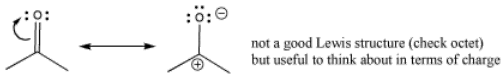


Figure 3.25.1:

There is a general rule about cation stability on carbon atoms: a carbocation with more carbons attached to it is more stable than a carbocation with more hydrogens attached to it.

This observation is sometimes explained as an inductive effect. The positively charged carbon is more electronegative than the uncharged carbons, so it draws electrons away from them. It can polarize the neighbouring carbons, drawing some negative charge towards itself and leaving some positive charge on the other carbons. In that way, it s charge is delocalized and stabilized.

In a more sophisticated explanation, the cation becomes stabilized by a molecular orbital interaction involving the empty p orbital on the carbocation and C-H bonds on the neighbouring carbons.

A similar situation results in the partially positive carbon in the carbonyl. The carbonyl carbon in the ketone is a little more stable than the carbonyl carbon in the aldehyde.

- The partial positive charge on an aldehyde carbonyl carbon is less stable than the partial positive charge on a ketone carbonyl carbon.
- Again, aldehydes are more reactive than ketones.

Exercise 3.25.1

Rank the following carbonyl compounds from most reactive to least reactive towards nucleophilic addition. Explain your reasoning.

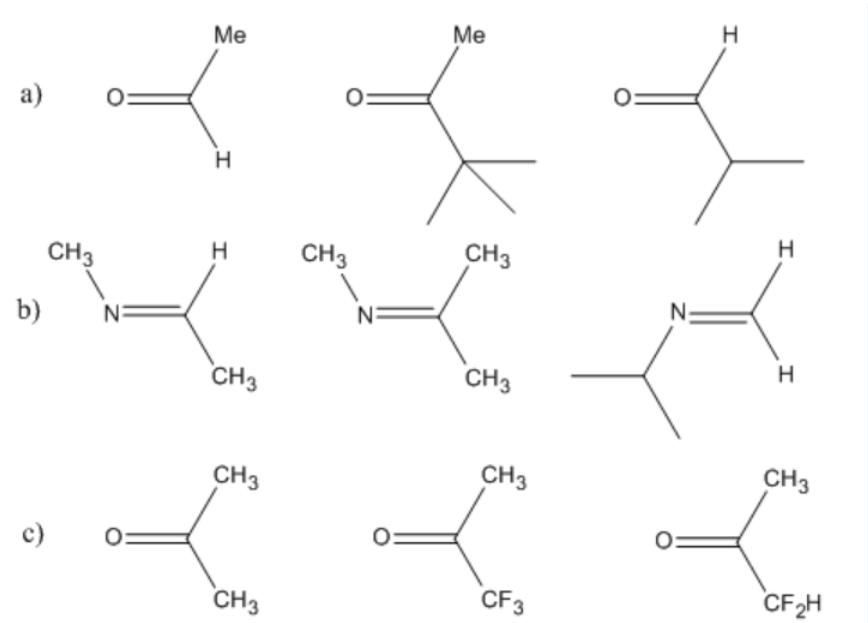


Figure 3.25.2:

Answer a

On the basis of steric crowding, the first one is most reactive, then the last one, then the middle.

Answer b

On the basis of steric crowding, the last one is most reactive, then the first one, and then the middle.

Although there is a large group on the nitrogen in that last compound, the site of reactivity is the carbon, which is less crowded.

Answer c

On the basis of electronics, the middle one is most reactive, then the last, and then the first. The fluorine atom is very electronegative and pulls electron density towards itself. That leaves more positive charge on the nearby carbonyl carbon. The more fluorines on that nearby carbon, the more positive the carbon. The more positive the carbon, the more it attracts electrons from a nucleophile.

Exercise 3.25.2

Provide names for the following aldehydes.

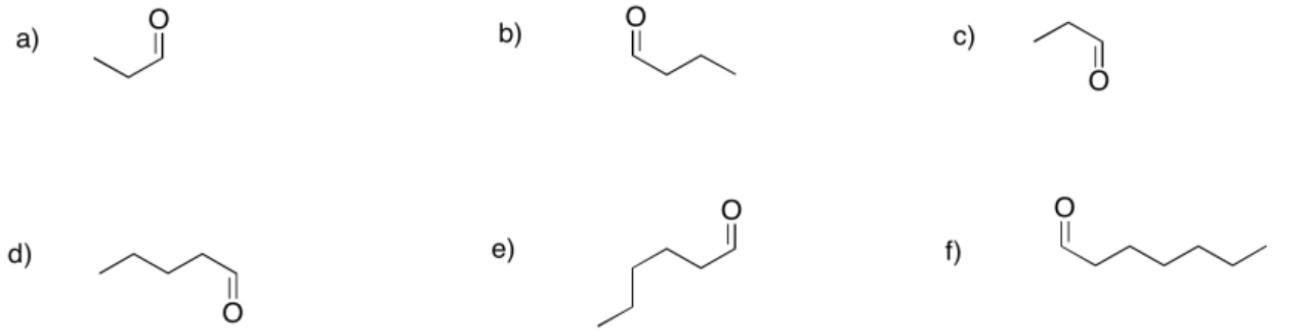


Figure 3.25.3:

Answer a

propanal

Answer b

butanal

Answer c

propanal, again!

Answer d

pentanal

Answer e

hexanal

Answer f

heptanal

Exercise 3.25.3

Problem CO6.3.

Provide names for the following ketones.

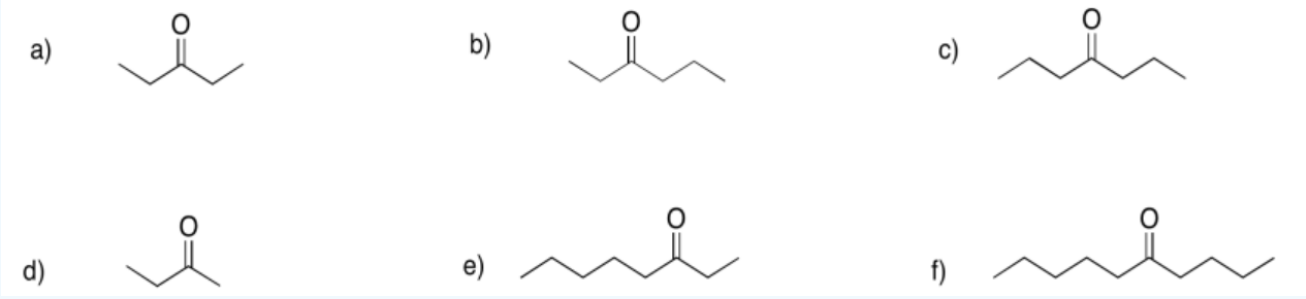


Figure 3.25.4:

Answer a

3-pentanone

Answer b

3-hexanone

Answer c

4-heptanone

Answer d

2-butanone

Answer e

3-octanone

Answer f

5-decanone

Exercise 3.25.1

Problem CO6.4.

Provide names for the following ketones.

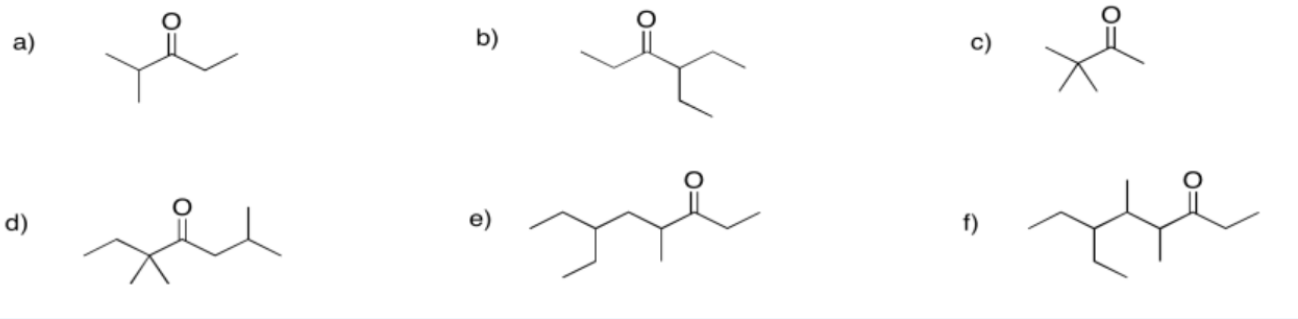


Figure 3.25.5:

Answer a

2-methyl-3-pentanone or 2-methylpentan-3-one

Answer b

4-ethyl-3-hexanone or 4-ethylhexan-3-one

Answer c

3,3-dimethyl-2-butanone or 3,3-dimethylbutan-2-one

Answer d

2,5,5-trimethyl-4-heptanone or 2,5,5-trimethylheptan-4-one

Answer e

6-ethyl-4-methyl-3-octanone or 6-ethyl-4-methyloctan-3-one

Answer f

6-ethyl-4,5-dimethyl-3-octanone or 6-ethyl-4,5-dimethyloctan-3-one

3.26: The Mechanism of Carbonyl Addition- Step One

Carbonyls act most importantly as electrophiles. They attract a pair of electrons from a nucleophile. When that happens, a bond forms between the nucleophile and the carbonyl carbon.

At the same time, the carbon-oxygen bond breaks. We think of that as a consequence of donating a pair of electrons into the LUMO of the carbonyl. The LUMO on the carbonyl is the C-O pi antibonding orbital. When that orbital is populated, there is no longer a net lowering in energy due to the pi interaction between the carbon and oxygen. The pi bond breaks. The electron pair from the pi bond goes to the oxygen, the more electronegative of the two atoms in the original bond. It becomes a lone pair.

After the pi bond breaks, the reaction reaches a branching point or decision point. The reaction may go forwards or backwards.

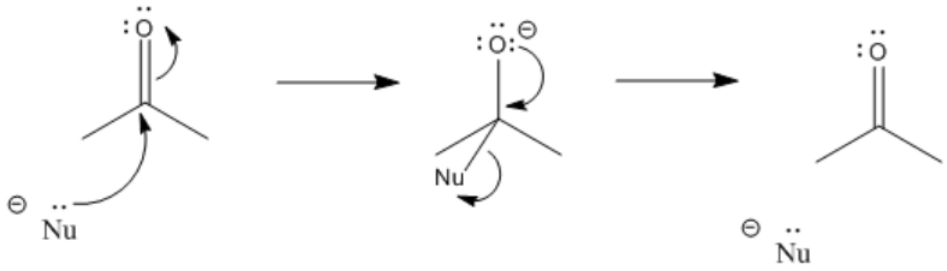


Figure 3.26.1:

In other words, this reaction can occur in equilibrium.

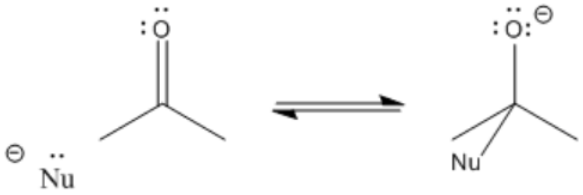


Figure 3.26.2:

To go backwards, the reaction simply slides into reverse. A lone pair on the oxygen donates to the carbon, forming a pi bond again, and pushes the nucleophile off. Whether the reaction ends up going forward or sliding backward depends partly on the relative stability of those two ends of the reaction. That's often very difficult to assess qualitatively, because there are too many factors involved. However, one factor that plays a role is charge stability. Because an "O minus" or alkoxide is produced in this reaction, if the original nucleophile was a more reactive ion than an alkoxide, the reaction probably goes to the right.

For that reason, many of the best nucleophiles for these reactions involve carbon anions or hydrogen anions. Those anions are less stable than oxygen anions.

Figure 3.26.3:

If the nucleophile were less reactive than alkoxide, the reaction could easily go to the left again. For that reason, stable halide ions (fluorides, chlorides, bromides, iodides) are not very good nucleophiles for these reactions. They have lone pairs, they even have negative charges, but the anion that would be produced would generally be less stable than the original halide ion.

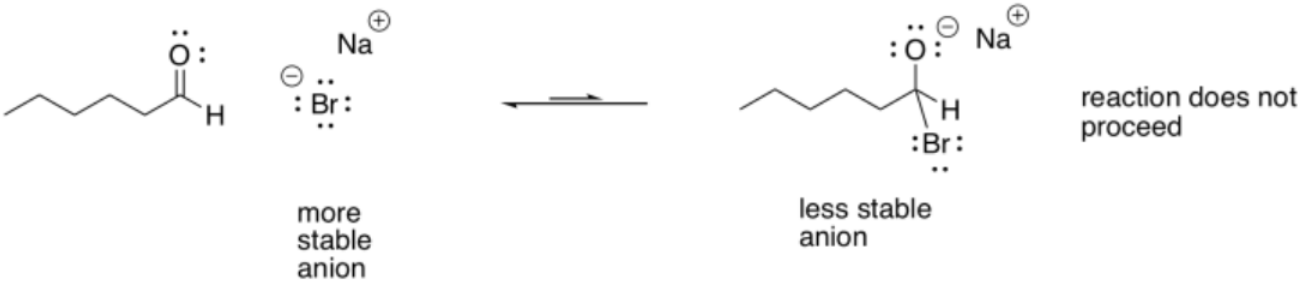


Figure 3.26.4:

Exercise 3.26.1

Provide curved arrows and predict the direction of equilibrium in the following cases.

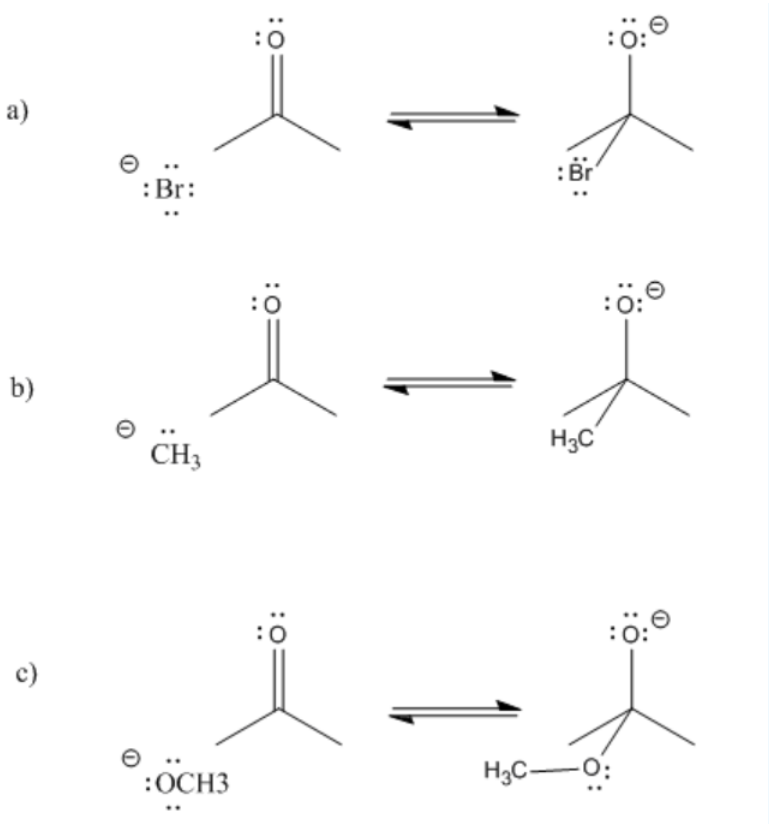
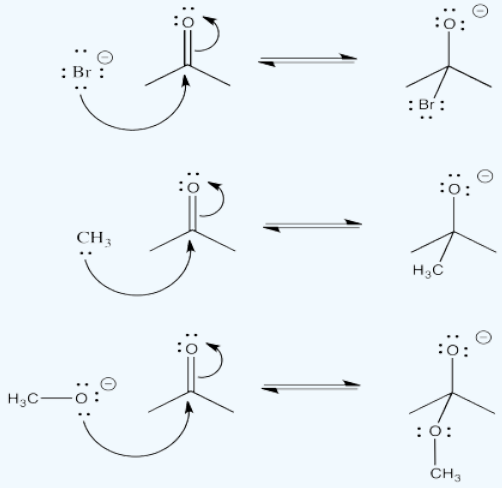


Figure 3.26.5:

Answer



- More reactive nucleophiles push the equilibrium to the right
- Less reactive nucleophiles do not push the reaction to the right; the reaction remains on the left

What happens after the initial equilibrium? In most cases, the alkoxide that is formed will become protonated. It will pick up a proton to become an alcohol. The source of the proton may be an acid, deliberately added to provide the H^+. Alternatively, it may just be a very slightly acidic molecule such as water or another alcohol.

3.27: Protonation of the Alkoxide Anion

After the addition of an anionic nucleophile, reaction mixtures are usually treated with or water or dilute aqueous acid. The acid provides a proton that can be picked up by the alkoxide ion formed in the nucleophilic addition. An alcohol is formed as a result. Overall, carbonyl addition reactions usually involve addition of a nucleophile to the carbonyl carbon and addition of a proton to the carbonyl oxygen.

The order of these steps can be very important. On paper, a carbonyl could be turned into an alcohol by adding a proton to the carbonyl oxygen, and then adding a nucleophile to the carbonyl carbon. However, things might not work out that way in reality. The potential problem lies in the fact that anionic nucleophiles can be pretty basic. If protons are added first, the anionic nucleophile is likely to pick up a proton rather than donate to the carbonyl. Once the nucleophile has picked up a proton, it is no longer anionic, and is less attracted to the partially positive carbonyl. Furthermore, it may have donated its only lone pair to the proton, leaving it completely unable to donate to the carbonyl.

What is the source of protons? In most cases, a dilute aqueous solution of a strong acid is used. That is, a little bit of strong acid is dissolved in water to provide plenty of protons to form the alcohol. The most common strong acids are hydrochloric acid, HCl, and sulfuric acid, H_2SO_4.

Figure 3.27.1:

Actually, just the water itself would be enough to donate protons. Water has a polar O-H bond and so it can transfer a positive hydrogen ion to an anion. However, that would result in the exchange of one oxygen anion for another. Energetically, there wouldn't be much difference between having the negative charge on the reaction product, the alkoxide, or on the hydroxide ion from the water. That's why a strong acid is usually added.

In terms of le Chatelier, if you added enough water, you should be able to drive that equilibrium to the right. However, there would always be a little unprotonated alkoxide left over at the end.

Exercise 3.27.1

Problem CO8.1.

Provide curved arrows and predict the direction of equilibrium in the following cases.

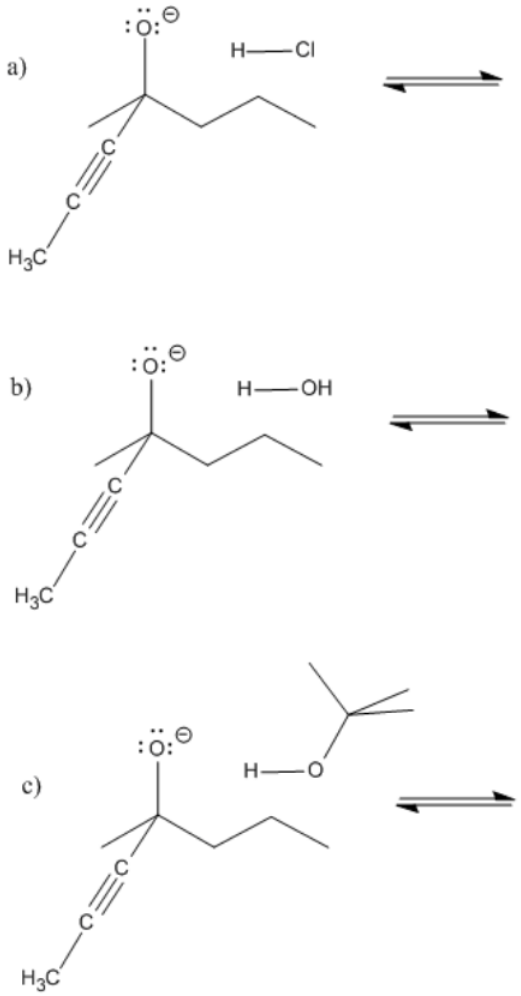
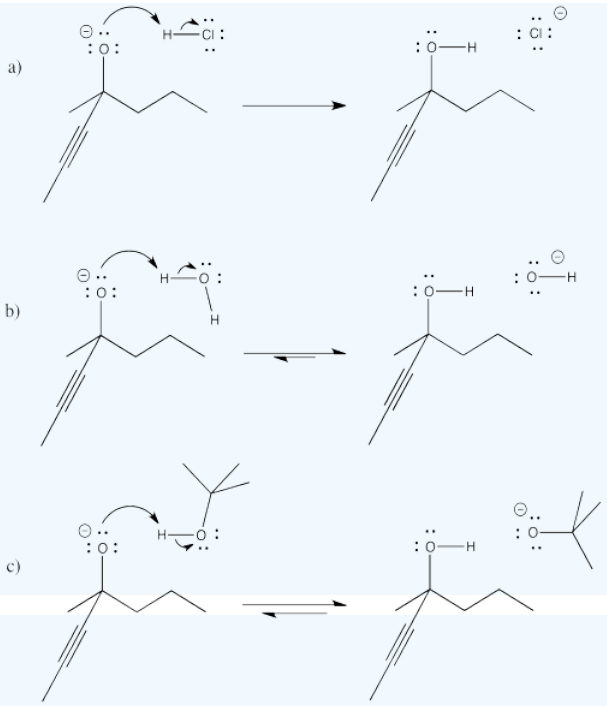


Figure 3.27.2:

Answer



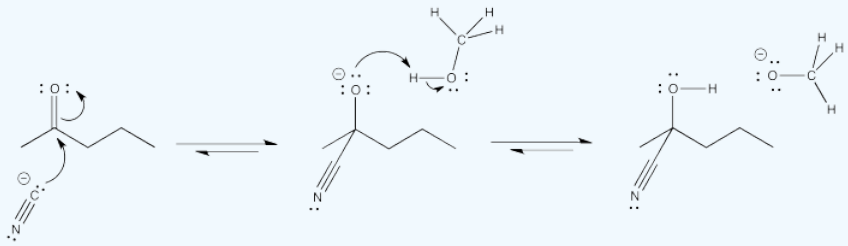
Exercise 3.27.2

Problem CO8.2.

Suppose nucleophilic addition was performed in methanol (10 mL) as a solvent, using 25 microliters of cyclopentanone and an equimolar amount as the of sodium cyanide (that means the same number of moles of sodium cyanide as cyclopentanone).

a. Show the mechanism for the reaction, using curved arrows in each step.
b. Comment on how the use of methanol *as a solvent* (rather than just adding an equimolar amount of methanol) would influence the direction of equilibrium for the final protonation step.

Answer

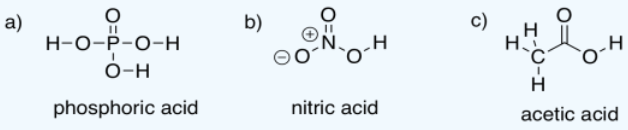


Exercise 3.27.3

Provide structures for the following acids. They are moderately strong acids, but not as commonly used in this context as hydrochloric and sulfuric acid. Note that, like sulfuric acid, they all contain polar OH groups.

a) phosphoric acid, H_3PO_4 b) nitric acid, HNO_3 c) acetic acid, CH_3CO_2H

Answer



Sometimes, weak acids are used to protonate the alkoxide intermediate. These acids are more acidic than water, so the equilibrium in the protonation reaction lies more towards the alcohol side. However, because they are only weak acids, they are safer and easier to work with than strong acids. Commone examples include ammonium chloride and sodium bicarbonate.

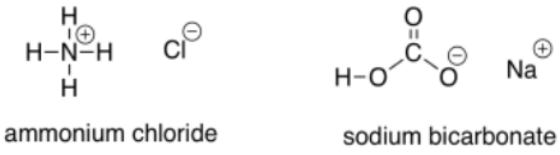


Figure 3.27.3:

Exercise 3.27.4

What factor makes each of these compounds mildly acidic?

Answer

Ammonium chloride has an N-H bond, normally less polar than the O-H bond of water. However, the positive charge makes this compound give up a proton more easily, because it results in a neutral (uncharged) ammonia molecule.

Sodium carbonate has a polar O-H bond, just like water. However, the anion that results from loss of a proton is resonance-stabilised. That makes this compound more acidic than water.

Exercise 3.27.5

Problem CO8.5.

Fill in the product or reagent for each of the following transformations. Remember there is always an acidic workup assumed.

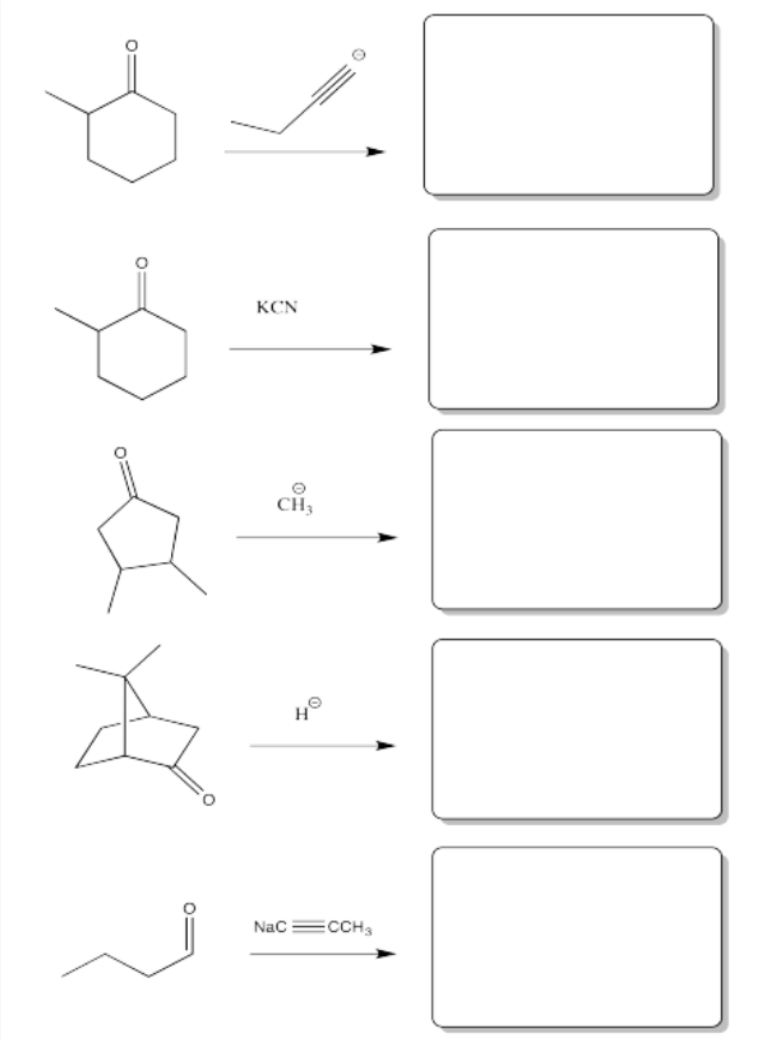


Figure 3.27.4:

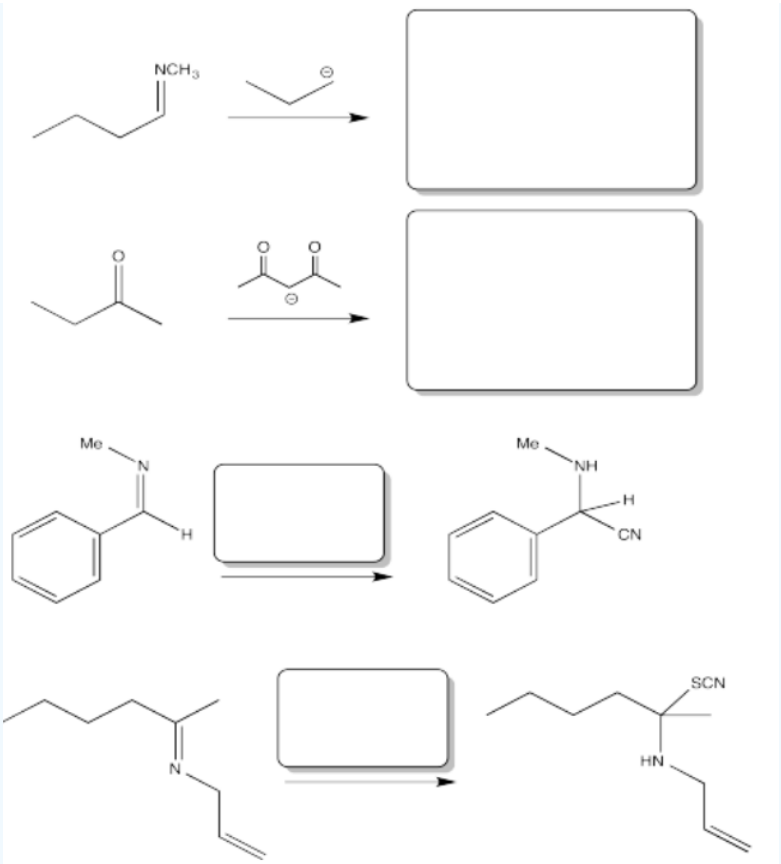
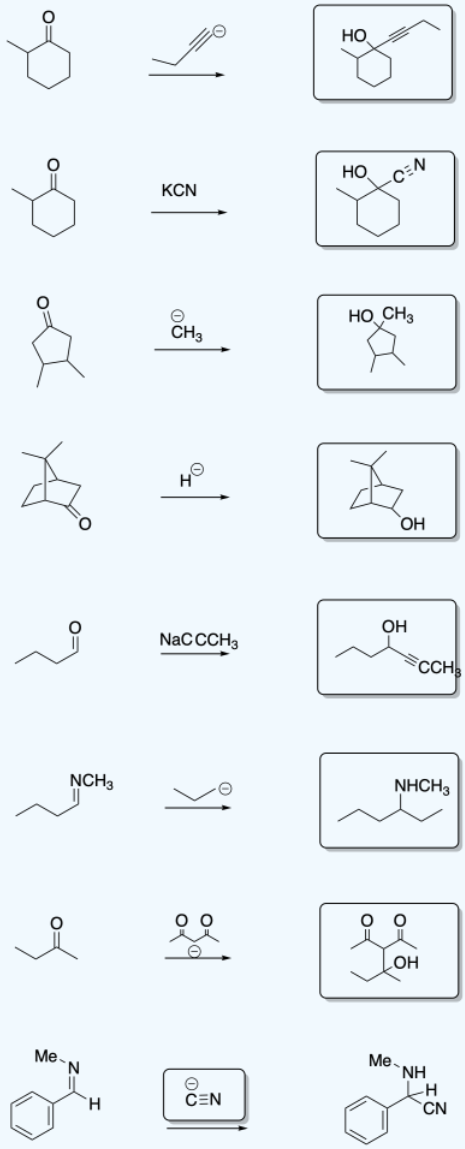


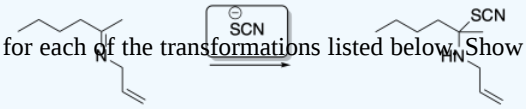
Figure 3.27.5:

Answer



Exercise 3.27.6

Draw a mechanism with curved arrows for each of the transformations listed below. Show all intermediates. Assume an acidic workup.



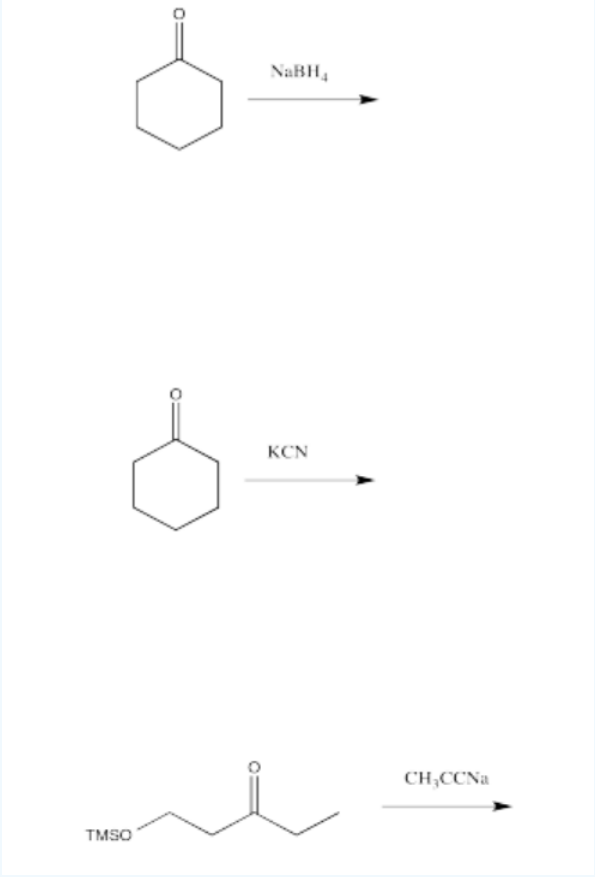


Figure 3.27.6:

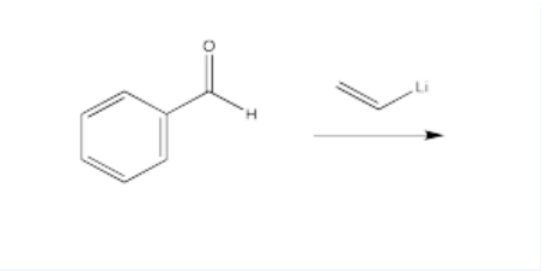
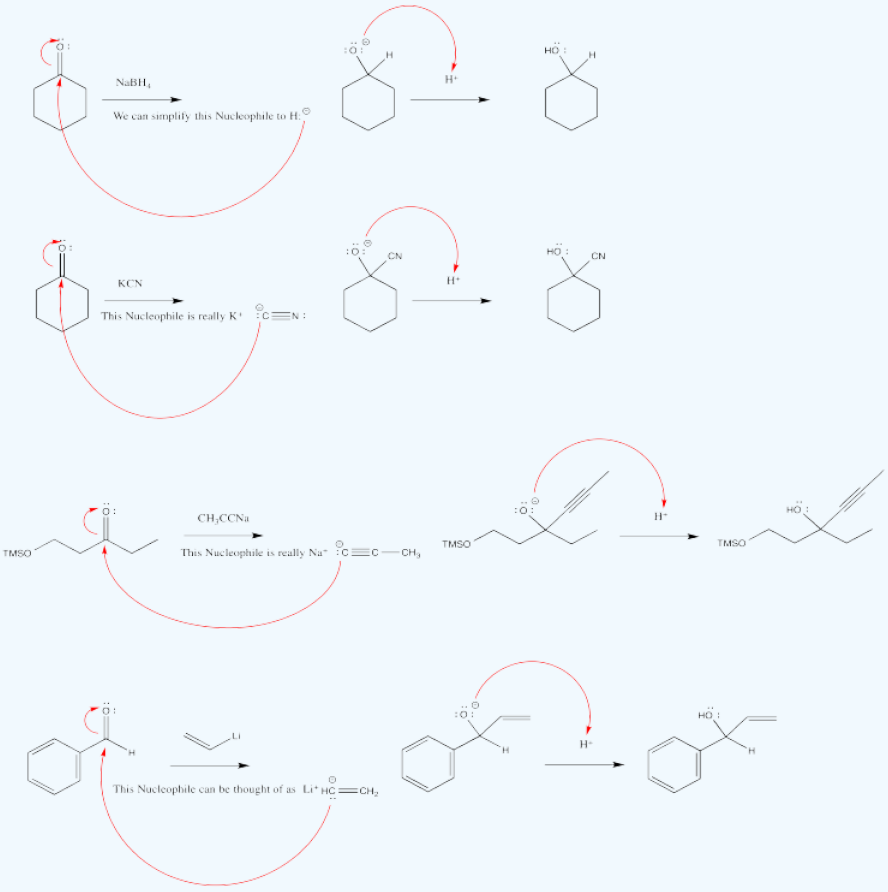


Figure 3.27.7:

Answer



3.28: What is a Nucleophile?

Lots of things can be nucleophiles. In principle, a nucleophile only needs a lone pair. However, some nucleophiles are better than others.

You already know something about nucleophiles if you know something about acidity and basicity. Nucleophiles are really Lewis bases. Some of the factors that account for basicity also account for nucleophilicity.

Halides are not very good nucleophiles for carbonyls. The negative charge on a halide is pretty stable, either because of electronegativity or polarizability. If a halide donates to a carbonyl, producing an oxygen anion, the reaction is uphill.

Hydroxide and alkoxide anions (such as CH_3O^-) are more reactive than halides. They are better nucleophiles. The sulfur analogues are similarly good nucleophiles (such as CH_3S^-). In addition, water, alcohols and thiols are nucleophilic, because they all have lone pairs that could be donated to an electrophile.

Nitrogen also has a lone pair in most compounds. That means amines are good nucleophiles, too.

Carbon does not normally have a lone pair, unless it is a carbanion. Carbanions are usually not very stable. As a result, they are not very common, except for cyanide (CN^-) and acetylides (RCC^-, in which R is a hydrogen or an alkyl group). However, when carbon does have a lone pair (and a negative charge), it is a good nucleophile. Because carbon is less electronegative than other elements with lone pairs, it is able to donate its lone pair easily.

Carbon nucleophiles add to carbonyls because that less stable carbon anion is traded for a more stable alkoxide anion. The reaction is downhill energetically.

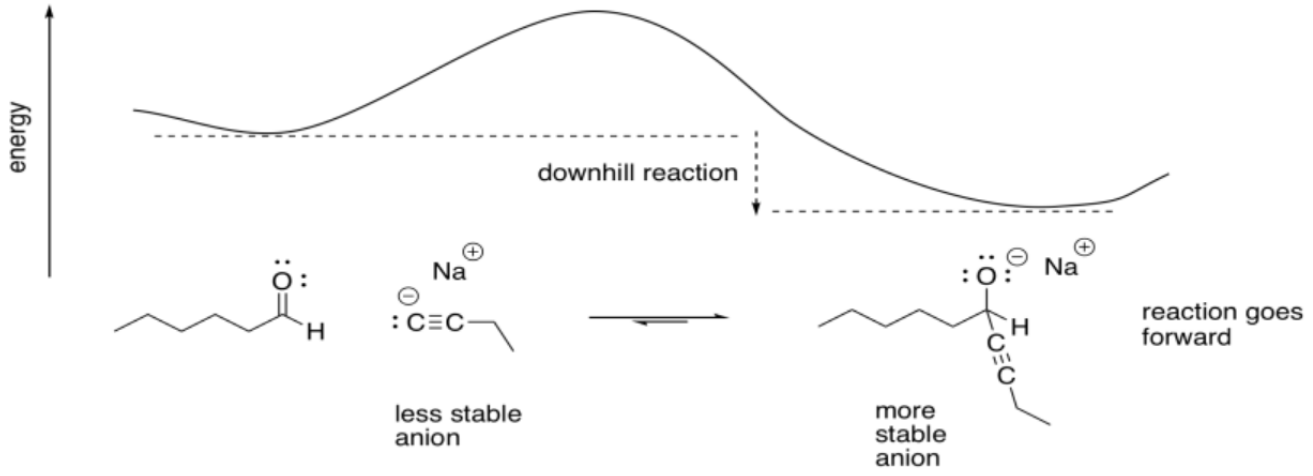


Figure 3.28.1:

Exercise 3.28.1

Carbanions such as CH_3^- (methyl anion) are very unstable and highly reactive. Explain why the following anions are more stable than a methyl anion.

a. Acetylide, HCC^-
b. cyanide, CN^-

Answer a

In acetylide, the lone pair is on a linear carbon or sp carbon. In methyl anion, the lone pair is on a tetrahedral carbon or sp^3 carbon. The description "sp" indicates that sigma bonding to neighbors involves a 2s orbital and a 2p orbital on carbon; there is a 50% contribution from the s orbital.

The description "sp^3", on the other hand, indicates that sigma bonding to neighbors involves a 2s orbital and three 2p orbitals; there is a 25% contribution from the s orbital.

The 2s orbital is lower in energy than the 2p orbital. The greater the s orbital contribution to the bond (or in this case to the lone pair), the lower it is in energy. Thus, a lone pair on an sp carbon is lower in energy than a lone pair on an sp^3 carbon.

Answer b

In cyanide, the same argument outlined in part (a) hold true. In addition, the nearby electronegative nitrogen stabilizes the charge by drawing electron density toward itself.

Other nucleophiles, such as halides, do not proceed. They are going uphill, from a more stable halide ion to a less stable alkoxide ion.

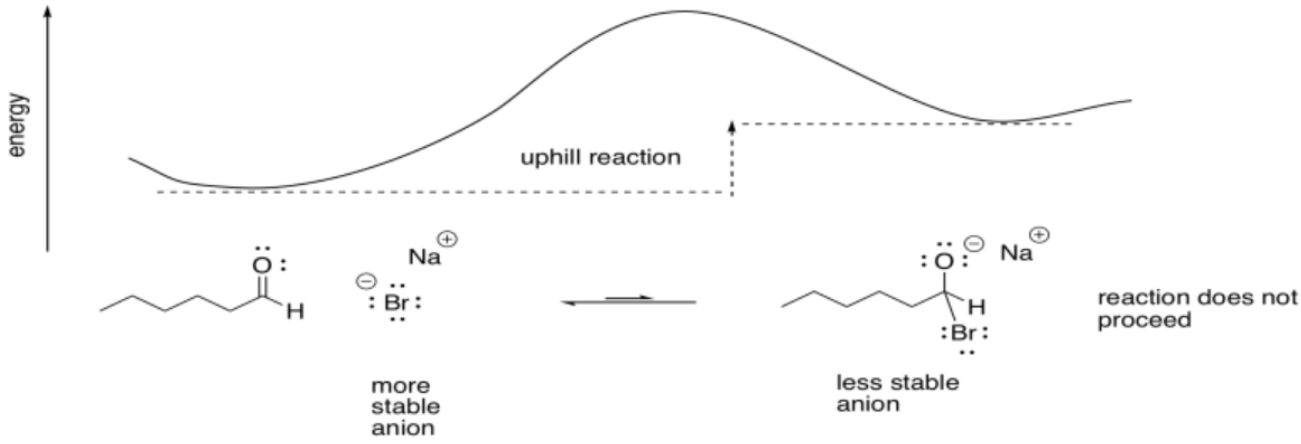


Figure 3.28.2:

If the nucleophilic atom were an oxygen anion, there might be an equilibrium. The reaction would be neither uphill nor downhill. It would result in a mixture of the original reactants and the new products.

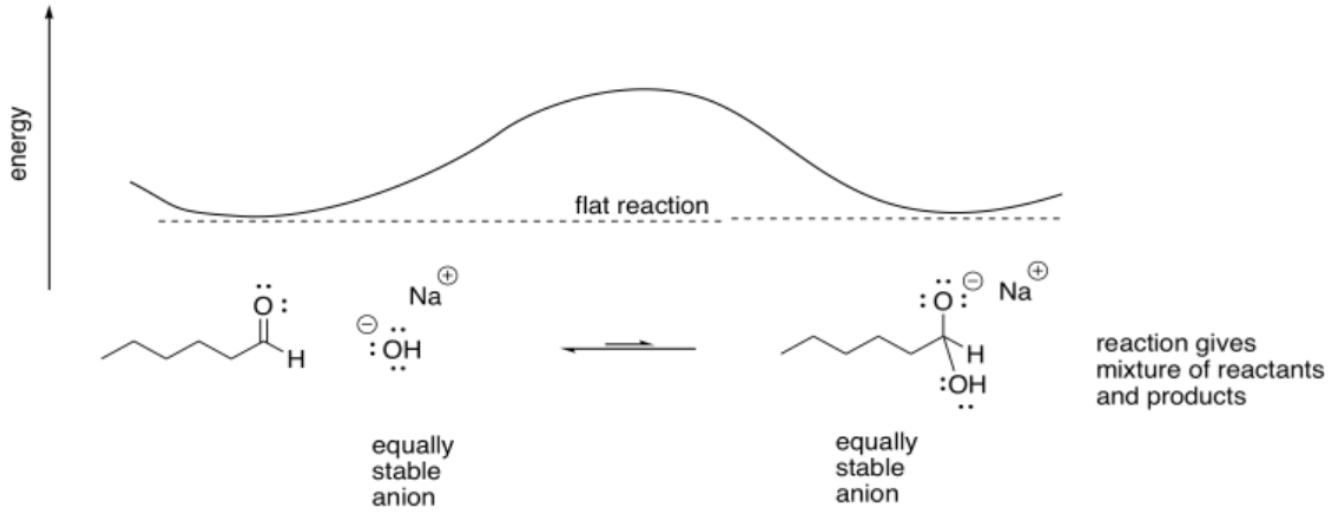


Figure 3.28.3:

Exercise 3.28.2

Nucleophilicity is the degree of attraction of a nucleophile to a positive charge (or partial positive charge). It is related to basicity. Choose the most nucleophilic item from each of the following pairs, and explain your answer.

a. CH_3OK or CH_3OH
b. CH_3OH or CH_3NH_2
c. NaCN or NaCCH
d. c-$C_6H_{11}ONa$ or c-C_6H_5ONa (c- in this case means "cyclo")

Answer a

CH_3OK, because of the ionic O-K bond. This is an anionic nucleophile. It is more reactive and nucleophilic than the corresponding neutral nucleophile.

Answer b

CH_3NH_2, because nitrogen is less electronegative than oxygen. Its lone pair is held less tightly and is more easily donated to the electrophile.

Answer c

NaCCH, because the neighbouring carbon in this case does not have the inductive electron-withdrawing effect that the nitrogen does in the case of NaCN. In that case, the lone pair is stabilized and made less reactive.

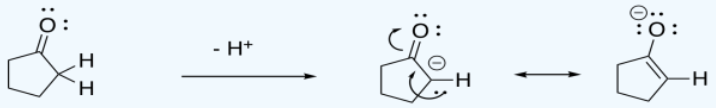
Answer d

c-$C_6H_{11}ONa$, because the negative charge is localized on one atom. In c-C_6H_5ONa, the negative charge is delocalized over four different positions in the molecule. Delocalization of charge stabilizes the anion and makes it less reactive.

Exercise 3.28.3

Carbonyl compounds such as aldehydes and ketones contain a very slightly acidic hydrogen next to the carbonyl. Some nucleophiles are basic enough to remove that proton instead of donating to the carbonyl. Show why the resulting anion is stable, using cyclopentanone as an example.

Answer



The resulting anion is stabilised by resonance.

Exercise 3.28.4

Accidental deprotonation (proton removal) alpha to a carbonyl (one carbon away from the carbonyl) can occur when a nucleophile is added to a ketone. One reason the proton might be taken instead is if the carbonyl is too crowded for the nucleophile to reach.

In the following cases, explain which nucleophile is more likely to add to the carbonyl in cyclohexanone and which is more likely to deprotonate it.

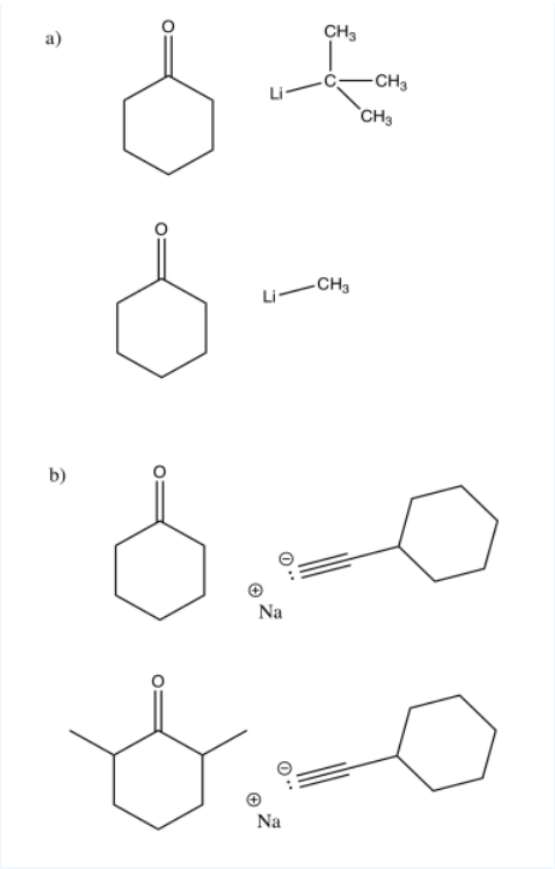
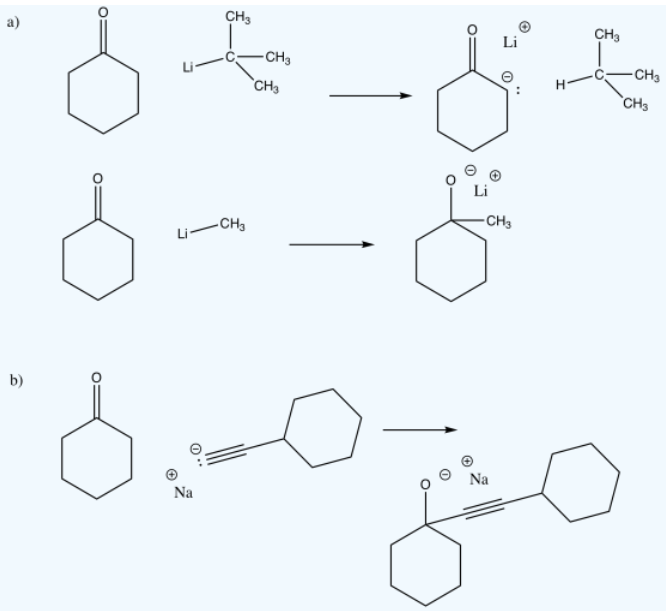
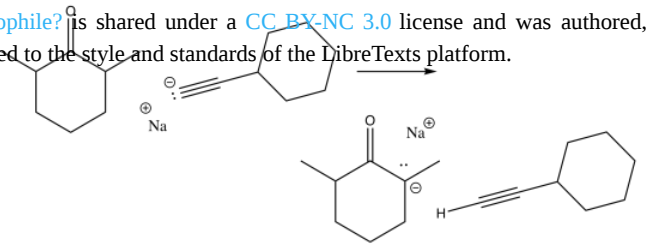


Figure 3.28.4:

Answer

The case with more steric crowding is more likely to result in deprotonation.





CHAPTER OVERVIEW

4: Insertion

4.1: Introduction

Insertions constitute a class of reactions involving transition metals. These reactions are important in some industrial processes that are catalyzed by transition metals. One of the most important processes that involves these reactions is hydroformylation. Hydroformylation is used to convert unsaturated hydrocarbons into aldehydes. These long-chain aldehydes are then converted into important commodities, such as detergents and fragrances.

There are two basic kinds of insertions: migratory insertions (or 1,1-insertions, more generally) and beta-insertions (or 1,2-insertions).

- Migratory insertions are related to the addition of nucleophiles to carbonyls.
- Migratory insertions involve transition metal compounds that bind to a carbon monoxide.
- The transition metal is bound to another group, such as an alkyl group or a hydride.
- The alkyl or hydride is transferred from the metal to the carbon of the bound carbon monoxide (figure 4.1.1).

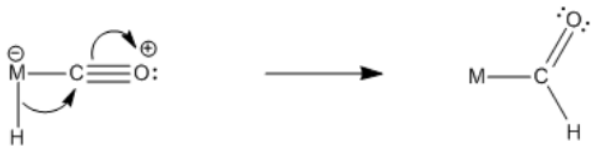


Figure 4.1.1: A general migratory insertion (or 1,1-insertion) reaction.

The other type of insertion, 1,2-insertion, often involves alkenes, or other ligands that can bind to a metal through two atoms instead of just one (Figure 4.1.2).

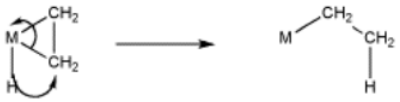


Figure 4.1.2: A general 1,2-insertion of an alkene.

Note that, in transition metal chemistry, formalisms are often used differently than in simple main group compounds involving carbon, oxygen and nitrogen..

- Sometimes, formal charges are not shown.
- Non-bonding electrons on metals are rarely shown.

Structures are often complicated enough that it becomes difficult to draw all the non-bonding electrons and formal charges and still have a clear picture. People who work in this area will keep count of electrons in their head, although they will frequently jot down the electron count on the metal beside the structure in order to keep track.

4.2: CO Binding

Migratory insertion involves the transfer of a hydride or alkyl group from a metal to a bound carbon monoxide. Because this reaction specifically involves bound carbon monoxide, we should take a look at how CO binds to transition metals. We should begin by reviewing the Lewis structure of carbon monoxide.

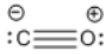


Figure 4.2.1: The Lewis structure of carbon monoxide.

Note the lone pair on carbon monoxide. It is a potential Lewis base or nucleophile. For a number of reasons, transition metals are almost always electrophiles: they are often positively charged ions, but in general they have an 18-electron octet that is difficult to fill, so they frequently need more electrons.

- Lewis: CO is a two electron donor
- Transition metals are electrophiles
- CO binds to metal atoms or ions
- The carbon is the usual donor atom; it has a lone pair and a negative formal charge

The donation of an electron pair to a metal cation is shown in figure 4.2.2.

Figure 4.2.2: Binding of CO to a metal cation.

Remember, because the 18-electron rule for transition metals makes them electrophilic, the electron pair does not need a positive charge to attract it (figure 4.2.3).

Figure 4.2.3: CO binding to a neutral metal atom.

Frequently, the formal charges and lone pairs are not even shown in the transition metal compound, because of the complexity of the picture.

Figure 4.2.4: A more commonly used picture of CO binding leaves out the formal charges.

Note that CO in the context of metal complexes is often referred to as carbonyl. For example, $Cr(CO)_6$ is called hexacarbonyl chromium.

Exercise 4.2.1

Draw structures for the following metal carbonyl compounds. For each compound, indicate

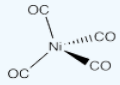
i) the electron count at the metal in the complex (show your work)

ii) the geometry at the metal

a. tetracarbonyl nickel, $Ni(CO)_4$
b. pentacarbonyl iron, $Fe(CO)_5$
c. hexacarbonyl chromium, $Cr(CO)_6$
d. tetracarbonyl cobalt anion, $Co(CO)_4^-$
e. tetracarbonyl cobalt hydride, $Co(CO)_4H$
f. octacarbonyl cobalt, $Co_2(CO)_9$ (there is a bond between the two cobalt atoms)

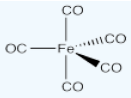
Answer

a)



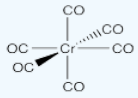
electrons on metal atom: 10
charge on metal: none
electrons on atom / ion: 10
electrons donated by ligands: 2 x 4 = 8
total: 18

b)



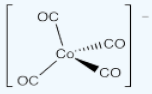
electrons on metal atom: 8
charge on metal: none
electrons on atom / ion: 8
electrons donated by ligands: 2 x 5 = 10
total: 18

c)



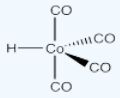
electrons on metal atom: 6
charge on metal: none
electrons on atom / ion: 6
electrons donated by ligands: 2 x 6 = 12
total: 18

d)



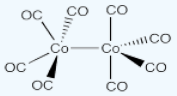
electrons on metal atom: 9
charge on metal: -1
electrons on atom / ion: 10
electrons donated by ligands: 2 x 4 = 8
total: 18

e)



electrons on metal atom: 9
charge on metal: +1
electrons on atom / ion: 8
electrons donated by ligands: 2 x 5 = 10
total: 18

f)

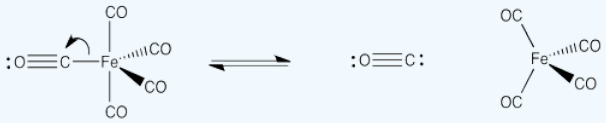


electrons on metal atom: 9
charge on metal: none
electrons on atom / ion: 9
electron donated from other metal 1
electrons donated by ligands: 2 x 4 = 8
total: 18

Exercise 4.2.2

Draw, with structures and arrows, the equilibrium between pentacarbonyl iron and tetracarbonyl iron, $Fe(CO)_4$ plus carbon monooxide.

Answer



An important aspect of CO binding is called "back-donation". In back-donation, not only does the ligand donate electrons to the metal, but the metal also donates to the ligand. We can think of the CO as donating a pair of electrons from a carbon-based orbital into an empty orbital on the metal, such as a p orbital (figure MI2.5). The metal has d orbitals that have good symmetry overlap with the pi antibonding orbitals in the CO. Electron density can be donated from a metal d orbital into the pi* level (figure MI2.6). Thus, binding to a metal actually weakens the CO bond because a pi* orbital receives electron density from the metal.

- MO picture: donation from carbon-based orbital into vacant metal p orbital
- MO picture, part 2: donation from occupied metal d orbital into CO pi* orbital
- this interaction weakens the C-O multiple bond

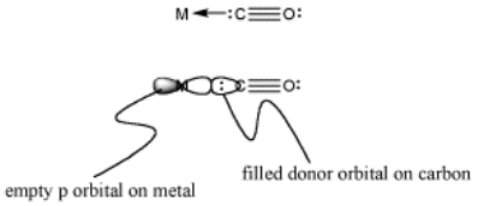


Figure 4.2.5: Donation from CO to metal in qualitative molecular orbital terms.

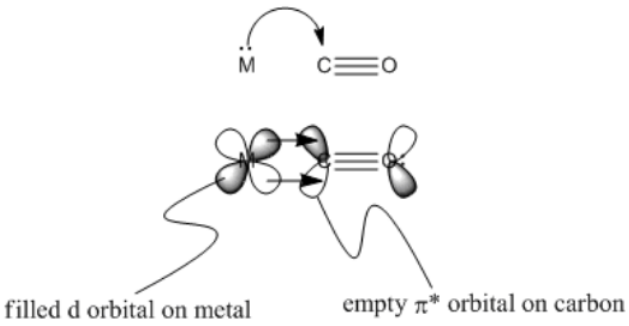
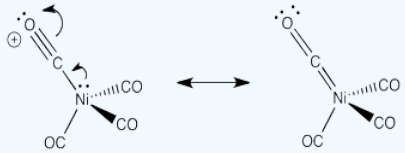


Figure 4.2.6: Donation from metal to CO in qualitative molecular orbital terms.

Exercise 4.2.3

Draw a Lewis structure that takes into account the effect of metal-to-carbonyl electron donation in tetracarbonyl nickel.

Answer



Exercise 4.2.4

Infrared spectroscopy is often used to assess bond order between specific atoms within a molecule. Because stretching frequencies are proportional to bond strength, a comparison of frequencies from a bond one molecule to a similar bond in another can give insight into the bond orders in each case.

a. A C-O bond in organic compounds shows up between 1000-1200 cm^{-1} in most cases. A C=O bond normally shows up near 1600-1700 cm^{-1}. Explain why these two bonds give rise to two different stretching frequencies.
b. Based on the Lewis structure, what do you predict for this bond frequency in a CO molecule?
c. What will happen to the CO stretching frequency in carbon monoxide if the molecule binds to a palladium atom?

Exercise 4.2.5

Explain the differences in CO stretching frequencies in the following pairs of compounds. (Note: the *number* of peaks is related to molecular symmetry and group theory; focus only on the difference in magnitude of the frequency.)

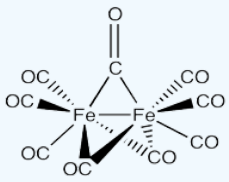
a. CO at 2143 cm^{-1} vs. $Mo(CO)_6$ at 2004 cm^{-1}.
b. $Ni(CO)_4$ at 2060 cm^{-1} vs. $Fe(CO)_4^{2-}$ at 1790 cm^{-1}.
c. $Cr(CO)_6$ at 2000 cm^{-1} vs. $Mn(CO)_6^{+}$ at 2090 cm^{-1}.
d. $(PF_3)Mo(CO)_3$ at 2055 & 2090 cm^{-1} vs $(PPh_3)Mo(CO)_3$ at 1835 & 1934 cm^{-1}.
e. $Cr(CO)_6$ at 2000 cm^{-1} vs. $(C_6H_5CH_3)Cr(CO)_3$ at 1963 and 1869 cm^{-1}.

Exercise 4.2.6

Sometimes, carbonyls can bridge between two metals. For example, the iron cluster Fe2(CO)9 contains six "terminal" carbonyls, bound to only one iron each, and three "bridging" carbonyls, each of which is bound to both iron atoms. This complex also features a metal-metal bond.

a. draw a structure for this compound.
b. explain why the terminal carbonyls display stretching frequencies of 2082 and 2019 cm^{-1}, but the bridging carbonyls display a stretching frequency of 1829 cm^{-1}.

Answer



"Organic" carbonyls, such as aldehydes and ketones, can also bind to transition metals, as you may have seen before. These compounds bind to transition metals in a very different way than carbon monoxide. Normally, we think of them as simple lone pair donors. The oxygen lone pair donates to the metal atom or ion. The resulting complexes are important because the carbonyl becomes "activated" or ready to accept nucleophiles.

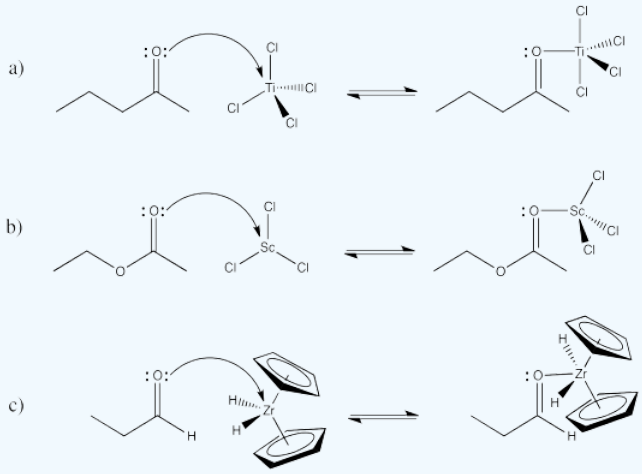
- Organic carbonyls can also bind to metal atoms or ions.
- Binding is usually via the heteroatom.

Exercise 4.2.7

Draw, with arrows, the coordination of the following organic carbonyl compounds to metal complexes.

a. 2-pentanone with $TiCl_4$.
b. ethyl acetate with $ScCl_3$.
c. propanal with Cp_2ZrH_2 (Cp = cyclopentadienyl anion, $C_5H_5^-$).

Answer



4.3: Hydride and Alkyl Migratory Insertions

Migratory insertion is a term to describe the transfer of a ligand from a metal to a carbon monoxide that is also bound to the metal. It is a special case of a 1,1-insertion. In a 1,1-insertion, a group is transferred from a metal to an atom attached to the same metal. A general 1,1-insertion is shown in figure 4.3.1.

Figure 4.3.1: A general 1,1-insertion. Formal charges would vary according to the specific groups X, Y and Z.

At the end of the 1,1-insertion, the ligand Z has attached to the 1st atom in the next ligand attached to the metal.

Carbonyl groups in organic compounds are electrophilic. The polar carbon-oxygen double bond places positive charge on the carbon, so the carbon atom attracts nucleophiles. One of the nucleophiles that can react with a carbonyl is a complex hydride, such as a borohydride ion or an aluminum hydride ion. Sometimes, these complex hydrides are anionic, making them more nucleophilic. An example is sodium borohydride, $NaBH_4$. Sometimes, the hydride compound is neutral, as in BH_3. However, the hydride is still nucleophilic even if the compound is not negatively charged, because of the electronegativity difference between the hydrogen and the boron (or the aluminum). A hydride ion is donated as a nucleophile to the electrophilic carbonyl. Transition metal hydrides, like boron and aluminum hydrides, are frequently nucleophilic. They can donate hydrides to electrophiles.

- A hydrogen attached to a metal atom frequently acts like a hydride.
- A nucleophilic hydride can donate to a carbonyl carbon.

Figure 4.3.2: CO binding to a metal ion.

"Inorganic carbonyls", or metal-bound CO compounds, behave in many ways like organic carbonyl compounds. In one sense, the bound CO can be thought of as having a positive formal charge on the oxygen, so it is easy to imagine it as an electrophile. It looks like an "activated" organic carbonyl (for example, a ketone that has been protonated, and has a positively charged oxygen). If a metal has a hydride attached to it (a nucleophile) as well as a CO (an electrophile), then a reaction can occur between them. The hydride can add to the carbonyl. This is one of the most useful things about transition metal chemistry: by binding different, reactive ligands, metals can organize reactants so that they react together.

- This reaction can occur intramolecularly; i.e. from a hydride to a carbonyl on the same metal.
- This event is called a migratory insertion.

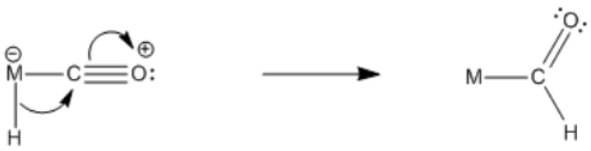


Figure 4.3.3: A metal hydride reacting with a carbonyl bound to the same metal.

Note that the metal does not have to be anionic for the hydride to act as a nucleophile. The electronegativities of transition metals vary from about 1.0 to 1.75, but the electronegativity of hydrogen is about 2.2. Hydrogen is more electronegative than the transition metals, and so a hydrogen attached to a transition metal is usually nucleophilic.

This reaction, migratory insertion of a hydride to a carbonyl, forms a metal "formyl" compound. The "formyl" is the CH=O group attached to the metal. Migratpry insertions can also take place with metal alkyls. Metal alkyls are also nucleophilic, just like metal hydrides. The alkyl carbon is usually more electronegative than the attached transition metal, so it has a partial negative charge.

- Nucleophilic alkyl groups can also undergo migratory insertion reactions.

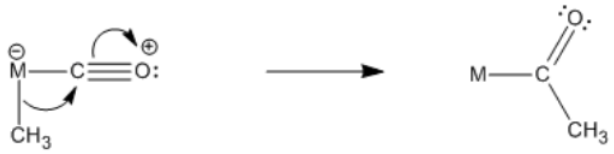


Figure 4.3.4: A migratory insertion reaction, this time forming an acyl compound.

In fact, migratory insertion to a carbonyl is actually much more common with alkyl ligands than it is with hydrides. Conceptually, the reactions are very similar. The reason alkyl migrations are much more common has to do with relative bonds strengths in the reactants compared to the products of the reaction.

Migratory insertion is industrially important. It is used in the manufacture of things many of us use every day. For example, the main component of body wash. sodium laureth sulfate and related compounds, is synthesized via a key hydroformylation process. The catalyst used for hydroformylation varies from one application to another and from one company to another. In the case of soap synthesis, a rhodium catalyst is usually employed.

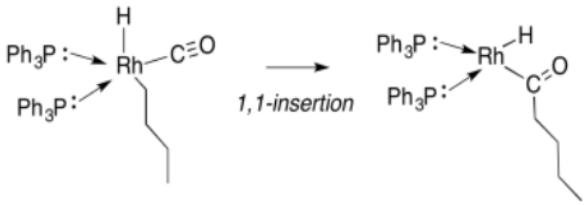


Figure 4.3.5:

Hydroformylation results in an alkene chain being lengthened by one carbon, with an aldehyde at the end of the chain. Overall, it results in the addition of a aldehyde fragment (CHO) to one end of the alkene double bond and a hydrogen atom the the other. A few additional steps are needed to extend the resulting aldehyde and cap the chain with a polar sulfonate group. Of course, the compound works by forming micelles when suspended in water. Those long tails gather together, with the polar heads interacting with the water. Stuff that won't wash off with plain water because it isn't polar enough to dissolve in water may instead dissolve among the soapy tails of the sodium laureth sulfate molecules.

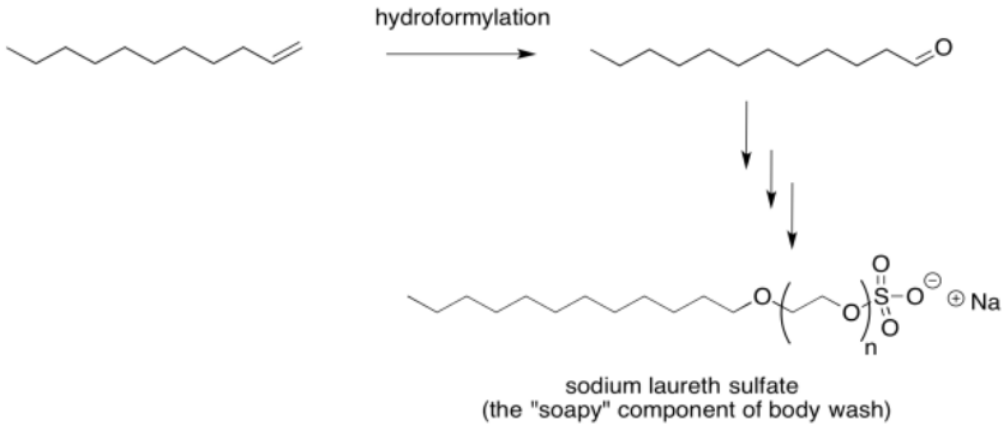


Figure 4.3.6:

? Exercise 4.3.1

Explain why a coordinated carbon monoxide acts as an electrophile.

? Exercise 4.3.2

Draw, with arrows, the reaction to give the 1,1- insertion products in the following cases.

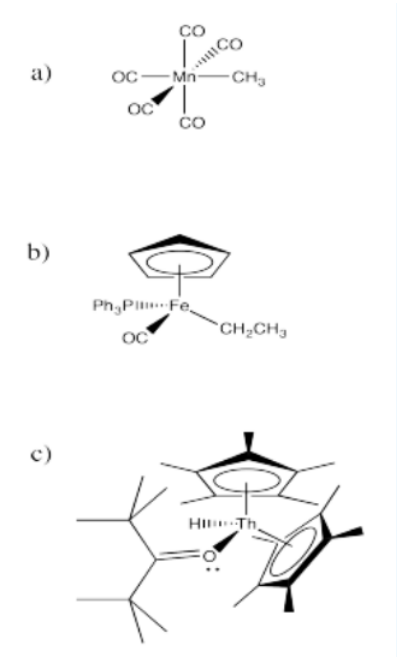
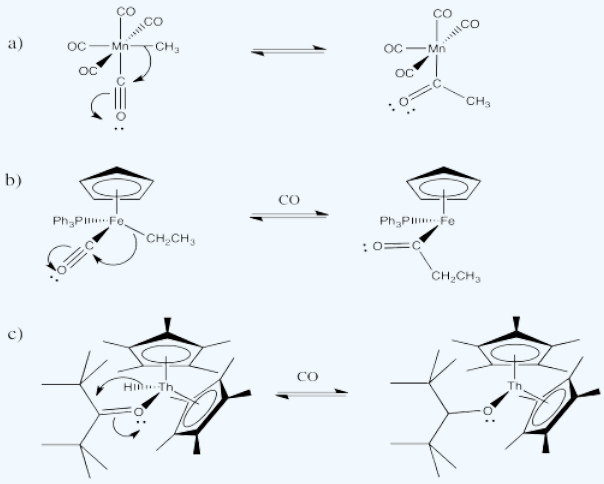


Figure 4.3.7:

Answer



Exercise 4.3.3

Binding or coordination to a metal may also occur with organic carbonyl compounds such as ketones, aldehydes, esters and so on.

a. Explain why a coordinated carbonyl compound, such as propanal, can be especially electrophilic.
b. Compare and contrast the electrophilicity of a coordinated organic carbonyl with the electrophilicity of coordinated carbon monoxide. What atom is the electrophile in each case? What will happen if a nucleophile donates electrons in each case?

Exercise 4.3.4

Provide products of the following migration reactions.

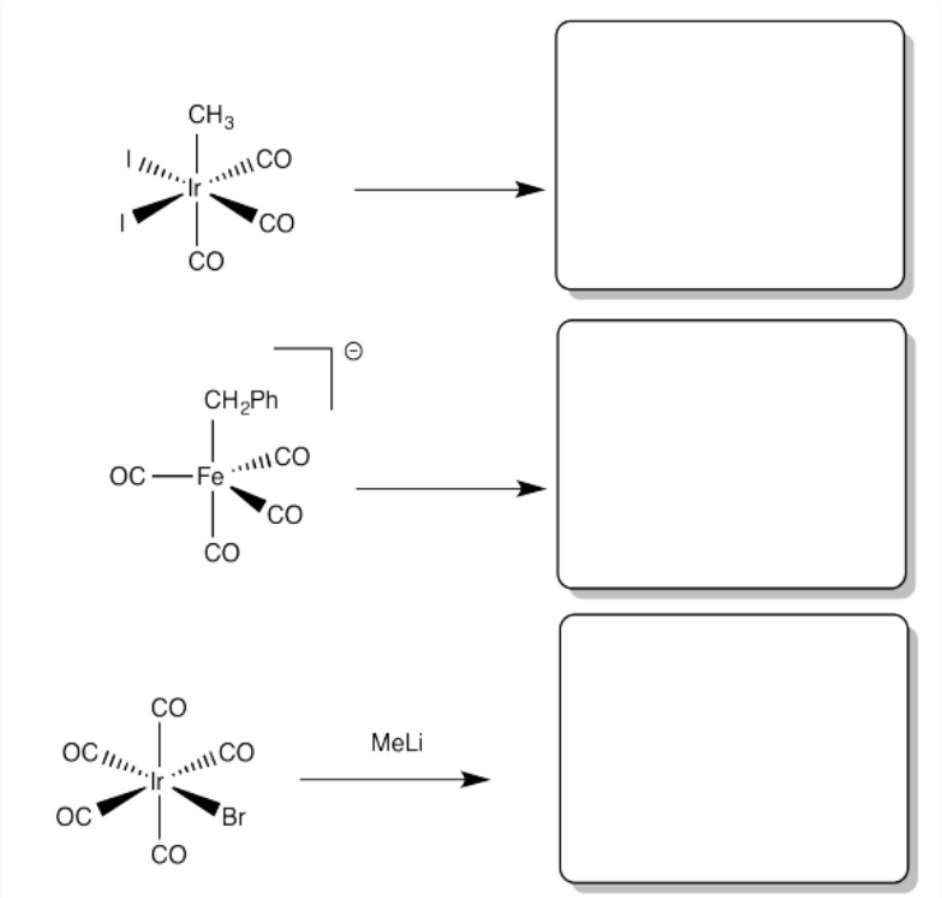


Figure 4.3.8:

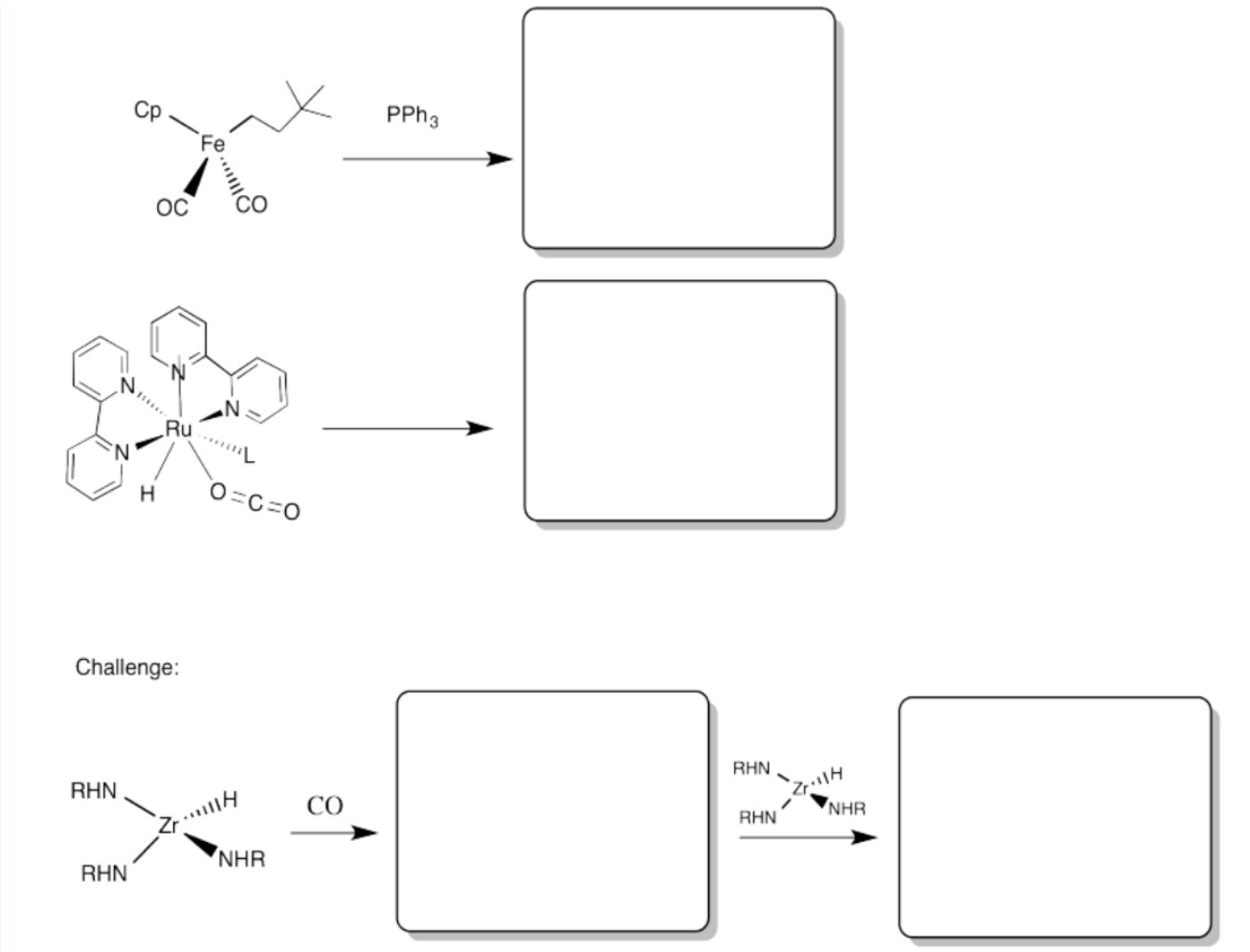
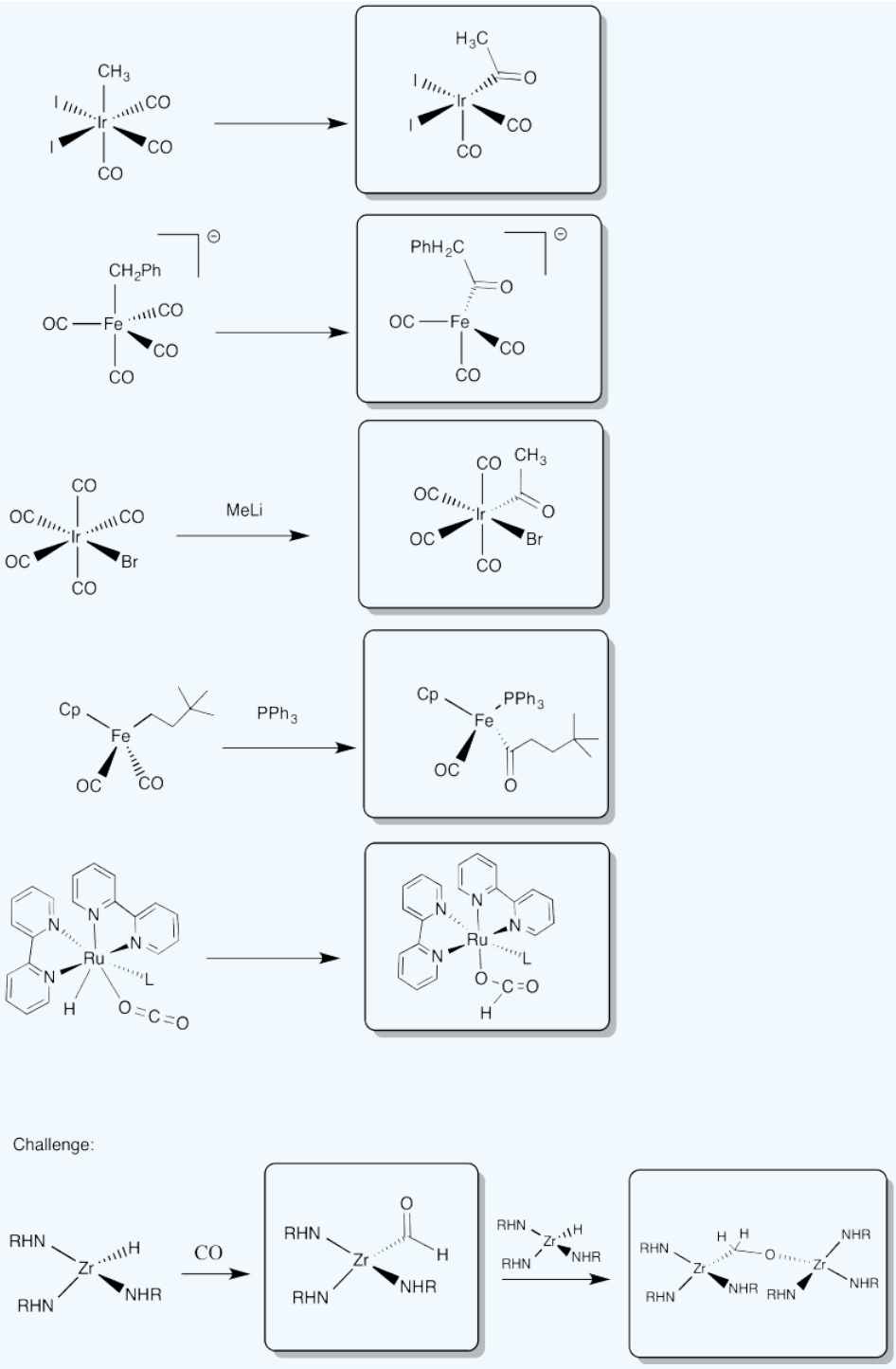


Figure 4.3.9:

Answer



Exercise 4.3.5

Provide the products of the following migration reactions.

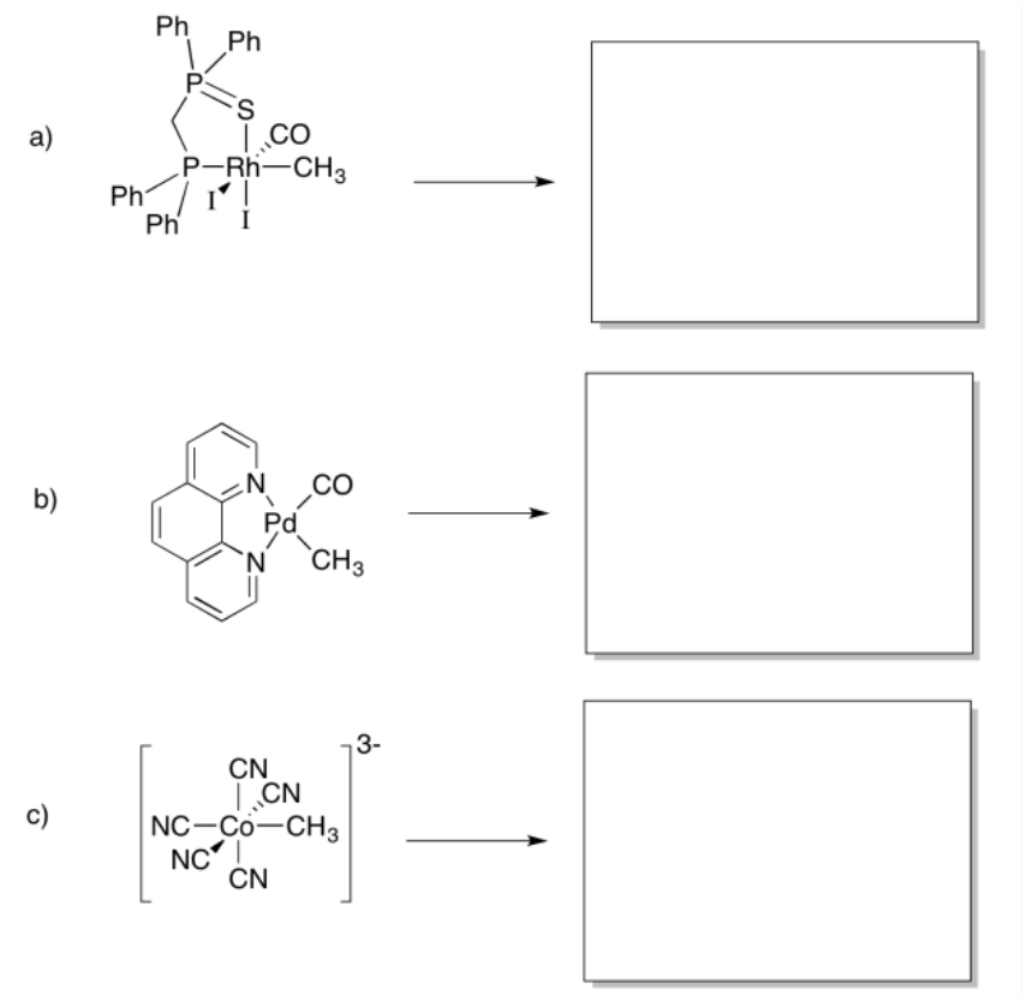


Figure 4.3.10:

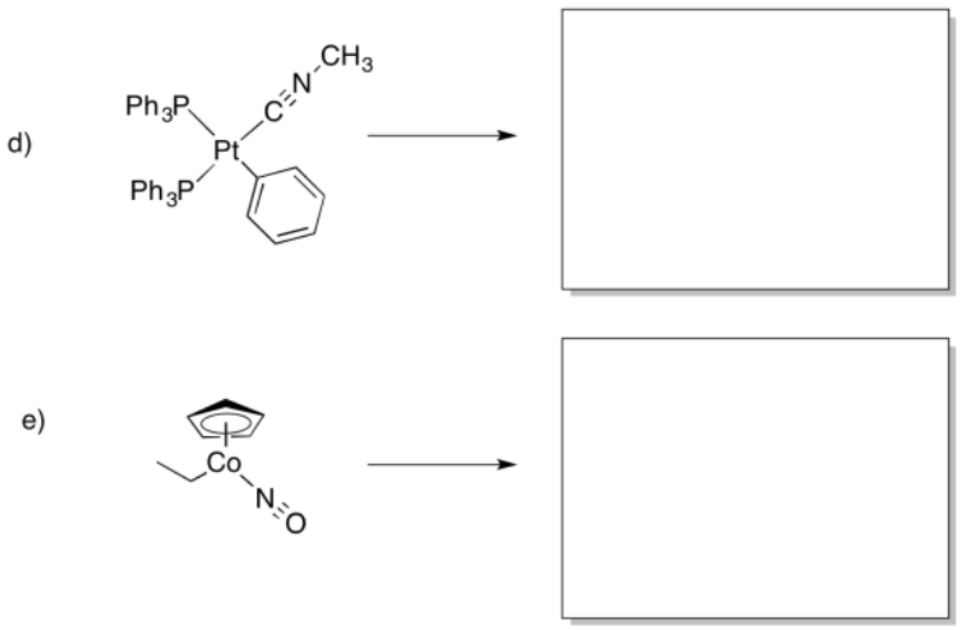
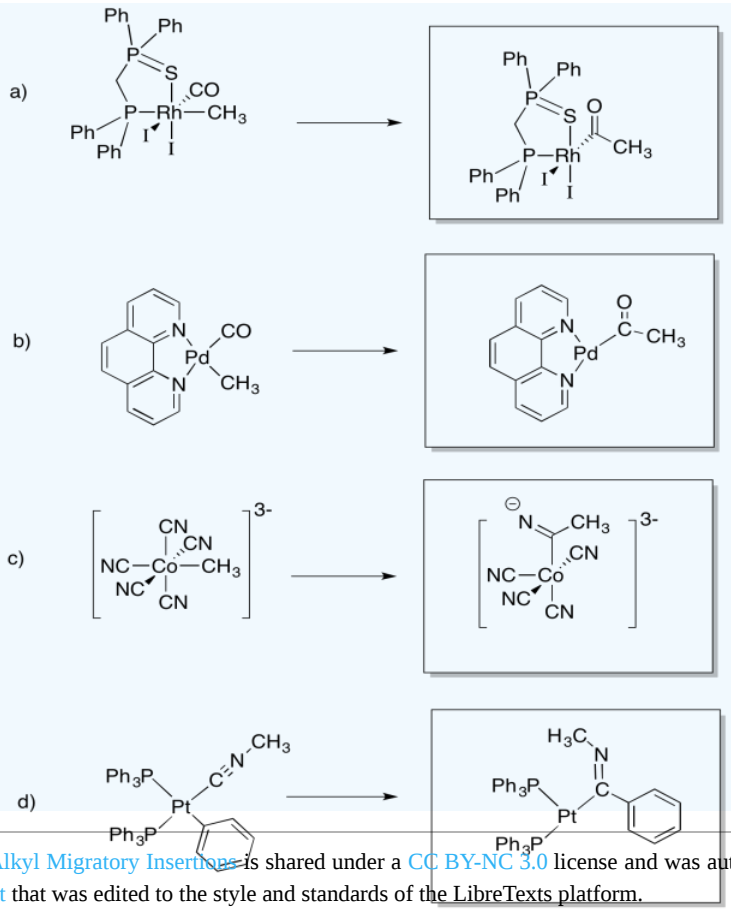


Figure 4.3.11:

Answer



4.4: β-Hydride Insertion and Beta-Hydride Elimination

Like a coordinated carbon monoxide molecule, a coordinated organic carbonyl is also electrophilic. This time, the oxygen can be thought of as having a formal positive charge because it is donating a lone pair to a metal.

Figure 4.4.1: Activation of an organic carbonyl by a metal ion.

Consequently, the carbonyl is activated. It becomes a better electrophile and is more likely to undergo an addition reaction, if there are any nucleophiles nearby that are able to donate a pair of electrons.

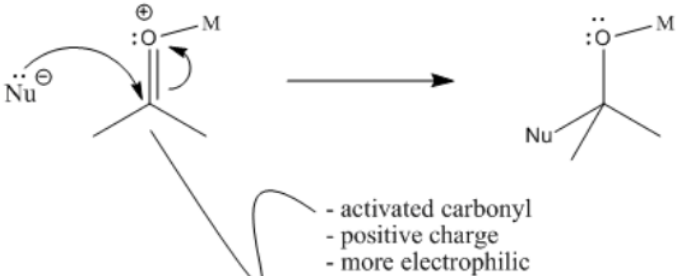


Figure 4.4.2: Coordination of an organic carbonyl to a metal ion makes the carbonyl more reactive towards nucleophiles.

A hydride attached to the metal can donate to the carbonyl. Remember, the hydride is nucleophilic, because the hydrogen atom is always more electronegative than a transition metal. Even the most electronegative transition metal, mercury, only has a Pauling electronegativity of 1.9, compared to 2.2 for hydrogen. When a hydride moves to the carbonyl from the metal, the carbonyl is turned into an alkoxide ligand.

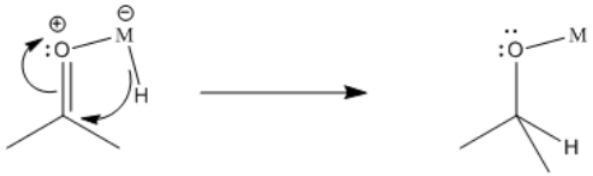


Figure 4.4.3: The intermolecular reaction of a coordinated organic carbonyl with a coordinated nucleophile.

Notice that there is a difference between migratory insertion, or 1,1-insertion, and this beta-insertion, which is sometimes called a 1,2-insertion. Unlike migratory insertion, the nucleophile does not move to the atom attached to the metal. The nucleophile moves to the *second* atom away from the metal: the 2 position or the beta position.

Furthermore, beta-insertions of hydride ligands are easily reversible. An alkoxide ligand attached to a metal can easily lose a beta hydrogen and become a ketone or aldehyde.

Figure 4.4.4: The reverse of a 1,2-addition is a 1,2-elimination.

- In this case, the insertion can be reversible.
- The reverse of an insertion is called a 1,2-elimination or a beta-elimination.

The Greek lettering refers to the number of atoms away from the metal. The first atom attached to the metal is called the alpha position. A hydrogen on that atom is called an alpha hydrogen. The next atom along the chain is called the beta position. The third

atom along the chain is the gamma position. A hydrogen attached to the beta position can undergo 1,2-elimination or beta-elimination.

- elimination leads to formation of a double bond.
- The double bond forms between the alpha and the beta position.

This nomenclature can be confusing because a carbonyl compound already has an alpha position and a beta position. The position is the carbonyl carbon and the position is the carbon next to the carbonyl. This Greek lettering system is a general way of designating positions and it is used in a number of different contexts; you need to be able to decide which context fits. If elimination is occurring, then the term, position, may mean one thing. If enolate formation is occurring, then the term, position, means something else.

Exercise 4.4.1

Problem MI4.1.

In the following structures, identify any alpha, beta or gamma positions on the groups attached to the metal. In each case, show the potential products of 1,2-elimination of hydrogen.

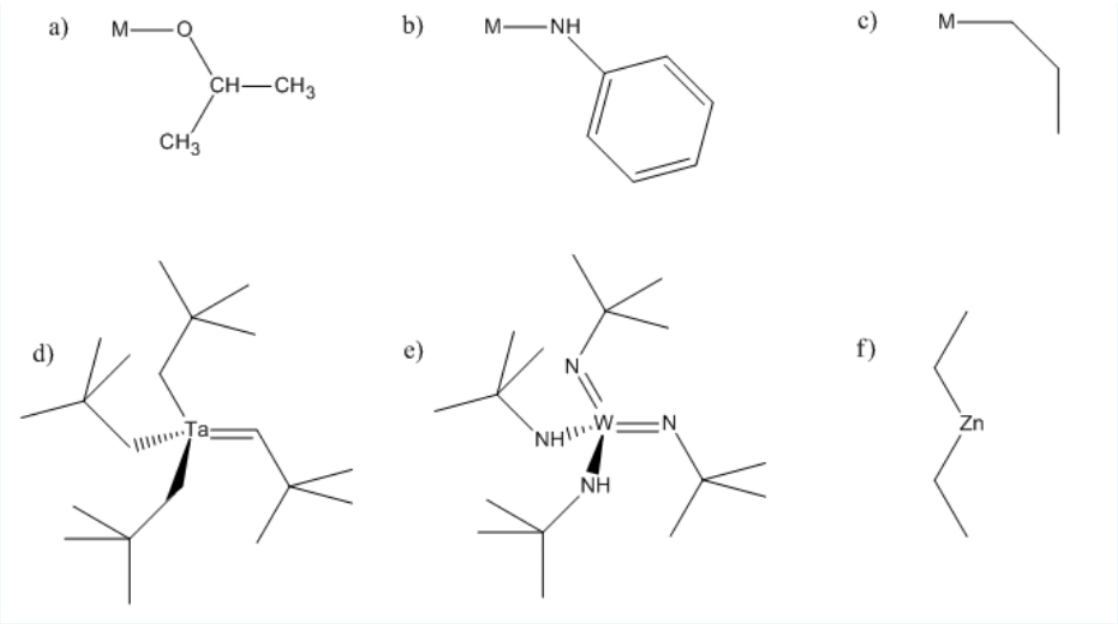
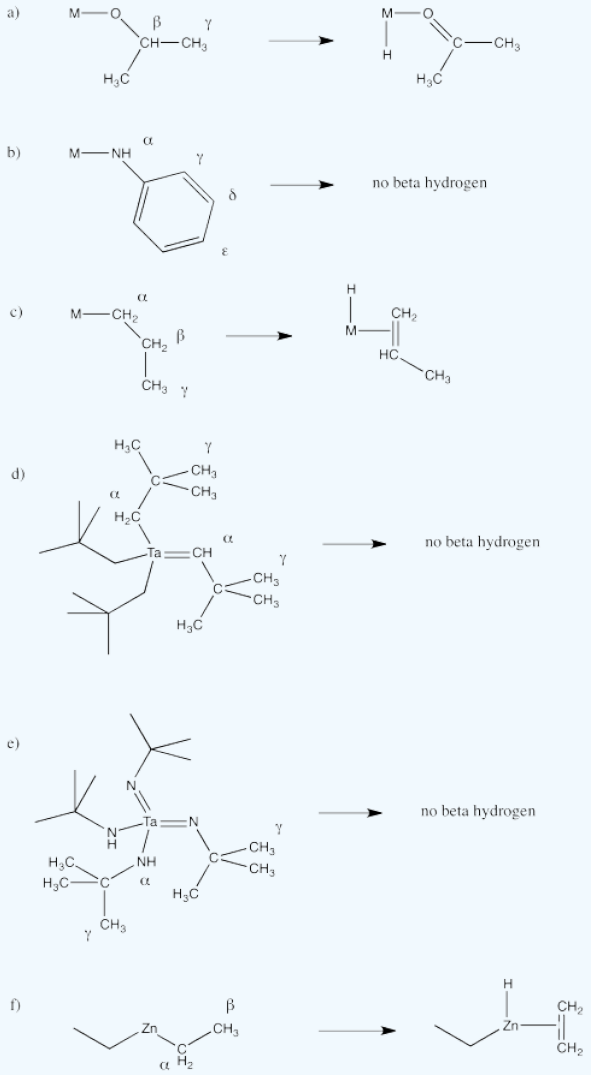


Figure 4.4.5:

Answer



Exercise 4.4.2

Problem MI4.2.

Hydride transfer reduction is a method of converting aldehydes or ketones to alcohols. This catalytic reaction involves the use of a sacrificial alcohol as the solvent. As the aldehyde or ketone substrate is converted into alcohol, the alcohol solvent is converted into ketone. The mechanism is quite complicated, but at a simple level it could be imagined as taking place through a series of binding steps, eliminations and insertions.

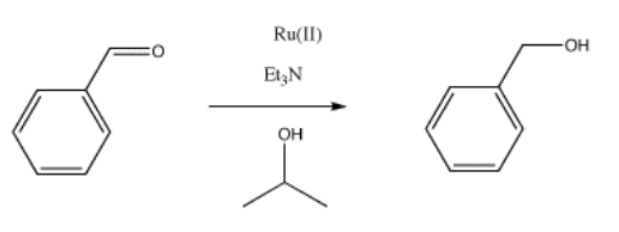
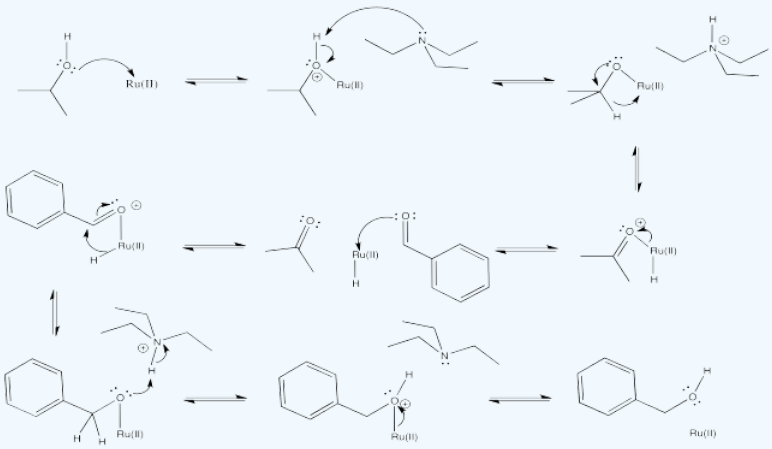


Figure 4.4.6:

Provide mechanisms based on the following descriptions for the reduction of benzaldehyde to benzyl alcohol.

a. The reaction involves binding of isopropanol or 2-propanol to a metal ion, such as Ru(II) or Ru^{2+}. A deprotonation ensues, followed by elimination, and 2-propanone dissociates from the metal ion.
b. The ruthenium hydride formed in step (a) binds to the substrate, benzaldehyde. An insertion occurs, forming a metal alkoxide.
c. The metal alkoxide is protonated, and the resulting alcohol dissociates from the metal.

Answer



Just like aldehydes and ketones, alkenes can undergo 1,2-insertions (also called beta hydride insertions). In terms of electrophiles and nucleophiles, this reaction is a little harder to imagine. However, we can still think of the hydride as a nucleophile. Maybe the alkene is an electrophile. Given that it is donating its pi electrons to the metal, we can think of it as "activated", a little bit like an activated carbonyl.

The formalisms of drawing a beta alkene insertion are tricky. If we use the metallacycle drawing of a bound alkene, it might look like this:

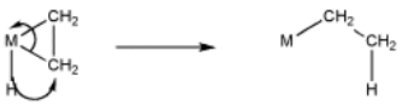


Figure 4.4.7:

More often, bound alkenes are drawn as shown as in the picture below. In that case, we could try to show the pi bond forming a new carbon-metal bond. The bond between the metal and alkene on the picture to the left does not really stand for a separate pair of electrons in this case; it just stands for the pi bond donating to the metal.

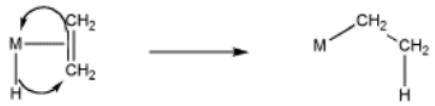


Figure 4.4.8:

- The reverse of elimination is insertion.
- A coordinated alkene is sometimes considered electrophilic because it is giving electrons to the metal.
- A coordinated alkene is activated, like a coordinated carbonyl compound.

So far, we have just looked at the 1,2-insertion of hydride ligands, but 1,2-insertions of alkyl ligands are also possible. In this case, an alkyl ligand would relocate onto the second atom in the former alkene. As a result, the alkyl chain attached to the metal would become two carbons longer.

Figure 4.4.9:

However, the opposite reaction, 1,2-elimination of an alkyl, is not very common. That reaction is usually restricted to movement of a hydrogen atom.

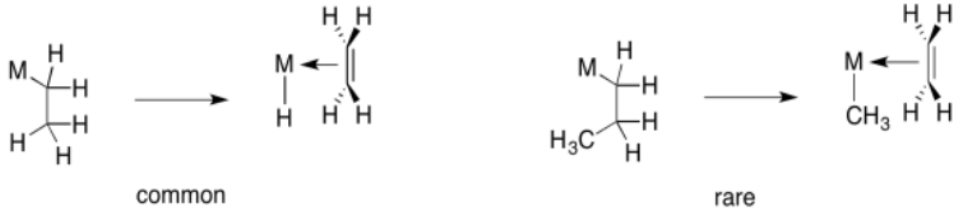


Figure 4.4.10:

Beta-insertion of hydride or alkyl ligands across alkenes is very important commercially. Many catalytic processes that are used to convert hydrocarbons into useful products depend on this reaction. Alkenes are readily made from petroleum or natural gas, so they are convenient starting materials to make more useful compounds. For example, ethene can be grown into longer carbon chains via a series of 1,2-alkyl insertions into coordinated ethene. This process is called "olefin oliomerization".

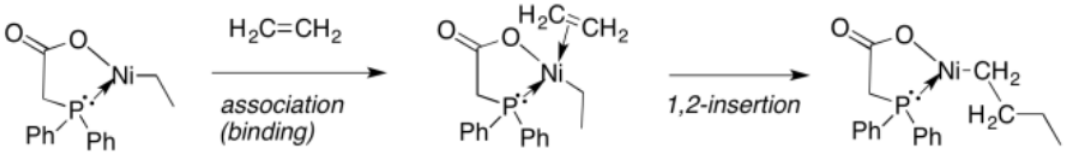


Figure 4.4.11:

That sequence of steps is crucial in the conversion of ethene into more valuable materials. It can be grown into hydrocarbon chains long enough to be used as fuels. However, more valuable products can be made such as soaps, detergents, and surfactants (via hydroformylation and other steps). In addition, the alkene may be functionalised in a variety of different ways if a long carbon chain needs to be incorporated into the synthesis of a more valuable commodity, such as a paint or a pharmacuetical.

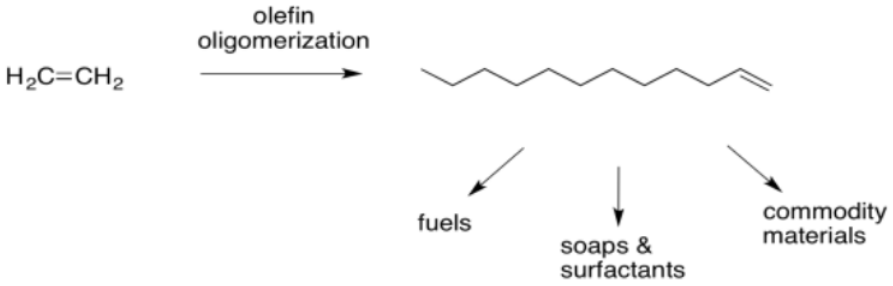


Figure 4.4.12:

Exercise 4.4.3

Provide the products of beta-elimination in each of the following cases. In each case, assume the elimination product is still bound to the metal.

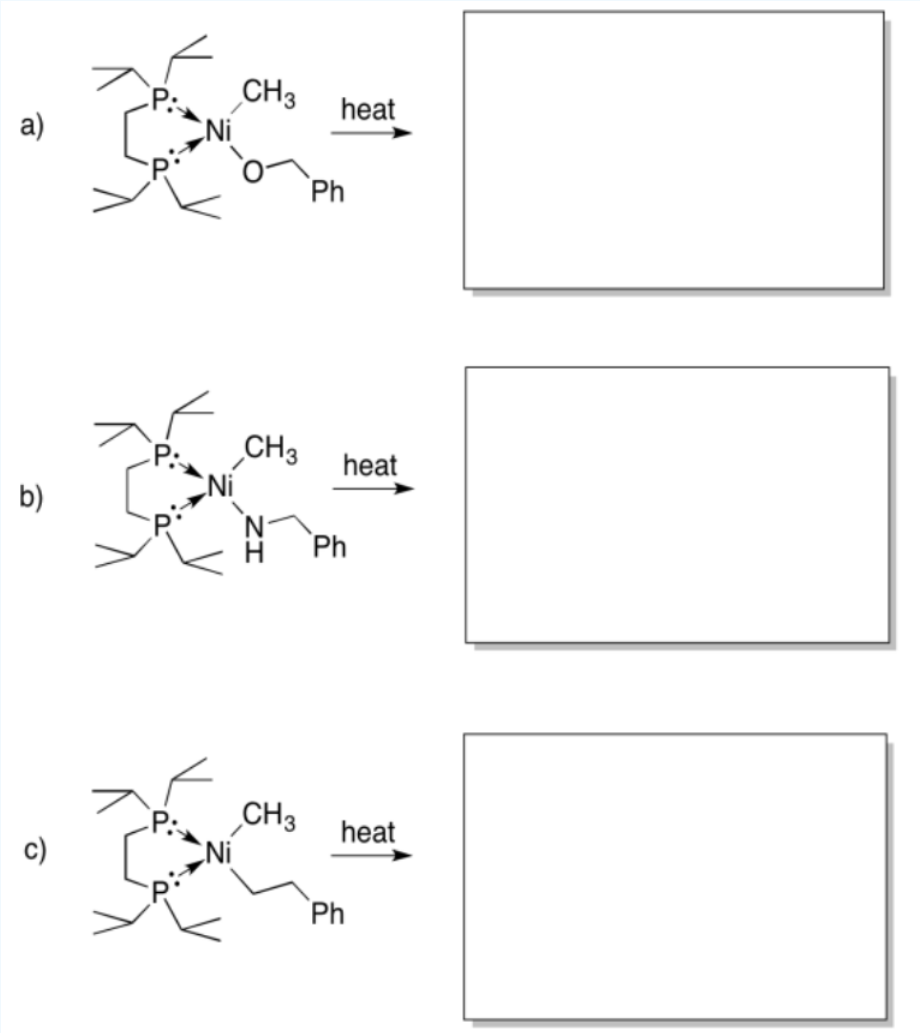


Figure 4.4.13:

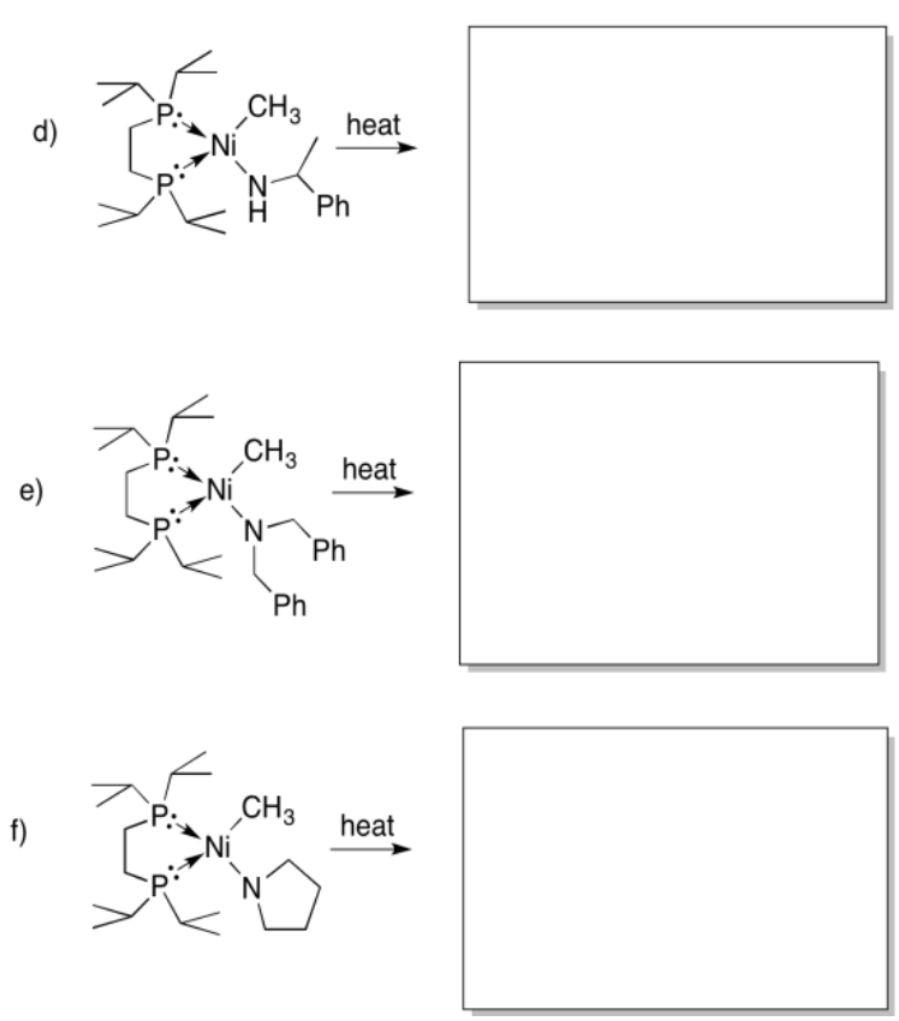
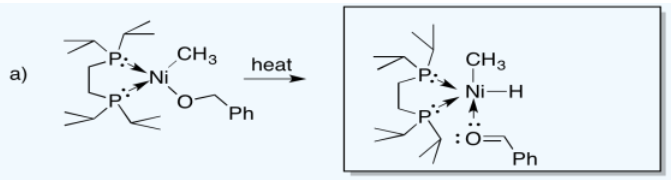


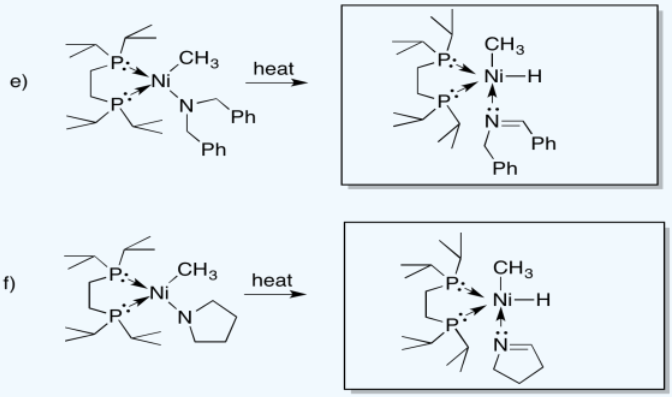
Figure 4.4.14:

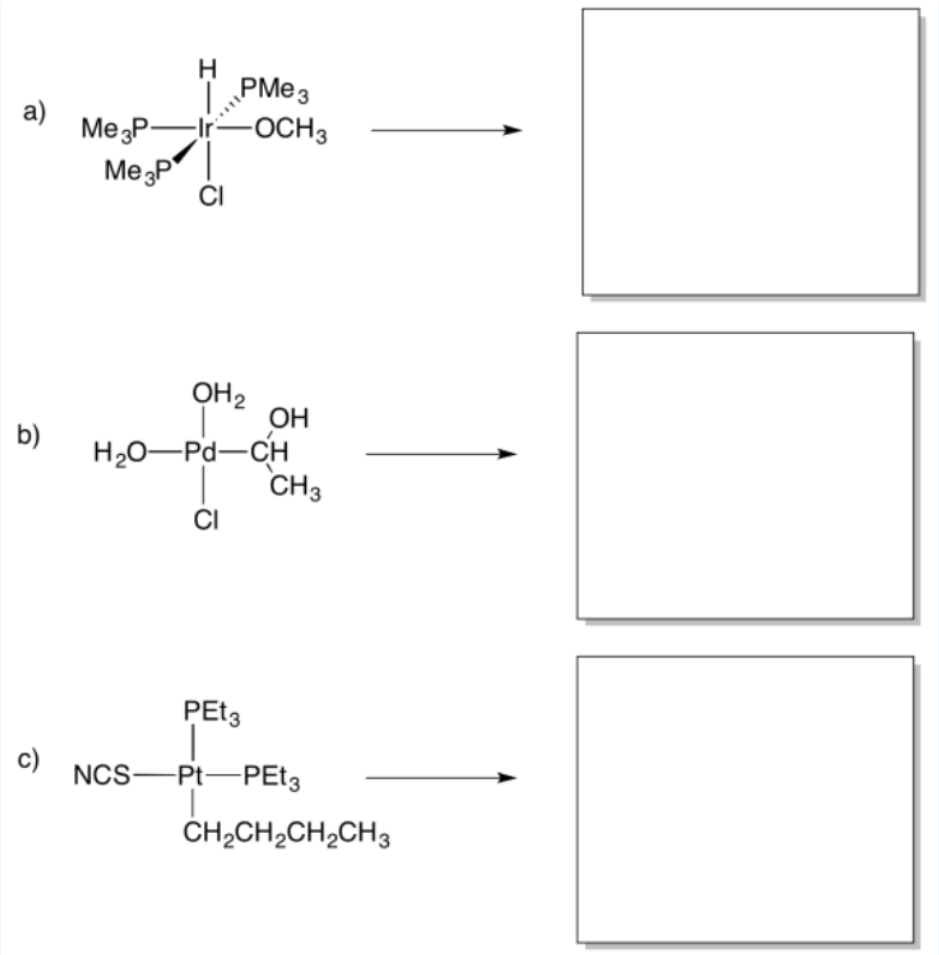
Answer



Exercise 4.4.4

Provide products of the following beta-eliminations. In each case, assume the elimination product has already dissociated from the metal.





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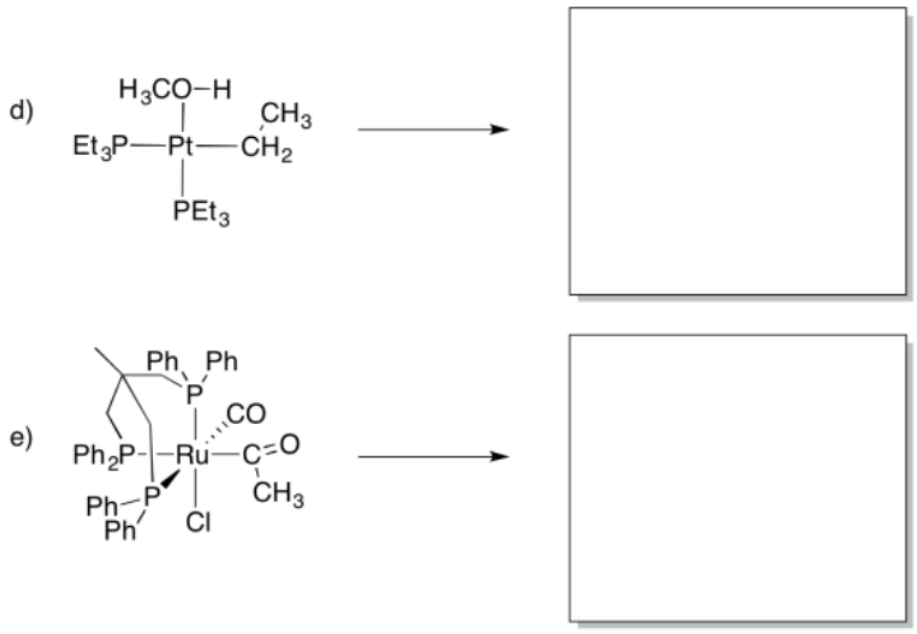
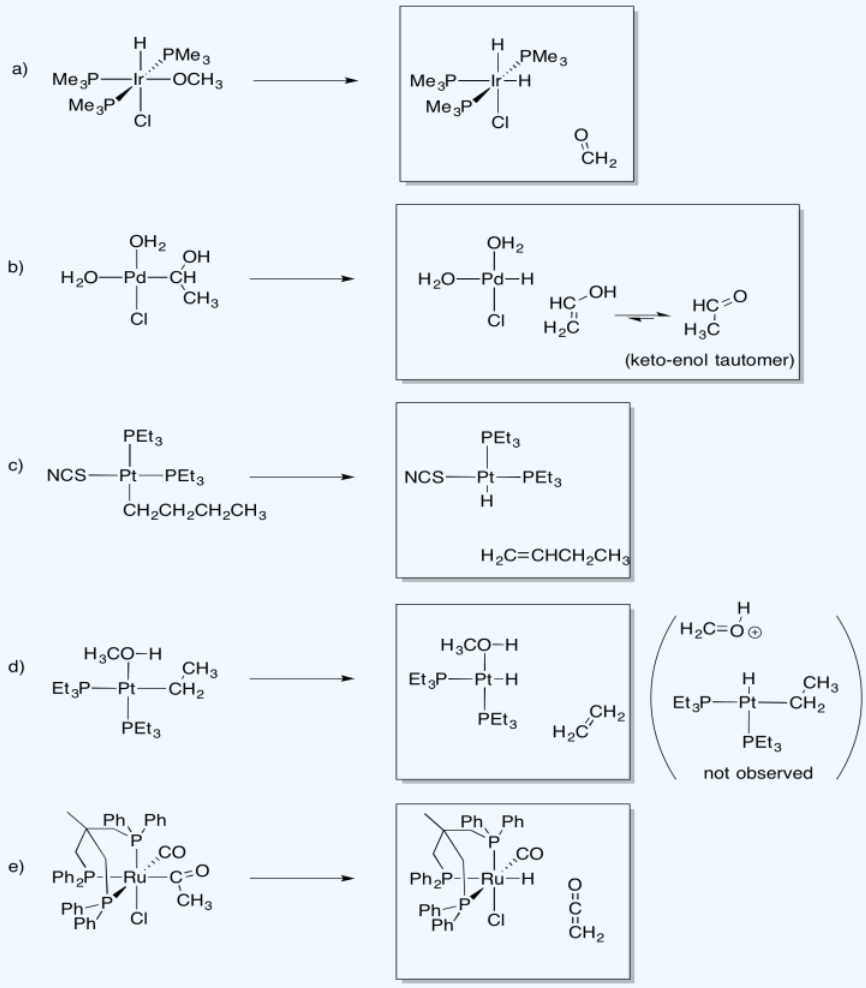


Figure 4.4.16:

Answer



Exercise 4.4.5

Provide products of the following insertion reactions.

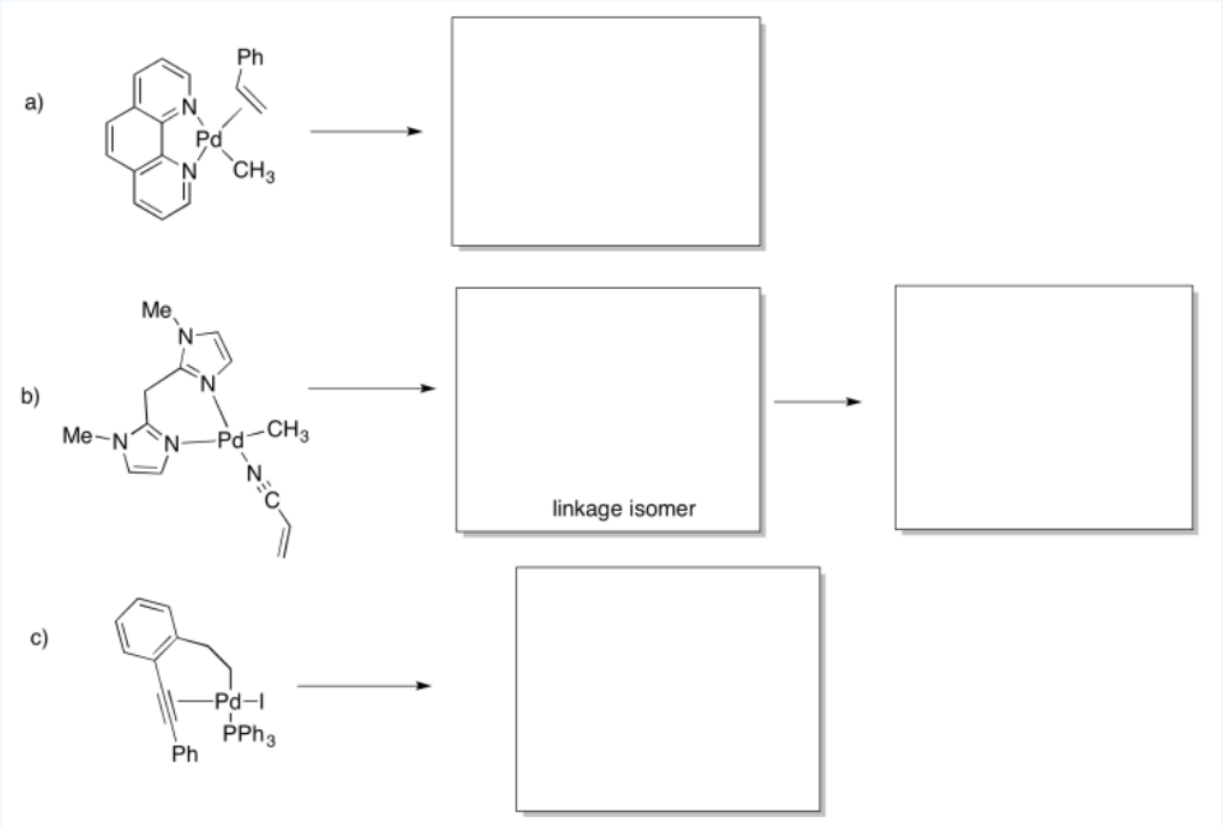
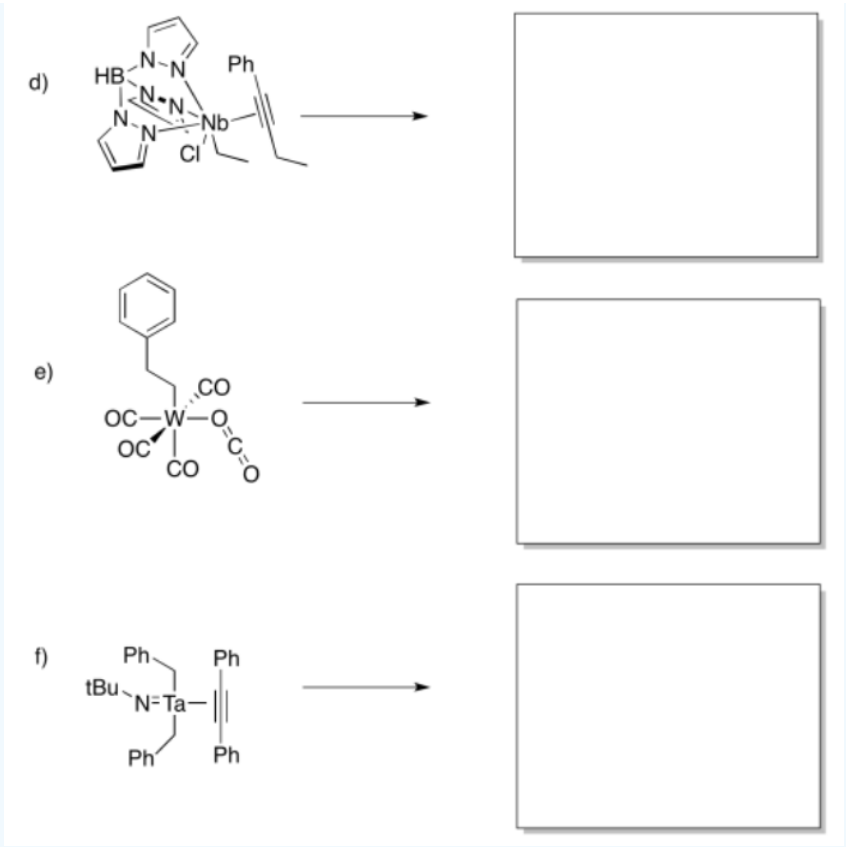


Figure 4.4.17:



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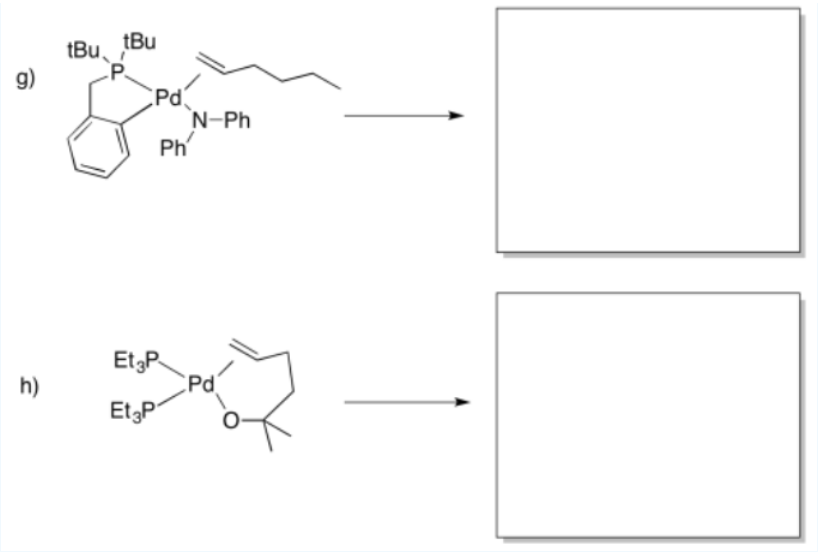
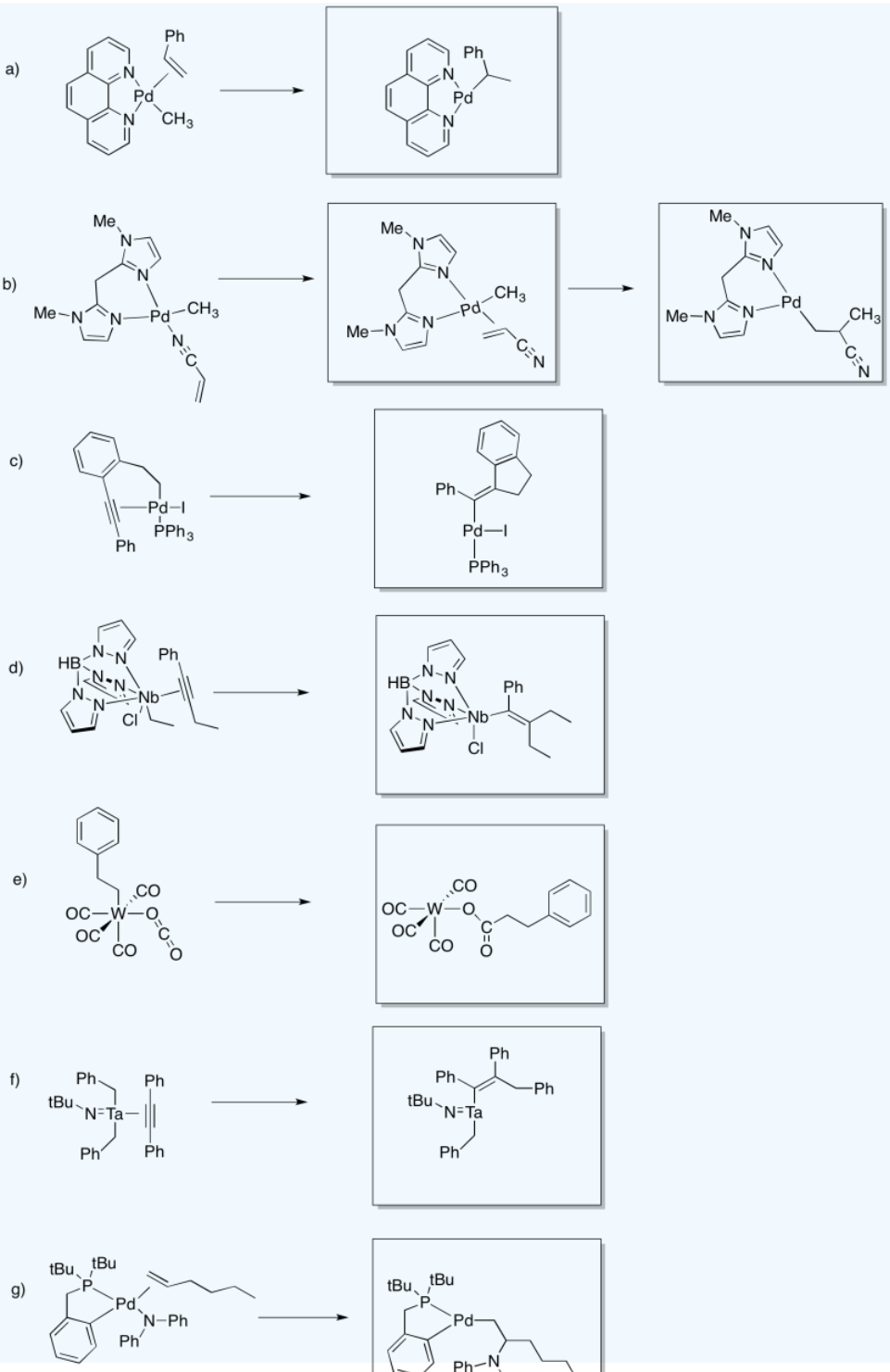


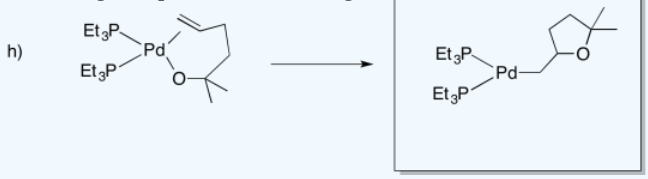
Figure 4.4.19:

Answer



Exercise 4.4.6

Predict whether the following compounds will undergo 1,1-insertion, 1,2-insertion, or beta-elimination.



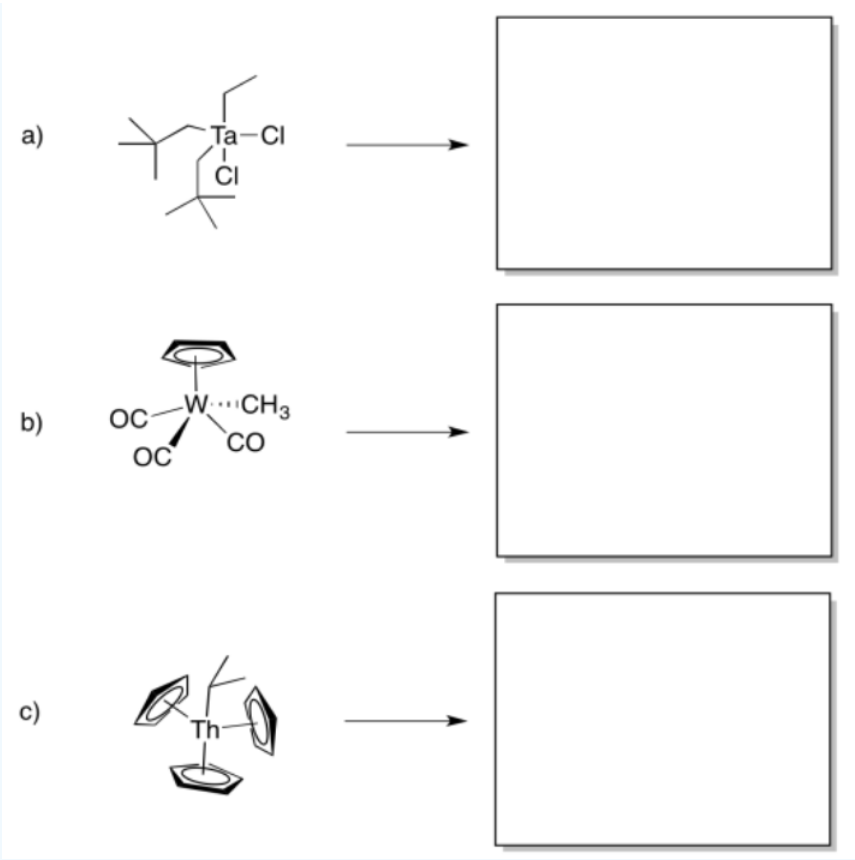


Figure 4.4.20:

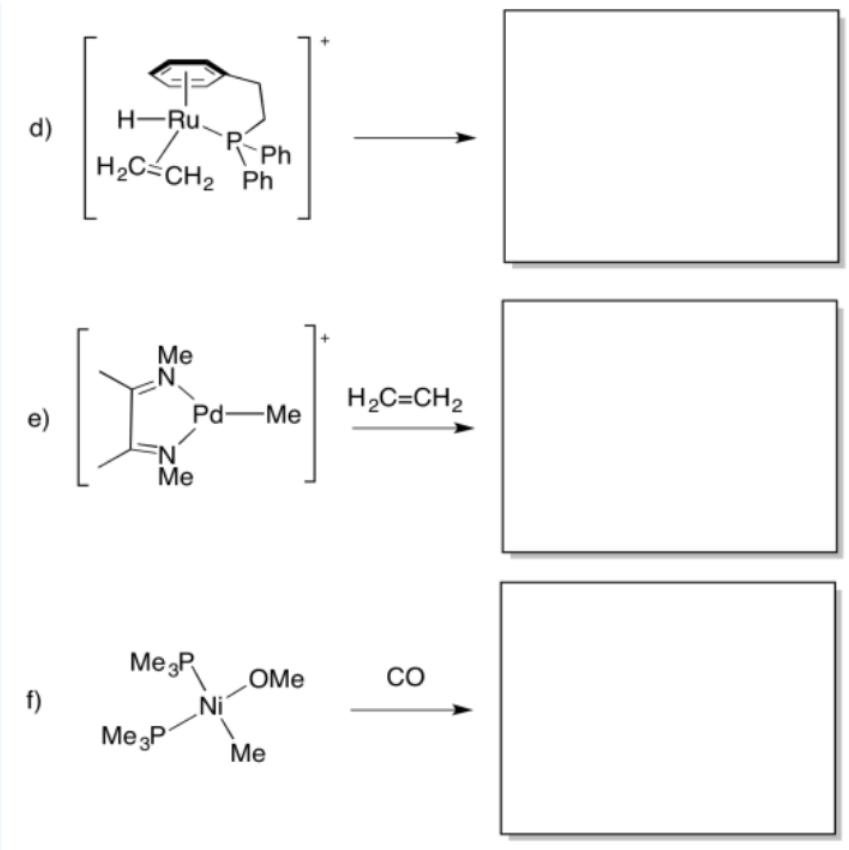
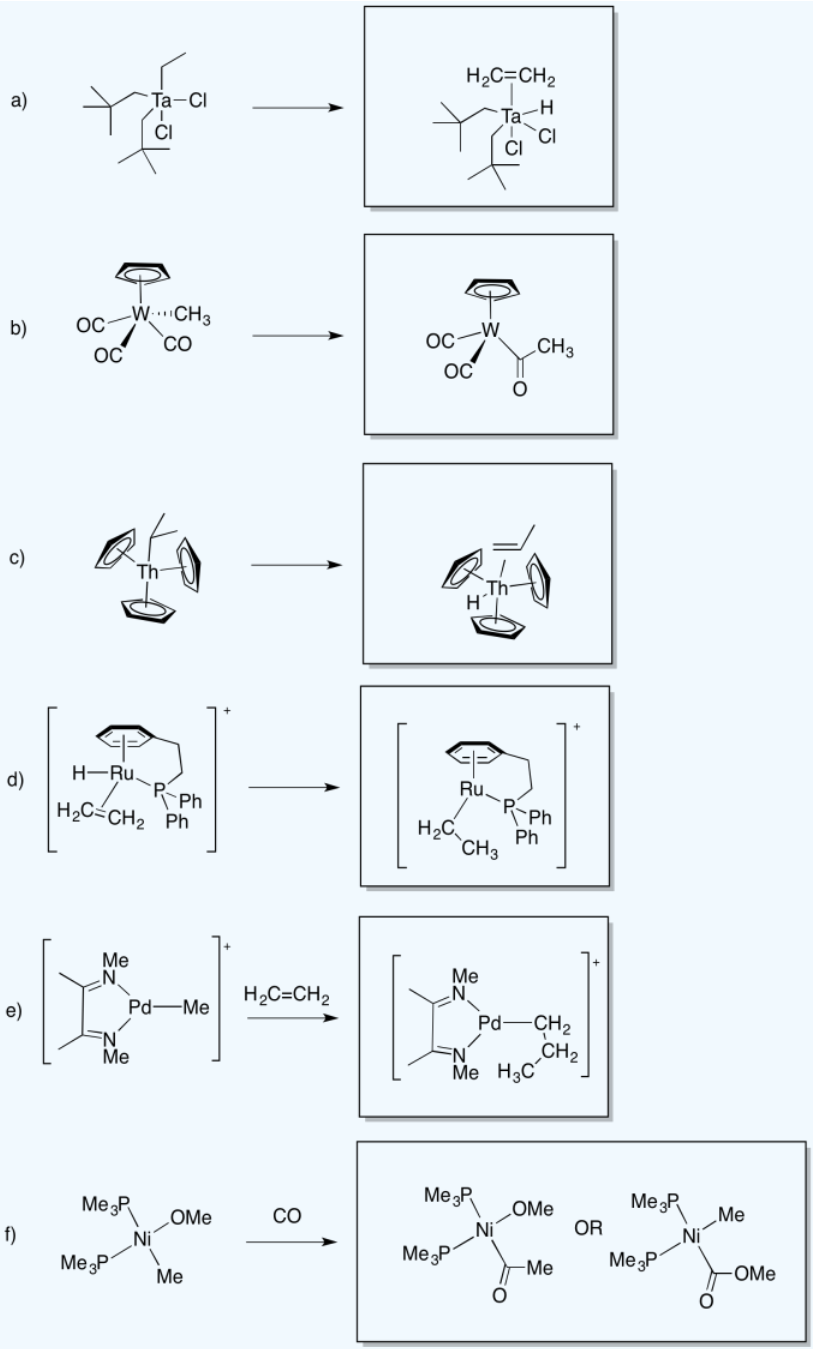


Figure 4.4.21:

Answer



Exercise 4.4.7

Insertion and elimination reactions can also occur on solid metal surfaces. Often, solid metals are used as catalysts in industrial processes.

a) Copper adopts a face-centered cubic structure. Show a unit cell of copper on the following template.

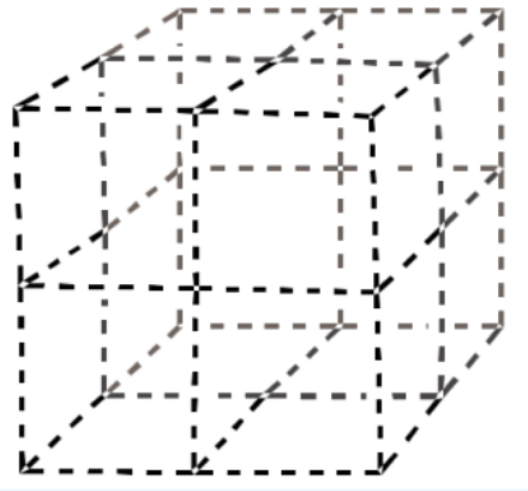
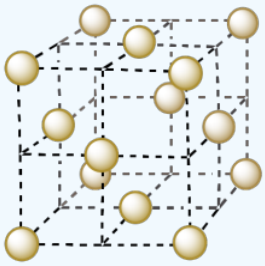


Figure 4.4.22:

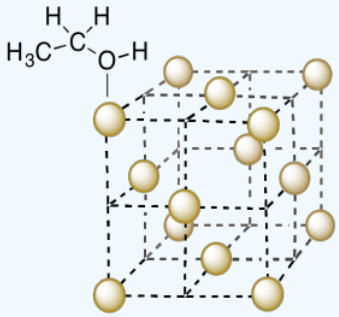
b) Alcohols such as ethanol can bind to the surface of the copper metal. Show an ethanol molecule binding to a copper in the unit cell.

c) The ethanol can undergo beta-elimination. Show the product of the reaction.

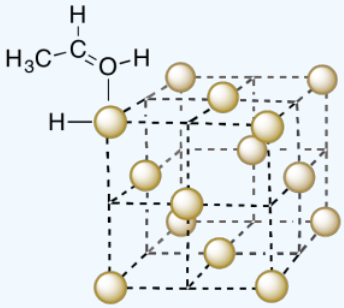
Answer a



Answer b



Answer c

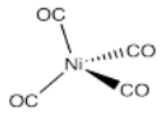


4.5: Solutions for Selected Problems

Note: In some cases, formal charge has been shown only on a particular atom to emphasize an aspect of its reactivity, but is left off other atoms.

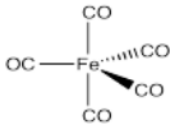
Exercise 4.2.1:

a)



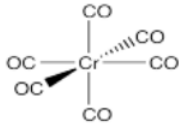
electrons on metal atom: 10
charge on metal: none
electrons on atom / ion: 10
electrons donated by ligands: 2 x 4 = 8
total: 18

b)



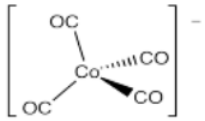
electrons on metal atom: 8
charge on metal: none
electrons on atom / ion: 8
electrons donated by ligands: 2 x 5 = 10
total: 18

c)



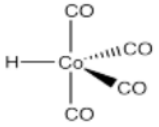
electrons on metal atom: 6
charge on metal: none
electrons on atom / ion: 6
electrons donated by ligands: 2 x 6 = 12
total: 18

d)



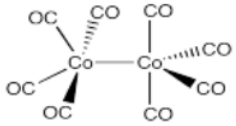
electrons on metal atom: 9
charge on metal: -1
electrons on atom / ion: 10
electrons donated by ligands: 2 x 4 = 8
total: 18

e)



electrons on metal atom: 9
charge on metal: +1
electrons on atom / ion: 8
electrons donated by ligands: 2 x 5 = 10
total: 18

f)



electrons on metal atom: 9
charge on metal: none
electrons on atom / ion: 9
electron donated from other metal 1
electrons donated by ligands: 2 x 4 = 8
total: 18

Figure 4.5.1:

Exercise 4.2.2:

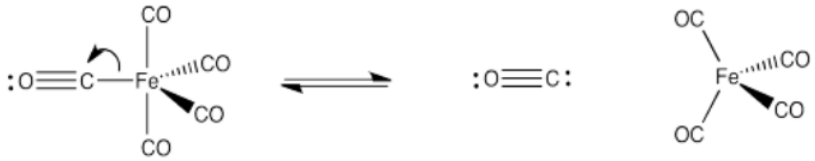


Figure 4.5.2:

Exercise 4.2.3:

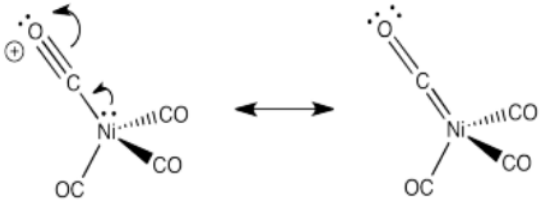


Figure 4.5.3:

Exercise 4.2.6:

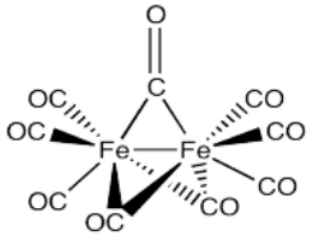


Figure 4.5.4:

Exercise 4.2.7:

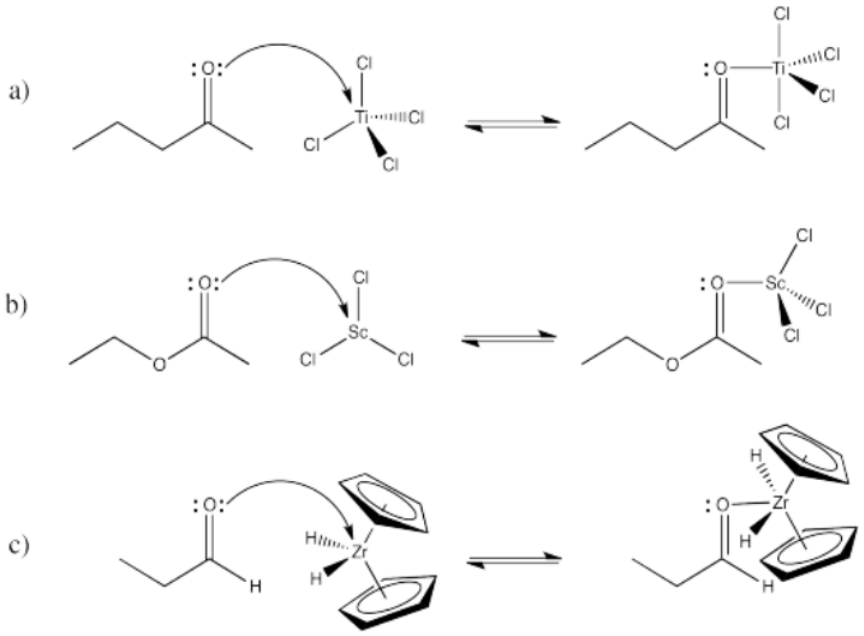


Figure 4.5.5:

Exercise 4.3.2:

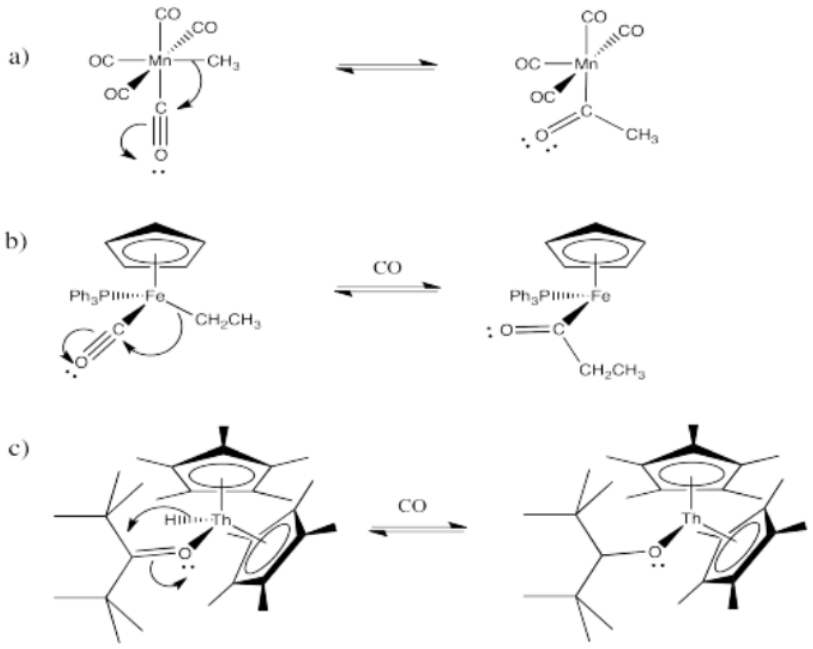


Figure 4.5.6:

Exercise 4.3.4:

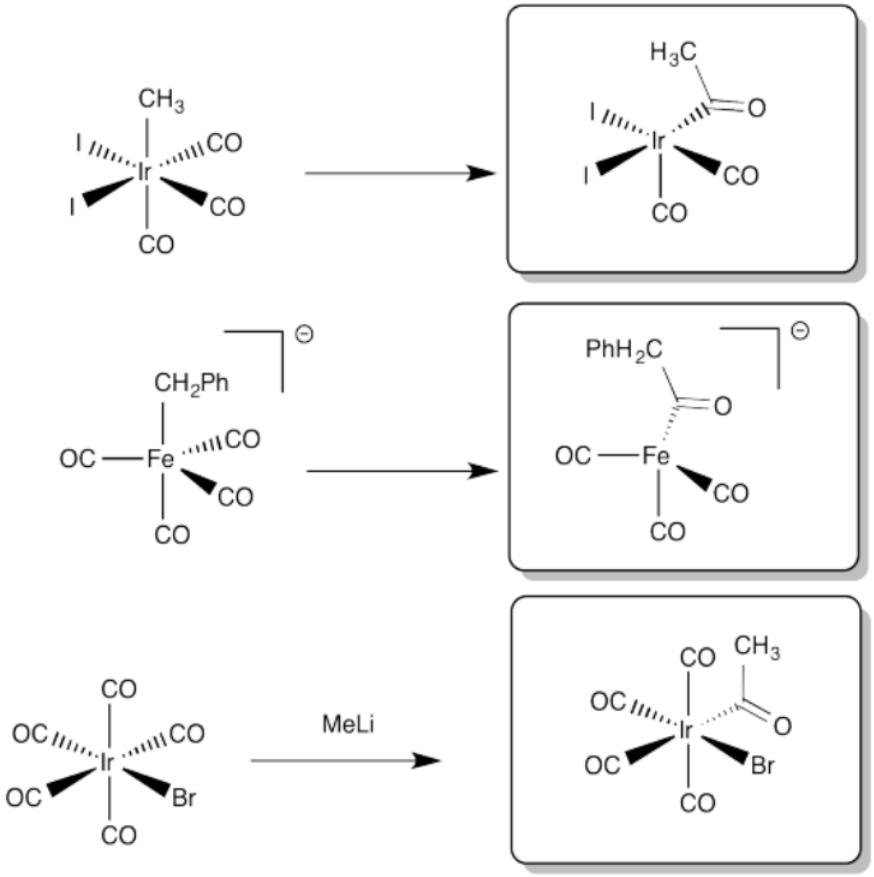


Figure 4.5.7:

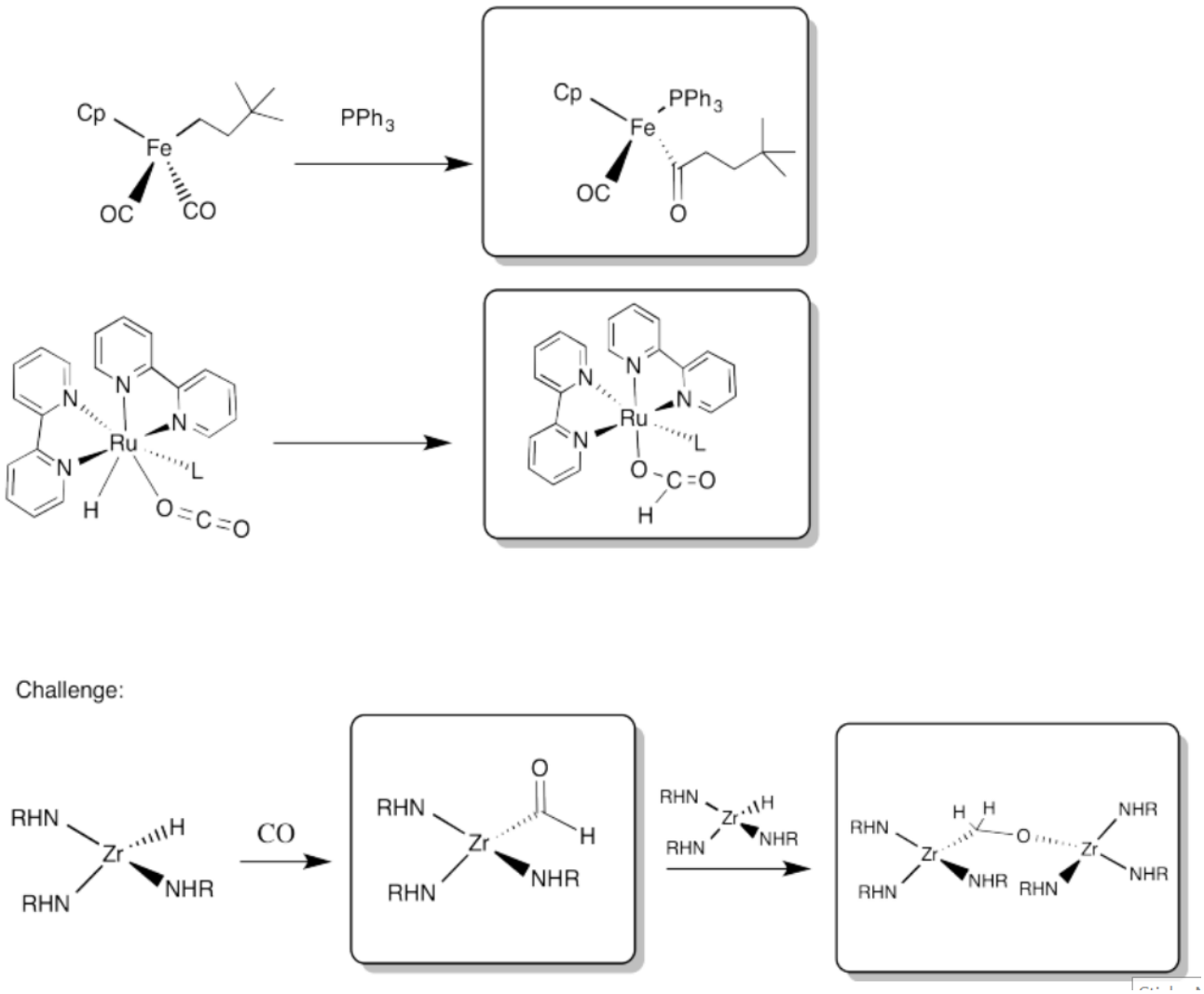


Figure 4.5.8:

Exercise 4.3.5:

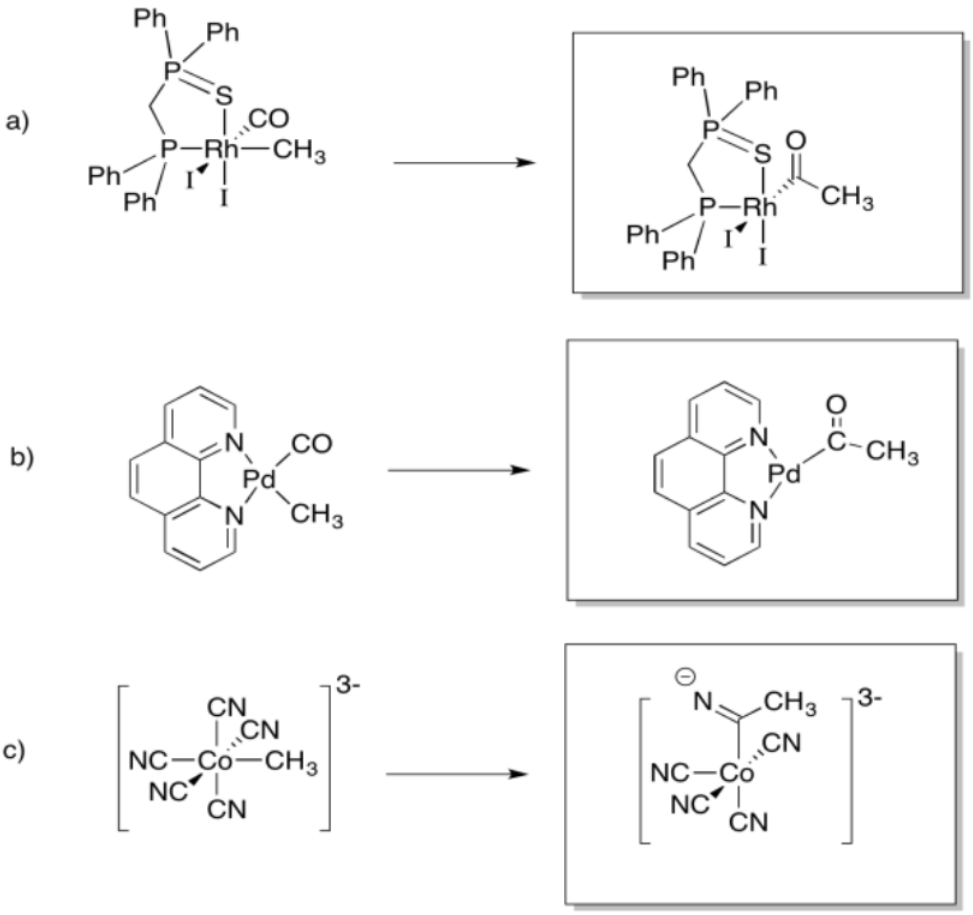


Figure 4.5.9:

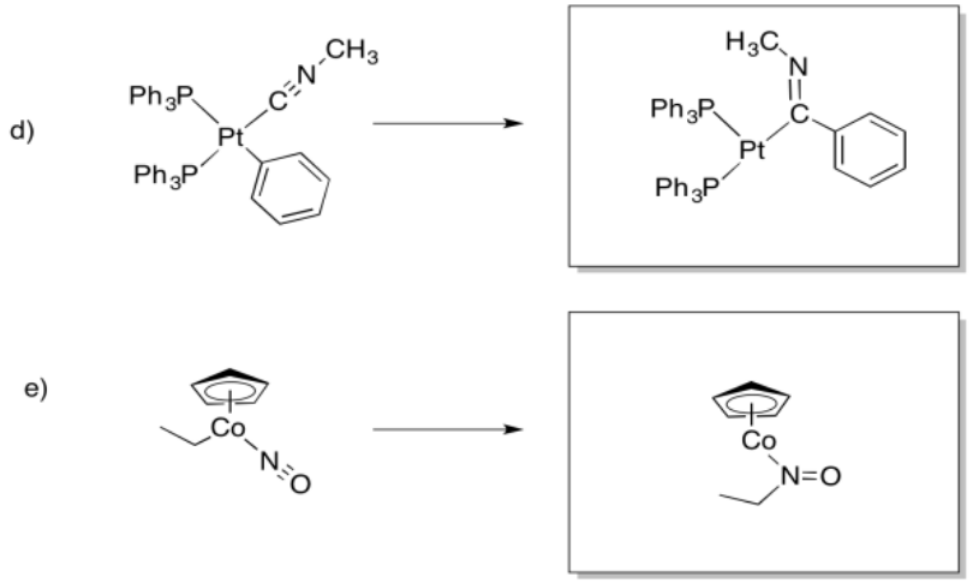


Figure 4.5.10:

Exercise 4.4.1:

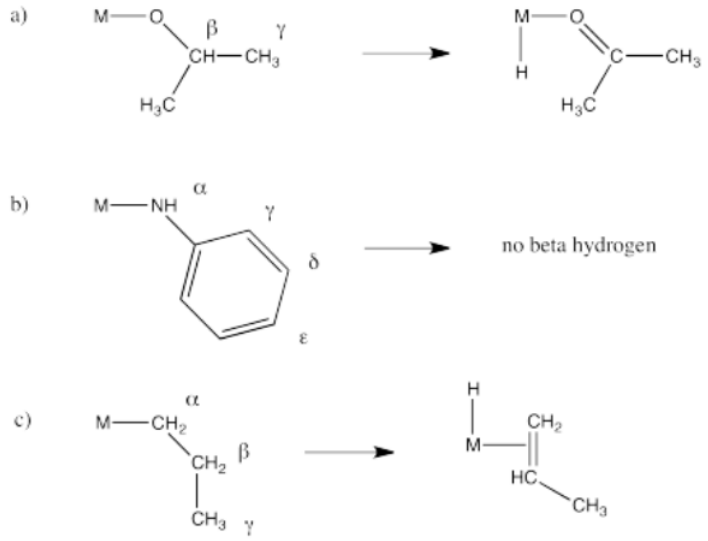


Figure 4.5.11:

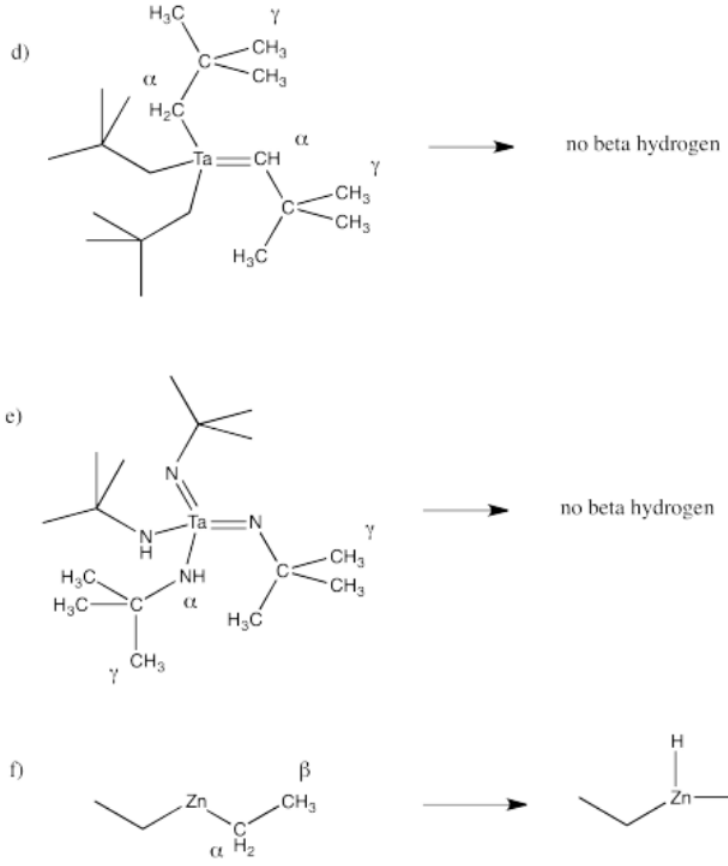


Figure 4.5.12:

Exercise 4.4.2:

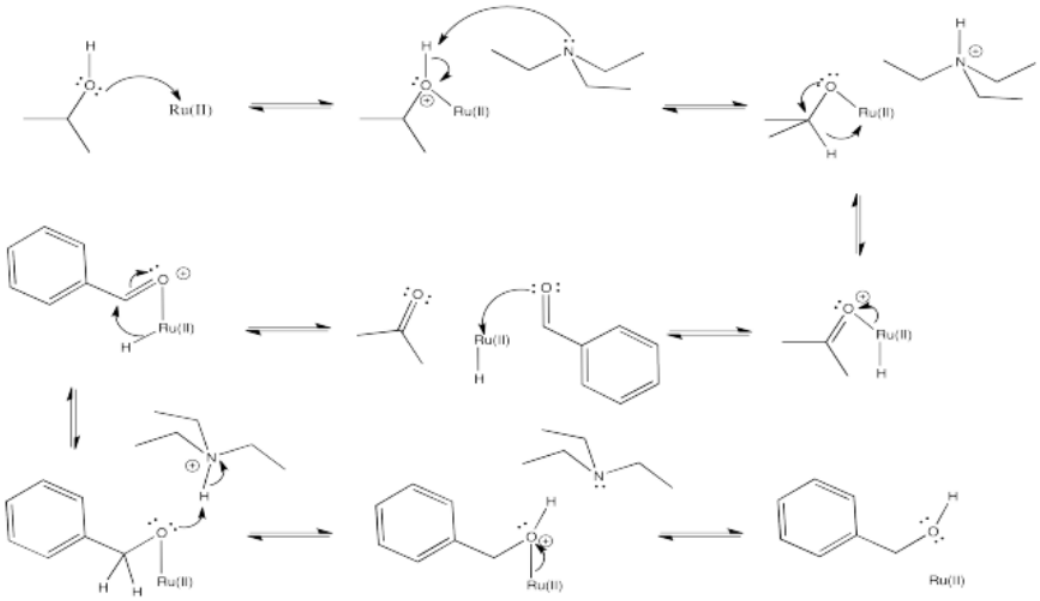
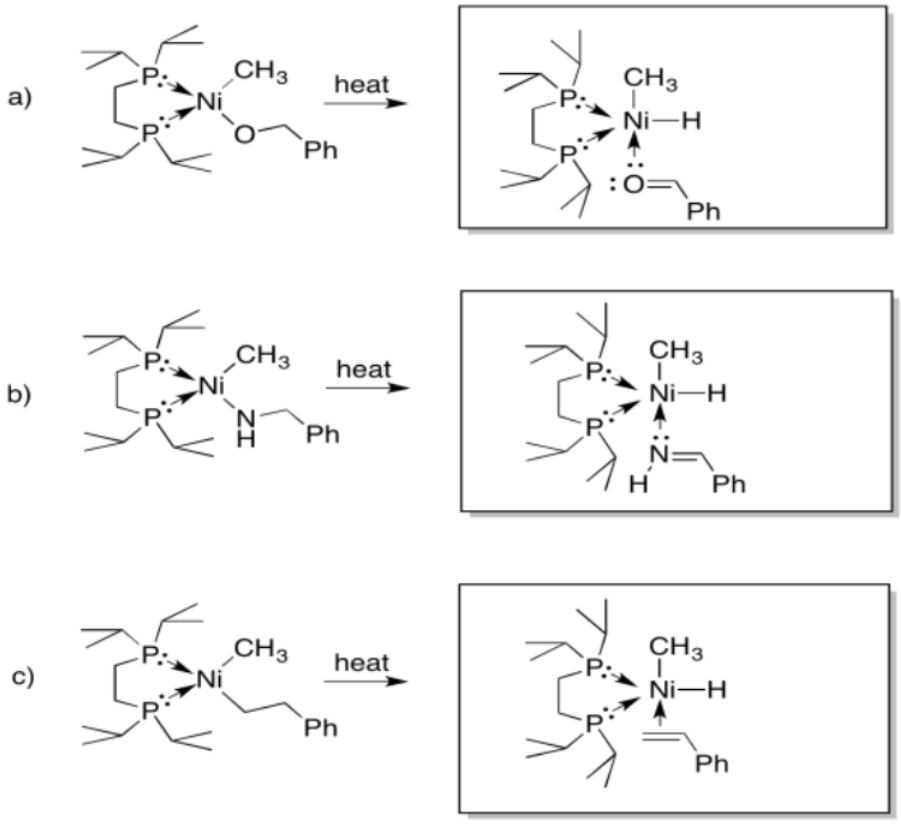


Figure 4.5.13:

Exercise 4.4.3:



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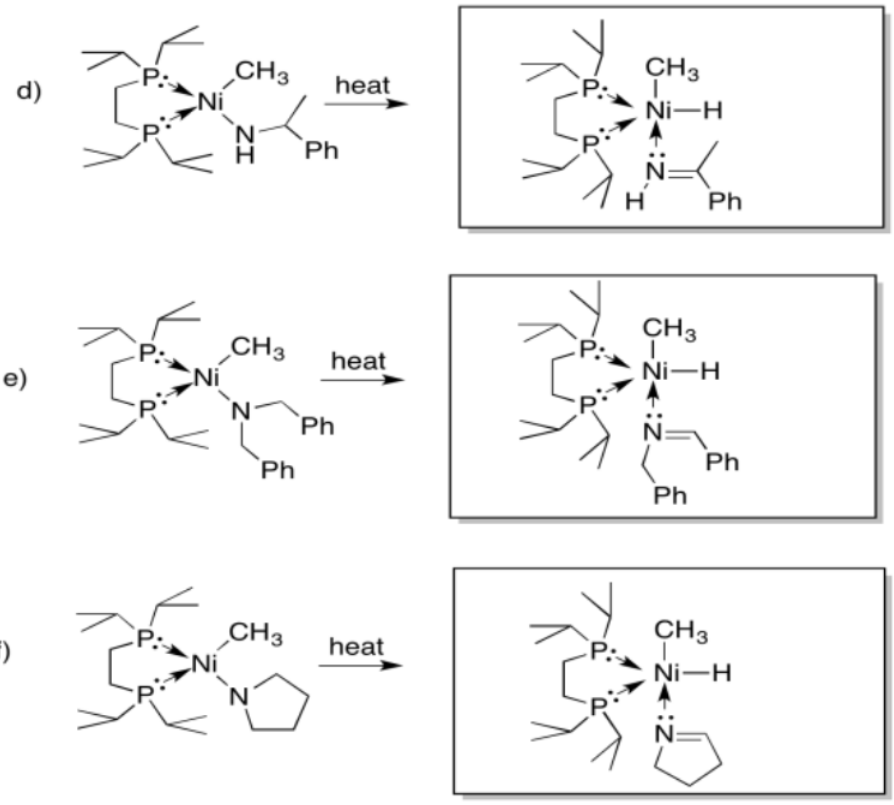
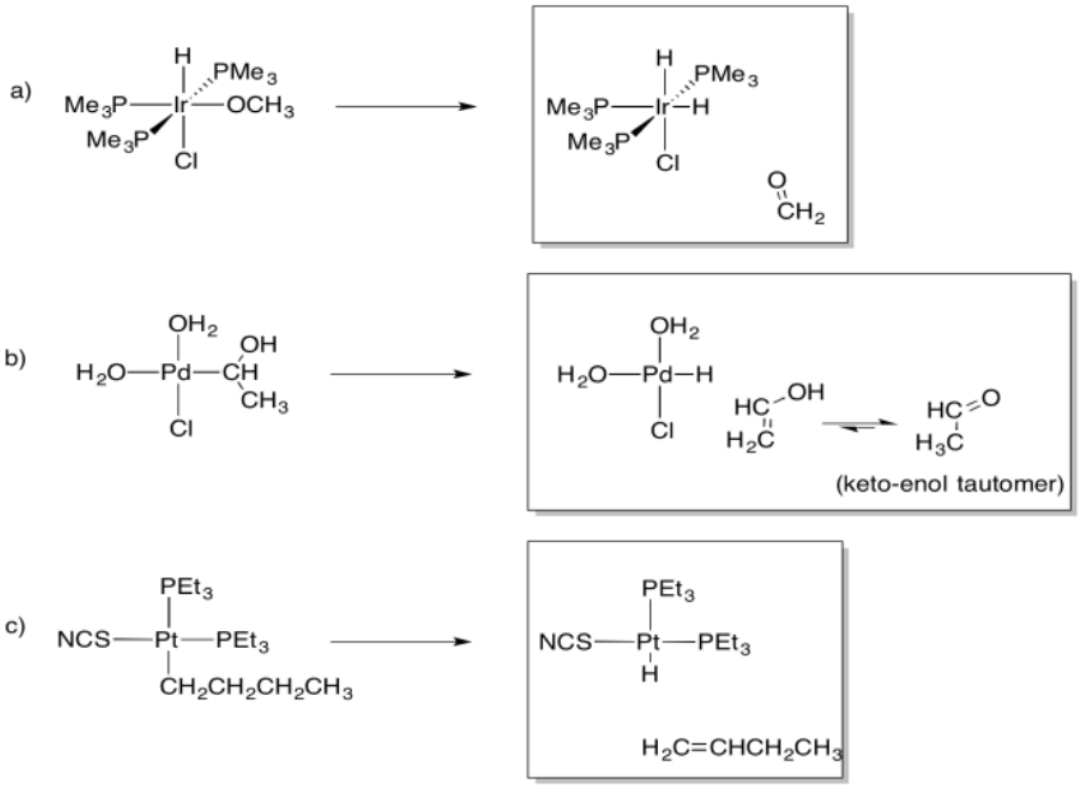


Figure 4.5.15:

Exercise 4.4.4:



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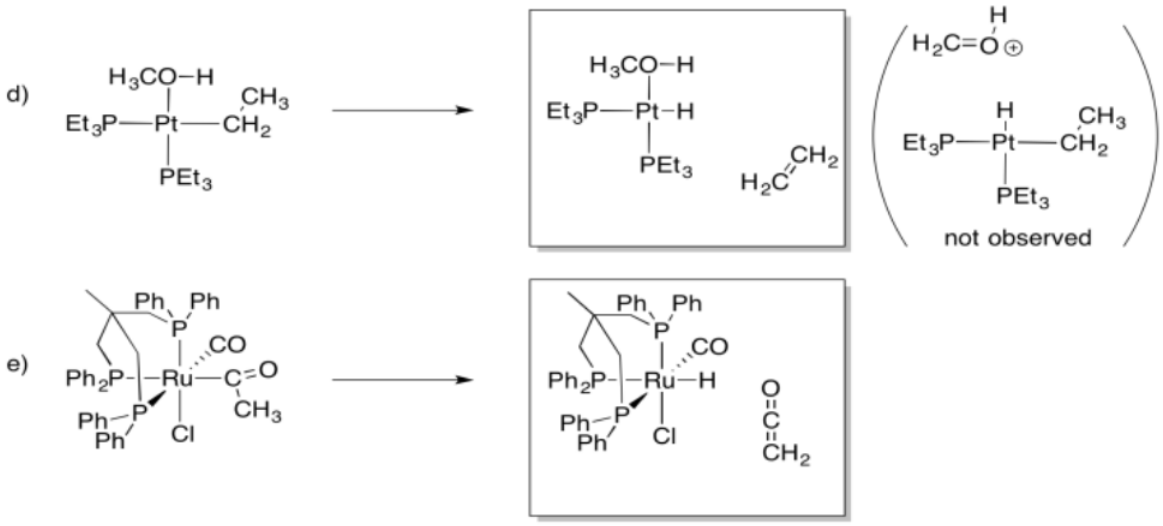


Figure 4.5.17:

Exercise 4.4.5:

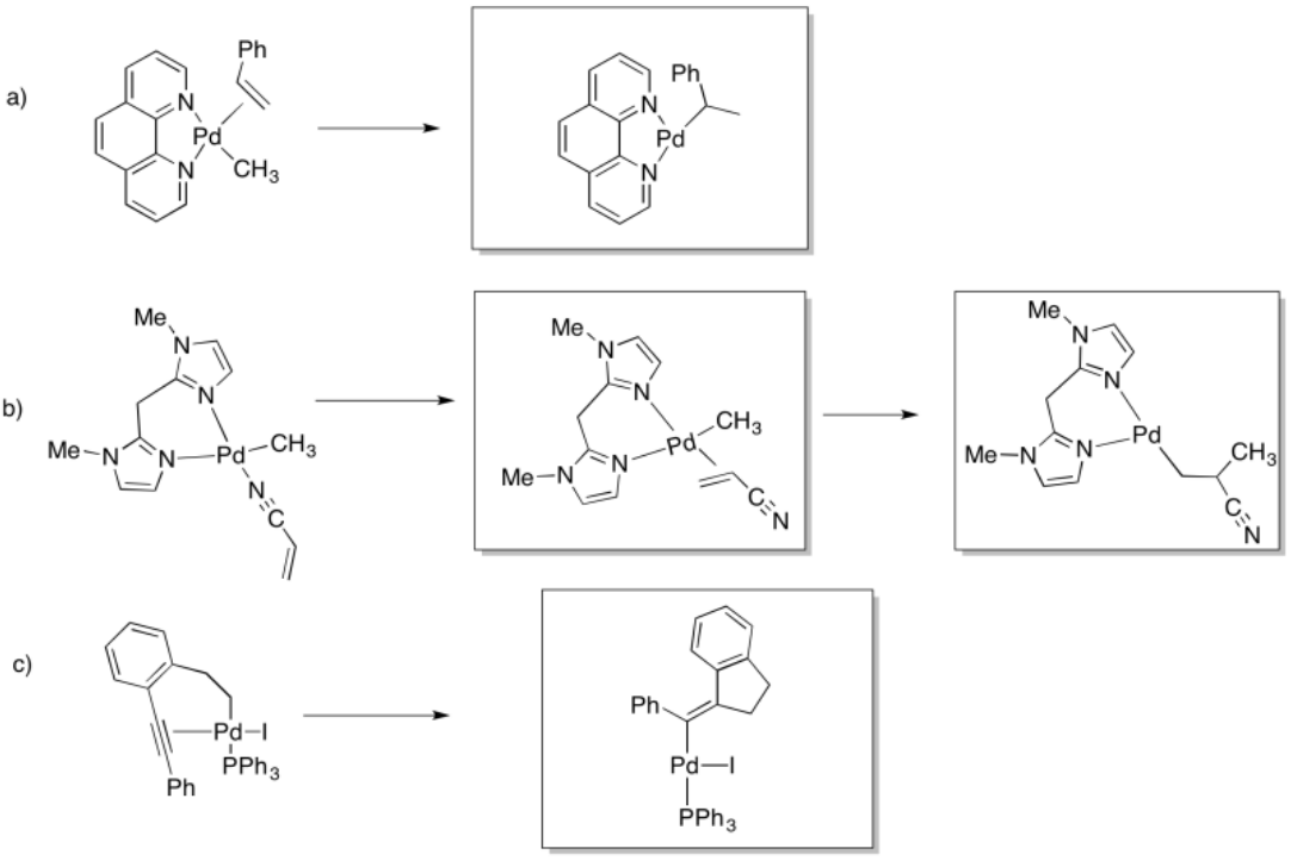


Figure 4.5.18:

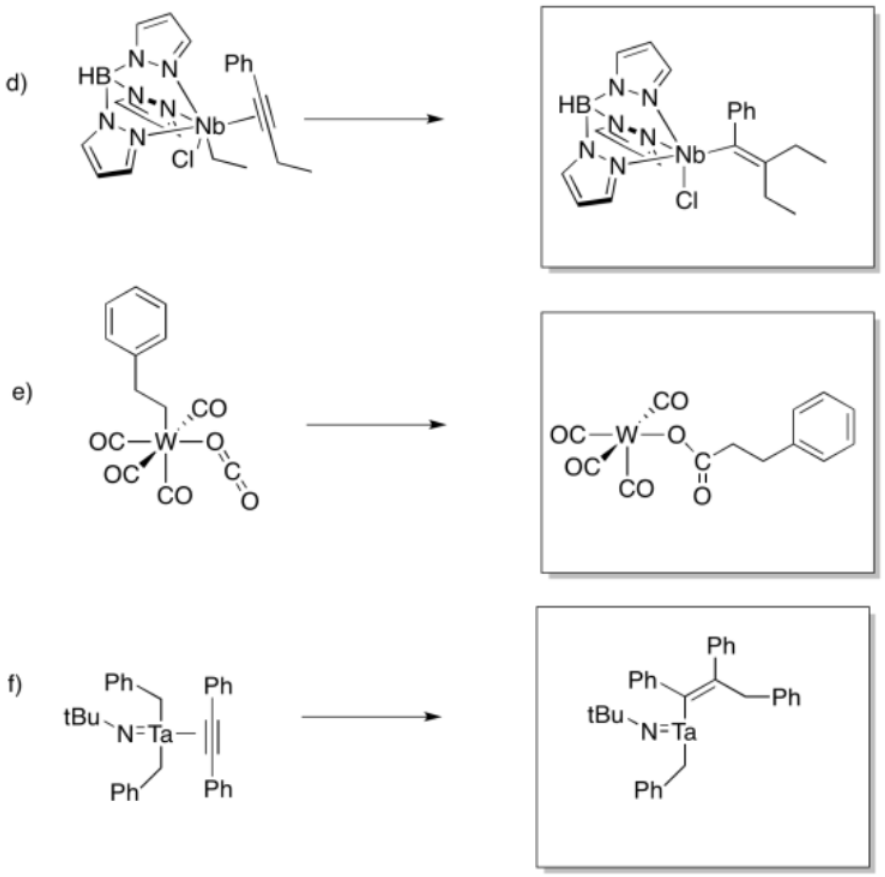


Figure 4.5.19:

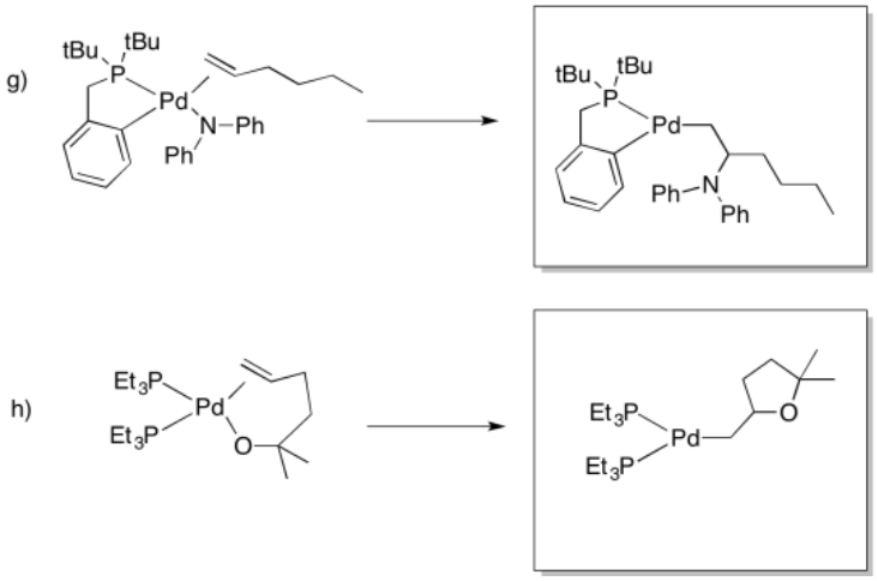


Figure 4.5.20:

Exercise 4.4.6:

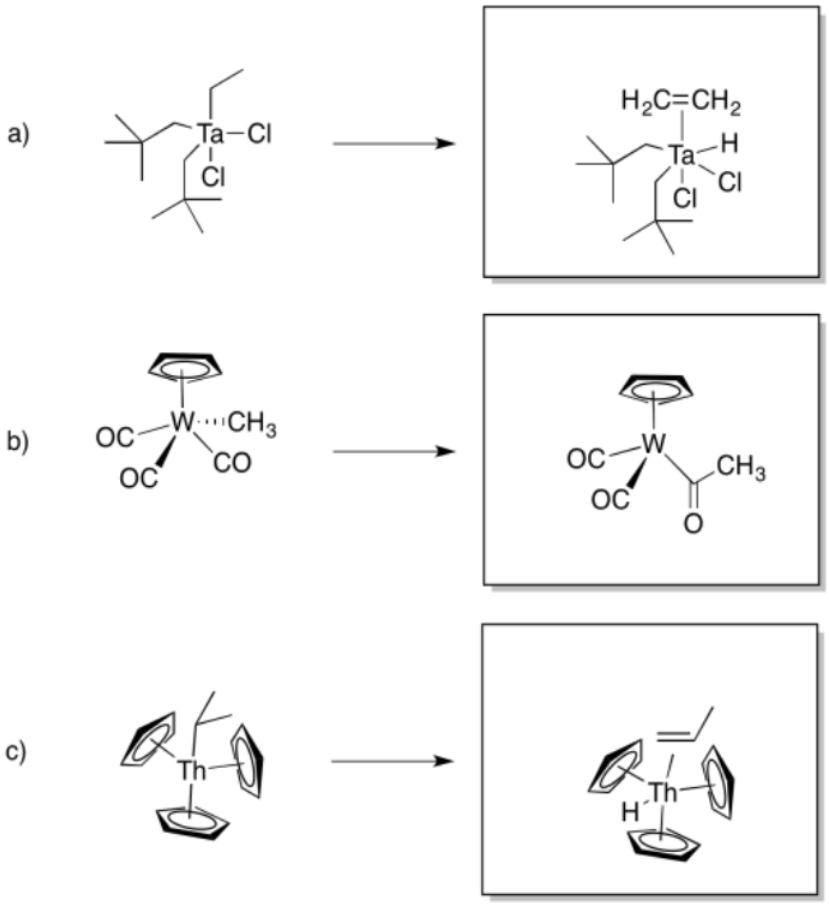


Figure 4.5.21:

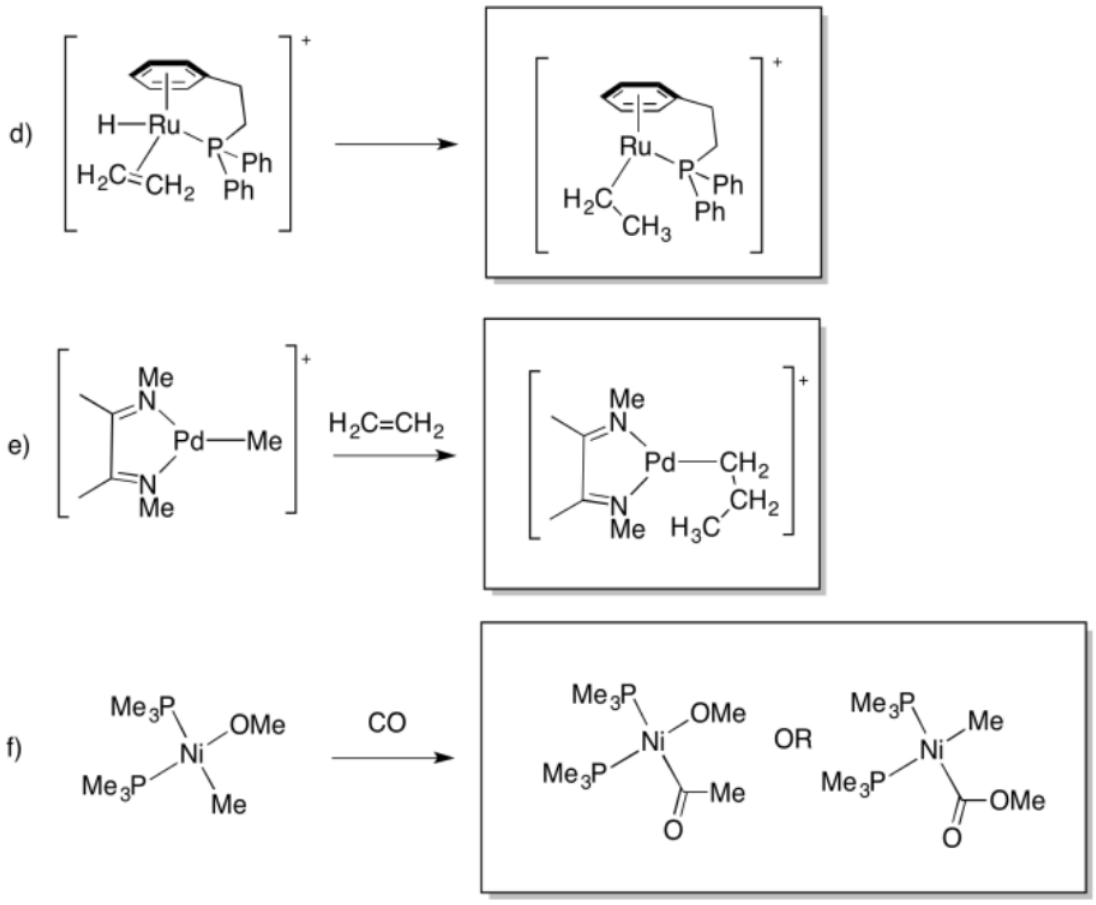


Figure 4.5.22:

Exercise 4.4.7:

a)

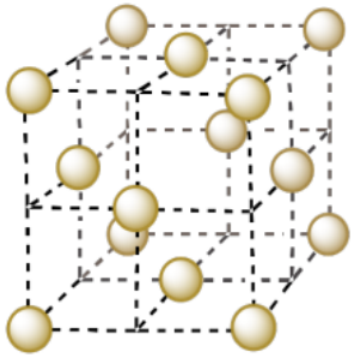


Figure 4.5.23:

b)

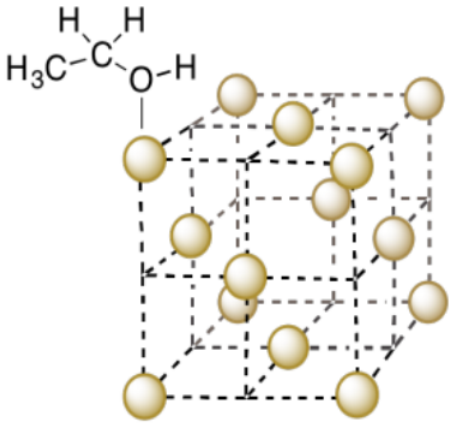


Figure 4.5.24:

c)

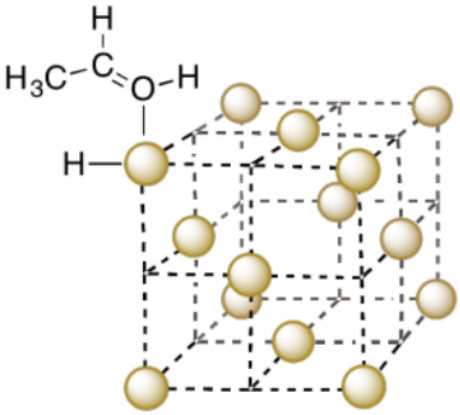


Figure 4.5.25:

CHAPTER OVERVIEW

5: Substitution at Carboxyloids

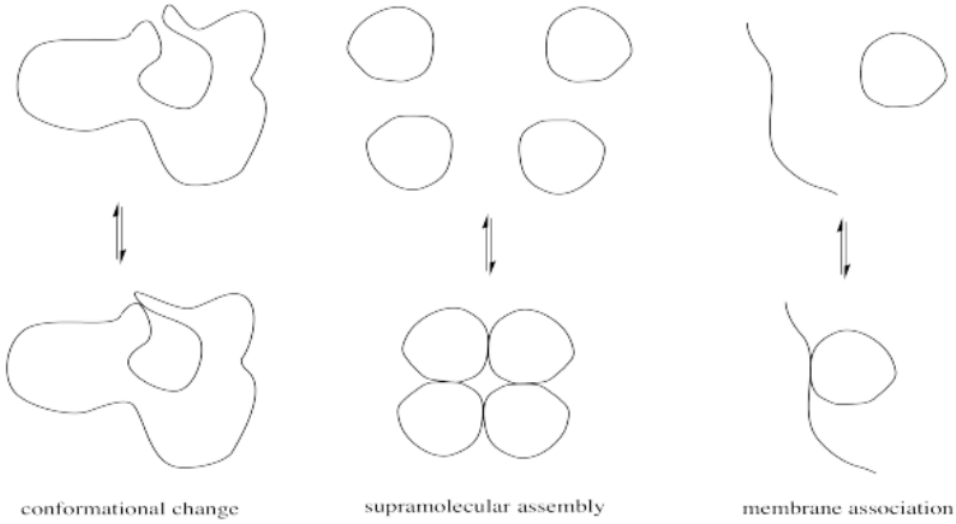
5.1: Biosynthesis of Proteins and Peptides

n/a

5.2: Protein Modification

After proteins are synthesized via transcription of DNA, their structures may be modified in a number of ways. This process, in general, is referred to as "post-translational modification". It might involve the attachment of small organic groups to the protein, attachment of other biomolecules, or even the complete alteration of an amino acid residue into another form, so that the protein actually contains a residue that does not exist in the basic beginner's amino acid alphabet.

Minor modifications of proteins can be very important in regulating enzyme activity. Modest changes in structure can have a big impact on the conformation of the protein, which in turn might open or close access into the enzyme's interior or alter the shape of the active site. Alternatively, these changes might affect the location of a protein by moving it from the cell membrane into the cell interior or vice versa. They might also result in the formation or dissociation of supramolecular assemblies, by increasing or decreasing the attraction between two separate biomolecules.

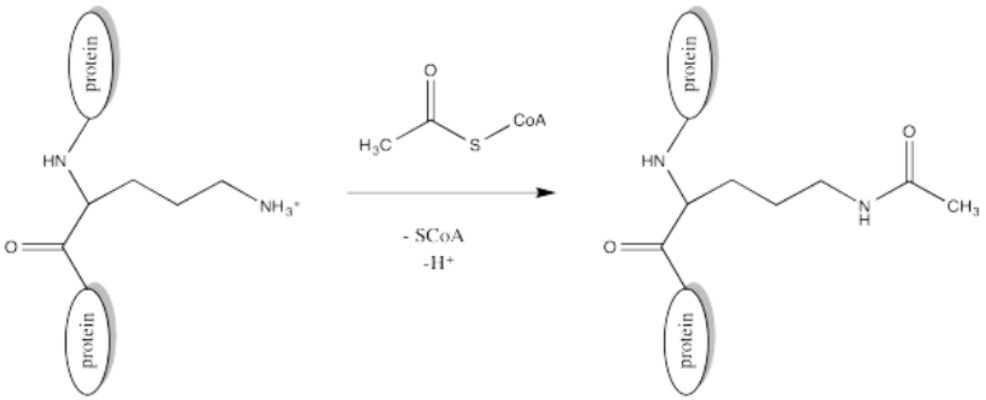


The physical reasons for these structure-property changes are based in simple intermolecular attractions or, in the case of a large, complicated protein, intramolecular attractions between different parts of the same protein. A hydrogen bonding interaction or ion-dipole interaction that holds the protein in one conformation may be disrupted if a key player in that interaction is suddenly masked. For example, a cationic ammonium side chain may react to become an amide group; the absence of a full positive charge on this group significantly alters its intermolecular attractions.

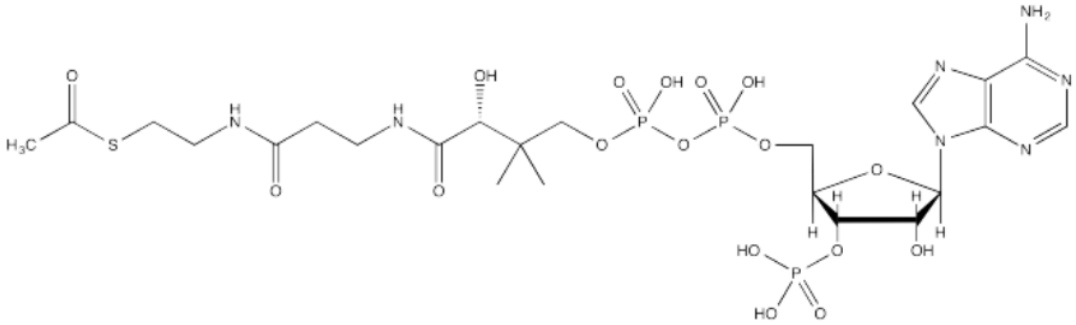
There are probably hundreds of ways in which proteins are modified. We will look at just a few different modifications that occur in proteins, some of which are closly tied to carboxylate substitution. Note that any of these modifications might act to turn an enzyme "off" or "on"; the details depend on the individual case.

Acetylation

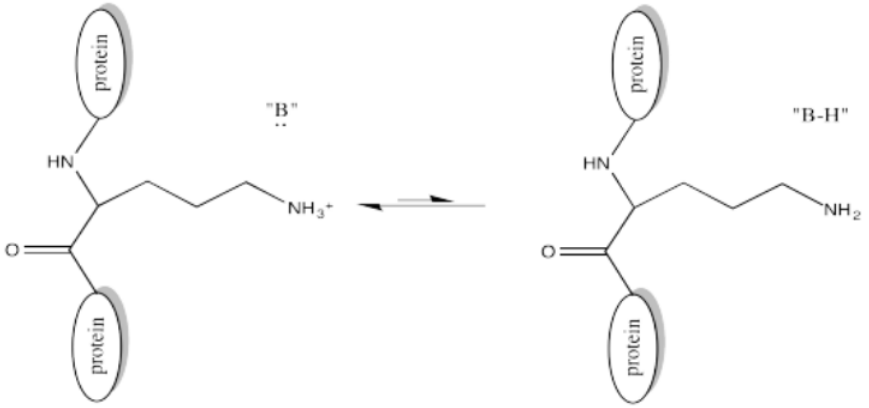
Acetylation is the attachment of an acetyl group, $CH_3C{=}O$, to another compound such as an amino acid residue. Serine and threonine groups might be acetylated to make esters, cysteine side chains might be acetylated to make thioesters, or amino groups. Frequently, acetylation refers specifically to reaction at an amino group, such as the N-terminus of a protein or in a lysine side chain, forming an amide.



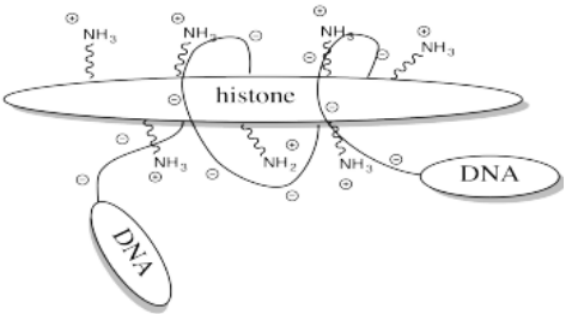
The source of the acetyl group is acetyl coenzyme A (AcSCoA, below), the thioester workhorse of the cell. This structure may seem a little bit complicated, but at the most basic level it is just a carboxyl electrophile ($CH_3C{=}O$) attached to a very large thiolate leaving group.



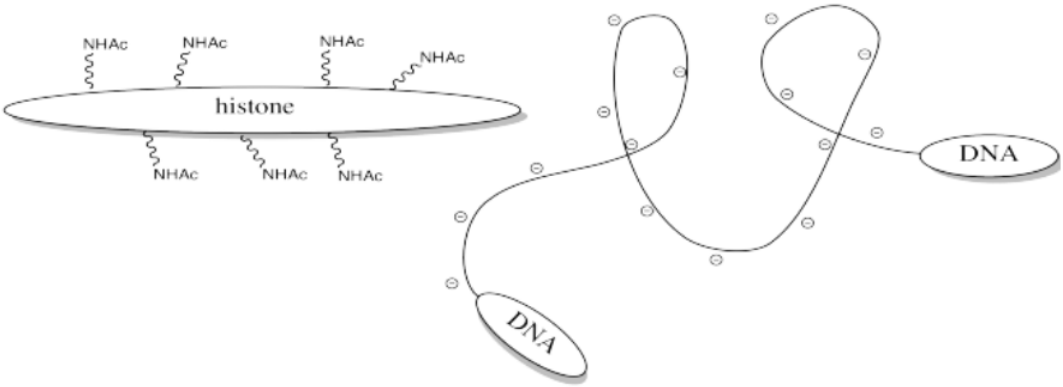
Of course, lysine side chains and the N-termini of proteins are usually in a protonated state under biological conditions. That means that there must be a deprotonation step along the reaction pathway.



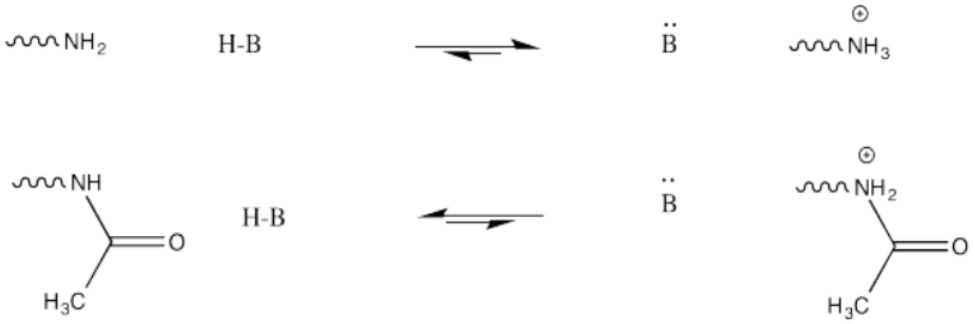
One example of the role of acetylation is seen in histones. Histones are proteins found in chromatin, the mixture of DNA and proteins in the cell nucleus. The already-coiled DNA helix is further wrapped around histones, bundling it up into a smaller package. DNA has many, many negative charges all along it because the phosphate units in its phosphate-sugar copolymer backbone are negatively charged at typical biological pH. The DNA interacts easily with the histones because they are rich in positively charged lysine residues.



Storing DNA in smaller bundles lets you keep more junk in your nucleus, but you don't want to just let the DNA sit there. Once in a while you want to take it out and do something with it, but how can you do that when it's stuck to those darned histones? The answer is, you just have to turn off the histones' force field. Get rid of that positive charge, and the DNA won't be stuck anymore. It's easy to do that by acetylating the histones.



This change in charge results because, although amines are easily protonated, amides are not. Thus, amines are likely to carry positive charge under biological conditions, whereas amides are likely to be neutral.

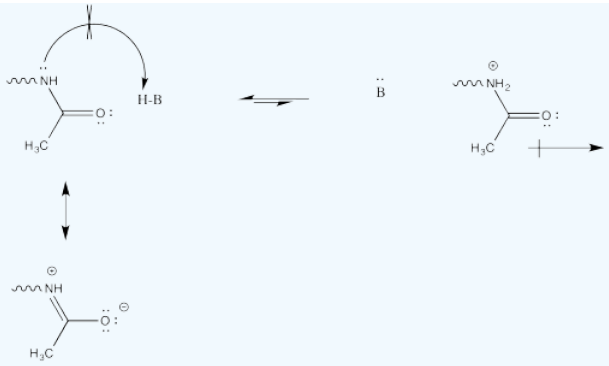


Exercise 5.2.1

Explain why an amine is easily protonated but an amide is not.

Answer

This change in charge results because, although amines are easily protonated, amides are not. Protonation of an amide would result in a cation adjacent to the very positive carbonyl carbon, leading to a buildup of localized positive charge. That wouldn't be easy. Furthermore, the amide nitrogen is not very likely to donate its electrons to a proton in the first place. Its protons are too busy. They are tied up in conjugation with the carbonyl, so they really aren't available to act as the lone pair of a base.

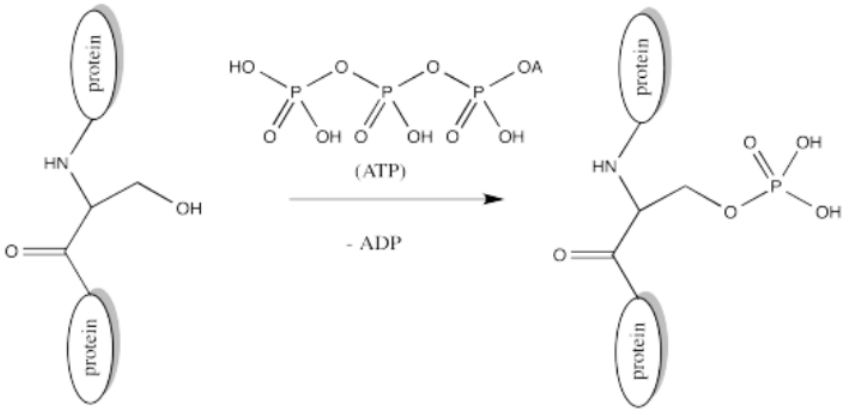


Exercise 5.2.2

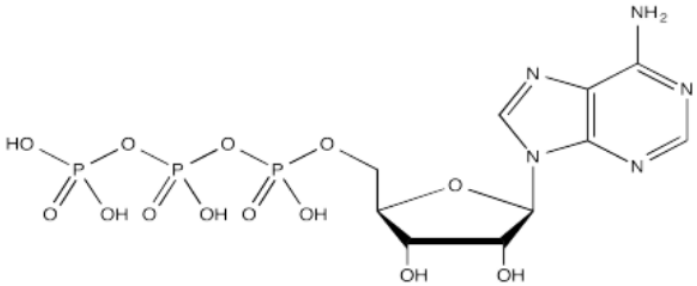
Provide a mechanism for the acetylation of a lysine side chain. Assume the presence of histidine and its conjugate acid, histidinium ion; these species are common proton shuttles in biological reactions.

Phosphorylation

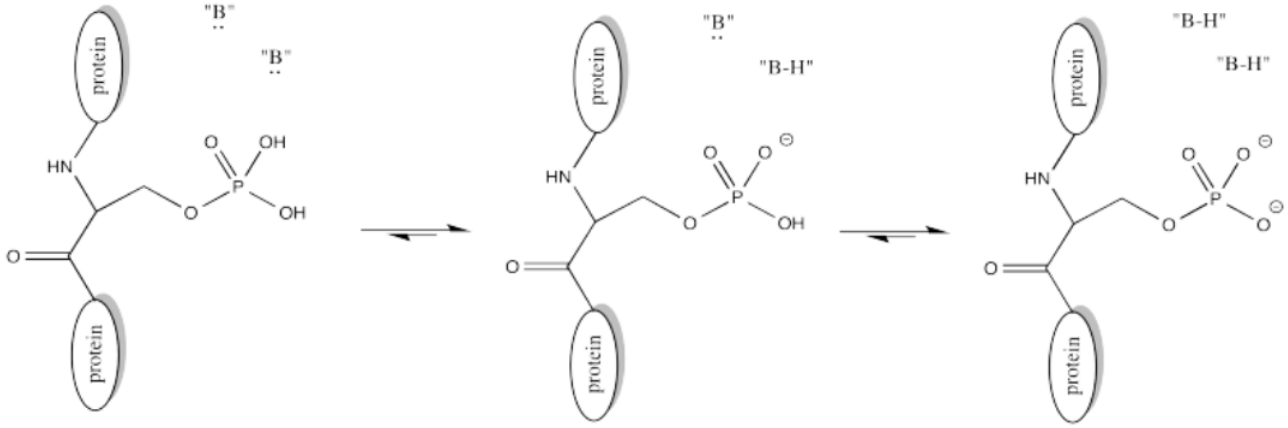
Serine, tyrosine and threonine residues are frequently modified by phosphorylation, which is the formation of a phosphate ester. The phosphorylation of these groups results in a change from a neutral side chain to an anionic side chain. The phosphate donor in these cases is another ubiquitous cellular performer, ATP.



The complete structure of ATP is shown here. It is a little less complicated than AcSCoA. Once again, at the most basic level of reactivity, it provides a phosphate electrophile, attached to a phosphate leaving group.



The anionic nature of the phosphate may not be apparent in the above drawing of ATP, but in reality, at biological pH, a phosphate would be deprotonated. Phosphates actually undergo multiple equilibria involving the loss of two protons.

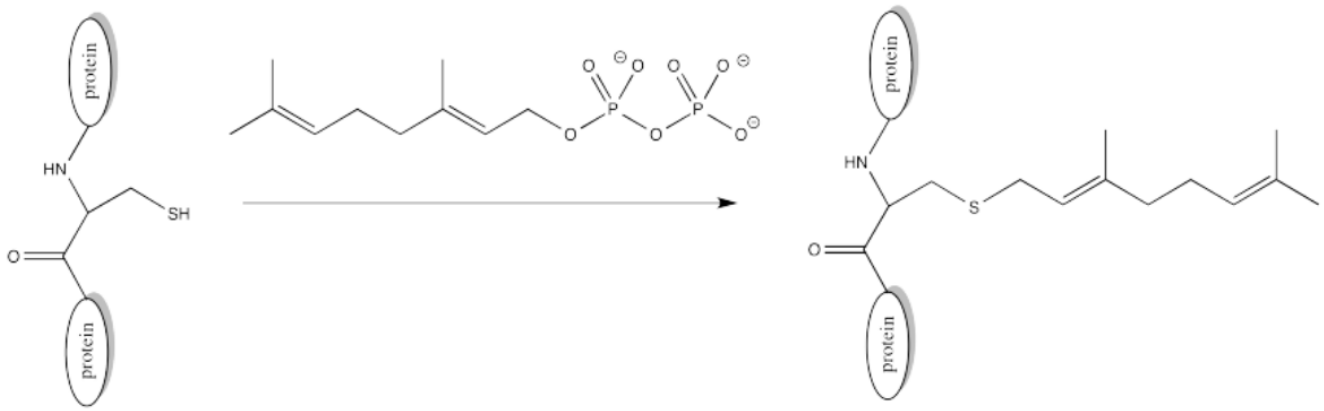


Exercise 5.2.3

Provide a mechanism for phosphorylation of serine in the presence of an appropriate biological proton shuttle.

Alkylation (Farnesylation)

There are other modifications that occur via different mechanisms. In a farnesylation, reaction does not even take place at a carbonyl. It does not take place at a phosphonate or a sulfonate.

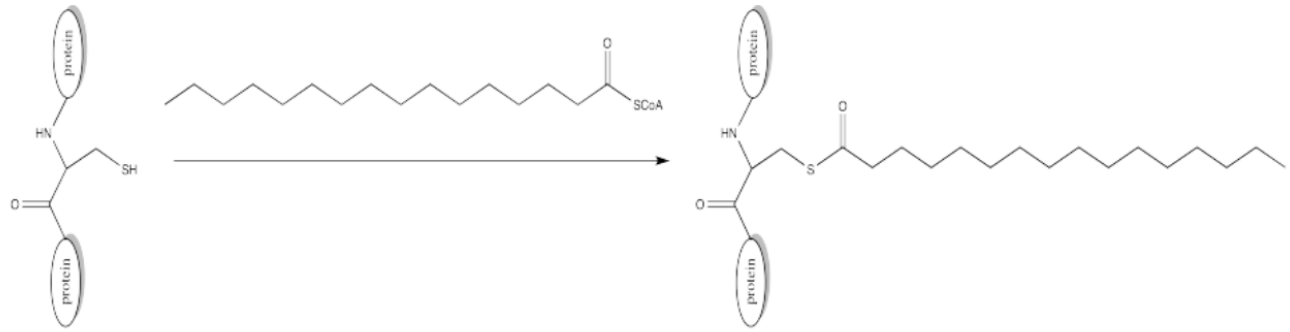


Exercise 5.2.4

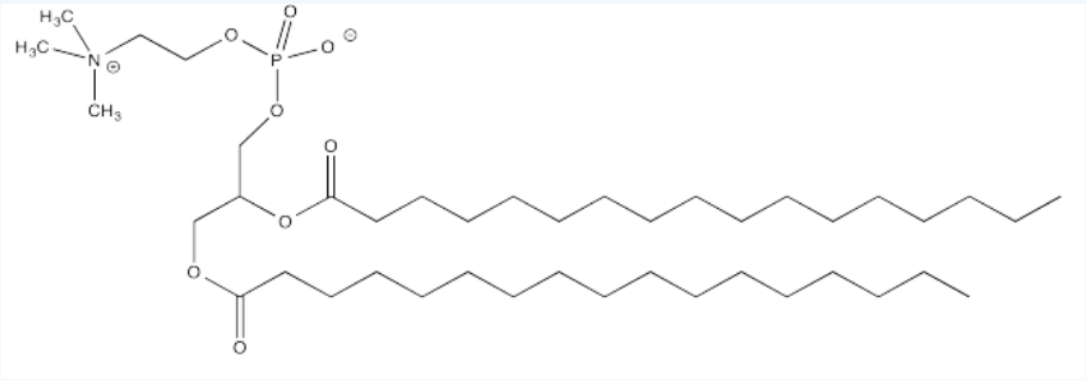
Sulfur is the nucleophile in the farnesylation shown above. Identify the electrophile and show a mechanism with curved arrows.

Exercise 5.2.5

Palmitoylation is closely related to acetylation, but the electrophile in this case is a palmitoyl group instead of an acetyl.



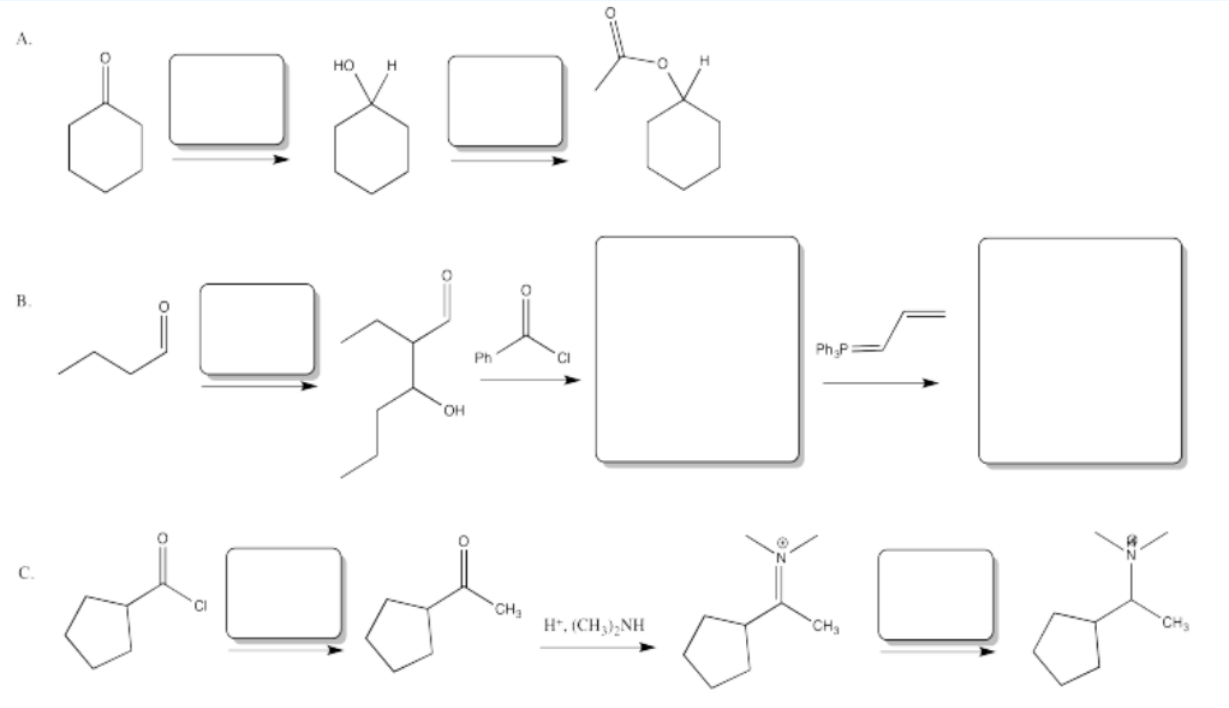
a. Provide a mechanism for palmitoylation of cysteine in the presence of an appropriate biological proton shuttle.
b. Explain how palmitoylation might influence the interaction of a protein with a cell membrane, composed of phospholipids like this one:



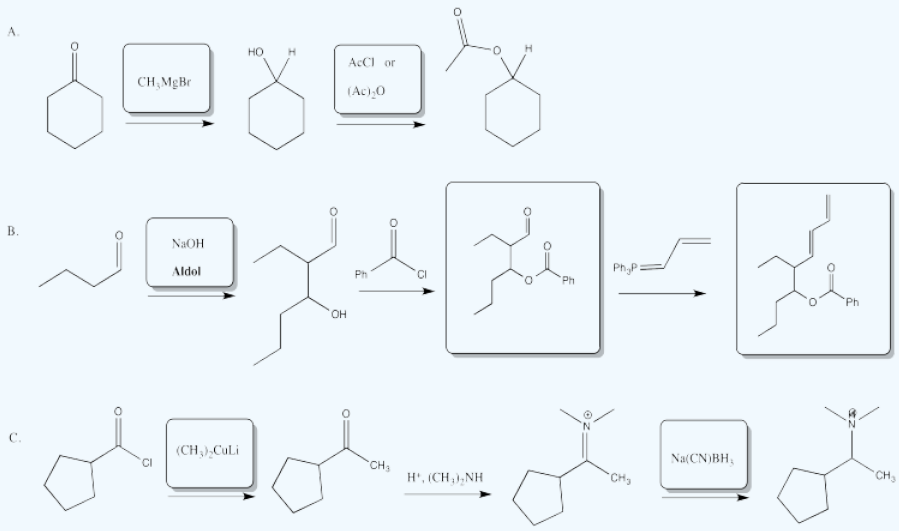
5.3: Additional Problems

Exercise 5.3.1

Fill in the blanks in the following syntheses.



Answer

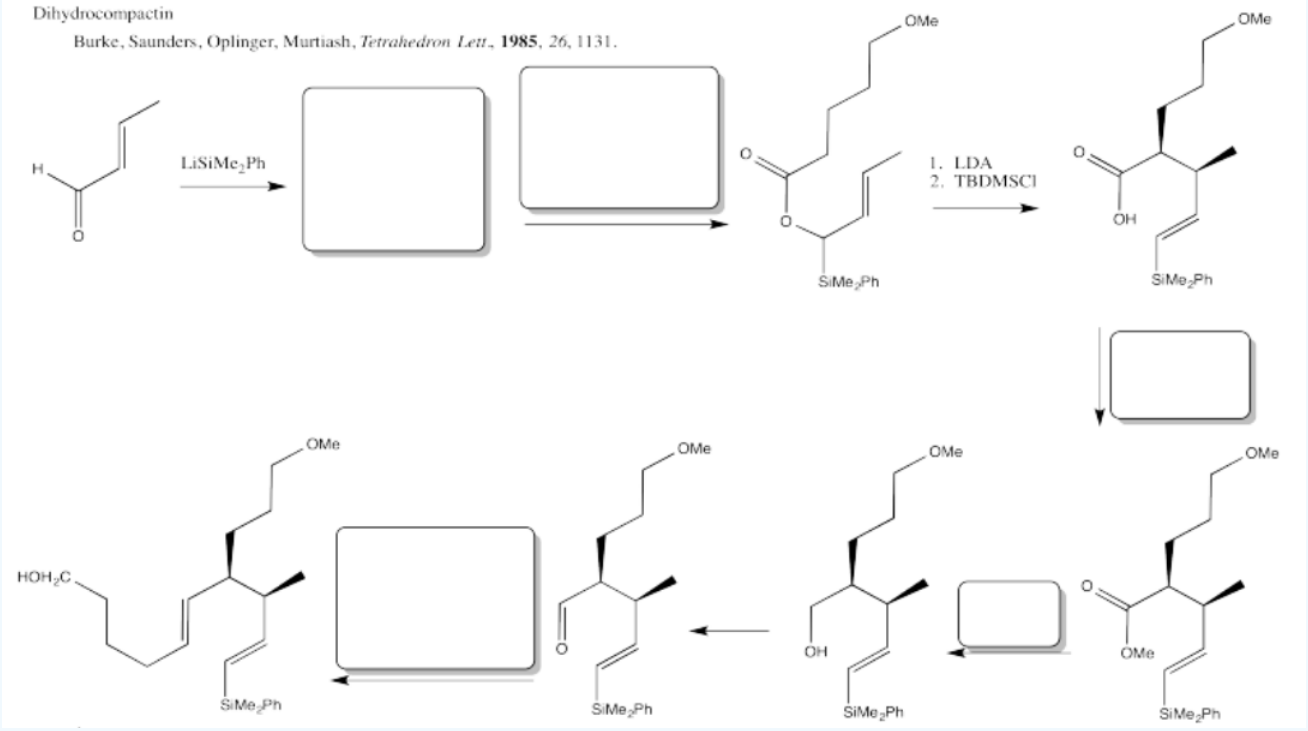


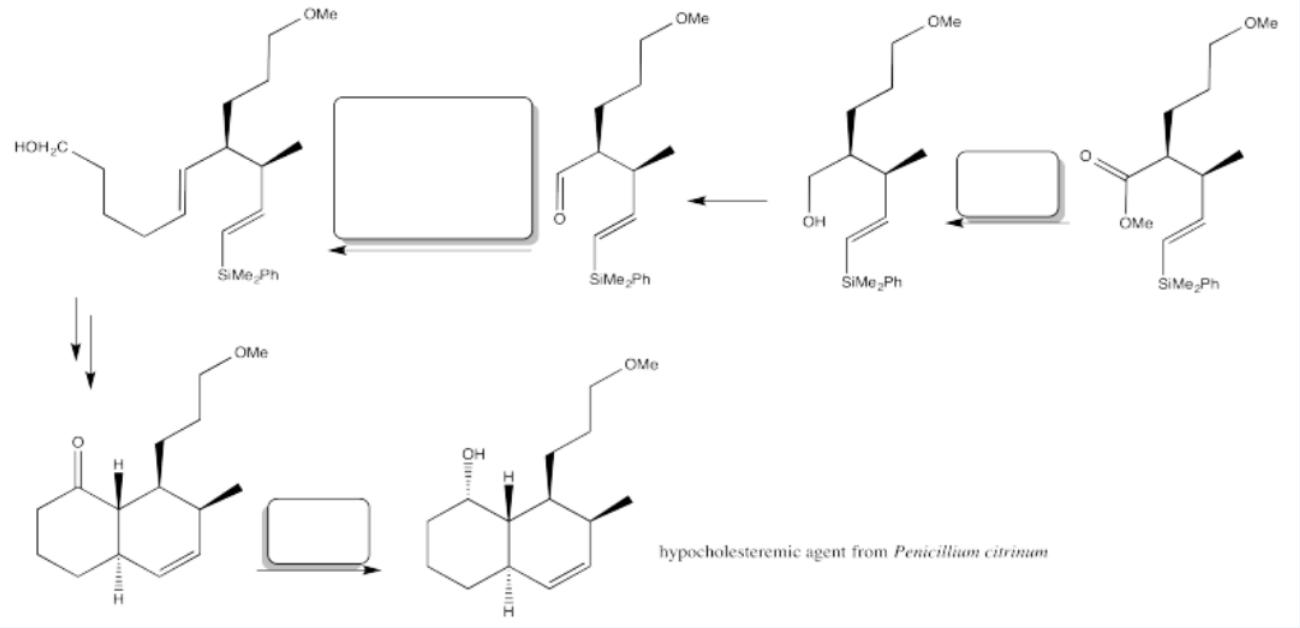
Exercise 5.3.2

Fill in the blanks in the following synthesis involving *anionic nucleophilic addition to carbonyl* and *nucleophilic substitution at carboxyl.*

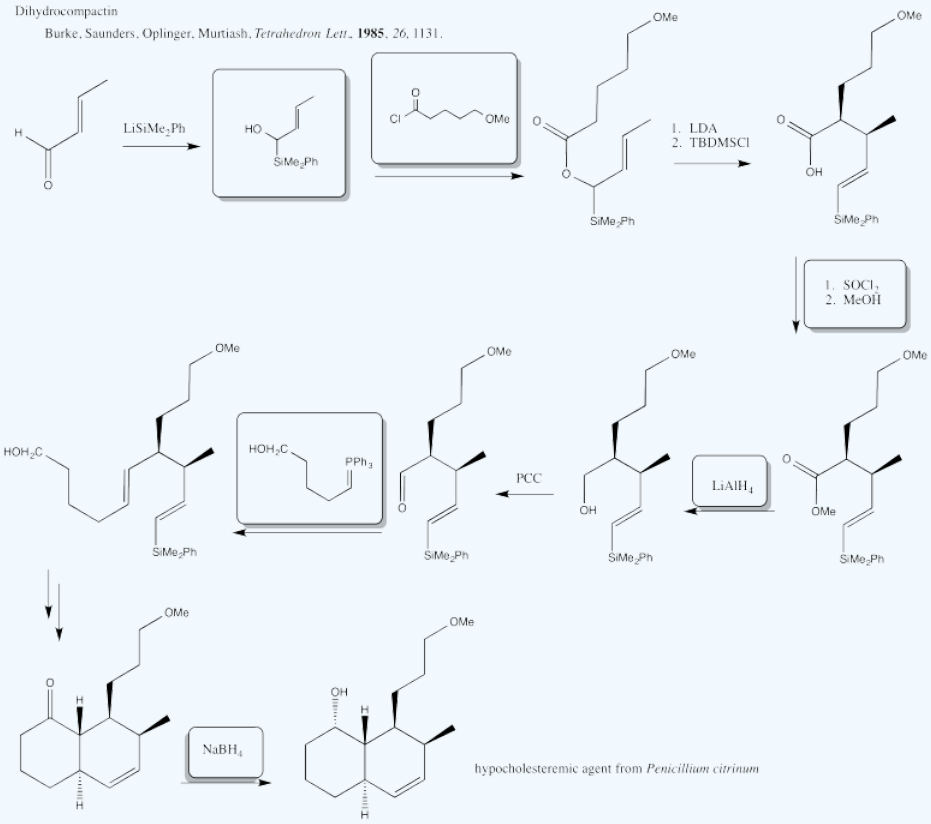
Dihydrocompactin

Burke, Saunders, Oplinger, Murtiash, *Tetrahedron Lett.*, **1985**, *26*, 1131.



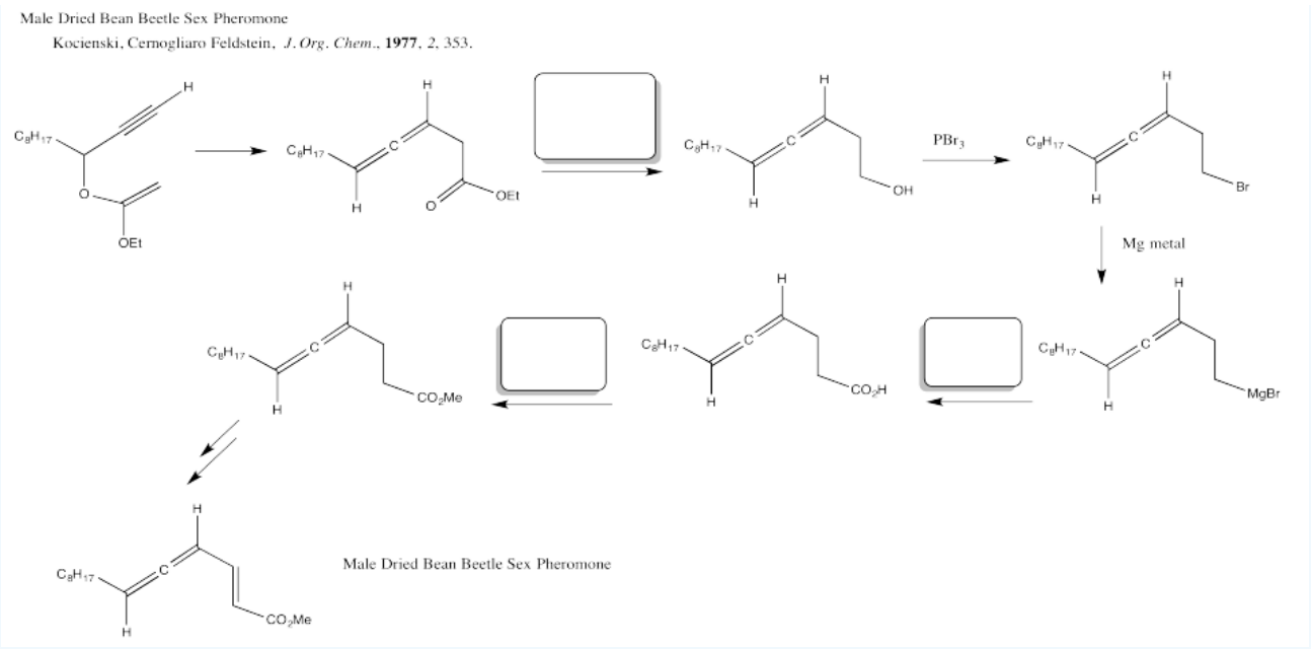


Answer

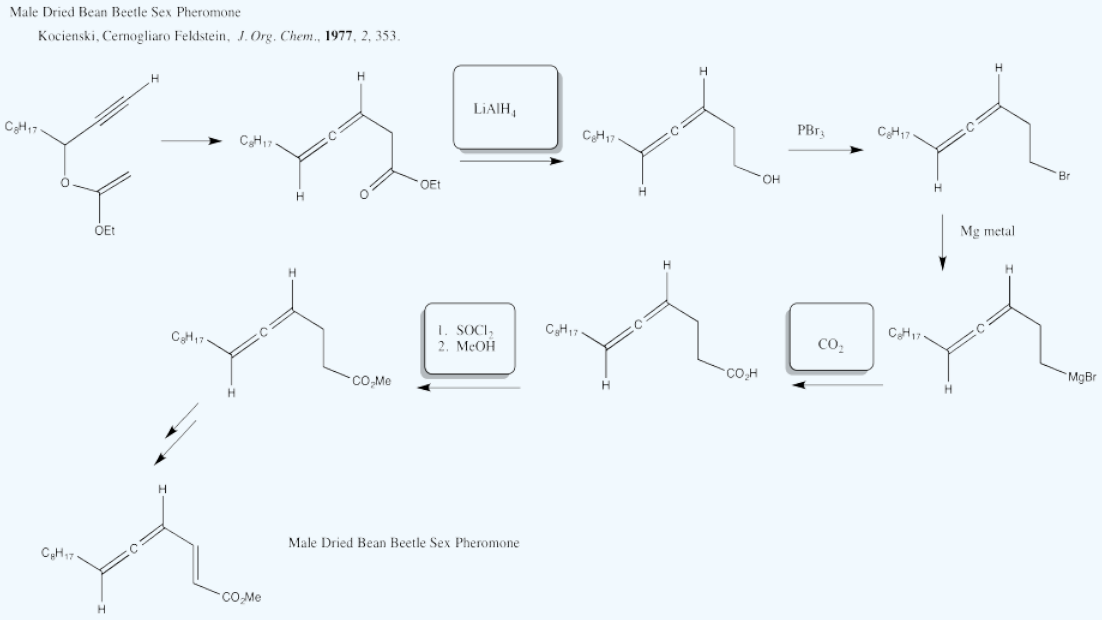


Exercise 5.3.3

Fill in the blanks in the following synthesis involving *anionic nucleophilic addition to carbonyl* and *nucleophilic substitution at carboxyl.*



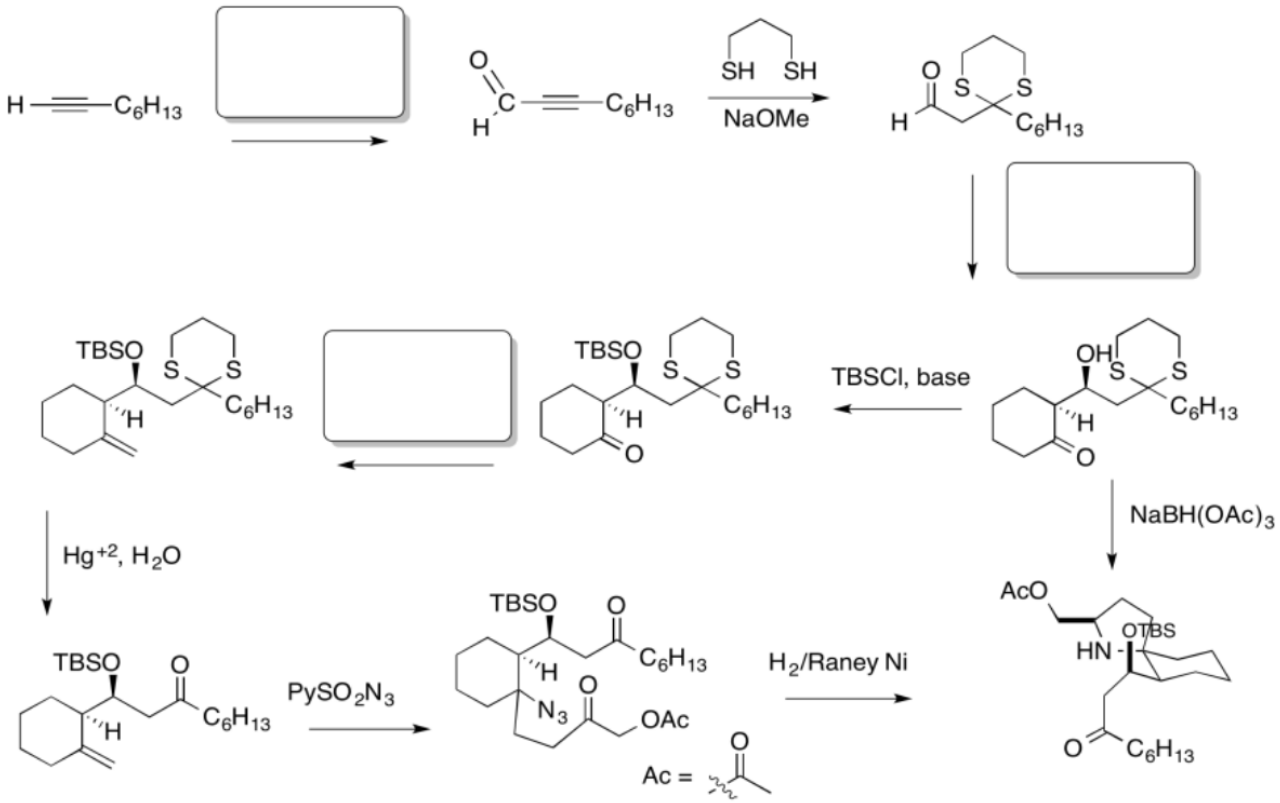
Answer

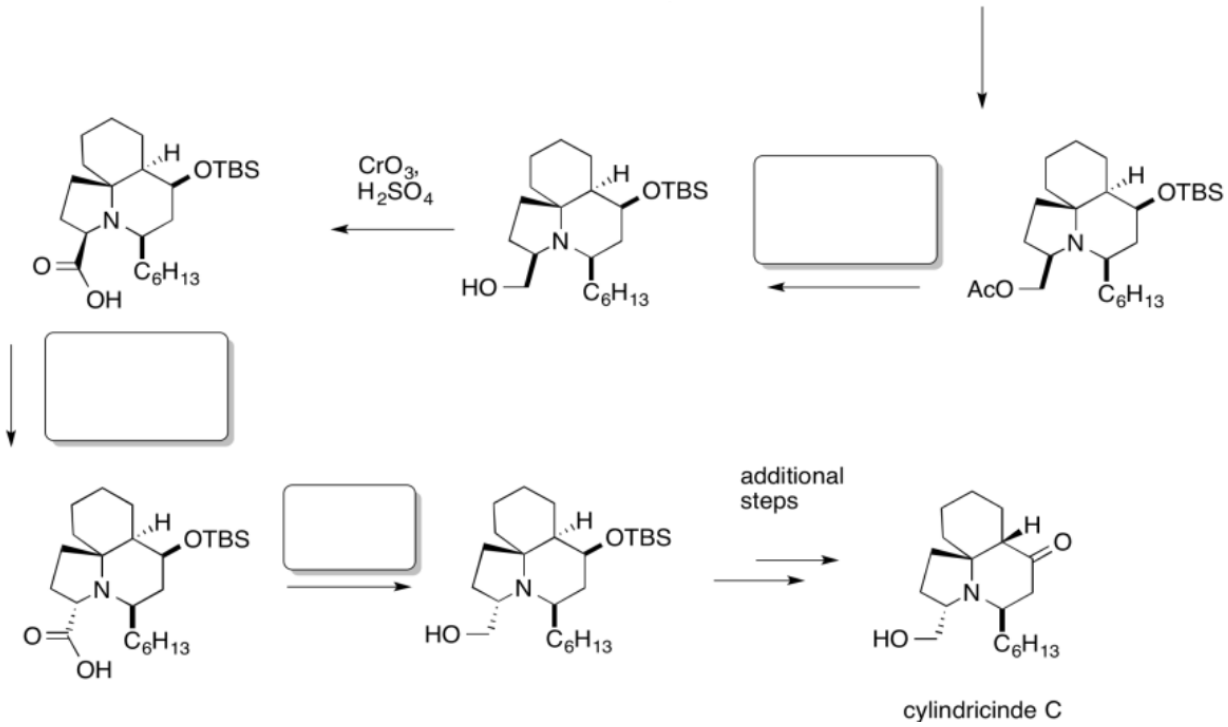


Exercise 5.3.4

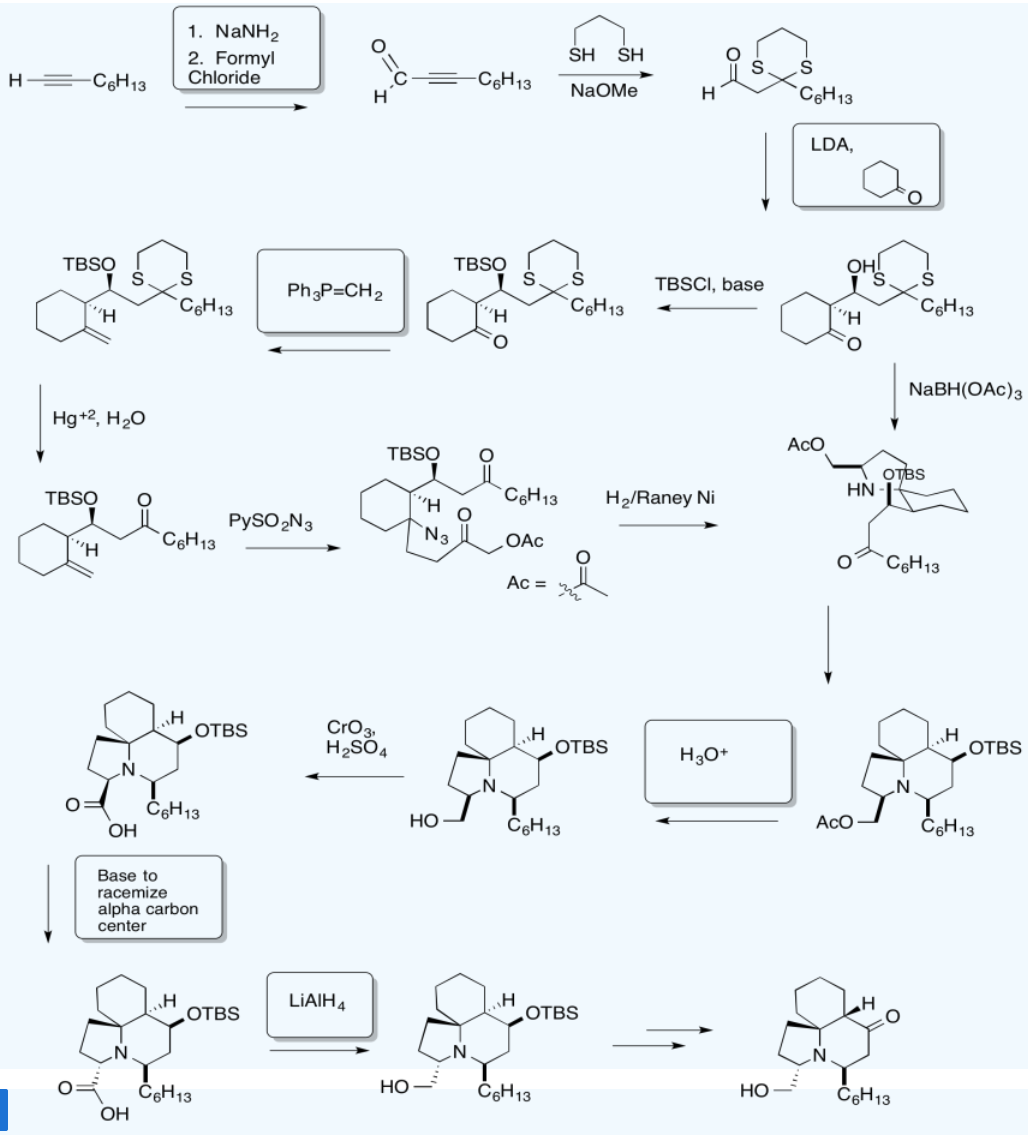
Fill in the blanks in the following synthesis involving *anionic nucleophilic addition to carbonyl* and *nucleophilic substitution at carboxyl* (including Wittig and aldol reactions).

Total Synthesis of Cylindricine C, Lapointe, Schenk, and Renaud, *Org Lett,* **2011**, *13*(18), 4774-4777.



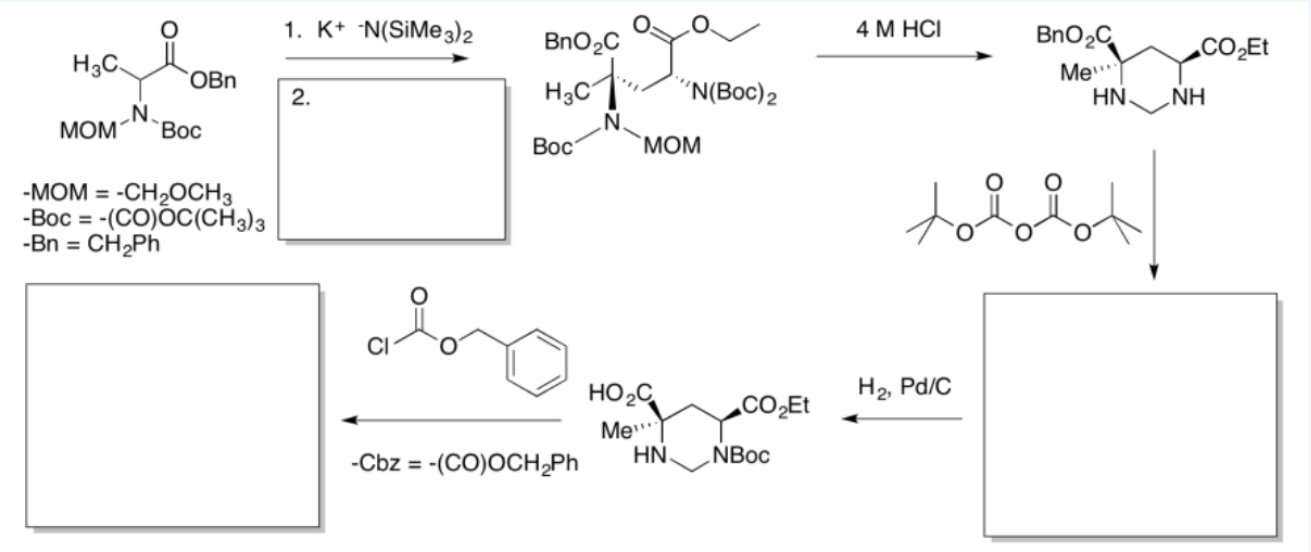


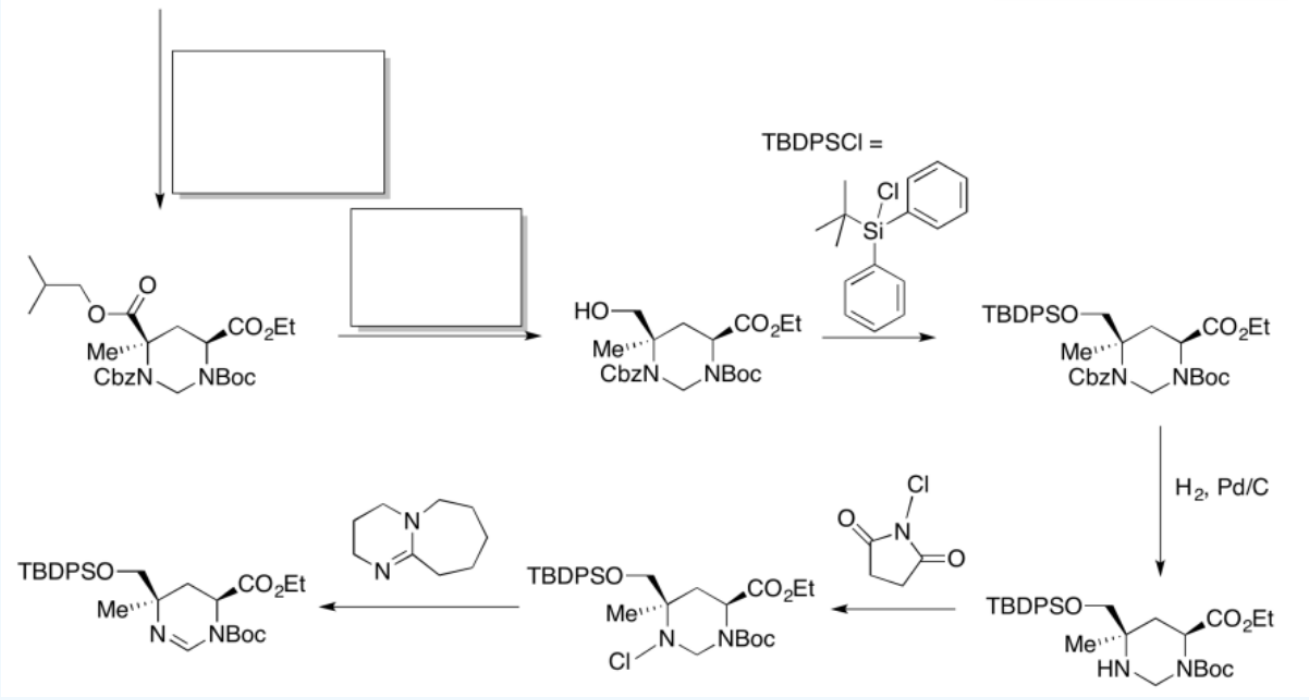
Answer

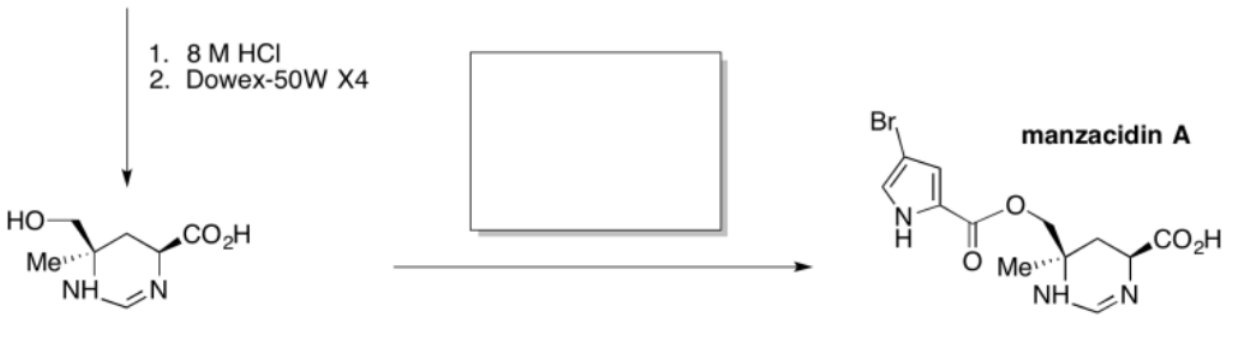


Exercise 5.3.5

Fill in the blanks in the following synthesis involving *nucleophilic substitution at carboxyl.*

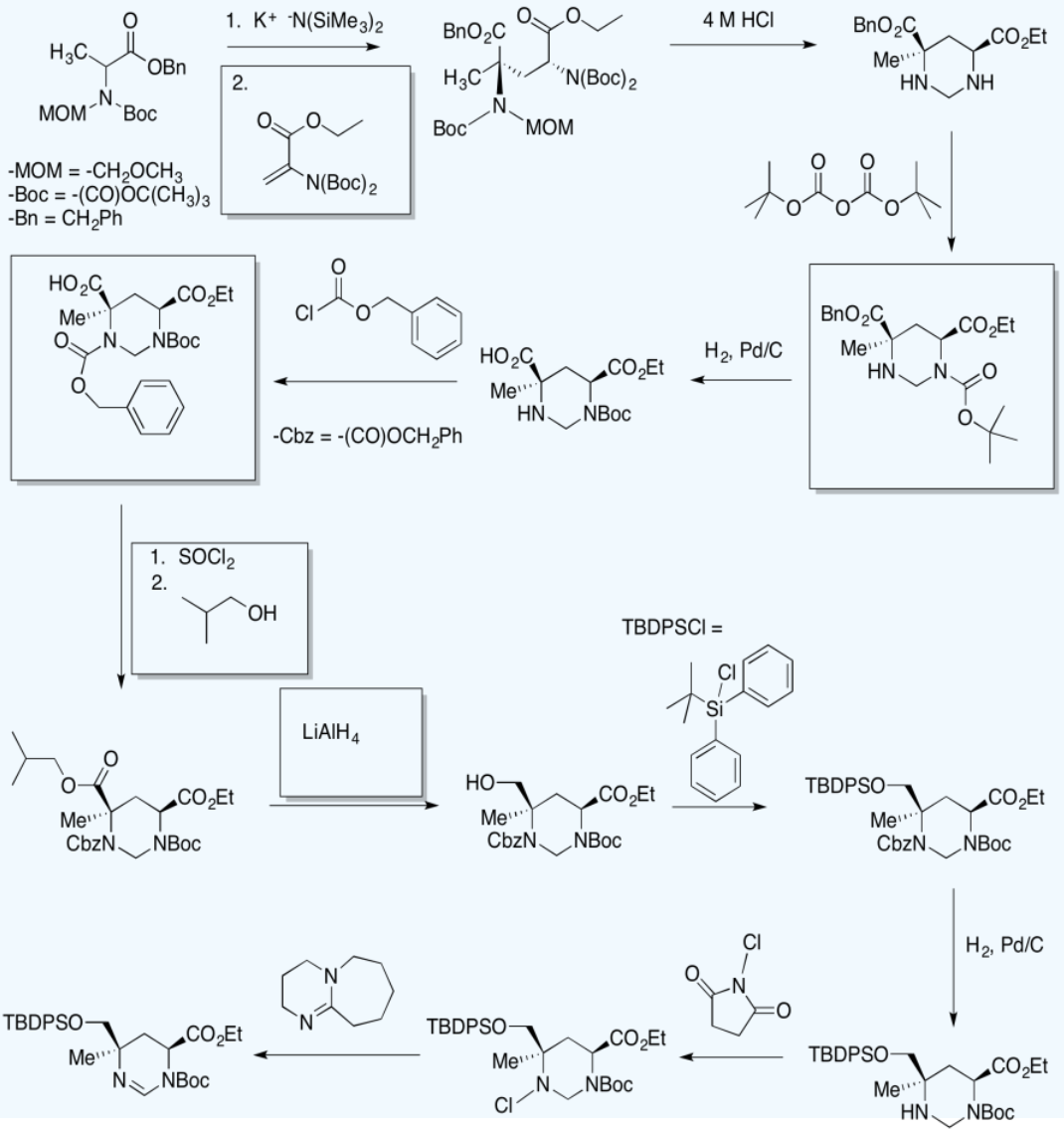






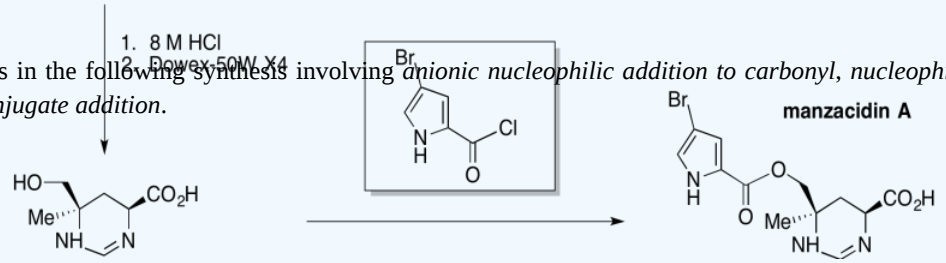
Answer

Total Synthesis of Manzacidin A (Kawabata, Kyoto University, 2013)
Isolated from Okanawan sponge *Hymeniacidon* sp. Extremely low isolated quantities prevented biological assays with naturally-available material.

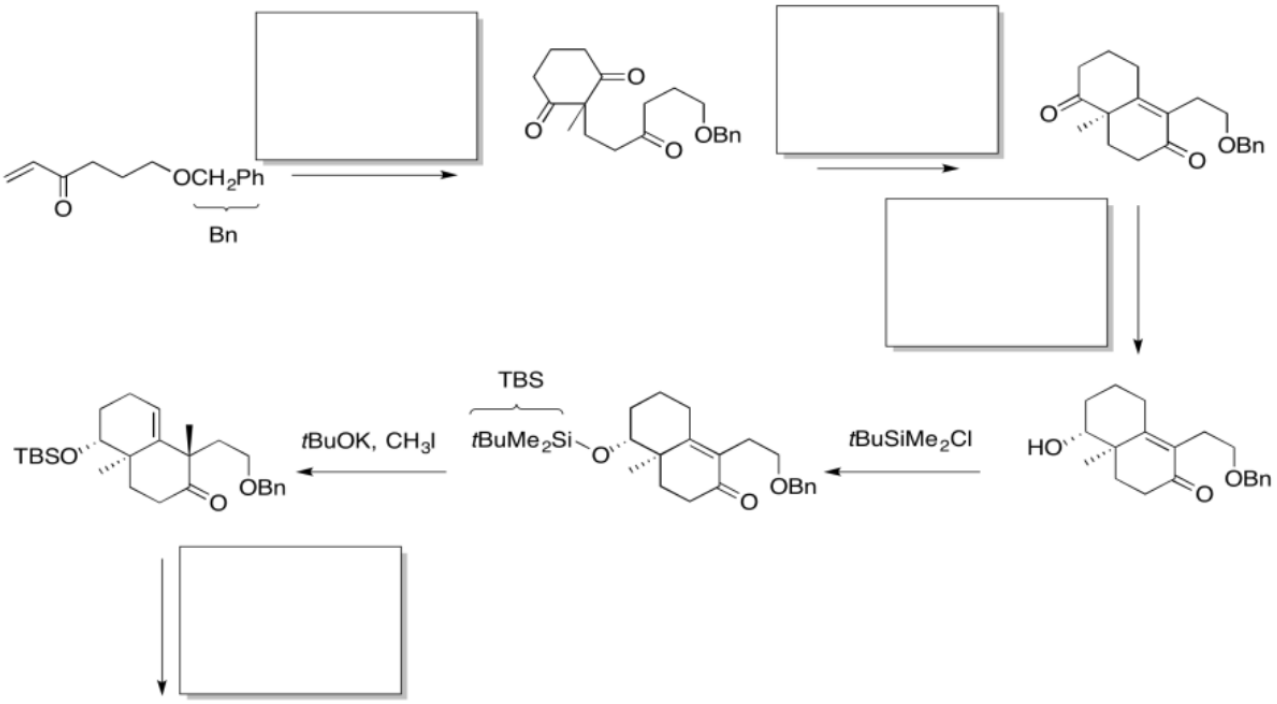


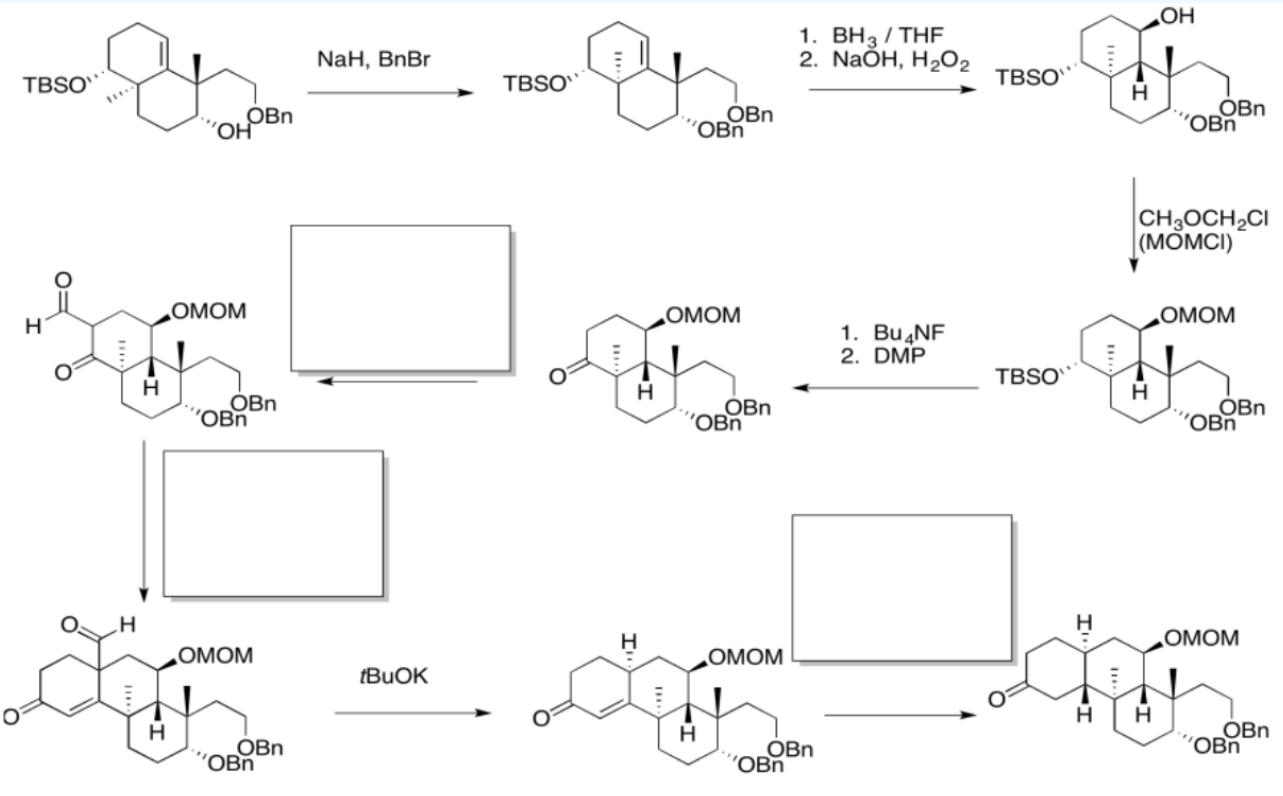
Exercise 5.3.6

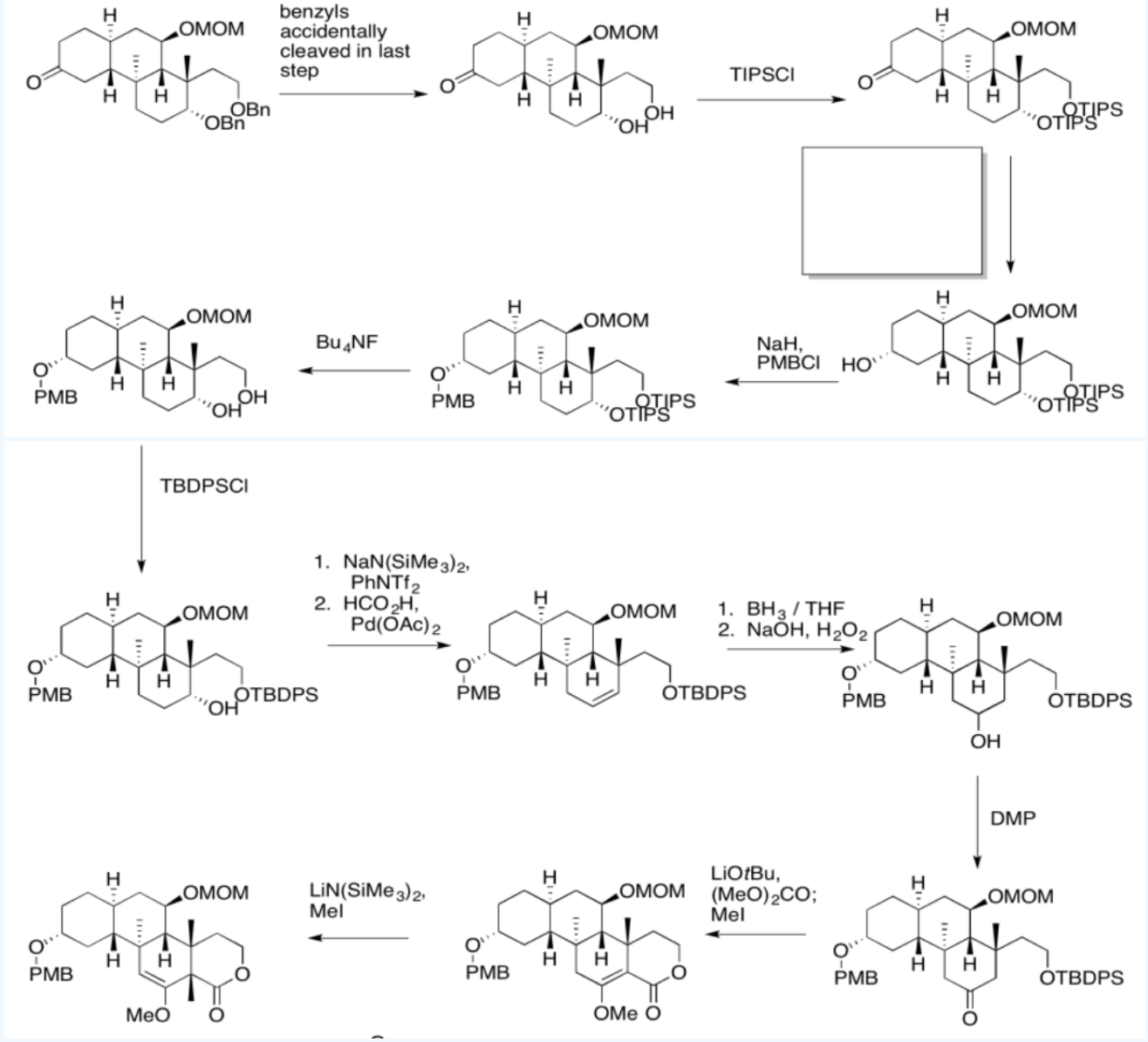
Fill in the blanks in the following synthesis involving *anionic nucleophilic addition to carbonyl*, *nucleophilic substitution at carboxyl* and *conjugate addition*.

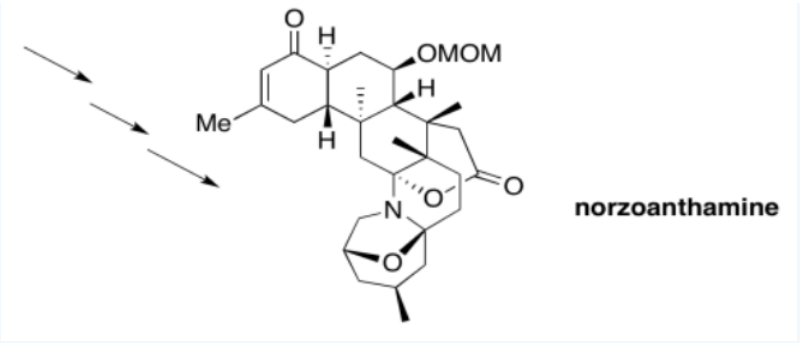


Partial Syntheses of Norzoanthamine (Thoedorakis, UCSD, 2011)
Marine natural product of *Zoanthus sp.* Demonstrated anti-osteoporotic effects in mice.



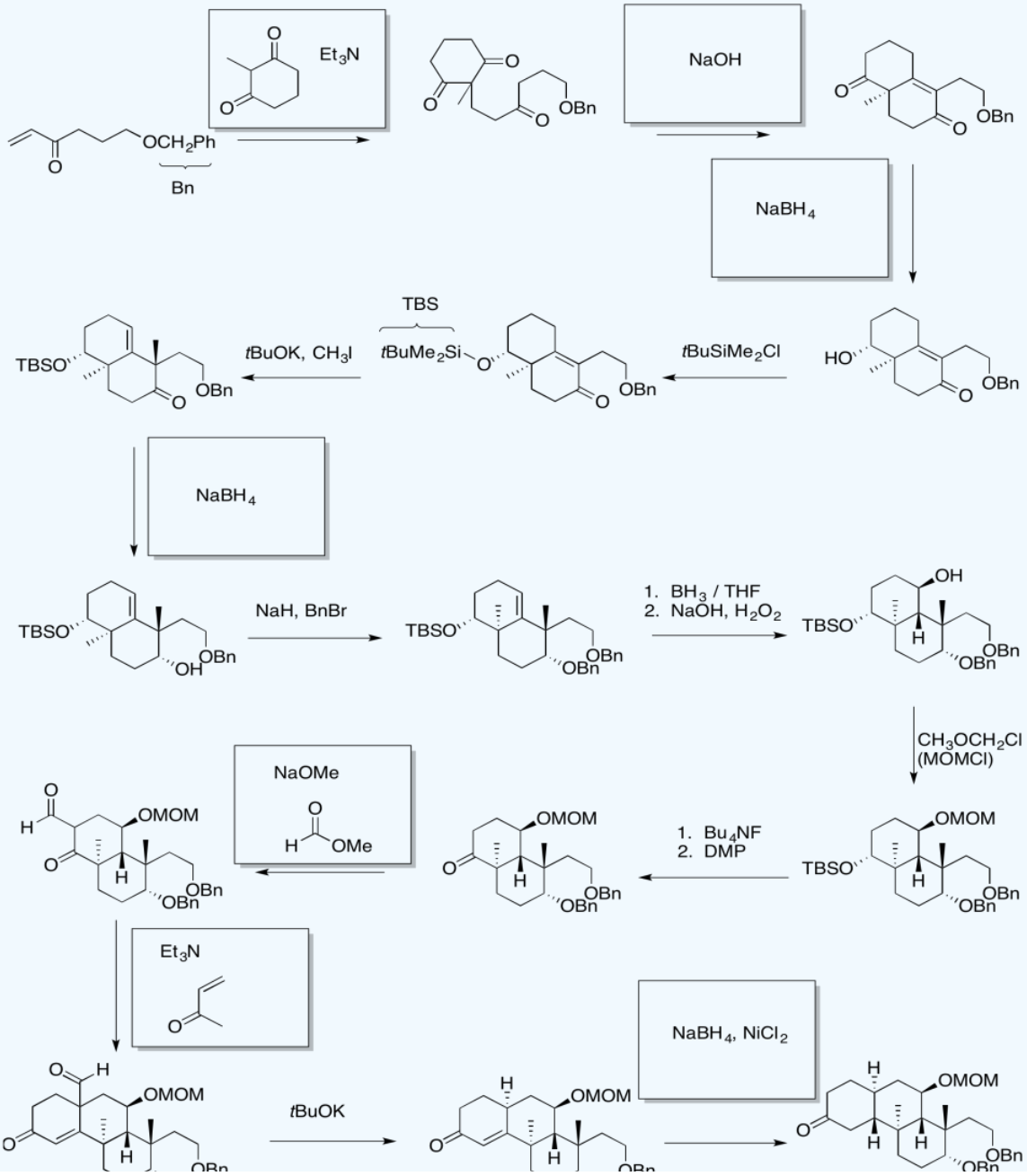


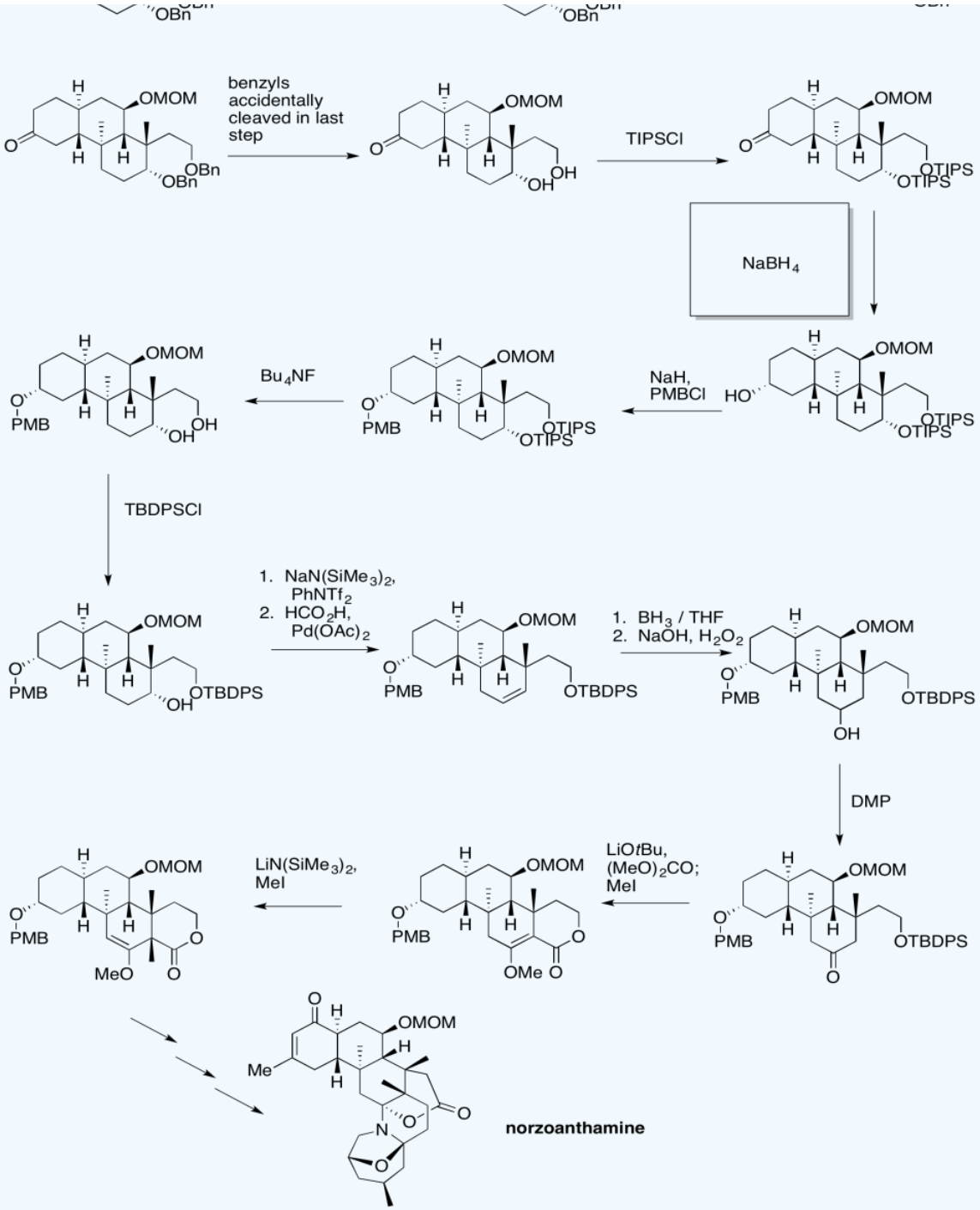




Answer

Partial Syntheses of Norzoanthamine (Thoedorakis, UCSD, 2011)
Marine natural product of *Zoanthus sp.* Demonstrated anti-osteoporotic effects in mice.



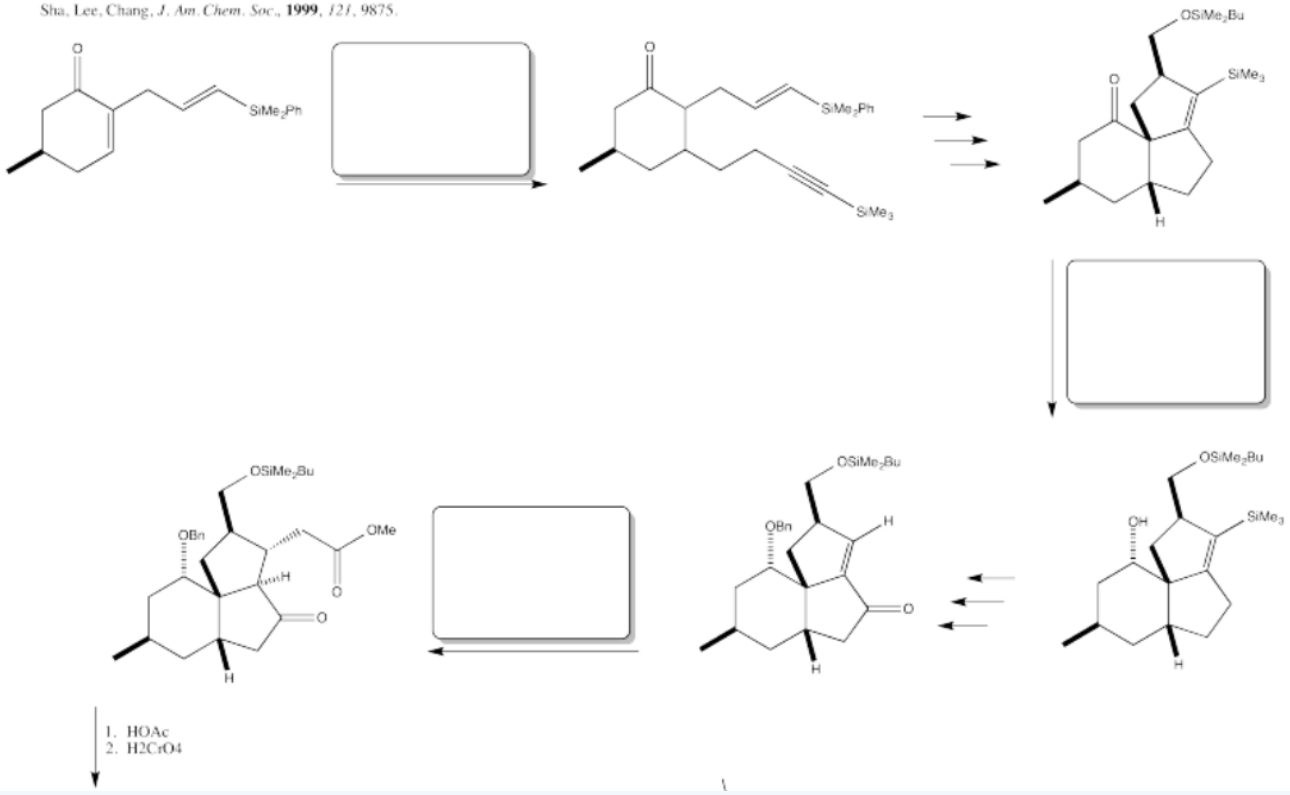


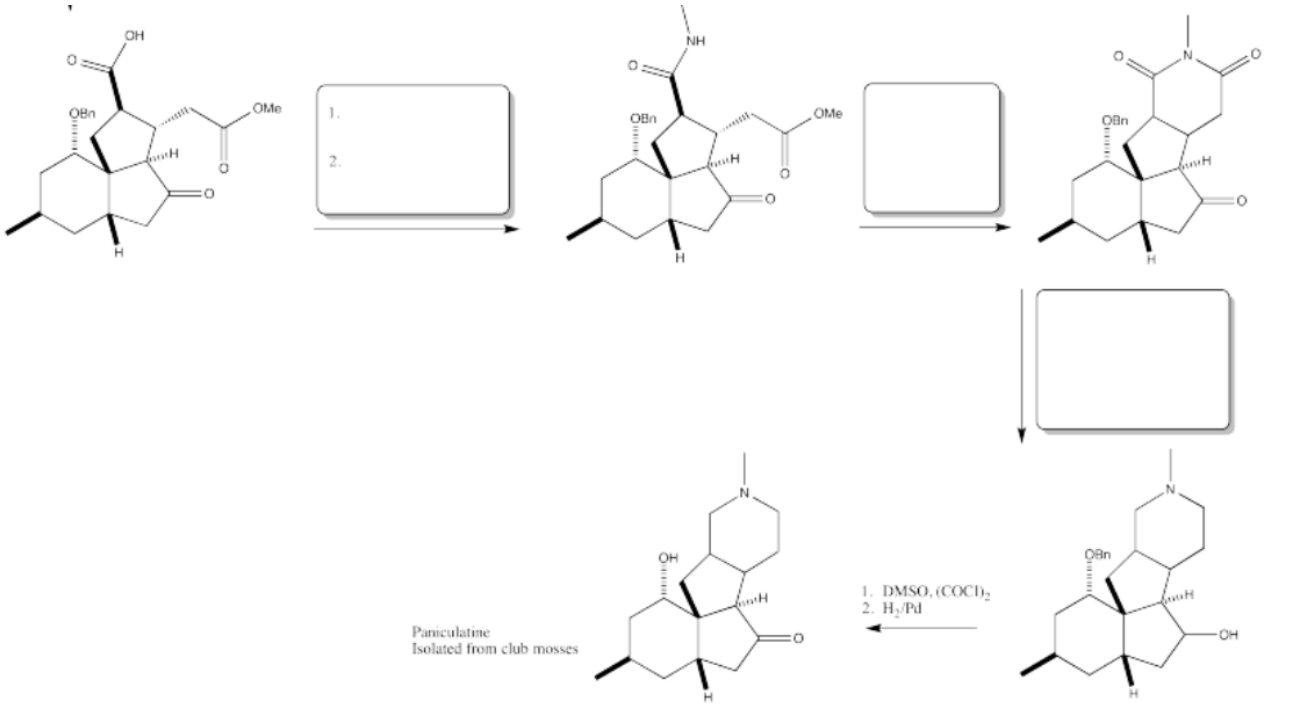
Exercise 5.3.7

Fill in the blanks in the following synthesis involving *anionic nucleophilic addition to carbonyl*, *conjugate addition* and *nucleophilic substitution at carboxyl*.

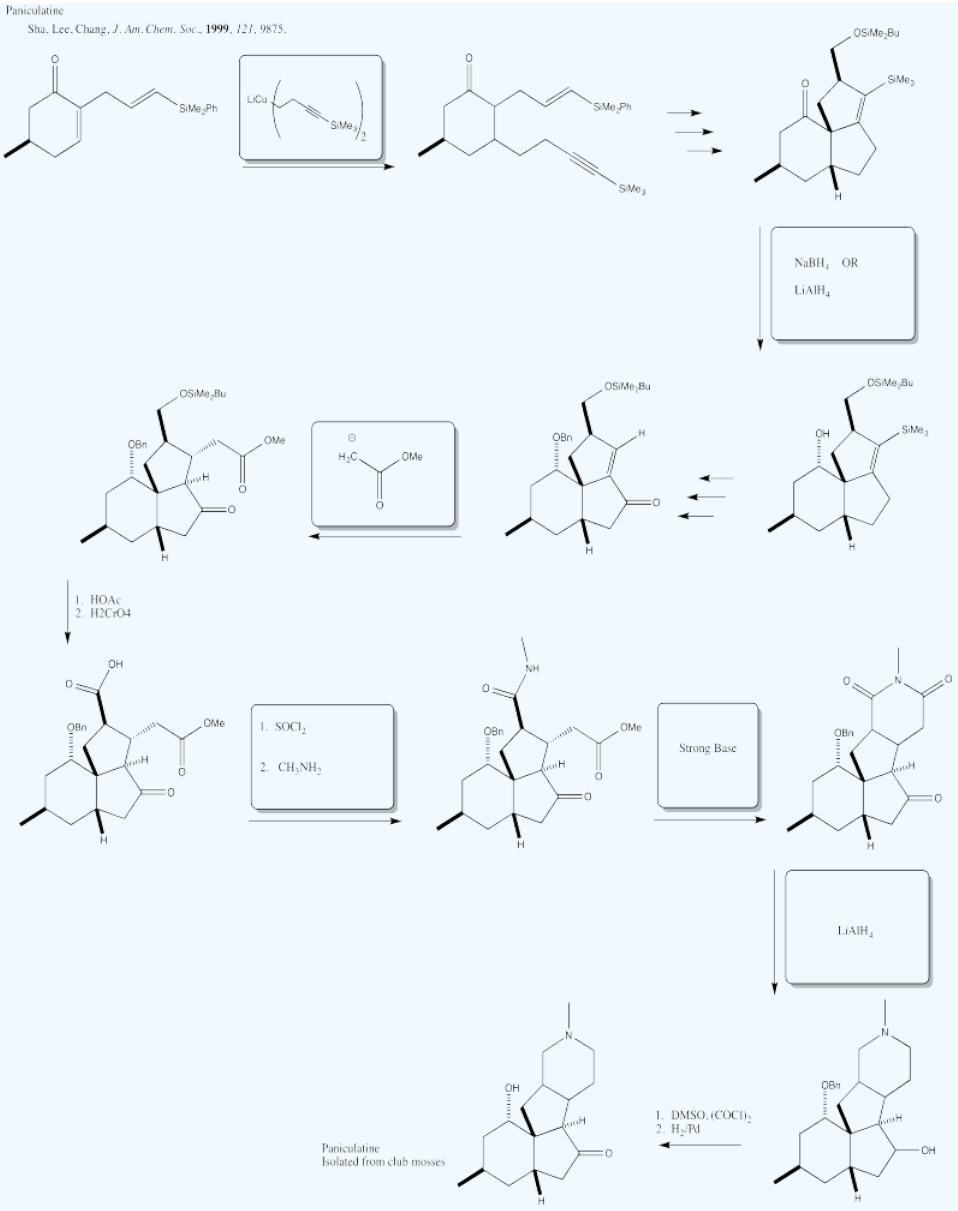
Paniculatine

Sha, Lee, Chang, *J. Am. Chem. Soc.*, **1999**, *121*, 9875.





Answer



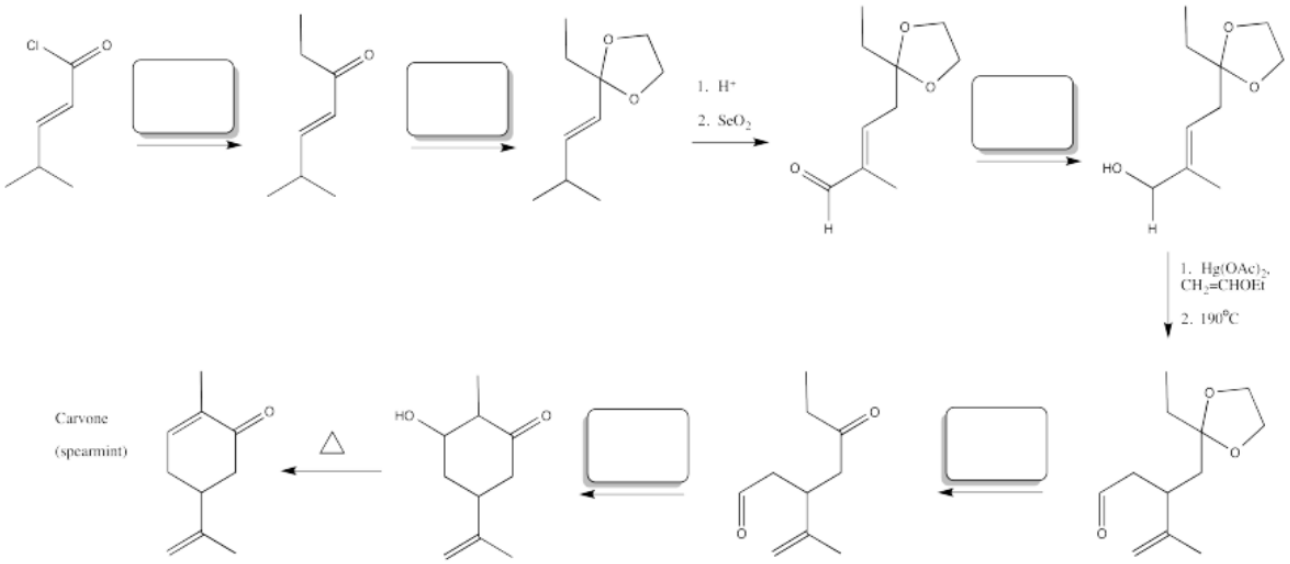
Exercise 5.3.8

Fill in the blanks in the following synthesis involving *anionic nucleophilic addition to carbonyl*, *nucleophilic substitution at carboxyl* and *neutral nucleophilic addition to carbonyl*.

Carvone

Nu Sub, Anionic Nu Add, Neutral Nu Add

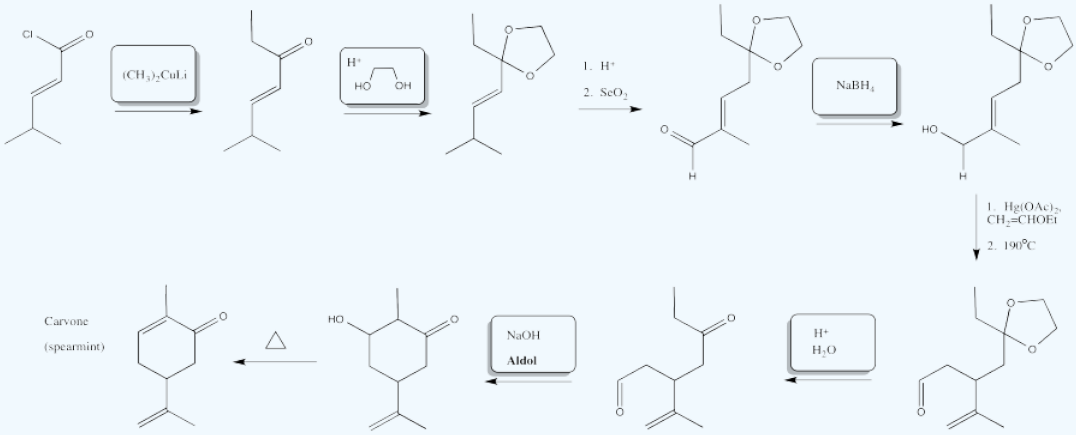
Vig, Sharma, Chander, Raj, *Ind. J. Chem.*, **1966**, *4*, 275.



Answer

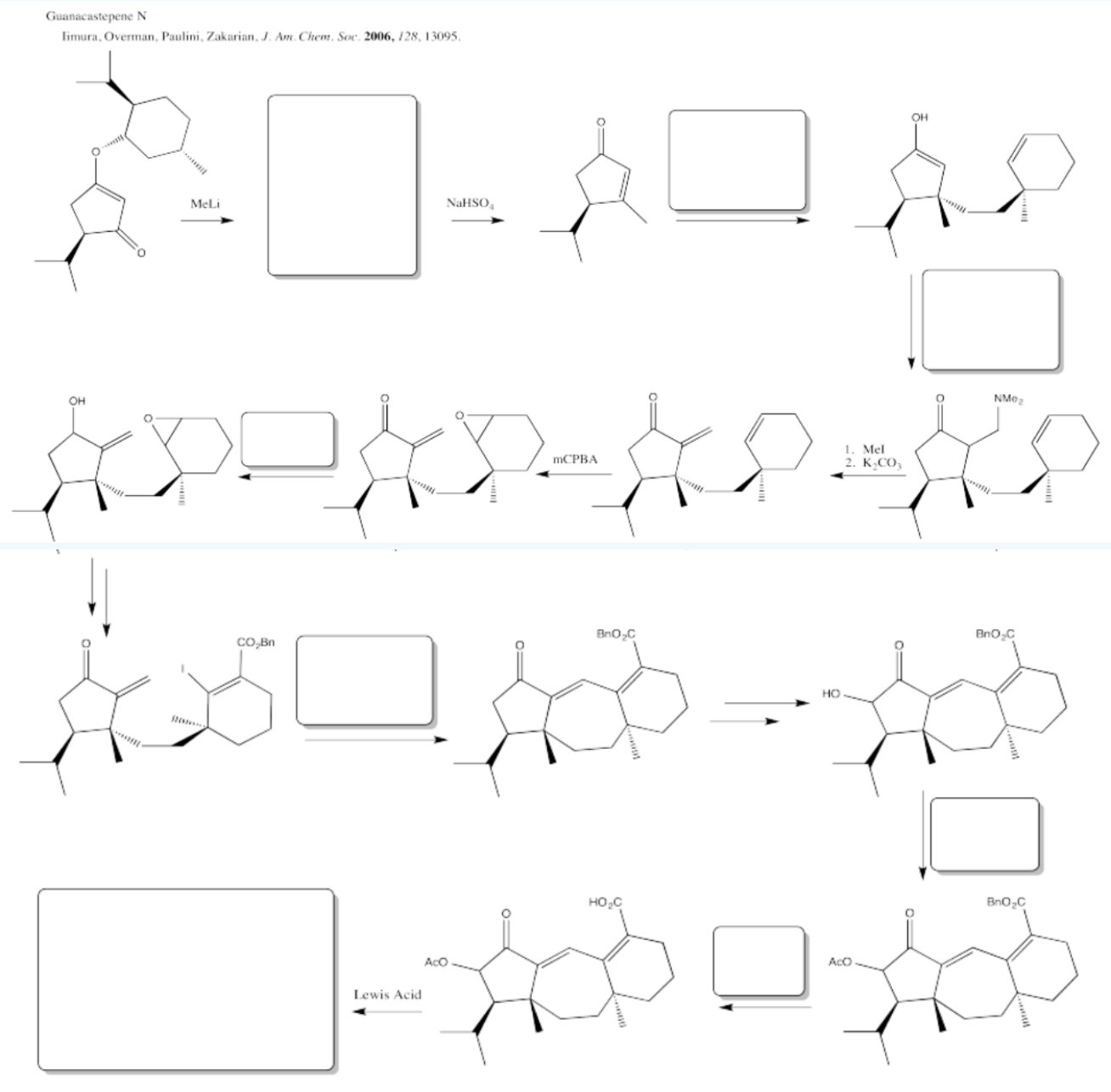
Carvone

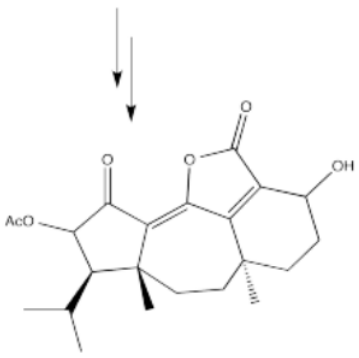
Vig, Sharma, Chander, Raj, *Ind. J. Chem.*, **1966**, *4*, 275.



Exercise 5.3.9

Fill in the blanks in the following synthesis involving anionic nucleophilic addition to carbonyl/em>, conjugate addition, nucleophilic substitution at carboxyl and transition metal-catalysed coupling.

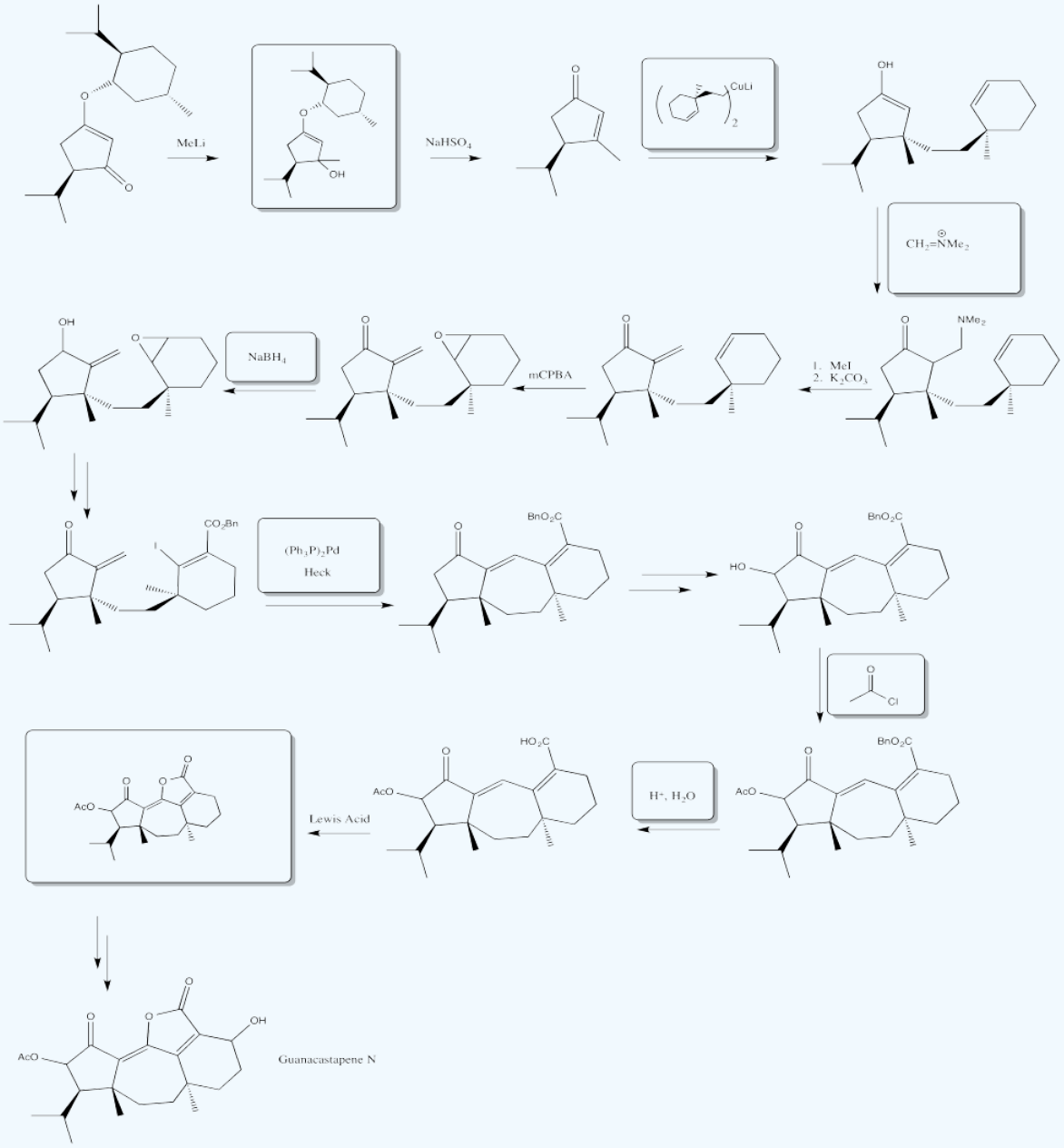




Answer

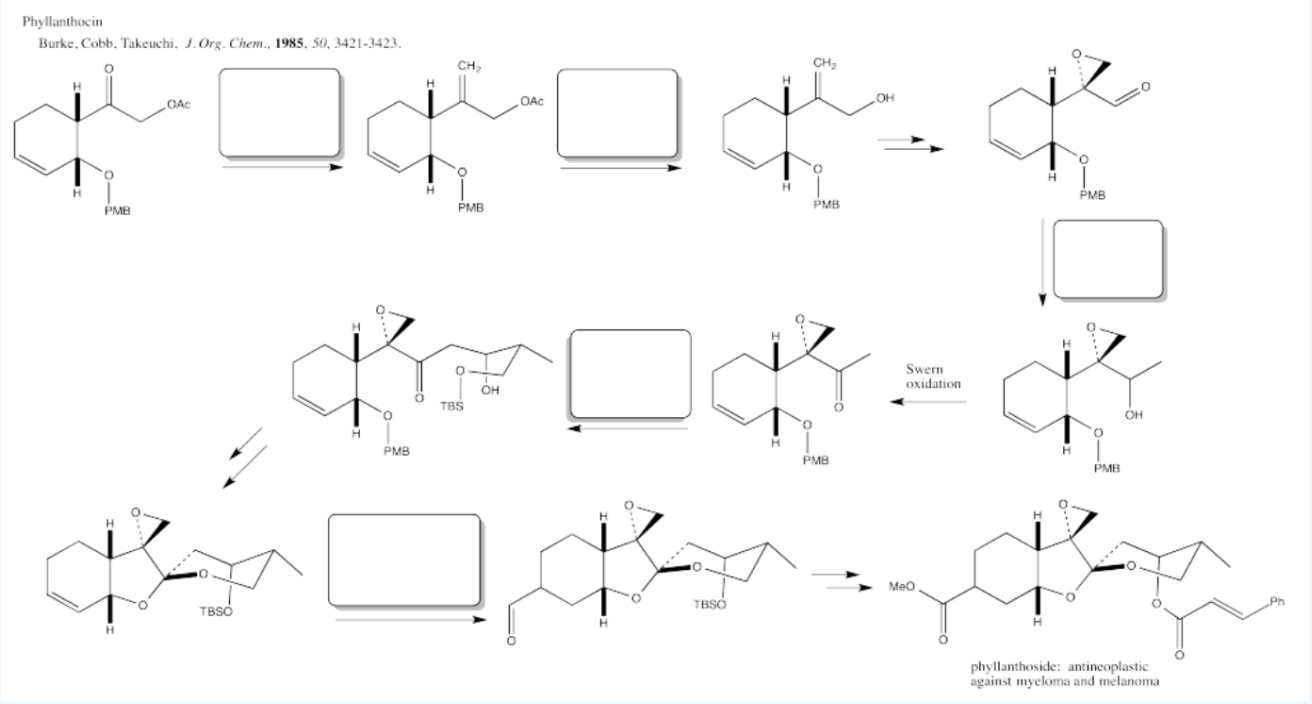
Guanacastepene N

Iimura, Overman, Paulini, Zakarian, *J. Am. Chem. Soc.* **2006,** *128,* 13095.

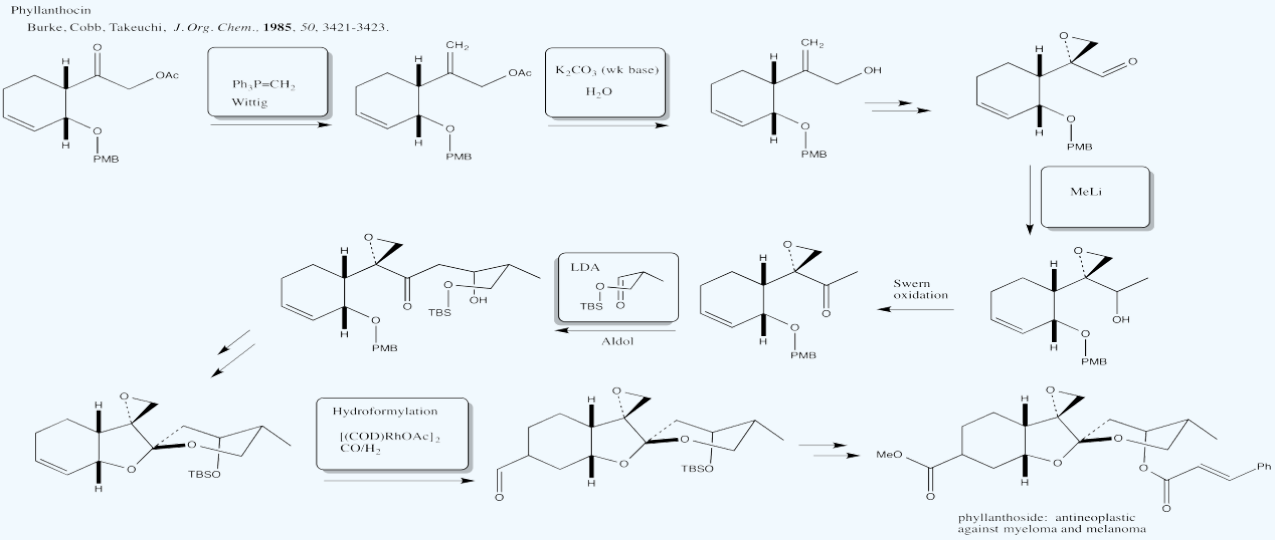


Exercise 5.3.10

Fill in the blanks in the following synthesis involving *anionic nucleophilic addition to carbonyl*, *conjugate addition*, *nucleophilic substitution at carboxyl* and *transition metal-catalysed coupling*.

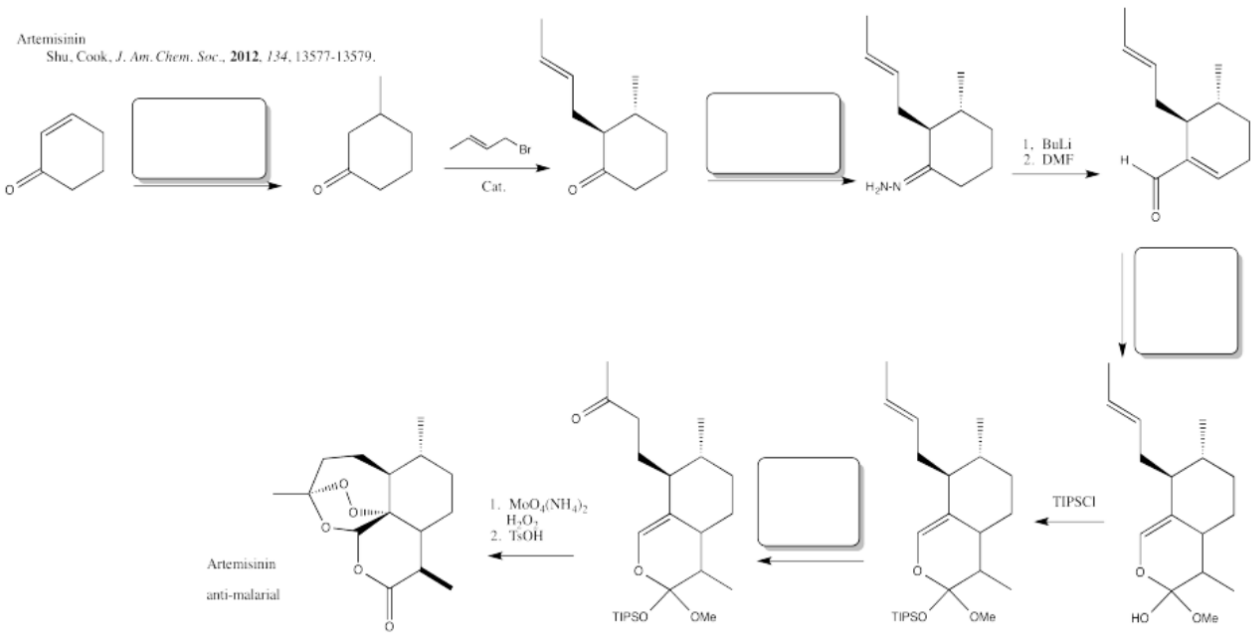


Answer

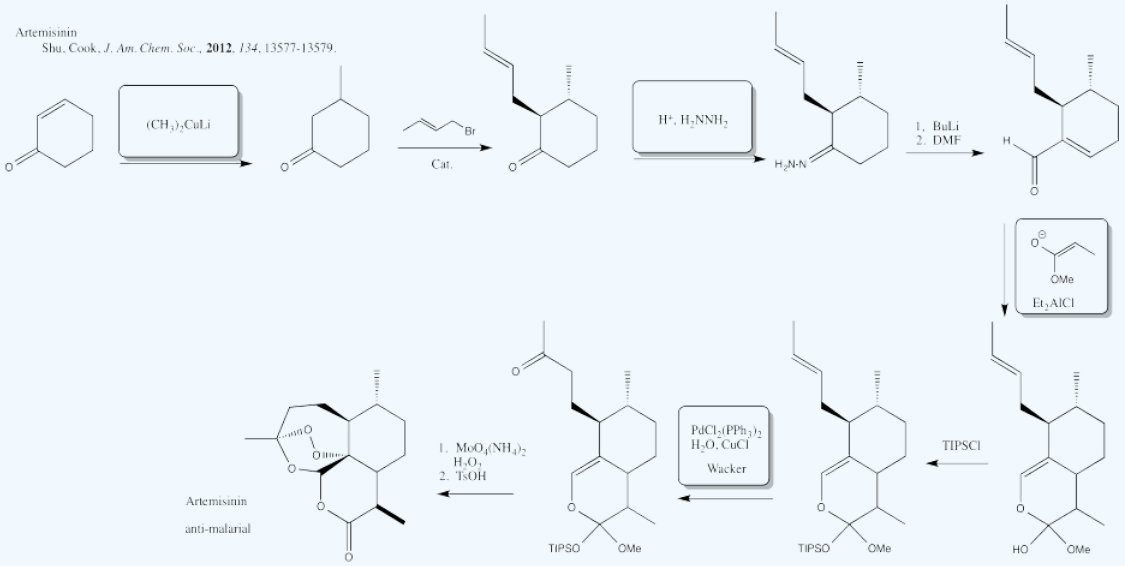


Exercise 5.3.11

Fill in the blanks in the following synthesis involving anionic nucleophilic addition to carbonyl, conjugate addition, nucleophilic substitution at carboxyl, transition metal-catalysed coupling and neutral nucleophilic addition to carbonyl.



Answer

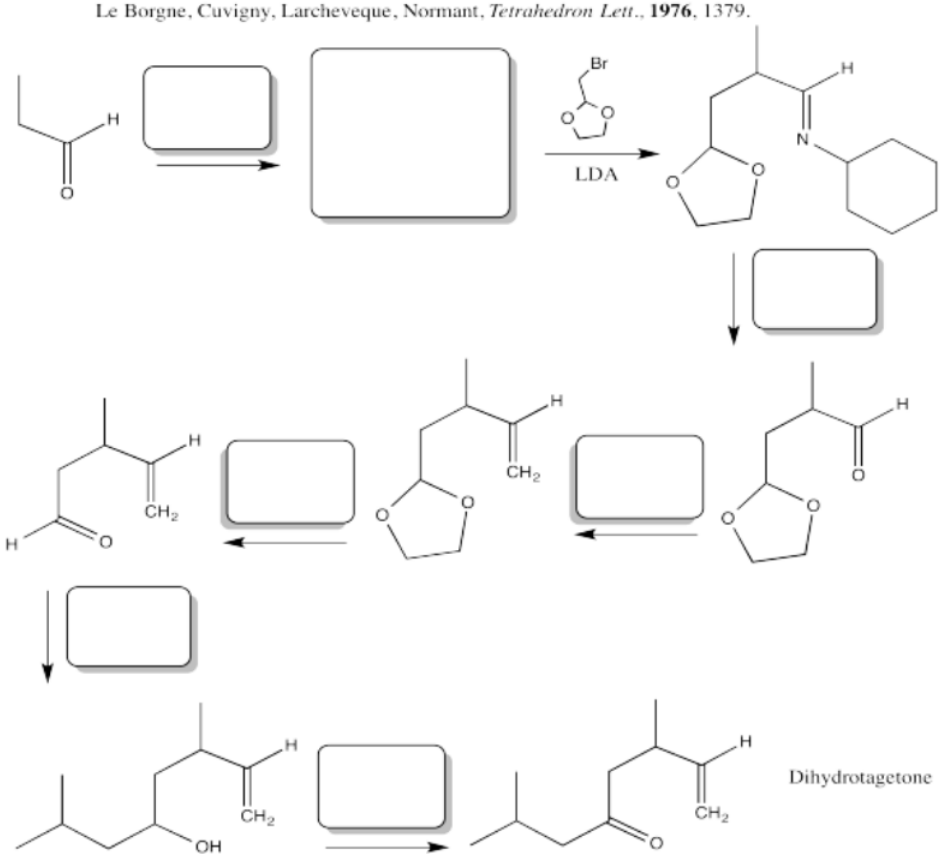


Exercise 5.3.12

Fill in the blanks in the following synthesis involving anionic nucleophilic addition to carbonyl, conjugate addition, nucleophilic substitution at carboxyl, transition metal-catalysed coupling and neutral nucleophilic addition to carbonyl.

Dihydrotagetone

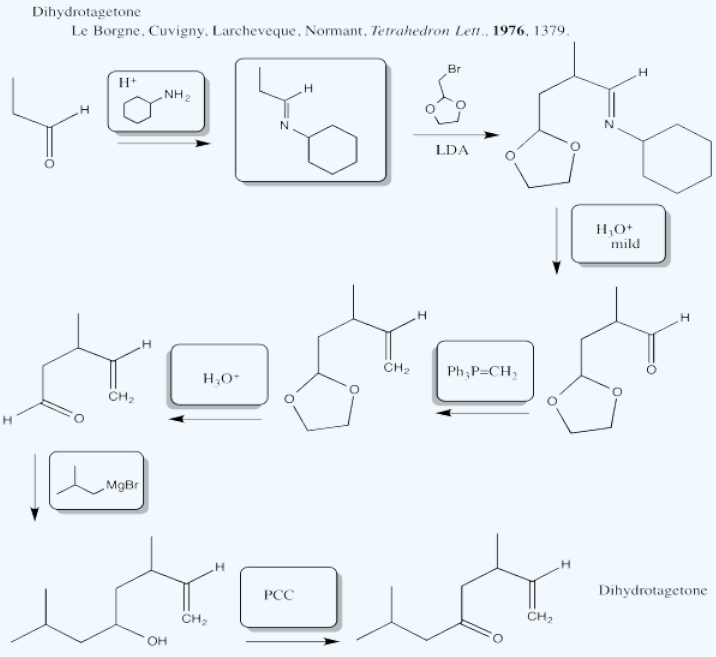
Le Borgne, Cuvigny, Larcheveque, Normant, *Tetrahedron Lett.*, **1976**, 1379.



Answer

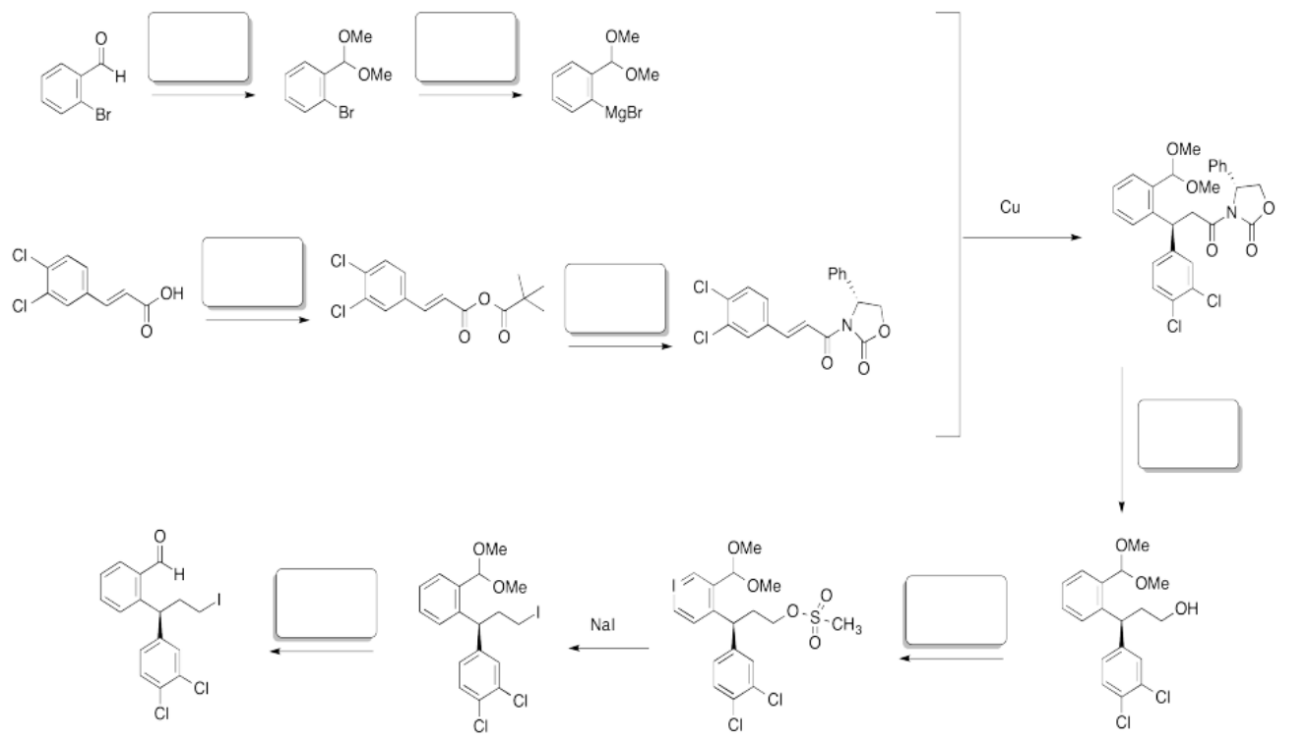
Dihydrotagetone

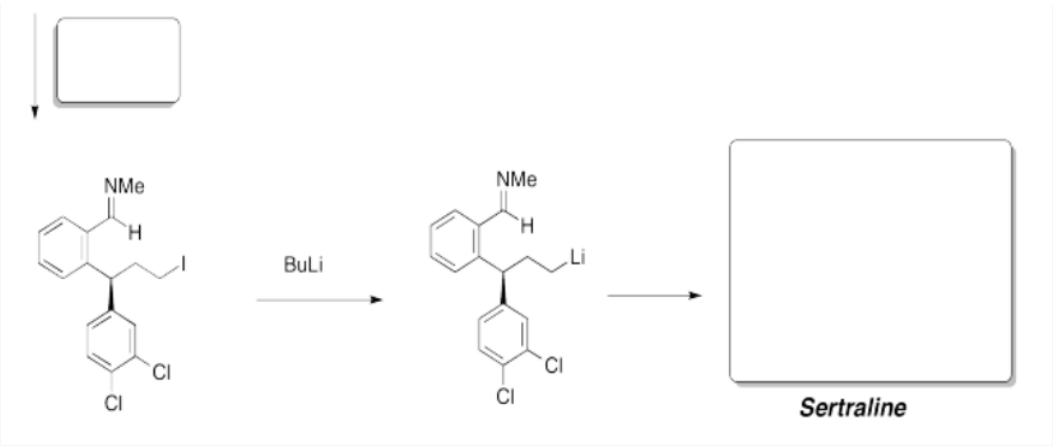
Le Borgne, Cuvigny, Larcheveque, Normant, *Tetrahedron Lett.*, **1976**, 1379.



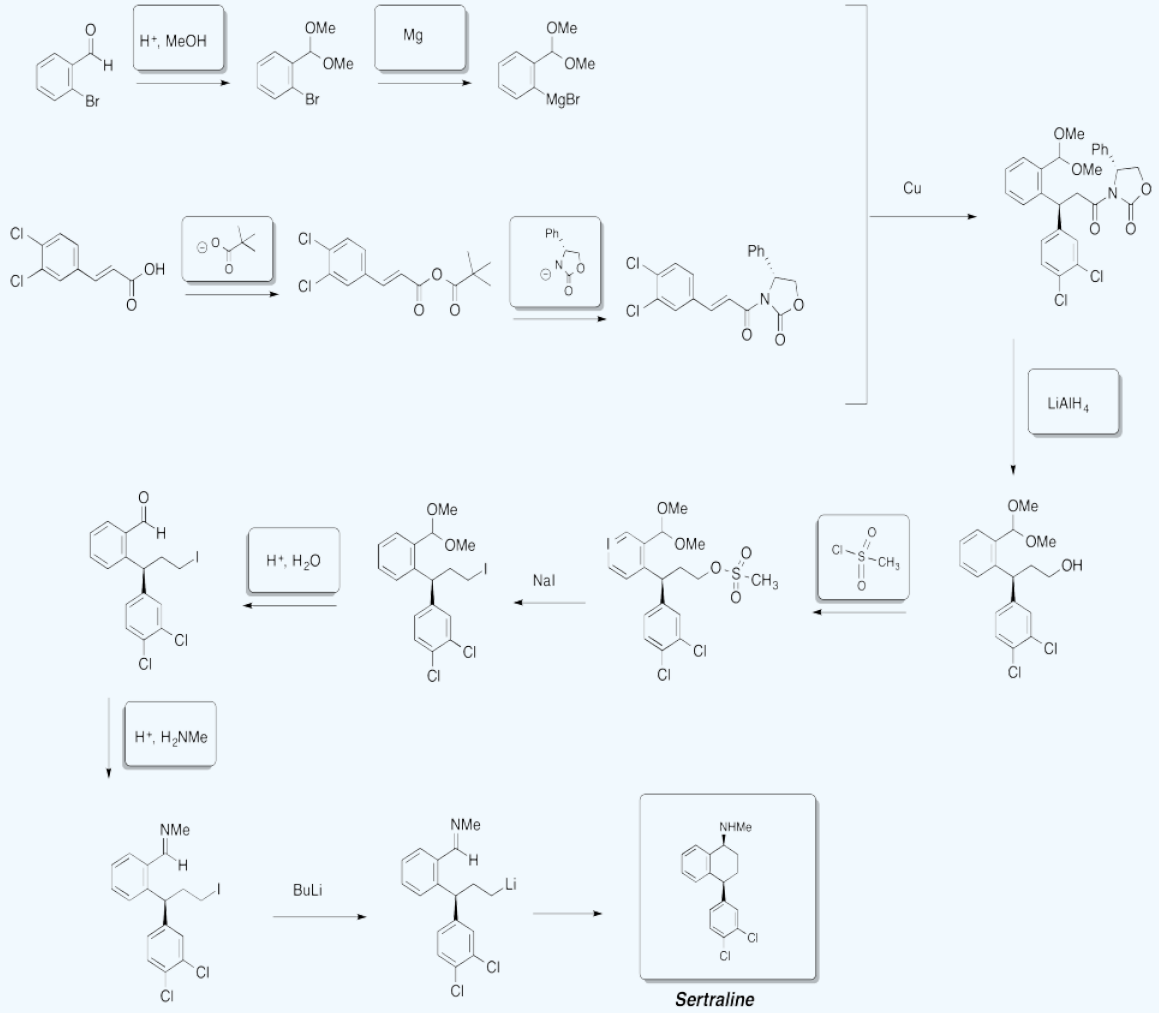
Exercise 5.3.13

Fill in the blanks in the following synthesis involving anionic nucleophilic addition to carbonyl, conjugate addition, nucleophilic substitution at carboxyl, transition metal-catalysed coupling and neutral nucleophilic addition to carbonyl.



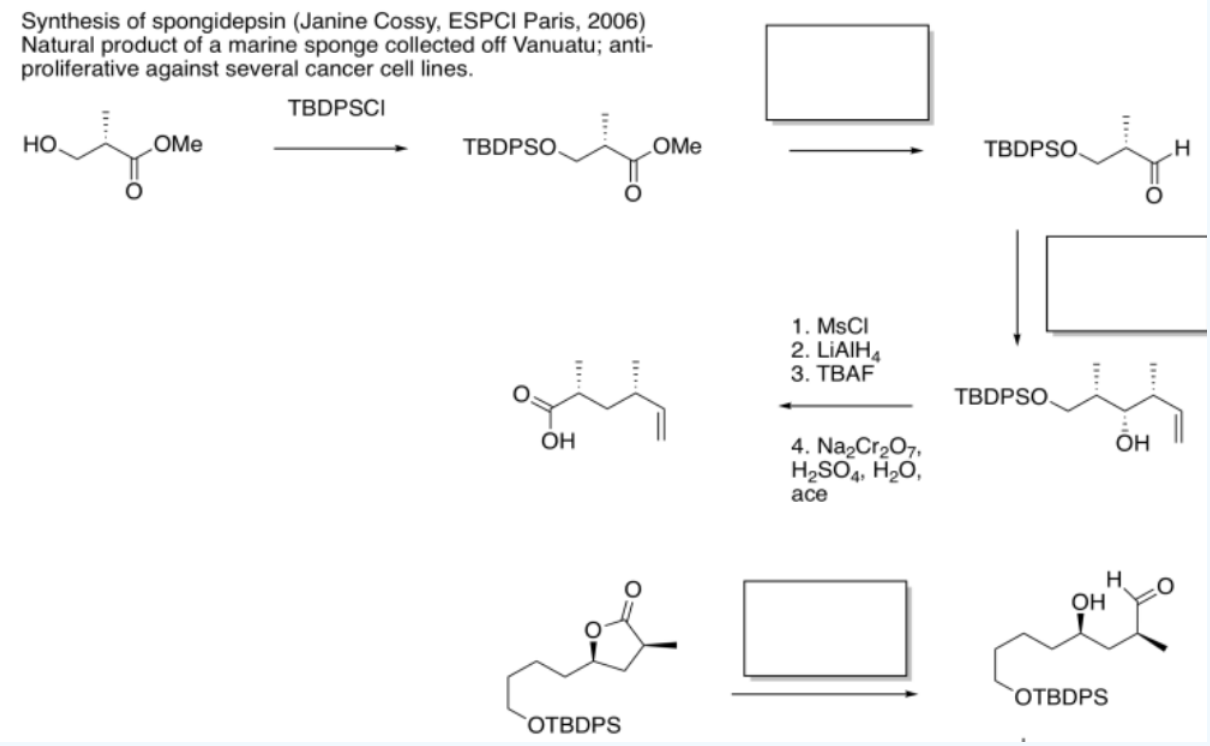


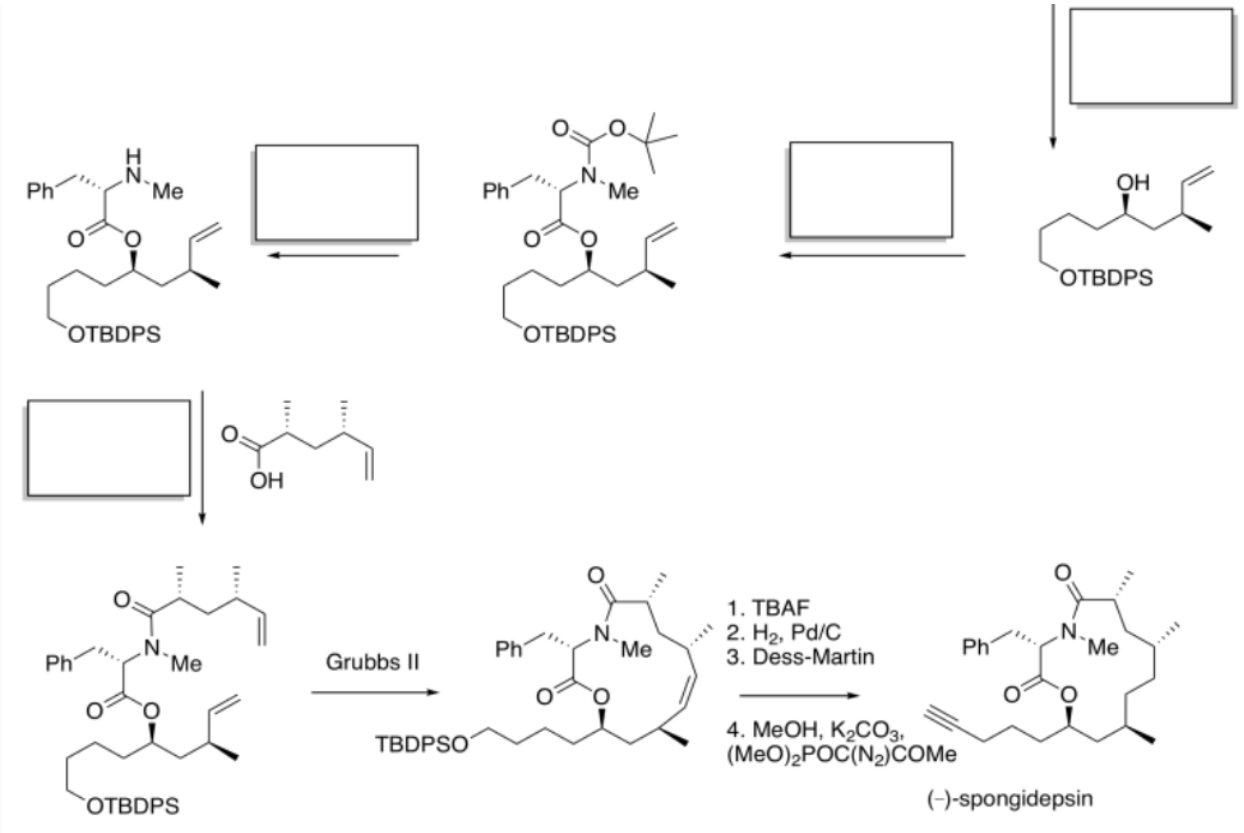
Answer



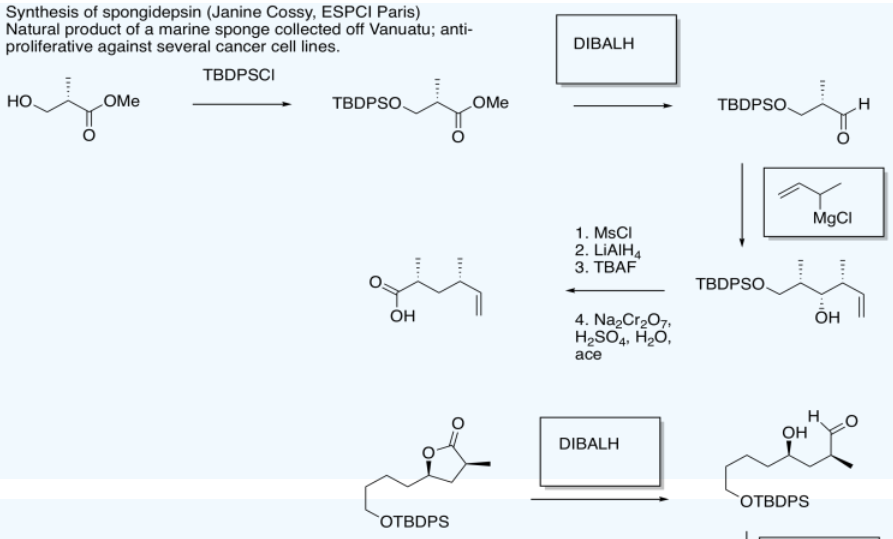
Exercise 5.3.14

Fill in the blanks. Requires knowledge of formation of esters and amides as well as Wittig or Horner-Wadworth-Emmons reactions.





Answer

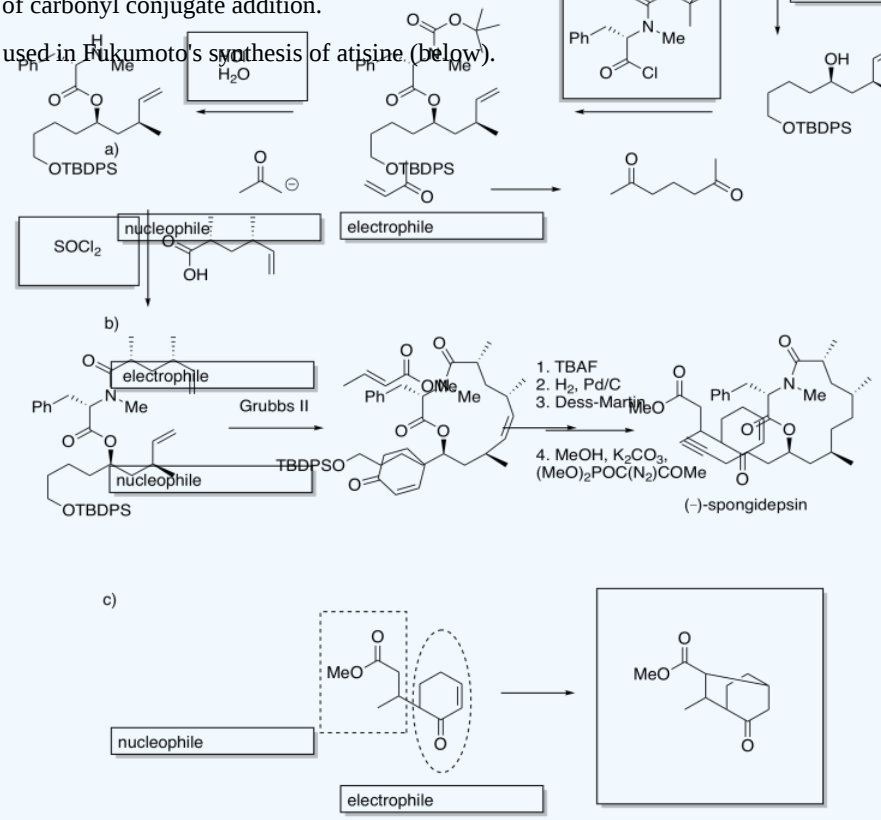


Exercise 5.3.15

In each case, analyse whether the starting material is a nucleophile or electrophile. Fill in the product in part (c). This question requires knowledge of carbonyl conjugate addition.

These strategies are used in Fukumoto's synthesis of atisine (below).

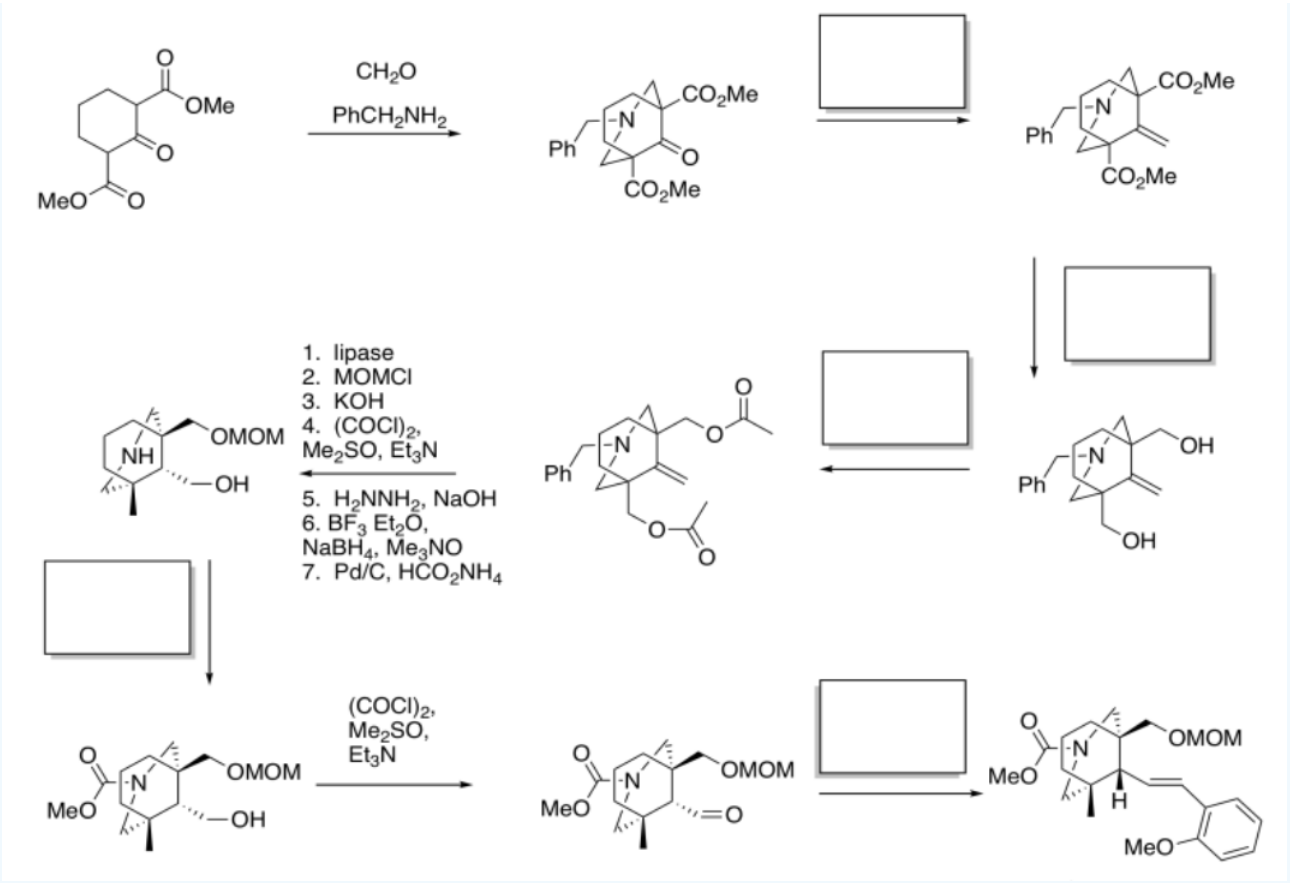
Answer

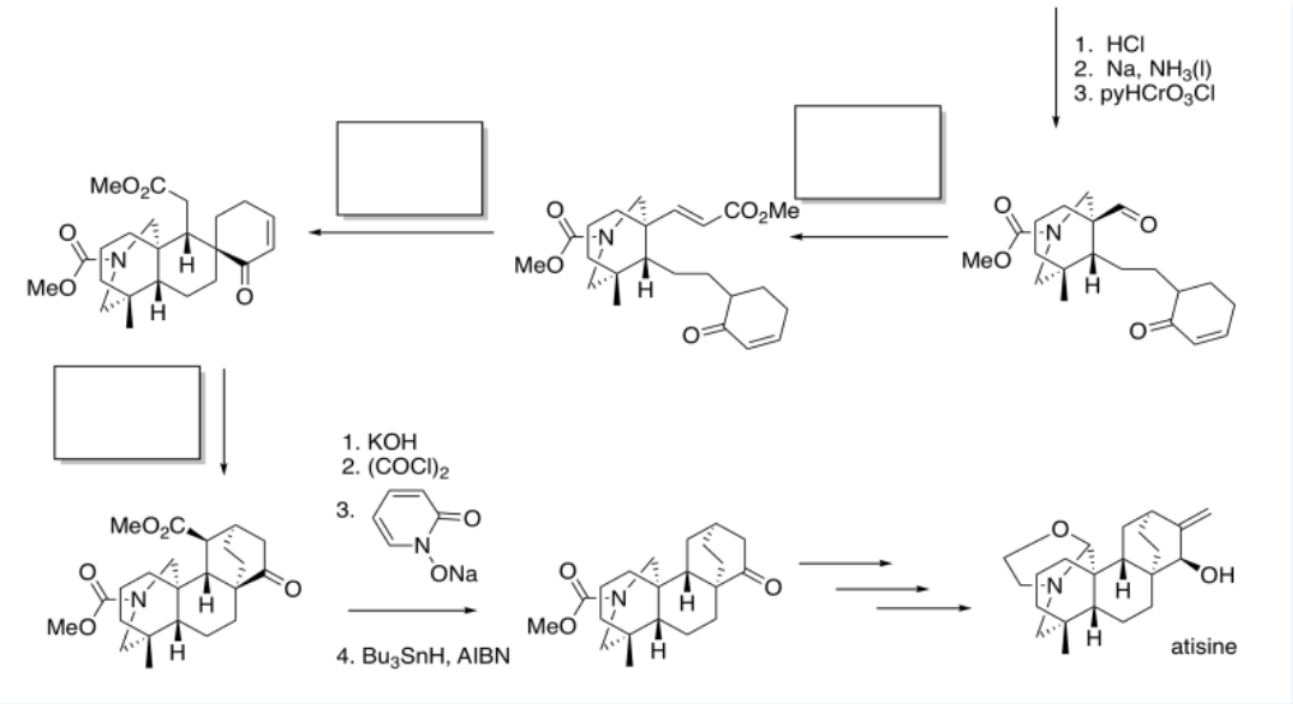


Exercise 5.3.16

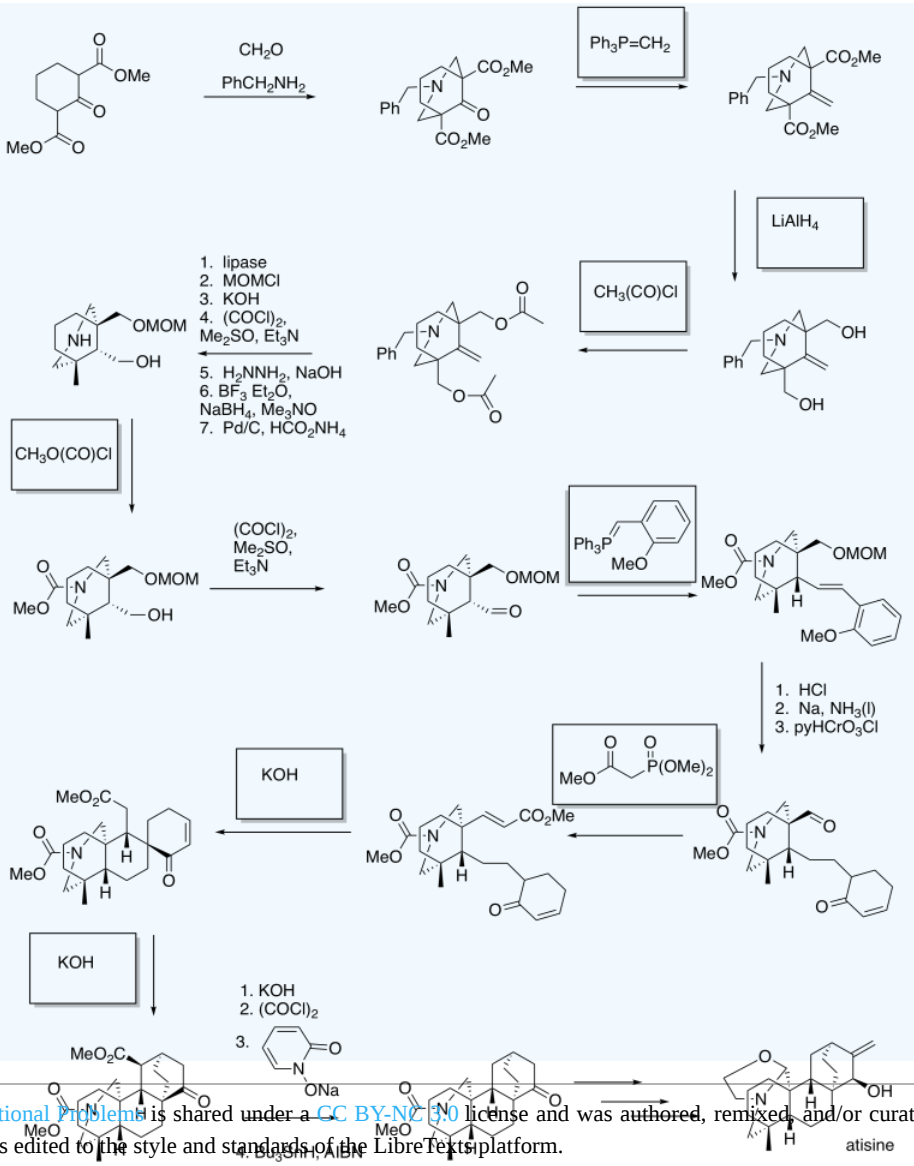
Fill in the blanks in the following synthesis of atisine (Keiichiro Fukumoto, Tohoku University). Atisine is a natural product of *Aconitum sp.*, the family of poisonous plants that includes wolfsbane.

Requires knowledge of conjugate addition / Michael reaction, ester reductions, formation of esters and amides, and Wittig or Horner-Wadworth-Emmons reactions.





Answer



5.4: Solutions For Selected Problems

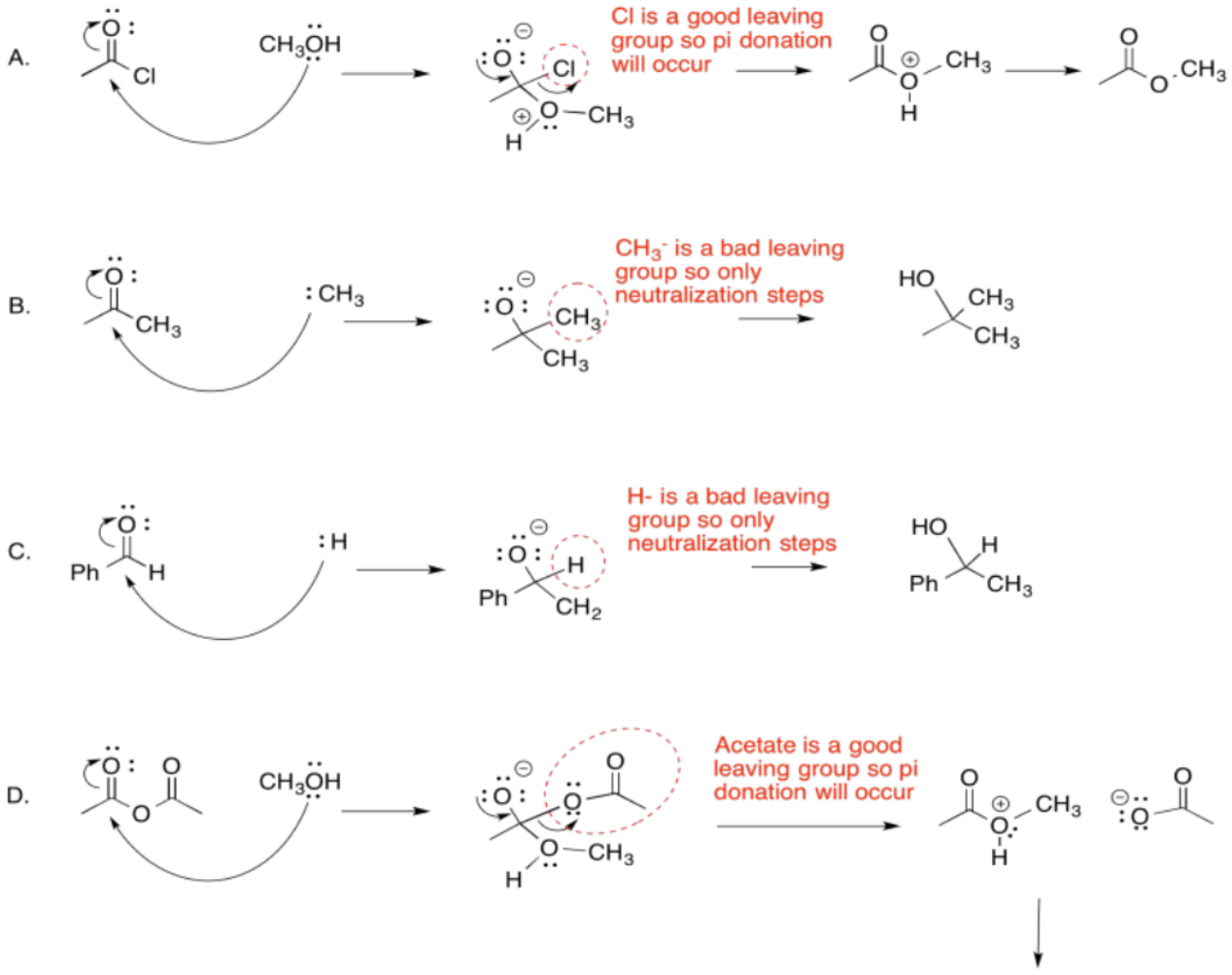
Exercise 5.1.1:

These heteroatoms are all found in the upper right-hand corner of the periodic table. They are all pretty electronegative and they all have lone pairs.

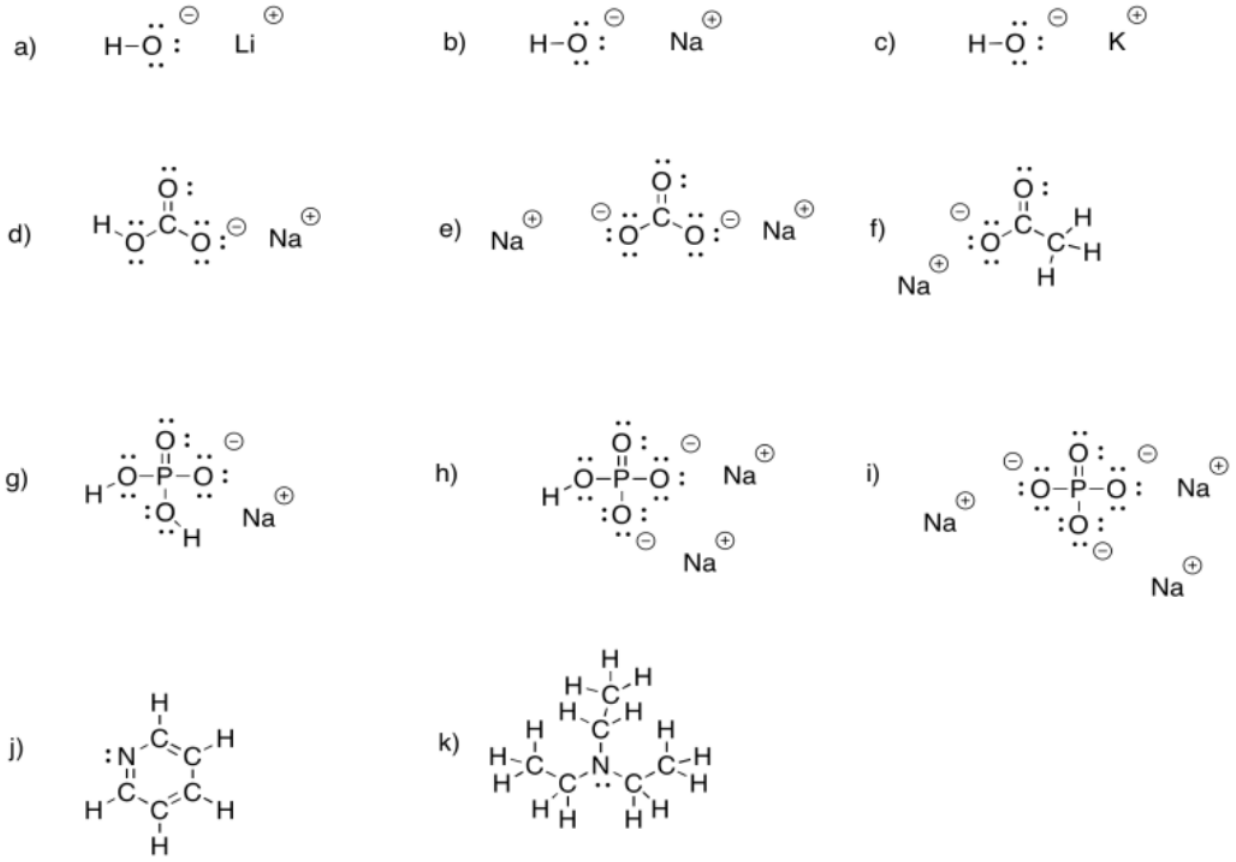
Exercise 5.2.2:

a. The electronegativity of the heteroatom attached to the carbonyl group in a carboxyloid is one factor that allows it to leave and form its own stable anion.
b. Although carbon and hydrogen are more electronegative than many of the elements in the periodic table, they are not stable enough as anions to form easily on their own.

Exercise 5.2.3:



Exercise 5.2.4:

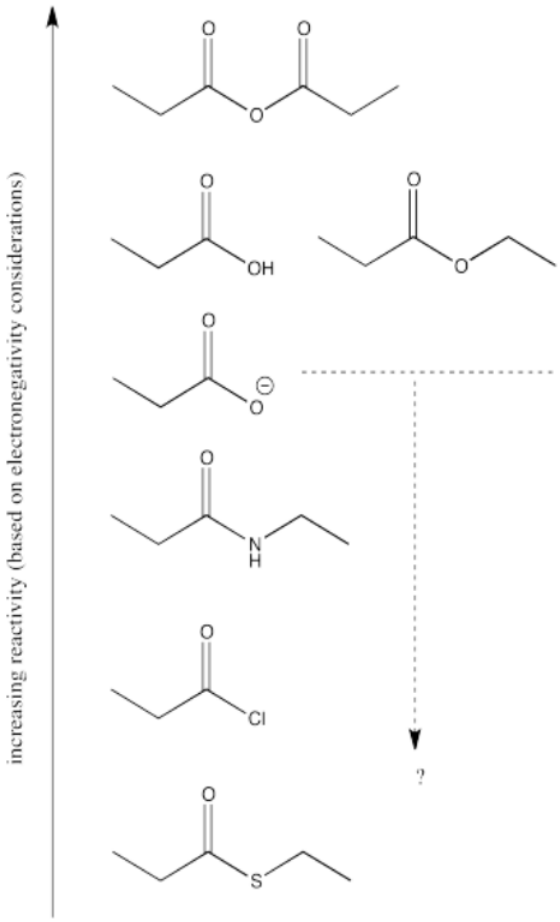


Exercise 5.3.1:

We might expect carboxyloids with the most electronegative elements attached to the carbonyl to be the most reactive and least stable towards substitution (in other words, carboxyloids with the most electronegative heteroatoms would become substituted the most easily).

In that case, we would predict that the carboxyloids with the most electronegative substituent (oxygen) would be the most reactive. There are a number of different kinds and we will think about how they relate to each other shortly.

After the oxygen derivatives we would predict either the nitrogen derivatives or the chloride, depending on what electronegativity scale we happen to use (remember, electronegativity is not an experimentally pure property, but the result of a calculation that can be performed in different ways). The sulfur derivative would be least reactive.



There are still several different oxygen derivatives to compare: carboxylic acids (OH), carboxylates (O-), esters (OR, in which R is an alkyl or carbon chain) and acid anhydrides (OC=O). The easiest to differentiate is the carboxylate, because of its negative charge. It must be less attractive to a nucleophile than the other oxygen derivatives, because it would offer more repulsion to an incoming lone pair.

However, we can't really predict whether it would be any less reactive than the nitrogen, chlorine or sulfur analogues, because who knows whether the charge or the nature of the atom matters more?

As it happens, the charge probably matters more. We learn that simply by looking at the experimental trend and seeing that the carboxylate is the least reactive of all the carboxyloids.

Turning to the other three oxygen derivatives, it would be difficult to differentiate between the effect of a remote hydrogen atom versus an alkyl chain in the ester versus the carboxylic acid, so we'll say those two are about the same. On the other hand, the additional electron-withdrawing carbonyl group in the acid anhydride probably has a profound effect, so we would expect that compound to attract nucleophiles more strongly.

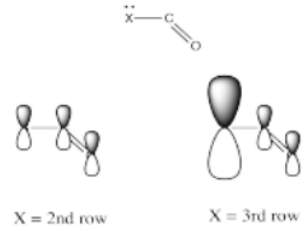
Of course, the series we have produced above is not the "right answer". It does not match the experimentally observed series of carboxyloid reactivities. Nevertheless, it is very useful in terms of building an understanding of carboxyloids. It tells us that electronegativity may play a role here, but that it can't be the only factor.

Some other factor is putting some of the derivatives out of order. In particular, the acid chloride (C=OCl) and the thioester (C=OSR) do not fit.

Exercise 5.3.2:

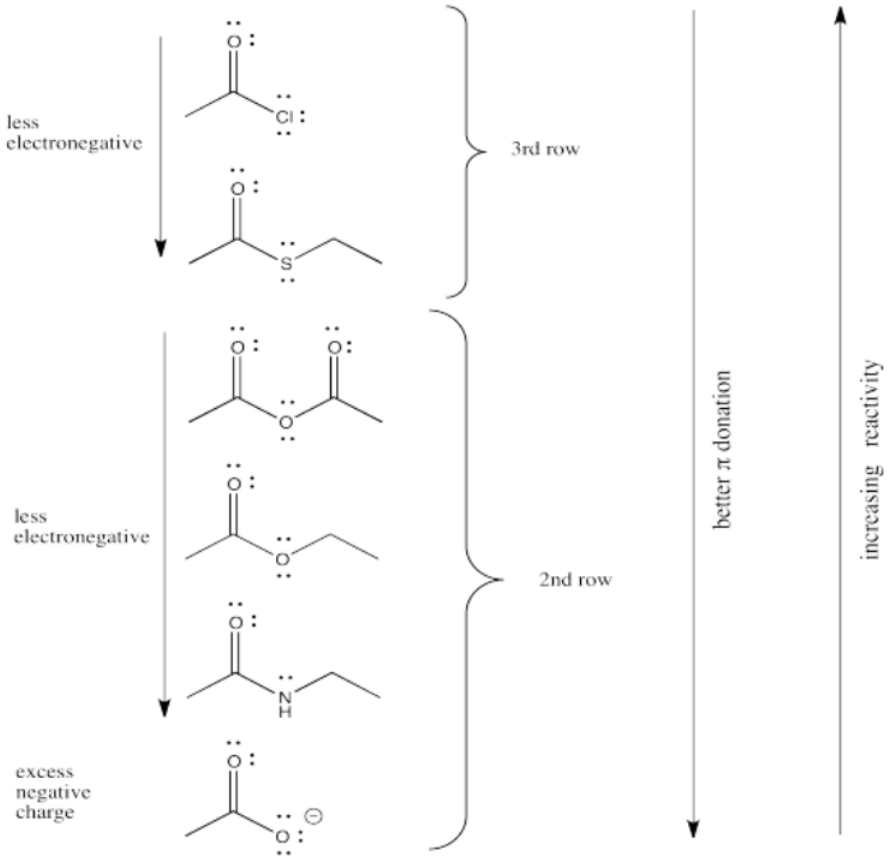
Electronegativity is an abvious factor that could influence an atom's ability to π-donate, but we just looked at that factor in the previous section, so let's look at another atomic property instead. Of course, different atoms have different sizes. In particular, if we look at the atoms involved in carboxyloid substituents, we can divide them into 2nd row atoms and 3rd row atoms.

It's actually well-documented that the degree of overlap between two orbitals influences how well they bond together. Since carbon is in the second row, it is about the same size as, and overlaps pretty well with, other second row atoms. Third row atoms are a little too big, on the other hand.



That factor breaks the carboxyloids into two different groups. Assuming π-donation is a major factor, sulfur and chlorine may be placed above the others in tems of reactivity. They cannot donate as well as oxygen or nitrogen can.

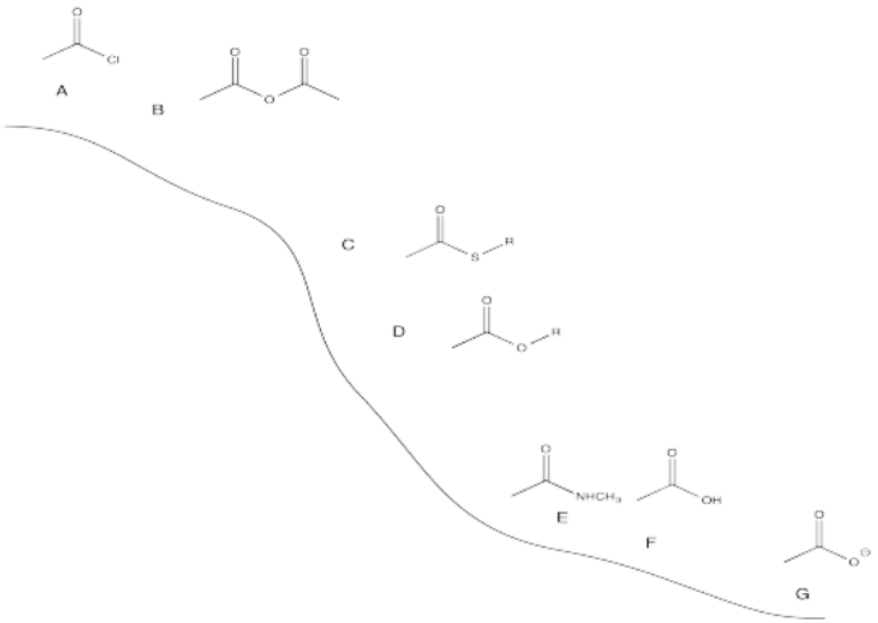
From there, differences among the atoms from the same row may be sorted out based on electronegativity differences.



Exercise 5.3.3:

Amide bonds are among the most stable carboxyloids possible. That stability makes them well-suited to form useful structures that will not decompose easily. Remember, any change that occurs in matter occurs through chemical reactions, including the formation and decomposition of biomaterials. Shutting down a potential chemical reaction means a material will be more durable.

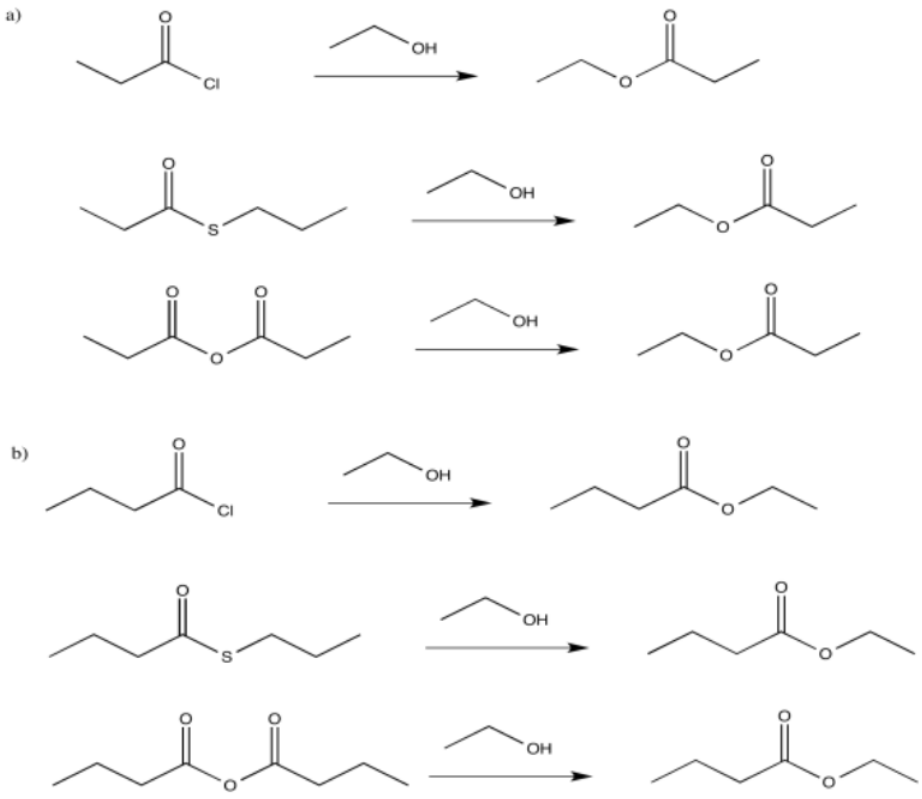
Exercise 5.3.4:

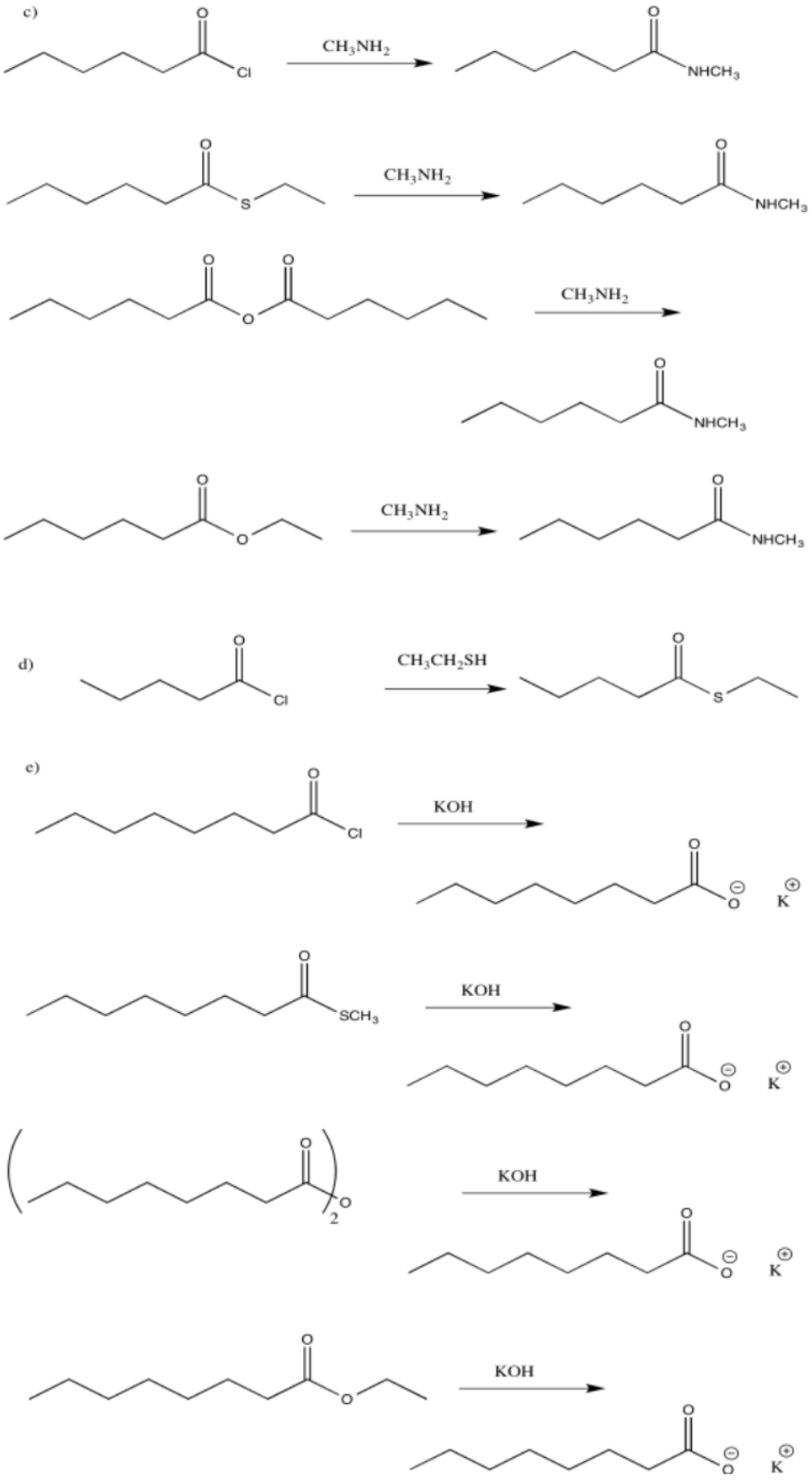


Exercise 5.3.5:

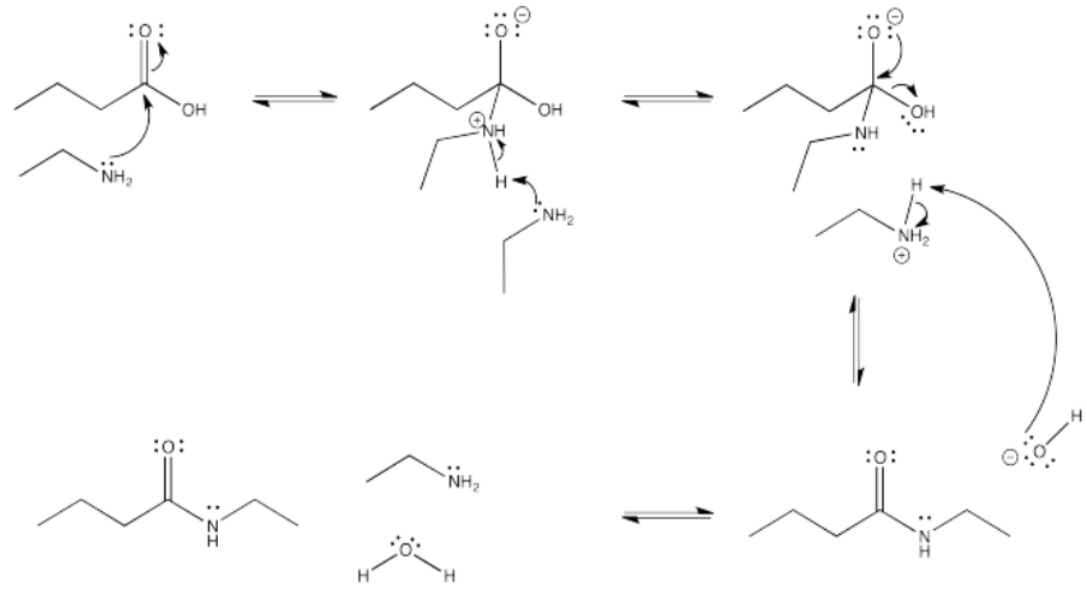
One possibility is the presence of an additional electronegative substituent. In the oxalyl chloride, the presence of an additional carbonyl next to the electrophilic acid chloride group would make each carbonyl even more electrophilic. In the thionyl chloride, the presence of two chlorines, instead of just one, could make this compound much less stable and more electrophilic.

Exercise 5.4.1:





Exercise 5.4.2:



Exercise 5.4.3:

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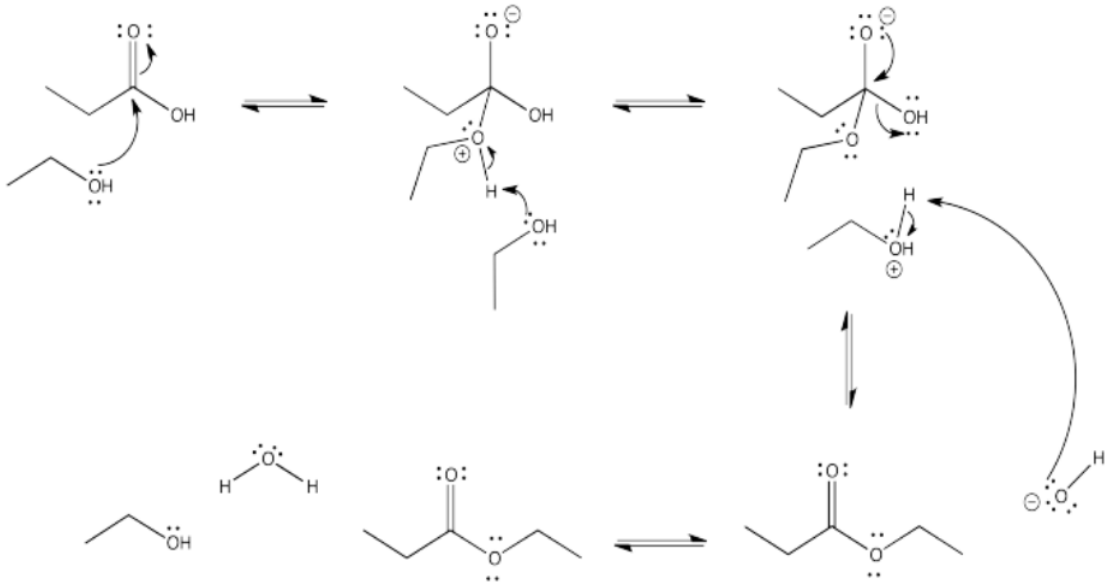

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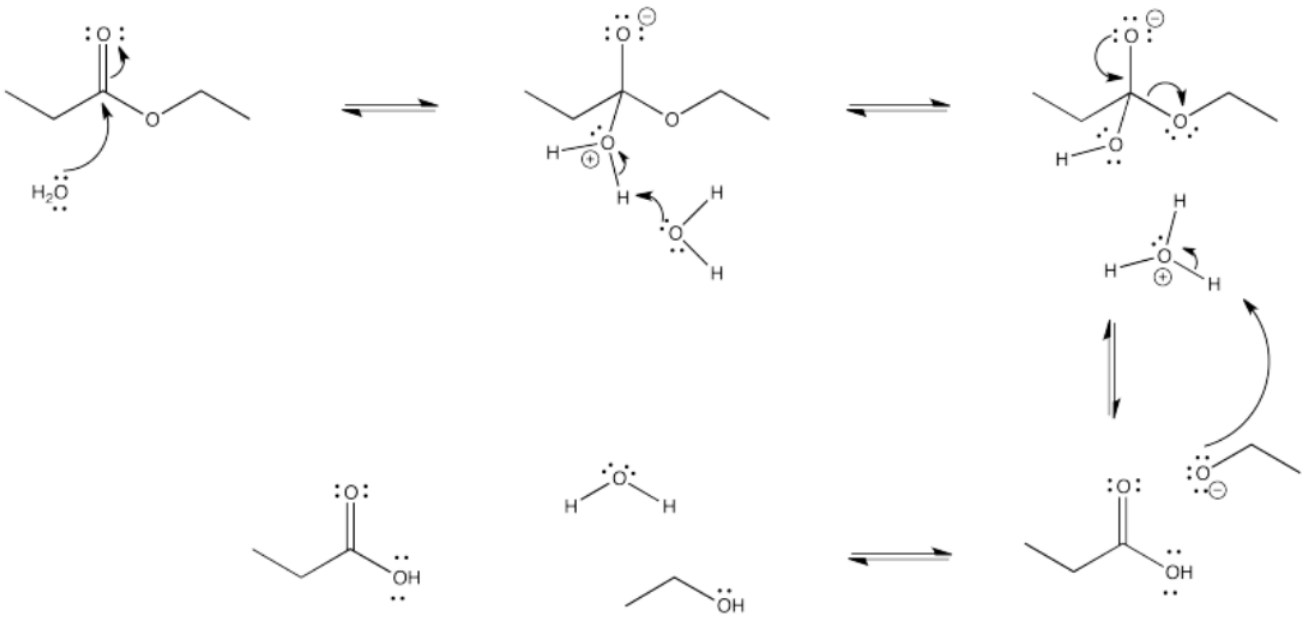
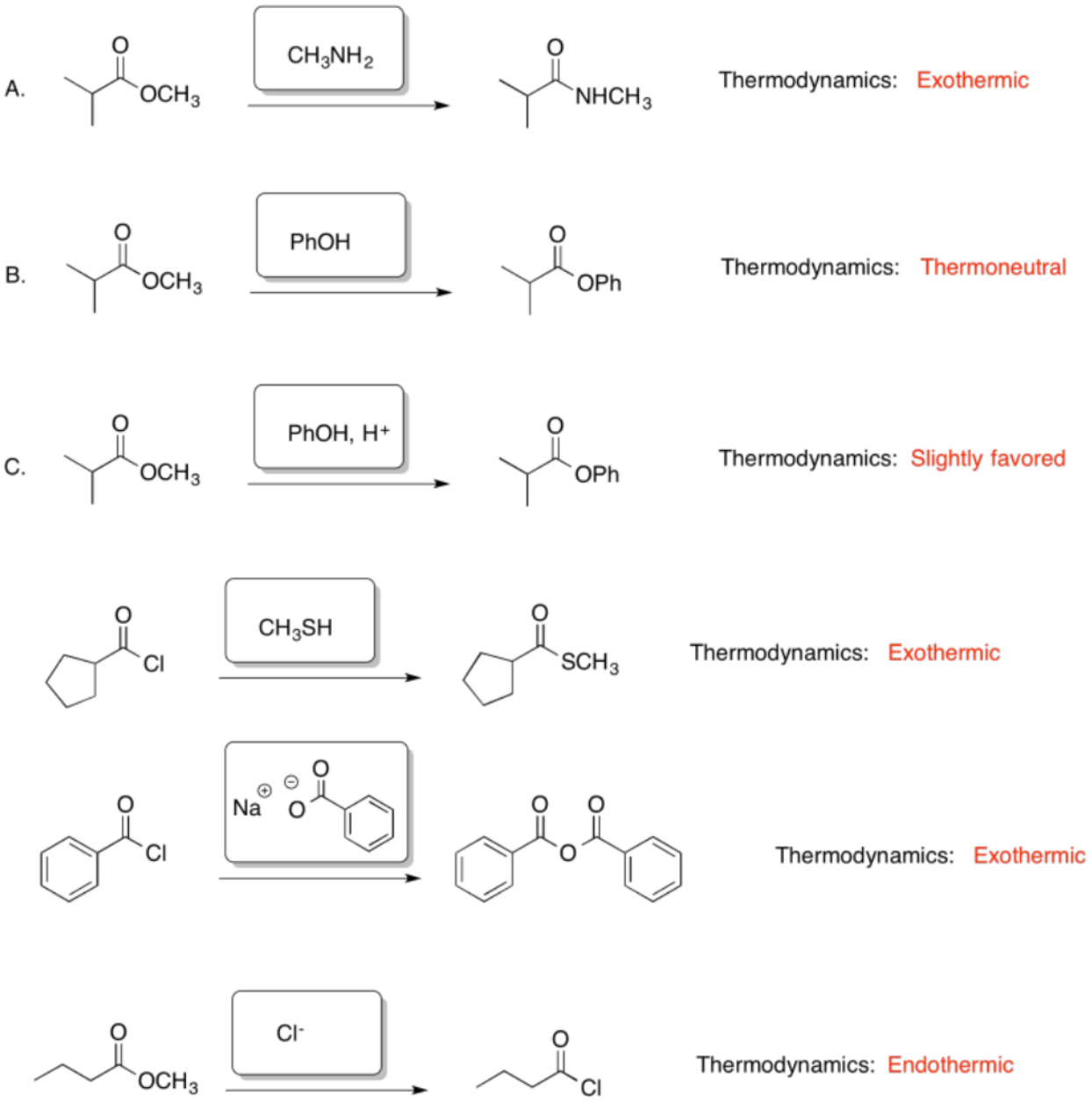


Exercise 5.4.4

Exercise 5.4.5:

Exercise 5.4.6:



Exercise 5.4.7:

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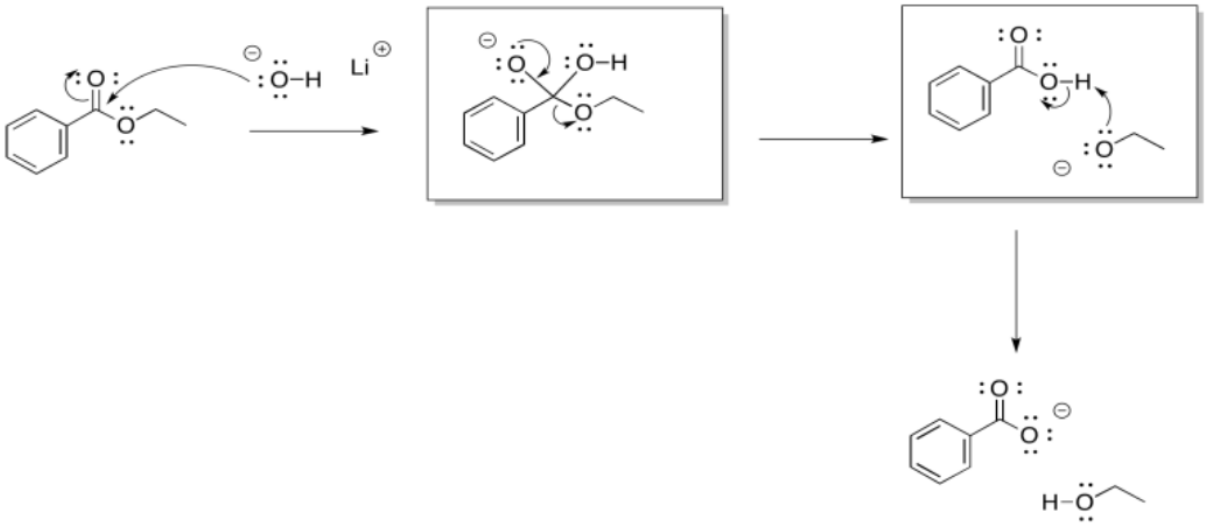

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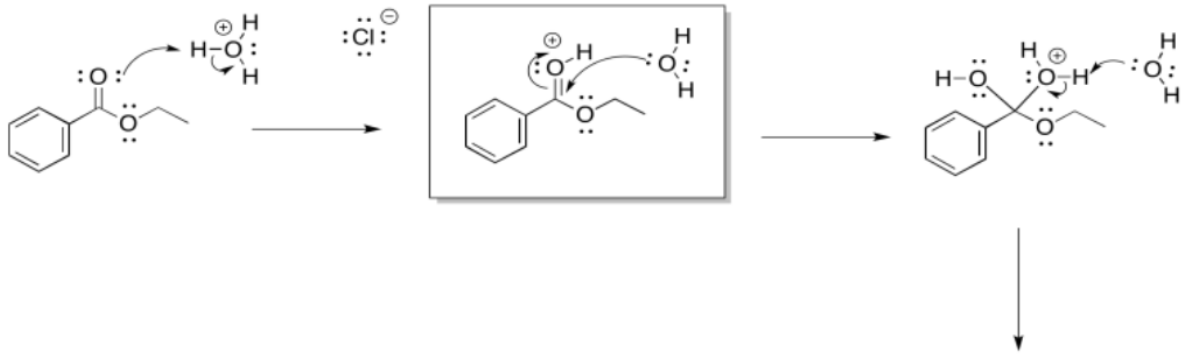

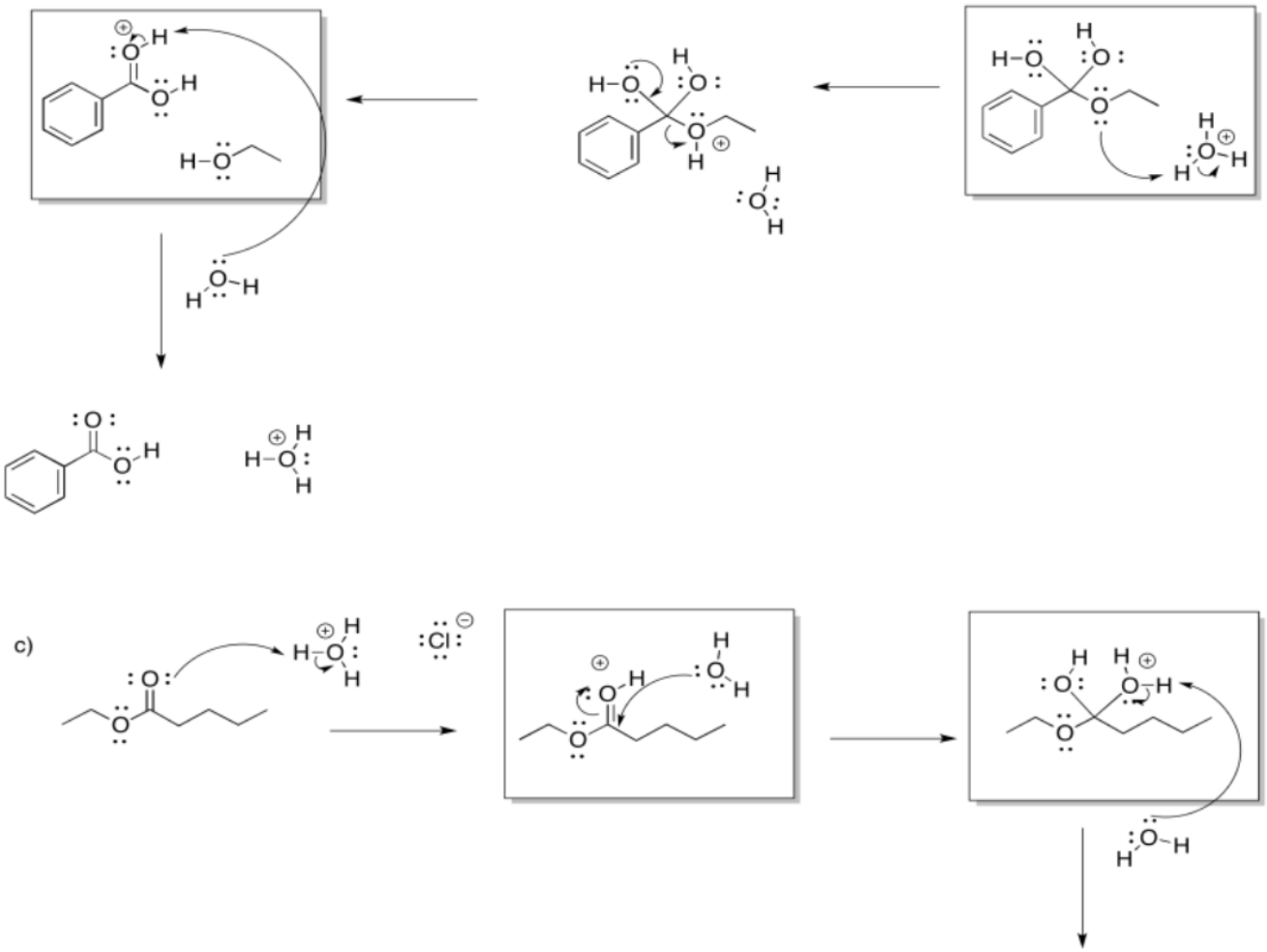

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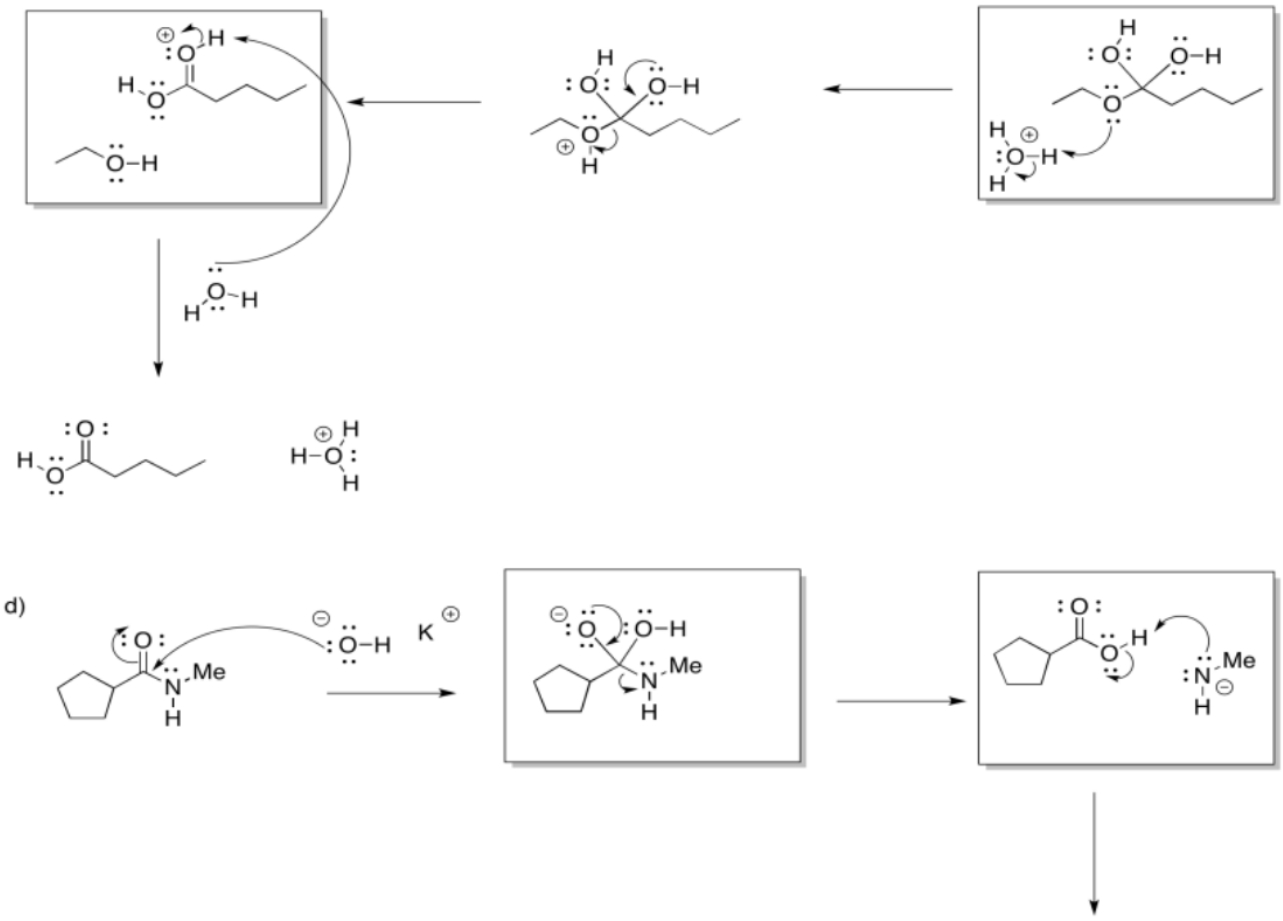

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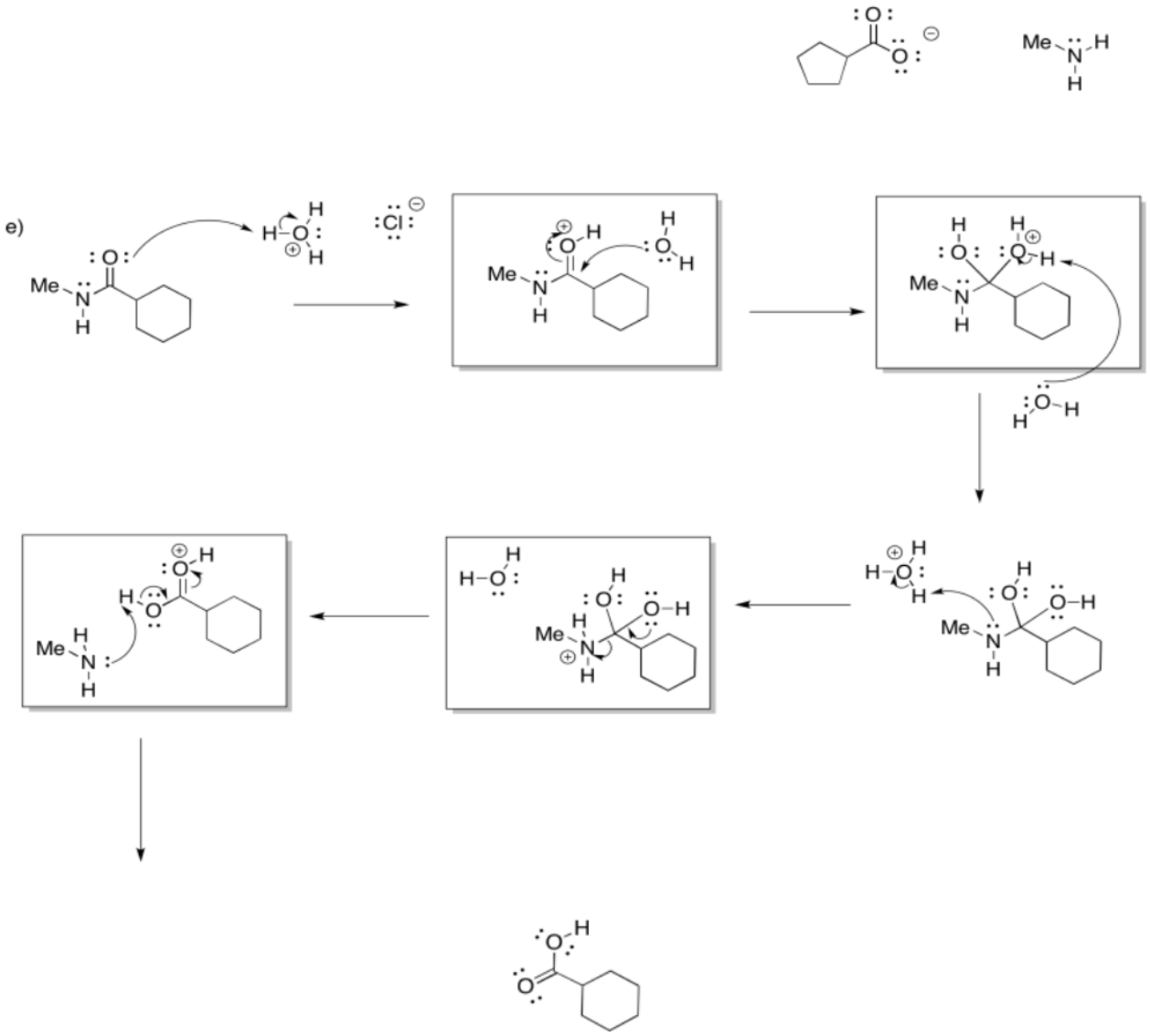
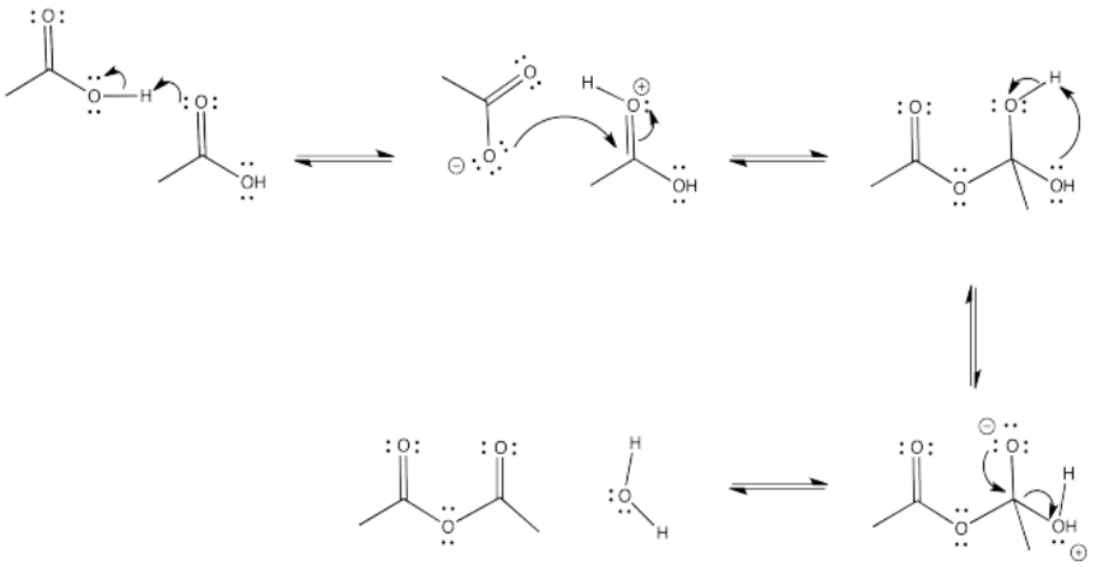


Exercise 5.5.4:



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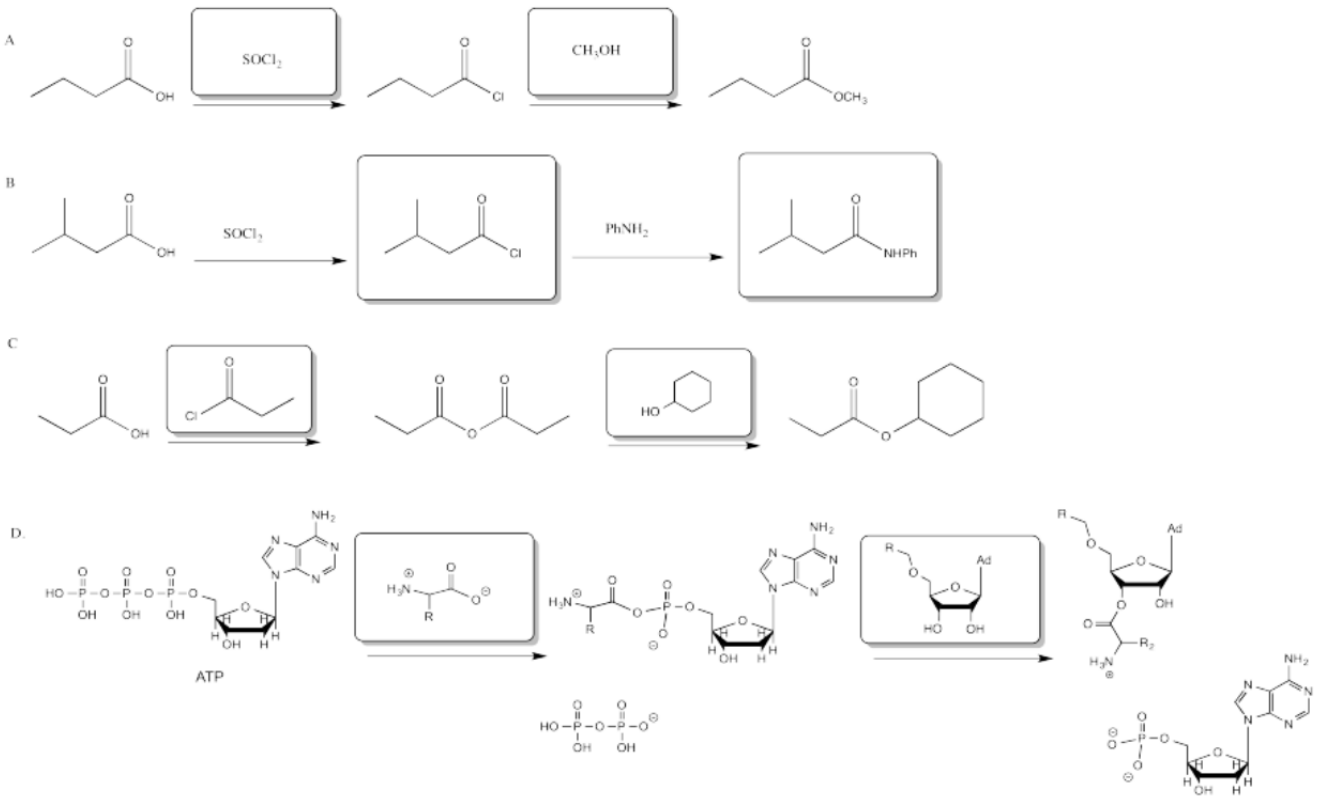
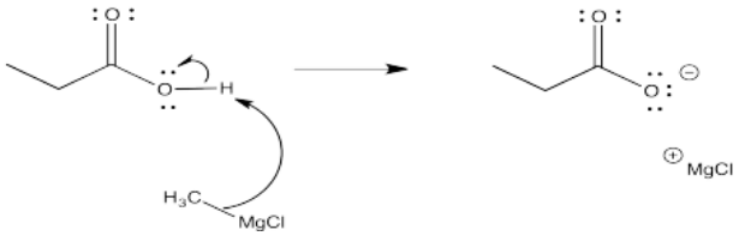


Exercise 5.6.1:

Because acid chlorides are at the top of the carboxyloid reactivity diagram (the ski hill), and other halides are likely to be similar in reactivity to the chloride, this reaction would be uphill from the other carboxyloids.

Exercise 5.6.4:



Exercise 5.6.5:

Amides and carboxylates are the least reactive carboxyloids, so it might not be too surprising that they do not react with these nucleophiles.

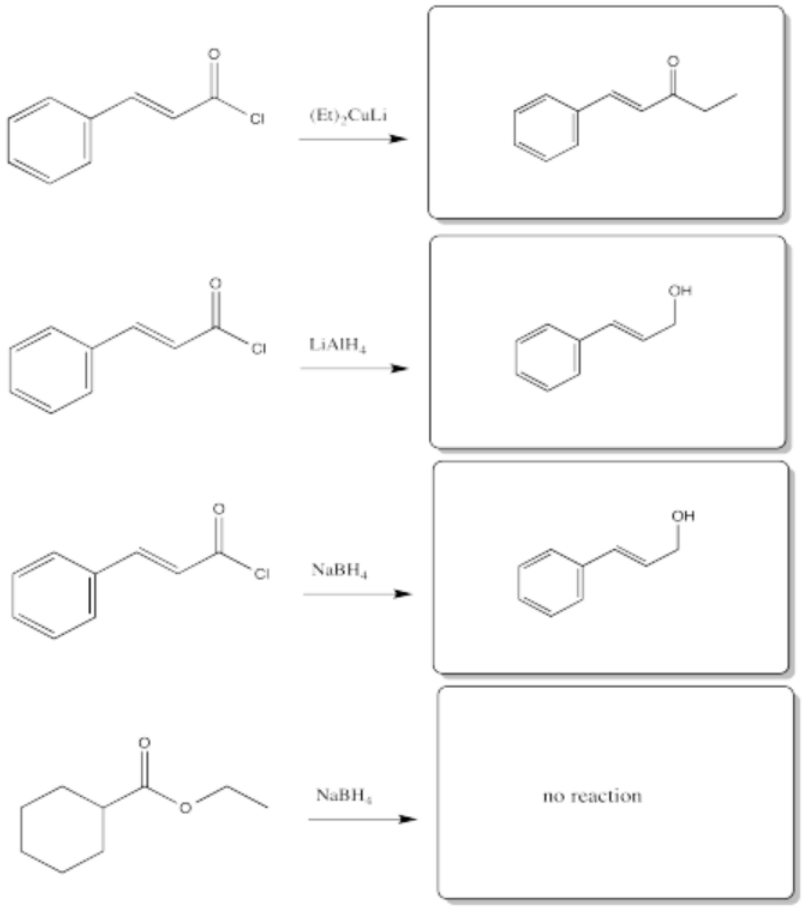
Exercise 5.6.6:

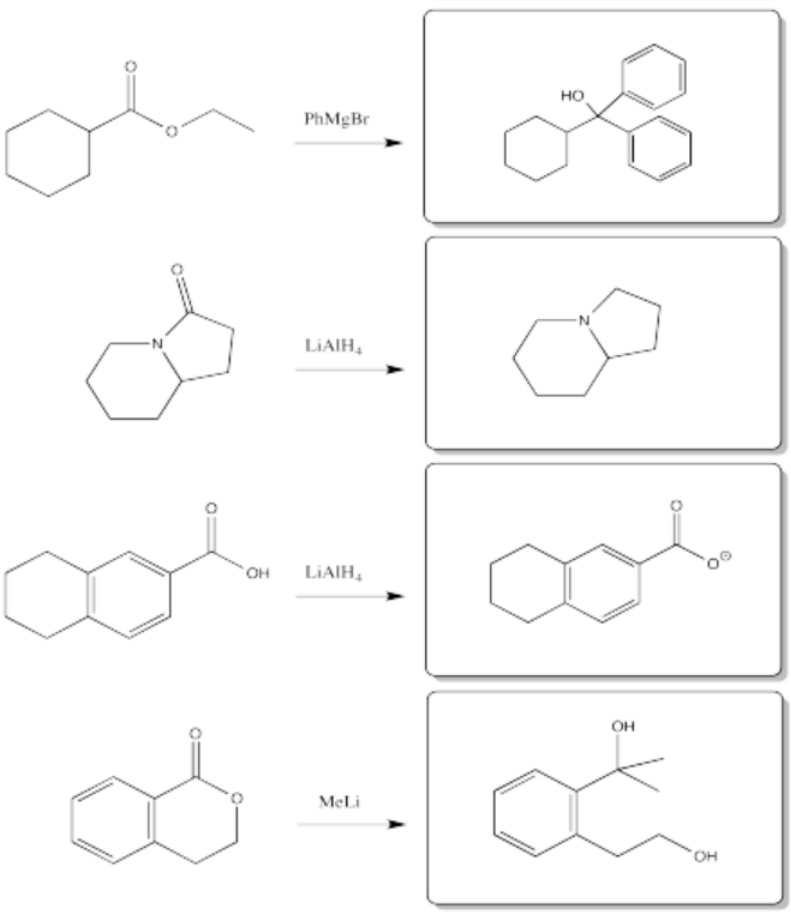
Acid chlorides typically react with these cuprate reagents.

Exercise 5.6.7:

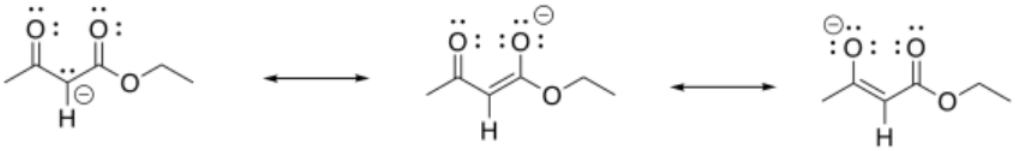
Borohydrides could presumably react with acid chlorides, anhydrides and thioesters, which are the most reactive carboxyloids. They probably can't react with amids or carboxylate ions, which are even farther downhill than esters.

Exercise 5.6.11:

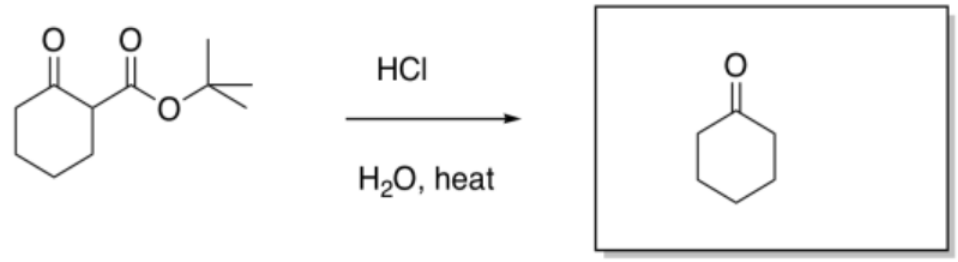




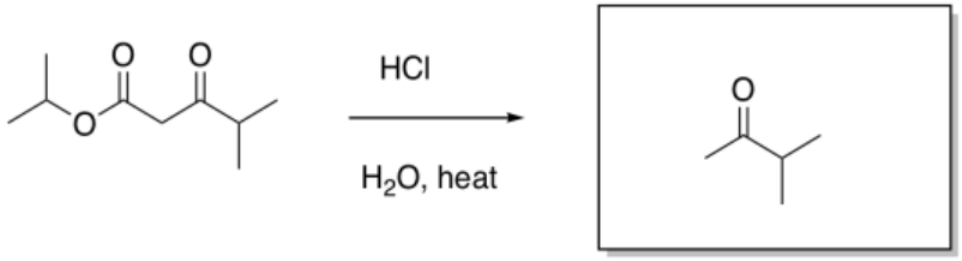
Exercise 5.7.1:



a)



b)



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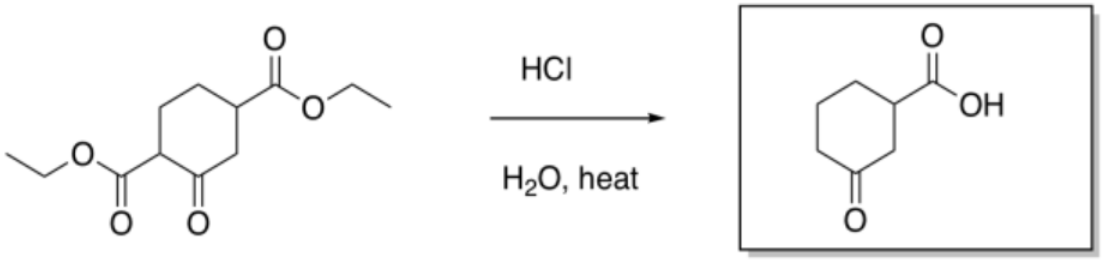

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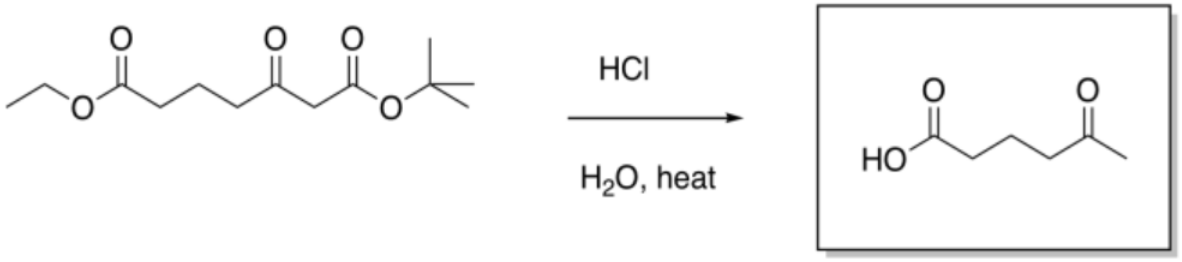
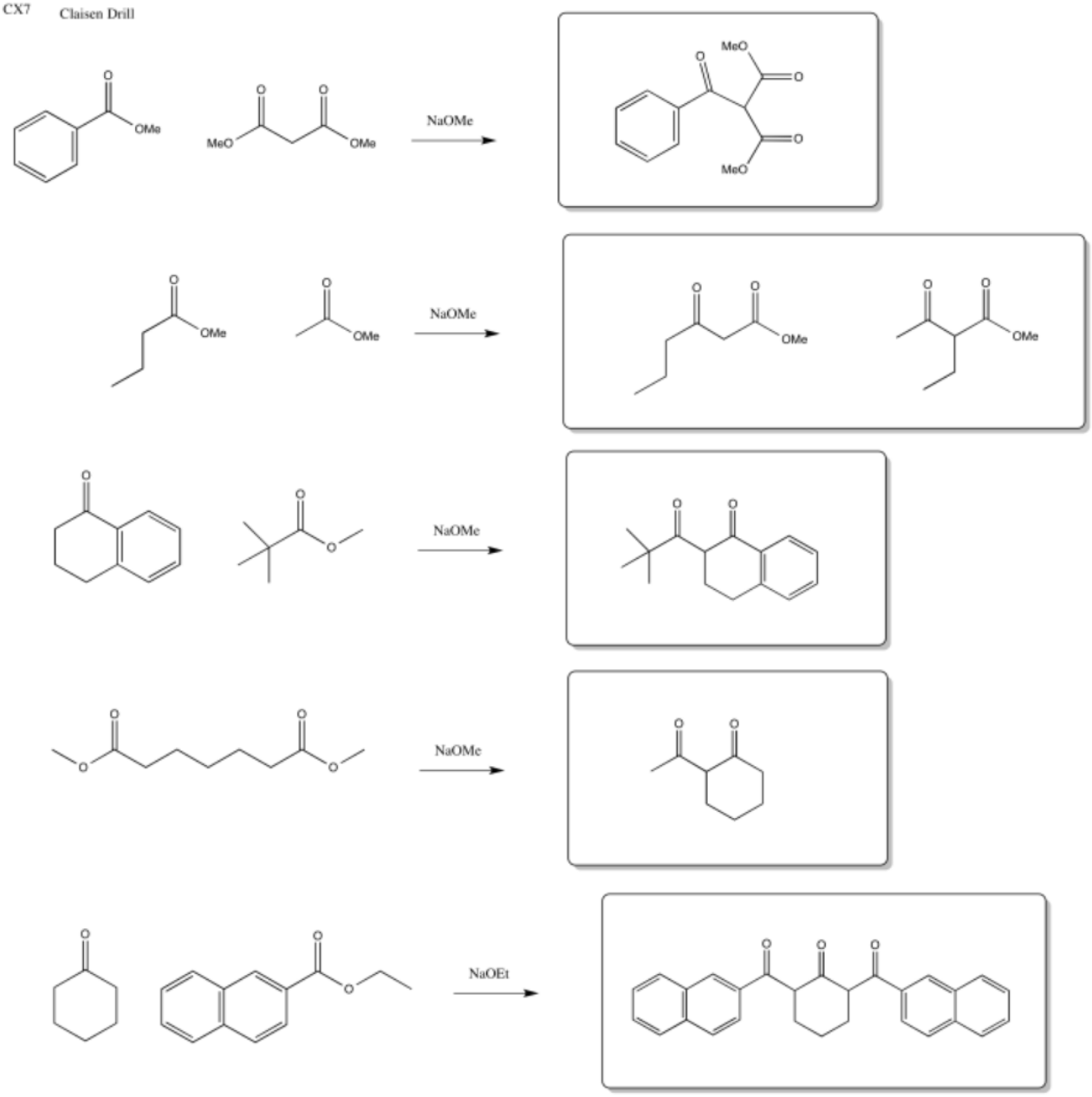
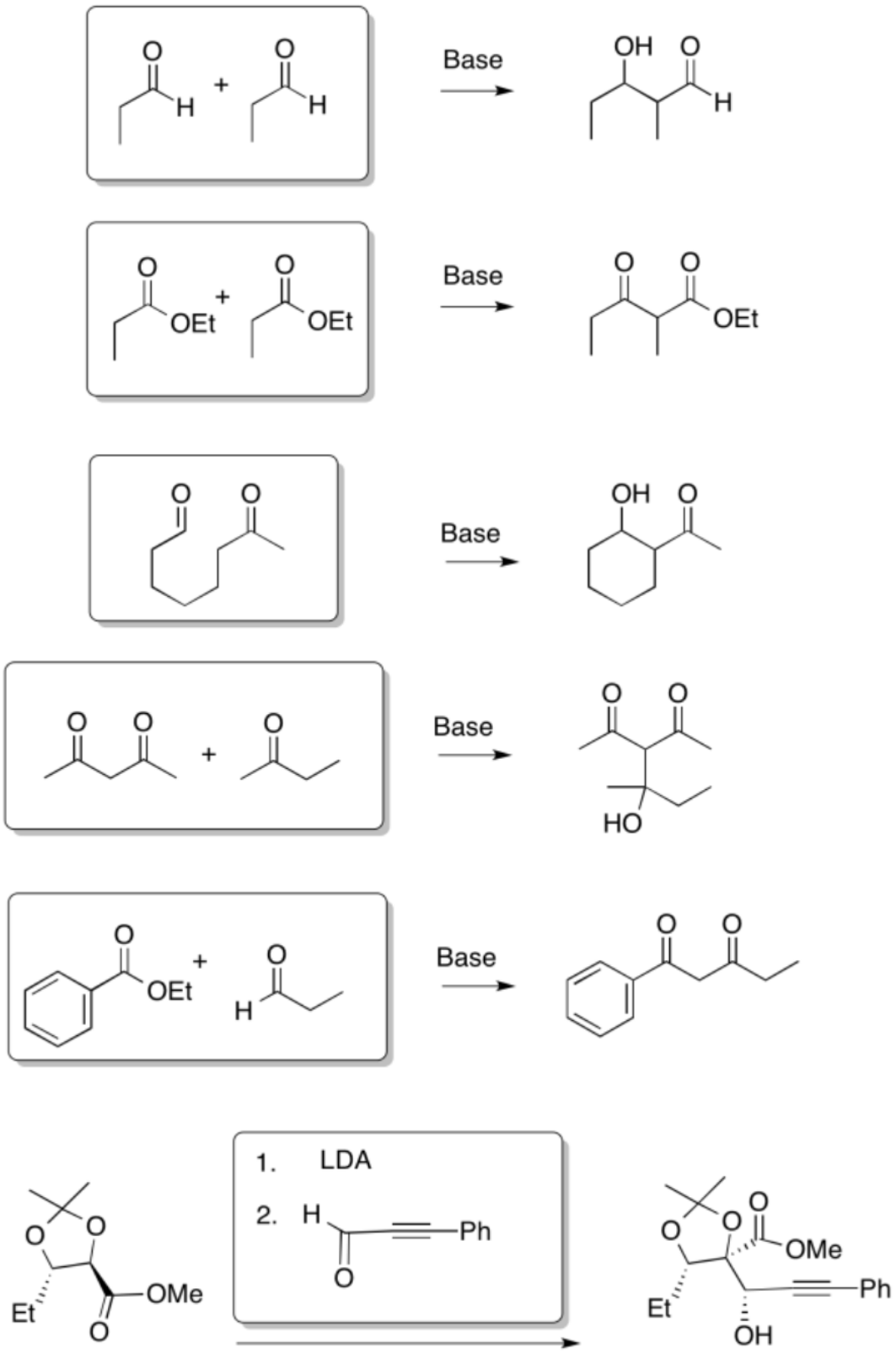
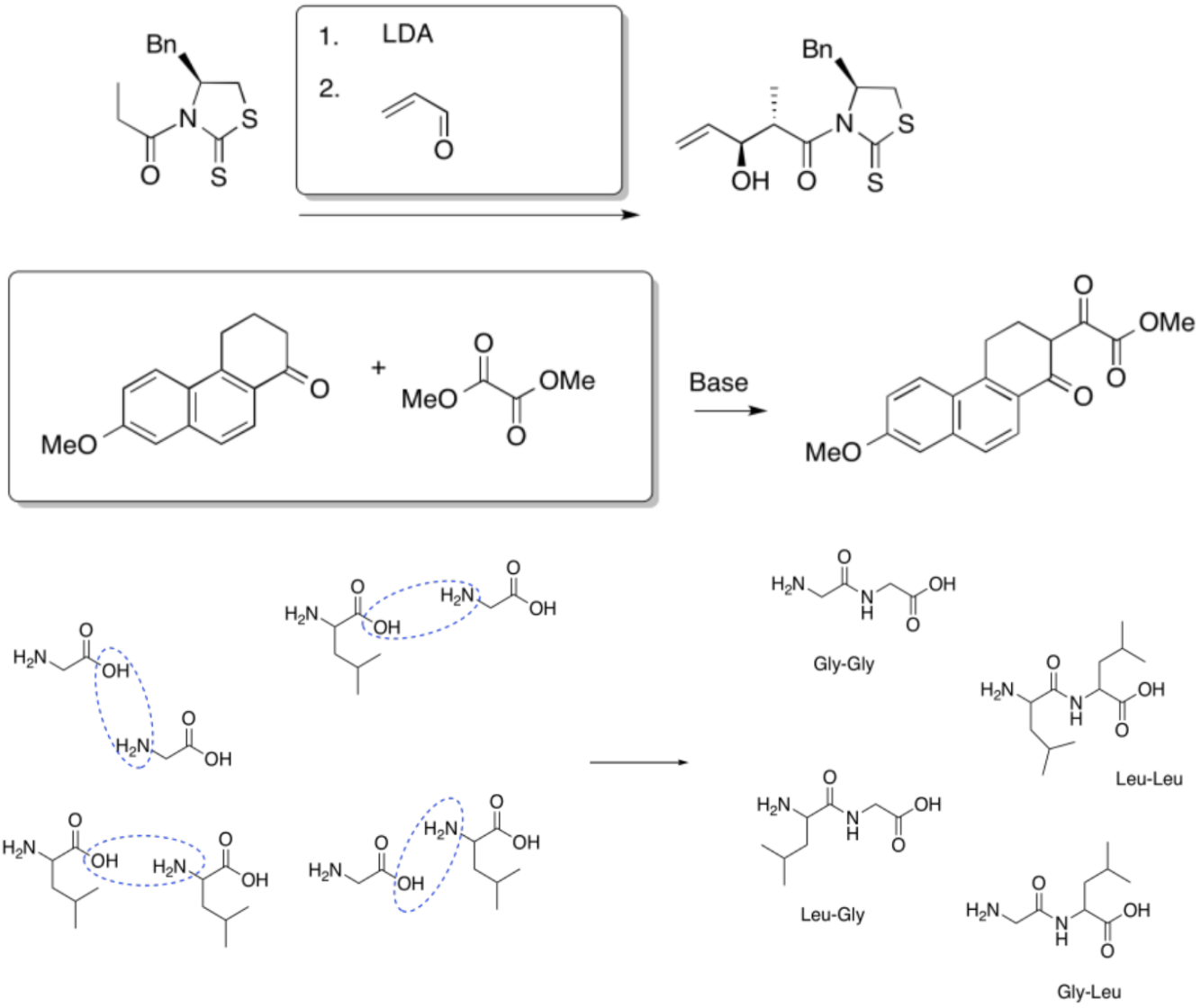


CX7 Claisen Drill







That combination would give thw following dipeptides:

ala-ala ala-gly ala-val

gly-gly gly-ala gly-val

val-val val-ala val-gly

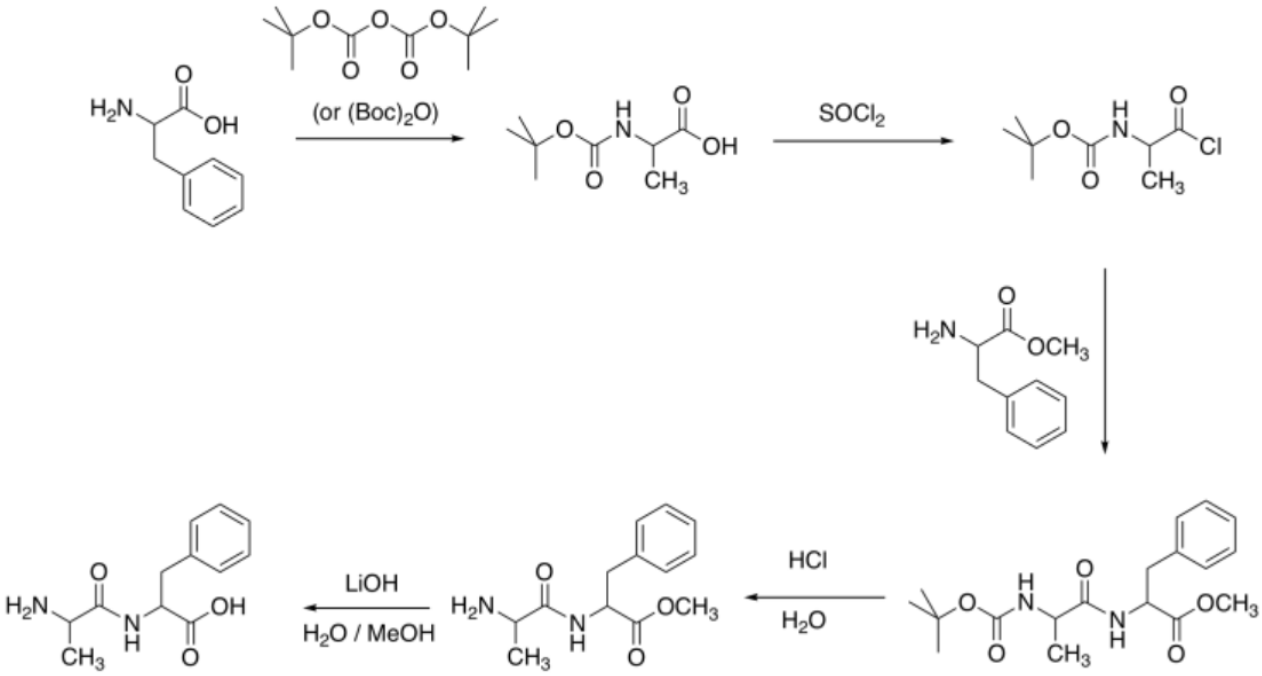
Of course, we might also get tripeptides, such as ala-ala-gly-val, and so on.

Carboxylic acids usually require activation before they can act as nucleophiles. That problem is actually complicated here because the carboxylic acid is in equilibrium with a carboxylate salt (read further on the page).

The relative reactivity of carboxyloids results from a balance between sigma electron withdrawing effects and pi-donation. An electronegative atom attached to a carbonyl tends to withdraw electron density, making the carbonyl even more positive and electrophilic. On the other hand, pi-donation from a neighbouring atom with a lone pair actually lowers electrophilicity by forming a stable, conjugated system.

In a carbamate, an additional electronegative atom is added to the carbonyl: it has an oxygen as well as a nitrogen adjacent to the C=O group. That atom draws electron density away from the carbonyl, making it more electrophilic. However, pi-donation from the additional oxygen does not result in a more stable conjugated system. The maximum pi system is still just three atoms long; it either involves conjugation of the O-C=O or the N-C=O unit. It does not, for example, lead to an even more stable conjugated system that is four atoms long.

As a result, the added oxygen probably contributes more to the electron-withdrawing effect than it does to stabilisation of the pi system.

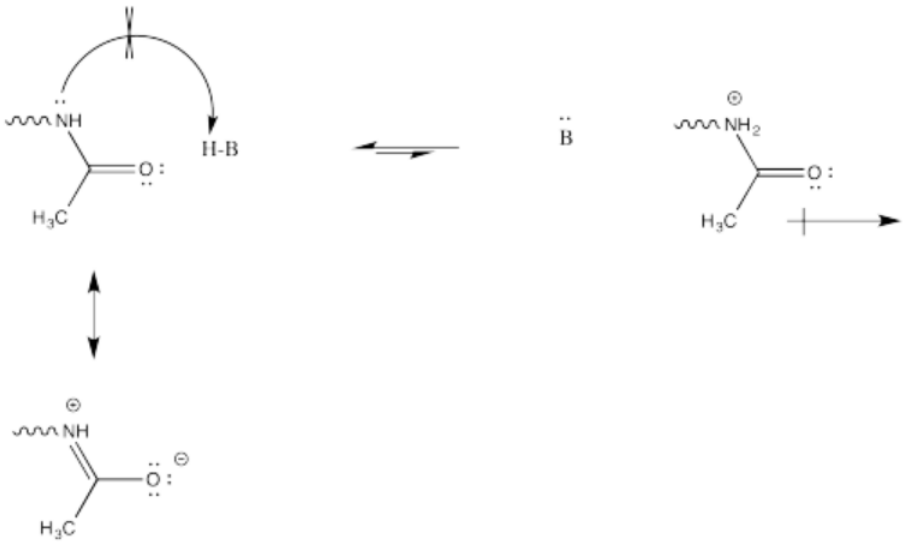


The more polar hydrochloride salt of EDCI is often used, as pictured. This more polar compound dissolves well in polar solvents, such as water, that also dissolve amino acids.

One can also imagine the amino group in EDCI acting as a site for catalysis, shuttling protons from one place to another.

Problem CX10.1.

This change in charge results because, although amines are easily protonated, amides are not. Protonation of an amide would result in a cation adjacent to the very positive carbonyl carbon, leading to a buildup of localized positive charge. That wouldn't be easy. Furthermore, the amide nitrogen is not very likely to donate its electrons to a proton in the first place. Its protons are too busy. They are tied up in conjugation with the carbonyl, so they really aren't available to act as the lone pair of a base.



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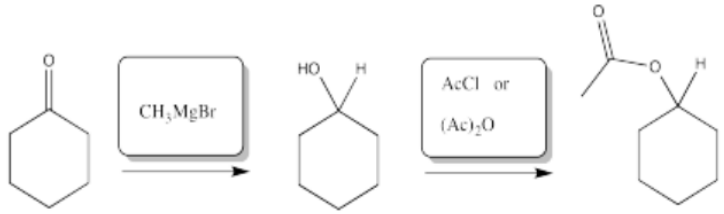

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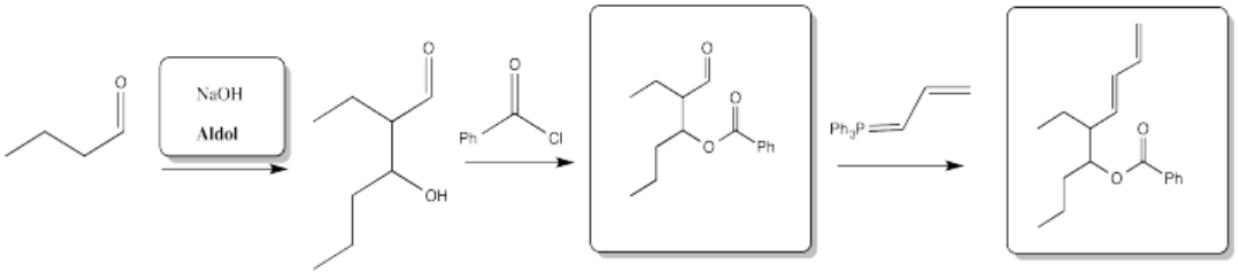

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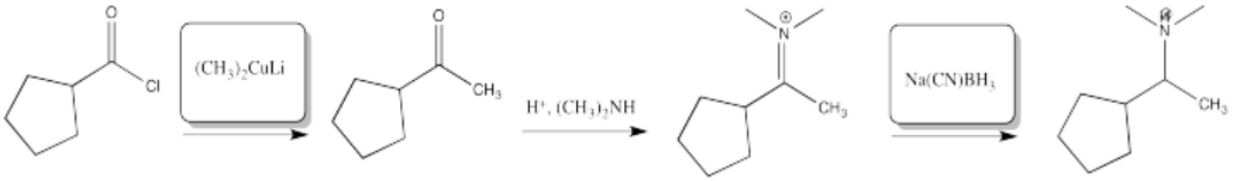
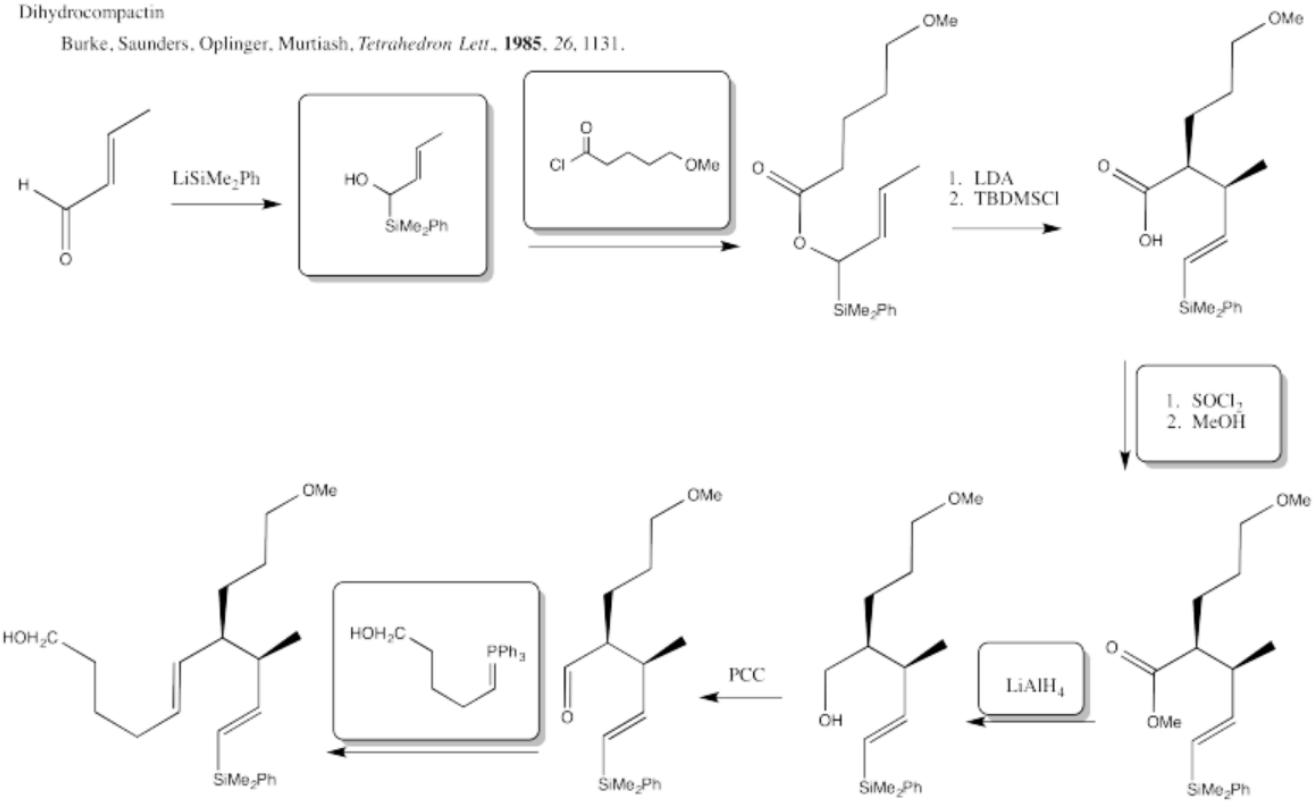
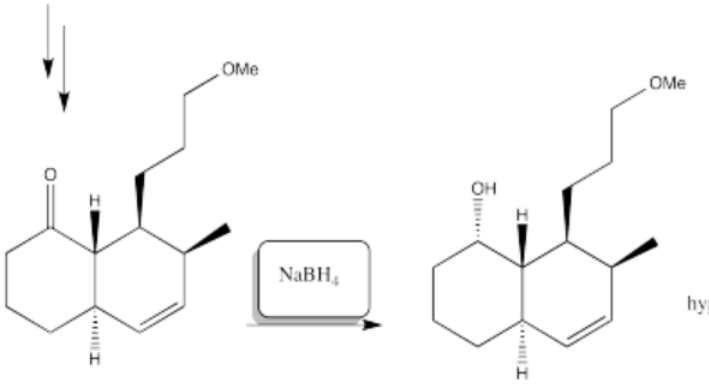


Dihydrocompactin

Burke, Saunders, Oplinger, Murtiash, *Tetrahedron Lett.*, **1985**, *26*, 1131.

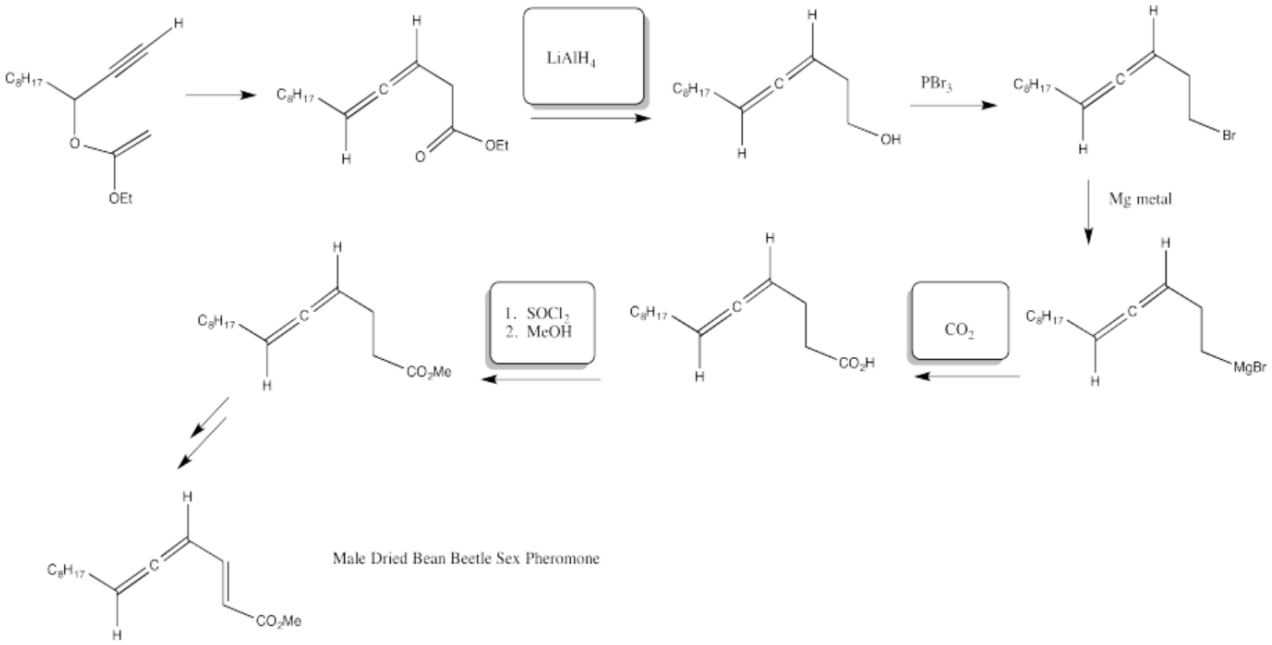




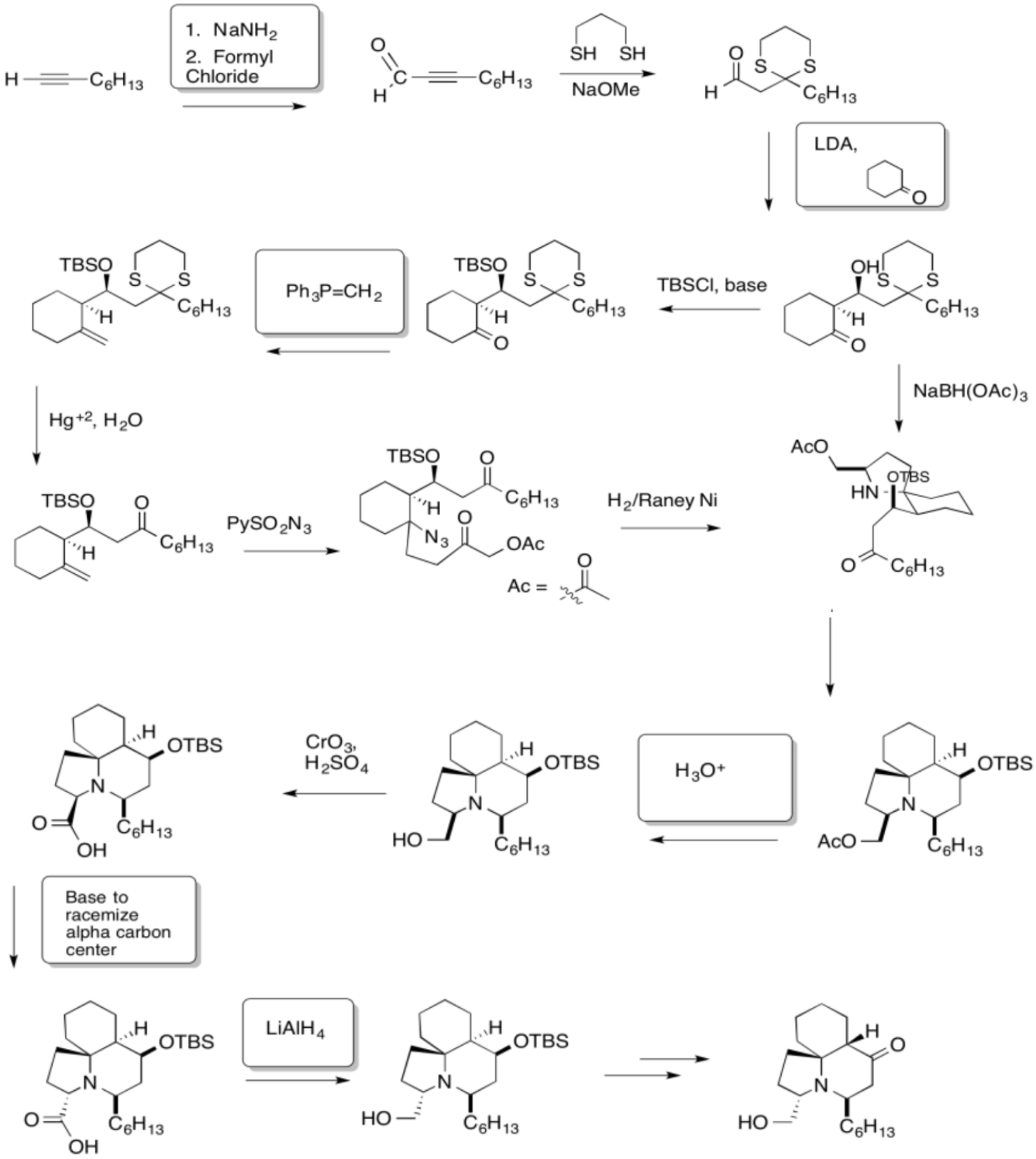
hypocholesteremic agent from *Penicillium citrinum*

Male Dried Bean Beetle Sex Pheromone

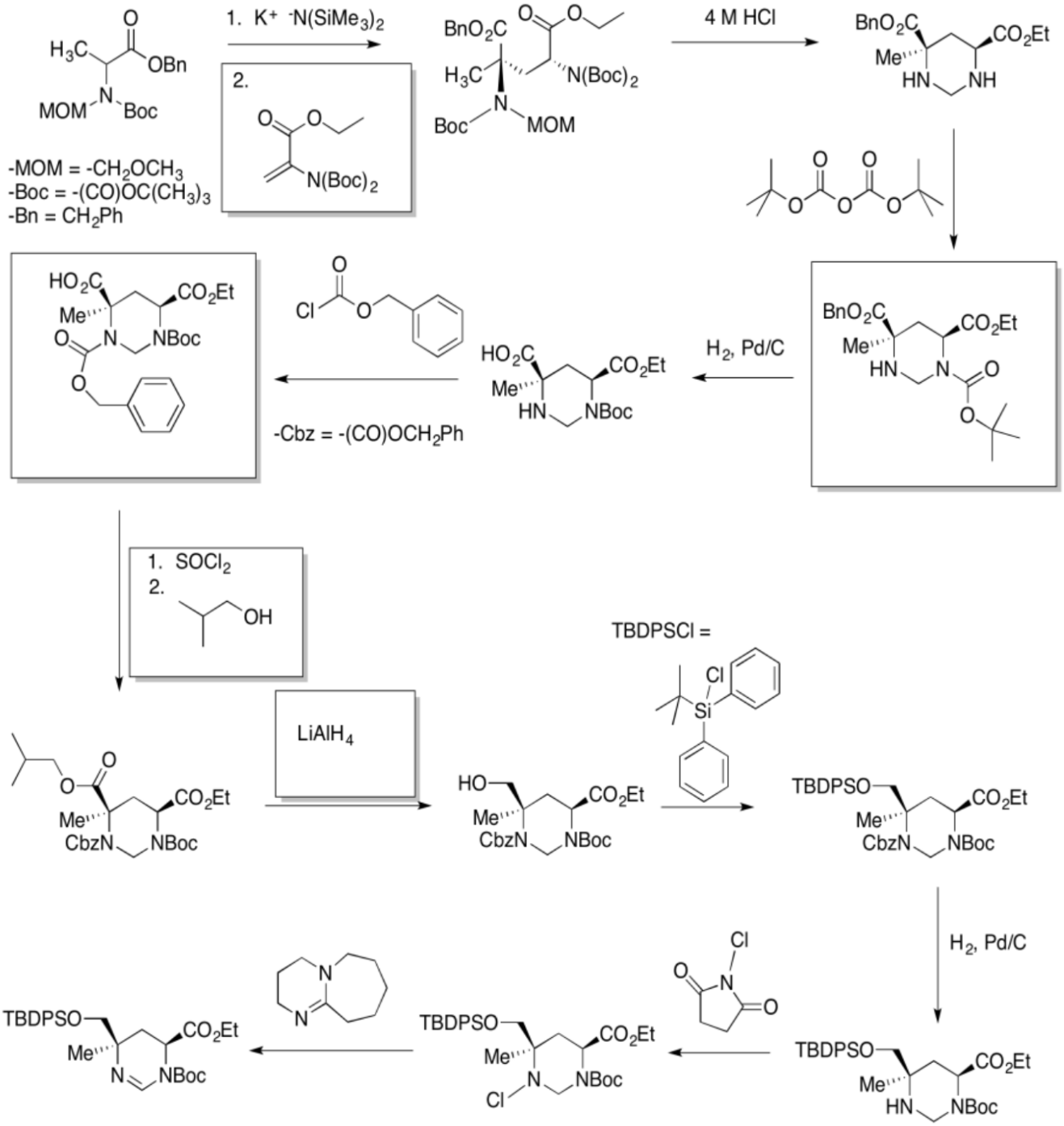
Kocienski, Cernogliaro Feldstein, *J. Org. Chem.*, **1977**, *2*, 353.

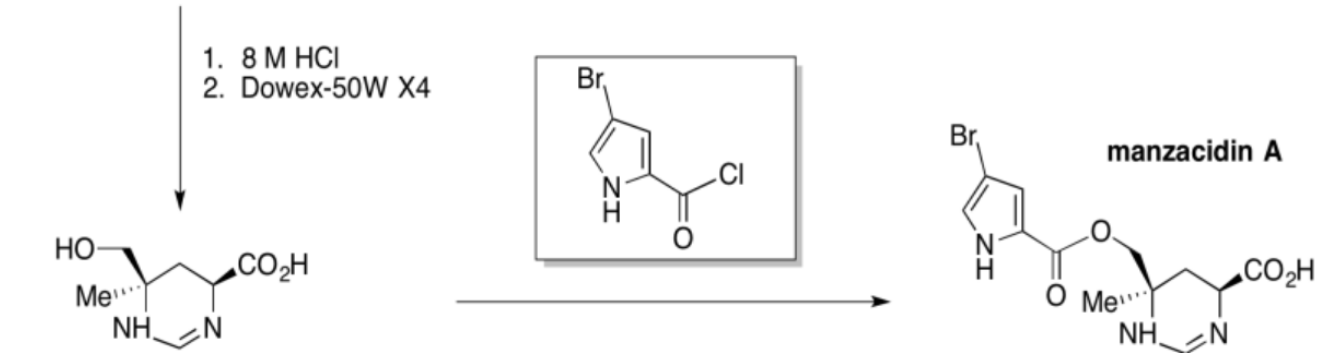


Male Dried Bean Beetle Sex Pheromone

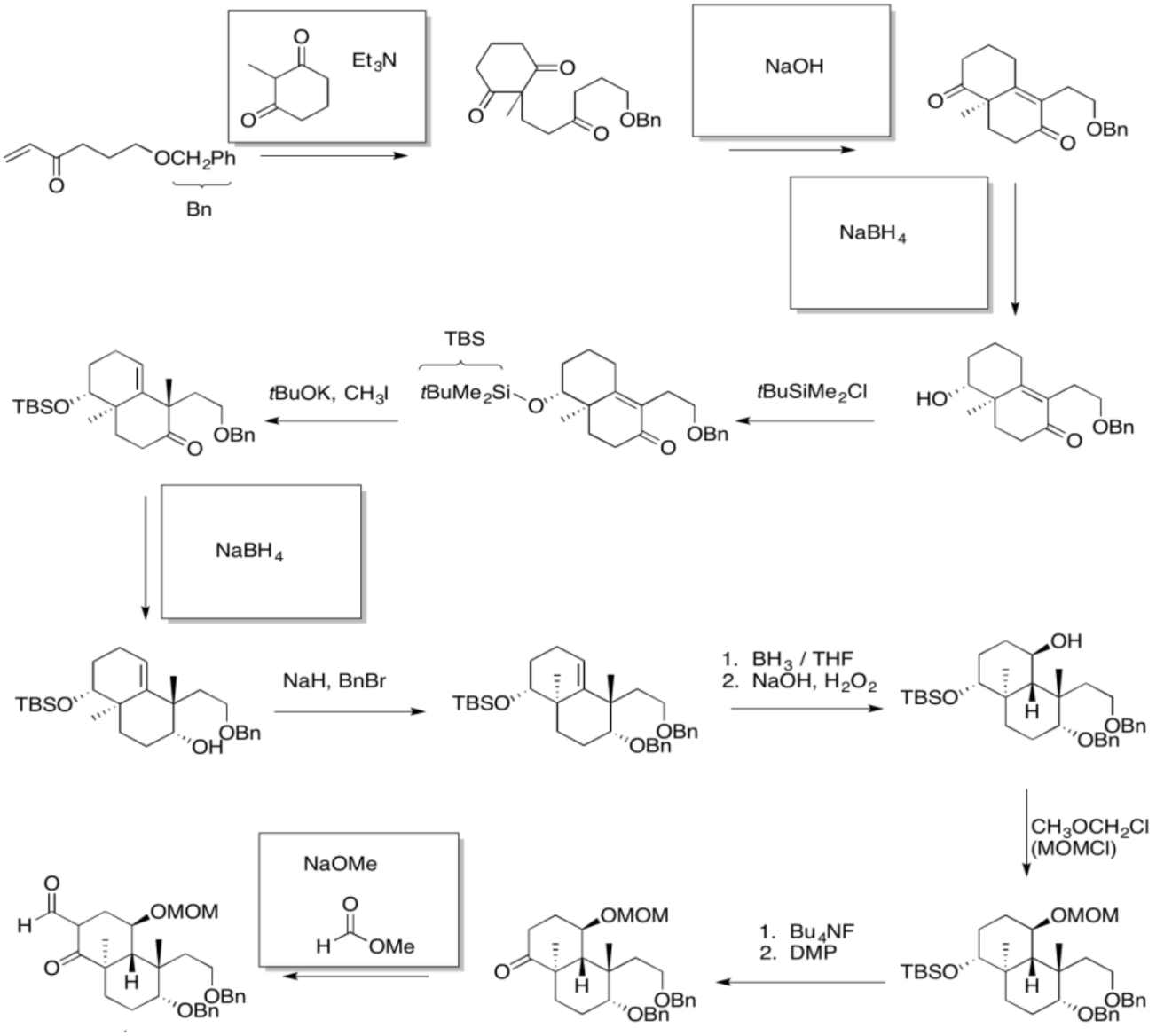


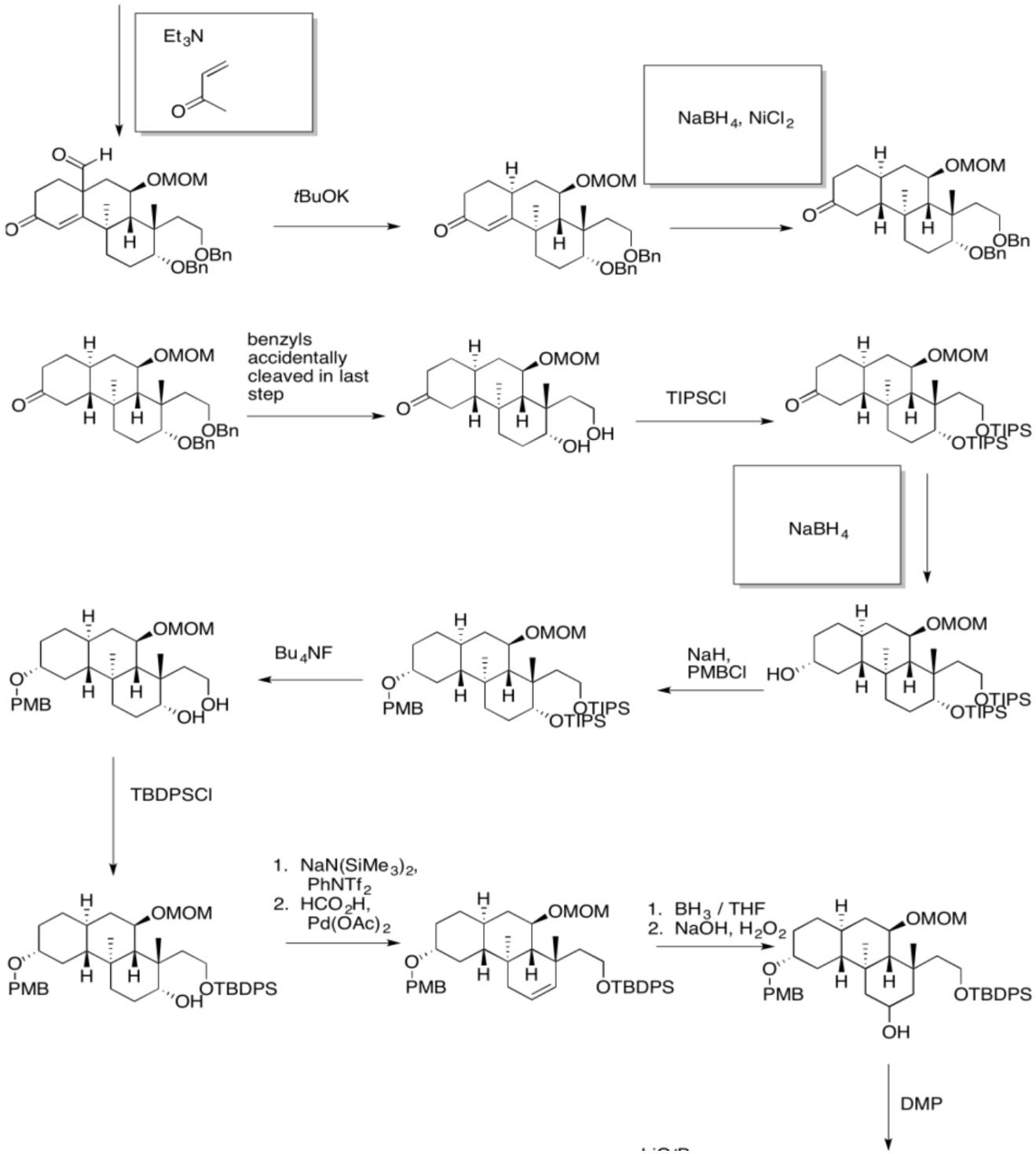
Total Synthesis of Manzacidin A (Kawabata, Kyoto University, 2013)
Isolated from Okanawan sponge *Hymeniacidon* sp. Extremely low isolated quantities prevented biological assays with naturally-available material.

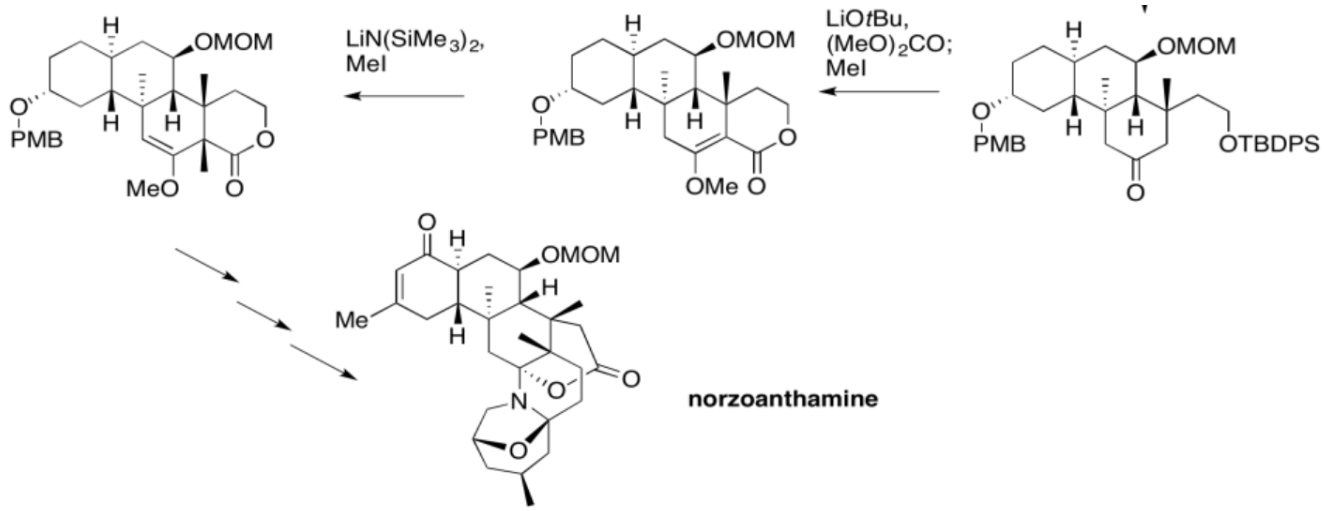




Partial Syntheses of Norzoanthamine (Thoedorakis, UCSD, 2011)
Marine natural product of *Zoanthus sp.* Demonstrated anti-osteoporotic effects in mice.

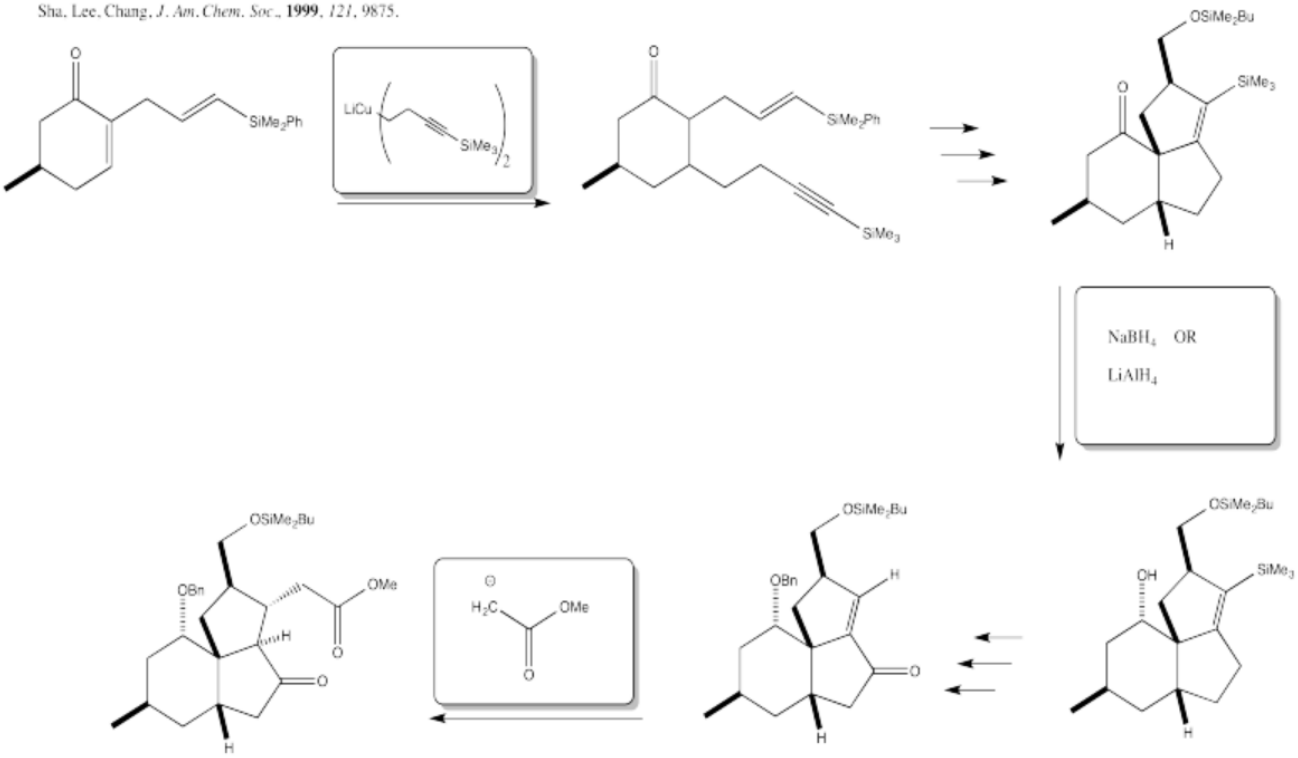


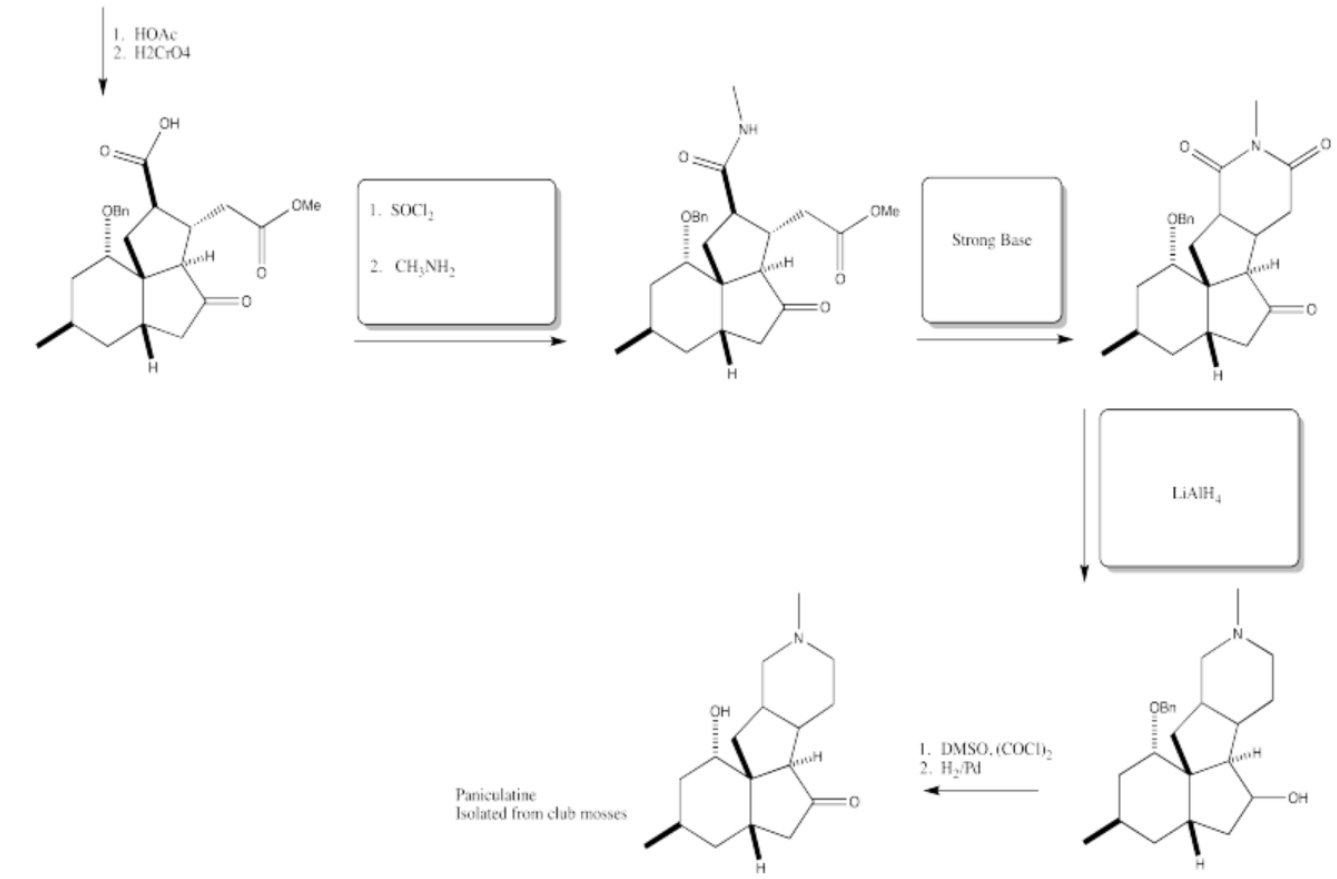




Paniculatine

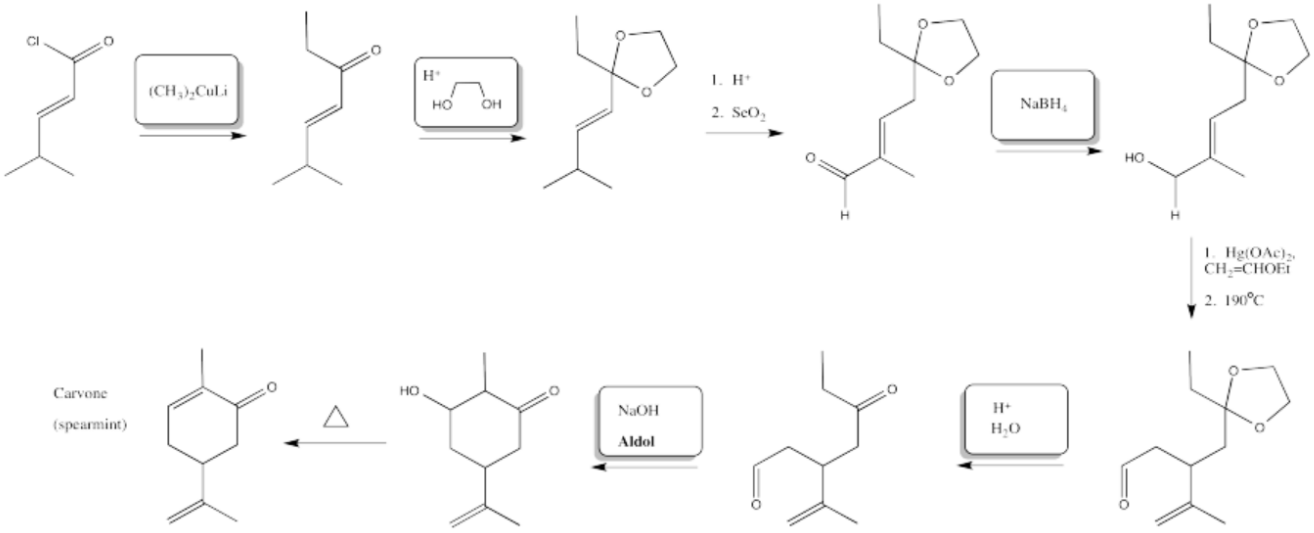
Sha, Lee, Chang, *J. Am. Chem. Soc.*, **1999**, *121*, 9875.





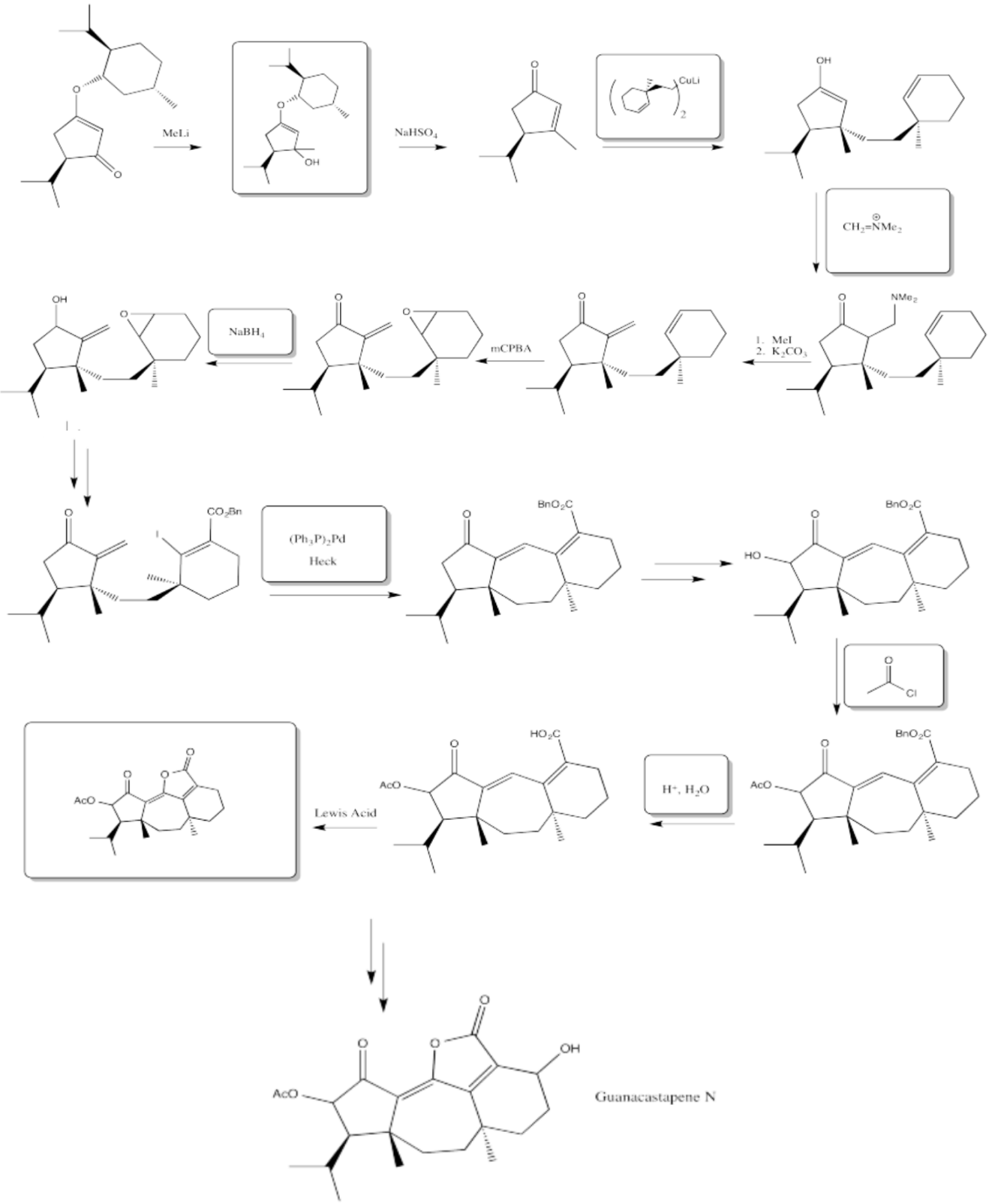
Carvone

Vig, Sharma, Chander, Raj, *Ind. J. Chem.*, **1966**, *4*, 275.



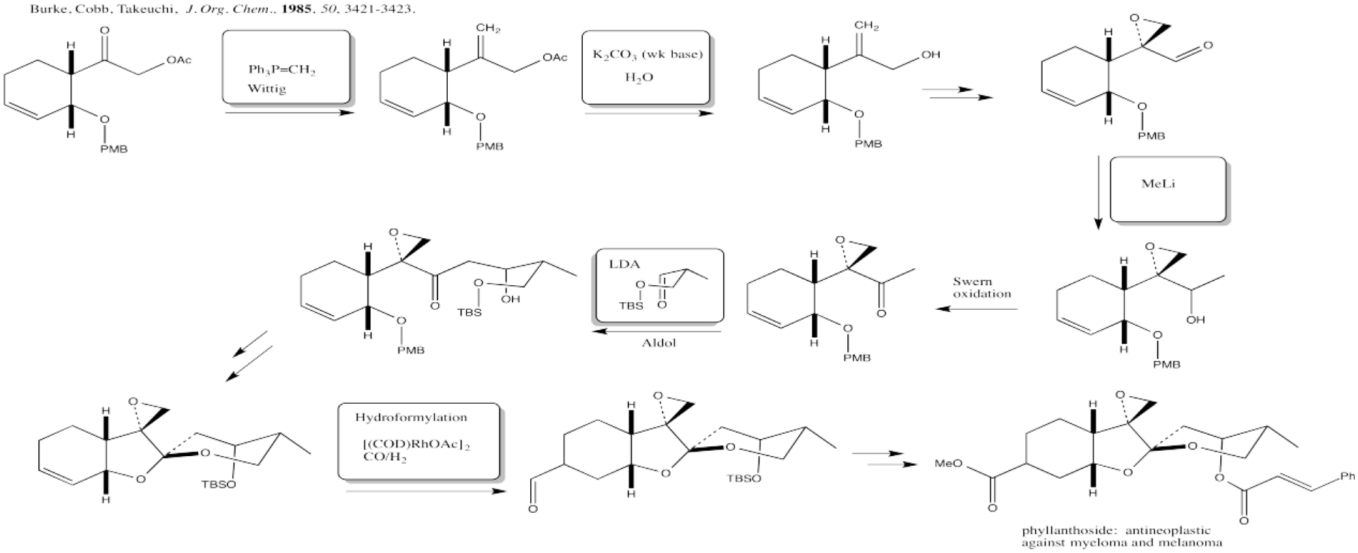
Guanacastepene N

Iimura, Overman, Paulini, Zakarian, *J. Am. Chem. Soc.* **2006,** *128*, 13095.



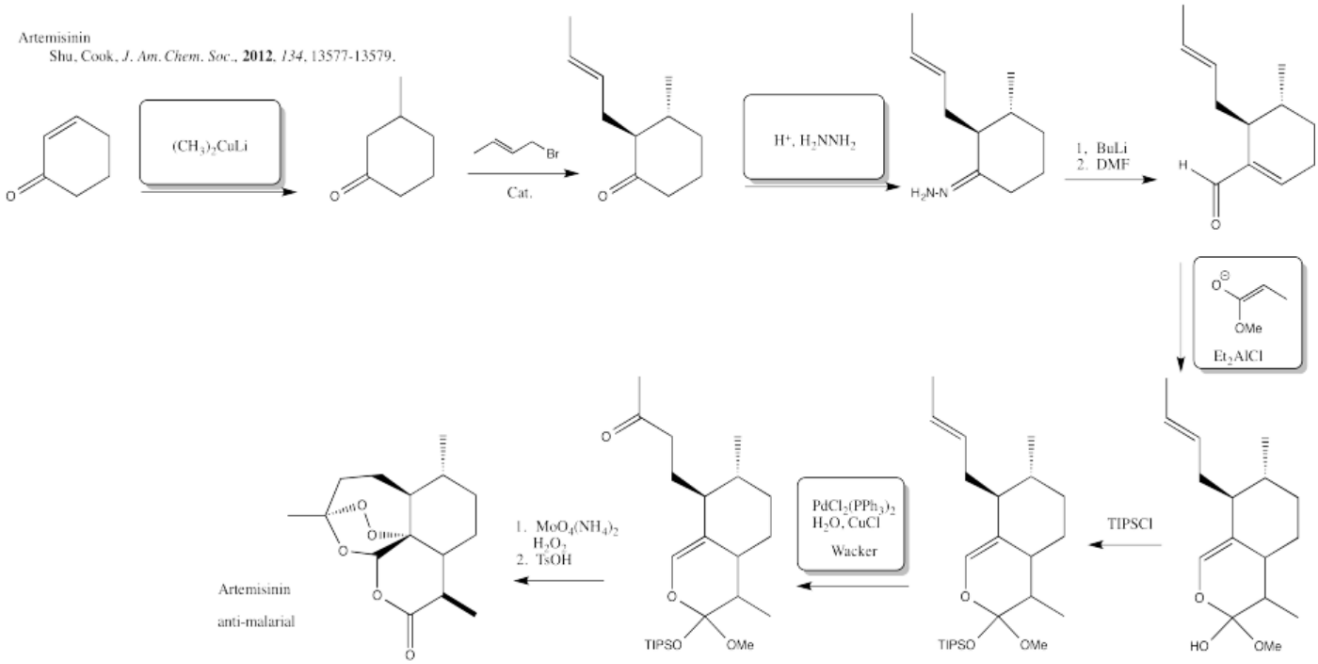
Phyllanthocin

Burke, Cobb, Takeuchi, *J. Org. Chem.*, **1985**, *50*, 3421-3423.



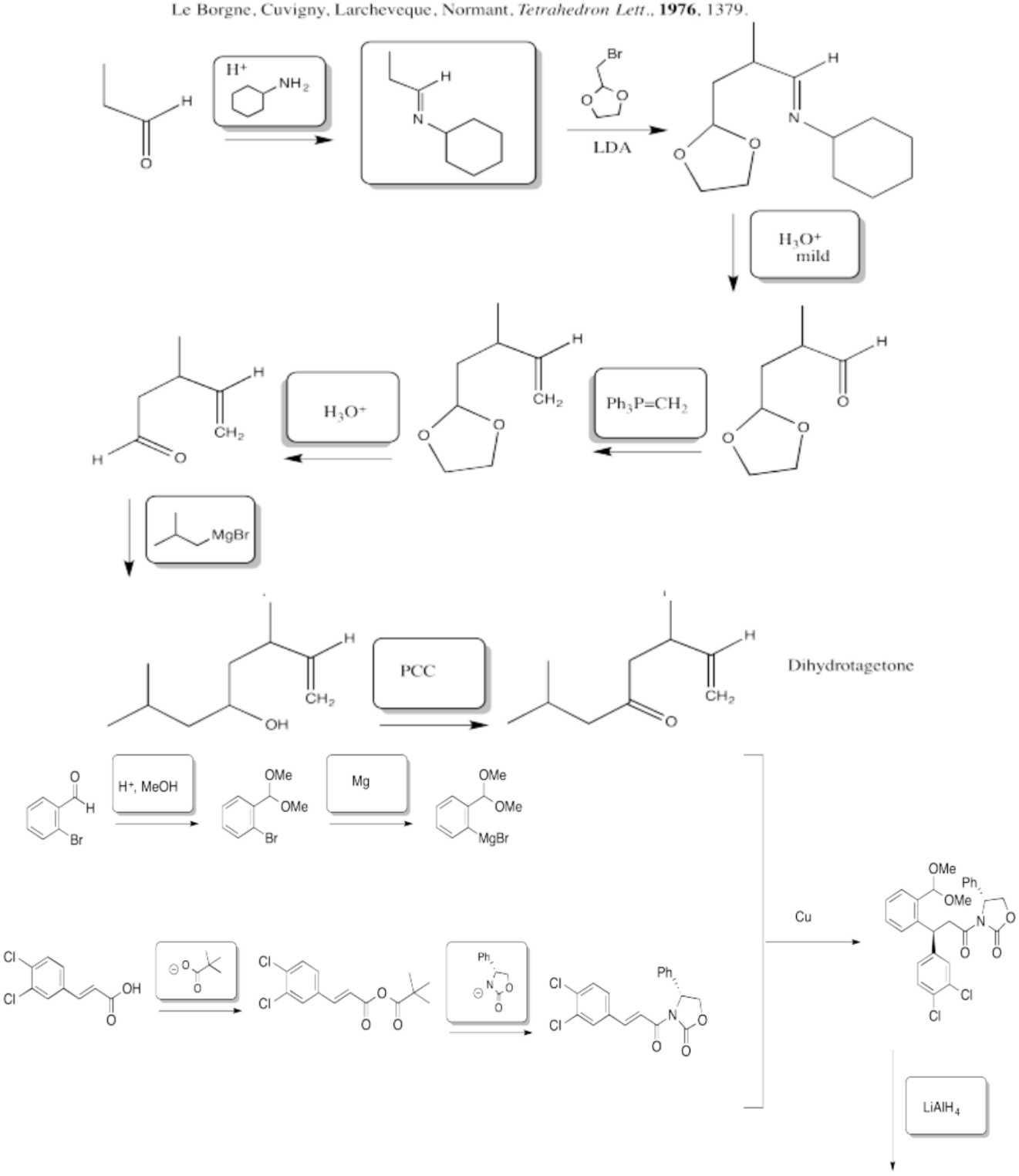
Artemisinin

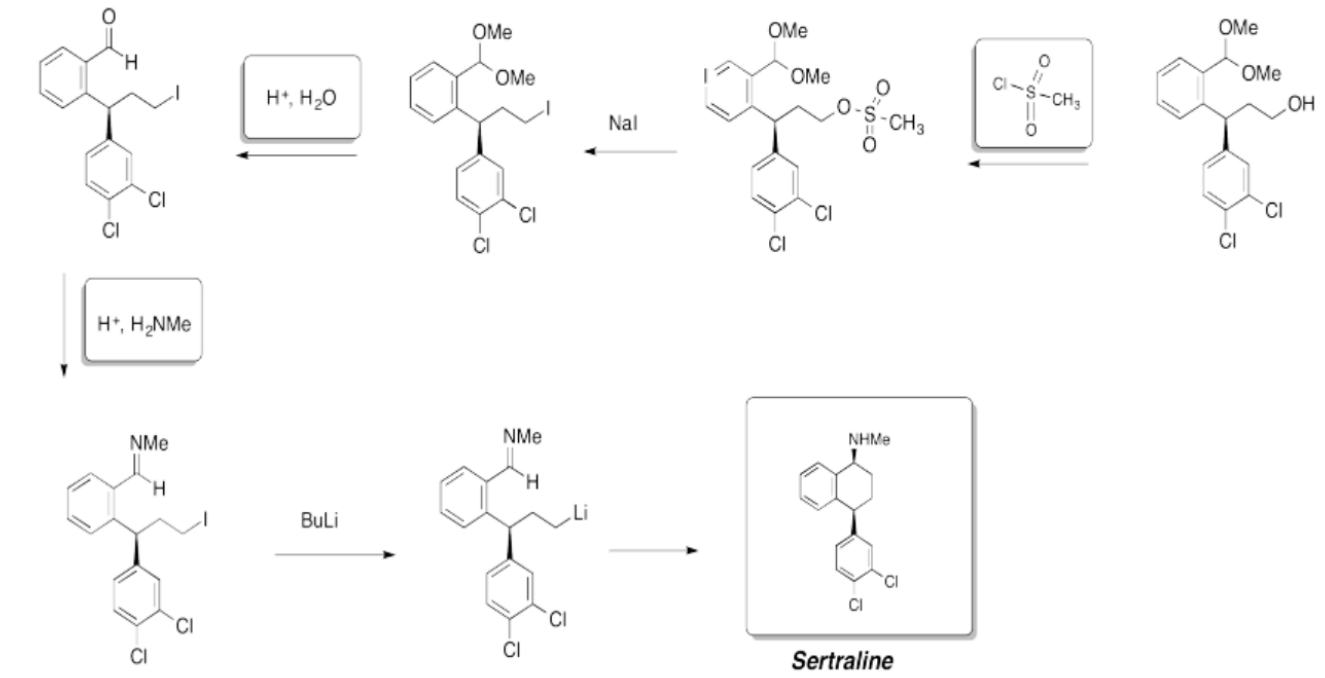
Shu, Cook, *J. Am. Chem. Soc.*, **2012**, *134*, 13577-13579.



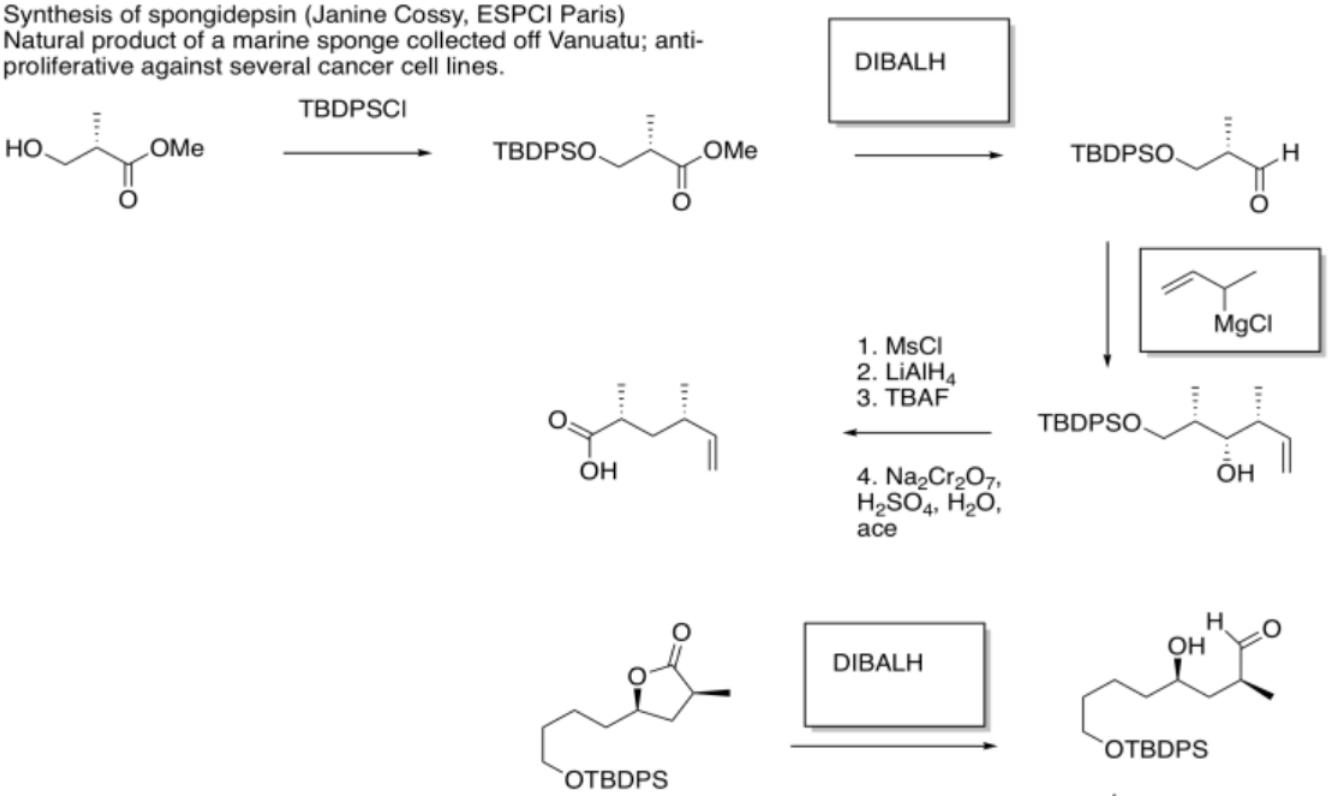
Dihydrotagetone

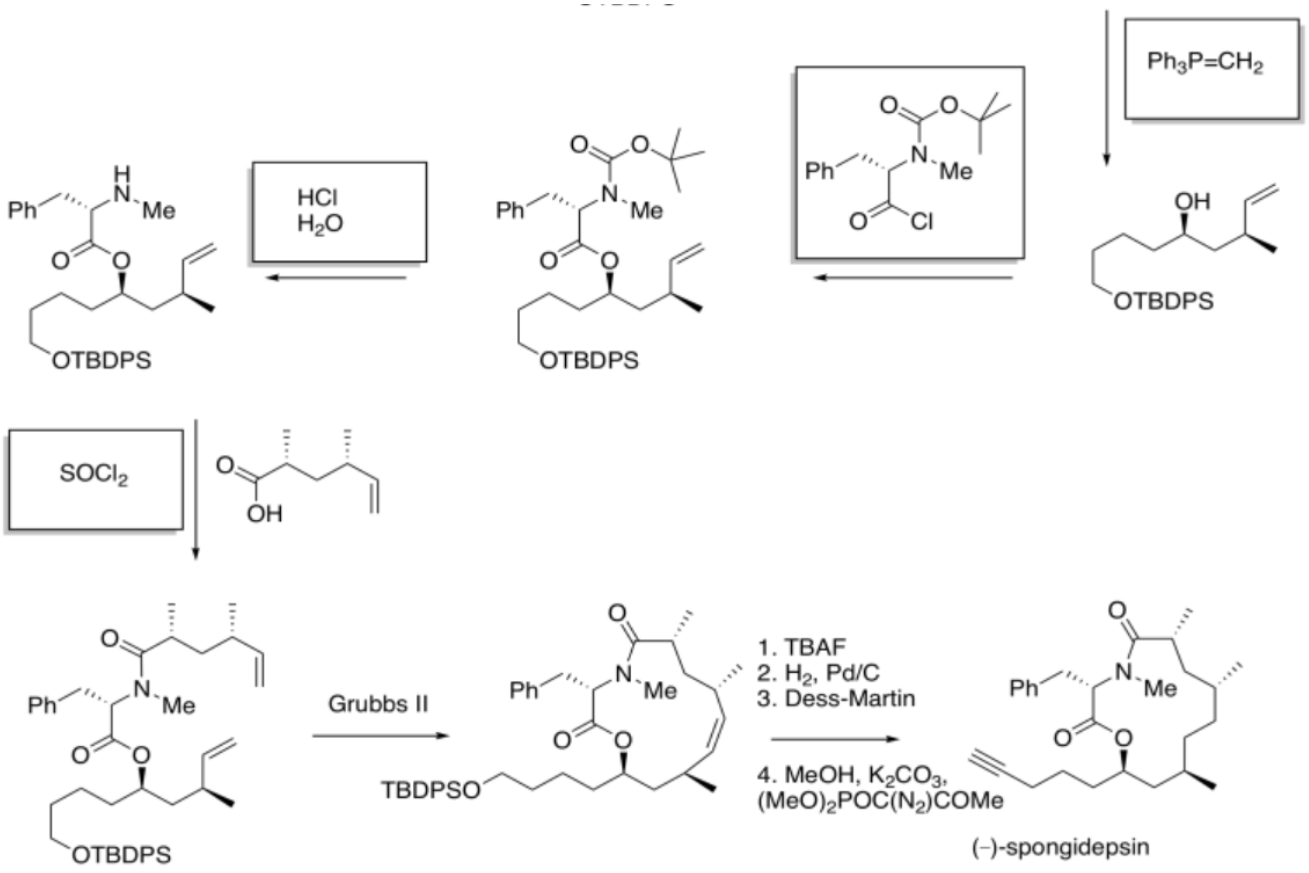
Le Borgne, Cuvigny, Larcheveque, Normant, *Tetrahedron Lett.*, **1976**, 1379.





Synthesis of spongidepsin (Janine Cossy, ESPCI Paris)
Natural product of a marine sponge collected off Vanuatu; anti-proliferative against several cancer cell lines.





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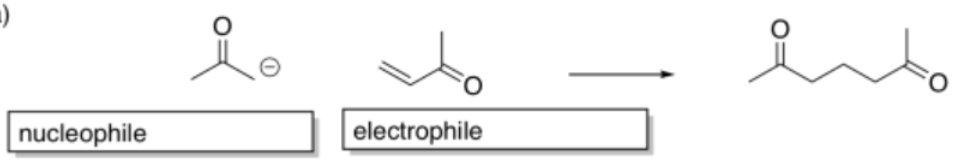

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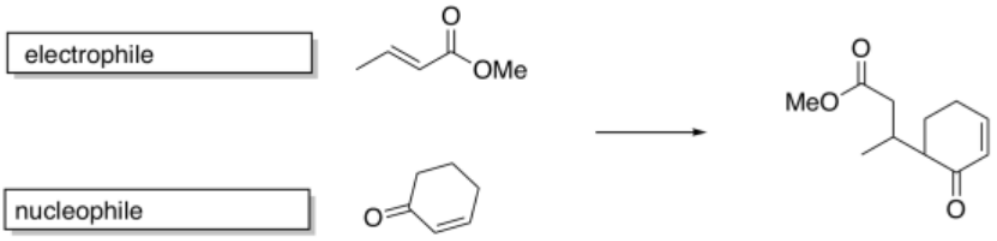

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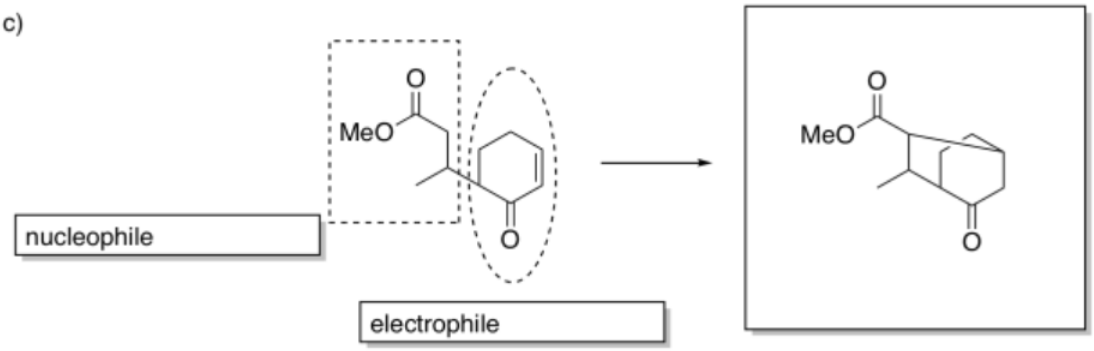
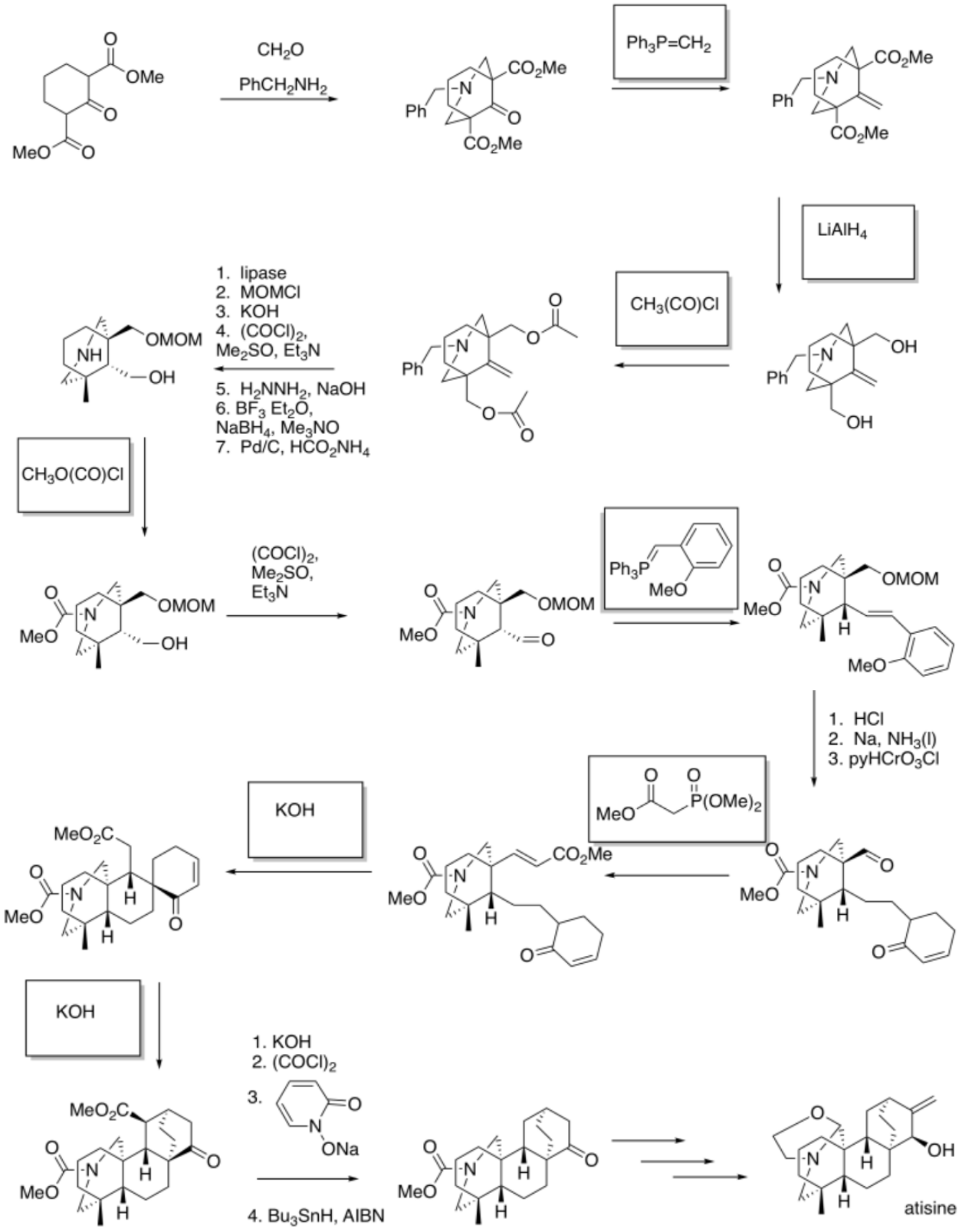




5.5: Introduction to Carboxyloids

Aldehydes and ketones are carbonyl compounds in which the carbonyl carbon is connected only to carbons atoms (in the case of a ketone) or to one carbon and one hydrogen atom (in the case of an aldehyde).

Carboxyloids, or carboxylic acid derivatives, are carbonyl compounds in which the carbonyl carbon is attached to one carbon and one heteroatom. Most commonly, the heteroatom is an oxygen, nitrogen, sulfur or chlorine.

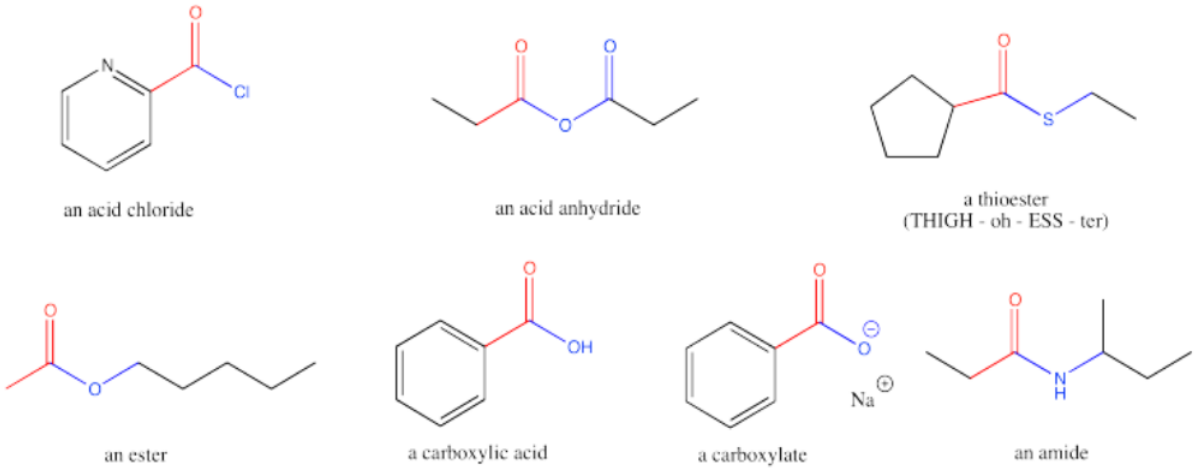


Figure 5.5.1:

Carboxylic acid derivatives were historically thought of as being made from carboxylic acids; hence the name. That name is a mouthful; we will use the term "carboxyloids", a term coined by the 20th century physical organic chemist, Christopher Ingold.

The reactivity of carboxyloids is typically different from aldehydes and ketones. Because of this difference it is useful to study these compounds separately from the simple carbonyls.

Exercise 5.5.1

What are some things that the heteroatoms involved in carboxyloids have in common?

Answer

These heteroatoms are all found in the upper right-hand corner of the periodic table. They are all pretty electronegative and they all have lone pairs.

Like simple carbonyls, carboxyloids react with nucleophiles. Just like simple carbonyls, the LUMO of a carboxyloid is usually the C=O pi antibonding orbital (the π^*). Populating this orbital with a pair of electrons from the nucleophile results in breaking the C=O pi bond, leaving only a C-O sigma bond.

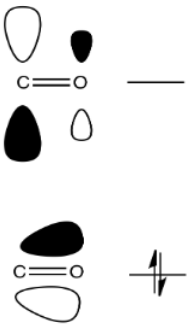


Figure 5.5.2:

Remember that this addition to the C=O bond is often reversible. In the case of carboxyloids, however, re-forming the pi bond can go through two pathways. In one pathway, the nucleophile can be displaced, returning to starting materials. In another pathway, the group attached to the carbonyl can be displaced instead. In that pathway, a new product results.

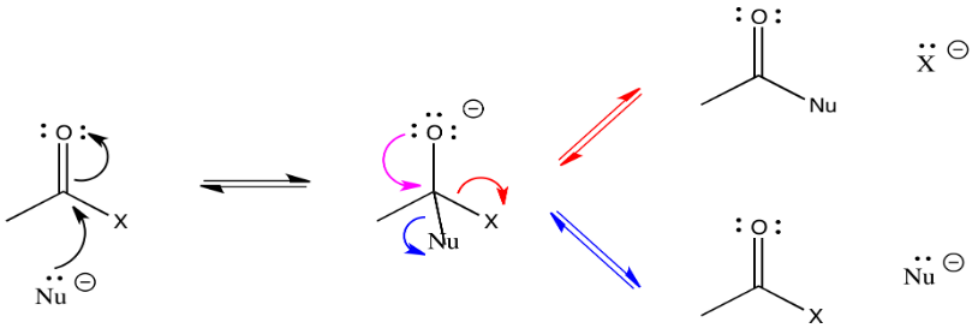


Figure 5.5.3:

5.6: General Reactivity Patterns

Just as a simple carbonyl is an electrophile, so is a carboxyloid. Carboxyloids react with many of the same nucleophiles that react with aldehydes and ketones. The overall result of the reaction is very different. However, the mechanism of the reaction is really quite similar.

Nucleophiles have the overall effect of adding across the carbonyl group of an aldehyde or ketone. Addition of a proton produces an alcohol. The C=O bond is parlty broken to a C-O bond. In some cases, the C=O bond is completely broken and after several steps the carbonyl oxygen is replaced by some other heteroatom. On the other hand, nucleophiles add to carboxyloids and end up replacing the heteroatom next to the carbonyl. The carbonyl itself remains intact after the reaction is complete.

The general pattern in carboxyloid chemistry is for nucleophiles to substitute for the heteroatomic group next to the carbonyl. In these reactions, the group next to the carbonyl is sometimes referred to as a "leaving group". That term simply means that this group has been replaced by the end of the reaction.

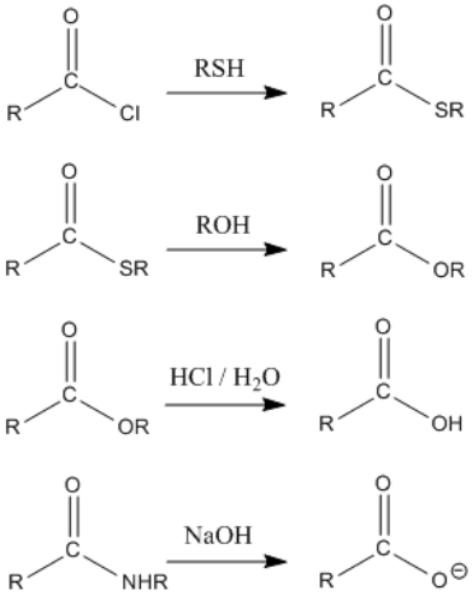


Figure 5.6.1:

Note that there is no reason to believe that the initial elementary reaction between a carboxyloid and a nucleophie is any different than that of a simple carbonyl with a nucleophile. An examination of the frontier orbitals in a carboxyloid suggests the pi antibonding level would be the site of population by a nucleophilic lone pair. The carbonyl pi bond would break as the nucleophile approaches.

However, an important feature of carbonyl chemistry is that two heteroatoms on one tetrahedral carbon cannot last. One always pushes the other off. If the former carbonyl oxygen pushes off the nucleophile, the system returns to the starting materials. However, if the former carbonyl oxygen displaces the heteroatomic group next to it, there is an overall change in bonding and a different product is formed. The net result is replacement of the group next to the carbonyl.

Exercise 5.6.1

The overall result of reaction with a carboxyloid is to displace the heteroatom group next to the carbonyl. This group is typically liberated as an anion.

a. What feature of the heteroatoms typically found attached to the carbonyl in carboxyloids allows them to be displaced from the molecule as anions?
b. Why doesn't this same reaction happen with aldehydes and ketones?

Answer a

The electronegativity of the heteroatom attached to the carbonyl group in a carboxyloid is one factor that allows it to leave and form its own stable anion.

Answer b

Although carbon and hydrogen are more electronegative than many of the elements in the periodic table, they are not stable enough as anions to form easily on their own.

Exercise 5.6.2

Suggest an order of reactivity for the carboxyloids: rank them from most reactive to least reactive. Provide a reason for your trend.

Exercise 5.6.3

For the following reactions

a. Draw mechanistic arrows for the nucleophilic addition. Clearly show the tetrahedral structure formed immediately after the nucleophile adds.
b. Determine if a leaving group is present. If so, show the pi donation step and resulting product. If not, draw the product in the neutral form.

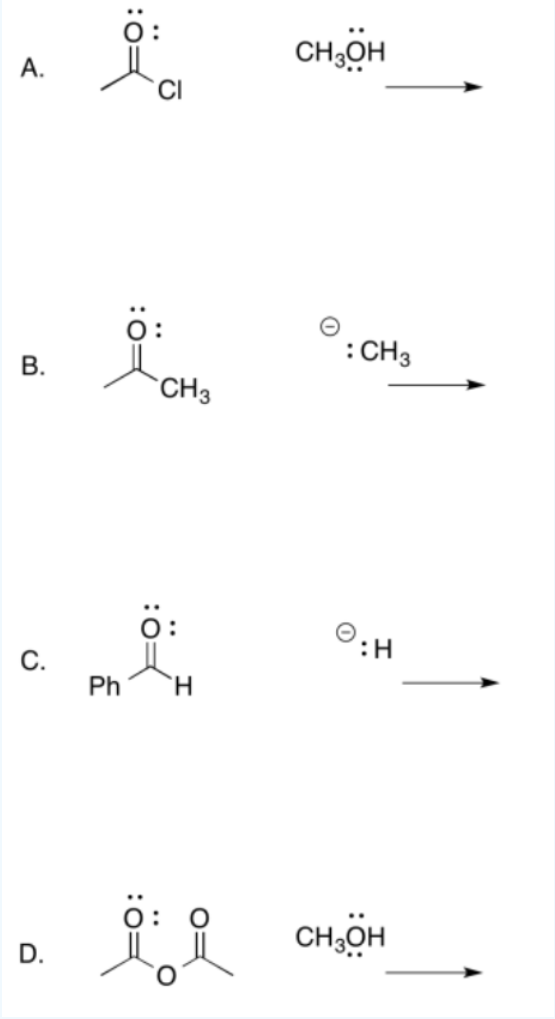
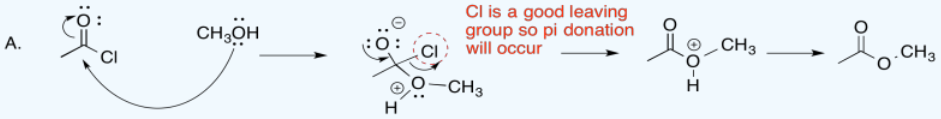
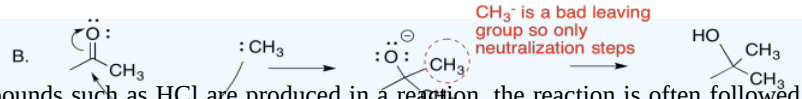


Figure 5.6.2:

Answer



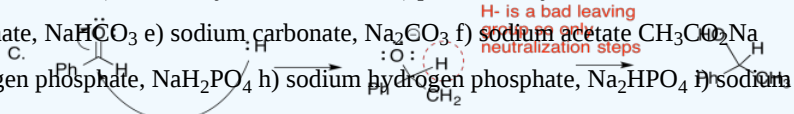
Exercise 5.6.4



When acidic compounds such as HCl are produced in a reaction, the reaction is often followed by treatment with a base that will neutralise the acid. Provide Lewis-Kekule structures of the following bases.

a) lithium hydroxide, LiOH b) sodium hydroxide, NaOH c) potassium hydroxide, KOH

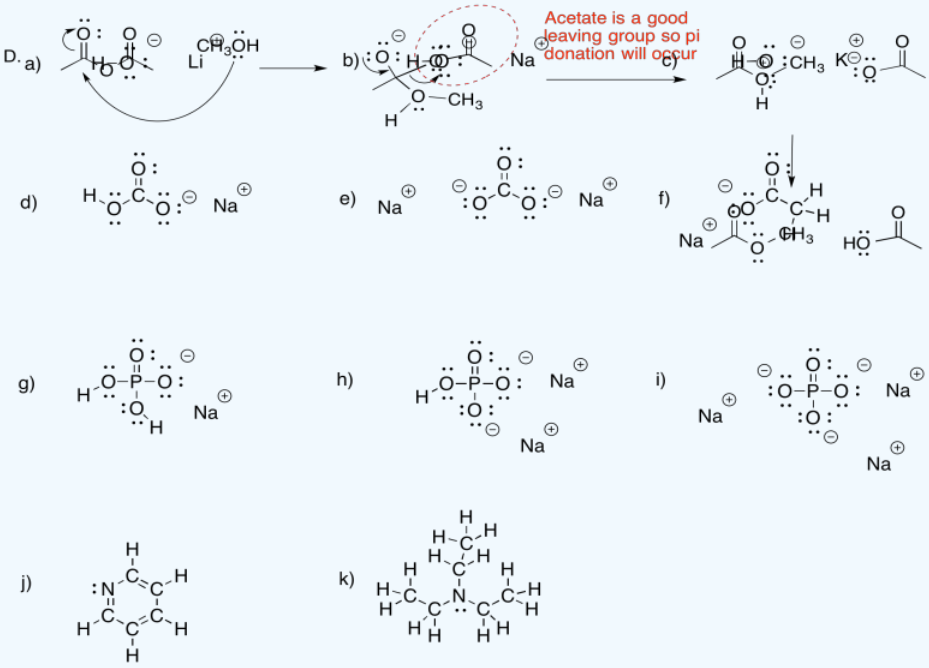
d) sodium bicarbonate, $NaHCO_3$ e) sodium carbonate, Na_2CO_3 f) sodium acetate CH_3CO_2Na



g) sodium dihydrogen phosphate, NaH_2PO_4 h) sodium hydrogen phosphate, Na_2HPO_4 i) sodium phosphate, Na_3PO_4

j) pyridine, C_5H_5N k) triethylamine, $(CH_3CH_2)_3N$

Answer



5.7: Comparative Energies- The Ski Hill

In most cases, the reactivity of carboxyloids involves converting one carboxyloid into another. This is done by replacing one heteroatom substituent with another. For example, the chloride in an acid chloride may be replaced by an alcohol or alkoxide ion to make an ester.

The fact that one carboxyloid can be converted into another suggests that there would be an equilibrium between them. The ratio of two carboxyloids at equilibrium would be determined by their relative stability, as well as the stability of other associated species in solution.

We can map out the stability of carboxyloids on a potential energy surface, as shown below. The higher energy, less stable, more reactive carboxyloids are shown at the top of the potential energy curve. The lower energy, more stable, less reactive carboxyloids are found lower down on the potential energy curve.

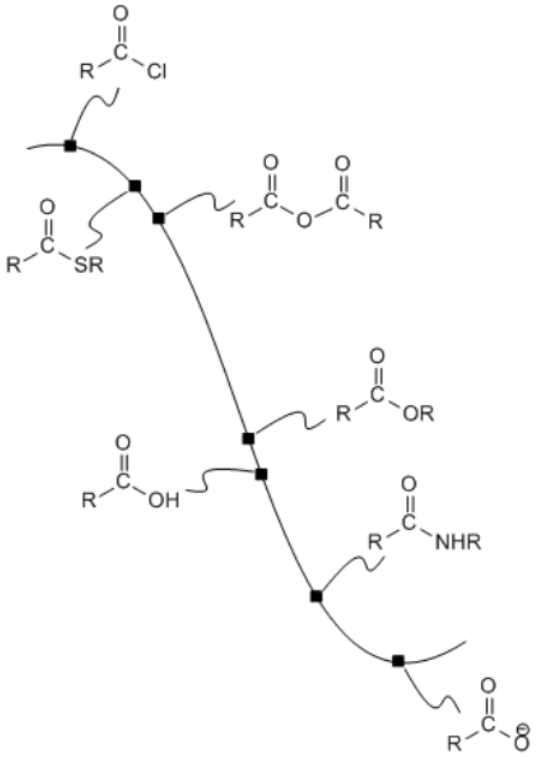


Figure 5.7.1: A potential energy curve showing relative reactivity of carboxloids.

The heteroatom attached to the carbonyl in a carboxyloid is always an electronegative atom with a lone pair. Either of those two features might be useful in understanding the reactivity trend illustrated above. For example, an electronegative atom would make the carbonyl carbon more positive. That carbon is already very positive because of the double bond to oxygen. Adding an additional electronegative atom should make it even more so. The amount of positive charge on the carbonyl carbon would be even greater if the atom attached to it were exceptionally electronegative.

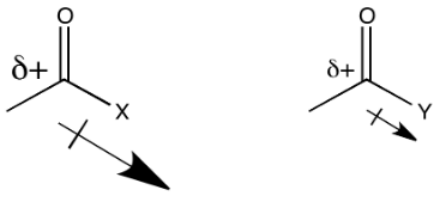


Figure 5.7.2:

On the other hand, a nearby lone pair might counteract the electron-attracting power of the carbonyl carbon. In a sense, we might think about that lone pair as competing with donation from a potential nucleophile.

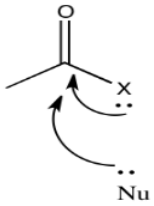


Figure 5.7.3:

The ability of an atom to π-donate, then, might have an influence on how strongly the carbonyl will attract nucleophiles. Of course, there is some trade-off involved in π-donation. Usually the atom that donates must take on a positive charge, since it is lending a pair of its own electrons to another atom. Factors that influence how easily this may happen could be important in determining carboxyloid reactivity.

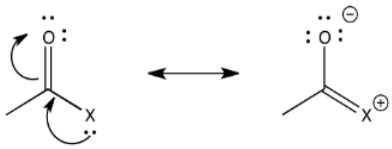


Figure 5.7.4:

Exercise 5.7.1

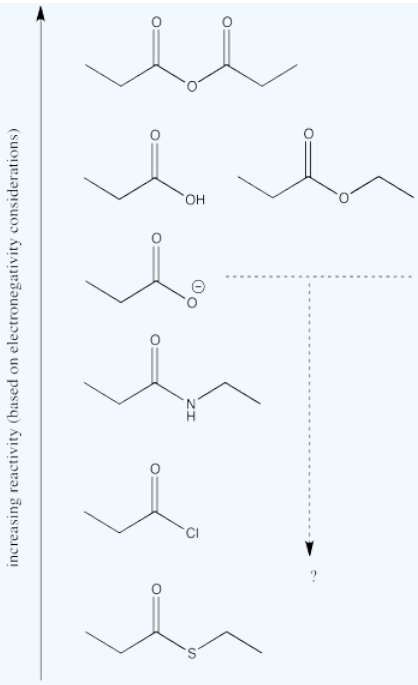
Based on electronegativity of the atom attached to the carbonyl carbon, we might expect a specific trend in carboxyloid reactivity. Explain how this factor would affect electrophilicity at the carbonyl carbon and predict the corresponding trend in reactivity. Compare this trend with the information in Figure 5.7.1 (CX3.1).

Answer

We might expect carboxyloids with the most electronegative elements attached to the carbonyl to be the most reactive and least stable towards substitution (in other words, carboxyloids with the most electronegative heteroatoms would become substituted the most easily).

In that case, we would predict that the carboxyloids with the most electronegative substituent (oxygen) would be the most reactive. There are a number of different kinds and we will think about how they relate to each other shortly.

After the oxygen derivatives we would predict either the nitrogen derivatives or the chloride, depending on what electronegativity scale we happen to use (remember, electronegativity is not an experimentally pure property, but the result of a calculation that can be performed in different ways). The sulfur derivative would be least reactive.



There are still several different oxygen derivatives to compare: carboxylic acids (OH), carboxylates (O-), esters (OR, in which R is an alkyl or carbon chain) and acid anhydrides (OC=O). The easiest to differentiate is the carboxylate, because of its negative charge. It must be less attractive to a nucleophile than the other oxygen derivatives, because it would offer more repulsion to an incoming lone pair.

However, we can't really predict whether it would be any less reactive than the nitrogen, chlorine or sulfur analogues, because who knows whether the charge or the nature of the atom matters more?

As it happens, the charge probably matters more. We learn that simply by looking at the experimental trend and seeing that the carboxylate is the least reactive of all the carboxyloids.

Turning to the other three oxygen derivatives, it would be difficult to differentiate between the effect of a remote hydrogen atom versus an alkyl chain in the ester versus the carboxylic acid, so we'll say those two are about the same. On the other hand, the additional electron-withdrawing carbonyl group in the acid anhydride probably has a profound effect, so we would expect that compound to attract nucleophiles more strongly.

Of course, the series we have produced above is not the "right answer". It does not match the experimentally observed series of carboxyloid reactivities. Nevertheless, it is very useful in terms of building an understanding of carboxyloids. It tells us that electronegativity may play a role here, but that it can't be the only factor.

Some other factor is putting some of the derivatives out of order. In particular, the acid chloride (C=OCl) and the thioester (C=OSR) do not fit.

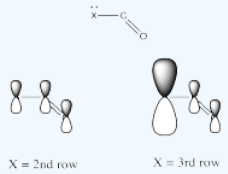
Exercise 5.7.2

Lone pair donation from the atom attached to the carbonyl carbon could also influence carboxyloid reactivity. Explain how this factor would affect electrophilicity at the carbonyl carbon and predict the corresponding trend in reactivity. Compare this trend with the information in Figure 5.7.1.

Answer

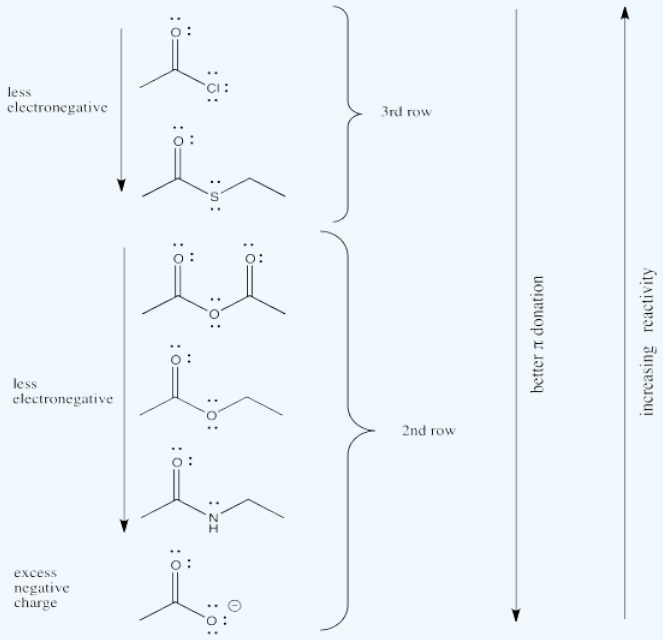
Electronegativity is an abvious factor that could influence an atom's ability to π-donate, but we just looked at that factor in the previous section, so let's look at another atomic property instead. Of course, different atoms have different sizes. In particular, if we look at the atoms involved in carboxyloid substituents, we can divide them into 2nd row atoms and 3rd row atoms.

It's actually well-documented that the degree of overlap between two orbitals influences how well they bond together. Since carbon is in the second row, it is about the same size as, and overlaps pretty well with, other second row atoms. Third row atoms are a little too big, on the other hand.



That factor breaks the carboxyloids into two different groups. Assuming π-donation is a major factor, sulfur and chlorine may be placed above the others in tems of reactivity. They cannot donate as well as oxygen or nitrogen can.

From there, differences among the atoms from the same row may be sorted out based on electronegativity differences.



Exercise 5.7.3

Using the information in Figure 5.7.1, explain why peptides (containing a number of amide bonds, R(C=O)N) are such a common structural feature in biology.

Answer

Amide bonds are among the most stable carboxyloids possible. That stability makes them well-suited to form useful structures that will not decompose easily. Remember, any change that occurs in matter occurs through chemical reactions, including the formation and decomposition of biomaterials. Shutting down a potential chemical reaction means a material will be more durable.

The potential energy curve in Figure 5.7.1 (CX3.1) is a useful index for the interconversion of carboxyloids. In general, it is easy to go downhill on the curve, but more difficult to go uphill. That means that compounds lower down on the ski hill can be made easily from compounds farther up the ski hill.

In general, pi donation from the heteroatom attached to the carbonyl is a primary factor that determines carboxyloid reactivity. The more able the heteroatom is to donate its pi electrons, the less electrophilic is the carbonyl. Nitrogen is very good at donating its lone pair. It is about the same size as the carbon atom it needs to donate to, and it only a little more electronegative than the carbon.

Oxygen (in esters and carboxylic acids) is next in line, since oxygen is more electronegative than nitrogen.

Chlorine and sulfur are a little too large to donate very well to a carbon atom. The size and energy mismatch between these atoms leads to poor pi bonding, and poor pi donation.

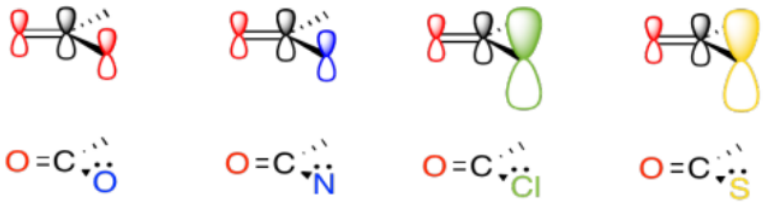


Figure 5.7.5:

Exercise 5.7.4

Place the following compounds in their relative positions on the ski hill.

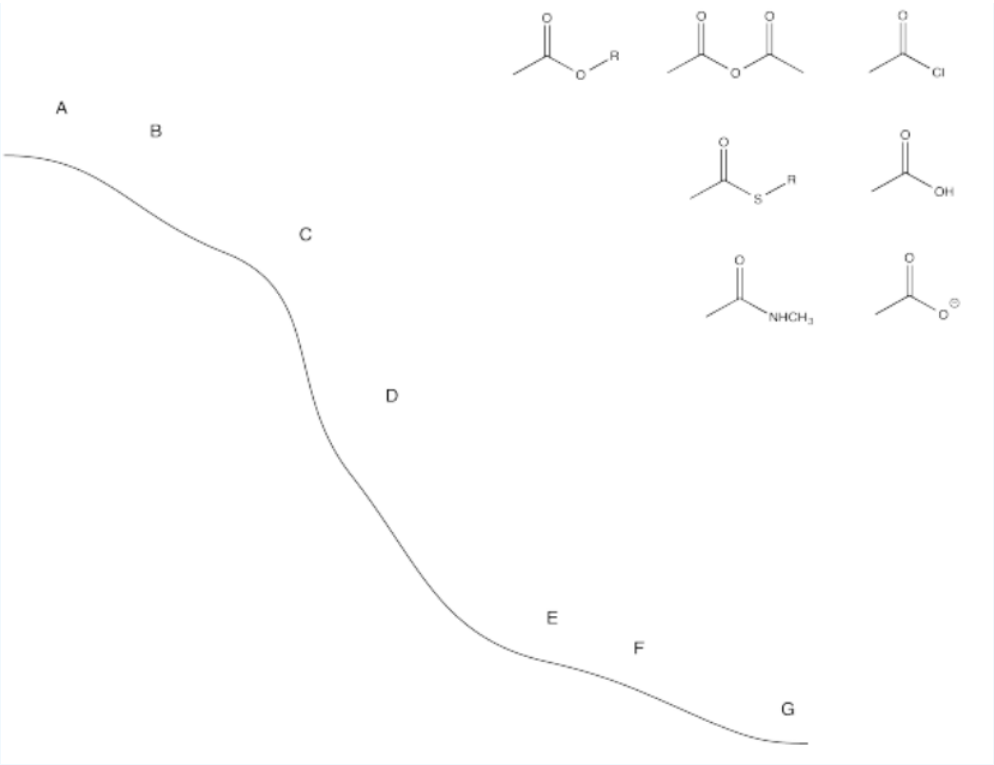
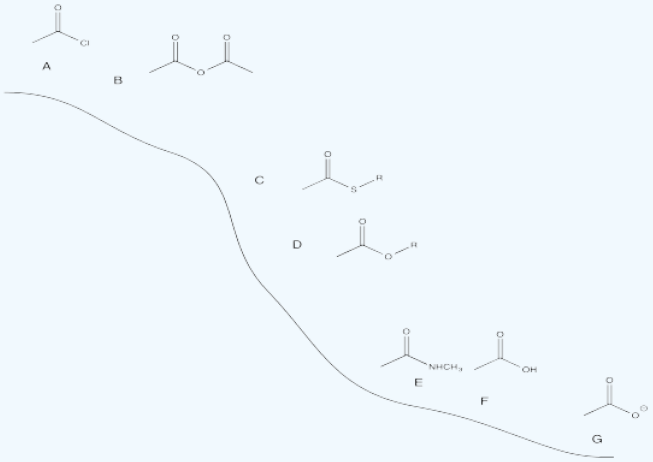


Figure 5.7.6:

Answer



Exercise 5.7.5

Oxalyl chloride (left) and thionyl chloride (right) are even higher on the ski hill than regular acid chlorides. Propose a reason that explains this relative instability as electrophiles.

Figure 5.7.7:

Answer

One possibility is the presence of an additional electronegative substituent. In the oxalyl chloride, the presence of an additional carbonyl next to the electrophilic acid chloride group would make each carbonyl even more electrophilic. In the thionyl chloride, the presence of two chlorines, instead of just one, could make this compound much less stable and more electrophilic.

5.8: Interconversion- Going Downhill

The potential energy curve linking the carboxyloids can be used as a guide to how these compounds can be interconverted. In general, it is possible to take a compound that is higher on the ski hill and convert it to a compound that is lower on the ski hill.

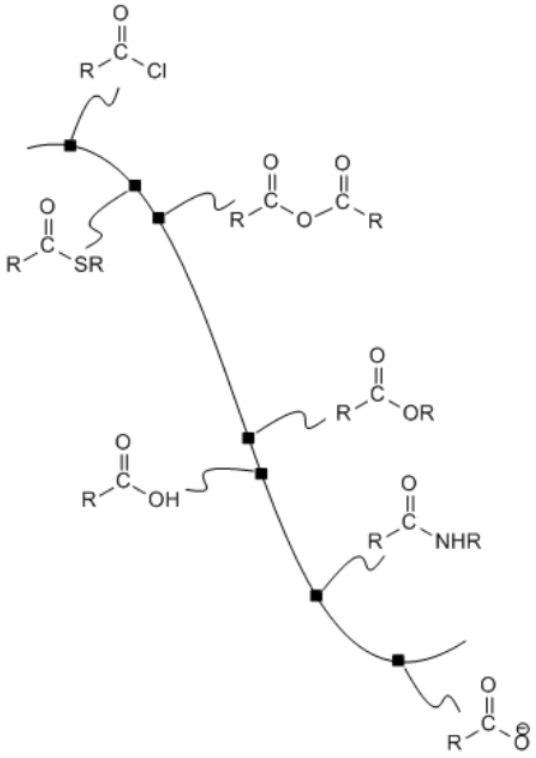
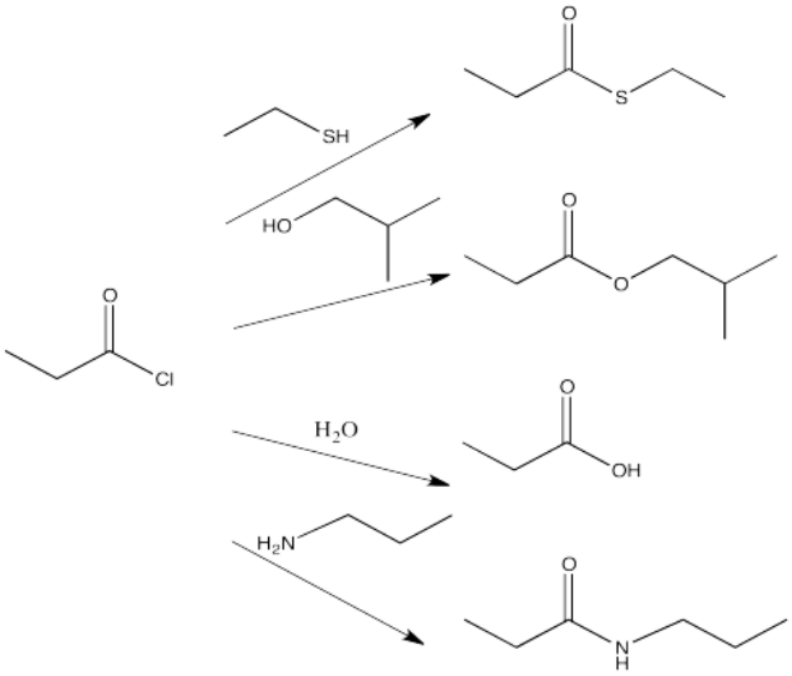


Figure 5.8.1: The potential energy surface linking carboxloids.

For example, acid chlorides are widely used to make other carboxyloids. By choosing the correct nucleophile, an acid chloride could be converted to any of the other derivatives. This is really the whole point of an acid chloride; it has no other function other than to provide an easy way to make other derivatives.



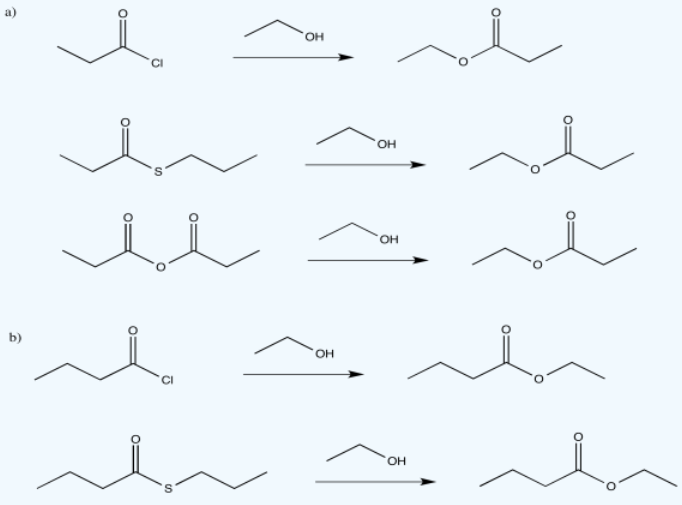
Acid anhydrides, also high on the potential energy curve, are also used in the same way. They could be used to make any of the derivatives lower than they are on the ski hill. In turn, acid anhydrides could conceivably be made from acid chlorides. However, because an acid anhydride plays the same role as an acid chloride -- providing a source with which to make the other derivatives -- we wouldn't normally make an acid anhydride from an acid chloride. We would either make one of the other derivatives directly from the acid chloride, or else make it from an acid anhydride that was obtained in another way.

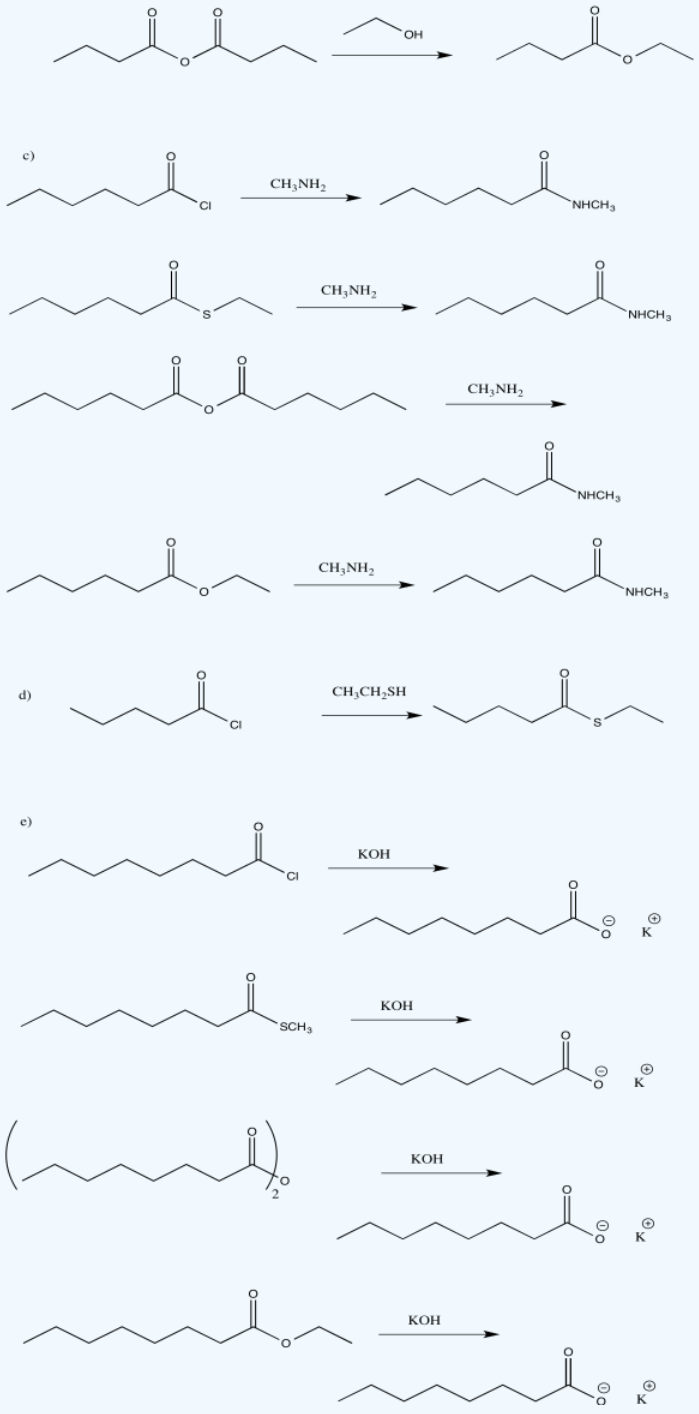
Exercise 5.8.1

Show all of the ways that you could make the following compounds by going down the ski hill. (Show the starting material, the reagent added and a reaction arrow going to the product.) For help with names, see the appendix.

a. ethyl propanoate
b. butanoic acid
c. N-methylhexanamide
d. thioethyl pentanoate
e. potassium octanoate

Answer



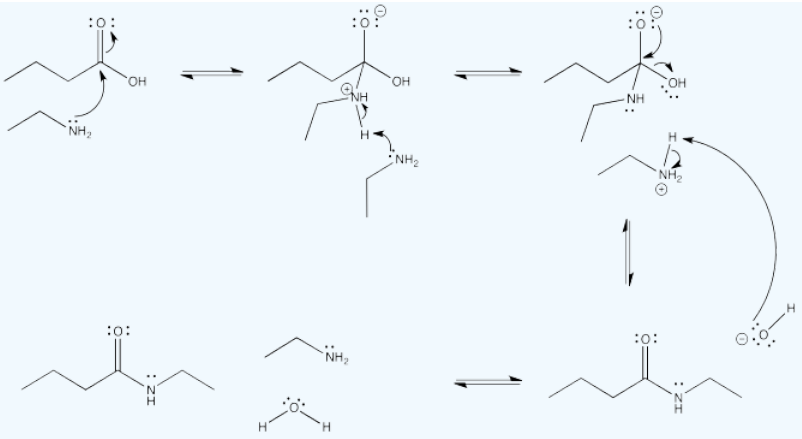


Exercise 5.8.2

Converting a carboxylic acid into an amide is complicated by a side reaction, as a result of which amide formation becomes an uphill process.

a. Show the mechanism for the conversion of butanoic acid into N-ethylbutanamide via the addition of ethylamine.
b. Show the side reaction that would easily occur between these two reactants.
c. Explain why amide formation becomes an uphill process as a result of this reaction.

Answer



Sometimes, two carboxyloids are close enough on the ski hill that it may be possible to convert in either direction between them. In other words, there is an equilibrium between these two compounds, and the equilibrium constant is close enough to unity (K = 1) that the equilibrium can be pushed in either direction.

For selected cases, we can choose which direction the equilibrium will go by changing the reaction conditions. To do so, we can use an important concept of equilibrium: le Chatelier's principle (luh sha-TELL-yay). According to le Chatelier, if conditions in the reaction cause the reaction to move away from equilibrium, the reaction will shift direction until it is back at equilibrium again. In other words, if the actual ratio of reactants to products strays from what it ought to be, the correct reaction will occur so that the ratio returns to normal.

le Chatelier's principle should be partly intuitive. If a reaction is occurring in both reactions, there are really two reactions, one going in each direction. The ability of these reactions to occur depends partly on the amount of reactants available for the forward reaction or the reverse reaction. If extra starting materials are added (on the left side of the reaction), there is too much reactant as defined by the equilibrium constant. The denominator gets bigger and the ratio of products to reactants goes down. However, because there is extra starting material for the forward reaction, more product is quickly made, until the ratio returns to normal.

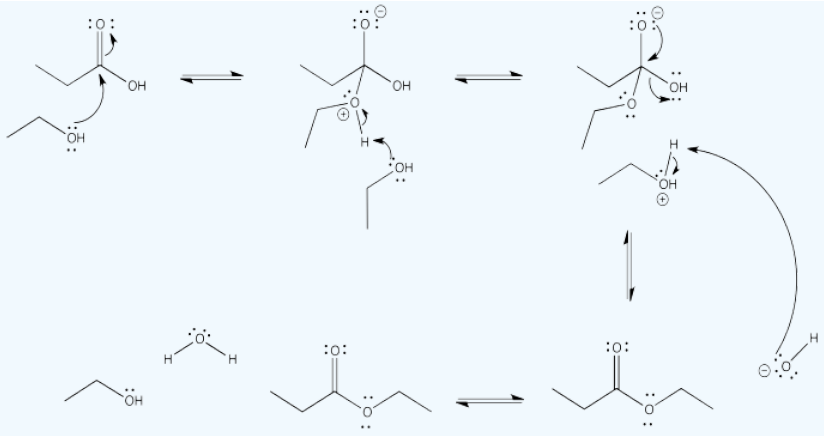
The opposite situation applies if too much product is made. *From the point of view of the reverse reaction*, those products of the forward reaction are really the reactants needed to go in the opposite direction. The reverse reaction has more material to work with, and this material can quickly be converted into the stuff on the left hand side of the reaction.

Exercise 5.8.3

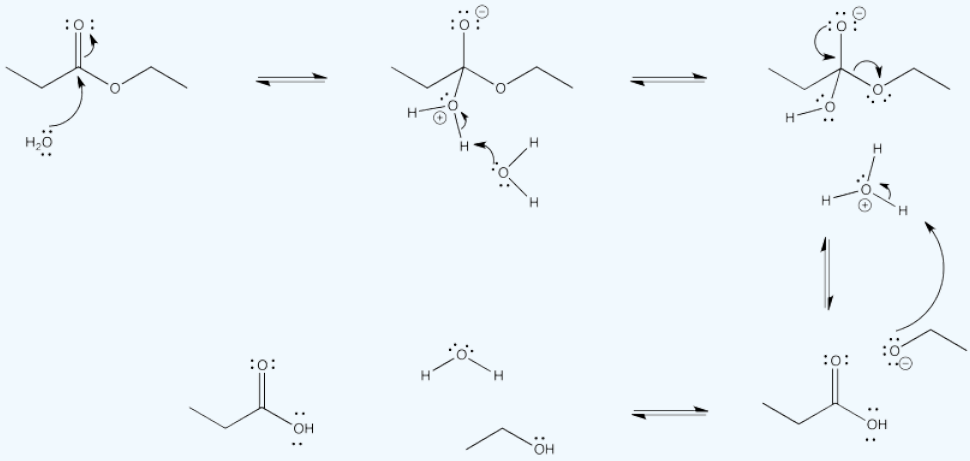
Draw the mechanism for the conversion of:

a. hexyl propanoate to propanoic acid.
b. propanoic acid to hexyl propanoate.

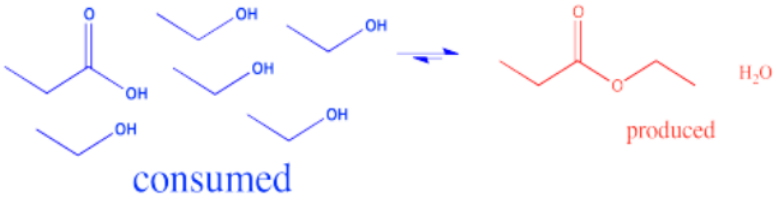
Answer a



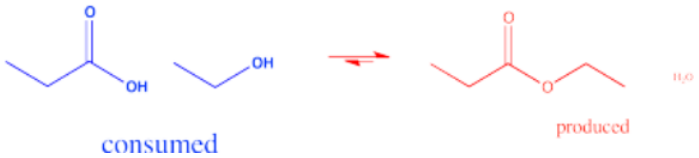
Answer b



In the interconversion of carboxyloids, equilibrium can be influenced in different ways. The conversion between esters and carboxylic acids can be influenced by the solvent used for the reaction. For example, an ester might be converted to a carboxylic acid under aqueous conditions, but a carboxylic acid might be converted to an ester using the appropriate alcohol as the solvent. In other words, because water and alcohol can be viewed as reactants in these cases, adding more can shift the reaction to one side. Solvent is usually present in concentrations many tens or hundreds or thousands of times higher than the reactants and products. Changing the solvent thus has a big impact on the direction of equilibrium.



Another strategy used to influence the equilibrium involves removal of product. For example, if water is a product of the reaction, a drying agent can be added to absorb the water. Drying agents include compounds such as $MgSO_4$ or zeolites (mixed aluminosilicates containing Al, Si, O and other metal ions such as Mg^{2+}, Ca^{2+} or Ti^{4+}).

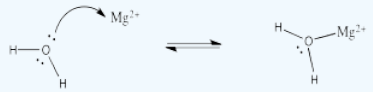


If a carboxylic acid is a product of a reaction, its concentration can be lowered by converting it to a carboxylate salt; this would happen easily in the presence of base. In either case, the disappearance of a product of the reaction (or a side product) would draw the reaction to the right in order to replace those products an re-establish the correct equilibrium ratio.

Exercise 5.8.4

Show, with curved arrows, how a magnesium ion could remove water from solution.

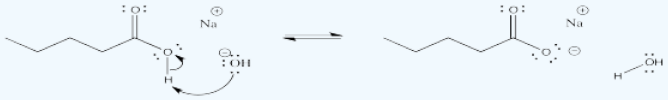
Answer



Exercise 5.8.5

Show, with curved arrows, how sodium hydroxide would remove butanoic acid from solution.

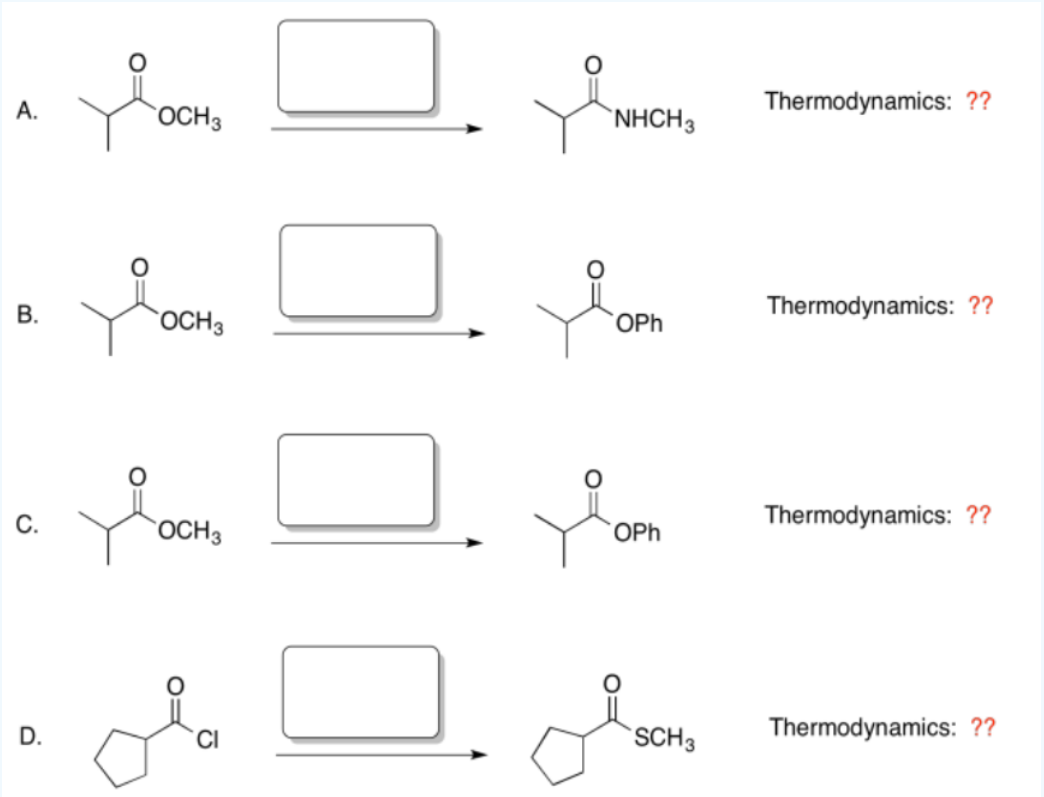
Answer



Exercise 5.8.6

For each of the following reactions:

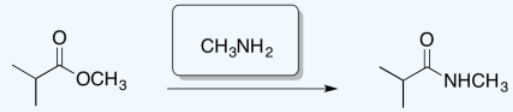
a. Predict the nucleophile that would be need to make this product.
b. Based on the location on the hill, would this reaction be thermodynamically favored?

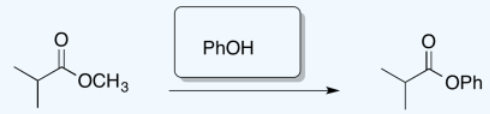


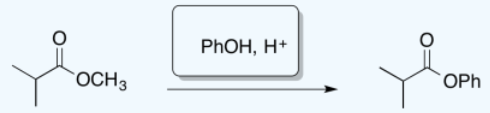
E.  Thermodynamics: ??

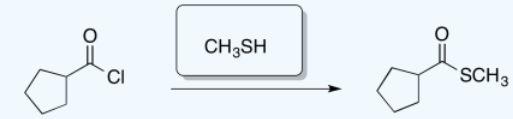
F.  Thermodynamics: ??

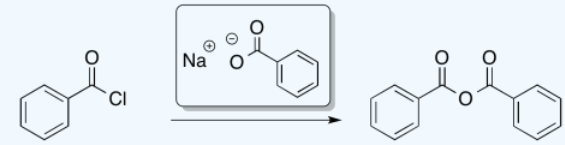
Answer

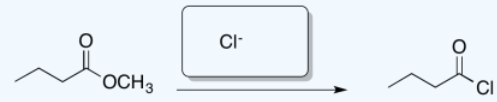
A.  Thermodynamics: Exothermic

B.  Thermodynamics: Thermoneutral

C.  Thermodynamics: Slightly favored

D.  Thermodynamics: Exothermic

E.  Thermodynamics: Exothermic

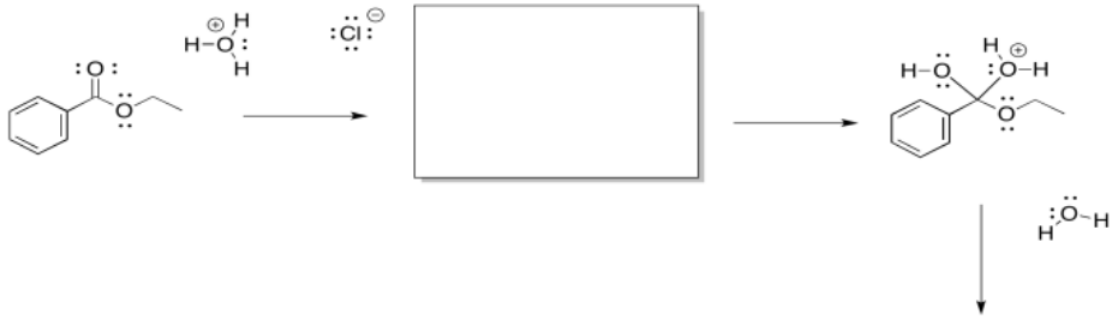
F.  Thermodynamics: Endothermic

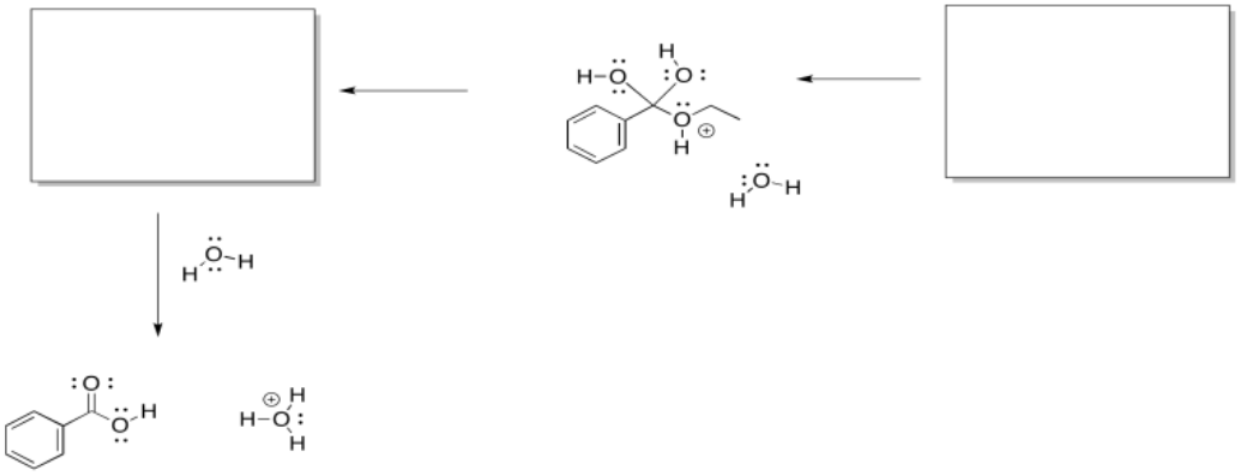
Exercise 5.8.7

Fill in the missing intermediates and add curved arrows to show electron movement.

a)

b)





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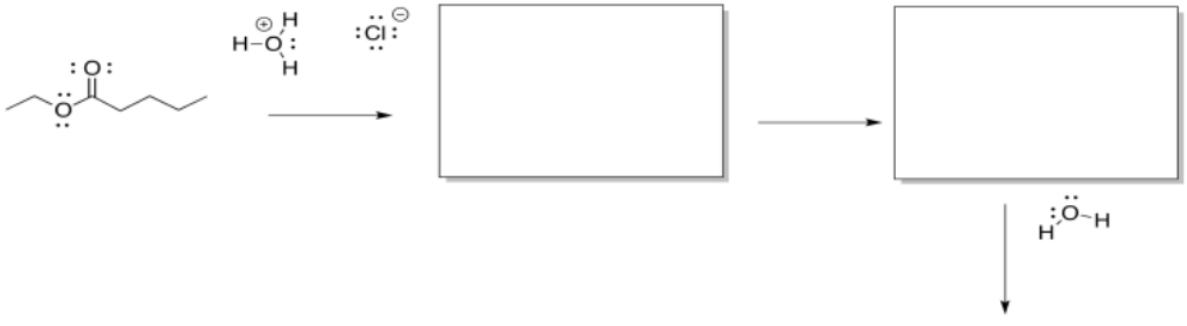
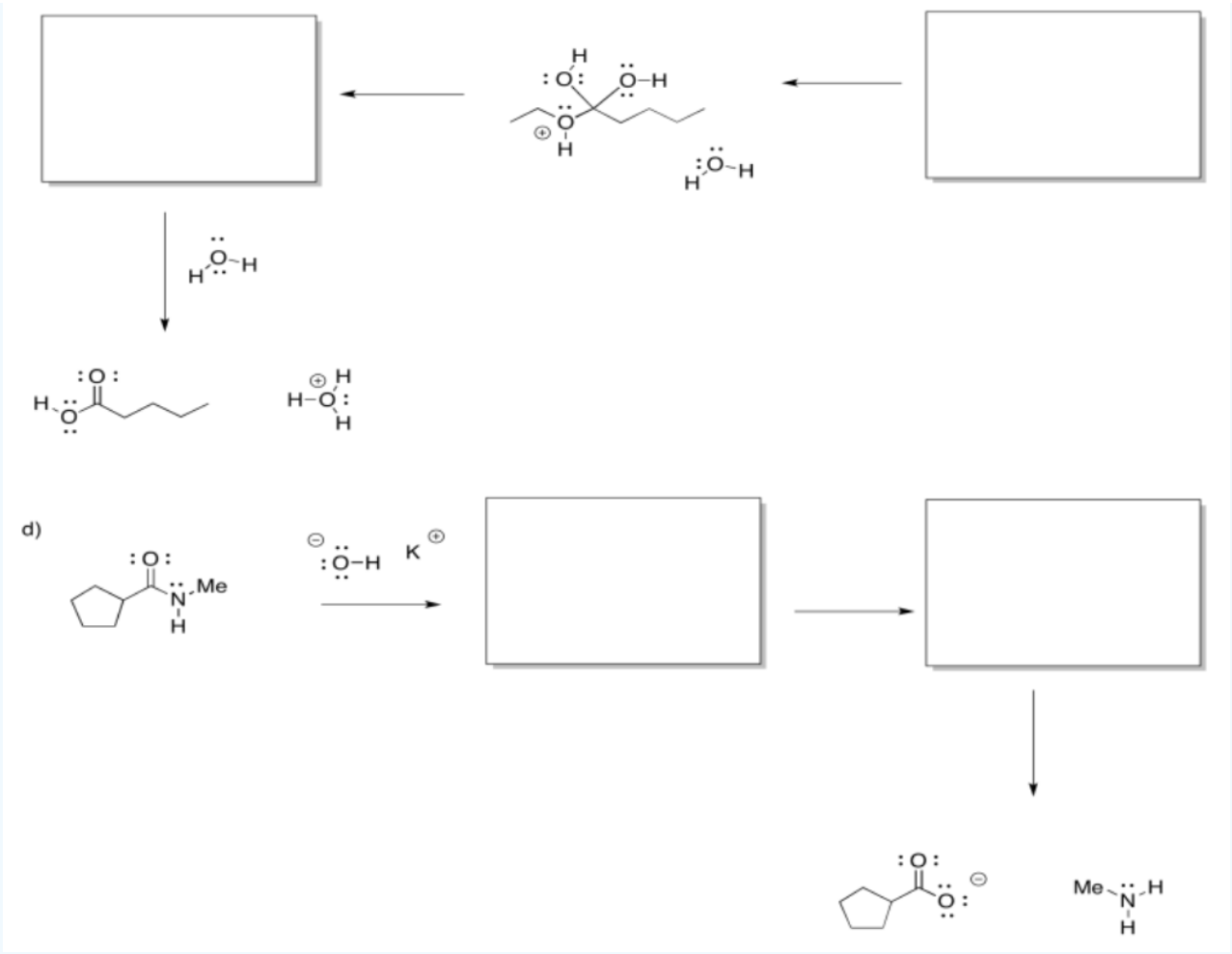
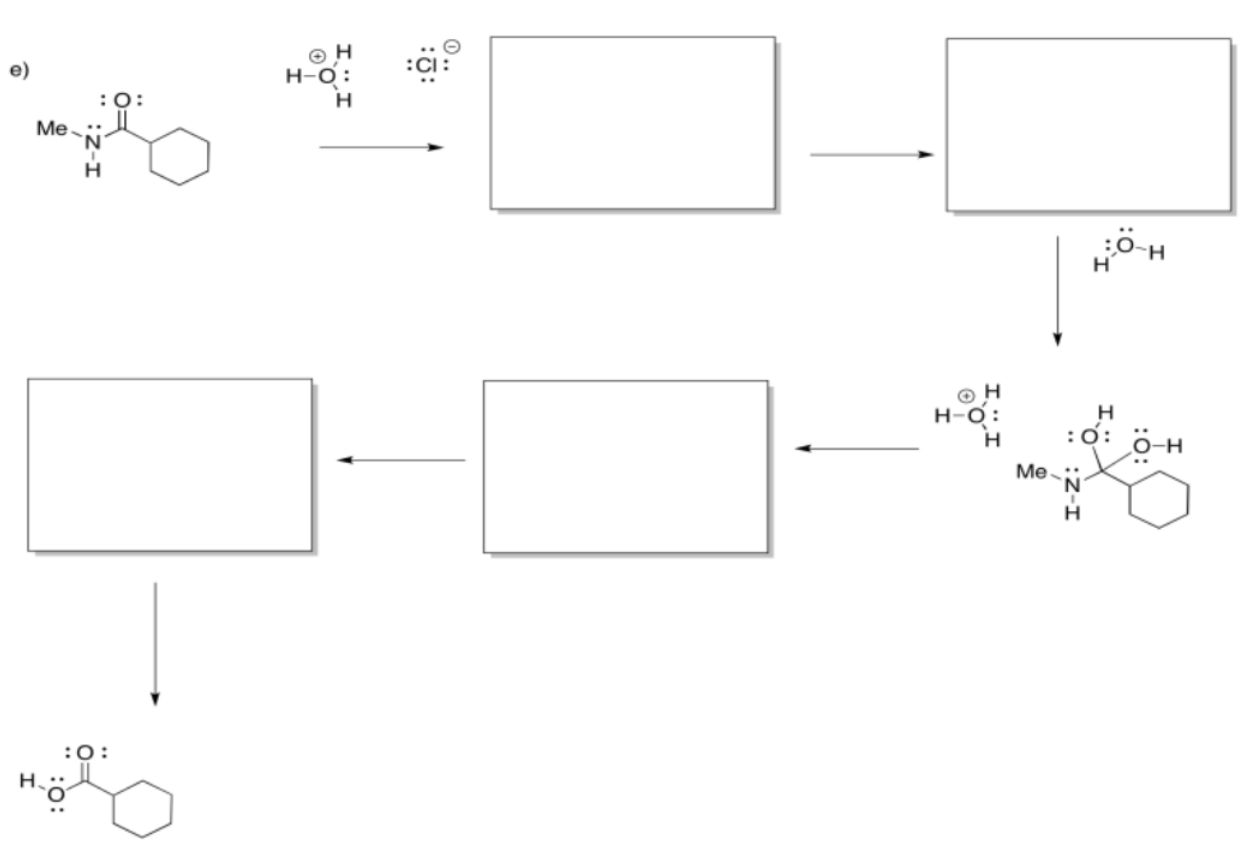
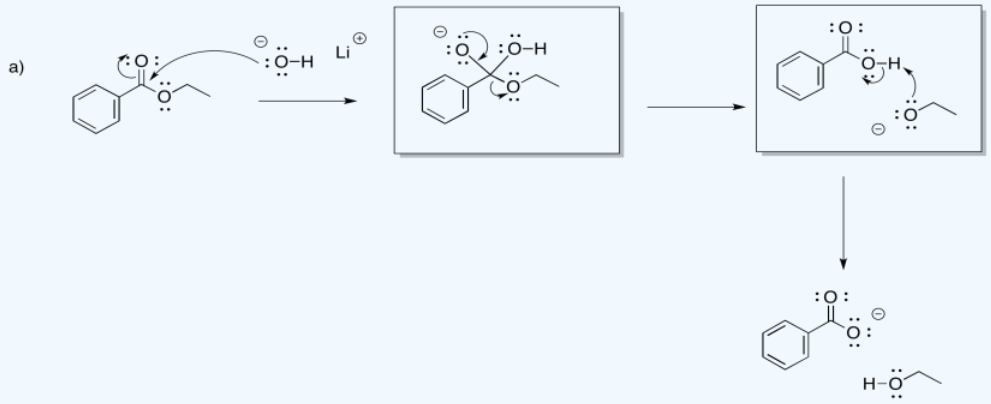
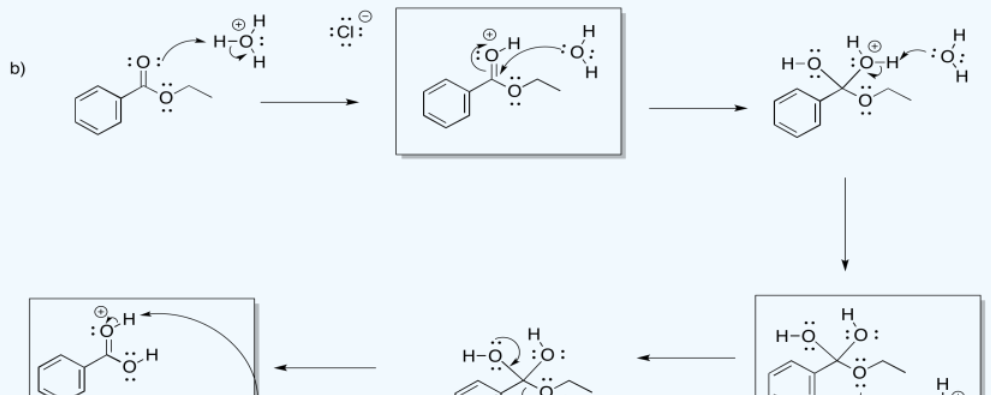


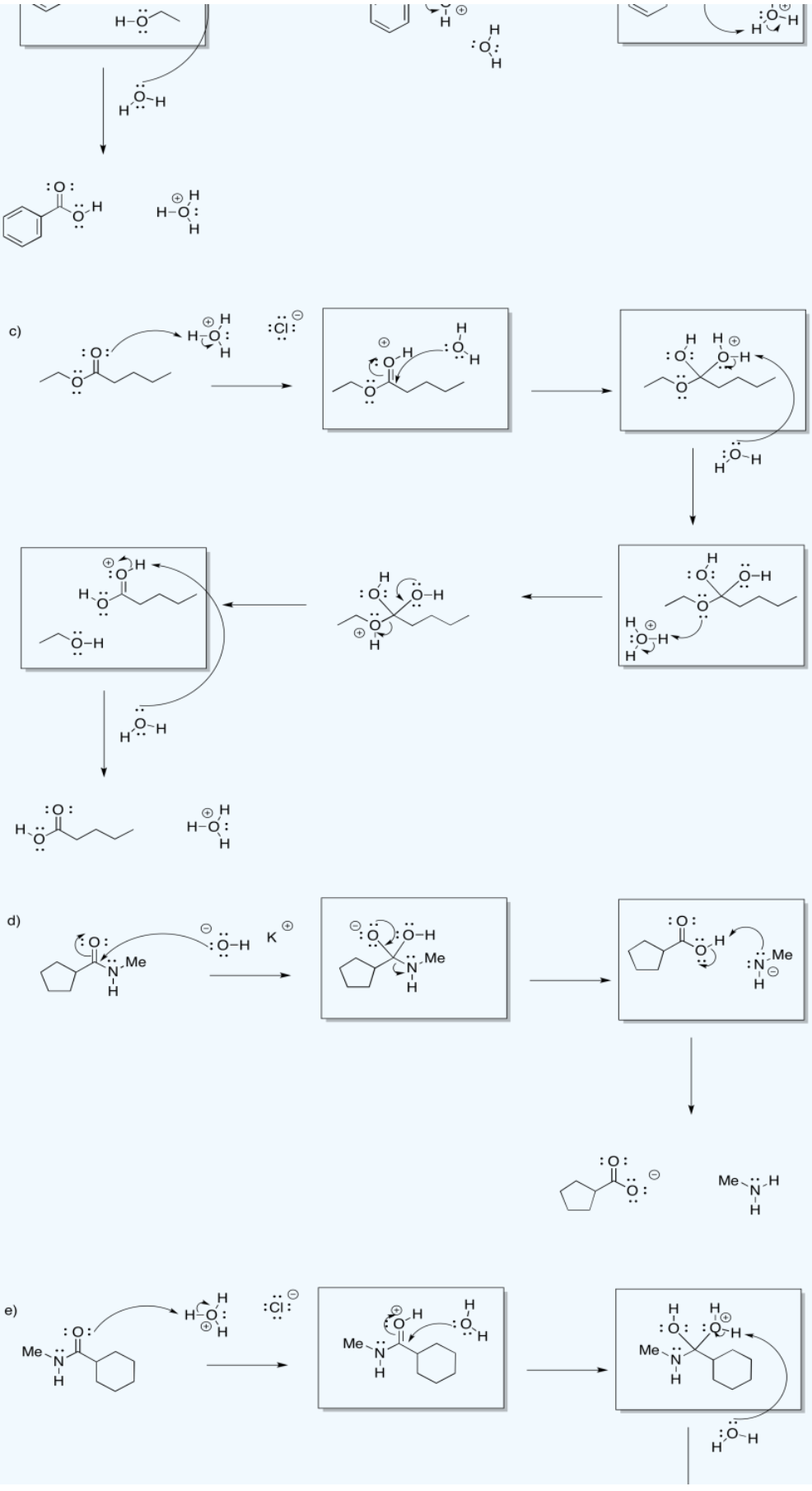


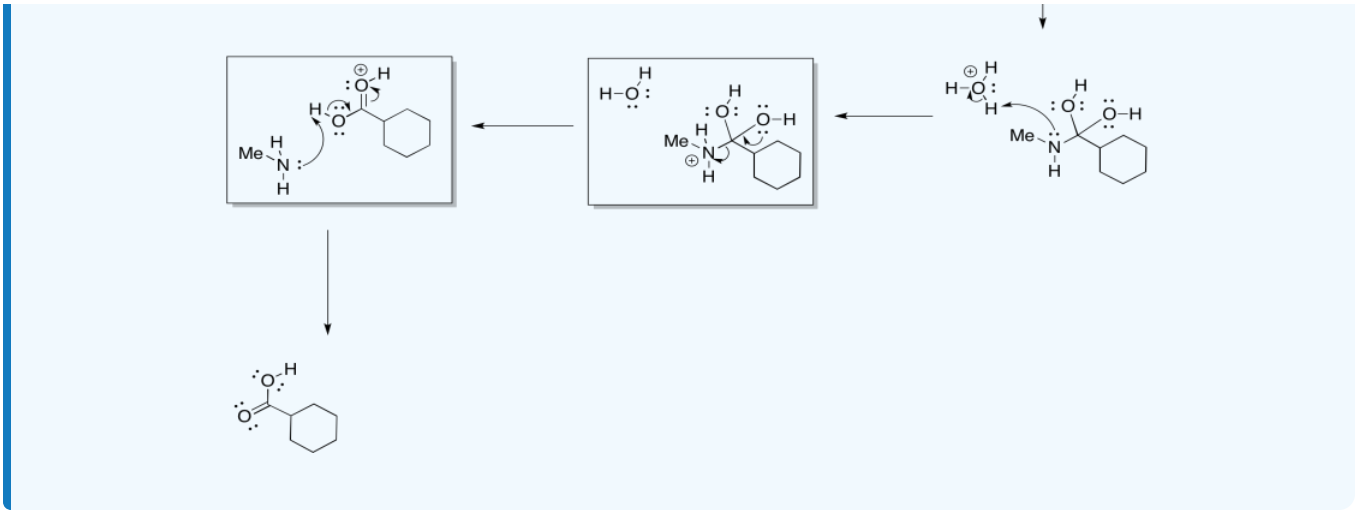


Answer









5.9: Getting Towed Uphill

The uphill carboxyloids are useful materials in terms of being able to make other compounds. For example, a thioester such as acetyl coenzyme A may be able to make a variety of acyl esters. In the laboratory, acid chlorides are very common starting materials to make other carboxyloids. However, if they are so far uphill, how are they formed in the first place?

The two most common methods of making acid chlorides are treatment with thionyl chloride or with oxalyl chloride.

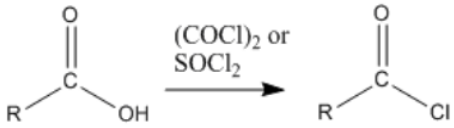


Figure 5.9.1: Possible syntheses of an acid chloride.

The key part of making the uphill acid chloride out of the downhill carboxylic acid is the reagent used. Structurally, the reagents can be compared to acid chlorides themselves. They can be though of as being a little bit like uphill carboxyloids themselves. Thus, as one compound gives its chloride and gets oxygenated on its way downhill, it provides the energy needed to drive the carboxylic acid uphill.

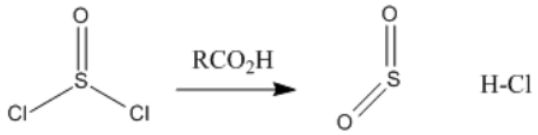


Figure 5.9.2: Conversion of thionyl chloride to sulfur dioxide and hydrochloric acid.

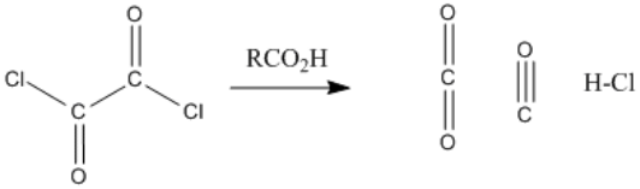
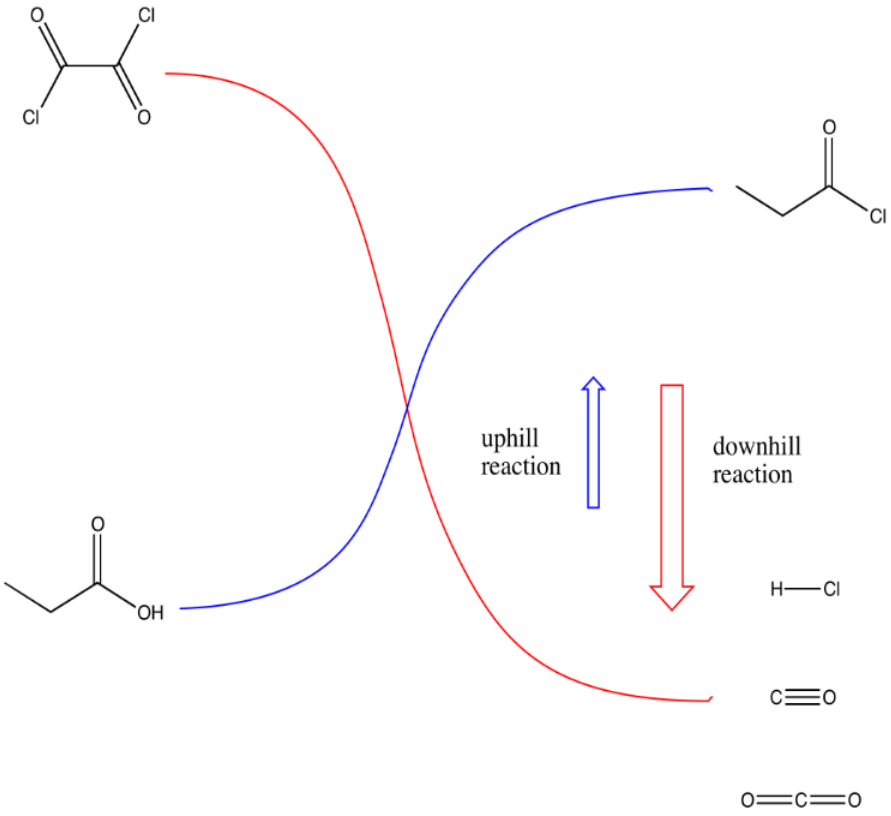


Figure 5.9.3: Conversion of oxalyl chloride to carbon dioxide, carbon monoxide and hydrochloric acid.



Exercise 5.9.1

Reaction of a carboxylic acid with oxalyl chloride starts with a carboxyloid substitution using the oxalyl chloride as electrophile and carboxylic acid as nucleophile. The chloride ion that is liberated then acts as a nucleophile in a cascade reaction that releases CO_2 and CO as an acid chloride forms. Draw the mechanism.

Exercise 5.9.2

Reaction of a carboxylic acid with thionyl chloride is very similar to reaction with oxalyl chloride, described above. Draw the mechanism of the reaction.

Exercise 5.9.3

Provide additional factors (such as energetics, equilibrium concepts) that explain why oxalyl chloride and thionyl chloride can drive the conversion of a carboxylic acid to an acid chloride.

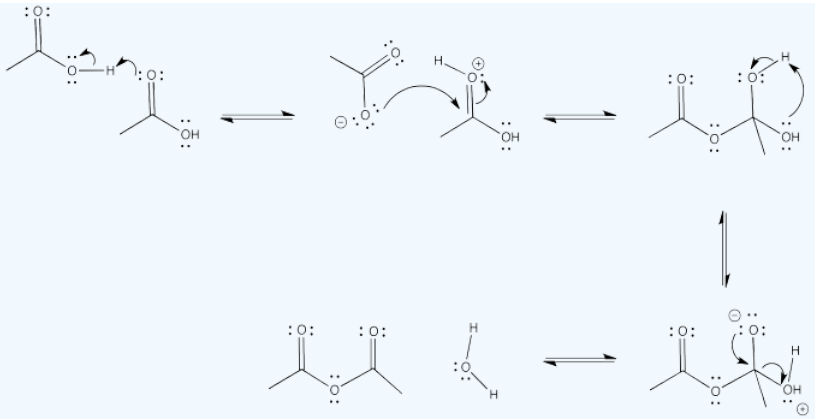
Acid anhydrides are usually made from the corresponding carboxylic acids. One molecule of carboxylic acid acts as a nucleophile and a second acts as an electrophile. Because the same kind of molecule acts as nucleophile and electrophile, acid anhydrides are typically symmetric: they havae a (C=O)O(C=O) unit in the middle, with the same alkyl groups on either side of it.

To aid formation of acid anhydrides, carboxylic acids are often heated strongly (well above 100 ^oC). Otherwise, they are sometimes heated in the presence of a strong drying agent, such as phosphorus pentoxide (empirically, P_2O_5). In the presence of water, phosphorus pentoxide is converted to phosphoric acid, H_3PO_4.

Exercise 5.9.4

Draw a mechanism for the conversion of ethanoic acid to ethanoic anhydride.

Answer



Exercise 5.9.5

Show the *reverse reaction* to the conversion of ethanoic acid to ethanoic anhydride (the same reaction, in the other direction). Which of the two directions do you think is favorable, based on the ski hill?

Exercise 5.9.6

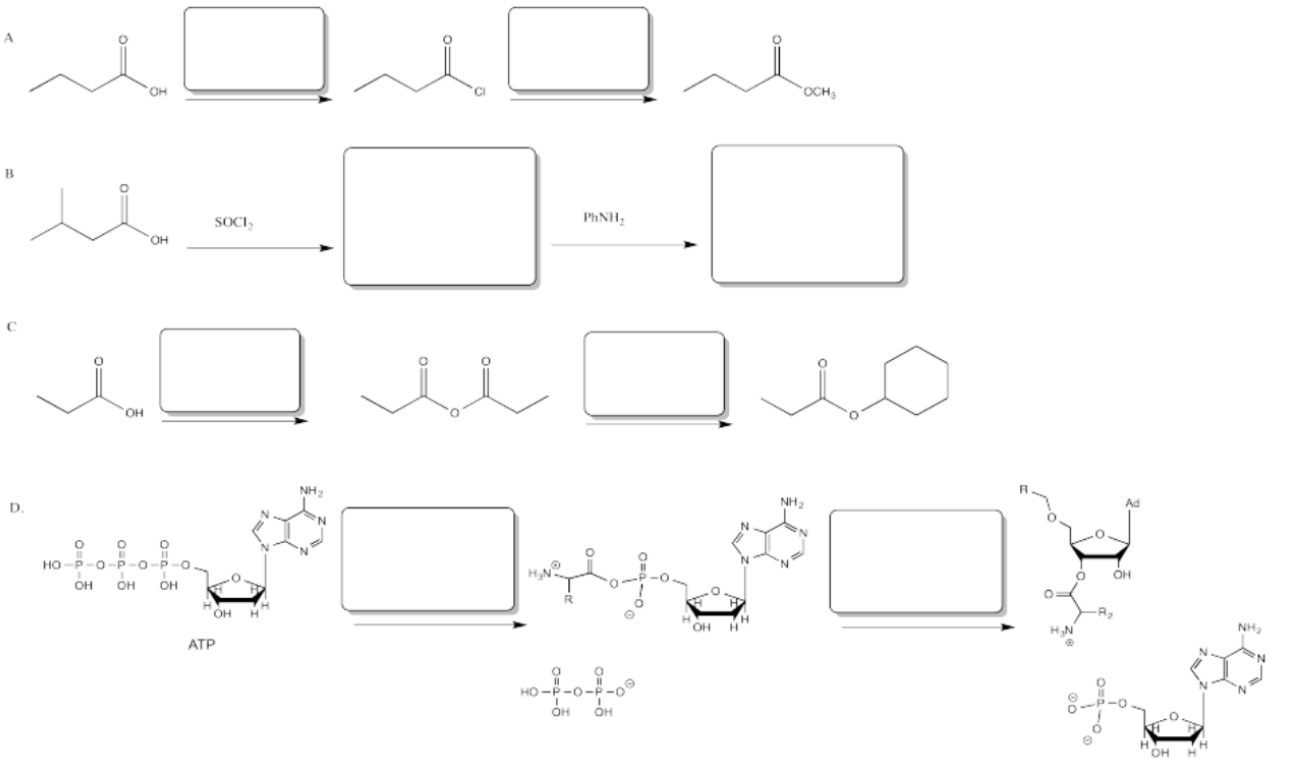
Draw a mechanism for the conversion of phosphorus pentoxide to phosphoric acid.

Exercise 5.9.7

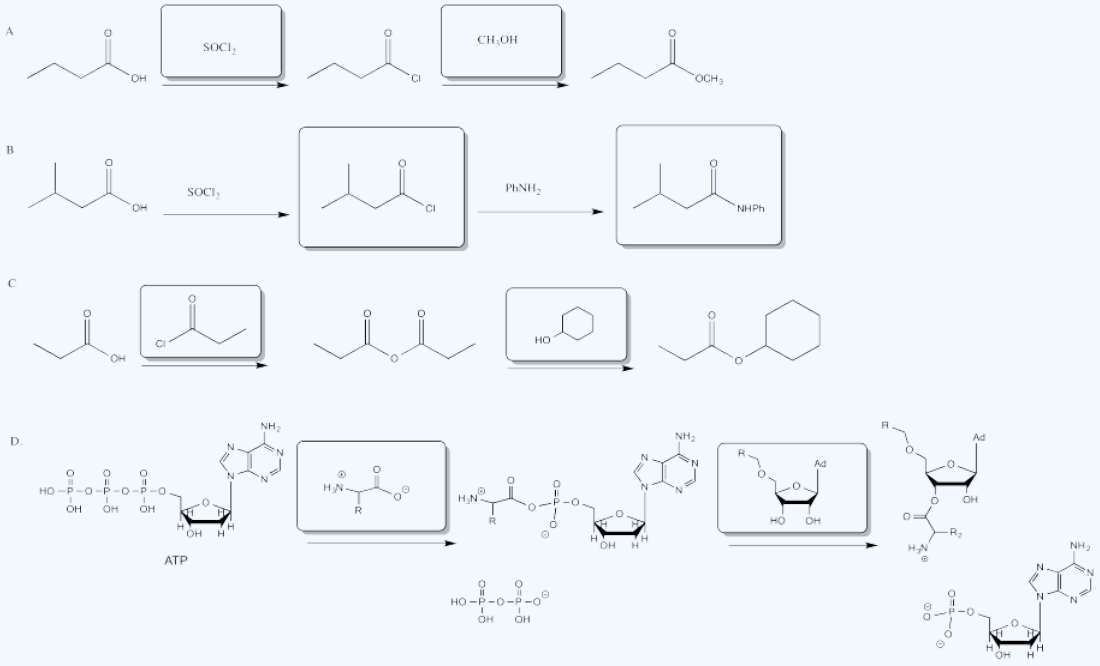
Explain why the conditions outlined above lead to acid anhydride formation.

Exercise 5.9.8

Fill in the blanks in the following problem.



Answer



5.10: Semi-Anionic Nucleophiles

Carboxyloids can be interconverted through addition of typical heteroatomic nucleophiles: amines, alcohols, thiols and water. In addition, other nucleophiles can displace the "leaving group" on a carboxyloid, provided the nucleophile is reactive enough.

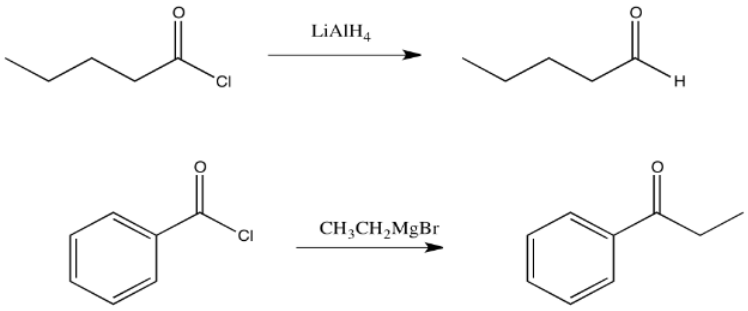
Exercise 5.10.1

Could a halide, such as bromide or chloride, replace a carboxyloid leaving group easily? Explain.

Answer

Because acid chlorides are at the top of the carboxyloid reactivity diagram (the ski hill), and other halides are likely to be similar in reactivity to the chloride, this reaction would be uphill from the other carboxyloids.

Carbon and hydrogen anions (or "semianions") are very good nucleophiles. Earlier, we saw how they can react with simple carbonyls. Although the lone pair on a carbon or a hydrogen is often masked in a covalent bond with a moderately electropositive metal such as aluminum or magnesium, that bonding pair of electrons is still nucleophilic enough to donate to a good electrophile. These nucleophiles can often react with carboxylic acid derivatives.



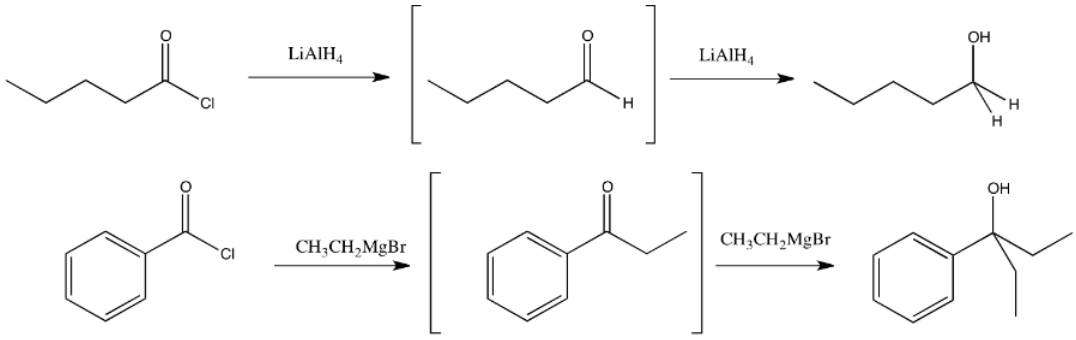
Exercise 5.10.2

Draw a mechanism for the replacement of the chloride in propanoyl chloride with a hydride from lithium aluminum hydride.

Exercise 5.10.3

Draw a mechanism for the replacement of the chloride in propanoyl chloride with a methyl from methylmagnesium chloride.

Addition of a Grignard reagent (alkylmagnesium halide) to a carboxyloid results in the formation of a ketone. Addition of a complex hydride reagent (such as lithium aluminum hydride) to a carboxyloid results in the formation of an aldehyde. We have already seen that these reagents can add to aldehydes and ketones to afford alcohols.



So, what happens if a Grignard reagent is added to an acid chloride or an acid anhydride? The carboxyloid would be converted to a ketone. If there are still more Grignard molecules around, they would probably convert the ketone into an alkoxide ion (and ultimately an alcohol via protonation). The thing is, it is very likely that there will be more Grignard molecules around. A reaction

tends to involve millions of reactant molecules, so by the time the first thousand or so molecules of carboxyloid have been converted to ketone, hundreds of those ketone molecules have already been converted to alkoxide.

In most cases, alkyl reagents and hydride reagents will add twice to carboxyloids. They will convert the carboxyloid into an aldehyde or ketone. Because aldehydes and ketones also react with hydride and alkyl nucleophiles, they will react a second time.

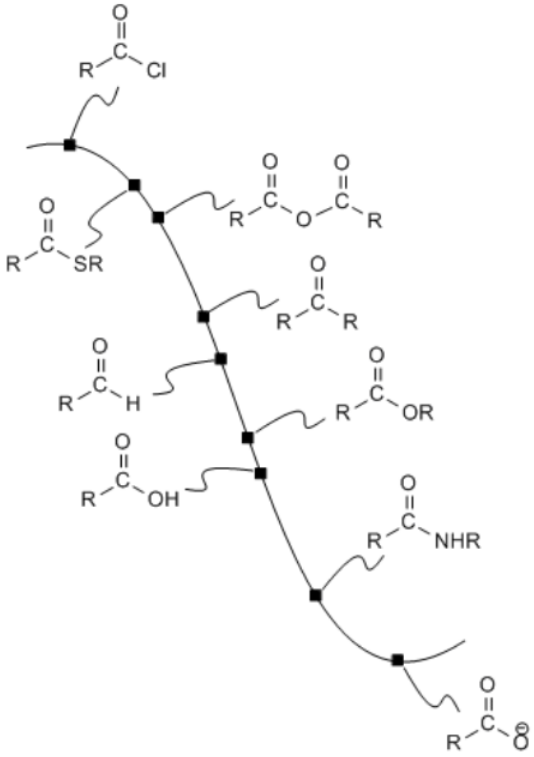
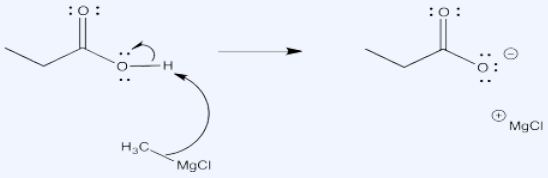


Figure 5.10.1: A modified potential energy surface that includes aldehydes and ketones.

Exercise 5.10.4

Grignard reagents will not effect leaving group replacement in carboxylic acids. Show why that particular reaction does not occur, with the help of a mechanism.

Answer



Exercise 5.10.5

Grignard reagents generally do not react with either amides or carboxylate ions. Explain why.

Answer

Amides and carboxylates are the least reactive carboxyloids, so it might not be too surprising that they do not react with these nucleophiles.

When a series of compounds varies from more reactive to less reactive in a particular reaction type, the possibility for selectivity arises. Some reagents may react with a few carboxyloids, but not with others. For example, organocuprates such as $(CH_3)_2CuLi$, which do not generally react well with aldehydes and ketones, are very selective in terms of which carboxyloids they will react with.

Exercise 5.10.6

Which carboxyloids do you think will react with $(CH_3)_2CuLi$? Show the reaction in each case (the reactant, reagent, and a reaction arrow going to the product). Explain your reasoning.

Answer

Acid chlorides typically react with these cuprate reagents.

Exercise 5.10.7

Complex hydride reagents can be very selective towards carboxyloids. For example, sodium borohydride is not powerful enough to react with esters.

a. Which of the carboxyloids can sodium borohydride react with? Explain.
b. What other carboxyloids can sodium borohydride NOT react with? Explain.

Answer

Borohydrides could presumably react with acid chlorides, anhydrides and thioesters, which are the most reactive carboxyloids. They probably can't react with amids or carboxylate ions, which are even farther downhill than esters.

Exercise 5.10.8

Lithium aluminum hydride can induce carboxylic substitution with carboxylate salts such as sodium octanoate.

a. What would be the ultimate product of this reaction? Explain.
b. What other carboxyloids can lithium aluminum hydride react with? Explain.

Exercise 5.10.9

a) Which is more reactive: lithium aluminum hydride or sodium borohydride?

a. Which is more selective: lithium aluminum hydride or sodium borohydride?
b. How can you explain the difference in reactivity between lithium aluminum hydride and sodium borohydride?

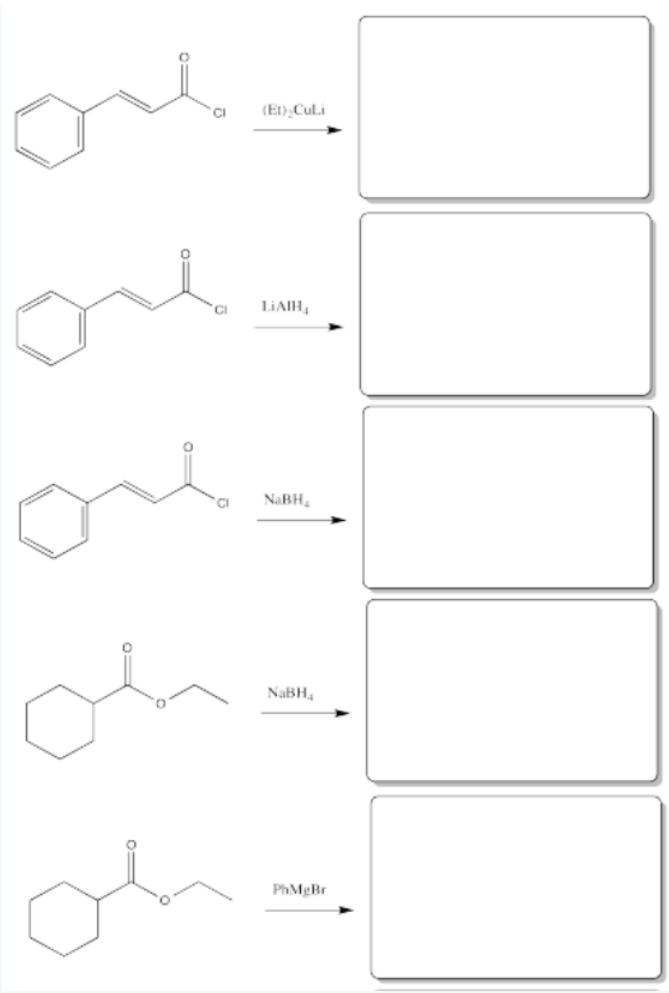
Exercise 5.10.10

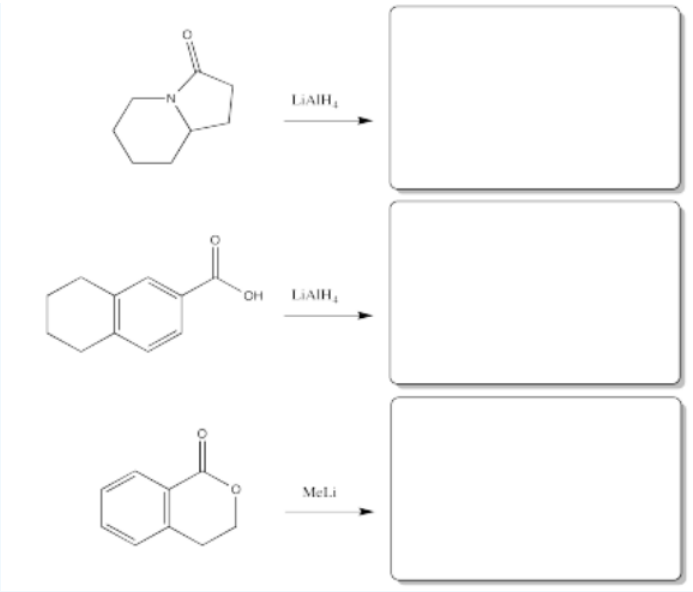
The reaction of lithium aluminum hydride with amides is unusual in that the final product of the reaction is generally an amine.

a. Why does this reaction seem to be different from other carboxyloid reactions?
b. Draw a mechanism for this reaction. (Hint: at some point, an oxygen atom donates a pair of electrons to aluminum.)
c. Propose a reason why this hydride reaction follows a different path than other reactions of hydrides with carboxyloids.

Exercise 5.10.11

Fill in the products of the following reactions.





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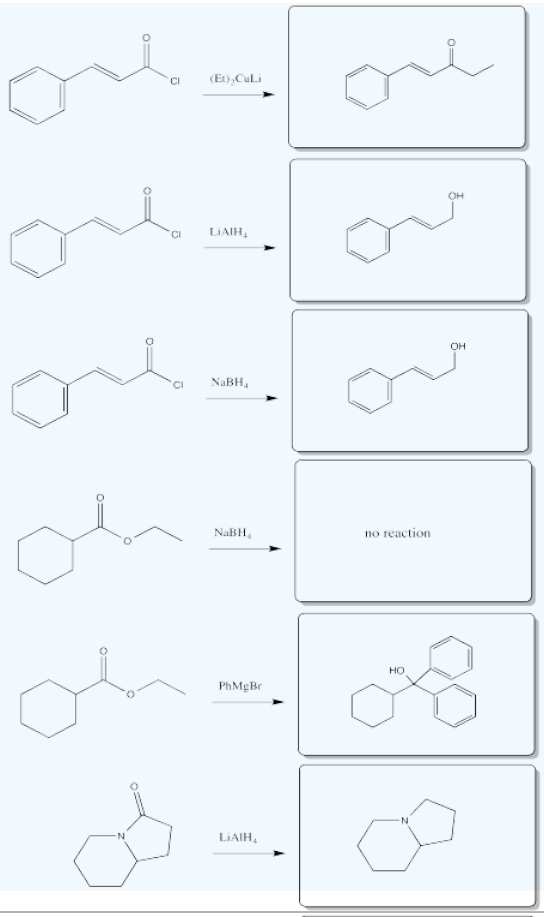
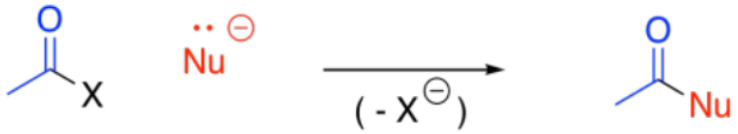


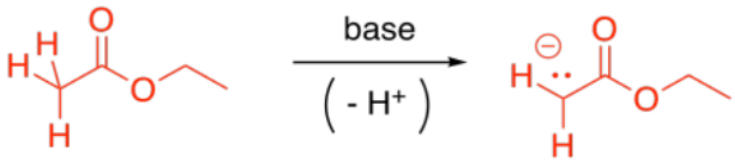
5.11: Enolates - Claisen Condensation and Decarboxylation

Alkylmagnesium reagents, alkylcuprates and complex hydrides can all react with carboxyloids. When they do, a carbon or hydrogen nucleophile bonds to the carbonyl carbon, usually replacing the leaving group at that position.

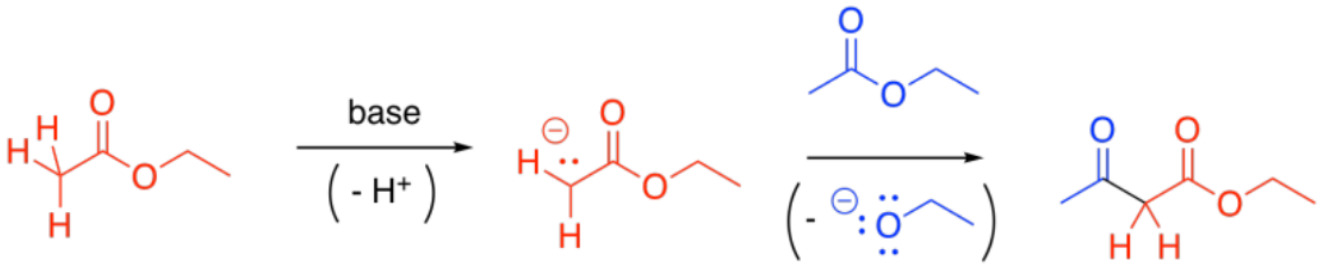


Another common carbon nucleophile is an enolate ion. Enolate ions can also react with carboxyloids, although not typically with amides.

Probably the most common enolate reaction involving carboxyloids is the reaction of esters. If a strong base is added to solution of ester, some of the esters will become deprotonated, forming enolate anions. These ions will be nucleophiles.

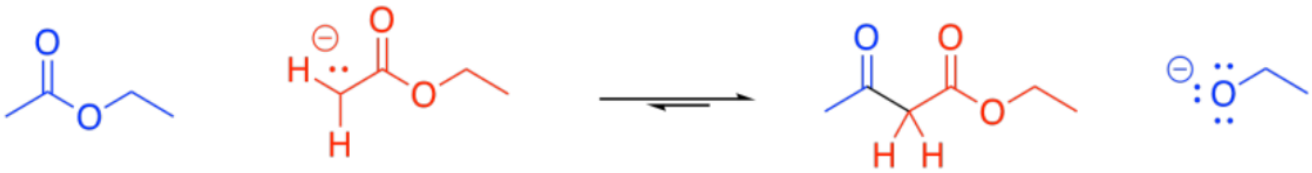


Some esters will remain protonated. These esters will be electrophiles. Donation of the enolate to the ester, with subsequent loss of the leaving group, leads to a beta-ketoester.

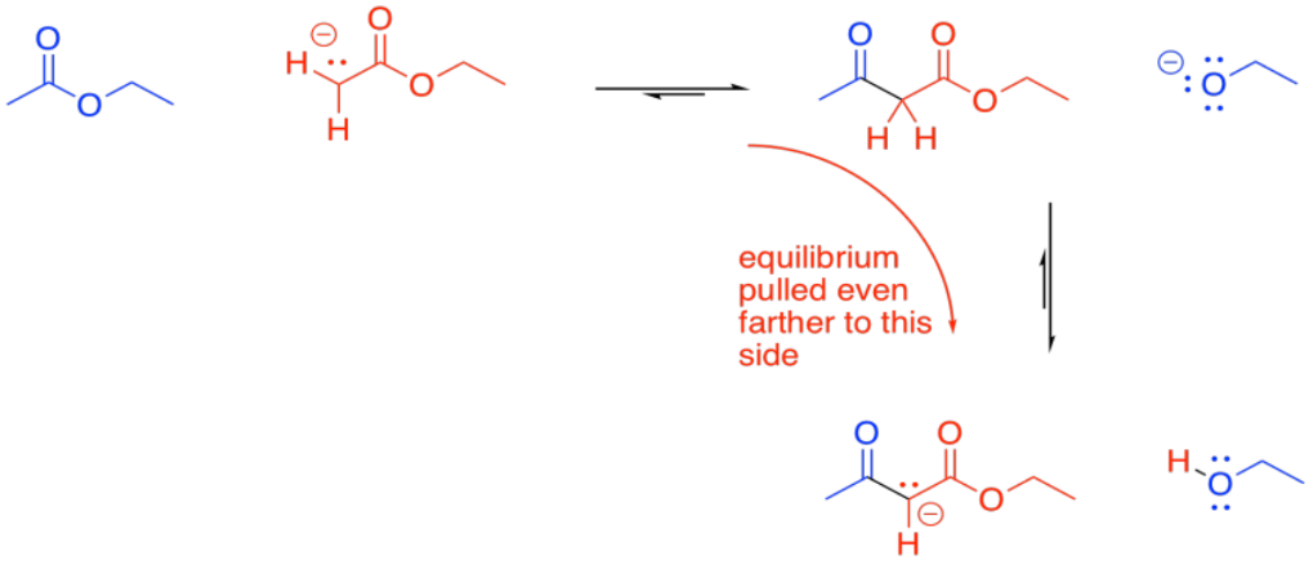


You are familiar with the term "alpha-position". That's the position next to a carbonyl. The "beta-position" is the next one after the alpha position. In a beta-ketoester, there is a ketone in the beta position of the ester. The formation of a beta-ketoester from two esters is called a "Claisen condensation".

In principle, this reaction could conceivably go backwards. The enolate ion could potentially be displaced by an alkoxide to get back to an ester and an enolate ion. That's because the enolate ion is a relatively stable ion, and a moderately good leaving group. However, that generally doesn't happen.



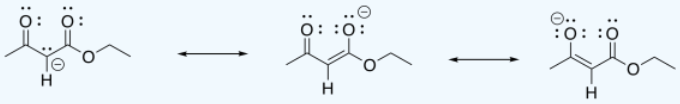
Under basic conditions, the beta-ketoester is usually deprotonated, forming a particularly stable ion. This ion formation acts as a "thermodynamic sink" for the reaction, pulling it forward until all of the ester has been consumed.



Exercise 5.11.1

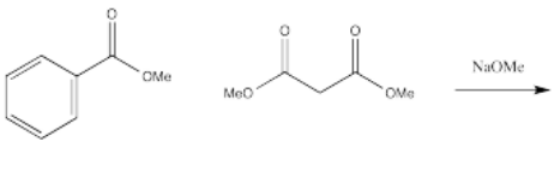
Show why the ion that results from deprotonation of the beta-ketoester is particularly stable.

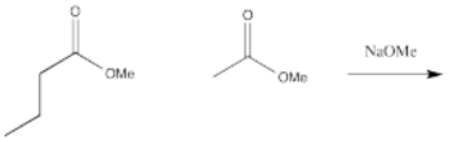
Answer

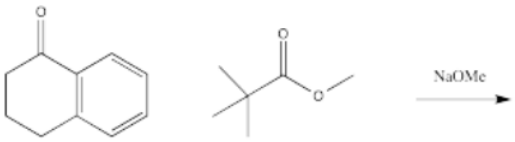


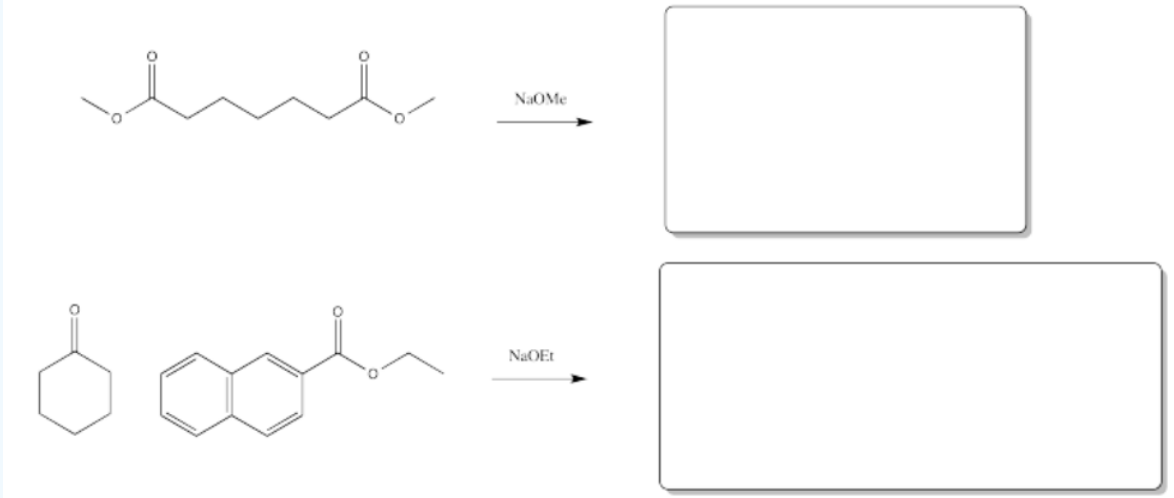
Exercise 5.11.2

Fill in the products of the following reactions.

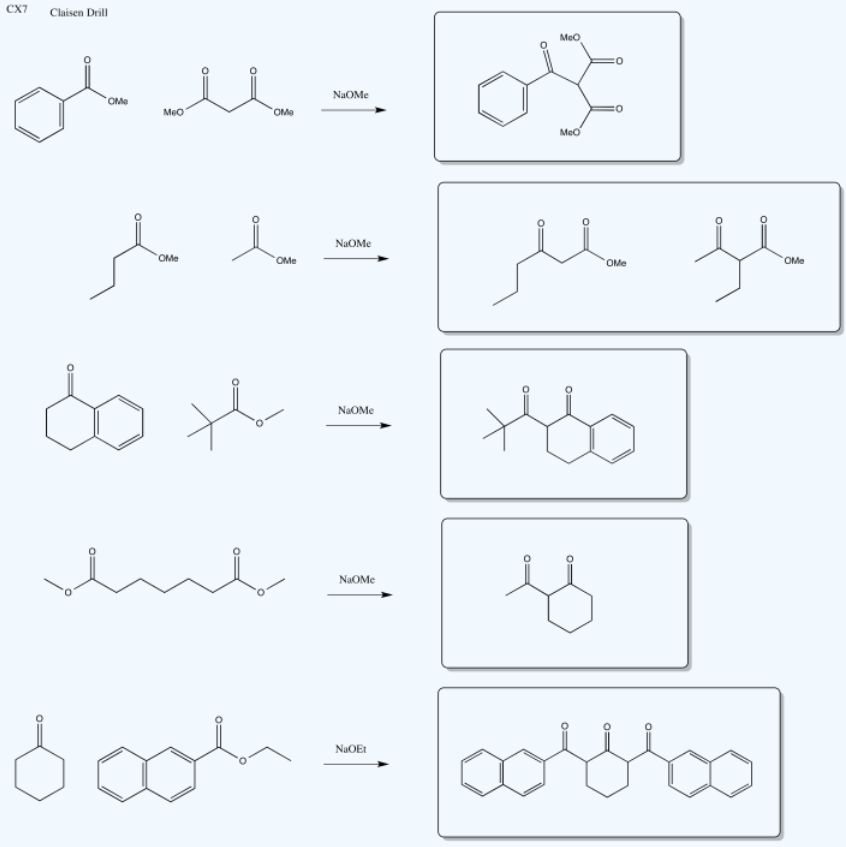






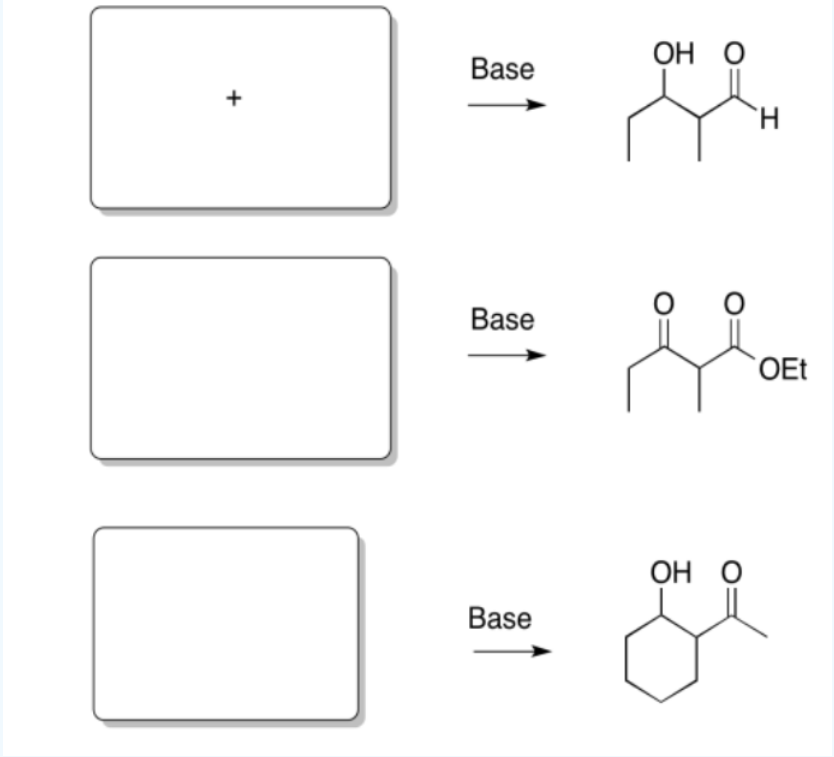


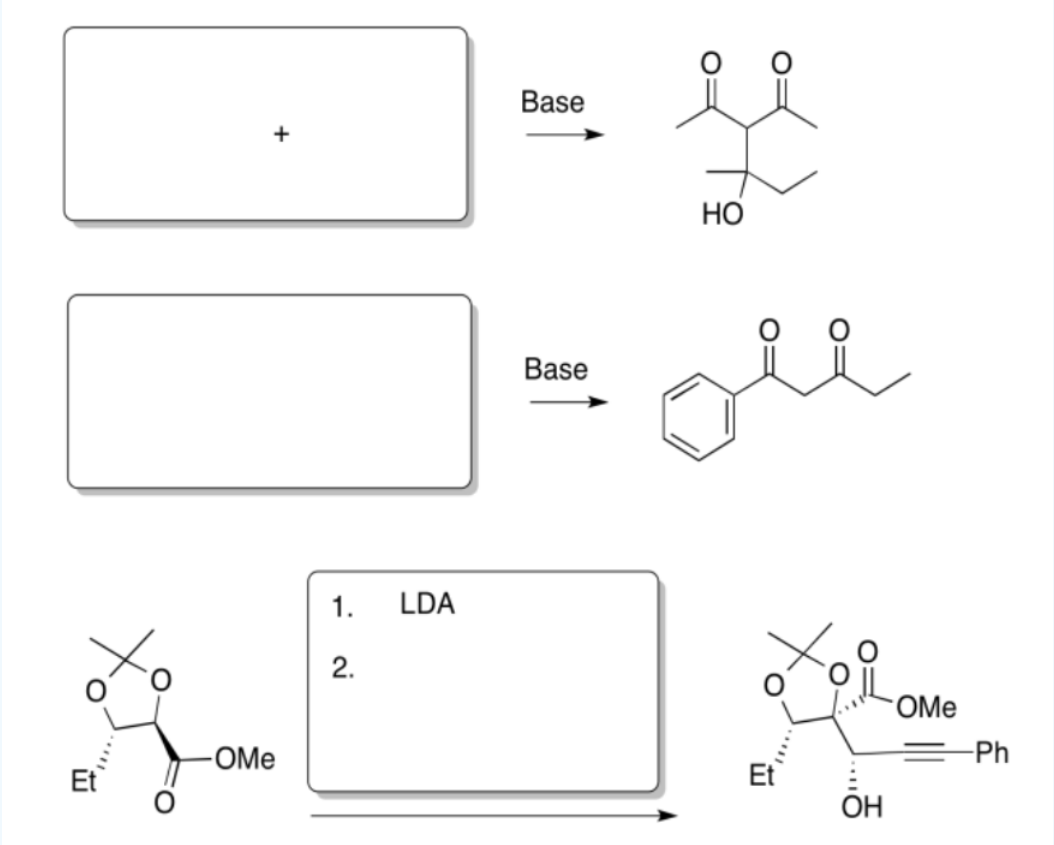
Answer



Exercise 5.11.3

Predict the reactants needed to make these products via a Claisen, Aldol or Crossed Aldol reaction.


+
Base
OH
O
H
Base
O
O
OEt
Base
OH
O


+
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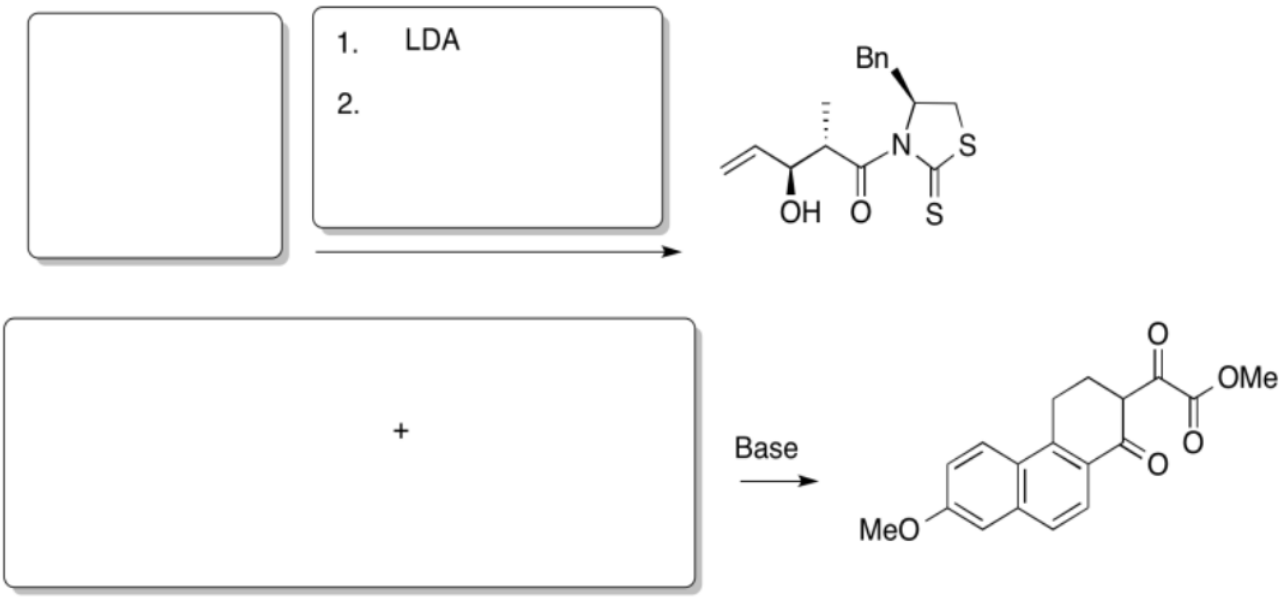
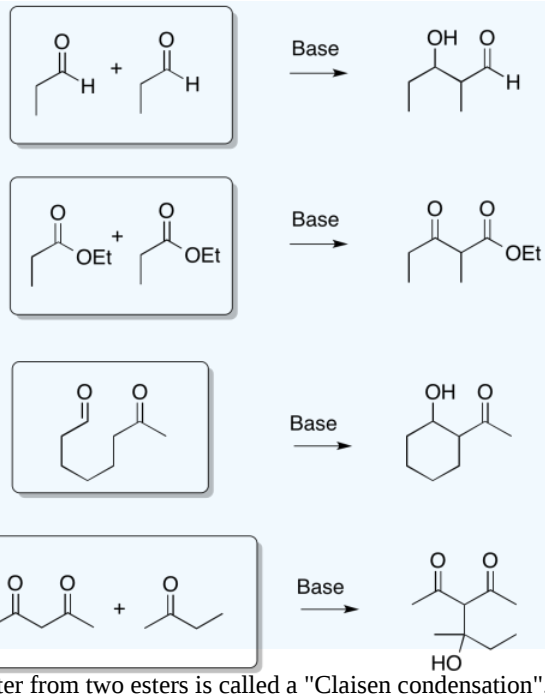
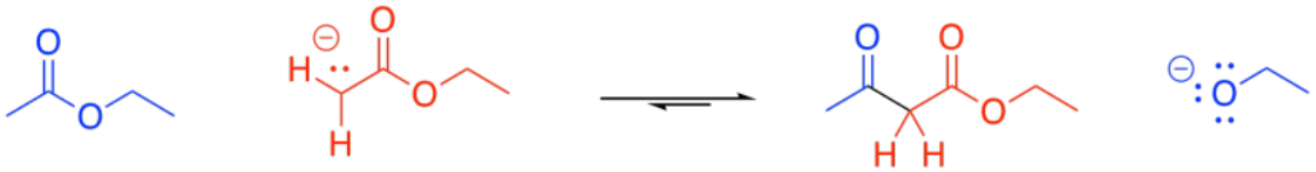


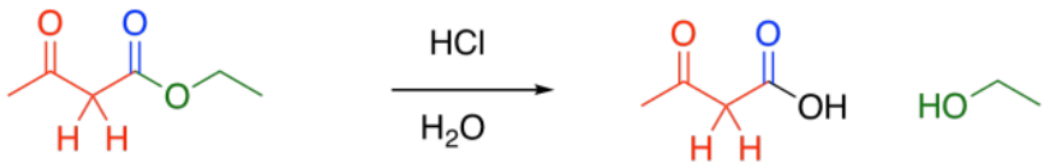
Answer



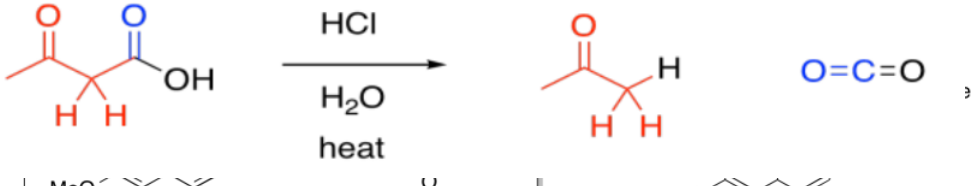
The formation of a beta-ketoester from two esters is called a "Claisen condensation".



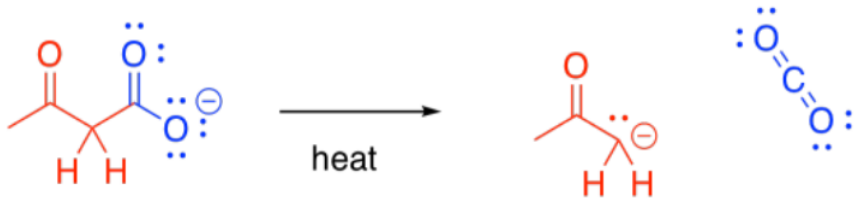
It is often followed by another important reaction: decarboxylation. If a beta-ketoester is treated with aqueous acid and heated, a couple of reactions take place. First, the ester portion of the molecule is converted into a carboxylic acid.



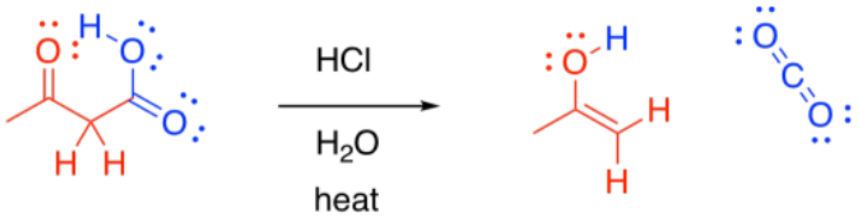
Second, the carboxylic acid is decarboxylated. Carbon dioxide is formed, and the organic molecule becomes a ketone. The carboxyl group is lost completely from the original molecule, and is converted into CO_2.



Decarboxylation is related to the retro-aldol reaction; formally, it can be thought of as leading to an enolate leaving group. Decarboxylation most commonly occurs in beta-ketoacids, rather than in other carboxylic acids. Otherwise, that leaving group could not occur. The ease of decarboxylation in beta-ketoacids is related to the stability of the enolate anion.



Under acidic conditions, of course, an enolate anion does not occur; instead, an enol is formed. However, enols are rapidly converted into the keto tautomers.



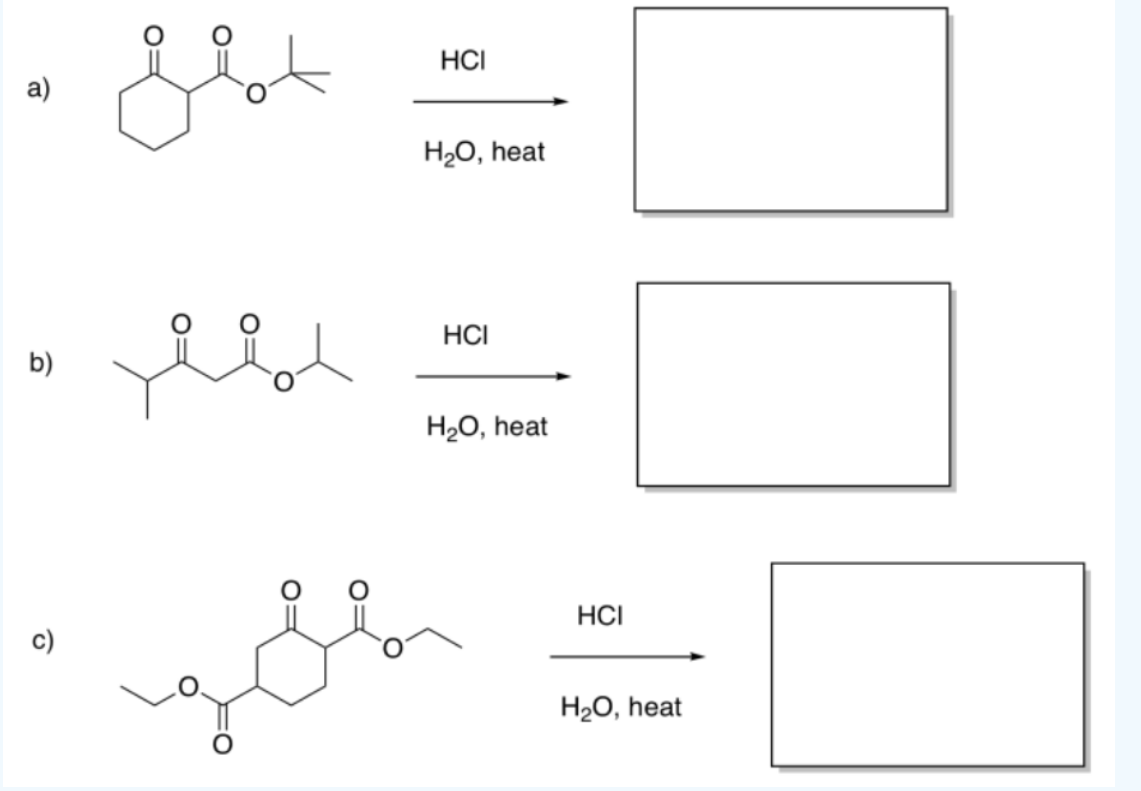
Exercise 5.11.4

Draw a mechanism for:

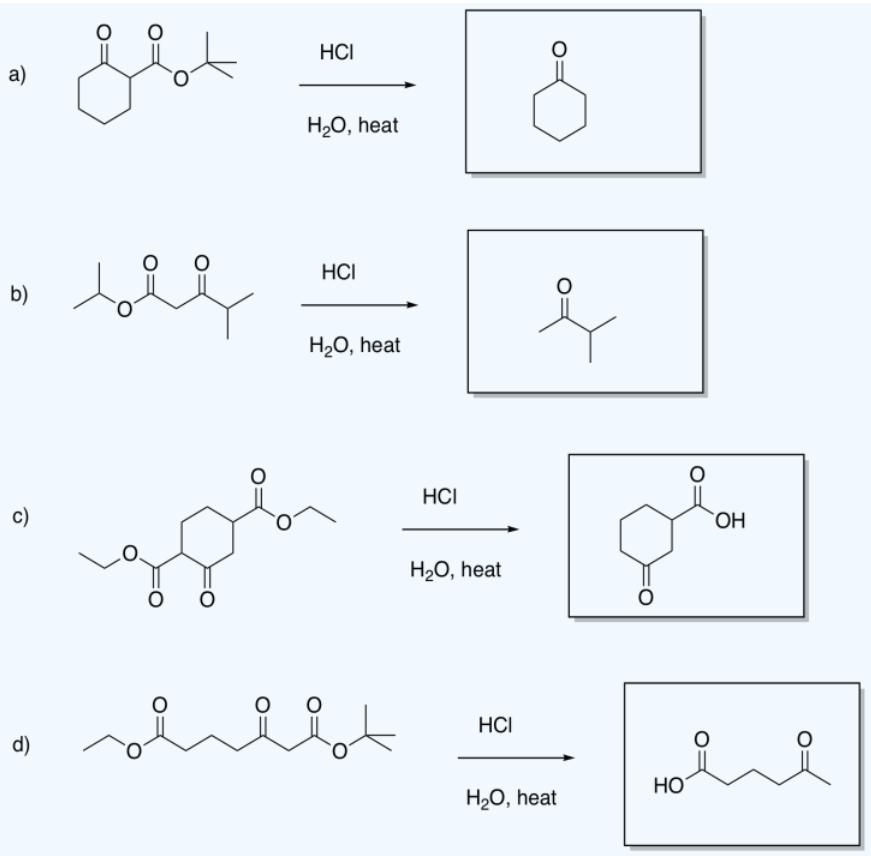
a. Conversion of ethyl-3-oxyhexanoate into 3-oxyhexanoic acid. (Oxy is a prefix meaning a ketone or aldehyde is foundalong the chain).
b. Decarboxylation of the resulting 3-oxyhexanoic acid.

Exercise 5.11.5

Fill in the products of the following reactions.



Answer



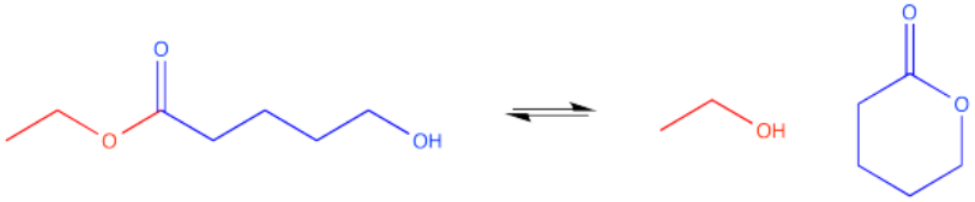
5.12: Condensation Polymers and Ring-Opening Trans-Esterification Polymerisation

Carboxyloids, such as esters, can interconvert with each other in the presence of the appropriate nucleophile. In the case of esters, an equilibrium will result. If an alcohol is added to an ester, under the right conditions we might get a new ester. A new alcohol would also appear, originating from the old OR group of the original ester. Two different esters and two different alcohols would be in equilibrium. This equilibrium might be perturbed in one direction or another, for example, by the addition of an excess of one nucleophile.

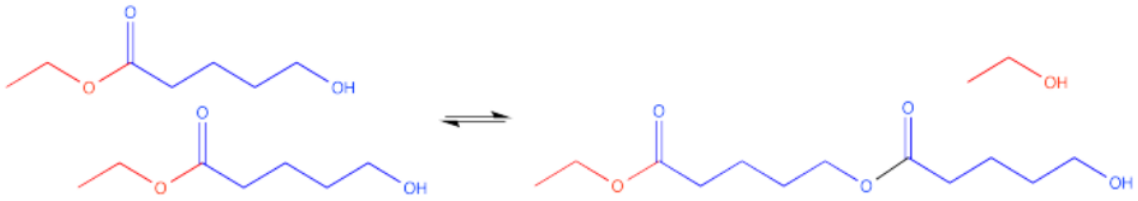
In the jargon of synthetic organic chemistry, an ester is a functional group. It is a site on the molecule at which reactions take place. It is also a site on the molecule that is easily subject to synthetic transformations. In other words, one functional group might easily be converted into another. In the case of a trans-esterification reaction, one ester simply gets converted into another.

Some compounds have more than one functional group. A compound could be both an ester and an alcohol, for instance. We might call this compound a hydroxyester. But wait -- if an alcohol can react with an ester, to make a new ester, doesn't this compound have both components of a reaction built in? Could it react with itself?

There are a couple of ways that could happen. If the chain between the carbonyl and the hydroxyl group is long enough (remember, a six-atom interaction between the hydroxyl oxygen and the carbonyl carbon may be optimal), the hydroxyl could wrap around and form a cyclic ester. That's an intramolecular reaction -- a reaction within one molecule.

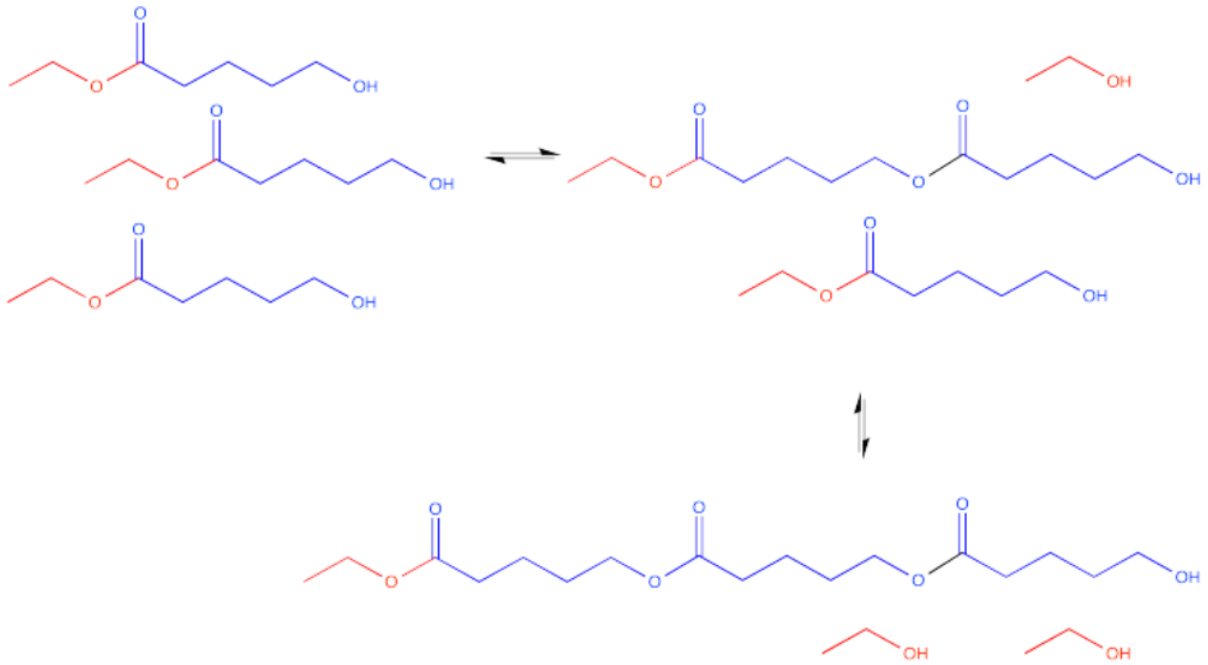


Alternatively, if there is another one of these molecules around someplace, an intermolecular reaction might occur. That's a reaction between two different molecules. The hydroxyl group on one molecule can reach out and react with the carbonyl on another molecule.



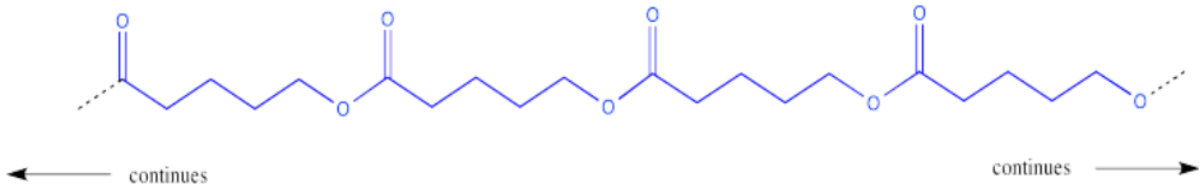
Now there are two molecules of the same kind bonded to each other. This double molecule is called a dimer. The individual molecules that have been linked togethr to make the dimer are called monomers.

That dimer has two esters in it, not just one. Of course, it still has a hydroxyl group on one end. That hydroxyl group can still react with another carbonyl on another molecule.

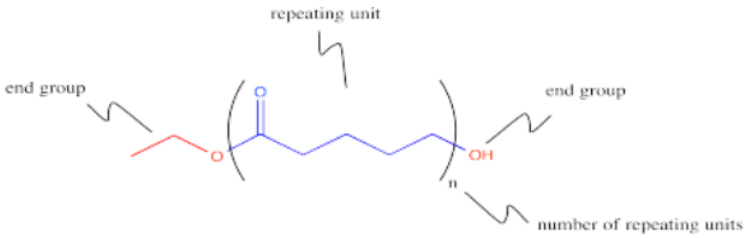


Now there are three molecules bonded together. This molecule is called a trimer.

This process could keep going on indefinitely, of course. We might end up with a very large molecule, composed of many individual (former) molecules that have bonded together. This very large molecule made up of repeating units is called a polymer. A polymer is built up from many monomers linked together. This particular kind of polymer is called a polyester.



This polymer is frequently drawn in a way that emphasizes the repeating pattern of monomers that have been incorporated into the chain.



Polyesters can also be made by co-polymerizing two different monomers together. One monomer could be a diester, for example. The other monomer could be a diol. These two molecules are ready to react together, with one molecule acting as an electrophile and the other molecule acting as the nucleophile.

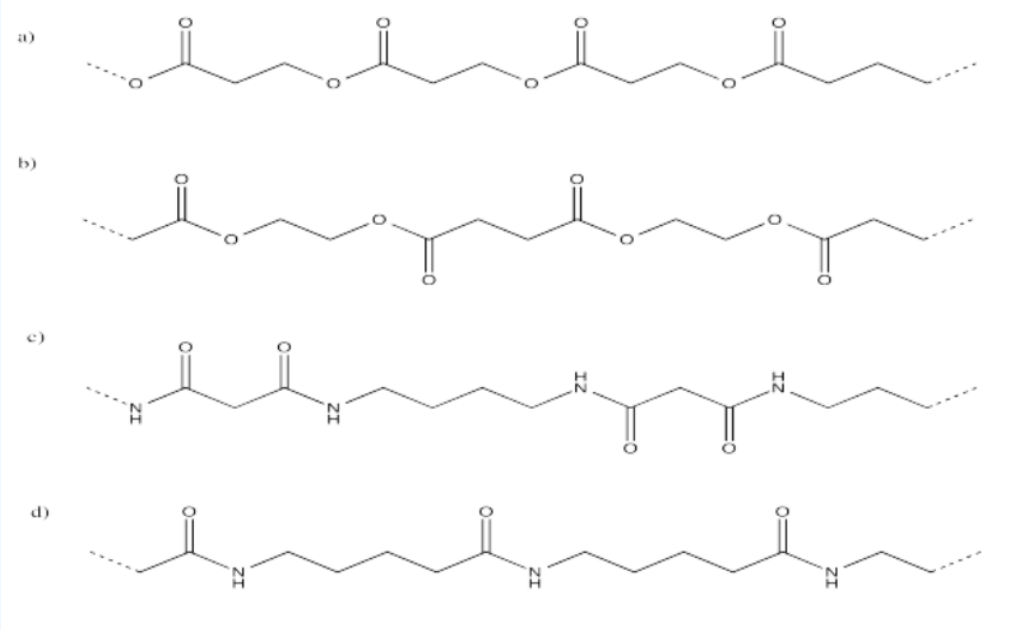
Together, the diester and the diol could be polymerized. The result would be an alternating copolymer, in which diester and diol monomer units alternate all along the polymer chain.

Polymers make up an important class of materials with many uses. Many polymers are lightweight, strong materials used to make parts for automobiles and other products. Polymers can also be very flexible or elastic. The physical properties of polymers are very different from the properties of other molecular compounds. These differences are a direct result of the very large size of polymer molecules. A polymer molecule might be thousands of monomers long, with a molecular weight in the millions.

Exercise 5.12.1

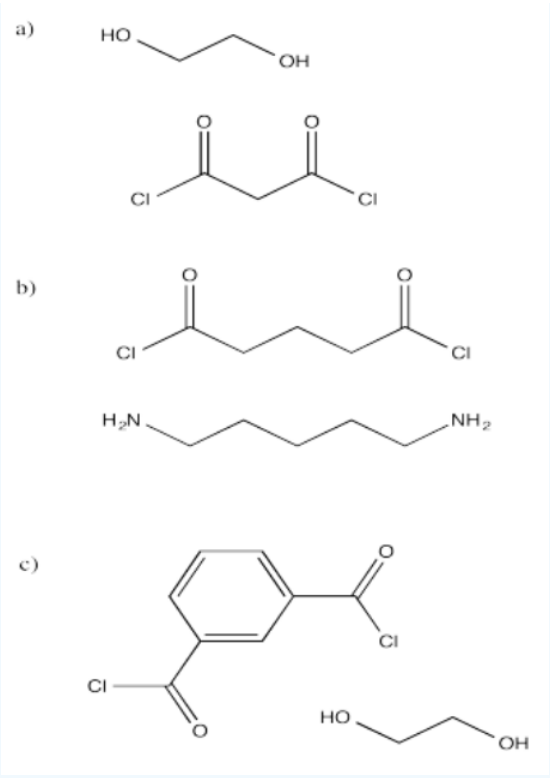
Problem CX8.1.

Express the following polymer structures in abbreviated structures showing *n* repeating units in parentheses.



Exercise 5.12.2

Show the structures of the polymers that would result from the following monomers. In each case, show a drawing with several enchained monomers.



Exercise 5.12.3

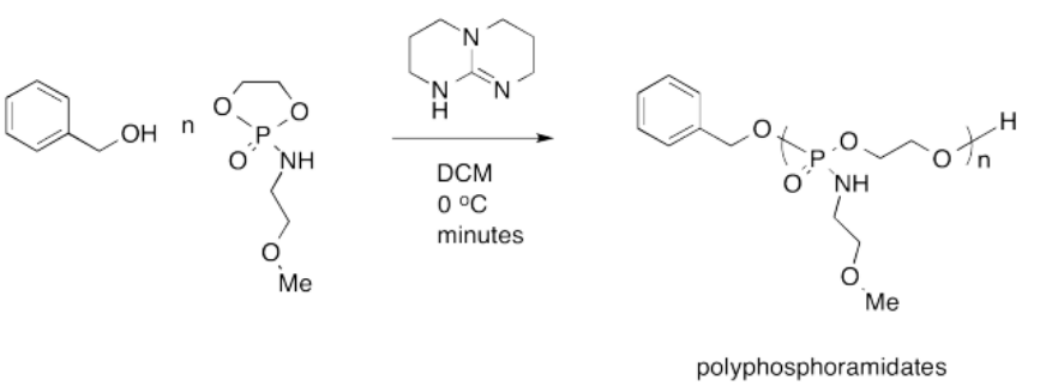
Ring-opening polymerization involves a multi-step reaction in which a cyclic compound, such as a lactone (below) is opened into a chain through the addition of a nucleophile (called the "initiator"). The resulting chain is able to act as a nucleophile and open the next lactone, and so on, until a polymer has formed. Show a mechanism for formation of the oligomer in which n = 3.

Exercise 5.12.4

Ring-opening polymerizations are frequently accelerated through the addition of small amounts of metal compounds, such as diethylzinc (Et_2Zn) or tin octoate ($Sn(O_2CCH(CH_2CH_3)CH_2CH_2CH_2CH_3)_2$. Explain the role of these compounds in the reaction mechanism.

Exercise 5.12.5

Karen Wooley at Texas A&M recently reported the following synthesis of a polyphosphoramidate for use as a pharmaceutical delivery agent. The goal is to use a benign delivery agent that is easily broken down and excreted by the body, resulting in low toxicity and minimal side effects.



a. Provide a mechanism for the synthesis.
b. Explain why the polyphosphoramidate is expected to be broken down and excreted easily by the body.

Difunctional molecules can sometimes polymerise, provided they have appropriate partners with which they can react on other molecules. For example, hydroxyesters might react with other hydoxyesters, with the hydroxyl group on one molecule reacting with the ester group on another, forming a polyester. Alternatively, there might be two different kinds of molecules that react with each other. For example, a diamine might react with a diacid chloride to form an amide.

In ring-opening polymerisation, the monomer is not difunctional. Instead, it is embedded in a ring. Ideally, there is a little ring strain in the molecule, bumping it up in energy just a little so that it will react more easily. Common examples include caprolactone and lactide, used to make biodegradable yard waste bags and produce containers, respectively (among many other applications). These cyclic esters are sometimes referred to as "lactones".

If an alcohol is added, it can act as an "initiator" in a "chain reaction". The alcohol is a nucleophile, and it donates to the carbonyl, eventually cleaving the carboxyl C-O bond and popping open the ring.

At some point, a proton gets transferred to the oxygen that used to be embedded in the ring. Now we have a new alcohol. What does it do? It reacts with another cyclic ester, popping it open and forming a new alcohol. The cycle repeats itself.

- A chain reaction keeps happenning over and over again.
- A chain reaction must be started by an initiator.
- A chain reaction leads to a product that looks just like an earlier reactant, so the product reacts again.

In reality, ring opening polymerisations don't really work if you just add an alcohol to a lactone. Typically, a catalyst is also added. Catalysts most commonly are Lewis acids, such as aluminum, iron or tin compounds. One of the most common catalysts is tin octoate, more properly called tin(II) 2-ethylhexanoate.

Exercise 5.12.6

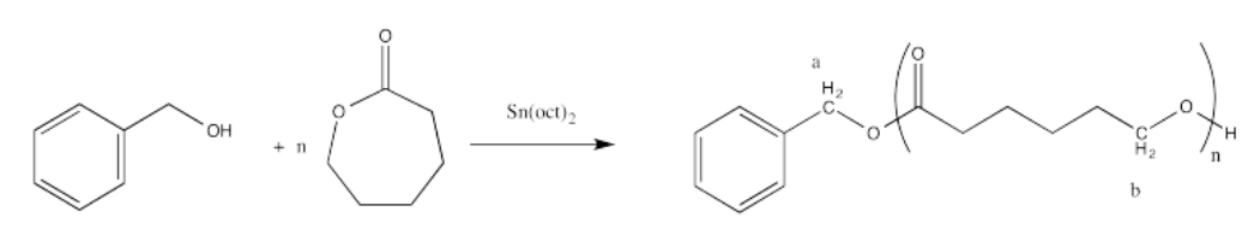
Provide a mechanism, with arrows, for the ring-opening polymerisation of caprolactone with tin octoate.

Exercise 5.12.7

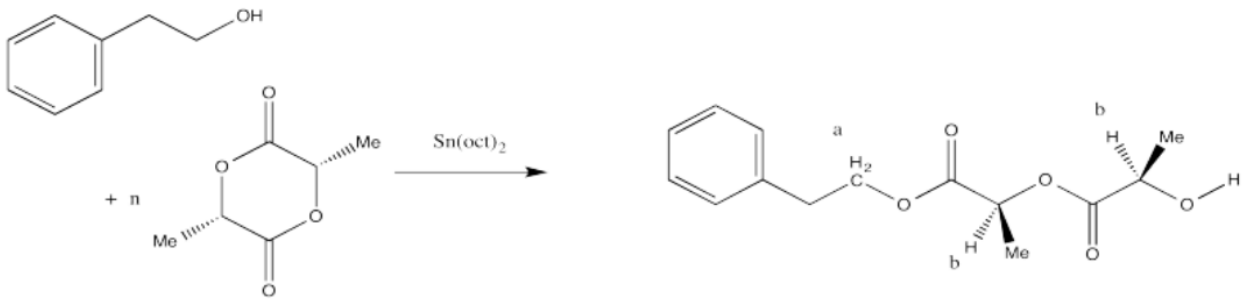
Perform end-group analysis in the following cases to determine

a. the degree of polymerisation (what is the value of "n"?).
b. the molecular weight.

i. The ratio of the integrals for the ^{1}H NMR peaks representing positions b:a is 50:1.

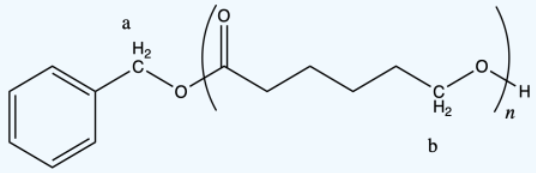


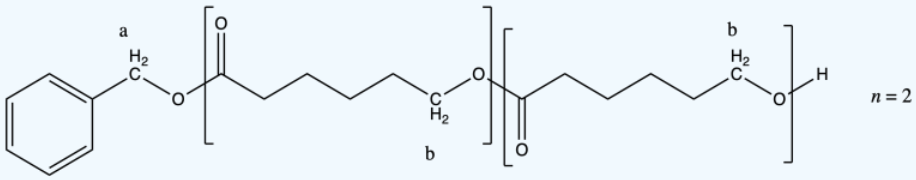
ii. The ratio of the integrals for the ^{1}H NMR peaks representing positions b:a is 80:1.



Answer i

In general, we compare a peak in the repeat unit (which occurs over and over) to a peak in an end group (which occurs only once in each chain) to find the number of repeat units or degree of polymerization. For example, if the chain were a dimer (n = 2) we would expect the integral for peak *b* to be twice as large as the integral for peak *a*.





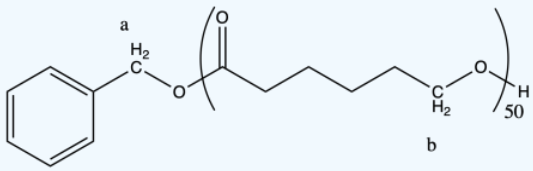
integral b : integral a = 4:2 = 2:1

degree of polymerization (= *n*) = ratio of integral from the repeat unit peak (b) to the end group peak (a)

It works out that way because in each repeat unit, peak *b* represents two hydrogens, and in the end group, peak *a* represents two hydrogens. It's the same number of hydrogens in each position, so comparing the integration of the two peaks tells you directly how many repeat units there are.

If that were not true (if peak *b* represented only 1H and peak 1 represented 2 H), then we would have to factor that difference into the answer.

The question states that the integration ratio of *b:a* is 50:1, so that means the degree of polymerization = 50.



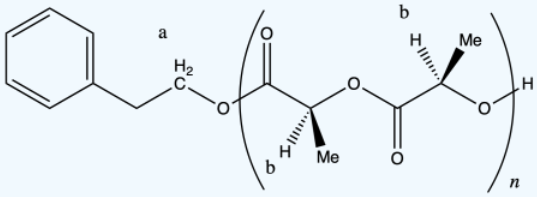
2H 100H

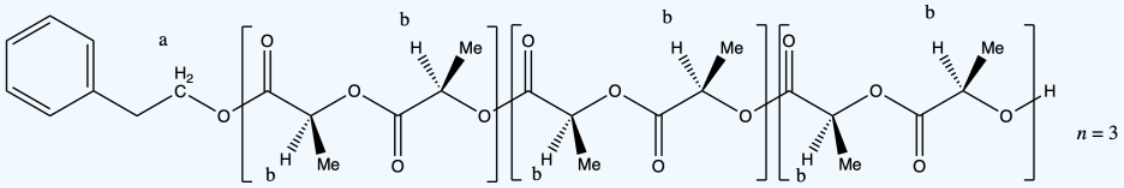
integration ratio b:a = 50:1

The molecular weight is therefore about 50 times the molecular weight of the monomer (114.4 g/mol), or 5,720 g/mol (sometimes expressed as 5,720 Da; a Dalton is just 1 g/mol). There are also end groups (from benzyl alcohol) that contribute a little weight, so the total molecular weight is 5,720 + 108 g/mol = 5,828 g/mol.

Answer ii

Once again, peak *a* represents two hydrogens, and so does peak *b* (although the peak b hydrogens occur at two different places in the molecule and differ stereochemically from each other). That means that, once again, the ratio of integrals of peak *b* to peak *a* tells us the degree of polymerization. If the ratio were 3:1, we would have $n = 3$.

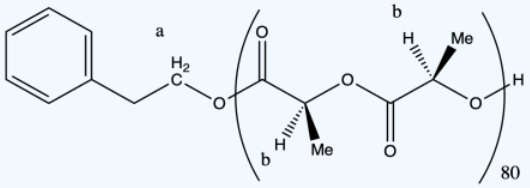




integral b : integral a = 6:2 = 3:1

degree of polymerization (= *n*) = ratio of integral from the repeat unit peak (b) to the end group peak (a)

The question states that the integration ratio of *b:a* is 80:1, so that means the degree of polymerization = 80.



2H 160H

integration ratio b:a = 80:1

The molecular weight is therefore about 50 times the molecular weight of the monomer (144.1 g/mol), or 11,530 g/mol. Adding in the end groups (from benzyl alcohol), the total molecular weight is 11,530 + 108 g/mol = 11,638 g/mol.

Note that in certain diastereomers of lactide (LLA or DLA) we could actually draw the repeat unit as a $C_3H_4O_2$ unit rather than as the larger $C_6H_8O_4$ unit, but in this case the two chiral centers are actually different, so we have to keep the larger repeat unit to show the presence of both stereochemical configurations.

5.13: Peptide and Protein Synthesis

Peptides and proteins are very important in biology. As a result, synthesis of these molecules has become very important, allowing for the laboratory study of model compounds that can give us insight into how proteins work, as well as pharmaceutically important compounds.

Insulin and glucagon are two important peptides (or small proteins) that regulate blood sugar. Insulin signals that blood sugar levels are high and that the body should begin storing this excess sugar. Glucagon signals that blood sugar levels are low and so the body may need to access its long-term energy stores. Both compounds are important in medicine.

Glucagon has a relatively simple structure, for a protein. It is a string of just 29 amino acids, connected together in the following order:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr.

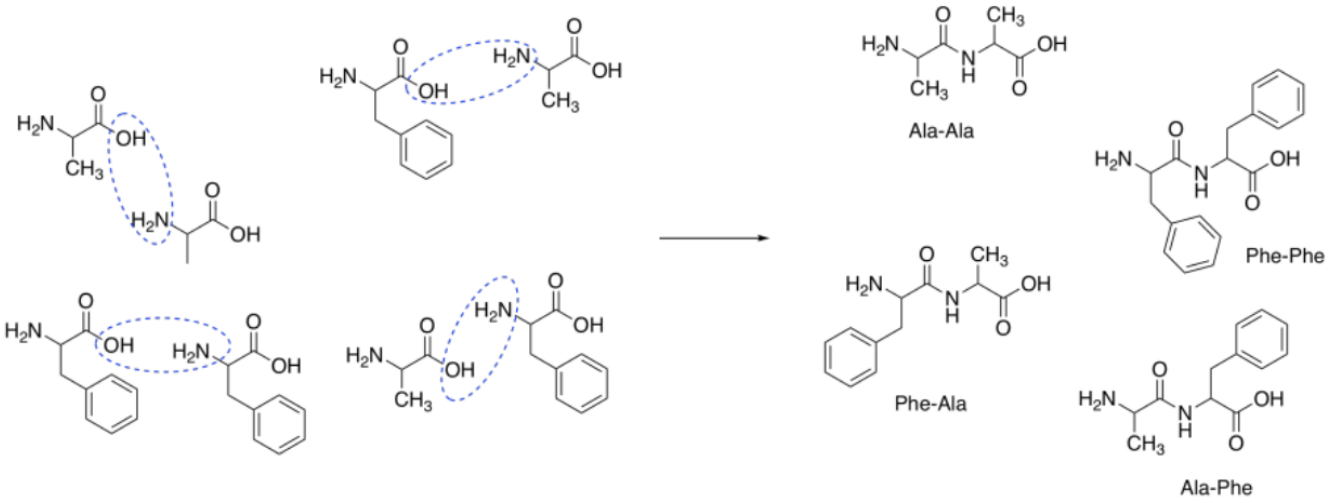
The structure is composed of readily-available starting materials. The amino acids are simple units that connect together to form a chain. Conceptually, it seems easy to put two amino acids together to make a side chain. When two amino acids come together, they lose a molecule of water together, and the remaining pieces are able to bond to each other to make the dipeptide. It ought to be just as easy to add a third, and so on.

Structurally, amide or peptide bonds are very stable and resistant to carboxyl substitution. That stability makes optimal structures from which to construct proteins. Despite being composed of very long chains of linked amino acids, proteins actually have some limits on their conformational flexibility (their "floppiness"). That allows proteins to more reliably hold a particular shape. The shape of proteins is crucial to their function as enzymes and other

Both the stability and the structural rigidity of peptides arises from the nature of the peptide bond. The pi donation that hinders nucleophiles from substituting at the carbonyl is pronounced enough that it can be considered to form an additional bond. Thus, peptides behave as though they contain C=N bonds rather than C-N bonds. X-ray structure determinations show that the peptide nitrogens in proteins are trigonal planar, not pyramidal. In addition, many peptides exhibit cis-trans isomerism. For every peptide bond, two different isomers can occur, depending on whether a substituent attached to nitrogen is on the same side of the C=N bond as the carbonyl oxygen or the opposite side.

The great stability of these structures does not mean they are easy to make. Part of the difficulty stems from the fact that amino acids are difunctional. In order to form long chain structures, amino acids must be able to react twice: once with an amine, to grow in one direction, and once with a carboxylic acid to grow in the other direction. In other words, an amino acid contains both a nucleophile and an electrophile.

Suppose we were to try to make the dipeptide, ala-phe. This peptide contains an alanine connected to a phenylalanine through a peptide bond. The peptide bond is formed between the carboxylic acid of alanine and the amine of phenylalanine.



Assuming the amino acids do react together to form the peptide, combining these two reactants would likely produce a mixture of four dipeptides:

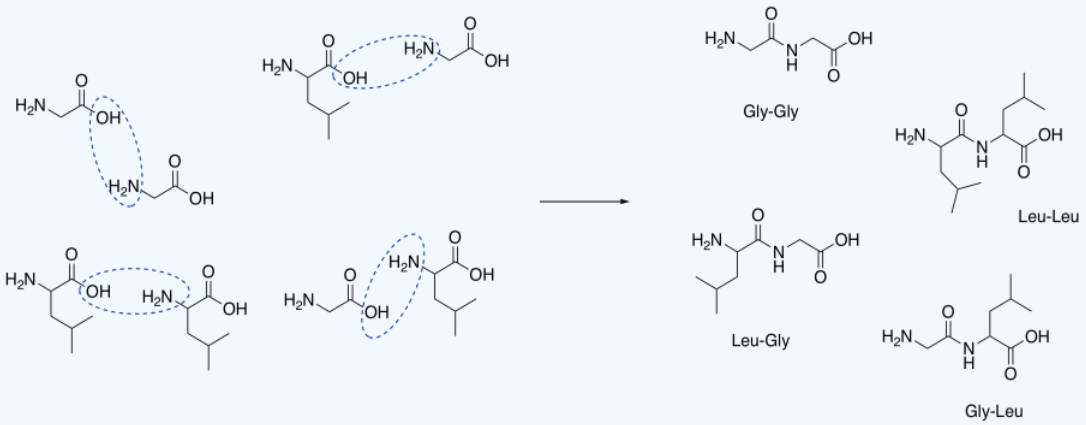
Ala-Phe Ala-Ala Phe-Phe Phe-Ala

In other words, peptide formation from amino acids is non-selective.

Exercise 5.13.1

Draw structures for the four peptides formed by combining glycine and leucine.

Answer



Exercise 5.13.2

What tripeptides would be produced by mixing Ala, Gly and Val?

Answer

That combination would give thw following dipeptides:

ala-ala ala-gly ala-val

gly-gly gly-ala gly-val

val-val val-ala val-gly

Of course, we might also get tripeptides, such as ala-ala-gly-val, and so on.

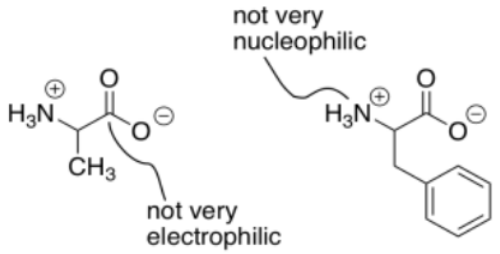
Exercise 5.13.3

Simply combining these peptides might not result in any peptide formation at all. Why not?

Answer

Carboxylic acids usually require activation before they can act as nucleophiles. That problem is actually complicated here because the carboxylic acid is in equilibrium with a carboxylate salt (read further on the page).

An additional complication in peptide synthesis is that amines and carboxylic acids do not really exist together. Instead, a proton is transferred from the carboxylic acid to the amine, forming a salt. The carboxylate is no longer very electrophilic, due to its negative charge. Because of its positive charge, the ammonium ion is no longer very nucleophilic.



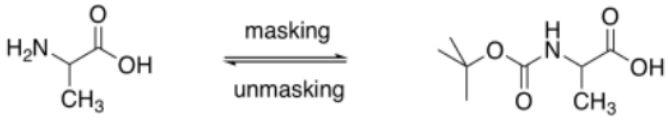
As a result, there are actually two distinct problems in peptide synthesis. There is a selectivity problem, because each amino acid has a nucleophilic part and an electrophilic part. There is no way to ask one compound to react only using its electrophile and another compound to react only using its nucleophile. There is also a reactivity problem: the carboxyl group in this case is a terrible electrophile, and the amine is a terrible nucleophile.

In laboratory syntheses, a number of techniques have been used to make peptide synthesis selective. Most frequently, protecting groups are used. A protecting group "masks" one of the two functional groups on an amino acid, but leaves the other one open. If one amino acid has its amine protected, it can only react via its carboxylic acid. If the other amino acid has its carboxylic acid protected, it can only react via its amino group. Only one combination will result.

The key to protecting groups is that the reaction used to mask one of the functional groups must be reversible. You must be able to take the protecting group back off when it is no longer needed.

Carboxylic acids are normally protected as esters. Esters can be removed via acid- or base-catalyzed hydrolysis (as can amides, but esters are more reactive, being farther up the ski hill).

Amines are normally protected as amides. However, we need to be able to remove specific amides her: the ones that mask the amines, not the ones that we have formed to link two amino acids together. As a result, in peptide synthesis, amines are usually protected as carbamates. Carbamates can be cleaved more easily than amides.



Boc-Ala

Exercise 5.13.4

Propose a reason for the relatively higher reactivity of carbamates compared to amides.

Answer

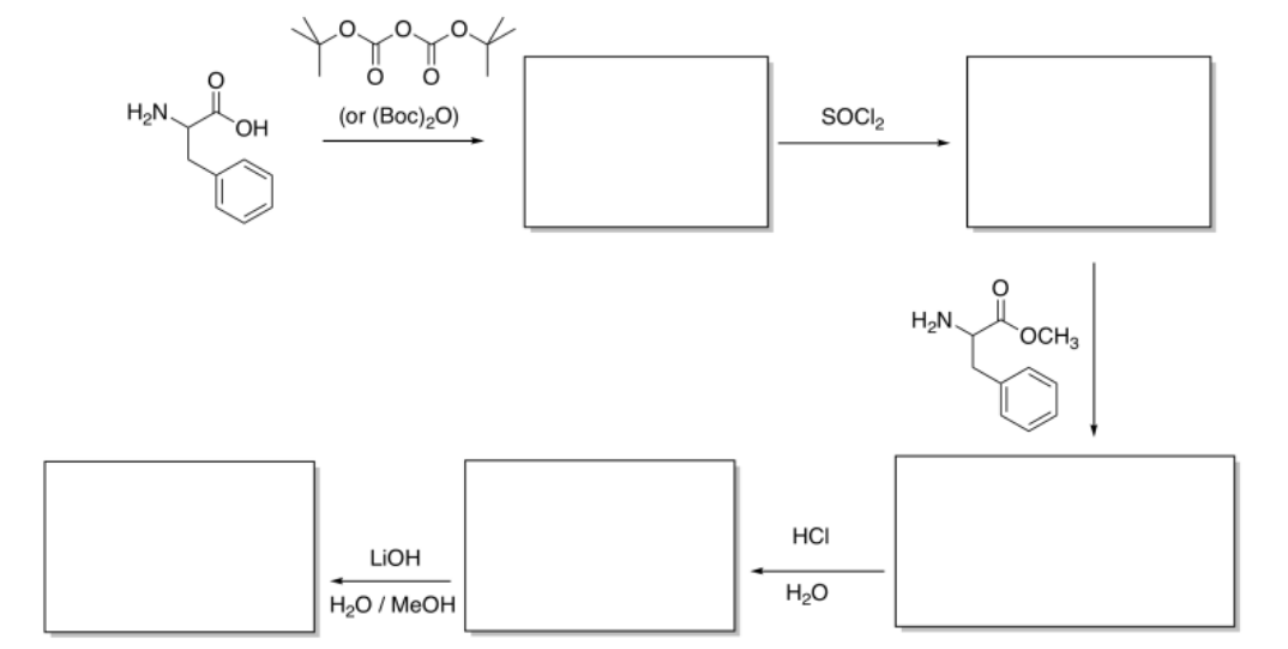
The relative reactivity of carboxyloids results from a balance between sigma electron withdrawing effects and pi-donation. An electronegative atom attached to a carbonyl tends to withdraw electron density, making the carbonyl even more positive and electrophilic. On the other hand, pi-donation from a neighbouring atom with a lone pair actually lowers electrophilicity by forming a stable, conjugated system.

In a carbamate, an additional electronegative atom is added to the carbonyl: it has an oxygen as well as a nitrogen adjacent to the C=O group. That atom draws electron density away from the carbonyl, making it more electrophilic. However, pi-donation from the additional oxygen does not result in a more stable conjugated system. The maximum pi system is still just three atoms long; it either involves conjugation of the O-C=O or the N-C=O unit. It does not, for example, lead to an even more stable conjugated system that is four atoms long.

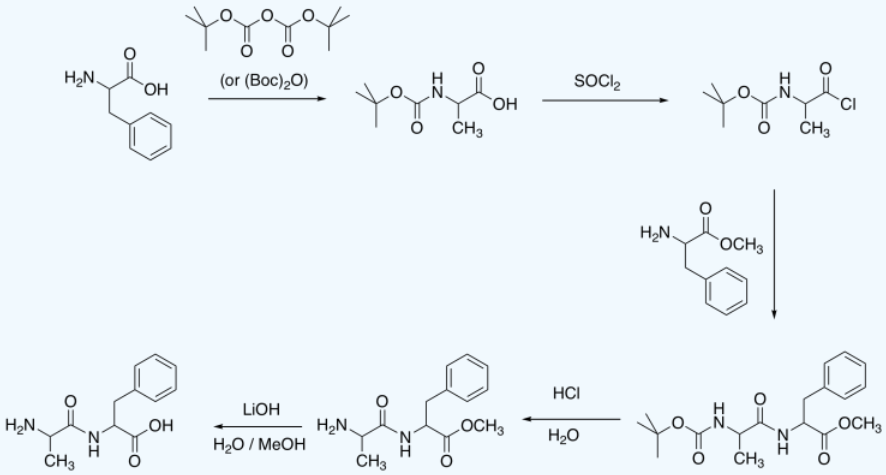
As a result, the added oxygen probably contributes more to the electron-withdrawing effect than it does to stabilisation of the pi system.

Exercise 5.13.5

Fill in the blanks in the following peptide synthesis.



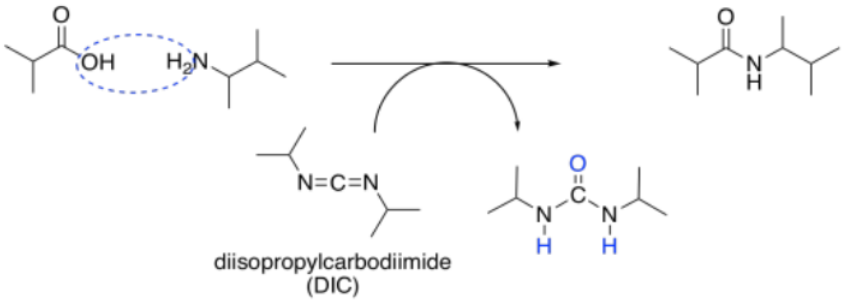
Answer



To get around the problem of low electrophilicity of the carboxylic acid, a number of coupling agents have been developed. A coupling agent can temporarily convert the carboxylate anion into a more reactive electrophile. To do so, it exploits the nucleophilicity of the carboxylate anion. After donating to the coupling agent, the carbonyl compound becomes more electrophilic.

Thionyl chloride ($SOCl_2$) can accomplish this goal, of course. It converts relatively non-electrophilic carboxylic acids into much more electrophilic acid chlorides. Thionyl chloride can be a little harsh, however, so chemists have sought to develop milder conditions that can knit two amino acids together without the necessity of forming a reactive acid chloride.

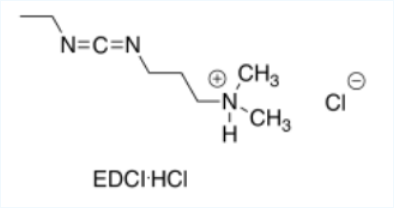
Some of the most commonly-used coupling agents for peptide synthesis are carbodiimides. These compounds contain an electrophilic N=C=N unit to act as an initial electrophile. Diisopropylcarbodiimide (DIC) and dicyclohexylacarbodiimide (DCC) were some of the earliest and simplest examples of these compounds developed for peptide synthesis.



Once a carboxylate has donated to the electrophilic carbon of the carbodiimide, a better leaving group is formed. The adjacent nitrogen atoms act as basic sites, picking up a proton from the carboxylic acid on one amino acid and from the ammonium ion intermediate formed by the other amino acid.

Exercise 5.13.6

Propose an advantage of EDCI as a coupling agent for amino acids.



Answer

The more polar hydrochloride salt of EDCI is often used, as pictured. This more polar compound dissolves well in polar solvents, such as water, that also dissolve amino acids.

One can also imagine the amino group in EDCI acting as a site for catalysis, shuttling protons from one place to another.

CHAPTER OVERVIEW

6: Enzyme Catalysis

6.1: Introduction to Enzymes

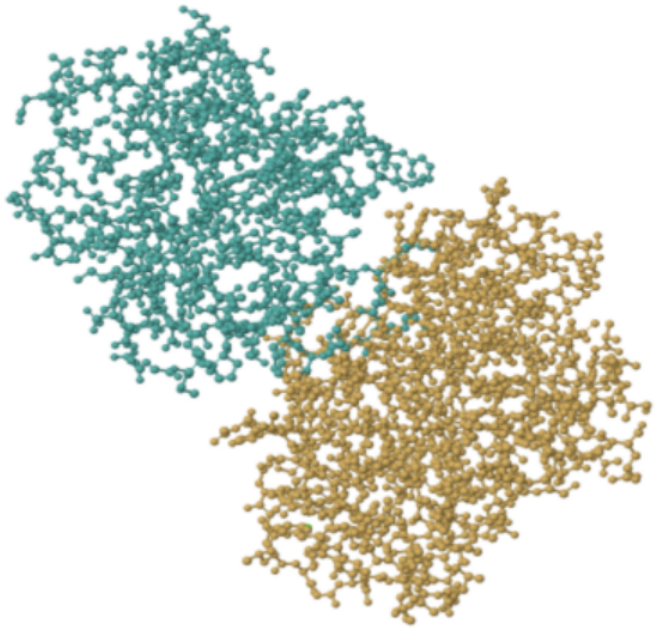
If you look around the laundry room cupboard, you might see some different household products that contain enzymes. That might seem a little strange at first; enzymes are found in the body, and have no business being in stain remover or drain cleaner. But enzymes are just molecules that are really, really good at performing specific tasks. In these household applications, enzymes are really good at breaking specific bonds and replacing them with new ones. In doing so, they are breaking down larger molecules, which might be causing a stain or a slow drain. Those bigger molecules turn into smaller molecules that can be washed away more easily.

What kind of molecules are enzymes? They are special proteins. Proteins play lots of roles in biology; they may provide structure, for example, or they might catalyse reactions. Enzymes are proteins that catalyse reactions. Proteins belong to a class of molecules called biopoylmers. Biopolymers are large molecules composed of smaller molecules that have been bonded together. The small building blocks of proteins are the amino acids. One of the important features of amino acids is the fact that they are chiral; they have very specific three-dimensional shapes, like a left-handed glove or a right-handed glove.

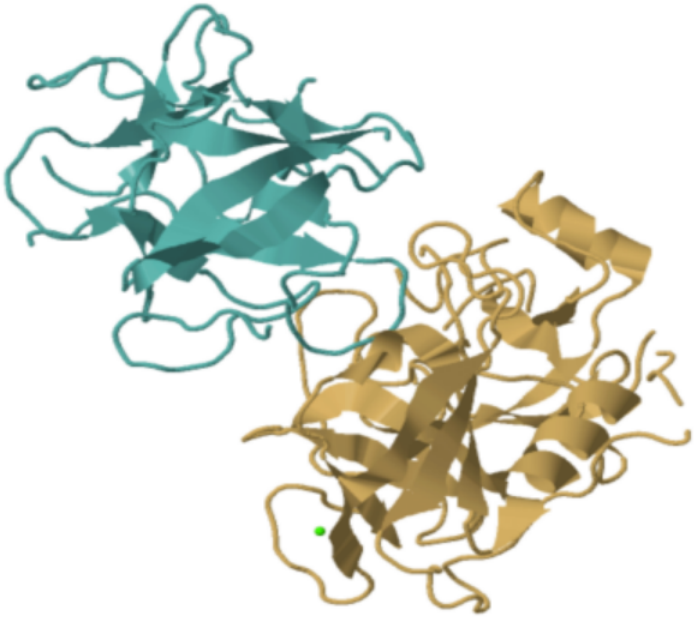
- Enzymes are proteins
- Proteins are composed of chiral amino acids
- Enzymes are great, big, chiral molecules

How big are these proteins, exactly? The biggest protein is titin, which is partly responsible for the elastic properties of muscle. Titin is composed of about 35,000 individual amino acids. The molecular weight of an amino acid is roughly 100 Da (100 Daltons or 100 amu), so that means titin has a molecular weight of about 35 million Da.

But titin is one of those structural proteins. Let's look at an enzyme. Trypsin is a really common enzyme, found in the gut. The picture below comes from a structure determination experiment involving pig trypsin. It's made of about 450 amino acids, so its molecular weight is about 45,000 Da.



That picture shows every atom other than the hydrogens in trypsin; the hydrogens are too small to bother with. Even so, it's a bit busy. More often we look at enzymes and other proteins in a simplified, cartoon form. The cartoon model of trypsin below highlights the beta sheets and alpha helices, the secondary structures within trypsin. In the cartoon model, you can get a better sense of the shape of things. You can see gaps and grooves in the protein, and you can see the chirality in those helices.



Trypsin belongs to a class of enzymes called hydrolases. Hydrolases break bonds with the help of a water molecule. Trypsin breaks specific amide or peptide bonds in other proteins (yes, it's a cannibal), converting the carbonyl side of the bond into a carboxylic acid. That starts breaking down proteins in food; it's an essential part of digestion.

But how does trypsin do that?

At the most basic level, enzymes bind their targets, called substrates, perform chemical reactions on them, and let them go. Binding the substrate is a key step, and it's one of the reasons the chirality of enzymes can be important. Some enzymes are extremely specific in what substrates they bind. For example, they might bind one enantiomer and not another.

Trypsin is also very specific; it specializes in breaking the amide bond next to either arginine or lysine residues. The reaction that it catalyses is not necessarily specific to that particular peptide bond, but the trypsin selectively binds at that site.

This role of specific binding in enzymes is often referred to as the "lock and key" mechanism. We think of enzymes as being unlocked or turned on when the proper key is inserted, causing the enzyme to spring into action. In the following sections, we'll take a closer look at how enzymes bind their substrates and carry out their reactions.

? Exercise 6.1.1

Problem EZ1.1.

Enzymes often have two-part names: the first part identifies the substrate, and the second part describes what the enzyme does with that substrate. See if you can tell what an enzyme would do if one of the following words was in its name:

Match each item in one column to an item in the other column.

a. isomerase i) add oxygen from O_2 into a molecule
b. hydrolase ii) add both oxygens from O2 into a molecule
c. oxygenase iii) oxidize or remove electrons from the substrate
d. dioxygenase iv) reduce or add electrons to the substrate
e. reductase v) reorganize atoms from one isomer into another
f. transferase vi) cleave a phosphate group off a protein
g. phosphatase vii) add water into a molecule, helping to break it down
h. oxidase viii) cause two molecules to be bound together
i. ligase ix) transfer a functional group to or from a molecule

Answer

a) isomerase v) reorganize atoms from one isomer into another

b) hydrolase vii) add water into a molecule, helping to break it down

c) oxygenase i) add oxygen from O_2 into a molecule

d) dioxygenase ii) add both oxygens from O_2 into a molecule

e) reductase iv) reduce or add electrons to the substrate

f) transferase ix) transfer a functional group to or from a molecule

g) phosphatase vi) cleave a phosphate group off a protein

h) oxidase iii) oxidize or remove electrons from the substrate

i) ligase viii) cause two molecules to be bound together

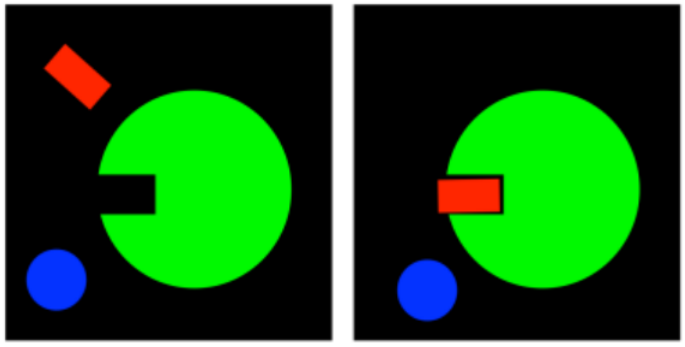
Trypsin Structure: PDB ID: 4AN7

Patil, D.N., Chaudhary, A., Sharma, A.K., Tomar, S., Kumar, P. Structural Basis for Dual Inhibitory Role of Tamarind Kunitz Inhibitor (Tki) Against Factor Xa and Trypsin. FEBS J. 2012, 279, 4547.

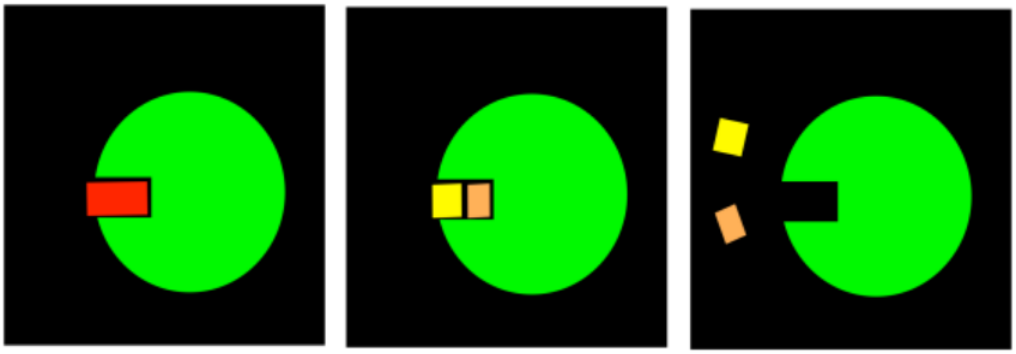
6.2: Enzyme Binding

The lock-and-key model of enzymes says that enzymes bind specific molecules and carry out reactions on those molecules. The enzyme recognizes the shape of its substrate and it is able to hold it in position in what is called the active site. The active site is the part of the enzyme that binds the substrate and carries out the reaction.

Enzyme specificity means that the enzyme only binds certain molecules that have the right shape. It will leave other molecules alone.



Once the molecule is bound, the enzyme carries out some change in the molecule. It might add new pieces on to the molecule or else take pieces off. After it carries out its work on the substrate, the products will be released. The enzyme is then regenerated into its original form and is ready to bind another substrate.



An enzyme is an example of a catalyst. It provides an alternative pathway for a reaction. It gives the substrate the tools to undergo a reaction that might not be possible otherwise. As a result, the reaction occurs much more quickly in the presence of the enzyme. However, one of the key features of a catalyst is that it remains unchanged at the end of the reaction (or, strictly speaking, it is regenerated into its original form). When the enzyme is finished with the substrate, it is ready to bind another one and repeat the process.

? Exercise 6.2.1

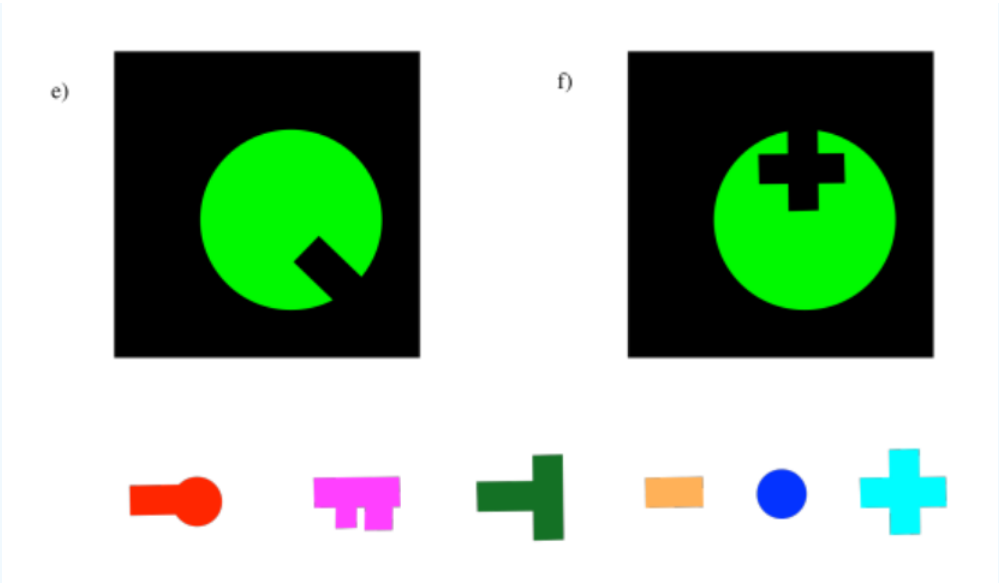
Identify the substrate that fits in each enzyme below.

a)

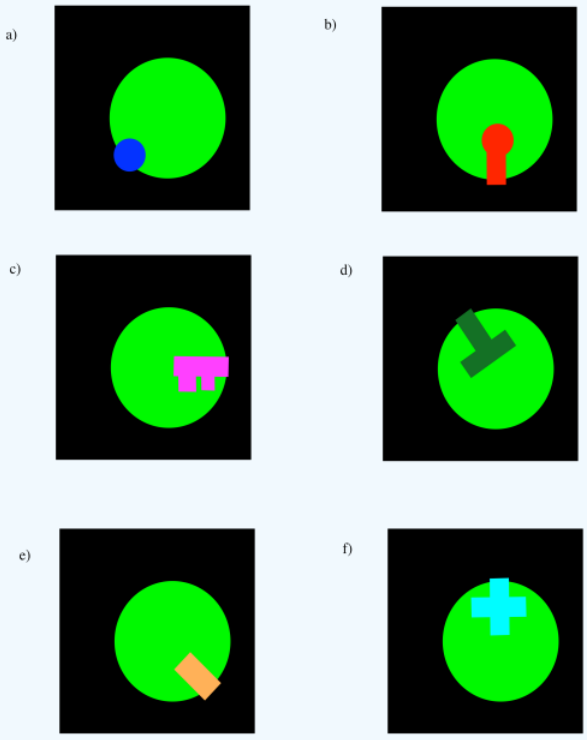
b)

c)

d)



Answer



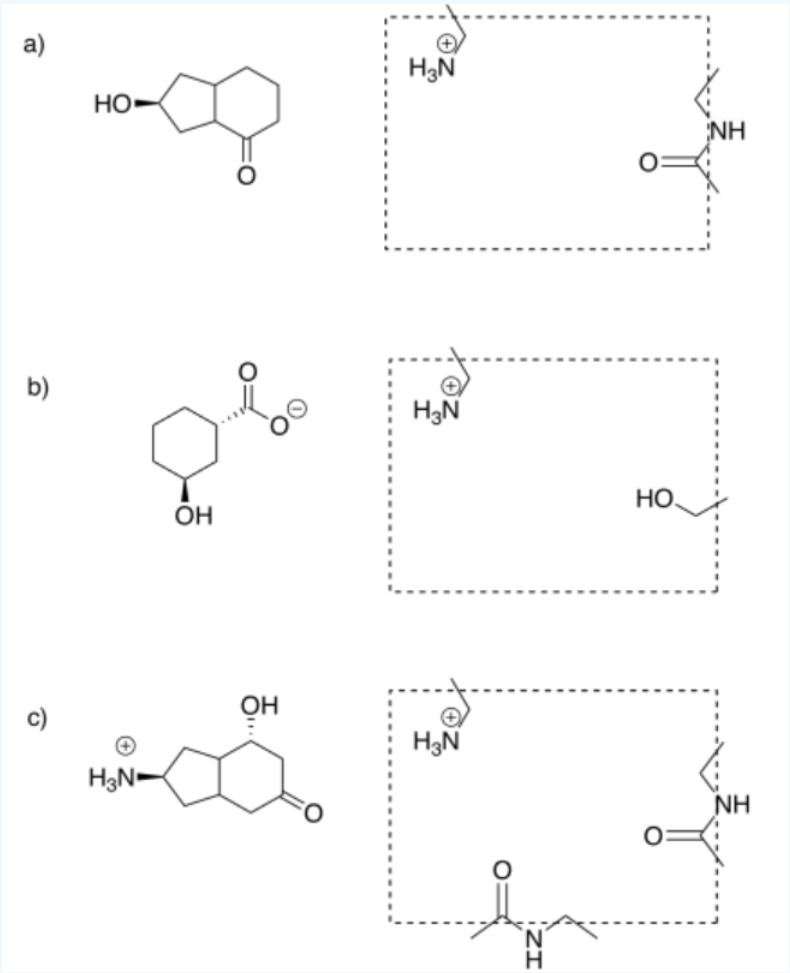
So far, we have been looking at some cartoons to get the idea of enzyme-substrate specificity. If you know anything about small, organic molecules, you may have some ideas about how their shapes might vary in reality. Maybe the substrate is chiral; the enzyme might bind the substrate but not its enantiomer or diastereomer, because those molecules do not have exactly the same shape. Fitting the wrong enantiomer into an enzyme might be like fitting a left hand into a right-handed glove.

Otherwise, functional groups on the substrate play a key role in binding to the enzyme. The functional groups are responsible for the intermolecular attractions between the substrate and the active site. We have been thinking of the active site as a very specific shape, like a circle or a square. In reality, it is often a fold or an opening in the enzyme, a space where a small molecule might settle

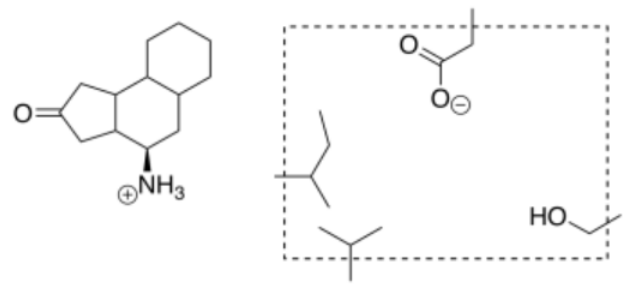
down. The amino acid side chains in that active site are situated to hold the substrate in place. Once everything is in place, the enzyme can get to work.

Exercise 6.2.2

The following are some hypothetical small molecules and their potential binding sites. In each case, orient the molecule within the binding site in order to maximize binding interactions.

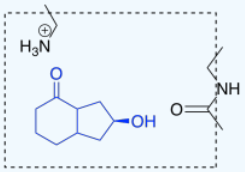


d)

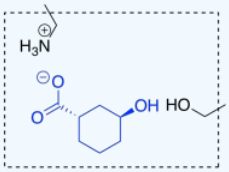


Answer

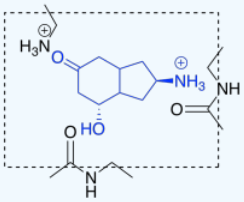
a)



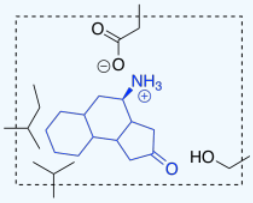
b)



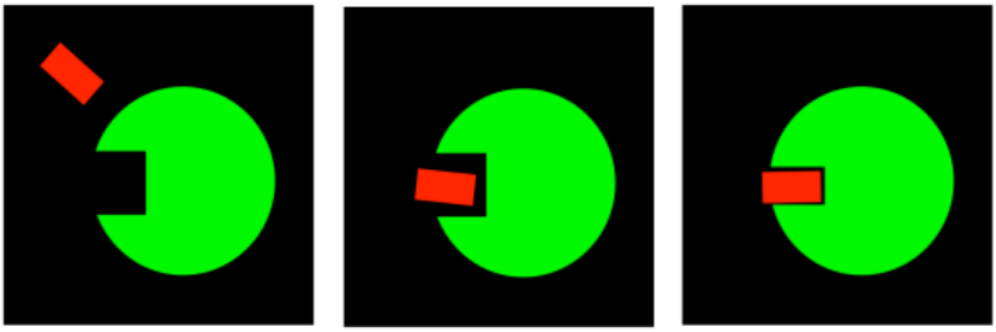
c)



d)



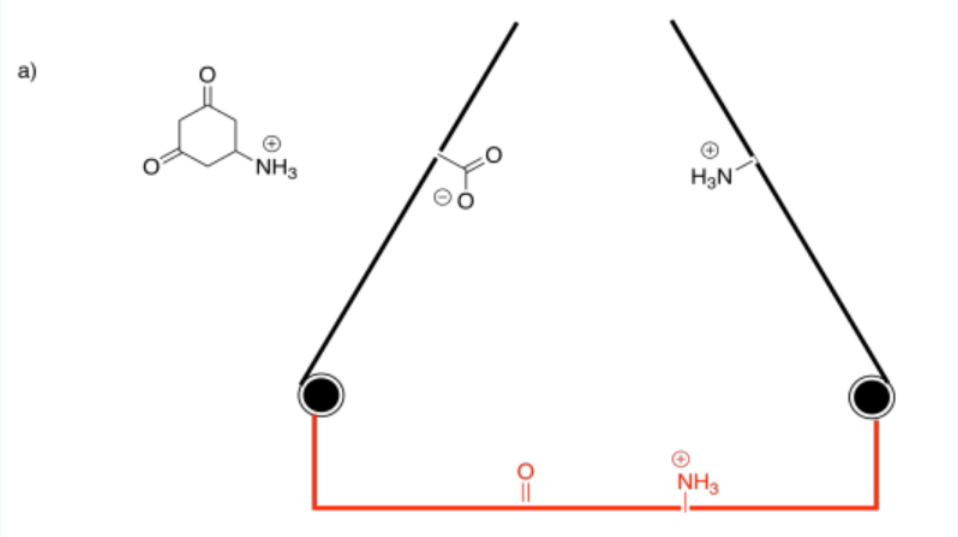
Things may be more subtle, still. Sometimes, binding a molecule causes a change in the shape of the enzyme. Enzymes are very large molecules. They are composed of long chains of amino acids; you can pictures those chains sliding past each other to make room for a guest molecule or to bind it more tightly. Frequently, enzymes are composed of more than one protein, stuck together, adding to the complexity of their shape. As a result, when a molecule binds to an enzyme, various changes might occur to trigger a reaction.

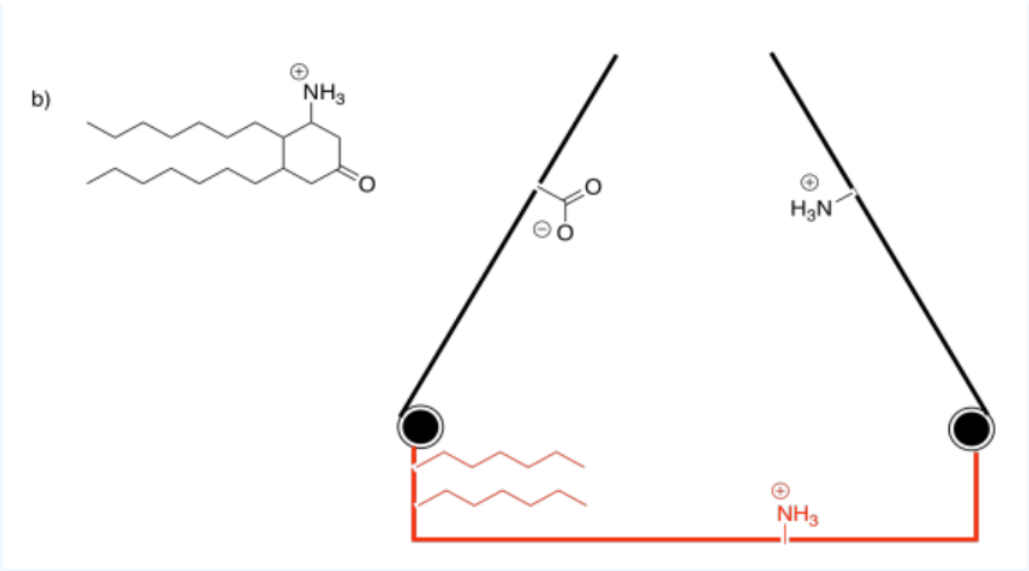


These changes in shape of the enzyme occur via conformational changes in the protein. Simple rotations around bonds cause changes in shapes of even small molecules. In large molecules such as proteins, these changes in shape can be dramatic.

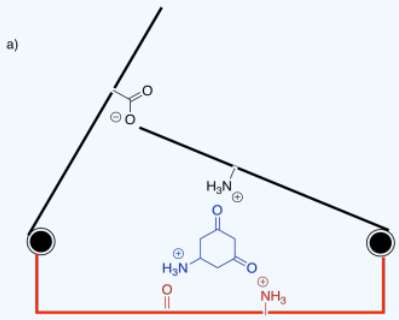
? Exercise 6.2.3

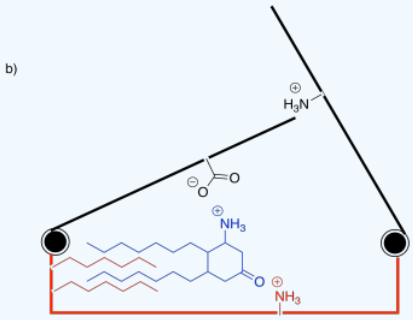
Binding the substrate in the active site (red) will cause one of the gates to close. Which one?





Answer





6.3: Strategies in Enzyme Catalysis

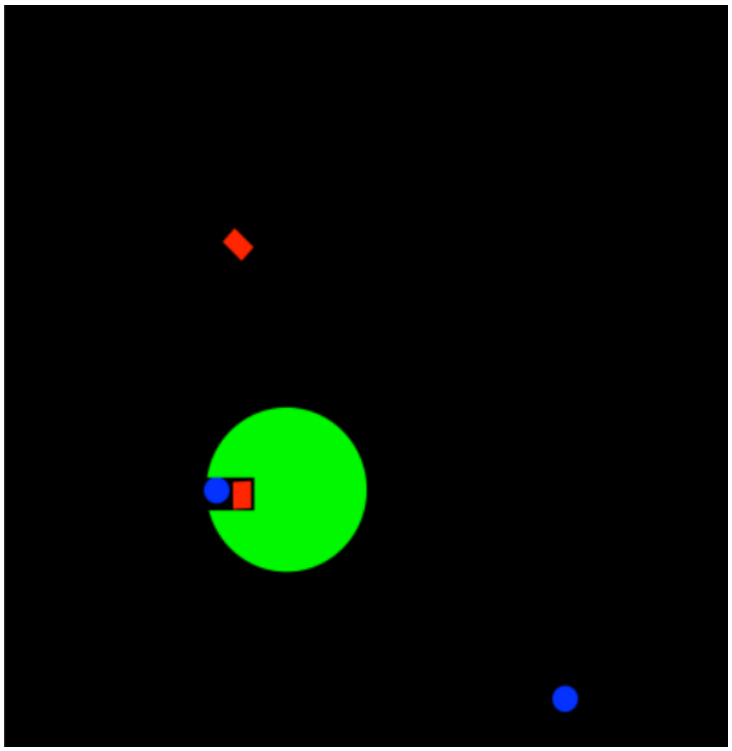
Once a substrate has been bound, it is the enzyme's job to quickly transform the substrate into product. The enzyme does so by carrying the substrate over a catalytic pathway. In a catalytic pathway, the reaction takes a different course than it would on its own. Sometimes the catalytic pathway is longer, involving additional steps, but because the energetic terrain is easier to traverse than in the un-catalyzed process, the catalytic reaction actually takes much less time.

Enzymes have a range of structures and reaction properties, so there are a wide number of different reactions they can catalyze. Nevertheless, there are a few common strategies displayed in catalytic reactions that are useful to know.

Approximation

When we make an approximation, we are getting close to the answer. If someone asks us what time it is, and it is 3:02 pm, we probably tell them it's about three o'clock. That's close enough.

In enzyme catalysis, approximation means getting things close to each other. If we have a substrate that is going to react with something, the enzyme can bind the substrate in such a way as to get the substrate in close proximity to the reactant. Sometimes, but not always, that might mean binding two substrates, so that they can more easily react with each other. If you want to meet your friend, it's a much better idea to say, let's meet at Cafe Santropol at 7:00, rather than wander the streets of Montreal, along with four million other people, hoping to bump into your friend. The reactant and substrate are much more likely to encounter each other in the protected confines of the enzyme than they are floating around in the wilderness of the cell.



- In approximation, two substrates are held close together within the enzyme
- This proximity makes them react together more easily

Sometimes, this idea can be a little more subtle. Imagine that the reactant is the enzyme itself, so that just by binding the single substrate, the reaction is already much more likely to occur. The substrate may be held in such a way that it is already in close proximity to amino acid side chains that will work on it and transform it into a new molecule.

- In approximation, the substrate is held in position so that subsequent reaction is much more likely

Approximation is really an entropy factor. By binding the substrate, we can limit its degrees of freedom, restricting its location or even its orientation so that there is no way the reactant can miss its intended target.

Of course, the substrates still have to find the active site of the enzyme. Sometimes, that task is aided by sticky surfaces on the enzyme; there can be groups on the surface of the enzyme that can interact with substrates, so that the substrates are less likely to

drift away after a random collision with the enzyme. With its movement thus restricted, the substrate is more likely to move into the active site than drift off through the cell once more.

Although we are discussing enzymes in the cell, other kinds of catalysis make use of approximation as well. For example, transition metal catalysis often makes use of solid chunks of metal to catalyze the reactions of gaseous vapors. The surface of the metal gives the gas-phase molecules a place to bind, giving them a place to gather, rather than wandering around in three dimensions in the gas phase. Once they are together in one place, they are more likely to react with each other or with additional species on the surface of the metal.

Acid-Base Catalysis

Acid-base catalysis is a very common phenomenon. So many reactions involve the addition or removal of protons, especially the carbonyl reactions that are so prevalent in biochemical pathways, that proton donors and acceptors become key players. Acidic and basic side chains of the amino acids in the protein naturally fill these roles.

? Exercise 6.3.1

Which amino acids are thought of as having "acidic" side chains?

Answer

Aspartic acid (abbreviations Asp or D) and glutamic acid (abbreviations Glu or E).

? Exercise 6.3.2

Which amino acids are thought of as having "basic" side chains?

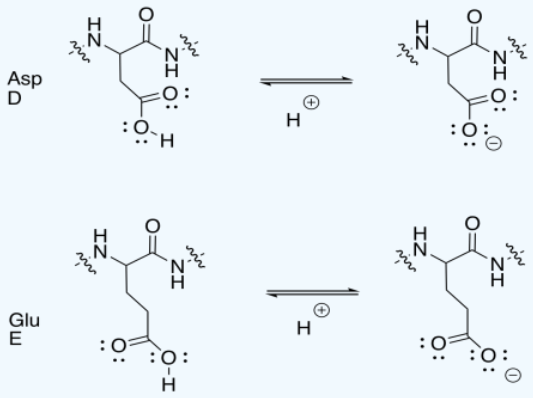
Answer

Histidine (abbreviations His or H), lysine (abbreviations Lys or K) and arginine (abbreviations Arg or R).

? Exercise 6.3.3

Draw the acidic amino acid side chains in both their acidic and conjugate basic forms.

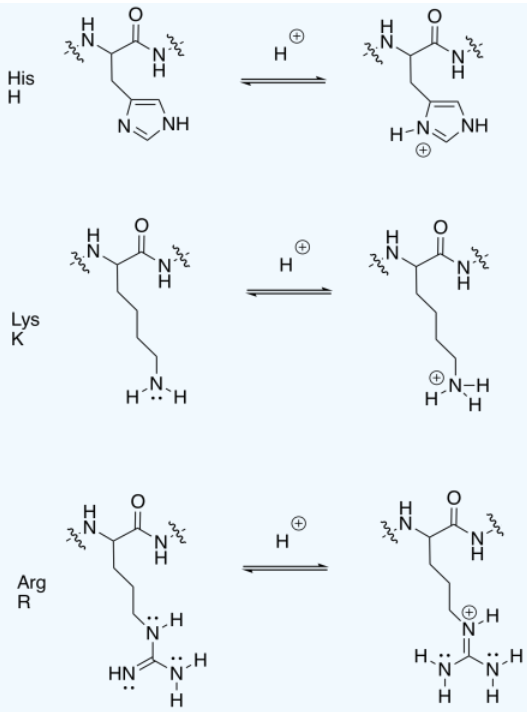
Answer



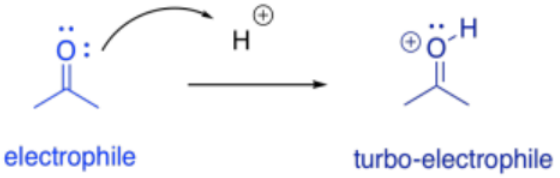
? Exercise 6.3.4

Draw the basic amino acid side chains in both their basic and conjugate acidic forms.

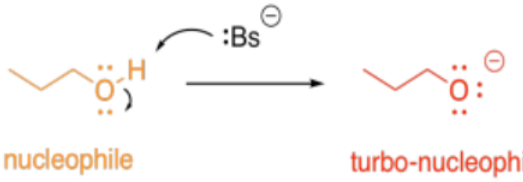
Answer



Acid-base catalysis can provide mechanistic advantages by rapidly enhancing the electrophilicity of a molecule. Any carbonyl compound is electrophilic, but if it gets protonated, the overall positive charge makes the carbonyl even more electrophilic.



Alternatively, acid-base catalysis might increase the nucleophilicity of a molecule. Any alcohol is nucleophilic, because it has lone pairs. However, if its proton is removed, it becomes even more nucleophilic, because of the overall negative charge.

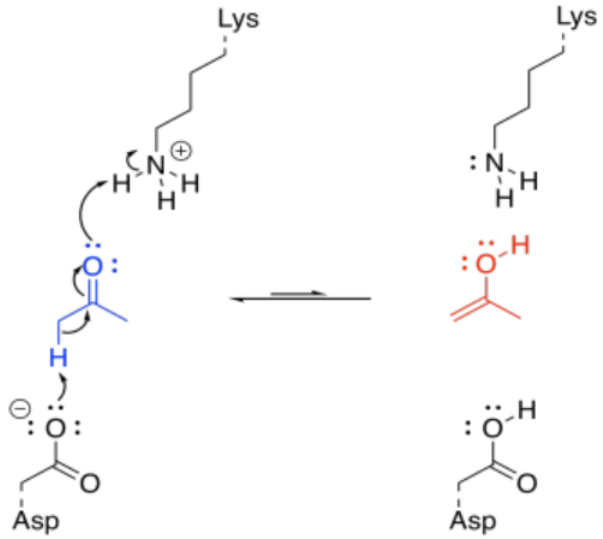


So, in the most straightforward case, adding a proton might accelerate a reaction involving an electrophile. Removing a proton might accelerate a reaction involving a nucleophile.

- Acid/base catalysis involves rapid proton shuttling
- Acidic side chains can activate electrophiles
- Basic side chains can activate nucleophiles

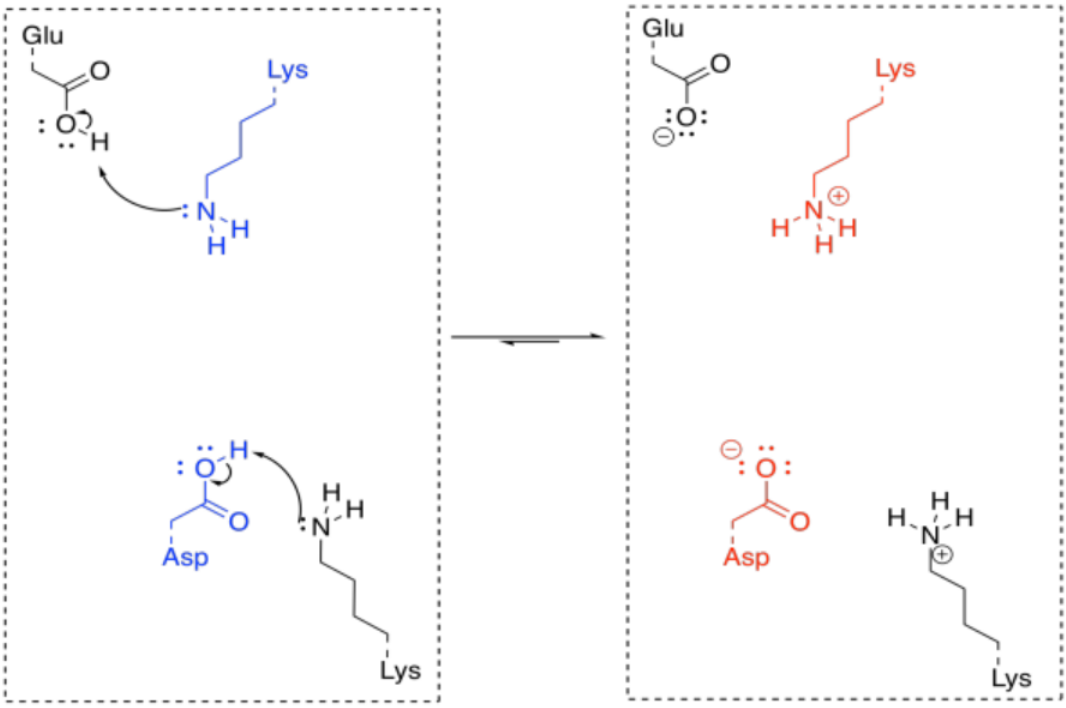
There are other variations on this approach. For example, consider a keto-enol tautomerism. We think of ketones classically as electrophiles, but their enol isomer is easily accessible in general, and the enol form is an excellent nucleophile. As part of a series of reaction, rapid conversion of a ketone into an enol might be a key step.

That's really a couple of different steps; you have to add a proton to the carbonyl oxygen, and then you have to take a proton away from the alpha position. You could do it the other way around, but it would still be two steps. Fortunately, enzymes have lots of acidic and basic sites, so there may be sources and sinks of protons that are readily available for a molecule bound in an enzyme. Furthermore, the molecule may be bound in such a way that these proton transfer steps are essentially simultaneous.



Under normal circumstances, this looks like three different molecules reacting together; that's basically impossible under normal circumstances. But if the lysine and the aspartate are part of the same enzyme, that reduces the problem to an interaction between two molecules; that happens all the time. If the ketone is already bound in the enzyme, the difficulty is reduced even further.

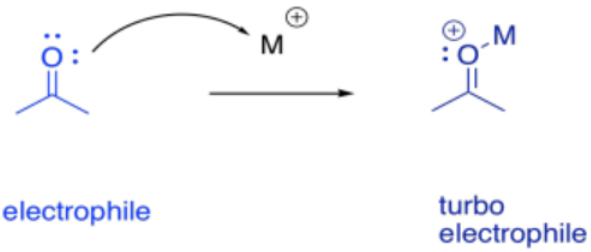
In order to make the reaction catalytic, the enzyme has to be regenerated. Again, that isn't a problem for enzymes, because of the number of acidic and basic sites available. A key site that is missing a crucial proton can pick one up from another amino acid side chain sitting nearby. Protonation states get reshuffled pretty quickly, and soon the enzyme is ready to go again.



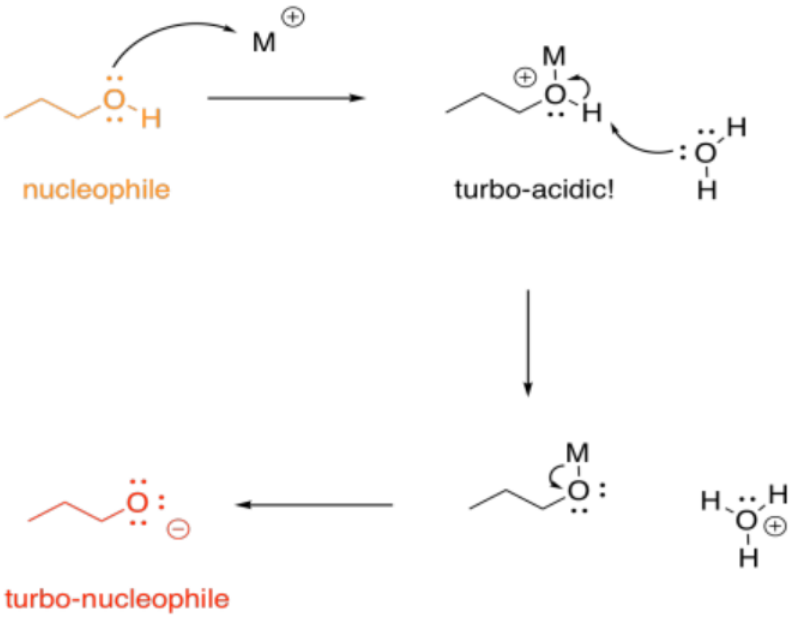
Acid-Base Catalysis: Metal Ion Catalysis

Metal ion catalysis can often be thought of as a special case of acid-base catalysis. With metal ions, we get Lewis acid catalysis. Lewis acid catalysis can accelerate reactions in a couple of different ways, in close analogy with general acid/base catalysis.

It sometimes helps to think of a metal as a great, big proton. That's an oversimplification, as we'll see in a moment. Nevertheless, it can be useful to keep the analogy in mind. When a compound binds to a metal ion, the effect can be similar to binding a proton. The compound has just donated a pair of electrons elsewhere (to the metal ion or to the proton), and so the compound suddenly looks electron-deficitient. It has enhanced electrophilicity.



On the other hand, we don't usually think of protonation as causing increased basicity; that would be completely backwards. With metals, though, that can happen, indirectly. If an alcohol, for example, donates a lone pair to a metal, the oxygen becomes positively charged. It becomes much more acidic. Suddenly, the alcohol can be deprotonated by a very, very weak base, such as water. That leads to formation of an alkoxide ion, which is much more nucleophilic than the original alcohol. Water would really never take a proton from an alcohol, but it can do it once the oxygen has a positive charge.

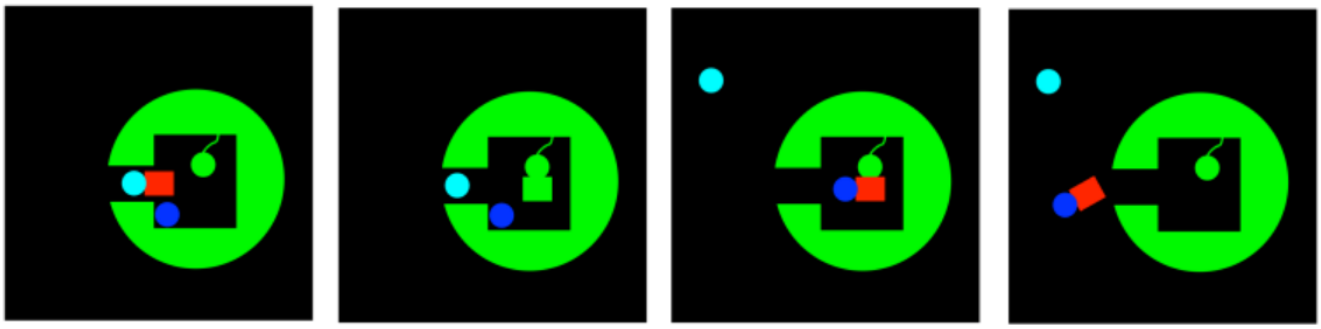


Metal ions can play a number of other roles in catalysis, but that's enough to get an idea of just some of the ways in which they might be useful. To learn more, we would have to explore more transition metal reactivity, including the ability of metals to donate and accept individual electrons.

Group Transfer

Group transfer, also called covalent catalysis, has something in common with approximation. It limits the degrees of freedom involved in a key step of the pathway to product. Rather than just binding two substrates near each other in the active site, or holding a substrate in a specific orientation, group transfer involves a reaction between the substrate and the enzyme such that the substrate becomes attached to the enzyme. It is attached via a covalent bond.

In a sense, like approximation, this mechanism limits the problem of two substrates bumping into each other -- an unlikely prospect in the roliing sea of the cell -- to two things coming together within the limited space of the active site. Of course, any time a molecule wanders into an active site, there is a chance it could wander off again; but that isn't true if you fasten it down. That's what group transfer does. It fastens one substrate to the enzyme, so that a second substrate is more likely to react with it.



That's not all. Sometimes when the substrate, or a group forming the crucial part of the substrate, is transferred to a side chain on the enzyme, it becomes modified in such a way as to become more reactive. For example, an aldehyde may be electrophilic to begin with. However, if it becomes attached to a lysine residue, it may be transformed into an imine. Now, an imine may seem less electrophilic than an aldehyde, because nitrogen is less electronegative than oxygen. However that same feature also makes nitrogen much more basic than oxygen. As a result, imines are very likely to rest in a protonated state; aldehydes are much less likely to be protonated. That protonated iminium ion, of course, is much more electrophilic than an aldehyde, because the iminium has a full positive charge.

Group transfer may even result in complete reversal of reactivity in the substrate. Again, in the case in which an aldehyde becomes tethered to a lysine residue, the aldehyde may be transformed into an enamine. The difference between forming an enamine and an imine is just the difference in which of the protons is removed. In an enzyme, that decision is easily settled by the positioning of the amino acid side chain that removes the proton. In one enzyme, this side chain removes the nearest proton, leading to an imine. In another enzyme, another side chain, situated in a different place, removes the nearest proton, leading to an enamine.

Of course, the consequence of forming an enamine rather than an imine is much like having an enolate or enol rather than an aldehyde. The former is nucleophilic, even though the latter is electrophilic. So, group transfer can even flip something from an electrophile into a nucleophile.

A very different example that is also pretty common involves a set of amino acid side chains called "the catalytic triad". These three groups -- aspartate, histidine, and serine -- are frequently observed in group transfer catalysis. With the catalytic triad, it is the serine that acts as the nucleophile, rather than a lysine. As a result, it is the serine that becomes bonded to the substrate. The role of the aspartate and histidine is to act as a proton relay, helping to activate the serine so that it becomes a more effective nucleophile.

Transition State Stabilization

We think of enzymes as being perfectly suited to bind a particular substrate, but that may not be the case at all. If you think about it, an enzyme that perfectly matches its substrate would pick up its substrate, snap it into place and... that would be all. Nothing else would ever happen. The substrate would sit there forever. Why mess with perfection?

Instead, it is thought that, at least in some cases, the enzyme is ideally suited to bind something a little further down the path. The idea is that the substrate will change shape as it goes through the reaction, and if the enzyme actually better fits the shape of something else to come, it will exert pressure on the substrate to go ahead and react. Once the substrate gets to the right shape, it will be rewarded with perfect binding.

In the extreme case, we might think about the enzyme being a perfect match for the product. That way, the enzyme could coax the reaction along, and the strong binding interaction between enzyme and product would pull the reaction through its equilibrium all the way to the product side.

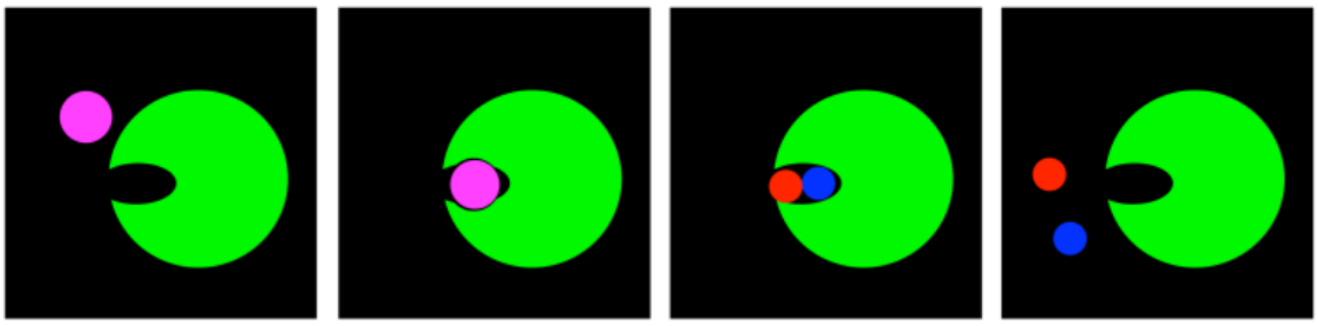
Well, if you think about it, that wouldn't work very well, either. Once the product forms, it would bind perfectly with the enzyme, which would never let it go. What good is it if the product is made but never gets released into the cell? The whole point of enzymatic catalysis is to quickly make things that the cell desperately needs; without these things, the cell will die.

But there is one kind of structure that could bind the enzyme perfectly, and we wouldn't have to worry about it getting stuck. It's a transition state. A transition state is an inherently unnatural structure; the molecule can't stay that way for long. It's just passing through on its way from one structure to another, and the transition state is the awkward, gangly phase in between, that horrid thing we glimpse in the dark when it thinks we aren't looking.

So if we stabilize that thing, then the substrate is pushed onward, a little further, and just when it reaches the perfect point, it finds it's gone too far. It must collapse. It's like Wile E. Coyote sublimely achieving his goal just as he passes over the cliff's edge.

Transition State Stabilization: Distortion

If transition state stabilization is the carrot, then distortion is the stick. Transition state stabilization coaxes the substrate further on; distortion pushes and prods until the substrate can take it no longer.



In distortion, the substrate finds itself in a binding site in which its shape is not quite right. Its geometry is subtly squeezed. The substrate itself is destabilized, whereas forming the product, or the transition state leading to the product, actually relieves that strain.

A good example is an atom that is supposed to be trigonal planar, but finds itself sitting in a place where it can't quite lay flat. Instead, it finds intermolecular interactions that are pushing it into another shape; maybe tetrahedral would be a better fit.

If a tetrahedral intermediate lies ahead, then by the time we reach the transition state, the geometry of that atom may actually look more like a tetrahedron than a trigonal plane. As a result, those intermolecular forces are distorting the otherwise stable structure of the substrate and bending towards the transition state.

6.4: Enzyme Inhibition

Compounds other than substrates can play important roles in interacting with enzymes. There are compounds that can either activate or inhibit enzymes, speeding up their activity or slowing them down, respectively. These compounds can be very important in naturally regulating enzymes in the cell. We can also exploit these compounds as medicines, treating illness by tuning the activity of enzymes until the body is back to normal.

Knowing for sure whether a compound is going to turn an enzyme on or off can get pretty complicated, so we are just going to start with a couple of simple ways in which enzymes can be turned off.

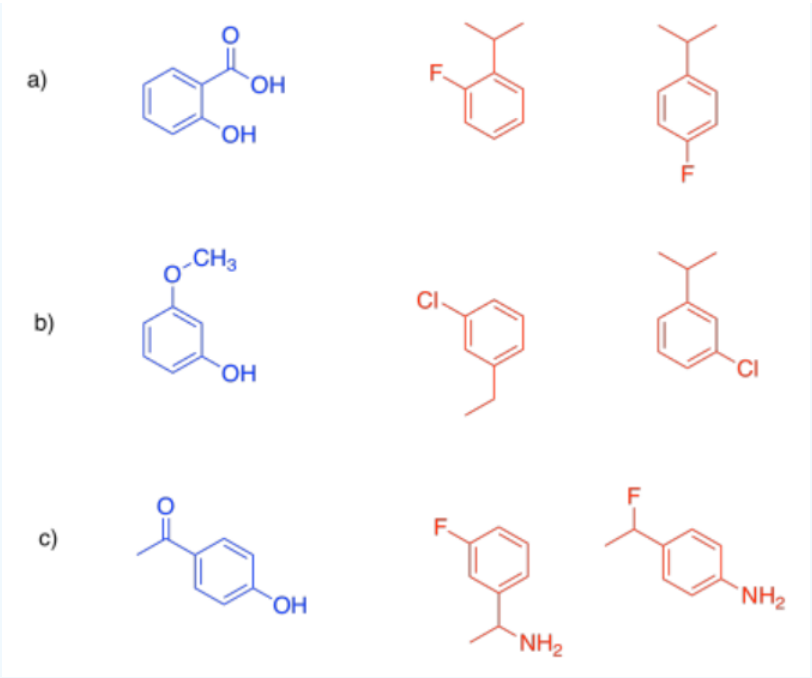
Reversible Inhibitors

There are several different ways in which compounds can inhibit enzymes. The simplest way is simply by taking up space in the active site. If something is blocking the active site, the true substrate can't get in, so the enzyme can't do its job.

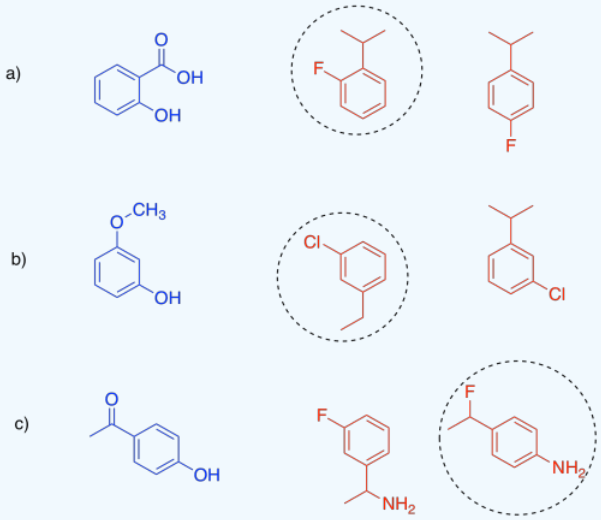
To block the active site, the inhibitor must also be a pretty good fit. It must have a similar shape, or in some way be able to interact with amino acid residues in the active site. That means it might not have a shape that is obviously familiar, but must be capable of intermolecular interactions that are similar to those of the substrate in the active site.

? Exercise 6.4.1

If the substrate is the compound in blue, indicate which of the red compounds would be a better competitive inhibitor.



Answer

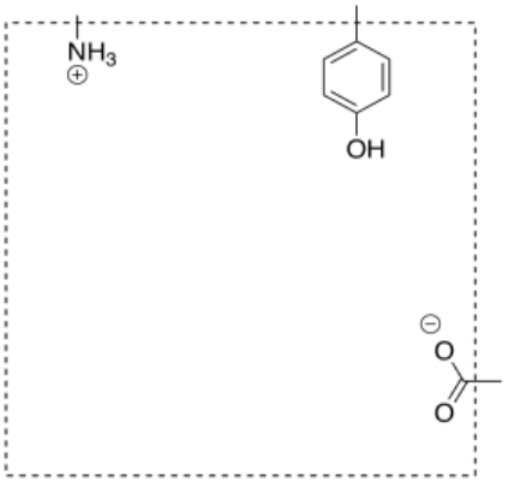


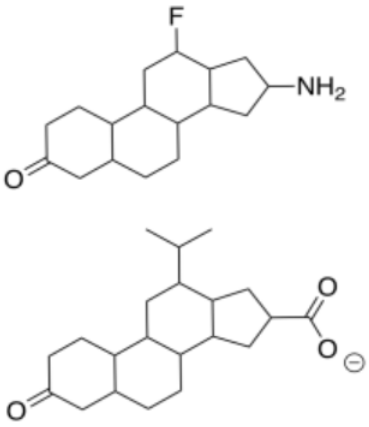
In drug design, the part of the enzyme that binds to the substrate is called the ***pharmacophore***. That's the feature that we will try to exploit in designing an inhibitor. The inhibitor will be designed so that it can also bind to the pharmacophore, either by fitting in terms of shape or by the intermolecular attractions it can supply.

? Exercise 6.4.2

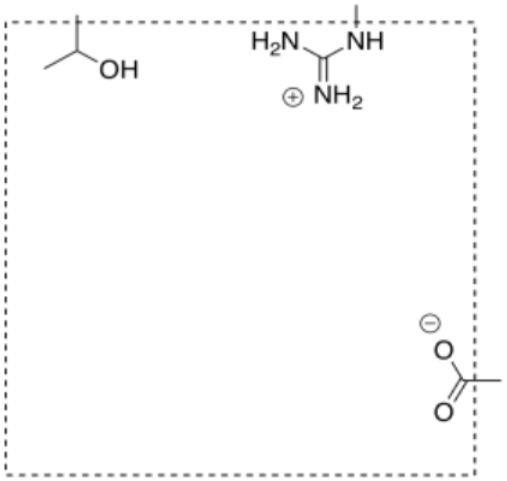
Select the compound that would more efficiently bind to the pharmacophore.

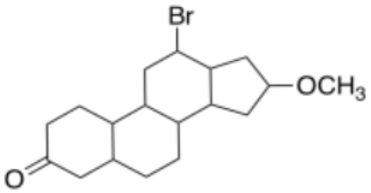
a)

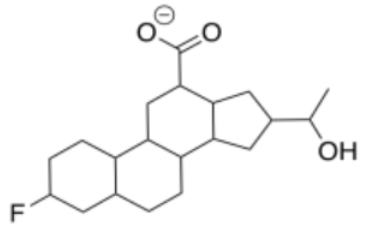


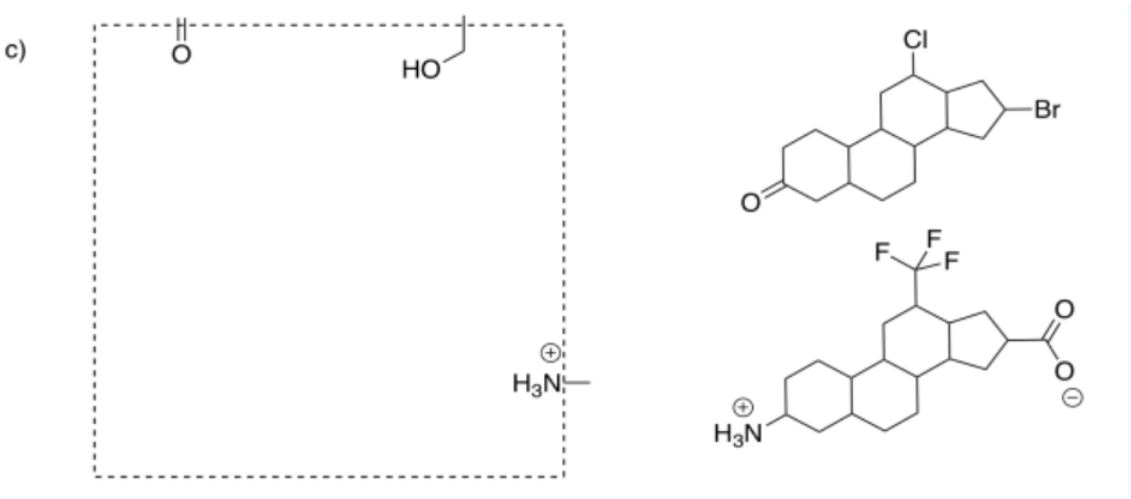


b)









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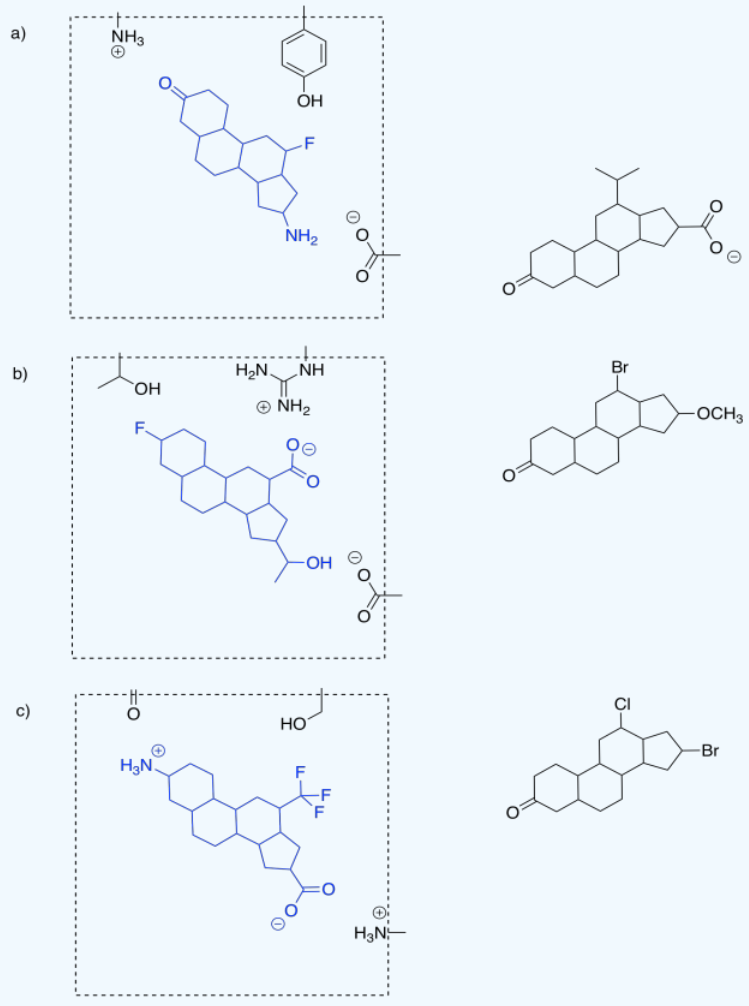
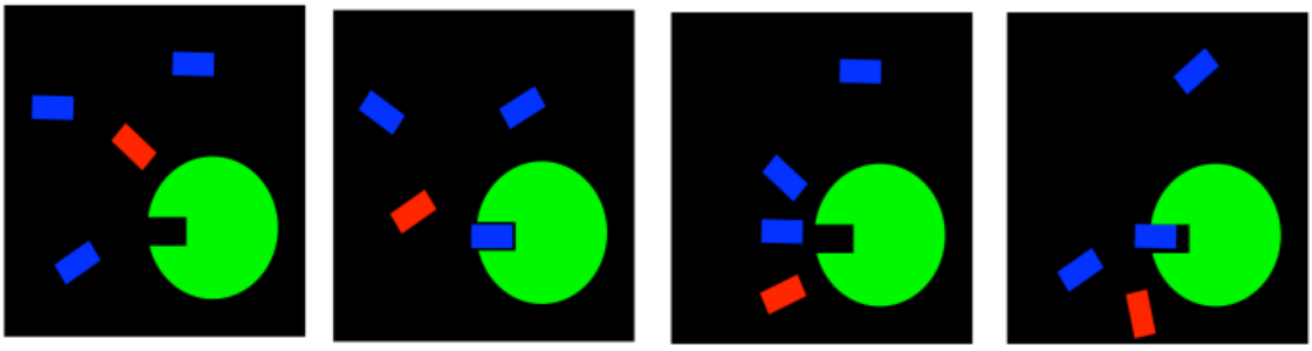


Most of the time, if we just want to moderate the effects of an over-active enzyme, we use what is called a reversible inhibitor. We don't want to block the active site of the enzyme permanently; we just want to slow things down, to get things back to normal. After all, the enzyme probably does something useful for us, and we may need it later. So, we use an inhibitor that will slow it down for a while, but whose effects can be reversed.



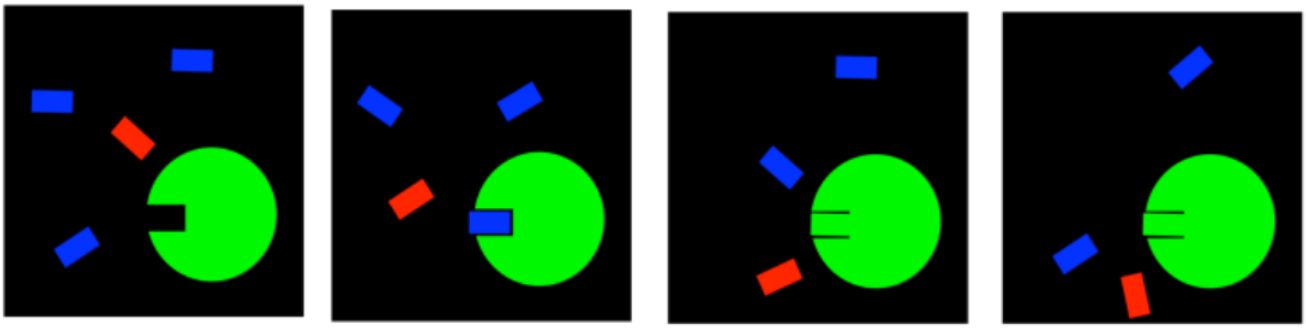
A competitive inhibitor simply competes with the substrate for the active site. Both the substrate and the inhibitor occupy the same niche, but they can't both sit there at the same time. In general, there is some equilibrium between bound and unbound states. That means that after a while, one molecule wanders back out of the enzyme, and the other one has a chance to enter.

We have mechanisms in the cell that scrub out molecules that shouldn't be there, so eventually, that's what happens to the inhibitor. While the concentration of inhibitor remains high, it can effective compete for the active site of the enzyme. As more and more of it gets removed, the enzyme gets back to its normal levels of activity. Hopefully, by that point, the disease state has eased off.

Irreversible inhibitors

Maybe a disease state is serious enough that we want to shut an enzyme down completely. That might be the case if we are fighting a bacterial or fungal infection, for example; we don't care whether the fungus needs that enzyme later. Causing big problems for the fungus is kind of the whole point at this stage.

In a case like this, we might use what is called an irreversible inhibitor. Once it goes into the enzyme, it never comes back out. It forms a permanent bond, hopefully in a place that blocks the active site or some other important feature of the enzyme.



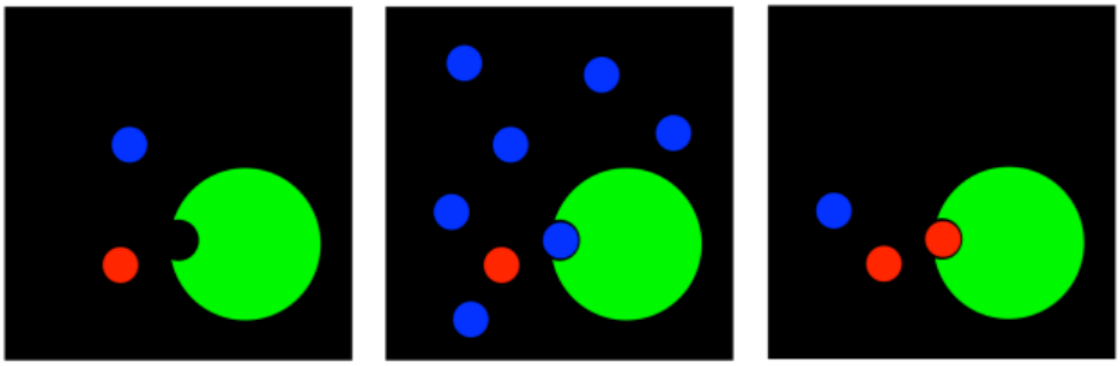
Attribution

- Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

6.5: Types of Reversible Inhibitors

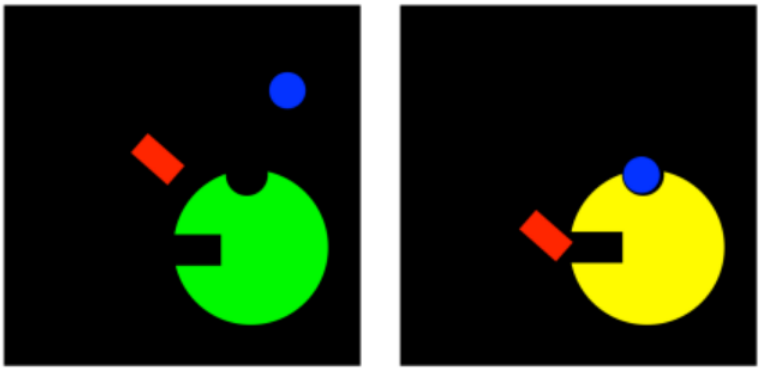
Reversible inhibitors are extremely important in regulating enzyme activity. Unlike irreversible inhibitors, they do no shut down an enzyme completely by permanently disabling it. They are much more subtle, just slowing it down temporarily. There are a number of different ways that the inhibitor could do that, however, and so we will take a look at those possibilities here.

The simplest idea is that an inhibitor can bind in the active site of the enzyme. If the inhibitor is already bound there, the substrate cannot. The inhibitor is in the way. This is called ***competitive inhibition***.

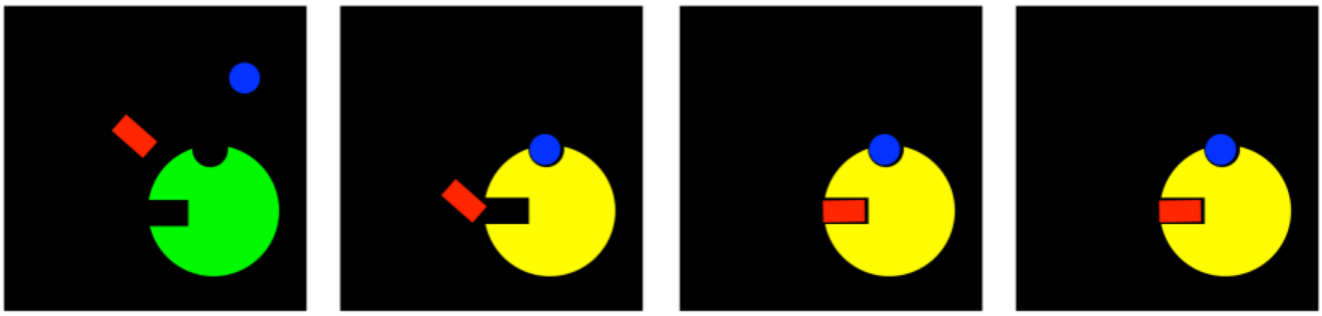


This case is a true competition. If there are more inhibitor molecules than substrate molecules, the inhibitors will probably win out, blocking the substrate from entering the active site. But if there are more substrate molecules than inhibitor molecules, then chances are the substrate will be able to bind, and the subsequent reaction will proceed.

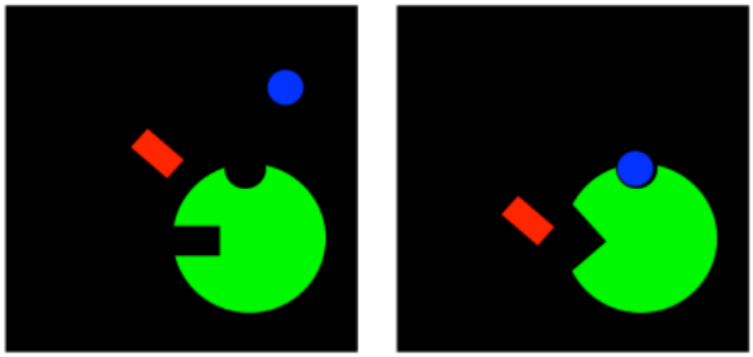
There are a number of cases, however, in which the inhibitor does not bind at the active site at all. It binds someplaces else on the enzyme, at a place called an allosteric site. When the inhibitor is bound at the allosteric site, it somehow interferes with the function of the enzyme. An inhibitor that binds at a site other than the active site is generally called an ***allosteric inhibitor***.



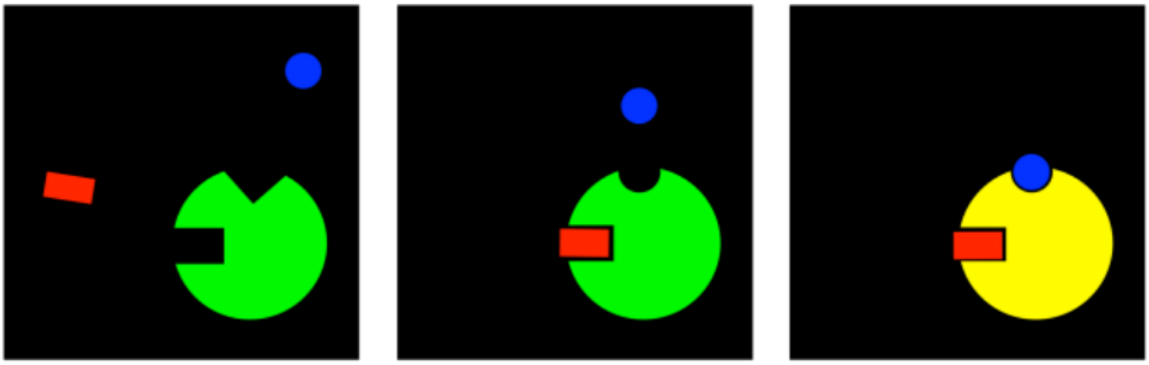
Allosteric inhibitors can work in a few different ways. In perhaps the simplest case, when the allosteric inhibitor binds to the enzyme, it causes some sort of conformational change that prevents the enzyme from carrying out reactions. It doesn't interfere with substrate binding, so the substrate can still complex with the enzyme, but nothing will happen after that. This type of inhibition is called ***noncompetitive inhibition***, or sometimes ***pure noncompetitive inhibition***, for the simple reason that the inhibitor is not interfering directly with the substrate; it's temporarily disabling the enzyme in some other way.



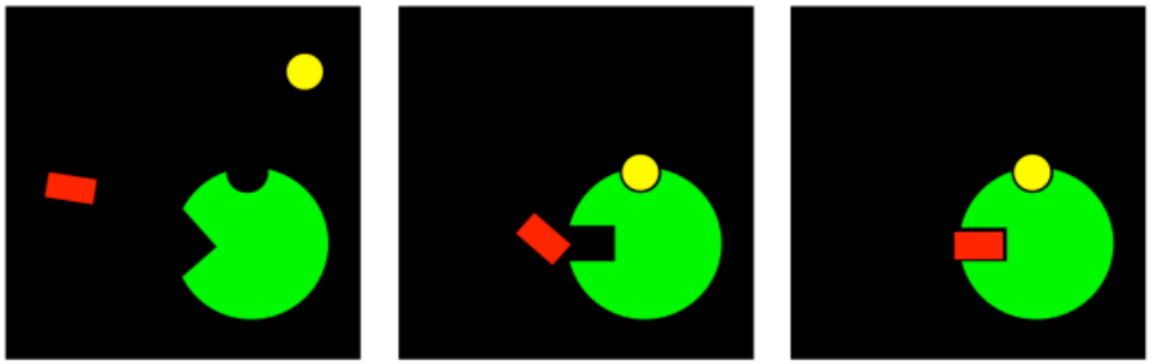
Noncompetitive inhibition interferes with the machinery of the enzymatic reaction, but leaves substrate binding alone. But if allosteric inhibitors cause some sort of conformational change in the enzyme, then it's easy to imagine they could somehow mess up the binding site. As a result, they might interfere with substrate binding, even without being in direct competition with the substrate. This mode is called ***mixed noncompetitive inhibition***. Although the inhibitor is not directly competing for the same binding site as the substrate, it ends up preventing the substrate from binding anyway.



Well, that game can go both ways. If an inhibitor can change the binding site of the substrate, maybe the substrate can change the binding site of the inhibitor. In ***uncompetitive inhibition***, the inhibitor is not able to bind to the free enzyme. However, when the substrate binds, it induces a conformational change in the allosteric site, allowing the inhibitor to bind. If the inhibitor binds, it interferes with the machinery of the enzyme, so the enzyme can't do its job, even though the substrate is bound.



There is one more case that is a complemetary idea; it isn't about inhibition at all. If a compound can bind at an allosteric site, changing the conformation of the active site so that a substrate can no longer bind, then maybe the reverse is true. Maybe a compound can bind at an allosteric site, allowing a substrate to bind that previously could not.



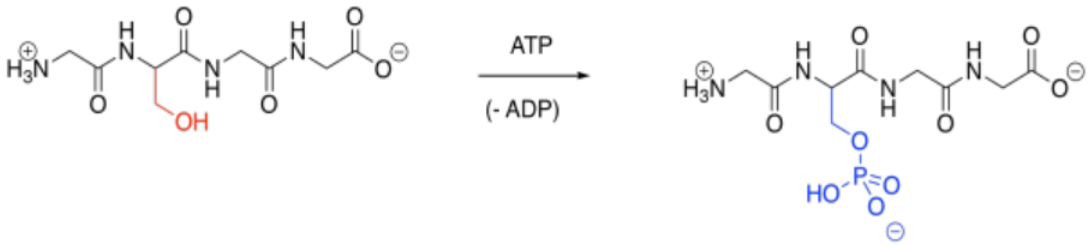
Instead of inhibiting the enzyme, this compound would be activating it. It would make binding possible, and suddenly the enzyme could do ts job. This compound is an ***allosteric activator***. As in inhibition, there may be different modes through which the allosteric activator could turn the enzyme on. The important thing is to know that in order to regulate an enzyme fully, there nood to be both on and off switches. Activators turn on enzymes that are waiting to be used. Inhibitors turn off enzymes that we don't need right now.

6.6: Covalent Modification

Reversible inhibitors are extremely important in regulating enzyme activity. They can turn enzymes on or off, acting as activators or inhibitors, respectively. In addition, enzymes can be regulated via ***covalent modification*** or ***post-translational modification***. That means that, after the enzyme has been assembled in the cell, its structure can be modified further by adding special groups to specific locations. In the case of regulation, these groups are added reversibly. Even though the group is added covalently -- it is bonded to the protein -- a reaction path exists for the removal of the group again.

There are three examples of these modifications that we will look at here. In each case, the behaviour of the protein is modified because of changes in the intermolecular attractions within the protein (or between the protein and another molecule).

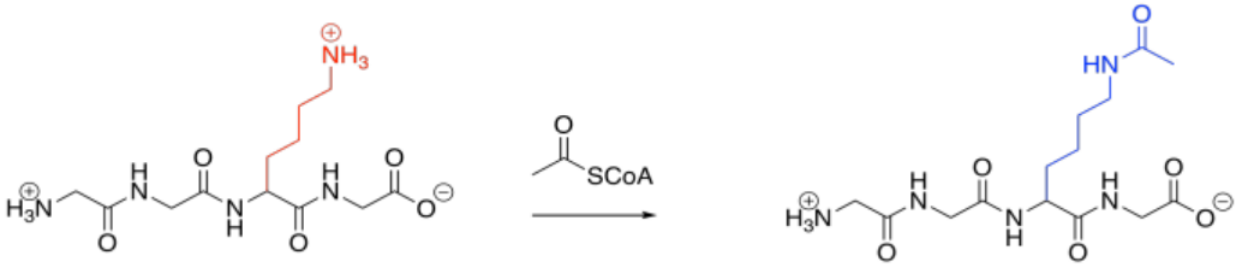
Phosphorylation is a very common modification. In phosphorylation, a phosphate group is attached to an amino acid side chain. The most commonly phosphorylated side chain is a serine. Tyrosine is often phosphorylated, too. Those sites are preferred because of the strong P-O bond formed during the reaction.



Phosphorylation is typically carried out under the control of another enzyme called a ***kinase***. That's right, one enzyme will bind another, tying a phosphate group onto it before releasing it again. A phosphate group can be removed again via another enzyme called a ***phosphatase***. The fact that these modifications are carried out by specific enzymes helps to explain their specificity. A particular kinase may bind to its target protein in a well-defined position, phosphorylating it only at that position (although some kinases may be less selective).

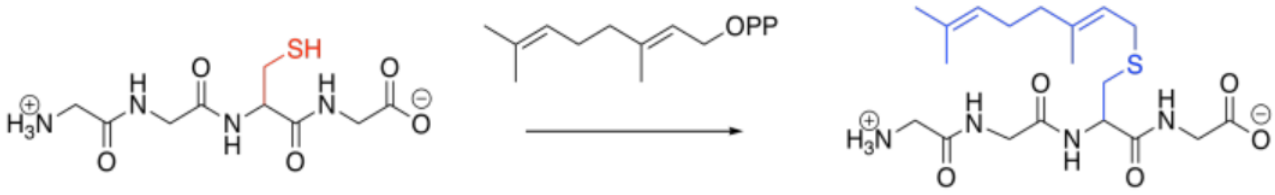
Of course, the key result of phosphorylation is that a neutral serine is suddenly masked by an anionic phosphate group. That negative charge alters intermlecular attractions quite starkly, because suddenly attractive and repulsive forces pop up where there were none before.

Acetylation is also quite common. Acetylation is the addition of an acetyl or ethanoyl group; usually, the group is added to a lysine. The forward reaction is driven by the strong amide bond that results.

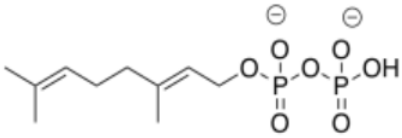


Acetylation is carried out by an **acetylase** or an **acyltransferase**. Like phosphatases, these are enzymes that bind their target proteins in order to modify their structures. Because lysines are normally positively charged at biological pH, acetylation results in the sudden disappearance of charged species because the are masked with neutral acyl groups. Intermolecular attractions can be dramatically affected as a result.

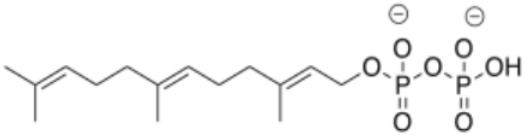
Prenylation is the addition of a hydrocarbon side chain, most often to a cysteine side chain. Sulfur is a particularly good nucleophile for carbon chains of this sort, enhancing selectivity for cysteine. As in the other cases, however, the reaction is carried out under the control of an enzyme (a ***geranyltrasnferase***, for example, or a ***farnesyltransferase***), and so other side chains might be targeted, instead.



Those enzyme types highlight two common groups that are added in these cases: the geranyl group and the related farnesyl group. These groups are structurally related, and are both in the terpenoid family of natural products. Terpenes are based on five-carbon building blocks, which you can easily trace out in the geranyl and farnesyl structures.



geranyl pyrophosphate
geranylOPP



farnesyl pyrophosphate
farnesylOPP

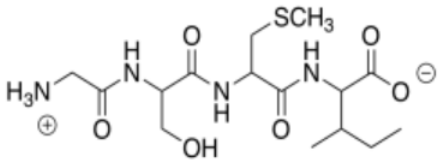
Changes in intermolecular attractions are more subtle in these cases, because prenylation is not accompanied by a full change in the charge of a side chain as it was in the other cases. Instead, addition of this group enhances the ***hydrophobicity*** of that part of the protein. A hydrophobic group is one that is completely incapable of interacting with water molecules, lacking ions, dipoles, or hydrogen bonding sites. As a result, it tends to get displaced or pushed out of the way by surrounding water molecules. That "pushing away" by water has the net effect of piling hydrophobic groups together.

What we tend to get, then, is hydrophobic groups sticking to each other, even though their attraction for each other (London forces) is actually pretty weak. Of course, because London forces are relatively weak, the amount of London forces, or the relative area of a molecule that can interact with another via London forces, becomes very important. Geranyl and farnesyl groups are moderately long, and so they exert significant amounts of London forces. As a result, two prenylated parts of a protein might stick together, or one newly prenylated part might huddle together with some hydrophobic side chains, such as valines, leucines, and isoleucines. Also, prenylation sometimes causes a protein that was formerly more water-soluble to migrate over to the cell membrane, where it could interact with the lipid bilayer. So, prenylation, despite causing seemingly modest changes in intermolecular attractions, can elicit dramatic changes in behaviour in the protein.

? Exercise 6.6.1

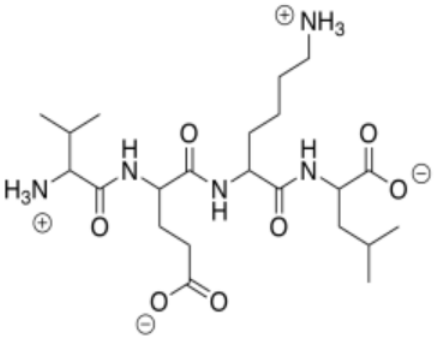
Show the products of the following modifications.

a)



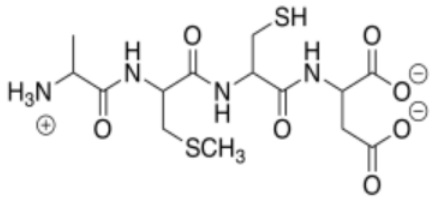
ATP →

b)



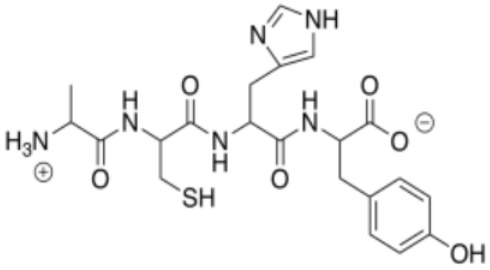
AcSCoA →

c)



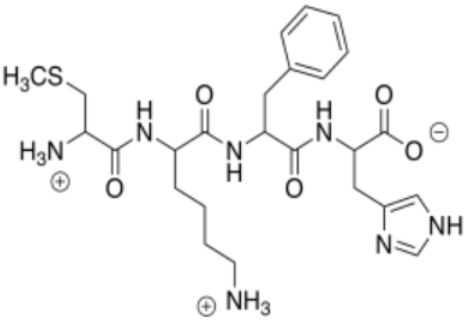
geranylOPP →

d)



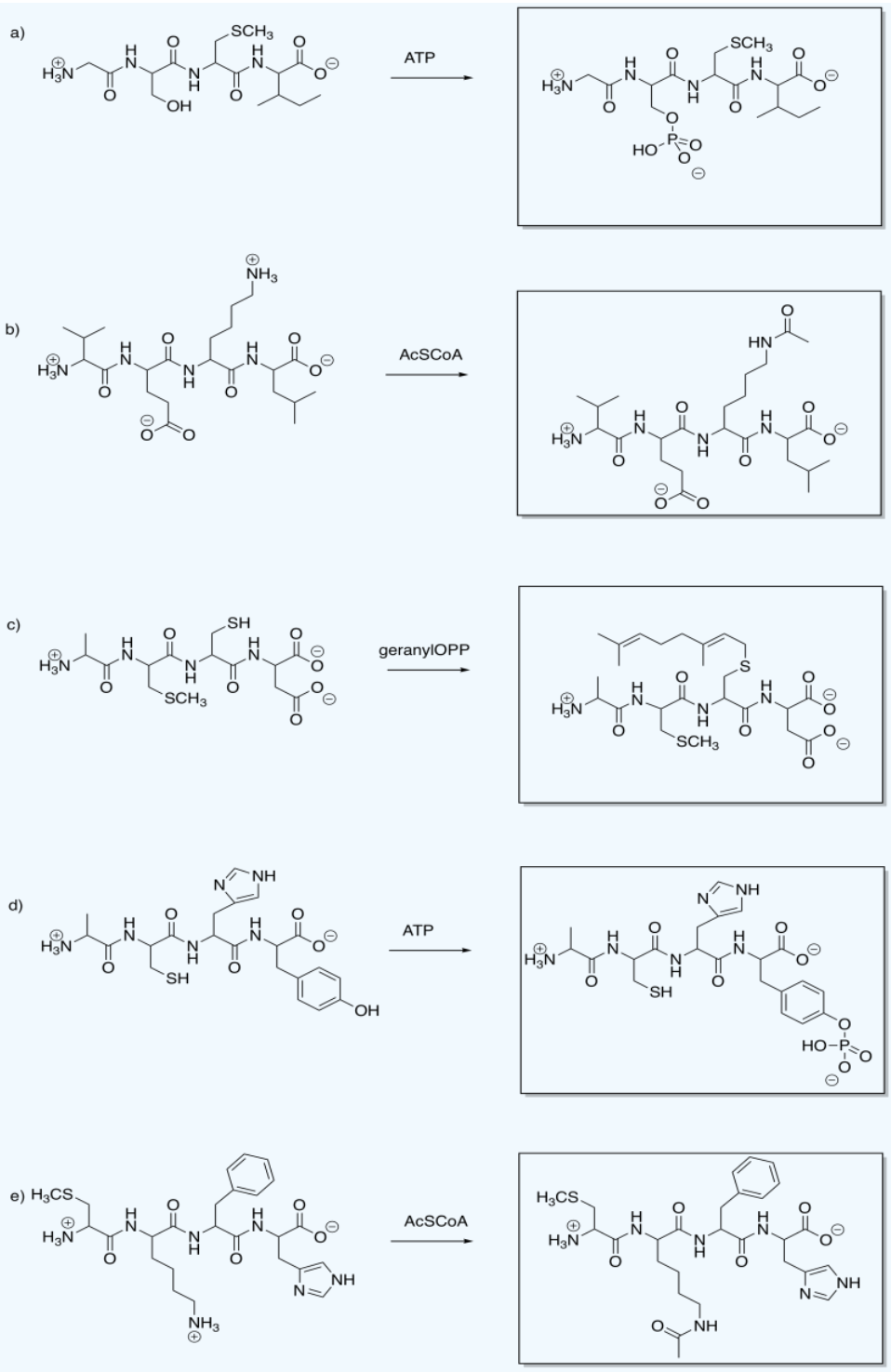
ATP →

e) H_3CS



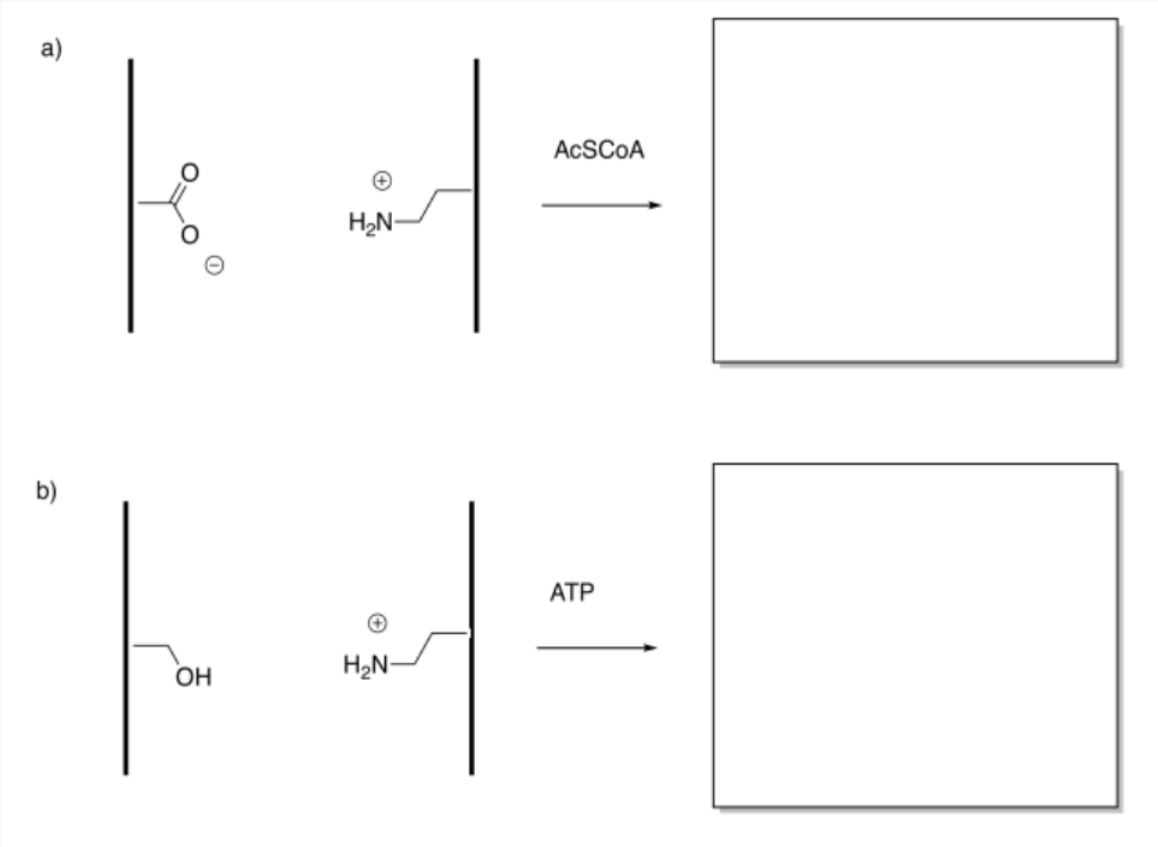
AcSCoA →

Answer

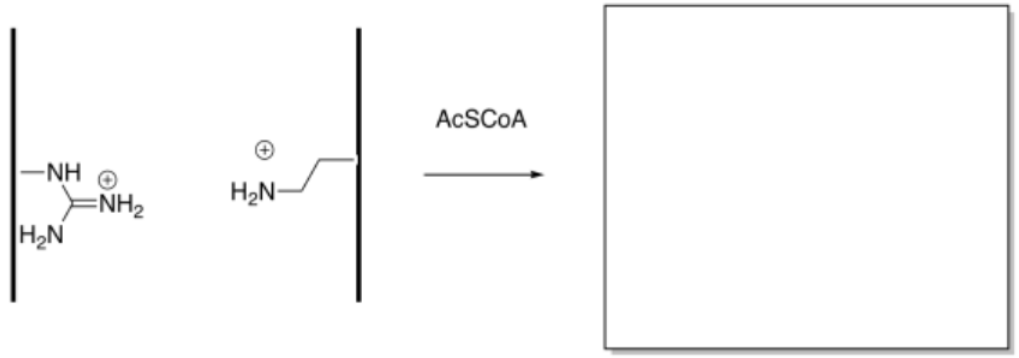


Exercise 6.6.2

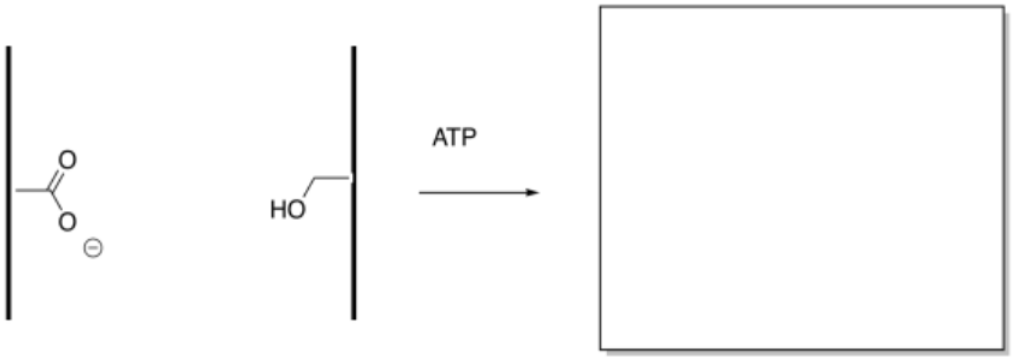
Indicate whether attraction between the strands would increase or decrease after modification.

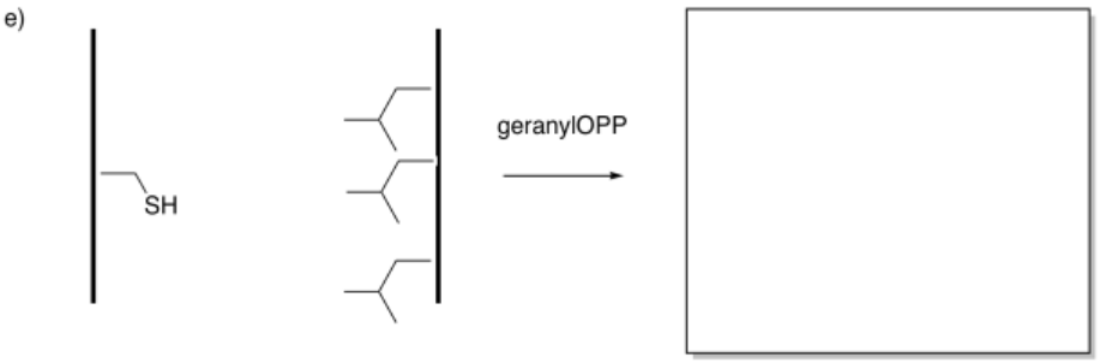


c)

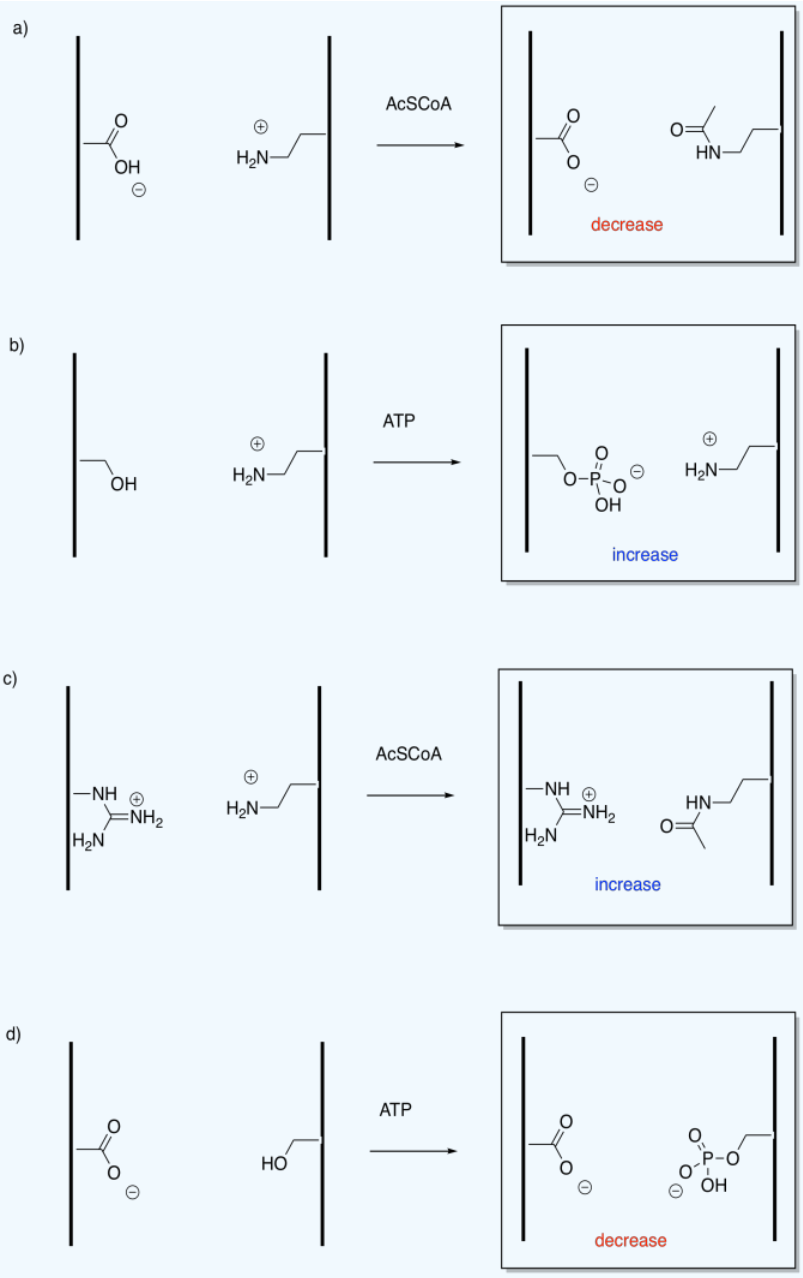


d)



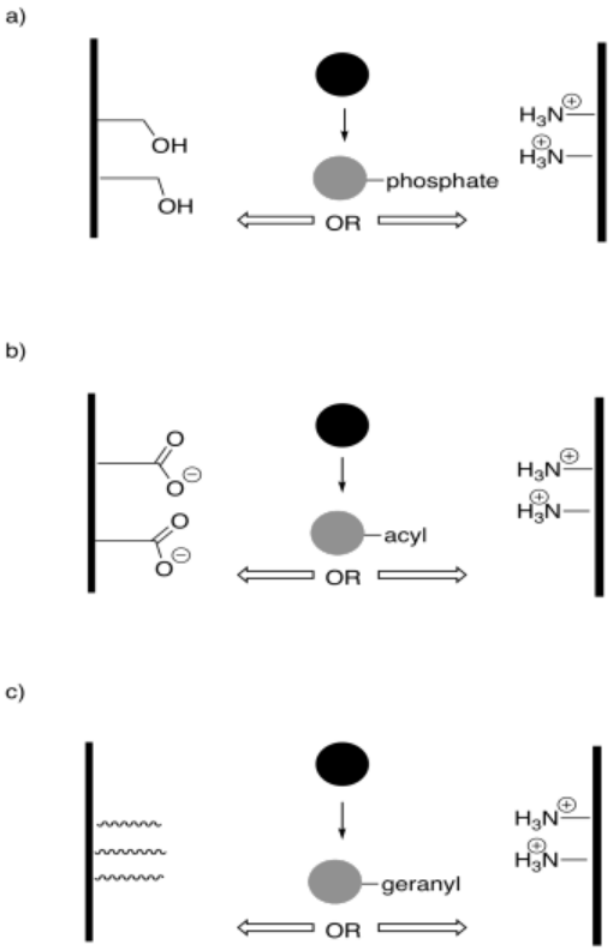


Answer

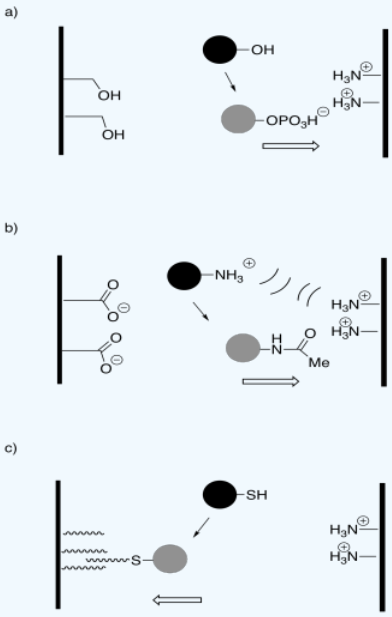


Exercise 6.6.3

In the following drawings, the object's interaction with one of the surfaces will change upon modification. This change in interaction will result in a net shift of the object to the left or to the right. The shift may result because of attractive or repulsive forces. Indicate the direction of shift in each case.

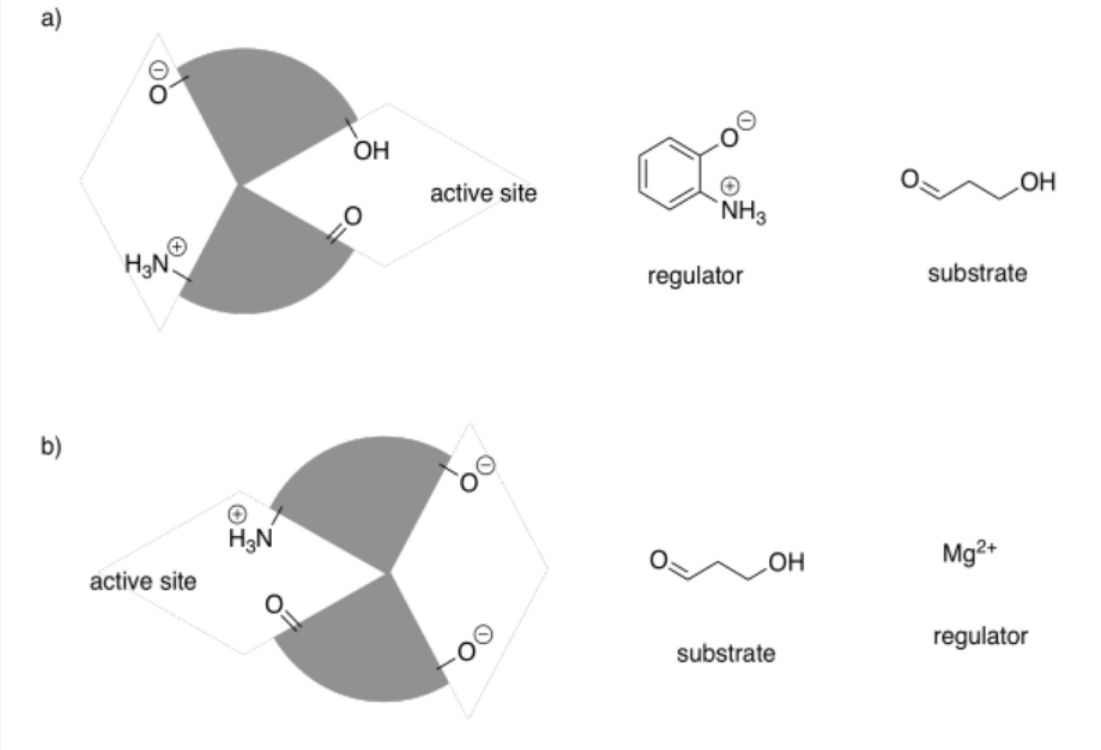

a)
OH
OH
phosphate
OR
H_3N
H_3N
b)
acyl
OR
c)
geranyl
OR

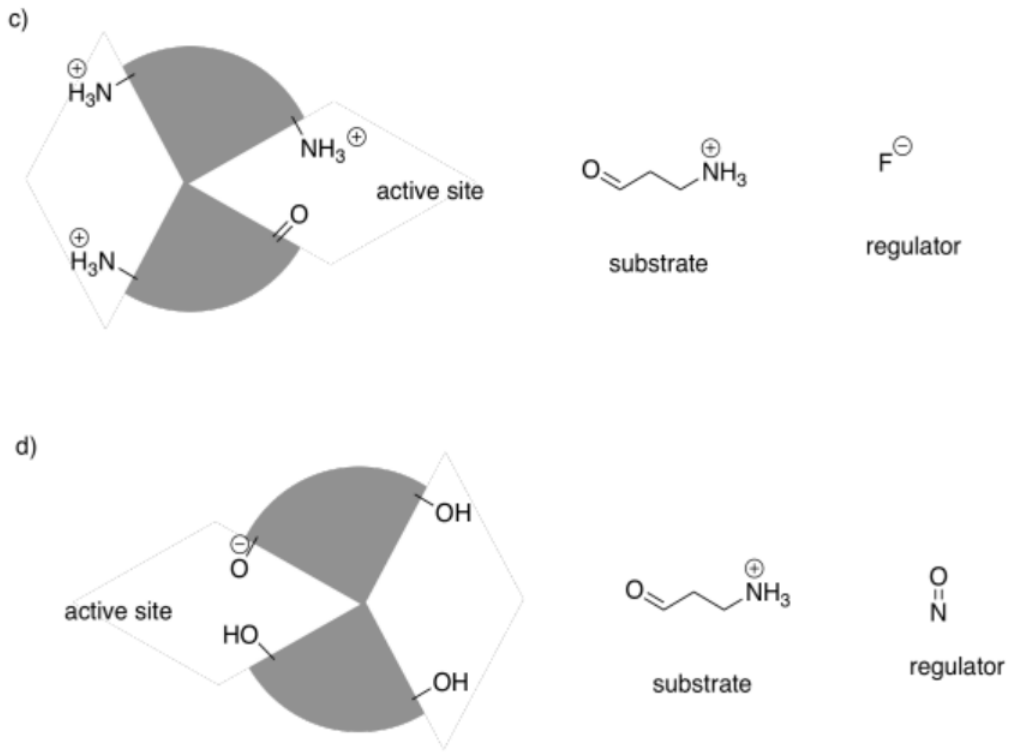
Answer


a)
OH
OH
OH
OPO_3H
b)
NH_3
Me
c)
SH
S

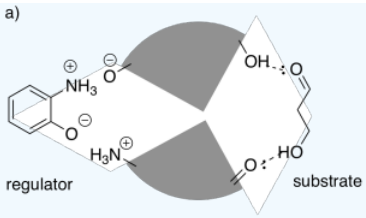
Exercise 6.6.4

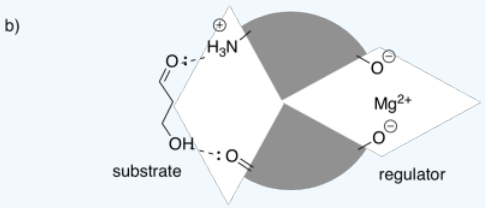
In the following drawings, the active site is closed. Show how the regulator will bind, causing the active site to open, and also show how the substrate will bind.

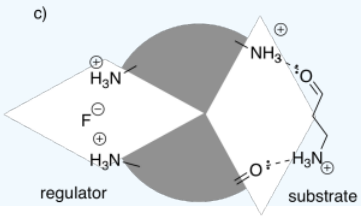



c)
H_3N
NH_3
active site
O
H_3N
substrate
F
regulator
d)
OH
O
active site
HO
OH
substrate
O
N
regulator

Answer

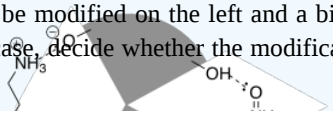




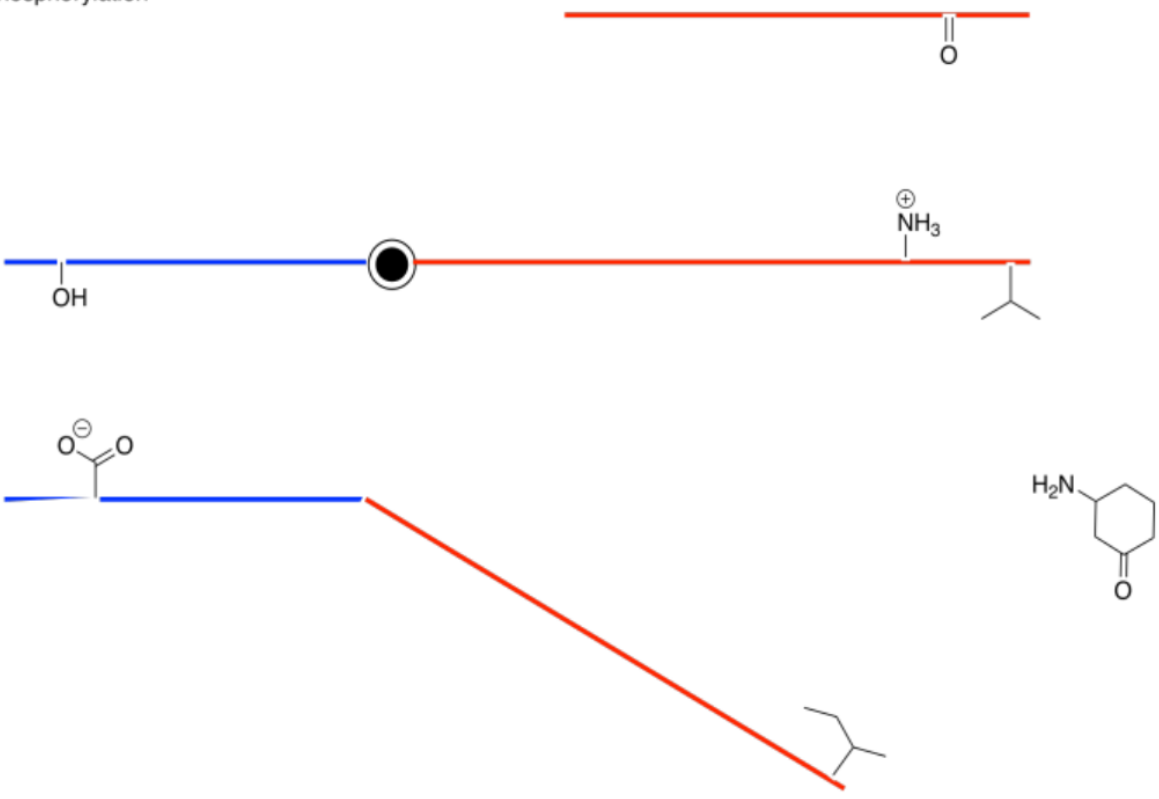


Exercise 6.6.5

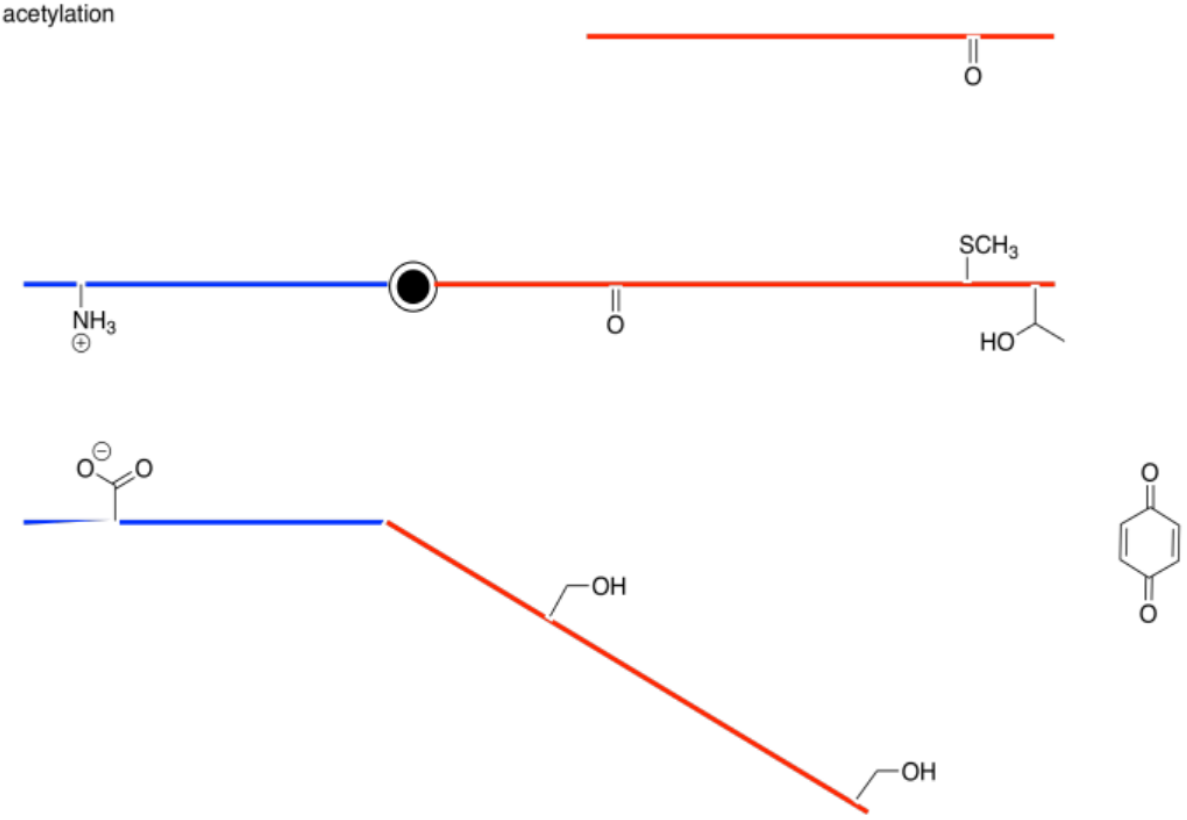
The following drawings depict an allosteric site that will be modified on the left and a binding site on the right. Imagine the middle bar is a see-saw that can tilt left or right. In each case, decide whether the modification will lead to tighter or to looser binding of the substrate.



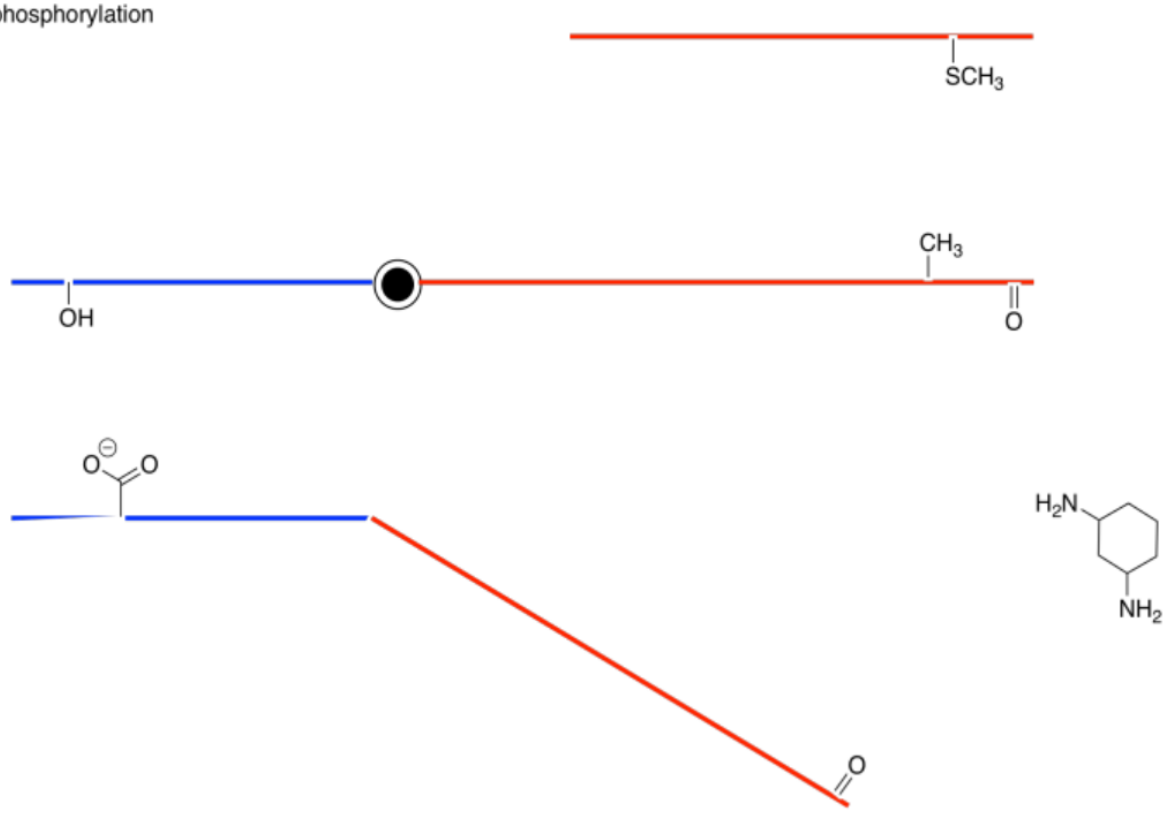
a) phosphorylation



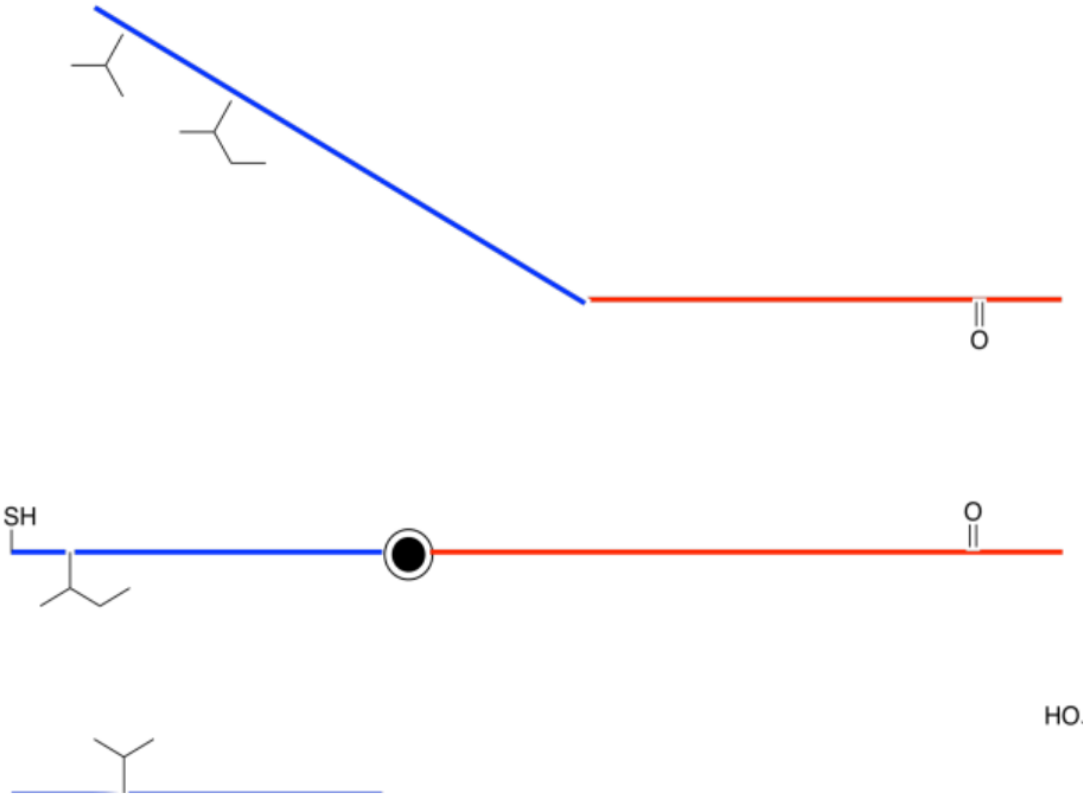
b) acetylation



c) phosphorylation

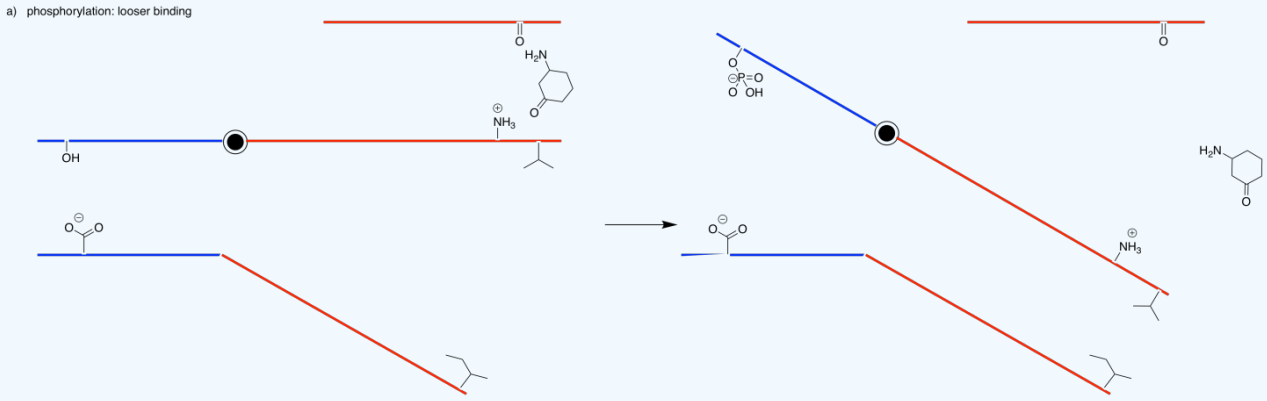


d) prenylation

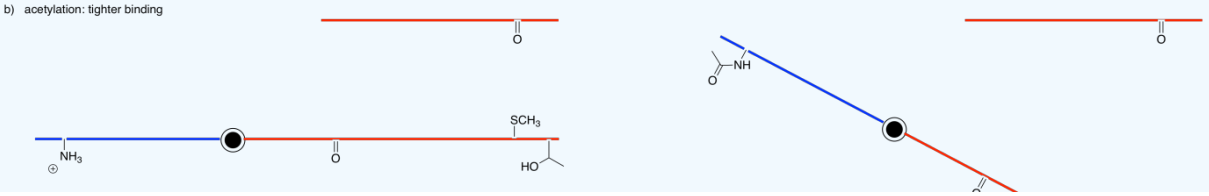


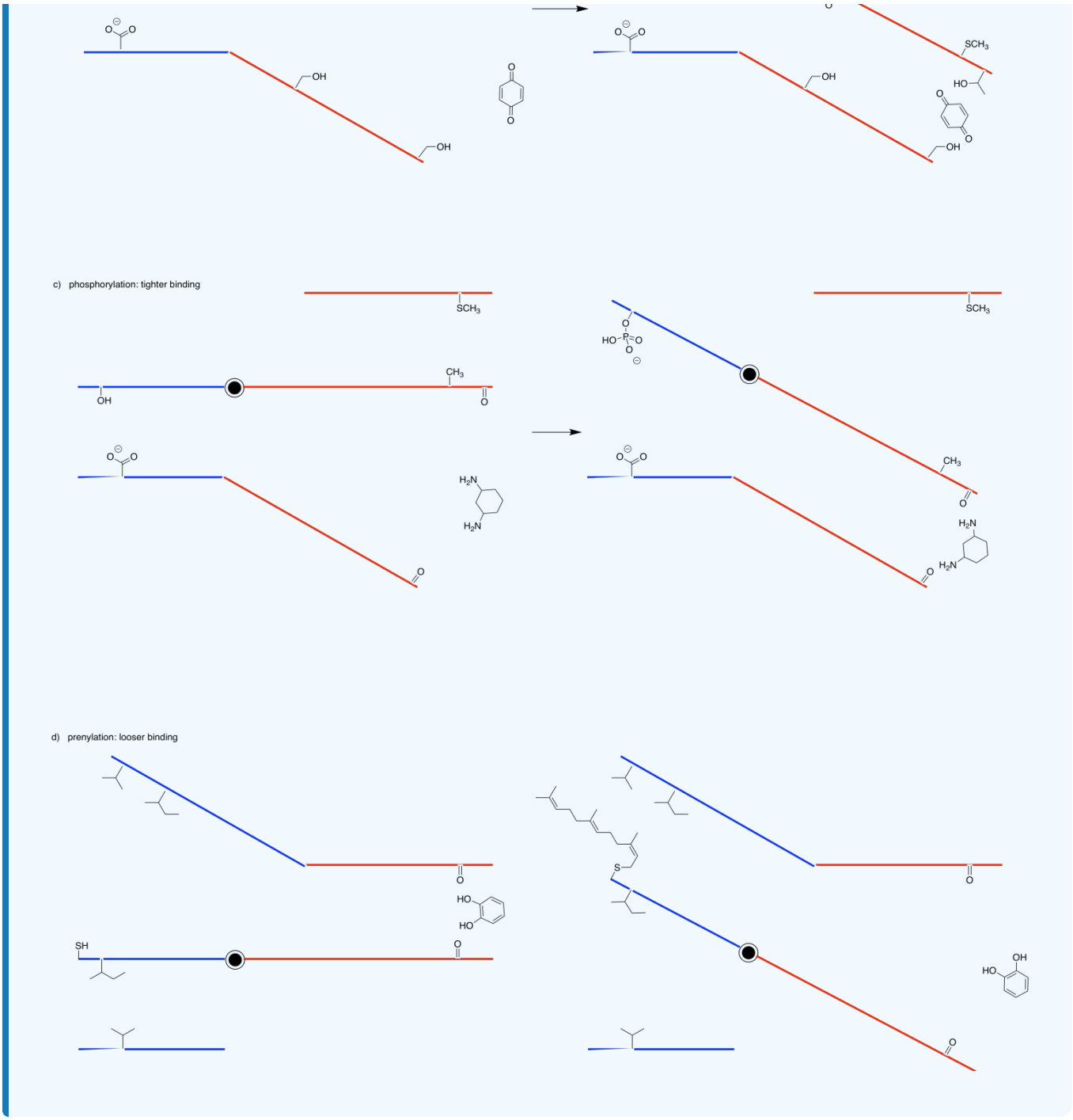
Answer

a) phosphorylation: looser binding



b) acetylation: tighter binding





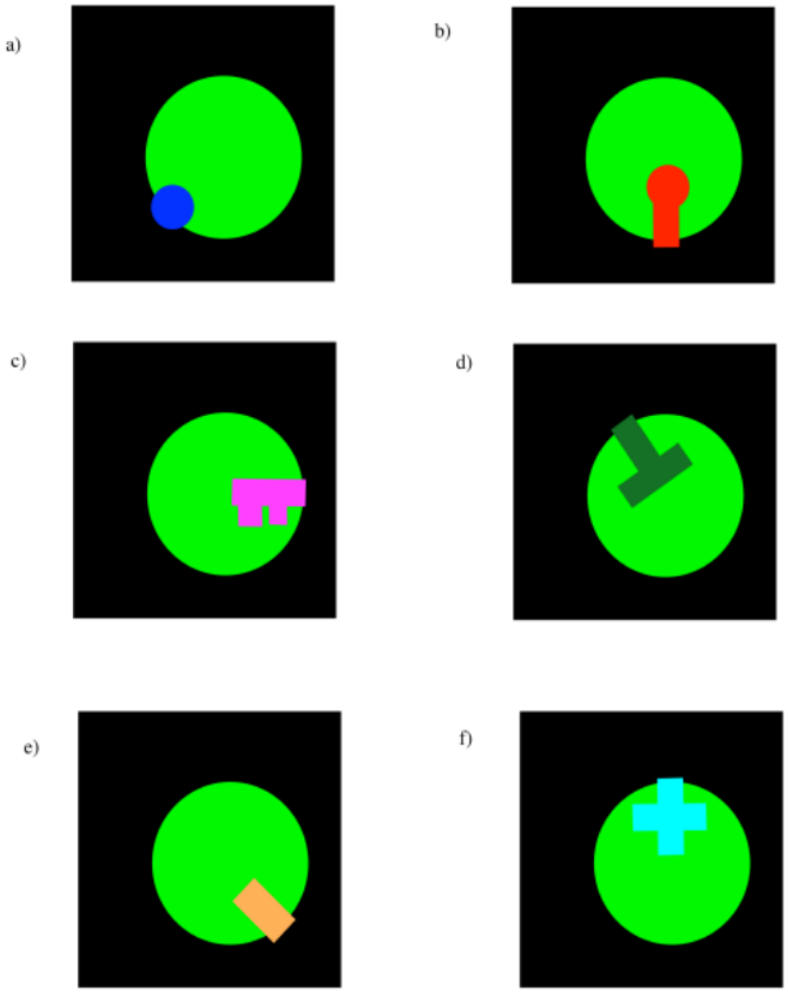
6.7: Enzyme Solutions

Exercise 6.1.1:

a. isomerase v) reorganize atoms from one isomer into another
b. hydrolase vii) add water into a molecule, helping to break it down
c. oxygenase i) add oxygen from O_2 into a molecule
d. dioxygenase ii) add both oxygens from O_2 into a molecule
e. reductase iv) reduce or add electrons to the substrate
f. transferase ix) transfer a functional group to or from a molecule
g. phosphatase vi) cleave a phosphate group off a protein
h. oxidase iii) oxidize or remove electrons from the substrate

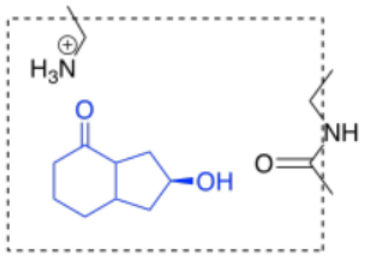
i) ligase viii) cause two molecules to be bound together

Exercise 6.2.1:

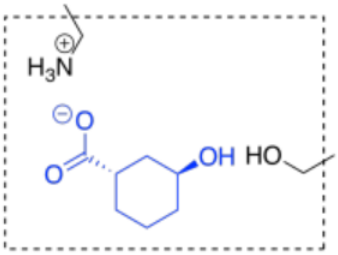


Exercise 6.2.2:

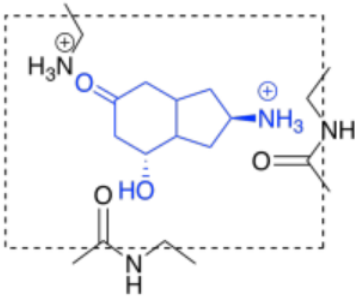
a)



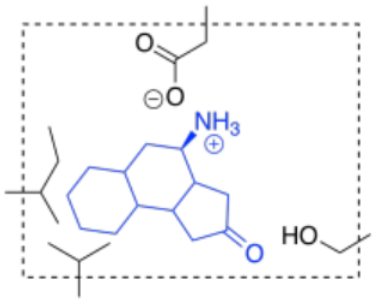
b)



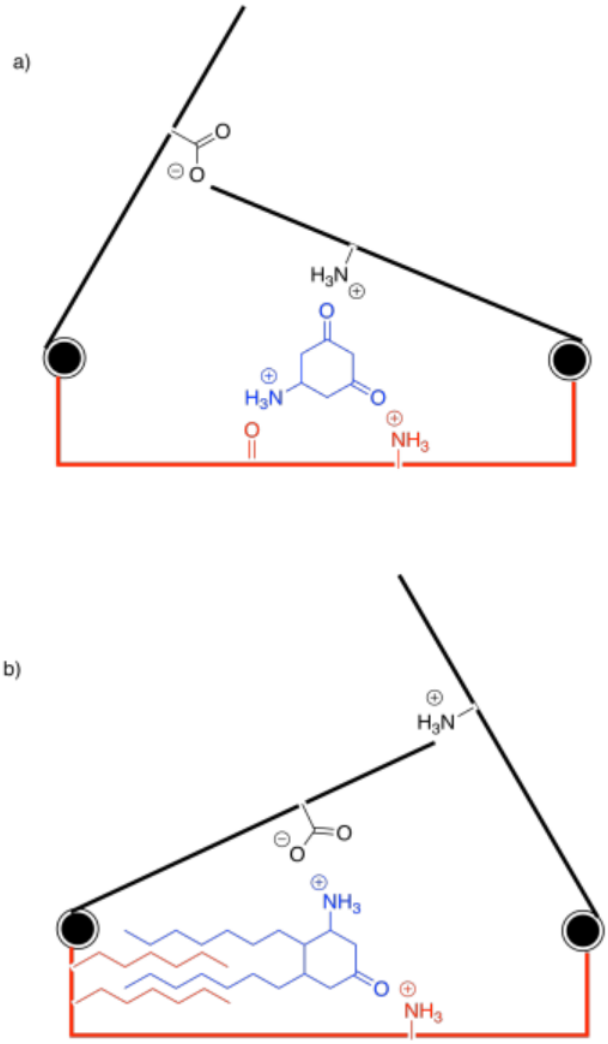
c)



d)



Exercise 6.2.3:



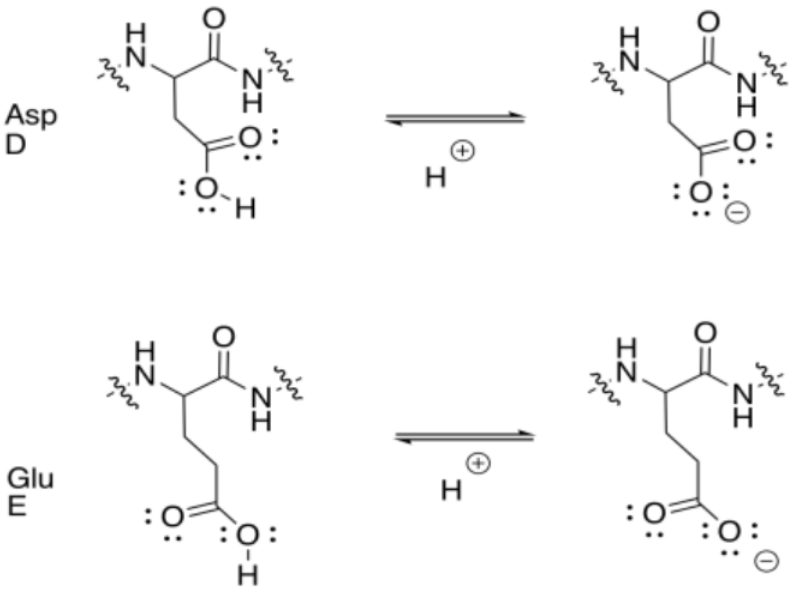
Exercise 6.3.1:

Aspartic acid (abbreviations Asp or D) and glutamic acid (abbreviations Glu or E).

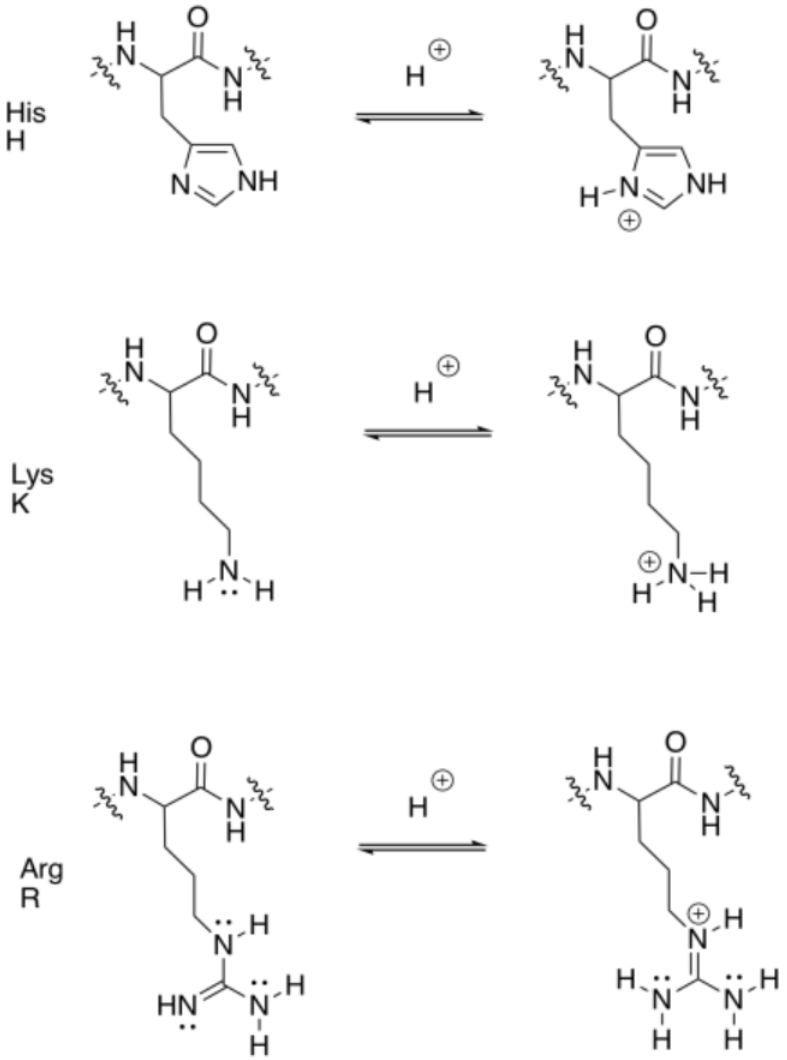
Exercise 6.3.2:

Histidine (abbreviations His or H), lysine (abbreviations Lys or K) and arginine (abbreviations Arg or R).

Exercise 6.3.3:



Exercise 6.3.4:



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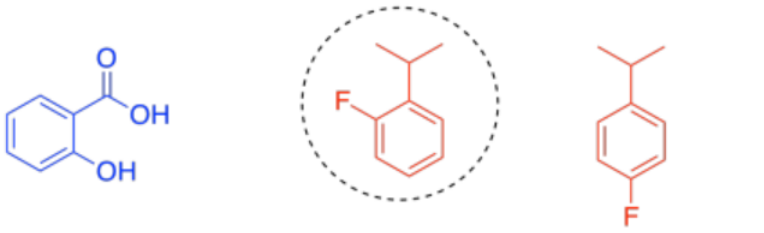

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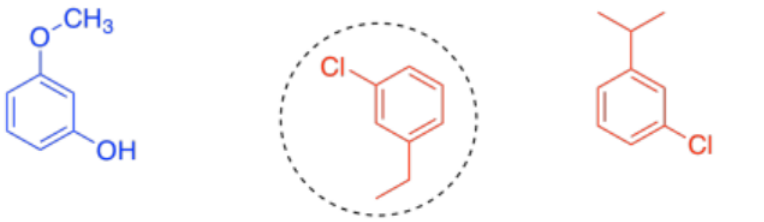

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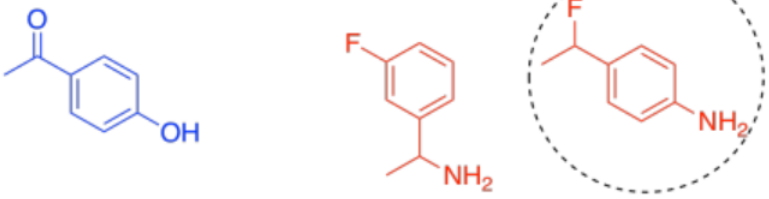

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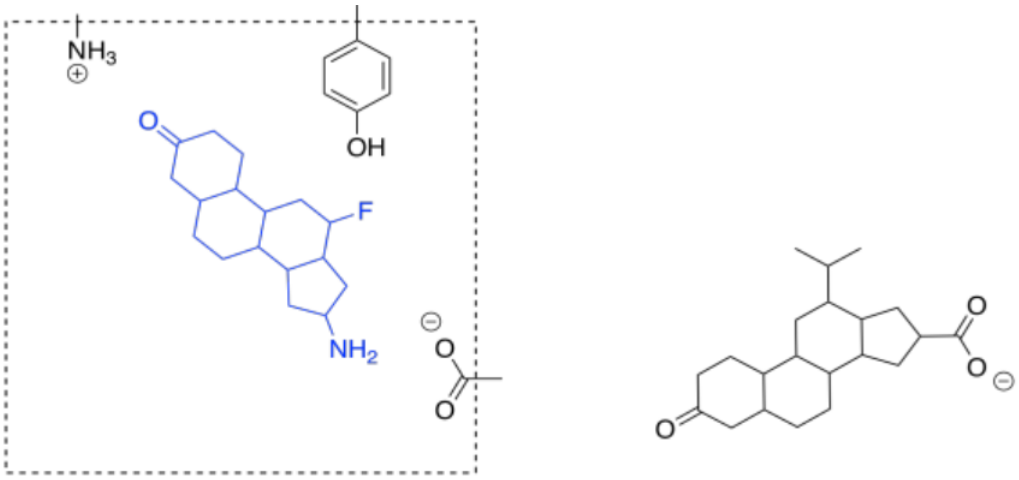

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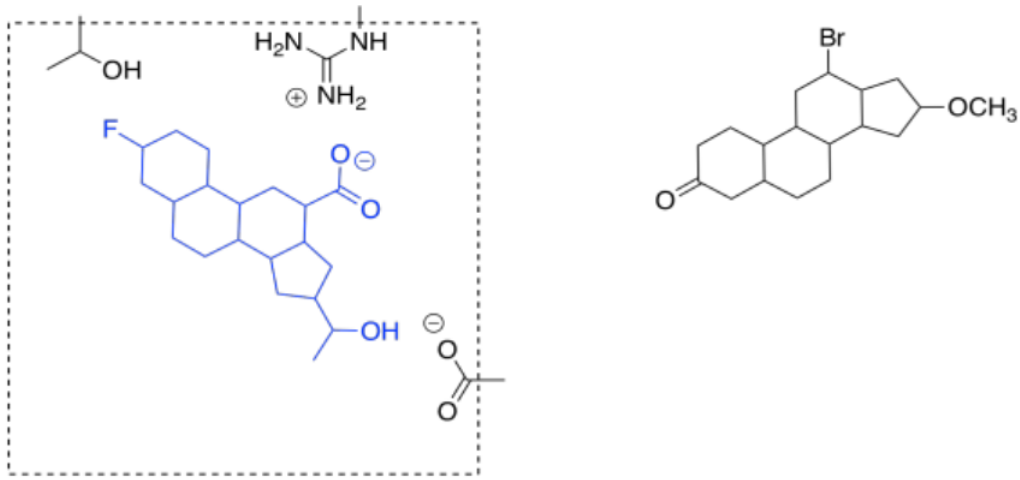

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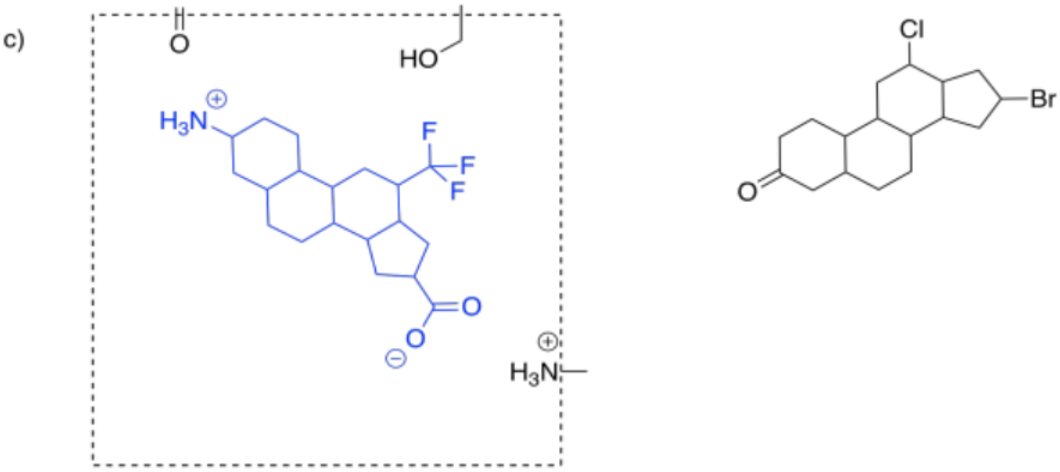

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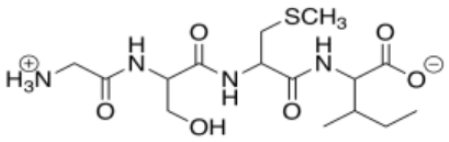

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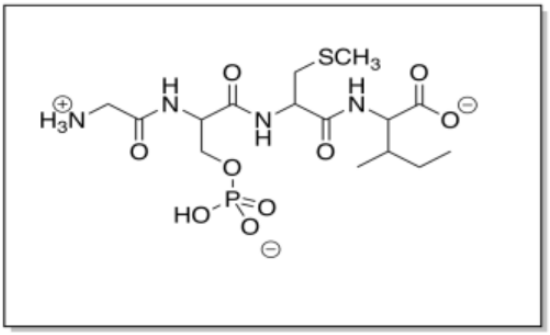

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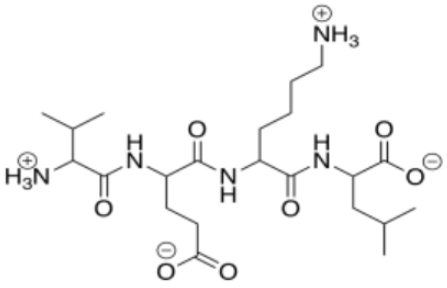

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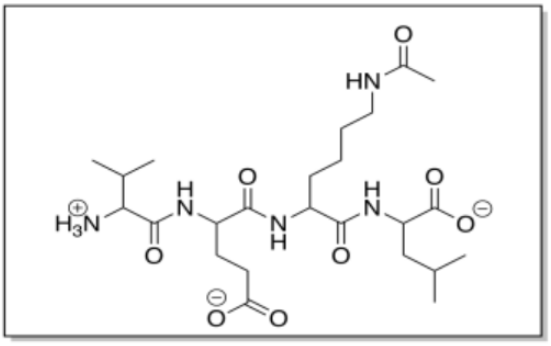

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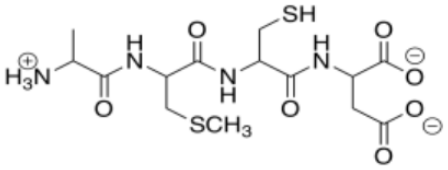

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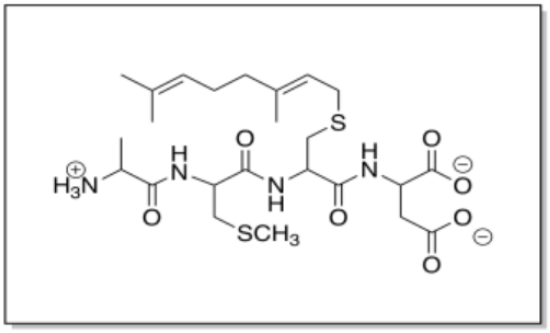

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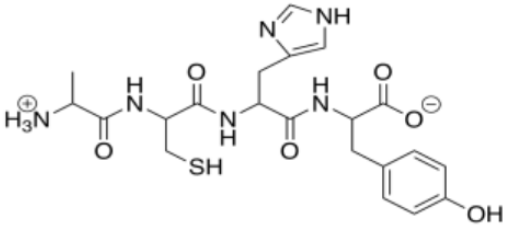

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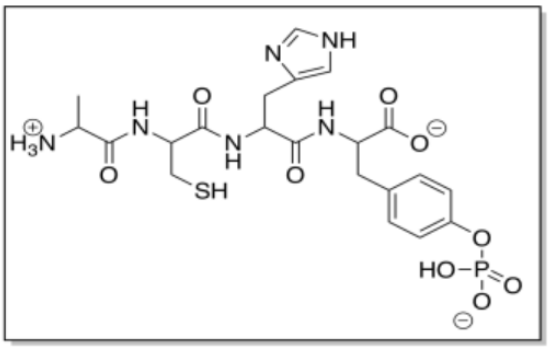

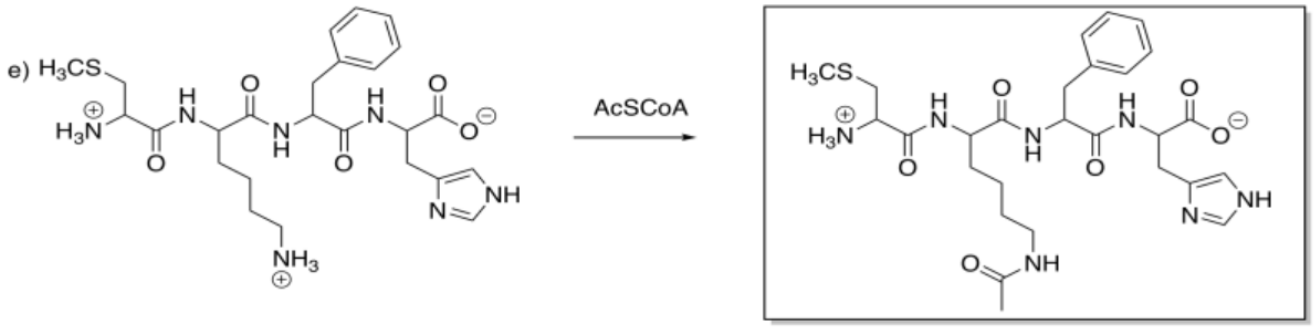

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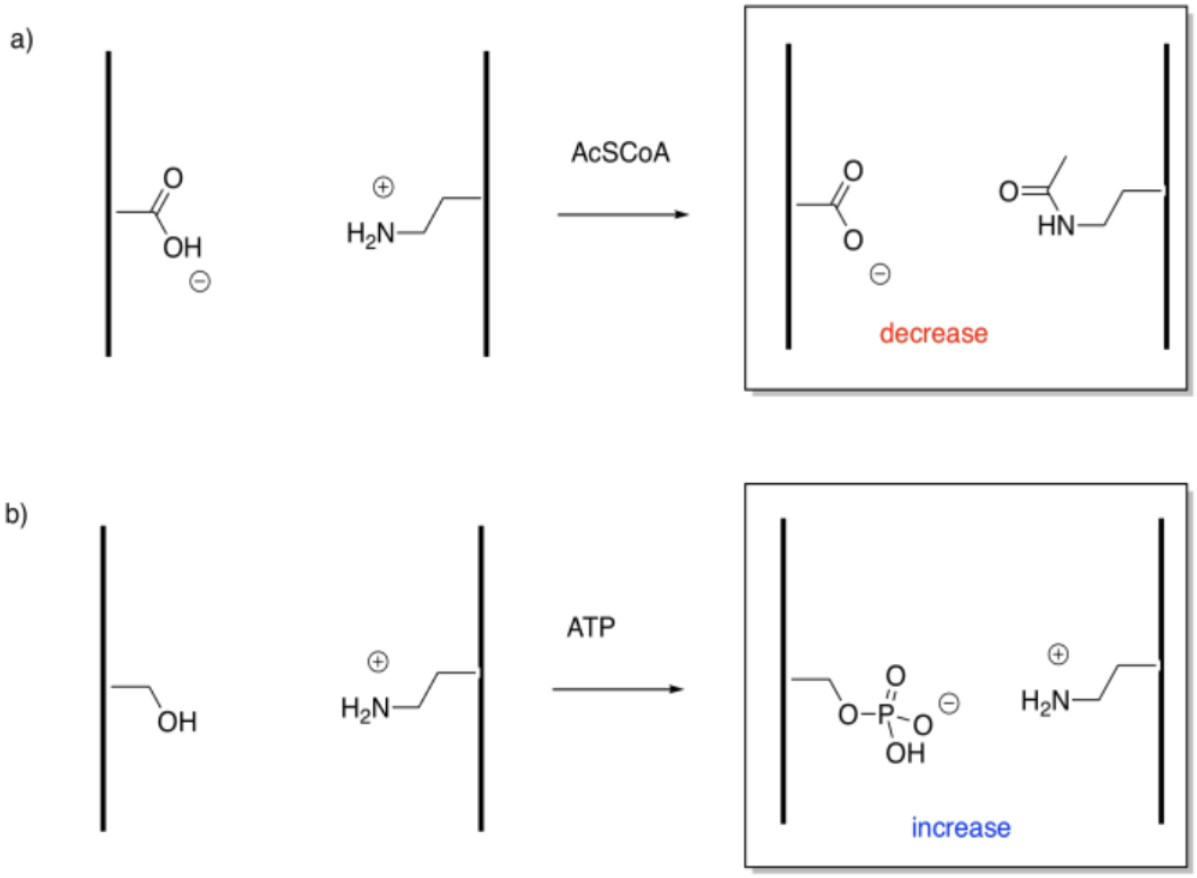

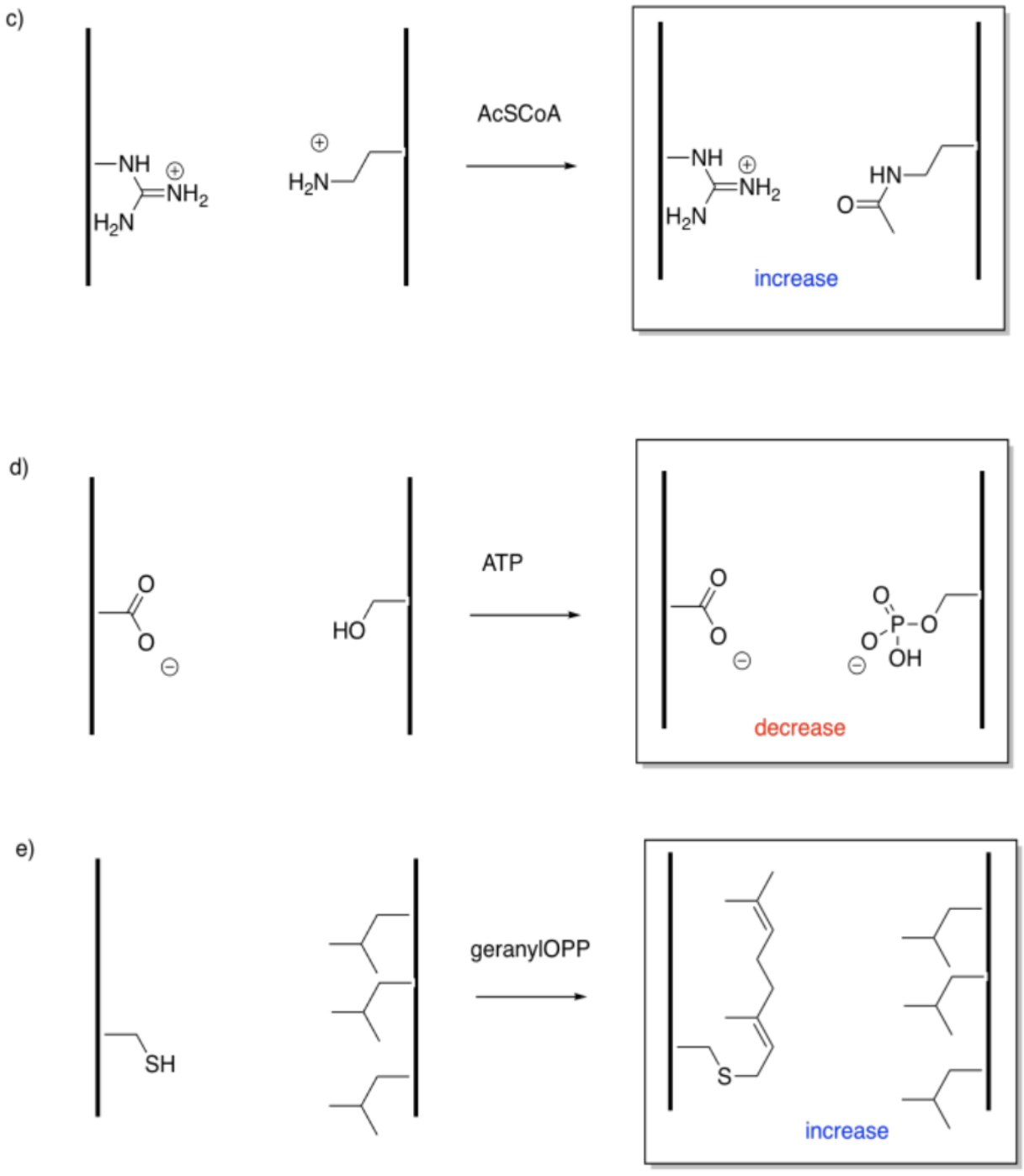

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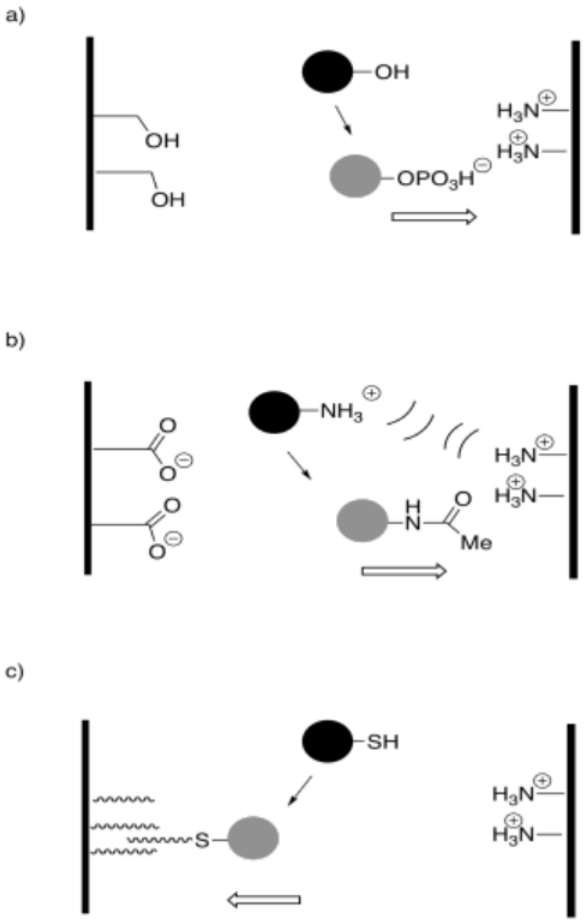

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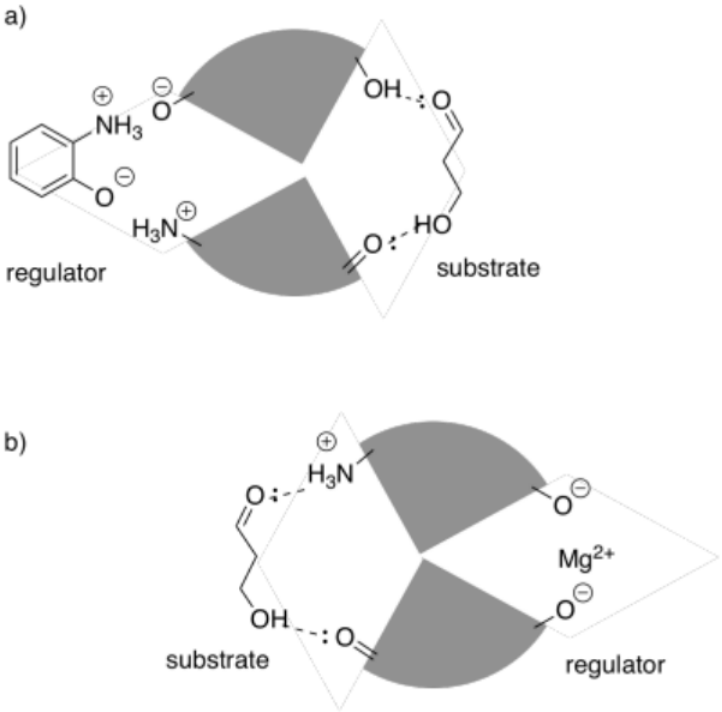

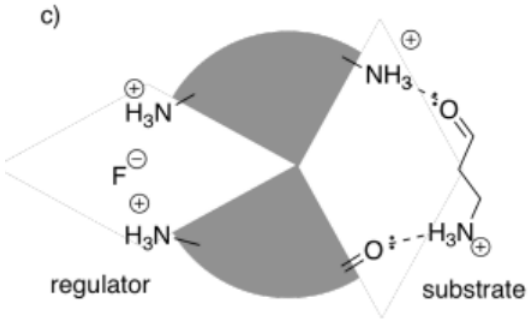

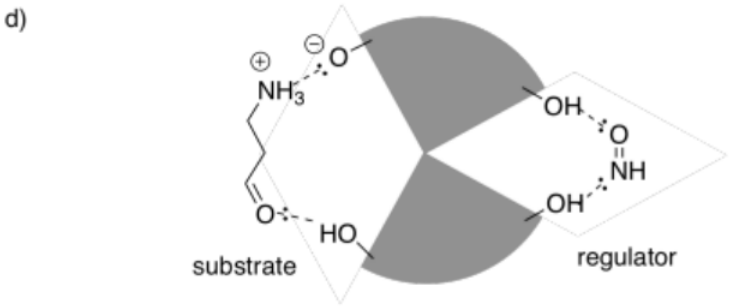

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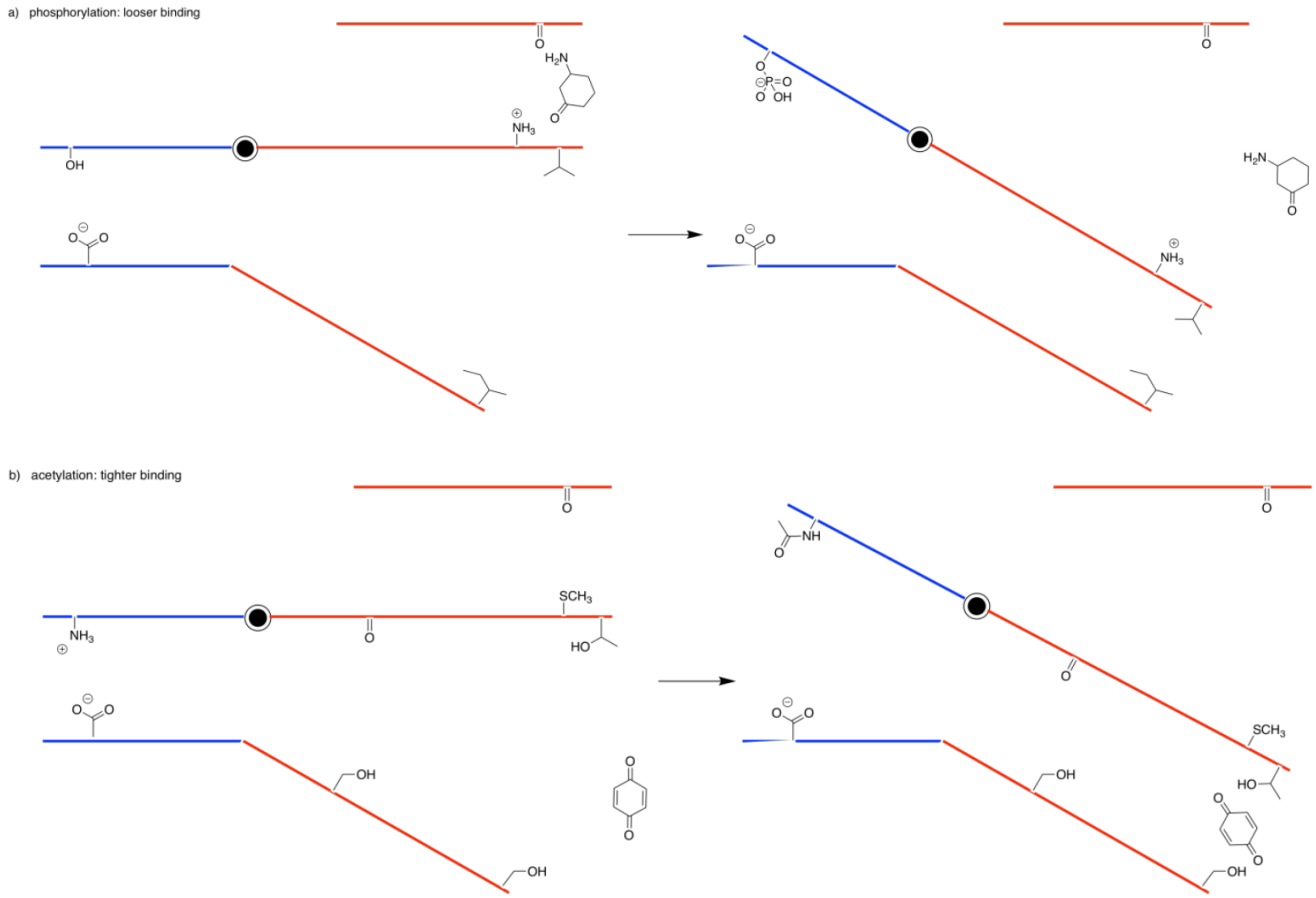
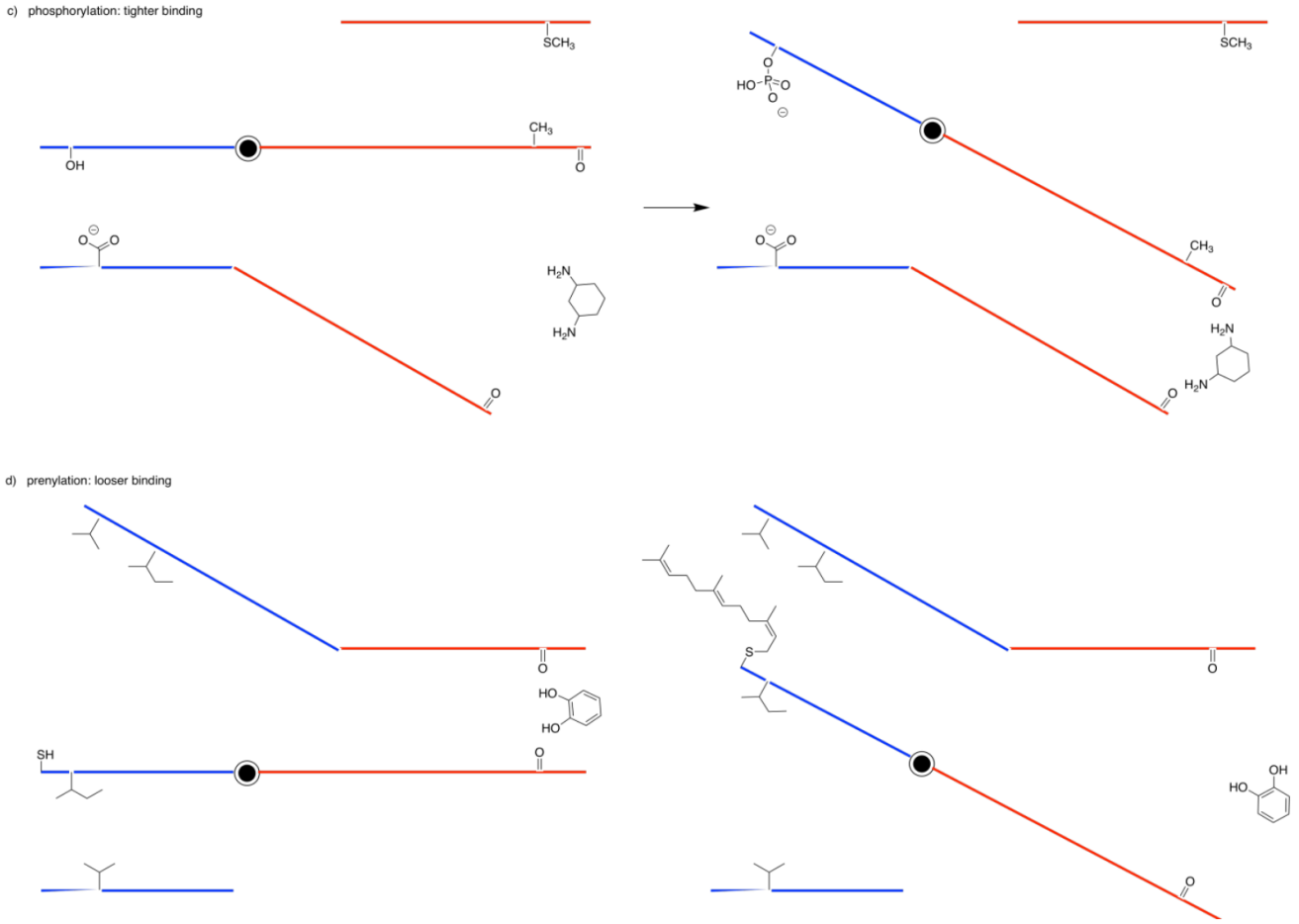




CHAPTER OVERVIEW

7: Metabolic Pathways

7.1: An Overview of Metabolic Pathways - Catabolism

Biological cells have a daunting task. They must carry out 1000s of different chemical reactions required to carry out cell function. These reactions can include opposing goals such as energy production and energy storage, macromolecule degradation and synthesis, and breakdown and synthesis of small molecules. All of these reactions are catalyzed by proteins and RNAs enzymes whose activities must be regulated, again through chemical reactions, to avoid a futile and energy wasting scenario of having opposing pathways functioning simultaneously in a cell.

Metabolism can be divided into two main parts, catabolism, the degradation of molecules, usually to produce energy or small molecules useful for cell function, and anabolism, the synthesis of larger biomolecules from small precursors.

CATBOLISM: Catabolic reactions involve the breakdown of carbohydrates, lipids, proteins, and nucleic acids to produce smaller molecules and biological energy in the form of heat or small thermodynamically reactive molecules like ATP whose further degradation can drive endergonic process such as biosynthesis. Our whole world is reliant on the oxidation of organic hydrocarbons to water and carbon dioxide to produce energy (at the expense of releasing a potent greenhouse gas, CO_2). In the biological world, reduced molecules like fatty acids and partially oxidized molecules such as glucose polymers (glycogen, starch), as well as simple sugars, can be partially or fully oxidized to ultimately produce CO_2 as well. Energy released from oxidative reactions is used to produce molecules like ATP as well as heat. Oxidative pathways include glycolysis, the tricarboxylic acid cycle (aka Kreb's cycle) and mitochondrial oxidative phosphorylation/electron transport. To fully oxidize carbon in glucose and fatty acids to carbon dioxide requires splitting C-C bonds and the availability of series of oxidizing agents that can perform controlled, step-wise oxidation reactions, analogous to the sequential oxidation of methane, CH4 to methanol (CH3OH), formaldehyde (CH2O) and carbon dixoxide.

- Glycolysis: This most primitive of metabolic pathways is found in perhaps all organisms. In glycolysis, glucose ($C_6H_{12}O_6$), a 6C molecule, is split (or lysed) into two, 3C carbon molecules, glyceraldehyde-3-phosphate, which are then partially oxidized under anaerobic conditions (without O_2) to form two molecules of pyruvate ($CH_3COCO_2^-$). Instead of the very strong oxidizing agent, O_2, a weaker one, NAD+ is used, which is reduced in the process to form NADH. Since none of the carbon atoms is oxidized to the state of CO_2, little energy is released compared to the complete oxidation to CO_2. This pathway comes to a screeching halt if all cellular NAD+ is converted to NADH as NAD+ is not replenished by the simple act of breathing as is the case with O_2 in aerobic oxidation. To prevent the depletion of NAD+ from inhibiting the cycle and to allow the cycle to continue under anaerobic conditions, excess NADH is reconverted to NAD+ when the other product of glycolysis, pyruvate is converted to lactate by the enzyme lactate dehydrogenase. Glycolysis occurs in the cytoplasm of the cell.

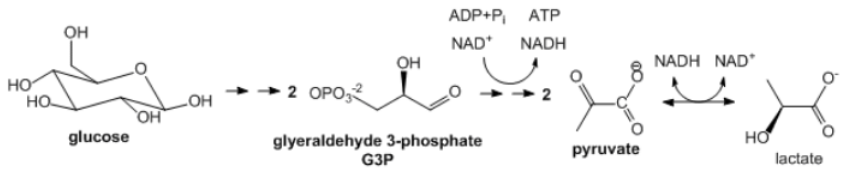


Figure 7.1.1: Summary of Glycolysis

- Tricarboxylic Acid (Kreb's) Cycle: The TCA cycle is an aerobic pathway which takes place in an intracellular organelle called the mitochondria. It takes pyruvate, the incompletely oxidized product from glycolysis, and finishes the job of oxidizing the 3C atoms all the way to CO_2. First the pyruvate moves into the mitochondria where is is oxidized to the 2C molecule acetylCoA with the release of one CO_2 by the enzyme pyruvate dehydrogenase. The acetyl-CoA then enters the TCA cycle where two more CO_2 are released. As in glycolysis, C-C bonds are cleaved and C is oxidized by NAD+ and another related oxidizing agent, FAD. What is very different about this pathway is that instead of being a series of linear, sequential reactions with one reactant (glucose) and one product (two pryuvates), it is a cyclic pathway. This has significant consequences since if any of the reactants within the pathways becomes depleted, the whole cyclic pathway can slow down and stop. To see how this happens consider the molecule oxaloacetate (OAA) which condenses with acetyl-CoA to form citrate (see diagram below). In this reaction, one OAA is consumed. However, when the cycle returns, one malate is converted to OAA so there is no net loss of OAA, unless OAA is pulled out of the TCA cycle for other reactions, which happens.

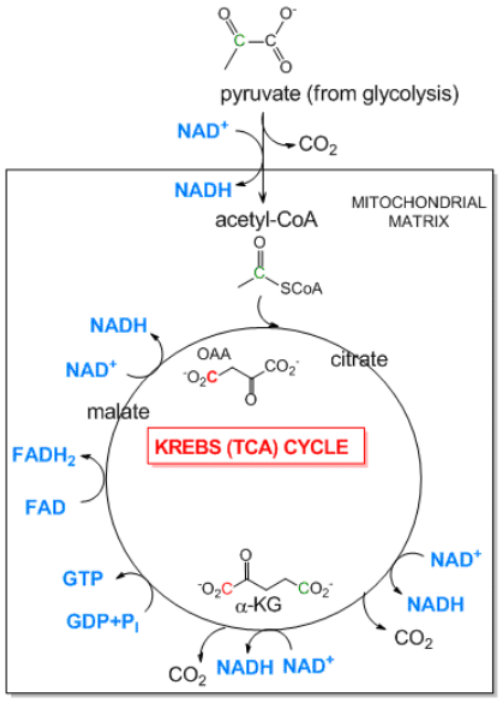


Figure 7.1.2: Pyruvate Dehydrogenase (mitochondrial) and the TCA Cycle

- Mitochondrial Oxidative Phosphorylation/Electron Transport: The TCA cycle accomplishes what glycolysis didn't, that is the cleavage of all C-C bonds in glucose (in the form of pyruvate and acetyl-CoA, and the complete oxidation of all C atoms to CO_2. Yet two problem remains. The pool of oxidizing molecules, NAD+ and FAD get converted to their reduced forms, NADH and FADH2. Unless NAD+ and FAD are regenerated, as was the case in anaerobic conditions when pyruvate gets converted to lacate, the pathway would again come to a grinding halt. In addition, not much ATP is made in the cycle (in the form of a related molecule GTP). Both these problems are resolved as the resulting NADH and FADH2 formed are reoxidized by mitochondrial membrane enzyme complexes which pass electrons from the oxidized NADH and FADH2 to increasingly potent oxidizing agents until they are accepted by the powerful oxidant O_2,which is converted reduced to water. The net oxidation of NADH and FADH2 by dioxygen is greatly exergonic, and the energy released by the process drives the synthesis of ATP from ADP and Pi by an mitochondrial enzyme complex, the F0F1ATPase.

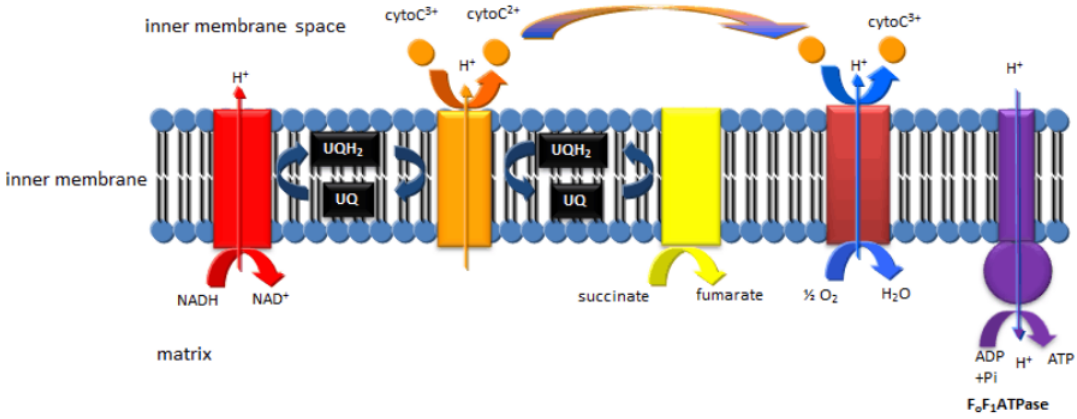
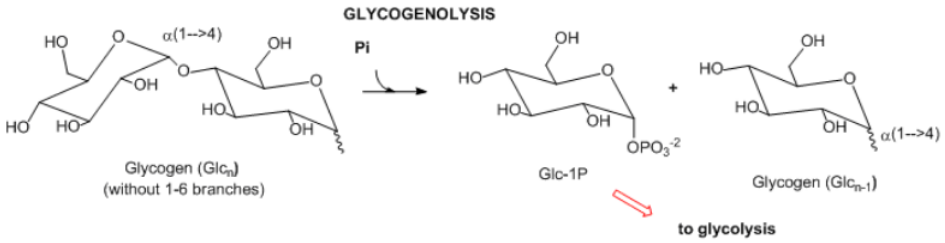


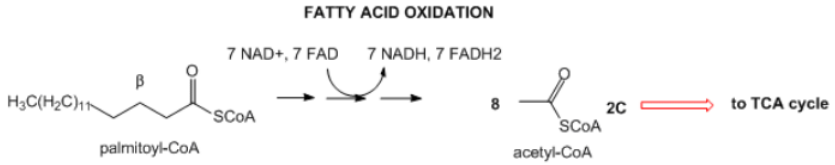
Figure 7.1.3: Mitochondrial Electron Transport/Oxidative Phosphorylation

Feeder Pathways: Other catabolic pathways produce products that can enter glycolysis or the TCA cycle. Two examples are given below.

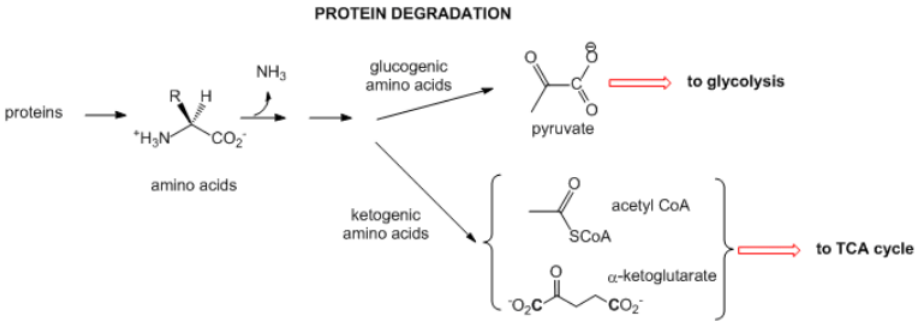
- Complex carbohydrates: In mammals, the major carbohydrate storage molecule is glycogen, a polymer of glucose linked a1-4 with a1-6 branches. The terminal acetal linkages in this highly branched polymer is cleaved sequentially at the ends not through hydrolysis but through phosphorolysis to produce lots of glucose-1-phosphate which can enter glycolysis.



- Lipids: Lipids are stored mostly as triacylglycerides in fat cells (adipocytes). When needed for energy, fatty acids are hydrolyzed from the glycerol backbone of the triacylglyceride, and send into cells where they broken down in an oxidative process to form acetyl-CoA with the concomitant production of lots of NADH and FADH2. These can then enter the mitochondrial oxidative phosphorylation/electrons transport system, which produces, under aerobic conditions, lots of ATP.



- Proteins: When intracellular proteins get degraded, they from individual amino acids. The amine N is lost as it enters the urea cycle. The rest of some amino acid structures can be ultimately converted to acetyl-CoA or keto acids (like alpha-ketoglutarate-a-KG) that are TCA intermediate. These amino acids are called ketogenic. Alternatively, some amino acids, after deamination, are coveted to pyruvate which can either enter the TCA cycle or in the liver be used to synthesize glucose in an anabolic process. These amino acids are called glucogenic. Chemical reactions such as these can be used to replenish intermediates in the TCA cycle which can become depleted as they are withdraw for other reactions.



7.2: An Overview of Metabolic Pathways - Anabolism

Anabolism: Anabolic reactions are those that lead to the synthesis of biomolecules. In contrast to the catabolic reactions just discussed (glycolysis, TCA cycle and electron transport/oxidative phosphorylation) which lead to the oxidative degradation of carbohydrates and fatty acids and energy release, anabolic reactions lead to the synthesis of more complex biomolecules including biopolymers (glycogen, proteins, nucleic acids) and complex lipids. Many biosynthetic reactions, including those for fatty acid synthesis, are reductive and hence require reducing agents. Reductive biosynthesis and complex polymer formation require energy input, usually in the form of ATP whose exergonic cleavage is coupled to endergonic biosynthesis.

Cells have evolved interesting mechanism so as not to have oxidative degradation reactions (which release energy) proceed at the same time and in the same cell as reductive biosynthesis (which requires energy input). Consider this scenario. You dive into a liver cell and find palmitic acid, a 16C fatty acid. From where did it come? Was it just synthesized by the liver cell or did it just enter the cell from a distant location such as adipocytes (fat cells). Should it be oxidized, which should happen if there is a demand for energy production by the cell, or should the liver cell export it, perhaps to adipocytes, which might happen if there is an excess of energy storage molecules? Cells have devised many ways to distinguish these opposing needs. One is by using a slightly different pool of redox reagents for anabolic and catabolic reactions. Oxidative degradation reactions typically use the redox pair NAD+/NADH (or FAD/FADH2) while reductive biosynthesis often uses phosphorylated variants of NAD+, NADP+/NADPH. In addition, cells often carry out competing reactions in different cellular compartments. Fatty acid oxidation of our example molecule (palmitic acid) occurs in the mitochondrial matrix, while reductive fatty acid synthesis occurs in the cytoplasm of the cell. Fatty acids entering the cell destined for oxidative degradation are transported into the mitochondria by the carnitine transport system. This transport system is inhibited under conditions when fatty acid synthesis is favored. We will discuss the regulation of metabolic pathways in a subsequent section. One of the main methods, as we will see, is to activate or inhibit key enzymes in the pathways under a given set of cellular conditions. The key enzyme in fatty acid synthesis, acetyl-CoA carboxylase, is inhibited when cellular conditions require fatty acid oxidation.

The following examples give short descriptions of anabolic pathways. Compare them to the catabolic pathways from the previous section.

- Glucose synthesis, better known as Gluconeogenesis: In glycolysis, glucose (C6H12O6), a 6C molecule, is converted to two, 3C molecules (pyruvate) in an oxidative process that requires NAD+ and makes two net ATP molecules. In a few organs, most predominately in the liver, the reverse pathway can take place. The liver does this to provide glucose to the brain when the body is deficient in circulating glucose, for example, under fasting and starving conditions. (The liver under these conditions can get its energy from oxidation of fatty acids). The reactions in gluconeogenesis are the same reactions in glycolysis but run in reverse, with the exception of three glycolytic steps which are essentially irreversible. These three steps have bypass enzymes in the gluconeogenesis pathway. Although the synthesis of glucose is a reductive pathway, it uses NADH instead of NADPH as the redundant as the same enzyme used in glycolysis is simply run in reverse. Gluconeogenesis, which also occurs in the cortex of the kidney, is more than just a simple reversal of glycolysis, however. It can be thought of as the net synthesis of glucose from non-carbohydrate precursors. Pyruvate, as seen in the section on catabolism, can be formed from protein degradation to glucogenic amino acids which can be converted to pyruvate. It can also be formed from triacylglycerides from the 3C molecule glycerol formed and released from adipocytes after hydrolysis of three fatty acids from triacylglycerides. However, in humans, glucose can not be made in net fashion from fatty acids. Fatty acids can be converted to acetyl-CoA by fatty acid oxidation. The resulting acetyl-CoA can not form pyruvate since the enzyme that catalyzes the formation for acetyl-CoA from pyruvate, pyruvate dehydrogenase, is irreversible and there is no bypass reaction known. The acetyl-CoA can enter the TCA cycle but since the pathway is cyclic and proceeds in one direction, it can not form in net fashion oxaloacetate. Although oxaloacetate can be remove from the TCA cycle and be use to form phosphoenolpyuvate, a glycolytic intermediate, one acetyl-CoA condenses with one oxaloacetate to form citrate which leads back to one oxaloacetate. Hence fatty acids can not be converted to glucose and other sugars in a net fashion.

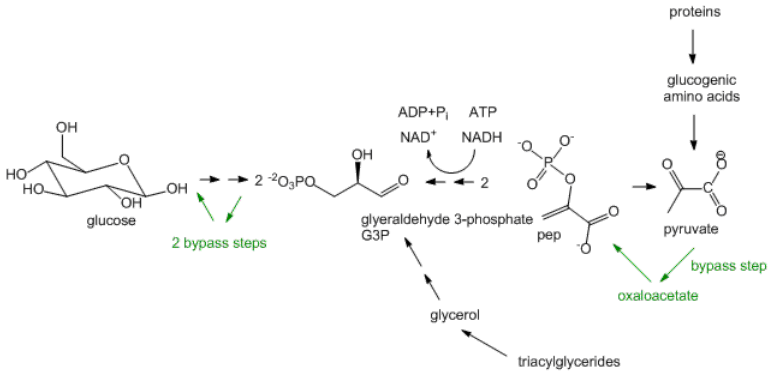
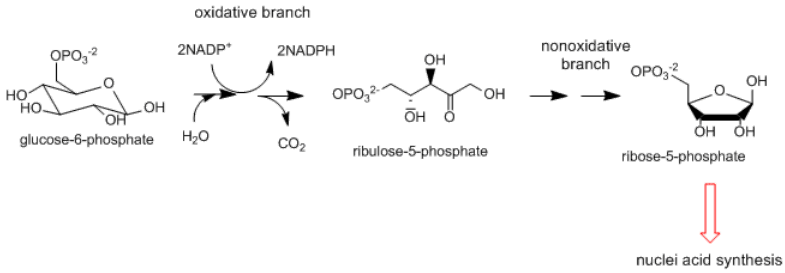
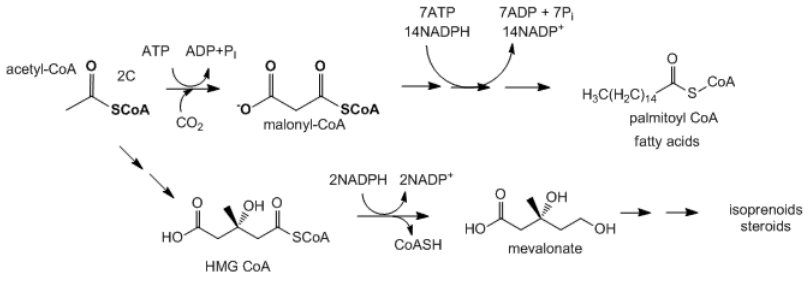


Figure 7.2.1: Gluconeogenesis

- Pentose Phosphate Shunt: This two-part pathway doesn't appear to start as a reductive biosynthetic pathway as the first part is the oxidative conversion of a glycolytic intermediate, glucose-6-phosphate, to ribulose-5-phosphate. The next, nonoxidative branch leads to the formation of ribose-5-phosphate, a key biosynthetic intermediate in nucleic acid synthesis as well as erthyrose-4-phosphate used for biosynthesis of aromatic amino acids . The oxidative branch is important in reductive biosynthesis as it is a major source of the reductant NADPH used in biosynthetic reactions.



- Fatty acid and isoprenoid/sterol biosynthesis: Acetyl-CoA is the source of carbon atoms for the synthesis of more complex lipids such as fatty acids, isoprenoids, and sterols. When energy needs in a cell are not high, citrate, the condensation product of oxaloacetate and acetyl-CoA in the TCA cycle, builds up in the mitochondrial matrix. It is then transported by the citrate transporter (an inner mitochondrial membrane protein) to the cytoplasm, where it is cleaved back to oxaloacetate and acetyl-CoA by the cytoplasmic enzyme citrate lyase. The oxaloacetate is returned to the mitochondria by conversion first to malate (reduction reaction using NADH), which can move back into the mitochondria through the malate transporter, or further conversion to pyruate, using the cytosolic malic enzyme, which uses NADP+ to oxidize malate to pyruvate which then enters the mitochondria. The acetyl-CoA formed in the cytoplasm can then be used in reductive biosynthesis using NADPH as the reductant to form fatty acids, isoprenoids, and sterols. The NADPH for the reduction comes from the oxidative branch of the pentose phosphate pathway and from the reaction catalyzed by malic enzyme. The liver cells can still run the glycolytic pathway as the NADH/NAD+ ratio is low in the cytoplasm while NADPH/NADP+ ratio is high.



Now its time to see how the various pathways fit together to form an integrated set of pathways.

7.3: Metabolic Maps Homepage

Now its time to see how the various pathways fit together to form an integrated set of pathways. Metabolic map pathways are by nature very messy and complex. I've created a series of maps below which display some important anabolic and catabolic pathways and how they connect. Many pathways have been omitted. These maps will evolve with time as more relevant information is added. The first maps show the interconnected pathways without much detail. Subsequent maps give increasingly amount of detail. Eventually, the most detailed maps will contain web links to show how given reactions are regulated and will display interactive Jmol molecular models of key enzymes.

These maps are tailored to support foundational courses in chemical reactivity that highlight specific metabolic pathways to illustrate how enzyme-catalyzed reactions can be explain using the language of organic and inorganic chemistry. Of course they are also useful for foundational level biochemistry courses which seek to give an overview of metabolic pathways and their connections. More detailed and comprehensive sites are available on the web. Once such site is the Kyoto Encylopedia of Gene and Genomes (KEGG) Pathway Data Base.

INTEGRATED METABOLIC PATHWAYS MAPS (pdf version)

- Lower resolution: Overview of catabolic and anabolic pathways
- Medium resolution: Overview showing structure of key shared pathway intermediates
- Higher resolution: Overview with more detailed pathway intermediates

INDIVIDUAL METABOLIC PATHWAY MAPS (pdf version)

Best viewed in Firefox as Safari. Some links don't show in Chrome or IE!

Catabolic

- Glycolysis:
- Pyruvate Dehydrogenase
- Tricarboxylic Acid Cycle (TCA):
- Variants of the TCA Cycle (New 4/11/12)
- Electron Transport/Oxidative Phosphorylation:
- Fatty Acid Oxidation

Anabolic

- Gluconeogenesis
- Pentose Phosphate Shunt
- Fatty Acid Synthesis
- Isoprenoid/Sterol Synthesis

Both

- Glycogen Synthesis/Mobilization
- Ketone Body Synthesis/Mobilization
- Triacylglyceride Synthesis/Mobilization
- Glutamine/Glutamate/NH3 Metabolism

ORGAN PROFILES

- Liver
- Brain
- Heart
- Muscle
- Adipose

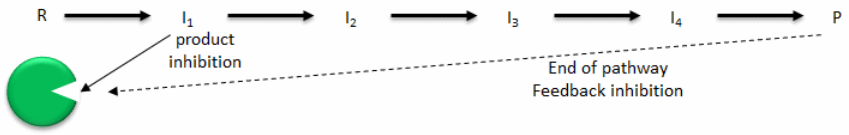
7.4: Regulation of Metabolic Pathways A - How is enzyme activity regulated?

Exquisite mechanisms have evolved that control the flux of metabolites through metabolic pathways to insure that the output of the pathways meets biological demand and that energy in the form of ATP is not wasted by having opposing pathways run concomitantly in the same cell.

Enzymes can be regulated by changing the activity of a preexisting enzyme or changing the amount of an enzyme.

A. Changing the activity of a pre-existing enzyme: The quickest way to modulate the activity of an enzyme is to alter the activity of an enzyme that already exists in the cell. The list below, illustrated in the following figure, gives common ways to regulate enzyme activity

1. Substrate availability: Substrates (reactants) bind to enzymes with a characteristic affinity (characterized by a dissociation constant) and a kinetic parameter called Km (units of molarity). If the actual concentration of a substrate in a cell is much less than the Km, the activity of the enzyme is very low. If the substrate concentration is much greater than Km, the enzyme active site is saturated with substrate and the enzyme is maximally active.
2. Product inhibition: A product of an enzyme-catalyzed reaction often resembles a starting reactant, so it should be clear that the product should also bind to the activity site, albeit probably with lower affinity. Under conditions in which the product of a reaction is present in high concentration, it would be energetically advantageous to the cell if no more product was synthesized. Product inhibition is hence commonly observed. Likewise it be energetically advantageous to a cell if the end product of an entire pathway could likewise bind to the initial enzyme in the pathways and inhibit it, allowing the whole pathway to be inhibited. This type of feedback inhibition is commonly oberved



3. Allosteric regulation: As many pathways are interconnected, it would be optimal if the molecules of one pathway affected the activity of enzymes in another interconnected pathway, even if the molecules in the first pathway are structurally dissimilar to reactants or products in a second pathway. Molecules that bind to sites on target enzymes other than the active site (allosteric sites) can regulate the activity of the target enzyme. These molecules can be structurally dissimilar to those that bind at the active site. They do so my conformational changes which can either activate or inhibit the target enzyme's activity.
4. pH and enzyme conformation: Changes in pH which can accompany metabolic process such as respiration (aerobic glycolysis for example) can alter the conformation of an enzyme and hence enzyme activity. The initial changes are covalent (change in protonation state of the protein) which can lead to an alteration in the delicate balance of forces that affect protein structure.
5. pH and active site protonation state: Changes in pH can affect the protonation state of key amino acid side chains in the active site of proteins without affecting the local or global conformation of the protein. Catalysis may be affected if the mechanism of catalysis involves an active site nucleophile (for example), that must be deprotonated for activity.
6. Covalent modification: Many if not most proteins are subjected to post-translational modifications which can affect enzyme activity through local or global shape changes, by promoting or inhibiting binding interaction of substrates and allosteric regulators, and even by changing the location of the protein within the cell. Proteins may be phosphorylated, acetylated, methylated, sulfated, glycosylated, amidated, hydroxylated, prenylated, myristolated, often in a reversible fashion. Some of these modifications are reversible. Regulation by phosphorylation through the action of kinases, and dephosphorylation by phosphates is extremely common. Control of phosphorylation state is mediated through signal transduction process starting at the cell membrane, leading to the activation or inhibition of protein kinases and phosphatases within the cell.

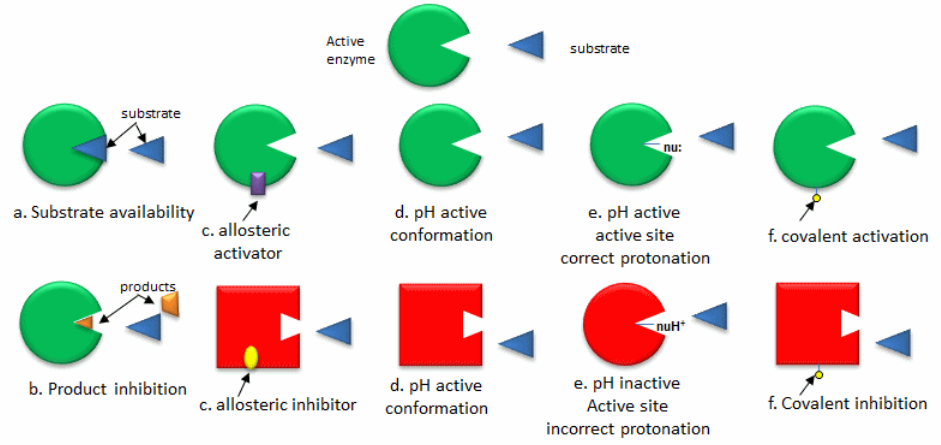


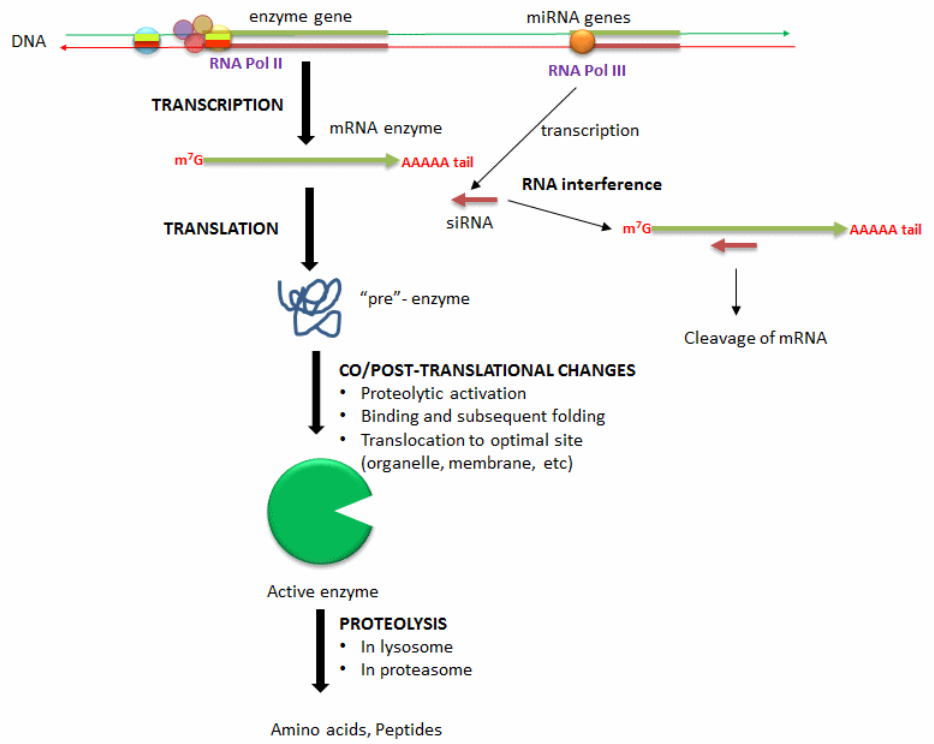
Figure 7.4.1: Regulation of the Activity of Pre-existing Enzymes

Extracellular regulated kinase 2 (ERK2), also known as mitogen activate protein kinase 2 (MAPK2) is a protein the plays a vital role in cell signaling across the cell membrane. Phosphoryation of ERK2 on Threonine 183 (Thr153) and Tyrosine 185 (Tyr185) leads to a structural change in the protein and the regulation of its activity.

Jmol: Erk2 -Structural Comparison of phosphorylated and dephosphorylated enzyme

B. Changing the amount of an enzyme: Another and less immediate but longer duration method to modulate the activity of an enzyme is to alter the activity of an enzyme that already exists in the cell. The list below, illustrated in the following figure, shows way in which enzyme concentration is regulated.

1. Alternation in transcription of enzyme's gene: Extracellular signal (hormones, neurotransmitters, etc) can lead to signal transductions responses and ultimate activation or inhibition of the transcription of the gene for a protein enzyme. These changes result from recruitment of transcription factors (proteins) to DNA sequences that regulate transcription of the enzyme gene.
2. Degradation of messenger RNA for the enzyme: The levels of messenger RNA for a protein will directly determin the amount of that protein synthesized. Small inhibitor RNAs, derived from microRNA molecules transcribed from cellular DNA, can bind to specific sequences in the mRNA of a target enzyme. The resulting double-stranded RNA complex recruits an enzyme (Dicer) that cleaves the complex with the effect of decreasing translation of the protein enzyme from its mRNA.
3. Co/Post translational changes: Once a protein enzymes is translated from its mRNA, it can undergo a changes to affect enzyme levels. Some proteins are synthesized in a "pre"form which must be cleaved in a targeted and limited fashion by proteases to active the protein enzyme. Some proteins are not fully folded and must bind to other factors in the cell to adopted a catalytically active form. Finally, fully active protein can be fully proteolyzed by the proteasome, a complex within cells, or in lysosomes, which are organelles within cells containing proteolytic enzymes.



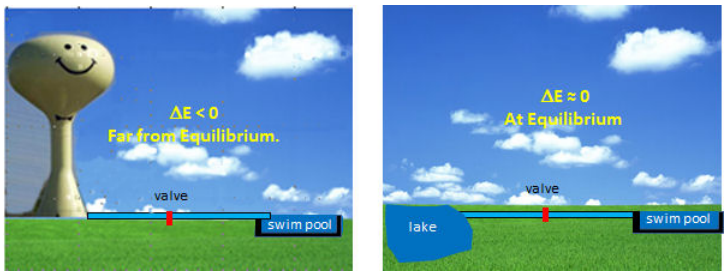
Next we will consider which enzymes in pathways make the best target for regulation.

7.5: Regulation of Metabolic Pathways B - Which Enzymes Are Optimal for Regulation?

All proteins are ultimately regulated, if only by modulating the rates of their synthesis and degradation. However, some enzymes positioned at key points in metabolic pathways are ideal candidates for regulation, as their activity can affect the output of entire pathways. These enzymes typically have two common characteristics, they catalyze reactions far from equilibrium and they catalyze early committed steps in pathways.

A. Regulation of enzymes for reactions not at equilibrium

The optimal enzymes for regulation are those at the beginning of pathways and that carry out thermodynamically favored reactions. Why is the latter so important? These enzymes control the flux of metabolites through pathway, so to understand their regulation we can use the analogy of flow (or flux) of water from one container to another. Let's say you wish to fill a swimming pool at any desired height you wish and you have two ways to do so (see figure below). You could open a valve that controls the flow from your towns water tower to the pool. In this the reaction (flow of water) is energetically (thermodynamically) favored given the difference in height of the water levels and the potential energy difference between the two. Even though flow (or flux) is cleared flavored, you can regulate it, from no flow, to maximal flow, by opening and closing the valve (analogous to activating and inhibiting an enzyme). Your choices in the other scenario, filling the pool from a lake, are not so great. It would be hard to fill the water to the desired level (especially if it was an above ground pool). It would be hard to regulate the flow.



By analogy, the best candidates for regulation are those enzymes whose reactions are thermodynamically favored (not at equilibrium) but which can be controlled by the mechanisms discussed in the previous section.

Which reactions are commonly not at equilibrium (i.e. $\Delta G^o < 0$ and usually also $\Delta G^o < 0$ if the ratio of products to reactants is not too high)? The answer is those that have reactants that are thermodynamically unstable compared to their reaction products. There are several types of reactions that often fit these criteria:

Hydrolysis (or similar reactions) of anhydride or analogous motifs: The figure below shows molecules with similar "anhydride" motifs and the ΔG^o for hydrolysis of the molecules. Those with more negative ΔG^o values can transfer their phosphate group to ADP to make ATP, which is necessary to drive unfavorable biological reactions. Metabolic reactions that involve hydrolysis (or other type of transfer reaction of these groups) usually proceed with a negative ΔG^o and ΔG, making them prime candidates for pathway regulation. Many textbooks label these types of molecules as having "high energy" bonds. This is confusing to many student as bonds between atoms lower the energy compare to when the atoms are not bonded. It takes energy to break the "high" energy phosphoanhydride covalent bond. What make hydrolysis of the molecules below so exergonic is that more energy is released on bond formation within the new products than was required to break the bonds in the reactants. In addition, other effects such as preferential hydration of the products, lower charge density in the products, and less competing resonances in the products all contribute to the thermodynamically favorable hydrolysis of the reactants.

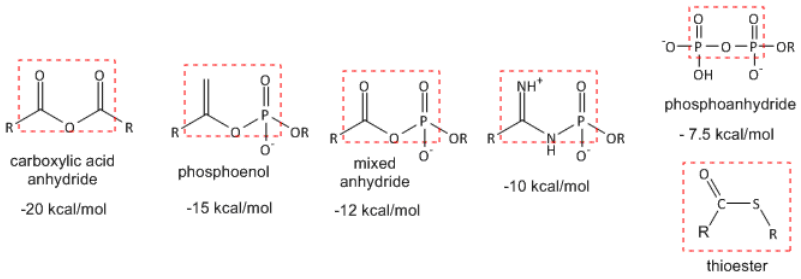


Figure 7.5.1: Thermodynamically Unstable Molecules (compared to their reaction products)

Thioesters (such as Acetyl-SCoA) are also included since that have the same negative ΔG^o of hydrolysis as ATP, even though the lack an "anhydride" motif. Thioesters are destabilized compared to their hydrolysis products and in comparison to esters made with alcohol since the C-S bond is weaker. Why?

Redox reactions: Everyone knows that redox reactions are thermodynamically favored if the oxidizing agent deployed is strong enough. The oxidation reactions of hydrocarbons, sugars, and fats by dioxygen are clearly exergonic (we do call these combustion reactions after all). What about redox reactions with less powerful oxidants? NAD+ is used frequently as a biological oxidizing agent. Are all these reactions as favored as combustion? Hardly so. Remember that in every redox reaction, an oxidizing and reducing agent react to form another oxidizing and reducing agent. Consider the following reaction:

$$\text{Pyruvate} + \text{NADH} \longrightarrow \text{Lactate} + \text{NAD}^+. \tag{7.5.1}$$

This reaction can go either way and is reversible. In the above form, it is written in the favored direction in aeroboic metabolism when both Pyr and NADH level are high. Although the ΔG^o actually favors the oxidation of lactate, given the high concentration of Pyr and NADH, the reaction is driven in the opposite direction and proceeds as shown. To determine if a redox reaction is favored and likely to occur, and possibly be regulated, the ΔG^o for a redox reaction should be calculated from standard reduction potentials, using the formula

$$\Delta G^o = -nFE^o. \tag{7.5.2}$$

B. Regulation of enzymes catalyzing committed steps in pathways:

The best enzymes to regulate are those that catalyze the first committed step in the reaction pathway. The committed step proceeds with a DG < 0 and is essentially irreversible. These reactions often occur from key metabolic intermediates that are immediately before or proximal to branches in reaction pathways. Two examples are shown below.

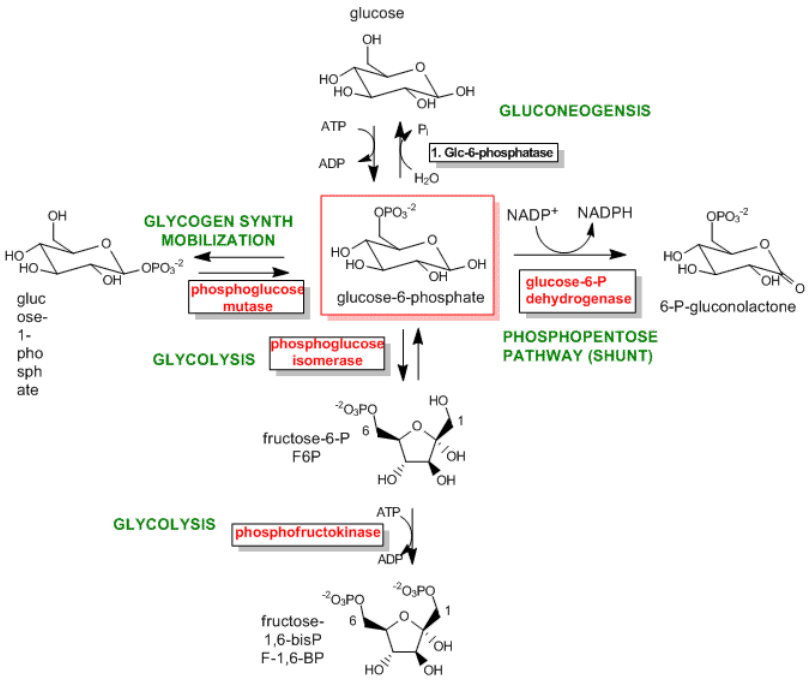


Figure 7.5.2: Reactions for Glucose-6-phosphate

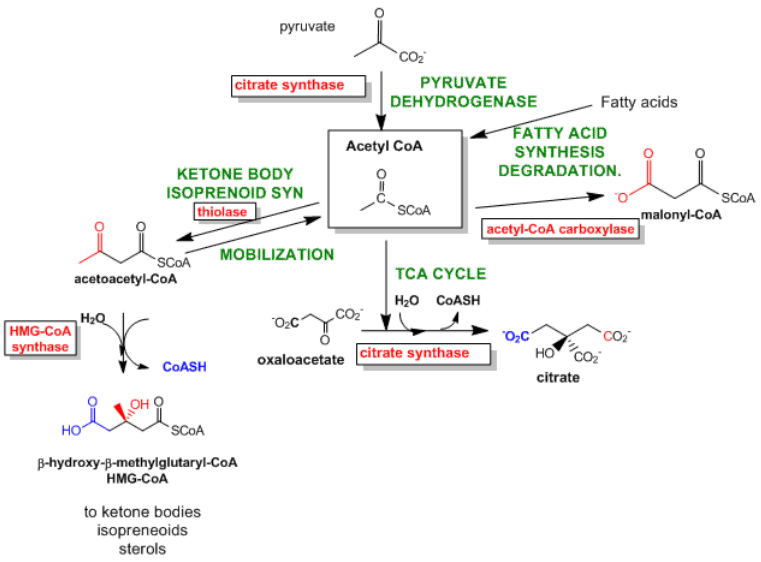


Figure 7.5.3: Reactions for Acetyl-CoA

CHAPTER OVERVIEW

8: Mechanisms of Glycolysis

8.1: Introduction to Glycolysis - Energy Storage

Glycolysis is a biochemical pathway in which glucose is consumed and ATP is produced. This pathway is an example of catabolism, in which larger molecules are broken down in the cell to make smaller ones. The opposite kind of pathway is anabolism, in which larger molecules are synthesized from smaller ones in the cell.

From the biologist's perspective, catabolism is associated with the breakdown of larger molecules to release energy. For example, in grade school science, you may have learned that most organisms derive their energy from the breakdown of carbohydrates. You may have seen the process of respiration expressed through the following equation of reaction:

$$\mathrm{C_6H_{12}O_{6(s)} + 6\,O_{2(g)} \longrightarrow 6\,CO_{2(g)} + 6\,H_2O_{(l)} + energy}$$

That idea gives rise to the slightly misleading paradigm that energy is stored in chemical bonds. The idea goes that, for example, when the single sugar molecule represented by the formula, $C_6H_{12}O_6$, is broken down to make six carbon dioxide molecules, the energy from all of those broken bonds is released for the benefit of the organism.

You may also have learned about another important energy-storage molecule, ATP. Like the breakdown of sugar, the breakdown of ATP is used to power other processes in the cell. That process might be expressed in the following expression:

$$\mathrm{ATP_{(aq)} + H_2O_{(l)} \longrightarrow ADP_{(aq)} + P_{i(aq)} + energy}$$

Once again, this can be considered a breaking-down process, in which an ATP molecule is split into a smaller ADP molecule and an inorganic phosphate.

From the chemist's perspective, it is wrong to suggest that energy is stored in chemical bonds. Instead, energy is released when bonds are formed. This chemical perspective is more than an idea; it represents physical reality. It can be demonstrated in a number of ways that energy is released when bonds are made, and energy must be used up in order to break bonds; apparently, this situation is the opposite of the biological viewpoint.

Some authors have suggested that this apparent disagreement is something like a difference of perspective. Think of an observer standing on the shore of the ocean, watching a ship sail away. From the observer's viewpoint, the ship eventually sinks below the ocean. After a while its hull is no longer visible; only its masts remain, and finally they, too, slip down and are gone. To a passenger on the ship, however, the ship is still sailing along on the surface of the ocean. Biologists and chemists think about bonding differently because they are looking at it from a different viewpoint.

Biologists say that energy is stored in chemical bonds because thinking about things that way is useful to them. It is useful to think of catabolic processes, such as the breakdown of sugars, as energy-releasing. It is useful to think of anabolic processes, such as photosynthesis or the synthesis of complex natural products, as energy-intensive.

Biologists are looking at things purely from the point of view of the biomolecule. Either it is breaking down into smaller pieces (its bonds are breaking), releasing energy, or else it is getting built up into something bigger (its bonds are being made), costing energy.

In a very loose sense, it is as if the reaction of carbohydrate breakdown is pared down to:

$$\mathrm{C_6H_{12}O_{6(s)} \longrightarrow 6\,CO_{2(g)} + energy}$$

And the reaction of ATP breakdown is abbreviated to:

$$\mathrm{ATP_{(aq)} \longrightarrow ADP_{(aq)} + P_{i(aq)} + energy}$$

In other words, part of the reaction is ignored. That viewpoint allows a focus on the biomolecule, but it neglects some important things. For example, in the breakdown of carbohydrates, it isn't the C-C bond breaking of the carbohydrates that is the source of energy. It is the formation of strong, new O-H and C=O bonds, and other, more subtle changes, that release the energy.

As always, we get more insight into a reaction by looking at the structural formulae in the equation, rather than condensed formulae. This way, we can actually see what bonds are being made and broken.

Figure 8.1.1: An equation of reaction for respiration, or the combustion of glucose, with structures.

The case of ATP is a little different. The bonds made and broken are pretty much the same in the breakdown of ATP; loosely, we just trade in one P-O bond for another. This case is more complicated, but the simplest explanation is that ATP cleavage relieves repulsion between the multiple negative charges in the ATP molecule. Energy decreases in the resulting molecules, and the rest of the energy that used to be in the reactants is released.

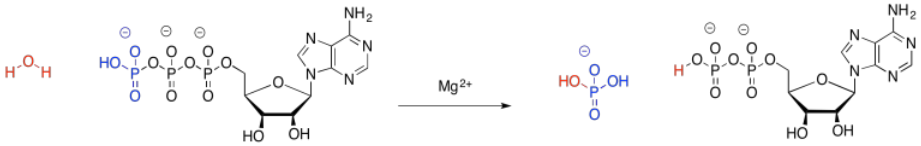


Figure 8.1.2: An equation of reaction for the hydrolysis of ATP, with structures.

In the reverse, when ADP is phosphorylated to make ATP, the system goes up in energy (the system just means everything in the reaction; it is everything on one side of the arrow or the other). That energy, however, is not really stored in any chemical bonds. It is distributed throughout the system, for example, in the motions of all of those atoms. The bonds may stretch, getting longer and shorter, but in addition the groups on the ends of the bonds can spin, and the molecules can tumble and zip around through space. There are lots of ways to distribute that energy throughout that entire collection of atoms; it isn't forced to sit in that one bond that was newly formed between two atoms.

So, although the idea of energy being stored in chemical bonds may be very useful in the biology classroom, it is only going to get in your way in the chemistry classroom. You need to be able to take off your biologist's hat and put on your chemist's lab coat when you need it.

? Exercise 8.1.1

Our economy is driven largely by the consumption of fossil fuels, such as heptane. Given the following reaction for the breakdown of heptane:

$CH_3CH_2CH_2CH_2CH_2CH_2CH_3 + 11\ O_2 \rightarrow 7\ CO_2 + 8\ H_2O$

Use the table of bond strengths to determine how much energy is released when a mol of heptane is consumed.

Bond	O=O	C-C	C-H	C=O	O-H
Average Bond Strength (kcal/mol)	120	80	100	190	110

a. Start by determining the energy needed to break bonds.
b. Determine the energy released when new bonds are made.
c. Determine the overall energy change.

Answer

Bonds Broken:

C-C 6 x 80 kcal/mol = 480 kcal/mol

C-H 16 x 100 kcal/mol = 1,600 kcal/mol

O=O 7 x 120 kcal/mol = 840 kcal/mol

Total: 2,920 kcal/mol

Bonds Made:

C=O 14 x (- 190 kcal/mol) = - 2,660 kcal/mol

O-H 16 x (- 110 kcal/mol) = -1,760 kcal/mol

Total: -4,420 kcal/mol

Overall: 1,240 - 4,420 kcal/mol = -1,500 kcal/mol

Exercise 8.1.2

Use the table of bond strengths to determine how much energy is released when a mol of octane is consumed.

$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_3 + 12.5\ O_2 \rightarrow 8\ CO_2 + 9\ H_2O$

Answer

Bonds Broken:

C-C 7 x 80 kcal/mol = 560 kcal/mol

C-H 18 x 100 kcal/mol = 1,800 kcal/mol

O=O 12.5 x 120 kcal/mol = 1,500 kcal/mol

Total: 3,860 kcal/mol

Bonds Made:

C=O 16 x (- 190 kcal/mol) = - 3,040 kcal/mol

O-H 18 x (- 110 kcal/mol) = -1,980 kcal/mol

Total: -5,020 kcal/mol

Overall: 3,860 - 5,020 kcal/mol = -1,160 kcal/mol

Exercise 8.1.3

Given an approximate C-O bond strength of 85 kcal/mol, use the table of bond strengths to determine how much energy is released when a mol of glucose is consumed.

Answer

Bonds Broken:

C-C 6 x 80 kcal/mol = 480 kcal/mol

C-H 7 x 100 kcal/mol = 700 kcal/mol

C-O 7 x 85 kcal/mol = 595 kcal/mol

O-H 5 x 110 kcal/mol = 550 kcal/mol

O=O 6 x 120 kcal/mol = 840 kcal/mol

Total: 3,165 kcal/mol

Bonds Made:

C=O 12 x (- 190 kcal/mol) = - 2,280 kcal/mol

O-H 12 x (- 110 kcal/mol) = -1,320 kcal/mol

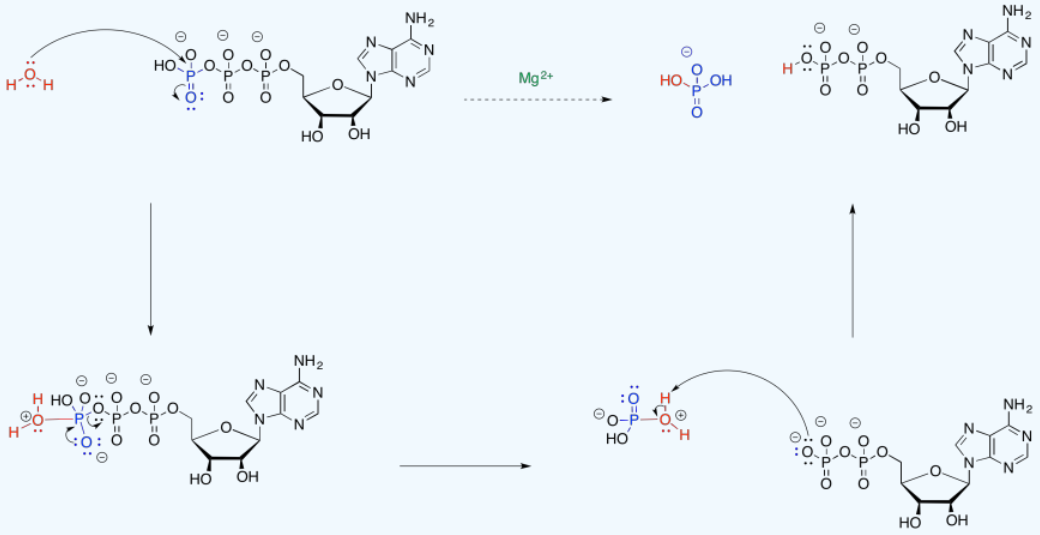
Total: -3,600 kcal/mol

Overall: 3,165 - 3,600 kcal/mol = -435 kcal/mol

Exercise 8.1.4

Provide a mechanism for the hydrolysis of ATP to ADP.

Answer



Exercise 8.1.5

Suggest a possible role for magnesium ion in the hydrolysis of ATP.

Answer

In the mechanism for hydrolysis, water acts as a nucleophile and ATP acts as an electrophile. That's a problem because ATP is negatively charged. It will not attract electrons very easily. By binding to magnesium ion (Mg^{2+}), the charge on the ATP will be lowered, accelerating the reaction with water.

8.2: Overview of Glycolysis

In the cell, carbohydrates are used as a source of energy. The carbohydrates might have been recently ingested, or they might be released from long-term storage. Carbohydrates can be stored in the form of glycogen, in animals, or starch, in plants. Glycogen and starch are biomacromolecules. They are composed of large collections of glucose molecules bonded together (or enchained) into one, much bigger molecule. They have different structures: starch is composed of very long chains of glucose molecules, whereas glycogen is a highly branched structure, more like a coral or a tree. Specific enzymes can be used to release glucose molecules, one by one, from these structures.

Glycolysis is a biochemical pathway in which glucose is consumed and ATP is produced. ATP is like the spring that powers all of the windup toys of the cell. To compress that spring, energy has to be expended, so glucose is sent through a series of reactions that eventually release some energy that can be used for this purpose. Once the spring is charged, it can release its energy rapidly.

The consumption of glucose is associated with the catabolic process of respiration. In respiration, glucose is combined with oxygen, the reactants are converted to carbon dioxide and water, and energy is released. We could write that reaction as follows:

$$\mathrm{C_6H_{12}O_6(s) + 6\,O_2(g) \longrightarrow 6\,CO_2(g) + 6\,H_2O(l) + energy} \tag{8.2.1}$$

However, that reaction is really the sum total of three different processes. In the first process, glycolysis, glucose is broken down partway, forming pyruvate. Some energy is released by the process. In the second process, the tricarboxylic acid (TCA) cycle or citric acid cycle, pyruvate is broken down further to release carbon dioxide. Again, some energy is produced by this process. Both of these pathways produce ATP. Both of these pathways also produce NADH. In the third process, oxidative phosphorylation, NADH is used to power an "electron transport chain", releasing additional energy that is harnessed in order to make more ATP. The TCA cycle will be covered in a later chapter in this section of the book. Oxidative phosphorylation is not discussed until the Reactivity III section of the book, which is concerned with single electron processes.

When looking at biochemical pathways, it is helpful to have a map of the process to get an overview of how all the steps fit together. Glycolysis is sometimes presented in two parts, so two maps are shown below. The first part, Phase One, actually consumes energy; this part is the initial investment needed for a later return.

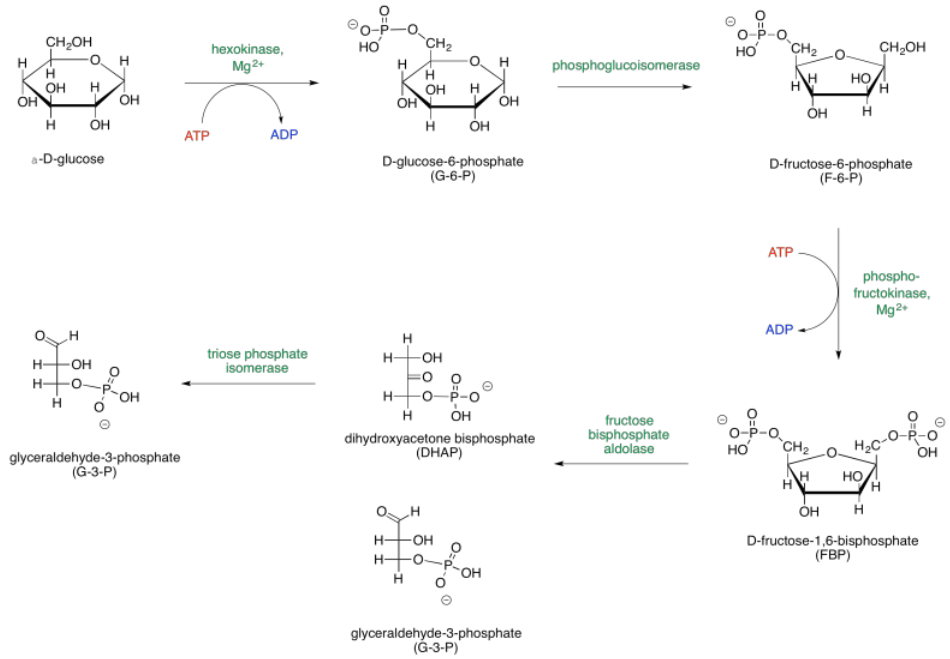


Figure 8.2.1: Phase One of glycolysis leads to the scission of a six-carbon sugar into two three-carbon sugars.

The map of phase one of glycolysis starts with glucose and leads eventually to the formation of two G3P molecules. Glucose is the initial input, and G3P is the final output; everything else along the way is just an intermediate that is consumed soon after it is made. Along the way, additional inputs to the reaction are shown in red, and outputs are shown in blue. Enzymes and other catalytic factors, which are not consumed by the reaction, are shown in green.

Exercise 8.2.1

Provide a net equation for phase one of glycolysis that shows all of the inputs on one side of the reaction arrow and all of the outputs on the other side of the reaction arrow.

Answer

glucose + 2 ATP → 2 G3P + 2 ADP

Note that the first phase of glycolysis actually consumes ATP rather than producing it. This initial investment of energy leads to a later return. The second part of glycolysis, Phase Two, occurs after the glucose has been cleaved in half; this phase leads to the release of energy.

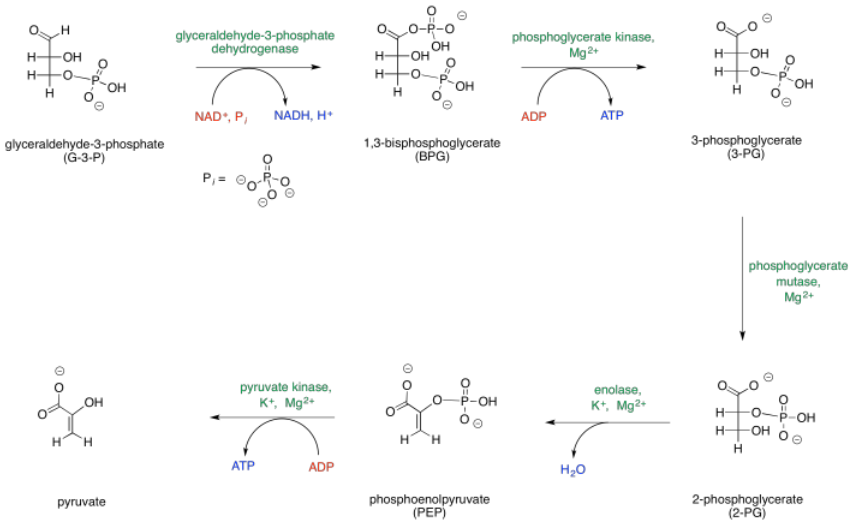


Figure 8.2.2: Phase two of glycolysis leads to production of ATP.

The map of phase two of glycolysis starts with G3P and leads eventually to the formation of pyruvate. G3P is the initial input, and pyruvate is the final output; everything else along the way is just an intermediate that is consumed soon after it is made. Along the way, additional inputs to the reaction are shown in red, and outputs are shown in blue. Enzymes and other catalytic cofactors are shown in green.

Exercise 8.2.2

Provide a net equation for phase one of glycolysis that shows all of the inputs on one side of the reaction arrow and all of the outputs on the other side of the reaction arrow.

Answer

$G3P + NAD^+ + PO_4^{3-} + 2\ ADP \rightarrow pyr + NADH + 2\ ATP + H_2O$

Exercise 8.2.3

Provide a net equation for glycolysis (both phases combined) that shows all of the inputs on one side of the reaction arrow and all of the outputs on the other side of the reaction arrow.

Answer

First we need to realise that one glucose gives rise to two molecules of G3P, so the second phase occurs twice for every glucose molecule consumed.

$2\ G3P + 2\ NAD^+ + 2\ PO_4^{3-} + 4\ ADP \rightarrow 2\ pyr + 2\ NADH + 4\ ATP + 2\ H_2O$

Adding the equations for the two phases together gives:

glucose + 2 ATP + 2 G3P + 2 NAD^+ + 2 PO_4^{3-} + 4 ADP → 2 G3P + 2 ADP + 2 pyr + 2 NADH + 4 ATP + 2 H_2O

That equation can be simplified, because some things appear on both the left and the right. It's just like algebra.

glucose + 2 NAD^+ + 2 PO_4^{3-} + 2 ADP → 2 pyr + 2 NADH + 2 ATP + 2 H_2O

It helps to be able to think about sugars in both cyclic and open chain forms. Phase One can be presented in an alternative way that depicts the carbohydrates as open chains rather than rings.

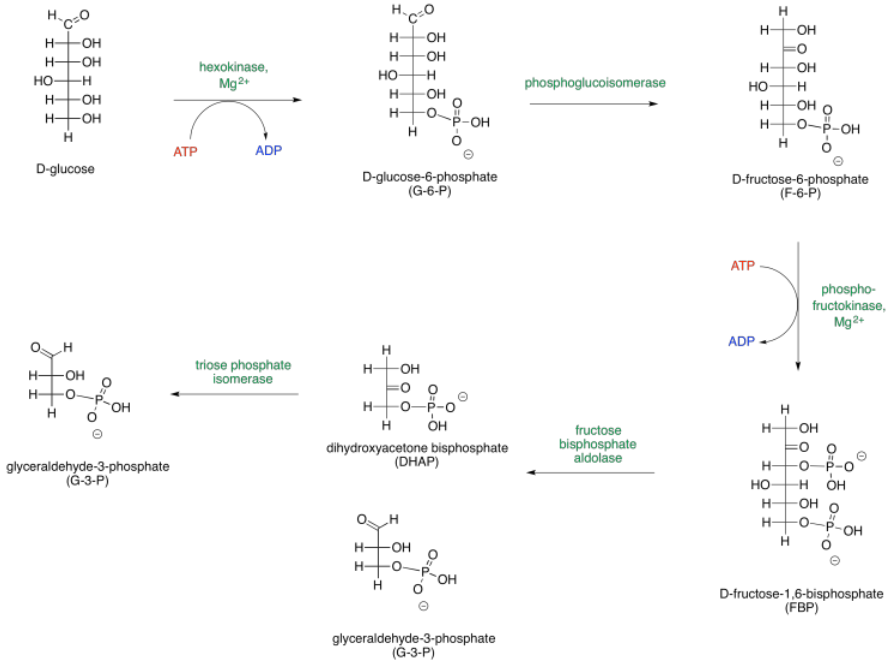


Figure 8.2.3: An alternative presentation of Phase One, showing the sugars in their open-chain forms.

These two different ways of depicting carbohydrates takes into account that most carbohydrates are dynamic structures. Rather than having one form, they have different forms that can interconvert between each other, and all of these forms are present at equilibrium. One form dominates, and that's usually a ring. For glucose, the six-membered ring or "pyranose" form makes up about 99% of molecules in solution. In water, the beta-form, in which the rightmost OH group in the Haworth projection is *cis*- to the CH_2OH group, makes up about two thirds of the pyranose form. In nonpolar environments the ratio is reversed, with the alpha-form dominating, in which the rightmost OH group in the Haworth projection is *trans*- to the CH_2OH group.

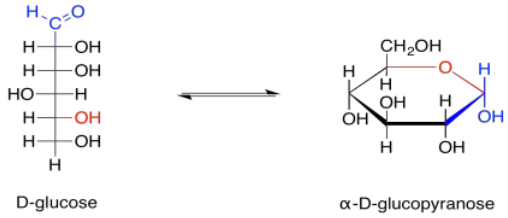


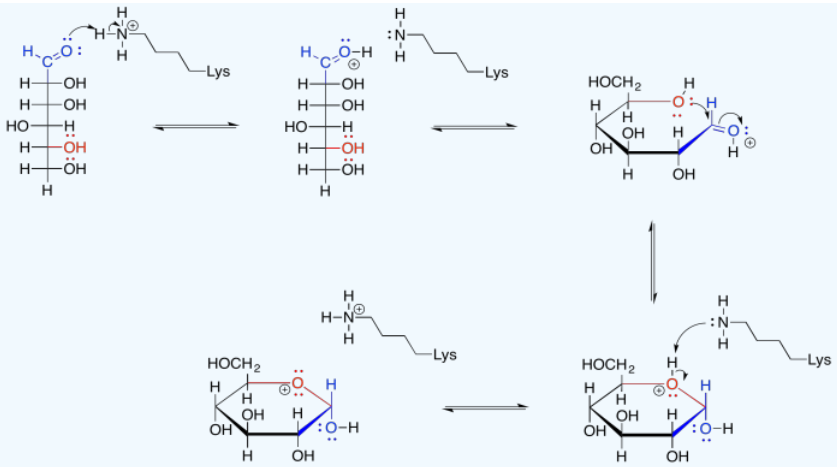
Figure 8.2.4: Equilibrium between the open chain and a cyclic form of glucose.

The open chain form makes up less than one percent of glucose molecules in solution. Nevertheless, sometimes it is the open-chain form that actually undergoes reaction, so it is useful to think of carbohydrates both ways.

? Exercise 8.2.4

Provide a mechanism for the formation of glucopyranose from the chain form of glucose. Assume biological conditions, such as the presence of a lysine residue to assist in proton transfer.

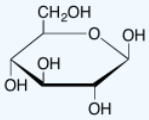
Answer



Exercise 8.2.5

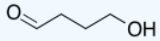
In the map of glycolysis, the α-D-glucopyranose form is shown. Draw β-D-glucopyranose.

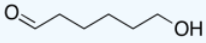
Answer

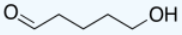


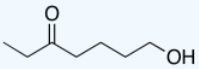
Exercise 8.2.6

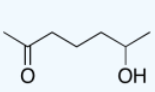
Show the hemiacetals that would form in the following cases.

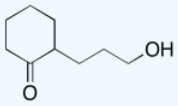
a) 

b) 

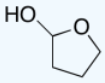
c) 

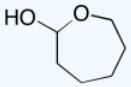
d) 

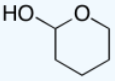
e) 

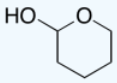
f) 

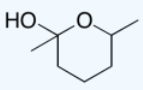
Answer

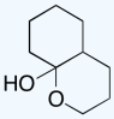
a) 

b) 

c) 

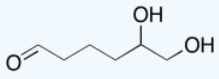
d) 

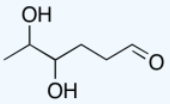
e) 

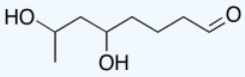
f) 

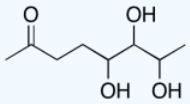
Exercise 8.2.1

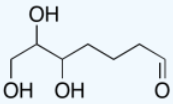
Show the pyran rings (six-membered rings with oxygen) that would form in the following cases.

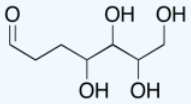
a) 

b) 

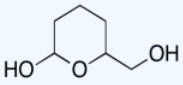
c) 

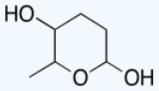
d) 

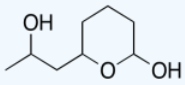
e) 

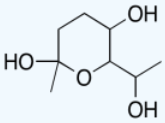
f) 

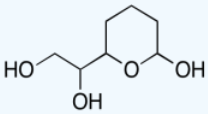
Answer

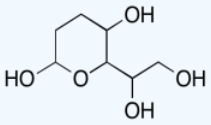
a) 

b) 

c) 

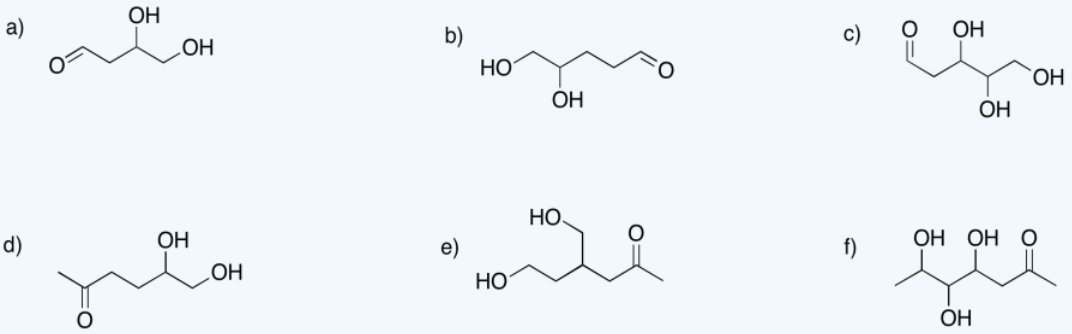
d) 

e) 

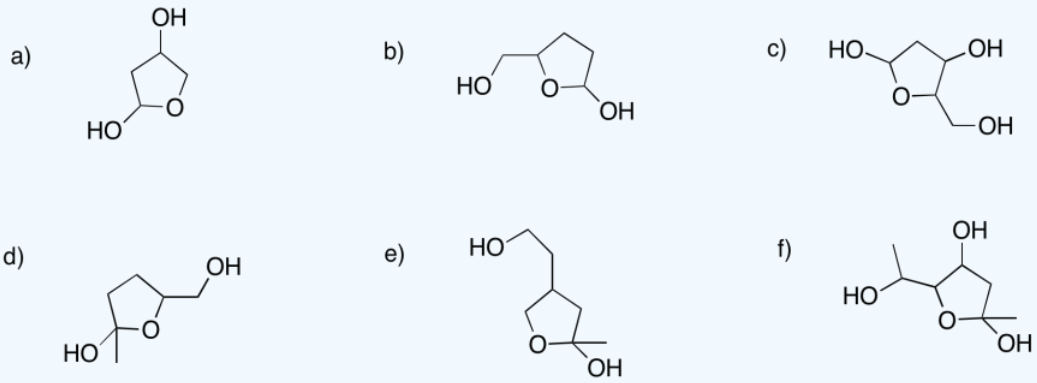
f) 

Exercise 8.2.8

Show the furan rings (five-membered rings with oxygen) that would form in the following cases.



Answer



8.3: Mechanisms of Phase One- Phosphorylation and Isomerisation

In the next couple of sections, we will look at the changes occurring in reactions of glycolysis and try to understand how those changes may be happening. In some cases, we will develop a formal understanding of the reaction, and return in a later section to see how that reaction is actually catalysed by an enzyme.

The first phase of glycolysis is all about taking the initial carbohydrate, glucose, and getting it into the right form for the energy-releasing, ATP-forming reactions of the second phase. All of the reactions of glycolysis are catalysed by enzymes. If you know anything about enzymes, you may know that there are many controls in place so that their reactions can be turned on or off.

One common element of enzyme control is phosphorylation. In phosphorylation, a phosphate group is added. The phosphate group could be added to the enzyme, or it could be added to the substrate -- the compound on which the enzyme carries out a reaction. If you look again at the map of Phase One, you will see a couple of phosphorylations taking place. Glucose is phosphorylated to start things off, and later on, a fructose phosphate is again phosphorylated to make a fructose bisphosphate.

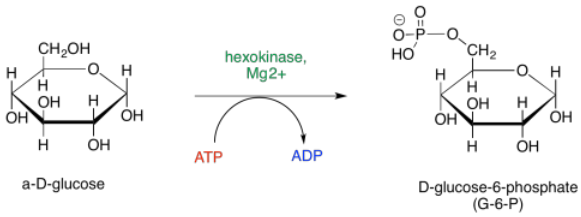


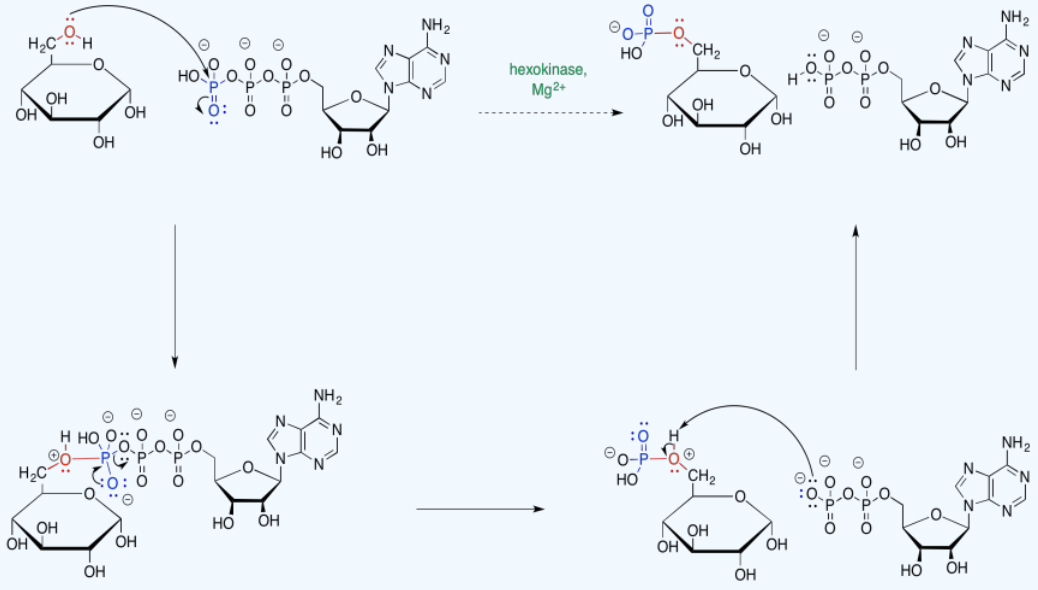
Figure 8.3.1: Phosphorylation of glucose.

Phosphorylation typically modifies the interaction of a substrate with its surroundings. It could be that phosphorylation, and the negative charge that results on the glucose, helps the glucose to bind more tightly with the next enzyme in the pathway. It is also believed that the anionic glucose phosphate is less likely to leave the cell, because it can't be taken up at the nonpolar membrane and transported across the membrane to the outside of the cell. A cell that needs energy would find it advantageous to prevent its glucose from escaping.

? Exercise 8.3.1

Provide a mechanism for the phosphorylation of glucose.

Answer



The second step of glycolysis is an isomerisation. The carbonyl of glucose, on the first carbon in the chain form, migrates to the second carbon in the chain.

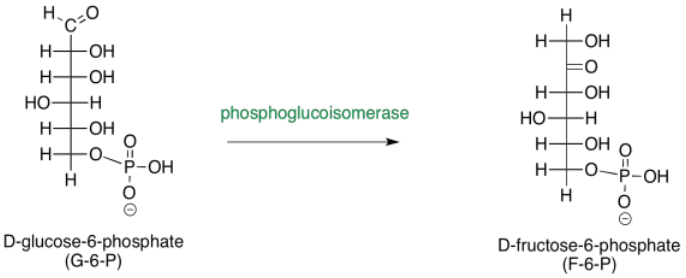


Figure 8.3.2: Isomerisation of glucose-6-phosphate.

The key to understanding this reaction is noting that, when the second carbon in the chain becomes a carbonyl, it loses a hydrogen.

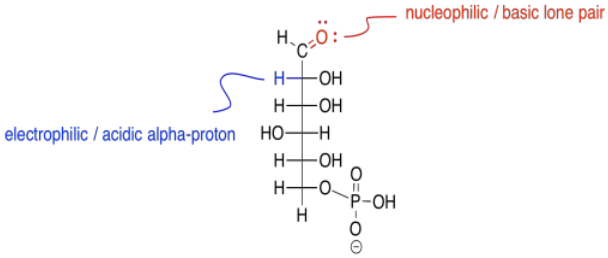


Figure 8.3.3: Reactive sites of glucose-6-phosphate.

The reaction actually occurs via an enol intermediate. Remember, an enol is just a tautomer of the original compound; that means it is an isomer in which the major difference is the position of one proton. In an enol tautomer, one proton has been moved from the alpha position, next to the carbonyl, over to the carbonyl oxygen.

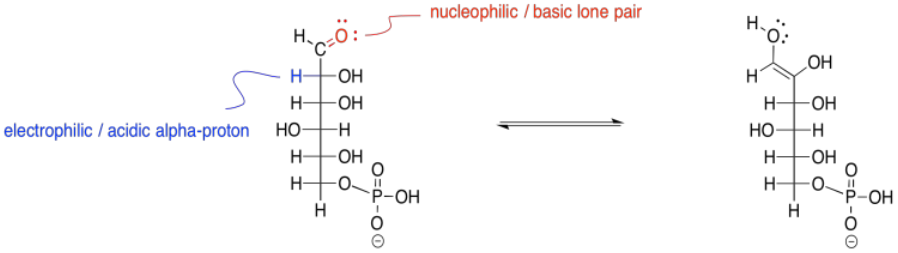


Figure 8.3.4: Keto-enol tautomerism to provide an enol intermediate.

? Exercise 8.3.2

Keto-enol tautomerism involves eventual transfer of a proton from one site to another within the same molecule. The reaction is subject to general catalysis, meaning it can be carried out either by acid or by base.

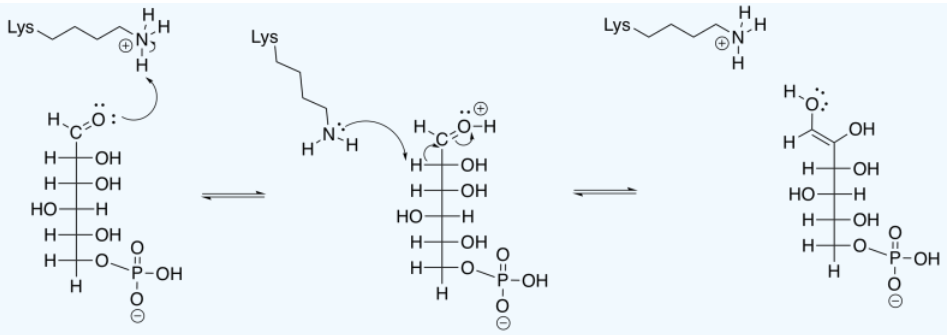
Provide a mechanism for the conversion of 2-propanone into its enol form in the presence of:

a. aqueous hydrochloric acid
b. aqueous sodium hydroxide

? Exercise 8.3.3

Provide a mechanism for the keto-enol tautomerism of glucose-6-phosphate. Assume acidic, biological conditions (for example, assisted by the acidic form of a lysine side chain).

Answer



Another enol-keto equilibrium is needed in order to complete the overall reaction. This time, it is the enol form going back into a keto form. That means the proton is being transferred from an OH group along the C=C bond (the enol position) back to the alpha position. But take a close look at this molecule. It actually has two different enol OH groups. Either one could lose its proton and turn back into a carbonyl. One of those events leads right back where we started from. The other one leads forward to fructose-6-phosphate.

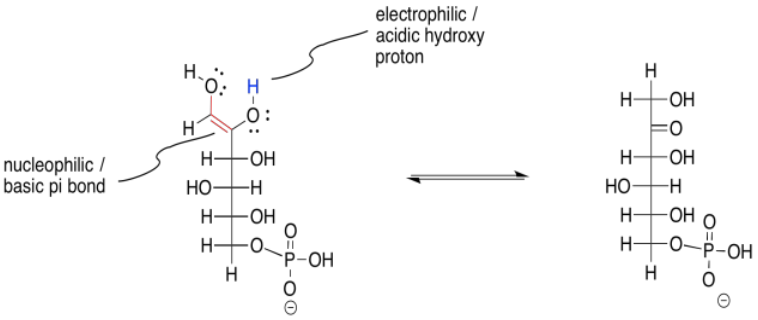


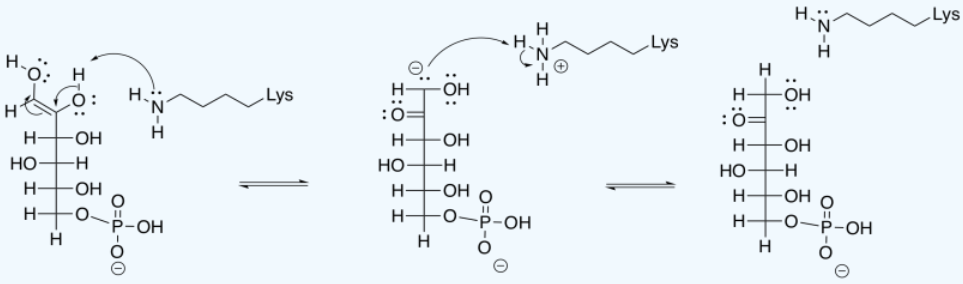
Figure 8.3.5: Keto-enol tautomerism completes the reaction to form fructose-6-phosphate.

Why did this step have to take place? Remember, the eventual end product of phase one of glycolysis is a three-carbon sugar, G3P. Right now we have a six carbon sugar (fructose, not glucose, but still a six-carbon sugar). The migration of the carbonyl from the first carbon to the second is what will allow the glucose molecule to break in half, between the third and the fourth carbon. It is going to break in an alpha position, next to a carbonyl. We have just moved the carbonyl to put the alpha position in the right place.

Exercise 8.3.4

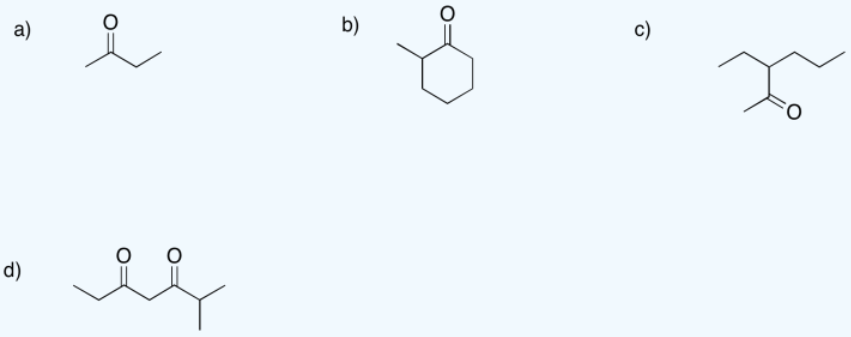
Provide a mechanism for the keto-enol tautomerism that forms fructose-6-phosphate. Assume basic, biological conditions (for example, assisted by the basic form of a lysine side chain).

Answer

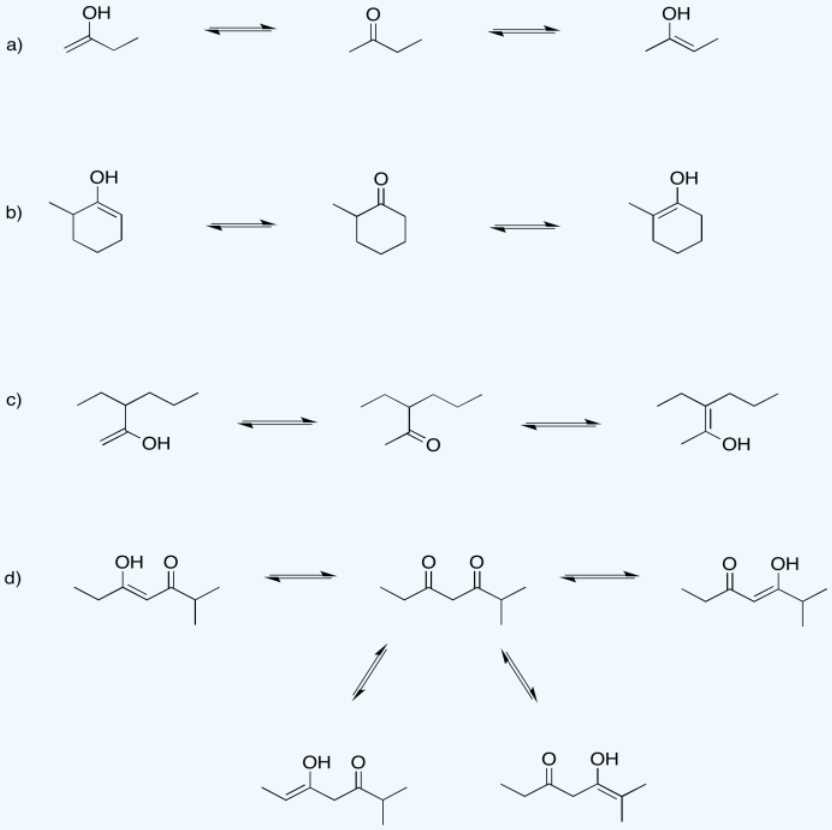


Exercise 8.3.5

Frequently, formation of an enol from a ketone could result in different products. Show the enol products (there are at east two in each case) that could form from each of the following compounds.

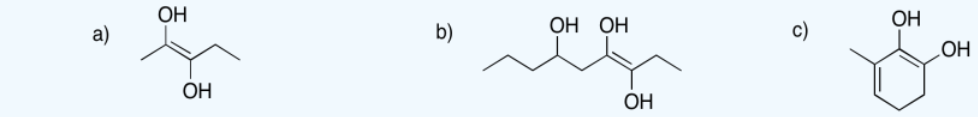


Answer

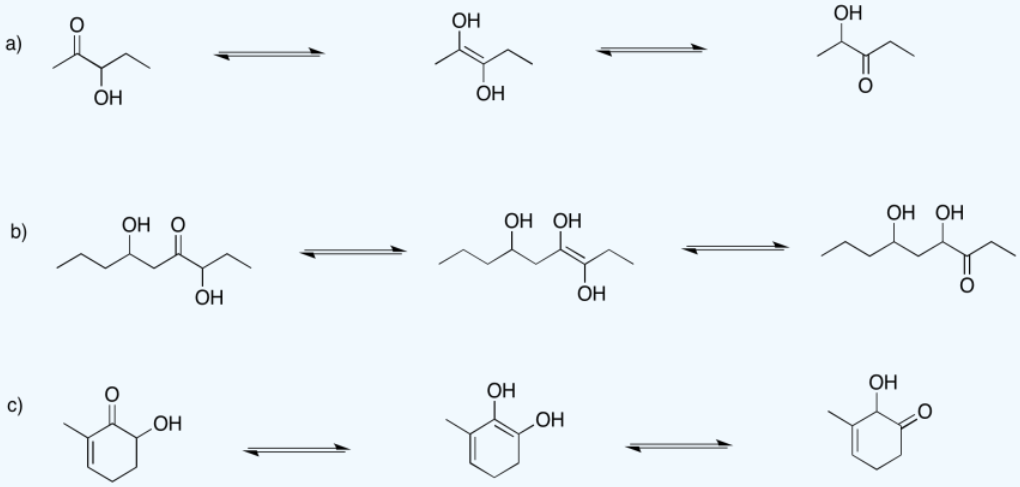


Exercise 8.3.6

Each of the following enols could form two different keto tautomers via keto-enol tautomerism. Show both products in each case.



Answer



The subsequent step in the pathway is that second phosphorylation, forming fructose-1,6-bisphosphate. The compound changes from an anion to a dianion, and that change has consequences in how the molecule interacts with its environment. Once again, the molecule becomes even less likely to move into the nonpolar cell membrane. Furthermore, it can now interact with different enzymes in a way it couldn't when it was just a monoanion.

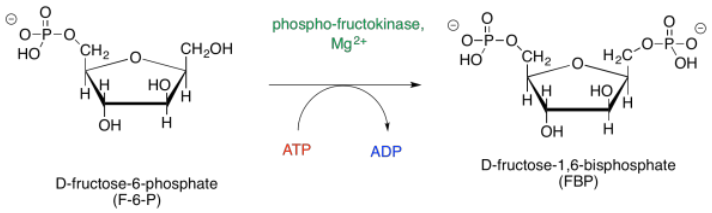


Figure 8.3.6: Another phosphorylation to form fructose-1,6-bisphosphate.

This phosphorylation requires the consumption of another molecule of ATP. Remember, this phase of glycolysis is not the energy-producing part. We are still getting ready for that part. It will happen in phase two, but we still have more to do in phase one on the next page.

? Exercise 8.3.7

Provide a mechanism for the formation of FBP from F6P.

8.4: Mechanisms of Phase One - Scission

The first few steps of glycolysis involve relatively minor changes. The sugar is phosphorylated, at two different stages, and a couple of keto-enol tautomerisations are employed to move the carbonyl position one carbon down the chain. The carbonyl migration allows the fructose molecule to undergo a scission or cleavage, in which the molecule is cut in half. That gives a couple of three-carbon sugars. Three-carbon sugars like these are important in phase two of glycolysis, the energy-producing phase.

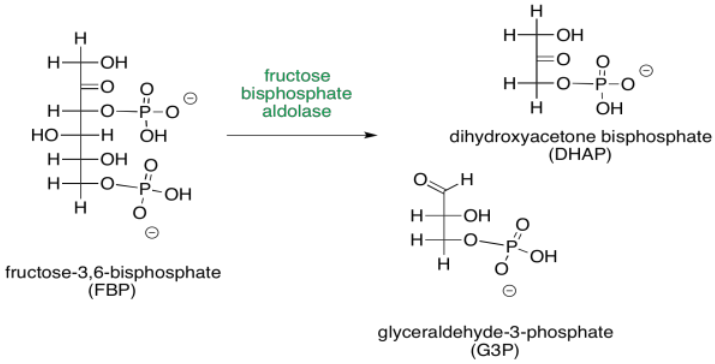


Figure 8.4.1: Cleavage of fructose into two three-carbon sugars.

To understand how the molecule splits in two, we're going to imagine a complementary case, because it might seem more familiar. The reaction shown below is called an aldol reaction. That's the one in which an enolate ion, with a negatively charged carbon next to a carbonyl, donates to a regular carbonyl. The enolate ion acts as the nucleophile, donating electrons to the neutral carbonyl, which acts as the electrophile. The electrophilic carbonyl pops open to make an alkoxide ion, which then picks up a proton to make the alcohol part of the aldol product.

Figure 8.4.2: A simple aldol reaction.

? Exercise 8.4.1

Show why the enolate ion is very stable, even though other carbon anions typically are not easy to form.

The products of aldol reactions bear a pattern that is easy to spot: there is always a carbonyl-carbon-alcohol sequence, O=C-C-C-OH. The middle carbon was the nucleophilic carbon; the carbon attached to the OH is the former electrophilic carbonyl carbon. The thing is, aldol reactions are reversible. They can go backward again, re-forming their starting materials. So if you look at an aldol product, with that carbonyl-carbon-alcohol sequence, you can imagine the molecule splitting apart, with a break between the middle carbon and the alcohol carbon.

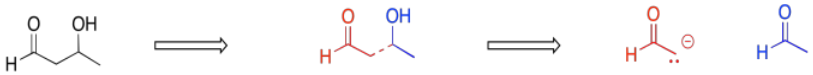
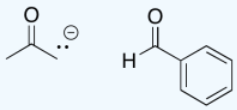


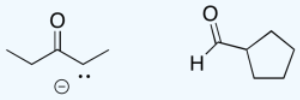
Figure 8.4.3: Retrosynthetic analysis of an aldol reaction, showing how a compound could be formed via an aldol reaction.

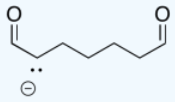
The open arrow in the picture above is a specific symbol in chemistry that means "can be made from". The aldol product can be made from the enolate and the carbonyl. But if an aldol reaction is reversible, then the reverse is also true: an enolate and a carbonyl can be formed from an aldol product, characterised by its O=C-C-C-OH pattern. This reverse reaction is called a retro-aldol reaction.

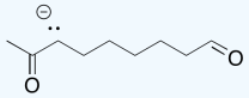
? Exercise 8.4.2

Predict the products of the following aldol reactions.

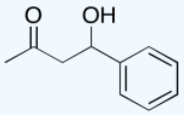
a) 

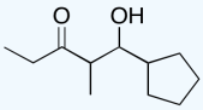
b) 

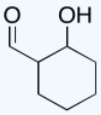
c) 

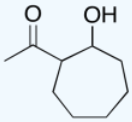
d) 

Answer

a) 

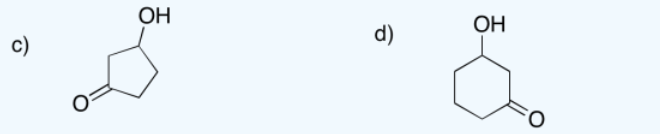
b) 

c) 

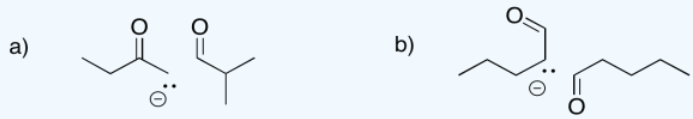
d) 

Exercise 8.4.3

Predict the precursors that could be used to form these compounds through aldol reactions.



Answer



What makes retro-aldol reactions possible? The same thing that made the forward aldol reaction possible: the stability of an enolate anion. Carbon-carbon bonds are actually pretty difficult to break, because the pair of electrons forming the bond aren't likely to shift one way or the other. The enolate provides a release mechanism. A pair of electrons can shift to the carbon next to the carbonyl, or the alpha position, because they will form a stable anion there.

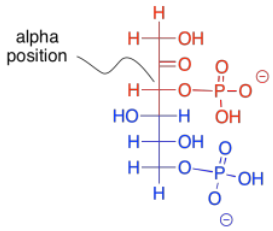


Figure 8.4.4: Frustose-1,6-bisphosphate depicted as a nucleophilic aldol precursor (red) and electrophilic aldol precursor (blue).

The enolate ion that would result from a retro-aldol reaction of FBP would be stable because the negative charge is delocalised. That charge delocalisation of an enolate anion is part of what makes retro-aldol reactions possible in the first place. You can't just have a C-C bond break in a random place and have one of the carbons form an anion; that would never happen. If the anion is somehow stabilised, however, then that changes everything.

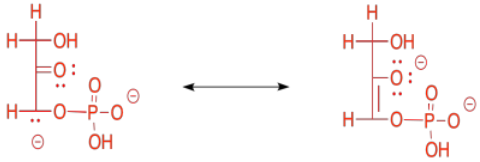
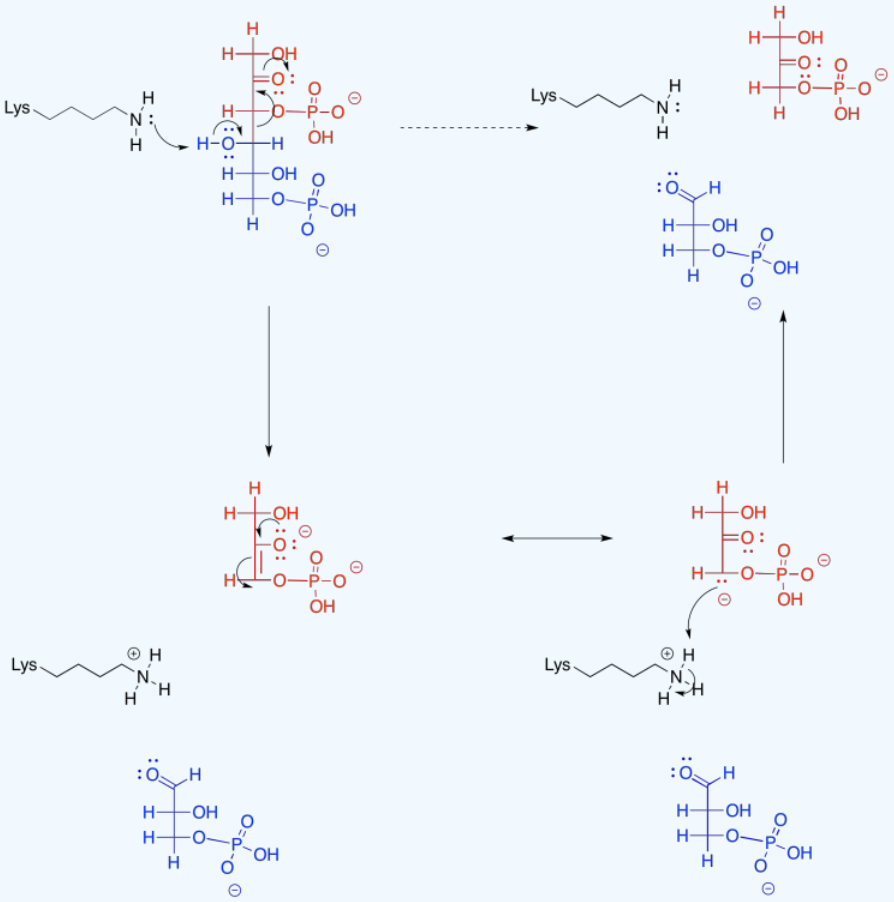


Figure 8.4.5: A key resonance structure.

Exercise 8.4.4

Provide a mechanism for the retro-aldol reaction of fructose-1,6-bisphosphate.

Answer



That's not the whole story, though. In reality, the retro-aldol reaction of FBP undergoes iminium catalysis. That means the reaction is accelerated through the action of a lysine residue in the enzyme, fructose bisphosphate aldolase. The lysine, which contains a nucleophilic amine side chain, transforms the carbonyl of fructose-1,6-bisphosphate into an iminium ion. Biochemists often call this kind of structure a Schiff base. Its structure is very similar to the original, but it contains a C=N group instead of a C=O group. At common biological pH, chances are that the nitrogen in the Schiff base is protonated.

How does that help things? Well, charge stability is always a key factor during reactions. It costs energy to stabilise charges. If we can avoid generating the negative charge of an enolate anion, even though it's relatively stable, that might make things easier. The Schiff base is already positively charged because of its basicity, so when it accepts a pair of electrons it becomes neutral. It has no charge to need stabilising. That step ought to be less difficult than a similar step that results in an anion.

So, by adding a couple of steps to the reaction -- adding the lysine onto the sugar and then taking it off again -- the reaction is accelerated. It can seem confusing that we add steps to the reaction, making the overall reaction longer, but the reaction gets faster. That's because, even though there are additional steps, each individual step is a lot easier than it was before. It's like the difference between jumping across a river and stepping across on a series of stones. Taking the extra steps may be the faster and surest way to get there.

The products of FBP cleavage are glyceraldehyde-3-phosphate (G3P) and dihydroxyacetone phosphate (DHAP). The dihydroxyacetone phosphate subsequently undergoes isomerisation to give another molecule of glyceraldehyde-3-phosphate. This reaction occurs via initial formation of an enol tautomer. It's similar to the isomerisation of glucose-6-phosphate to fructose-6-phosphate that we saw earlier.

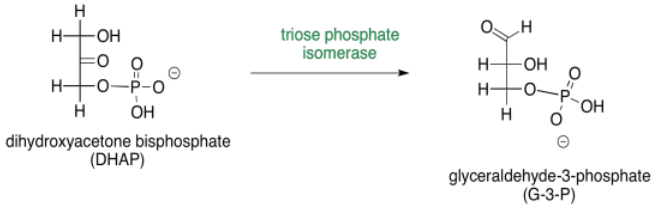


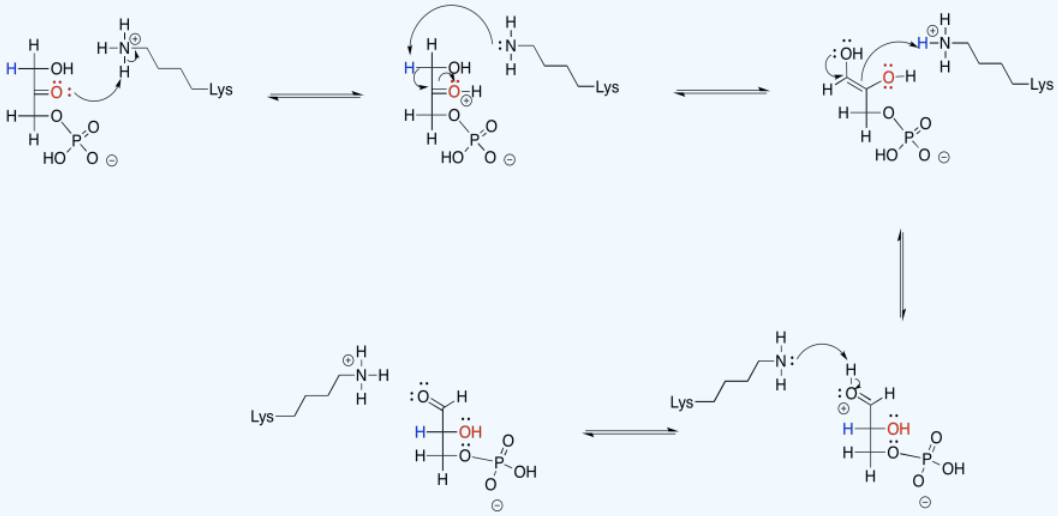
Figure 8.4.6: Isomerisation of dihydroxyacetone phosphate to glyceraldehyde-3-phosphate.

So, when the fructose-1,6-bisphosphate forms, it makes one molecule of glyceraldehyde-3-phosphate and one molecule of dihydroxyacetone phosphate, but that dihydroxyacetone phosphate molecule is then converted into another molecule of glyceraldehyde-3-phosphate. Thus, the overall outcome of this part of the reaction is to transform the six-carbon sugar (first glucose and later fructose) into glyceraldehyde-3-phosphate. This is where phase two of glycolysis begins.

Exercise 8.4.5

Provide a mechanism for the isomerisation reaction of dihydroxyacetone phosphate to glyceraldehyde-3-phosphate.

Answer

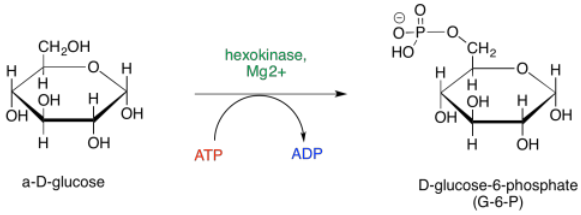


8.5: Catalysis in Phase One

Reactions in biochemistry are usually catalysed by enzymes. In a catalysed reaction, an alternative pathway is available that makes it easier to get from reactants to products. That doesn't mean that there are fewer steps. In fact, normally there are more steps in a catalysed reaction than there are in an uncatalysed one. It does mean that the overall energy needed to traverse the catalysed barrier is lower than the energy needed to surpass the uncatalysed barrier. It's like taking the stairs up to the second floor rather than taking a running leap at the window: more steps, but overall it will save time.

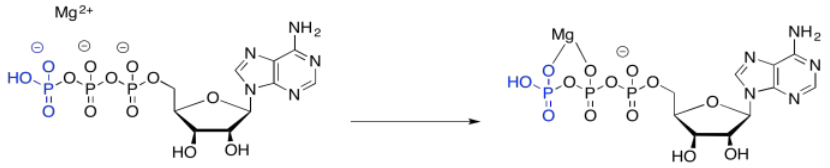
So far, the reactions we have seen in glycolysis are just the overall reactions. By looking at the overall reactions, we get a pretty good sense about what is happening at each stage of the pathway. We even get some sense of how those reactions might happen, because we can identify familar nucleophiles and electrophiles that appear to be involved. Here, we will take a more detailed look at the catalytic pathways taken during the first phase of glycolysis.

Essentially every step of glycolysis involves catalysis, and so the reactions entail cofactors and detailed steps that we have glossed over until now. The first step, phosphorylation of glucose to afford glucose-6-phosphate, requires the consumption of ATP. During that step, the terminal hydroxy group of glucose takes up phosphate from ATP, leaving ADP.

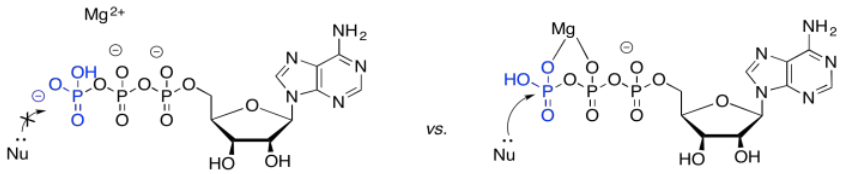


It seems like that first step should be pretty straightforward, because we think of ATP as this high-energy power source for the cell, so it must be really reactive. ATP is not quite as reactive as you might think, though. That's a good thing. If it reacted too readily, it couldn't travel around the cell at all; it would get hydrolysed the first time it encountered a water molecule, and there really are an awful lot of those in a typical cell. In order to react, the ATP needs to be activated.

Part of the catalysis of the phosphorylation of glucose simply involves binding ATP to a magnesium ion. Once bound to the magnesium ion, the ATP becomes more electrophilic, because of that positive charge on the magnesium ion.

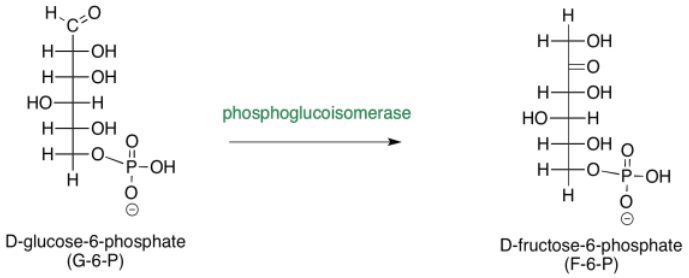


Although a nucleophile, such as water, is unlikely to donate to ATP -- partly because of the negative charge on the ATP -- it is more likely to donate to ATP once coordination takes place, because the magnesium ion has leveled out that negative charge.

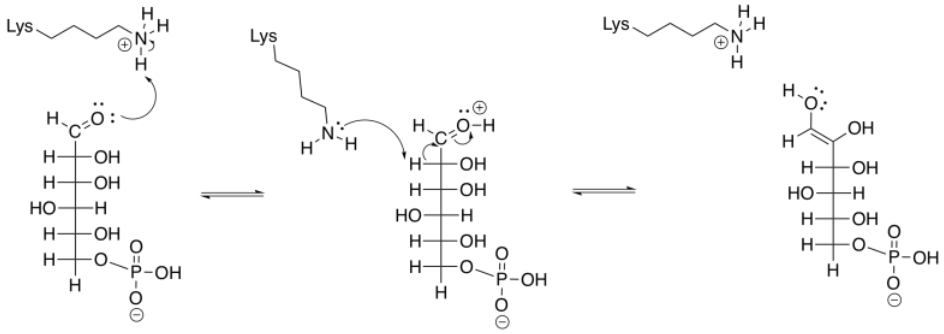


Another aspect of catalysis in the phosphorylation of glucose involves the removal of a proton. A hydroxyl group is converted to a phosphate, and a proton is lost. Acid-base catalysis is quite common in biochemistry. There are only a handful of amino acids that commonly participate in deprotonation steps: aspartate, glutamate, lysine, and histidine. All of these residues have two structures in equilibrium: a protonated one and a non-protonated one. The non-protonated form is ready to remove a proton when needed.

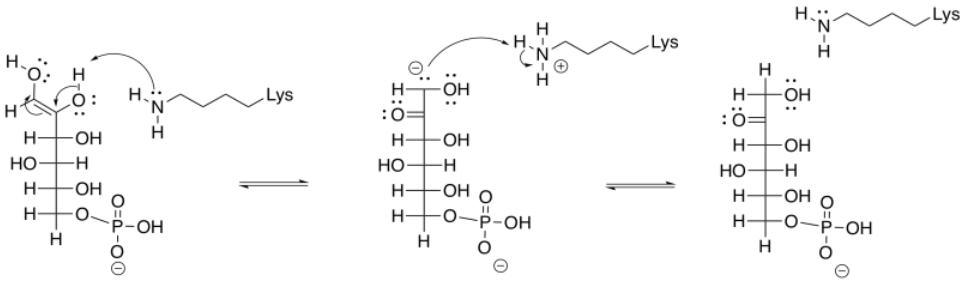
Similarly, acid-base catalysis is carried out by nearby amino acid residues in the active site of the enzyme that carries out the isomerisation of glucose-6-phosphate to fructose-6-phosphate.



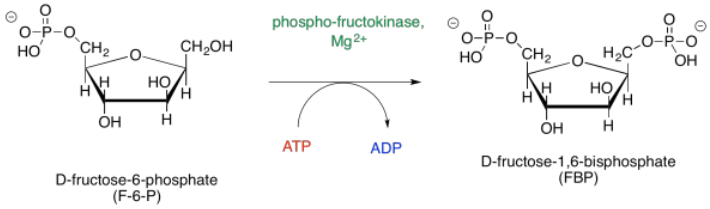
Phosphoglucoisomerase accomplishes this task by removing a proton from an alpha position, and also from an O-H group, as well as donation of protons to a different alpha position and a different oxygen.



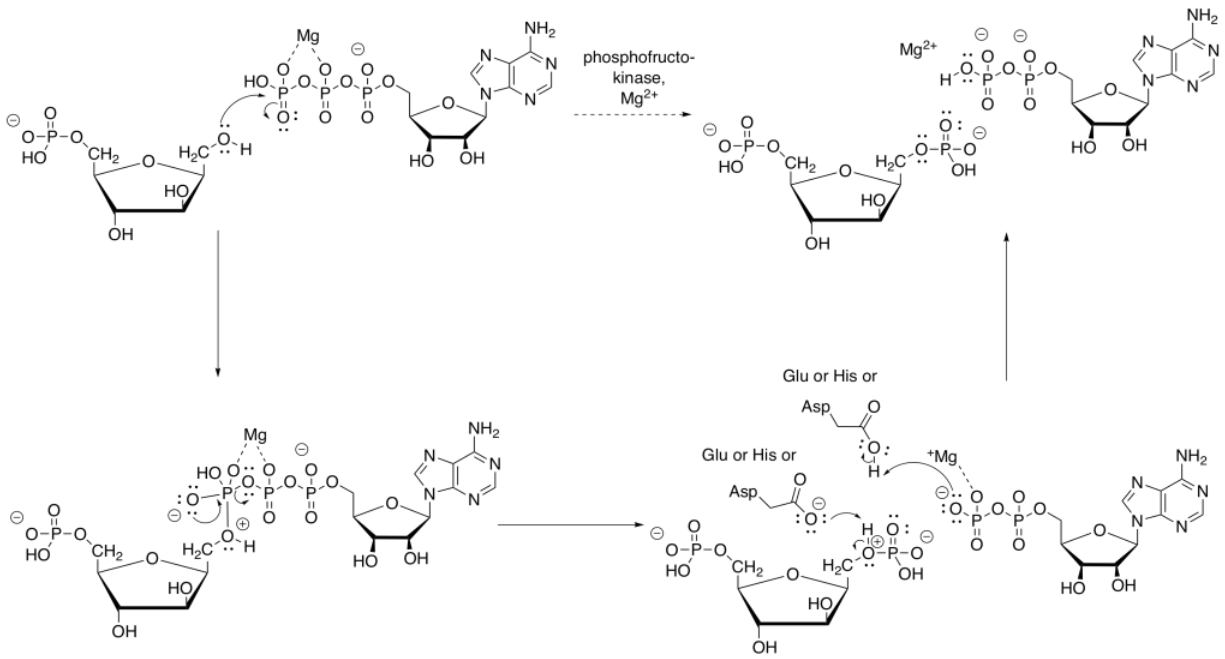
An enol intermediate is the halfway point between the two isomers. If the proton were to be removed from that end hydroxy group, and a proton put back in the alpha position again, the structure would return to the original G6P. If, instead, a proton is removed from the second hydroxyl group along the chain, a different structure results.



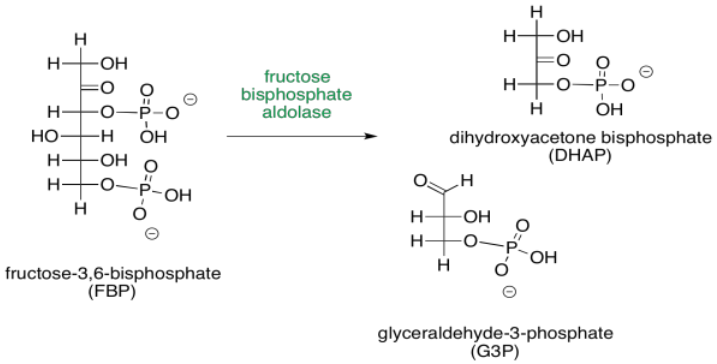
Of course, the same sort of catalytic requirements arise again during the conversion of F6P to FBP. ATP must be activated by magnesium, and proton transfers must be carried out by acidic and basic amino acid residues.



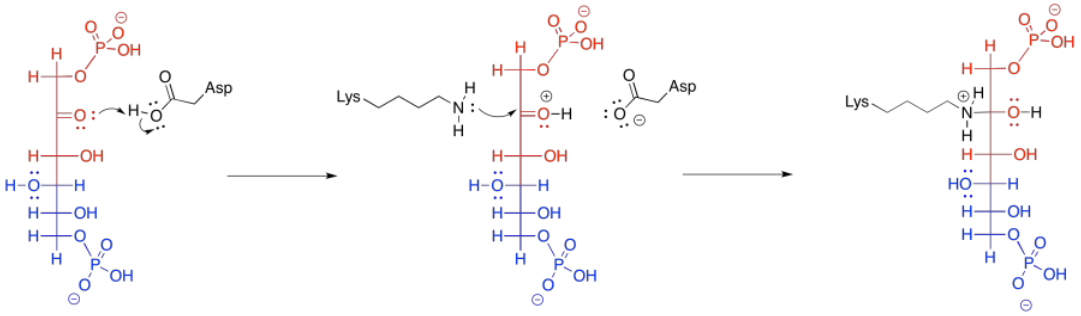
The magnesium will bind to the ATP in order to reduce the amount of negative charge. That way, the nucleophilic alcohol can donate electrons more easily. The proton from the alcohol group can be removed by an amino acid side chain, such as the negatively charged carboxylate of aspartate or glutamate, or a neutral histidine.



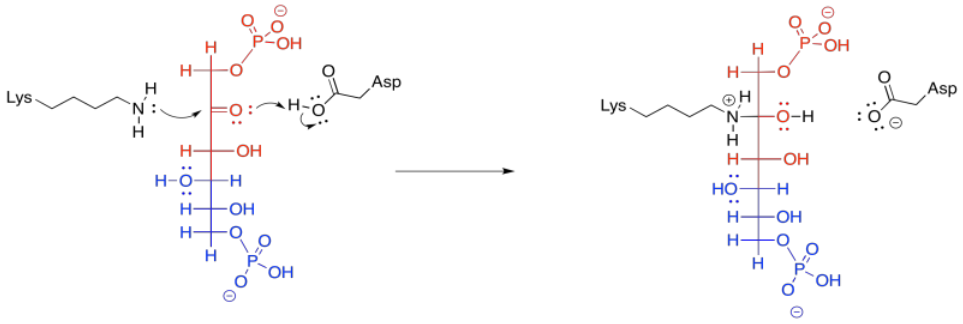
A completely different kind of catalysis occurs during the scission step of phase one, when the six-carbon sugar is cleaved into a pair of three-carbon sugars. You may recall that this cleavage is accomplished via a retro-aldol reaction: an aldol reaction goes into reverse, spitting out an enolate or enol and a carbonyl.



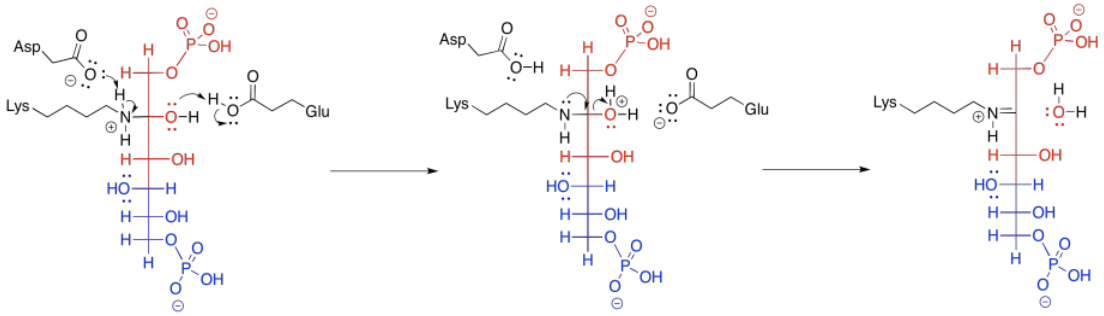
That retro-aldol step is accomplished via iminium ion catalysis. Very often in biochemical reactions, a lysine residue binds with a carbonyl to form either an iminium ion, containing an electrophilic C=N bond, or an enamine, with a nucleophilic N-C=C unit. The process begins with donation of the lysine, in its non-protonated form, to the carbonyl of FBP.



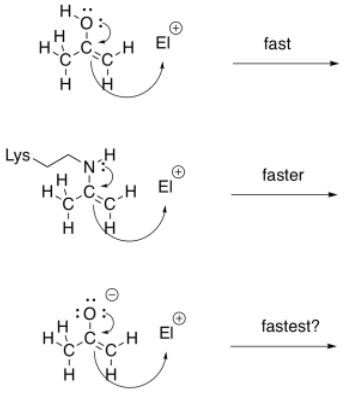
Frequently, enzymatic reactions are presented in a more condensed form. Multiple steps are shown at once; but not just any steps. In the example below, the FBP reacts with both the lysine and the aspartate at the same time. We never draw three molecules coming together at once, because the probability of three molecules colliding at the same time is just about nil. In this case, that's not a problem; the aspartate and lysine are both part of the same molecule. Furthermore, by this point, the FBP has already bound to the enzyme, so the whole thing is one big assembly.



Subsequently, the carbinolamine undergoes displacement of water to yield the imine, C=N.

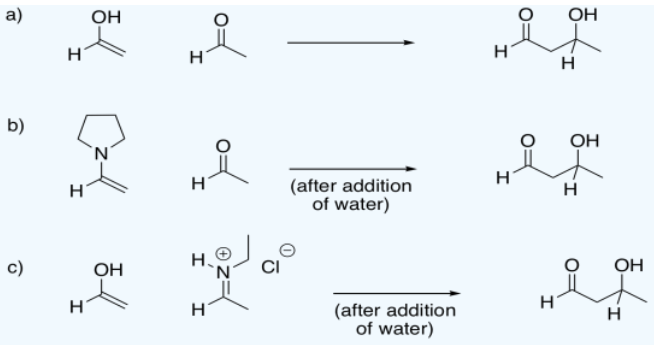


Imines and enamines are roughly equivalent to carbonyls and enolates, respectively. Enamines are very good nucleophiles, just like enolates. Enolates are a little better, because of the negative charge. However, even though they are neutral nucleophiles, enamines are almost as good, because the reaction is driven by a less electronegative nitrogen atom; which is more willing to donate its electrons. Furthermore, in the environment of the cell, enamines form much more easily than enolates. That's because there isn't a whole lot of LDA or even NaOH floating around inside your cells. As a result, enamines are often employed as nucleophile in cases where you might think of using an enolate.

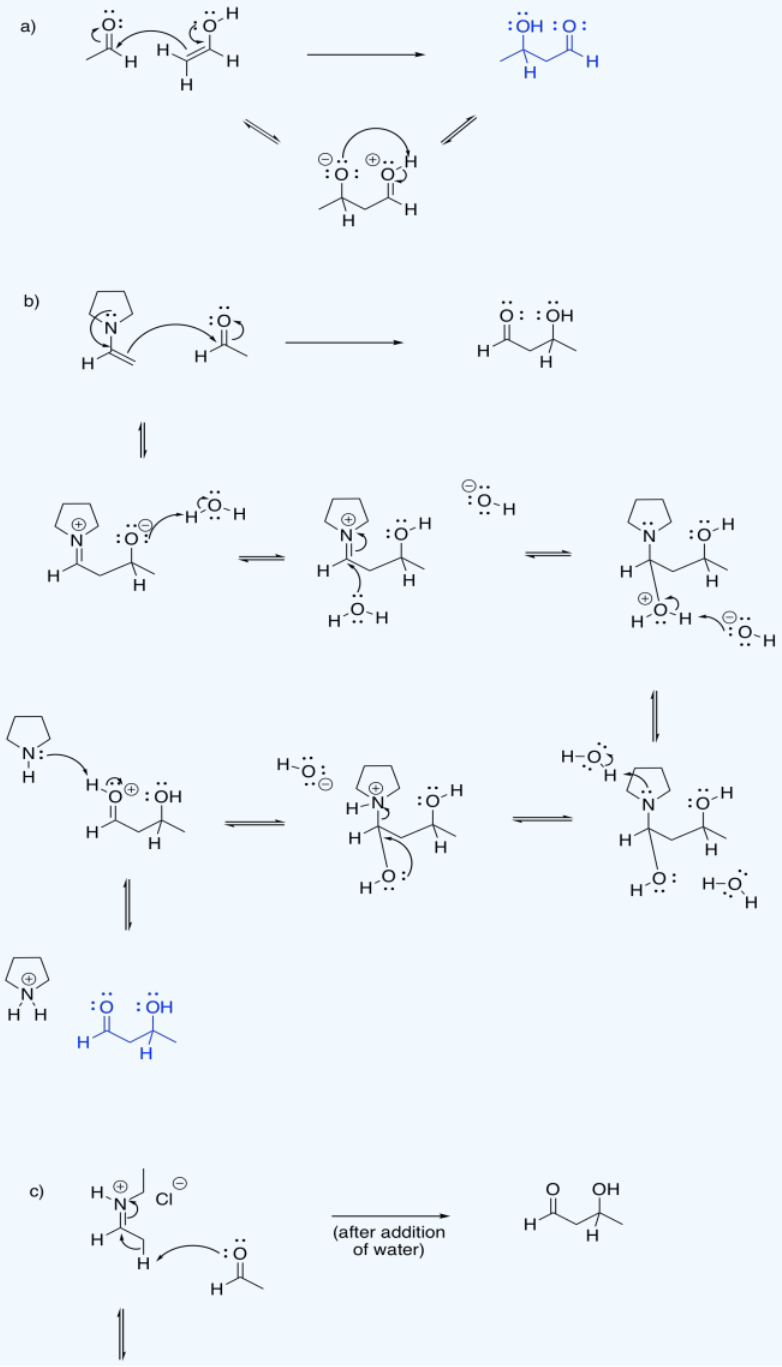


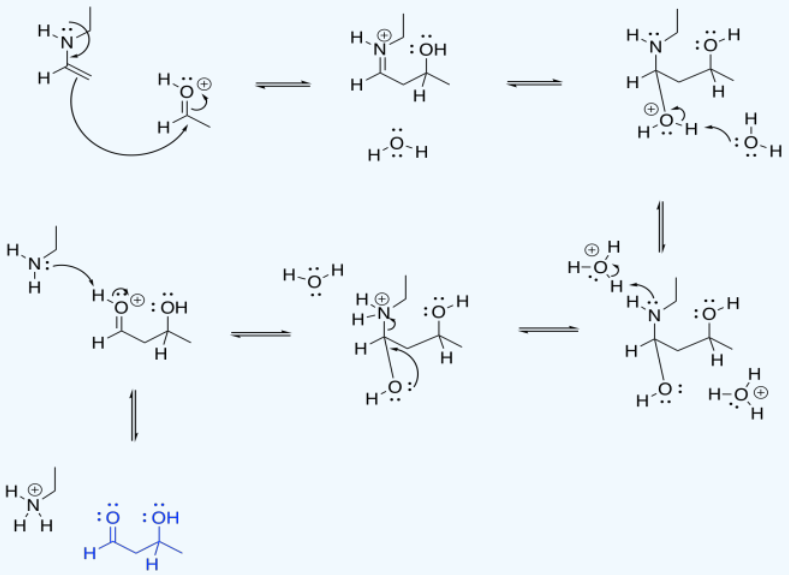
? Exercise 8.5.1

Provide mechanisms for the following aldol-like reactions.

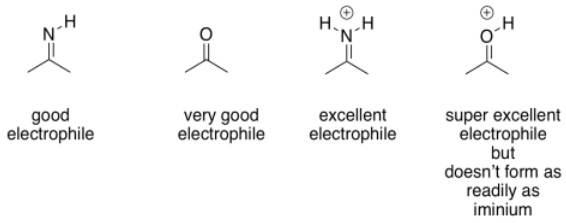


Answer





The imine unit isn't an inherently better electrophile than a carbonyl; after all, it contains a less polar C=N bond instead of a C=O bond. However, the nitrogen in an imine is much more basic than the oxygen in a carbonyl. It can be protonated quite easily under biological conditions. The resulting iminium ion, containing the $C=N-H^+$ unit, is an activated electrophile. Of course it reacts much more quickly than a regular carbonyl.

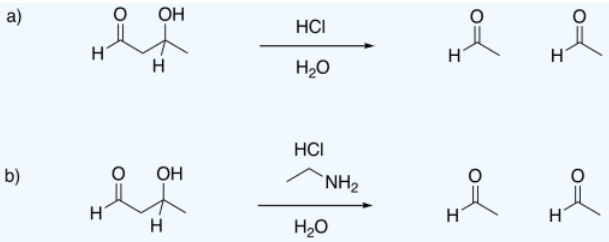


Because carbonyls can easily form either imines or enamines, they will often be converted into those compounds in order to do reactions. This process is called enamine and imine catalysis.

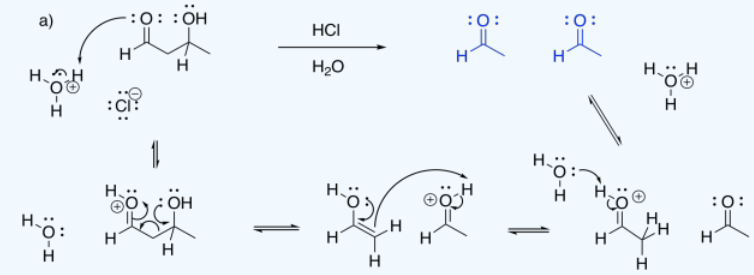
Aldol reactions are actually reversible. A retro-aldol reaction is just the aldol reaction going in reverse. In that case, an enolate or an enol or an enamine might come out as a leaving group, rather than acting as the initial nucleophile.

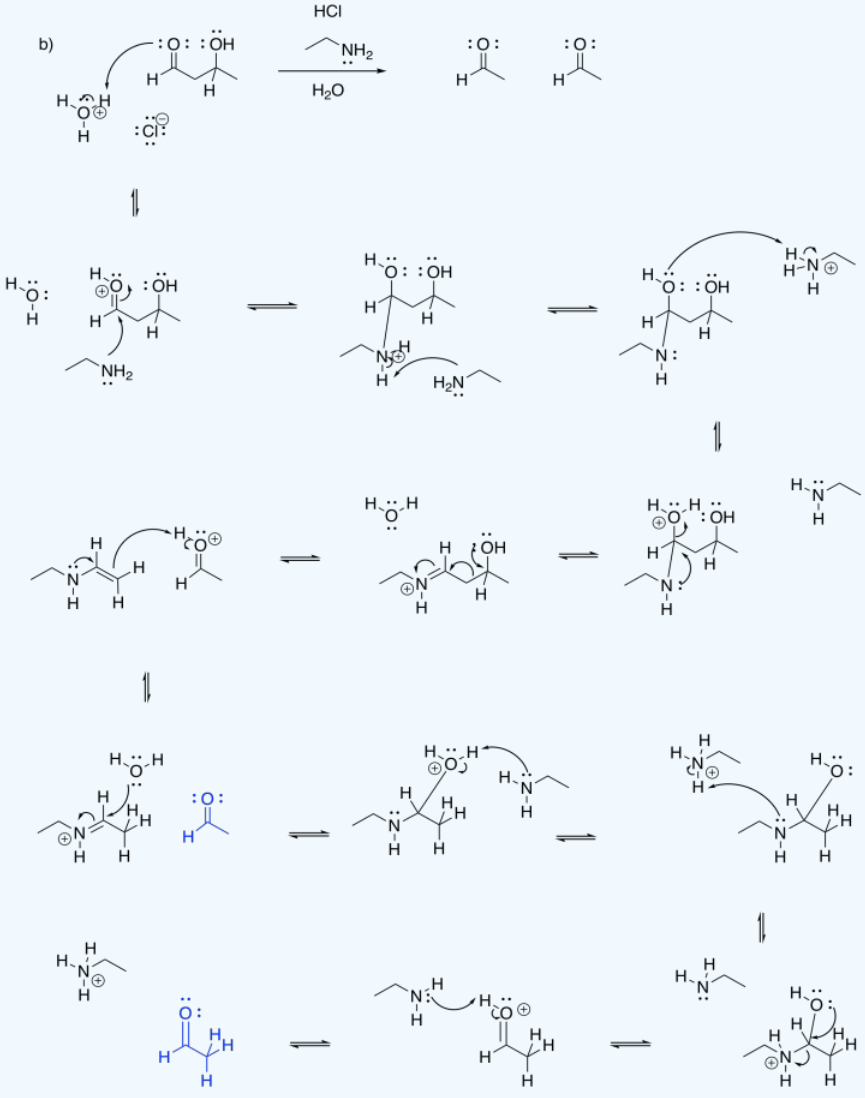
? Exercise 8.5.2

Provide mechanisms for the following retro-aldol reactions.

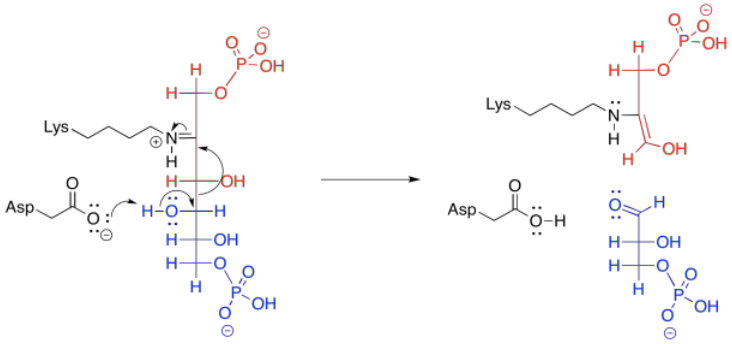


Answer

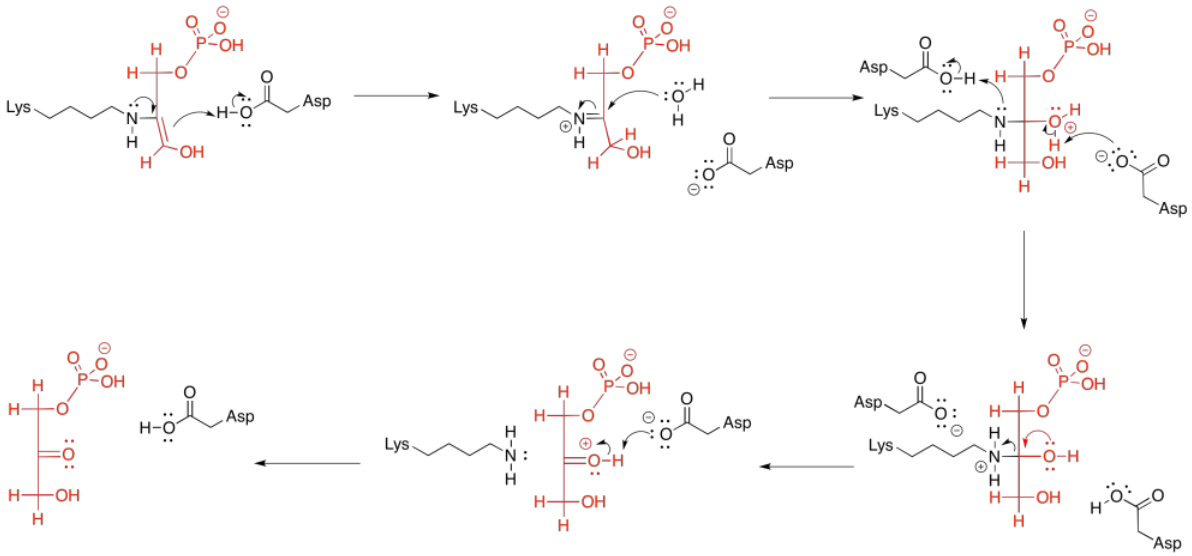




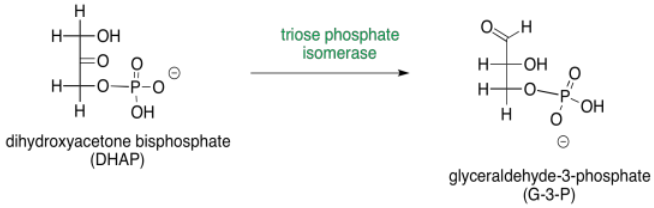
In the context of a retro-aldol reaction, we need to think about the catalysis backwards. Instead of an iminium ion acting as an activated intermediate to receive a nucleophile, it is accepting electrons to form a leaving group. Instead of having an enolate leaving group in the retro-aldol reaction, we have an enamine leaving group.



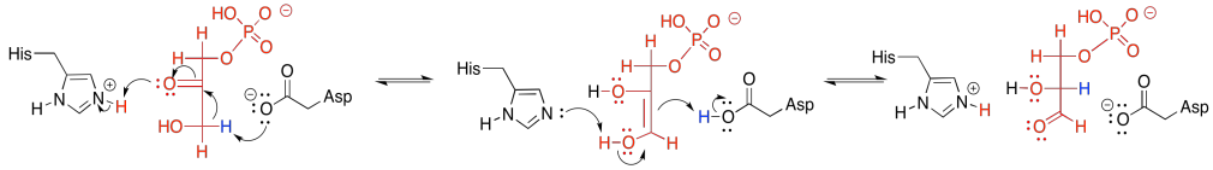
The lysine group, which just came on board to catalyse the reaction, is liberated by addition of a water molecule.



There is one last reaction in phase one, the fifth overall in glycolysis. It's the conversion of DHAP to G3P; but that's just another keto-enol tautomerism. The catalytic mechanisms will be very much like those seen in the conversion of G6P to F6P.



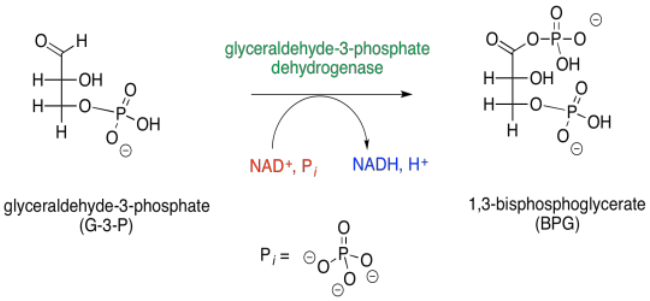
Basic amino acid sites such as neutral histidine and anionic aspartate can readily remove a proton, whereas the corresponding conjugates can supply a proton. Tautomerism simply requires removal of a proton from an alpha position. When a proton is returned, it goes to the other end of the double bond in the enol.



8.6: Mechanisms of Phase Two

Phase one of glycolysis is setting the stage. An initial investment of ATP is needed to get the system ready to produce more ATP; it's like a farmer who sows sunflower seeds in the spring to get a bigger crop of sunflower seeds in the fall.

Two molecules of glyceraldehyde-3-phosphate are produced in phase one of glycolysis. Both of those molecules enter into phase two. The first step in this phase is an oxidation reaction. In organic chemistry, the term oxidation suggests that a carbon atom is getting fewer bonds to hydrogen, or more bonds to oxygen. (The complementary term, reduction, suggests new carbon-hydrogen bonds are forming, or carbon-oxygen bonds are disappearing.) Notice that the carbonyl carbon, C=O, is becoming a carboxylic carbon, O-C=O.

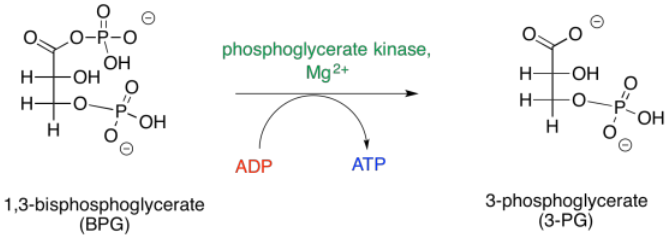


That isn't all that's going on. There is also a phosphorylation step here, but this time ATP is not required. The source of the phosphate group is a simple phosphate ion.

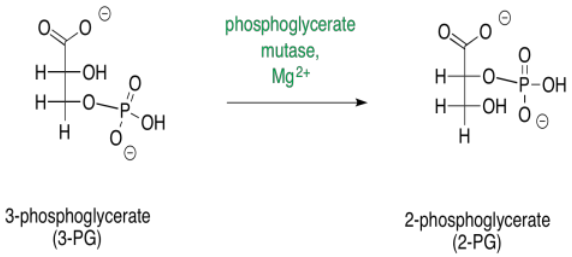
Furthermore, a molecule of NADH is produced. You might remember that NAD^+ can pick up a hydride ion (that's right, H^- instead of H^+) to become NADH. In this case, the hydride ion is coming from the aldehyde that is converted into a carboxyloid, the phosphoric anhydride group in BPG.

This first step has consequences for energy-packaging pathways further downstream. NADH is the starting material for oxidative phosphorylation, an elegant process in which electrons are passed from one metal ion to another within membrane-bound proteins; as the electrons move across the membrane, they draw oppositely-charged protons along with them. A proton gradient builds up, with protons on one side of the membrane outnumbering those on the other; this osmotic pressure is relieved when the protons find a channel to pour back through the membrane, but as they do so they turn a molecular millwheel that drives the production of more ATP. Remember, oxidative phosphorylation, along with glycolysis and the citric acid cycle, is one of the three pathways that together make up the process of respiration.

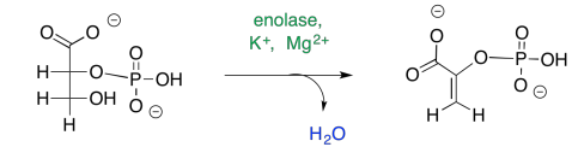
There is also a more immediate energy-packaging result. That first step produces 1,3-bisphosphoglycerate, which is primed to deliver a phosphate to a molecule of ADP. In addition to ATP, a molecule of 3-phosphoglycerate is left behind.



A slight modification of the 3-phosphoglycerate ensues. In this step, the phosphate group migrates from the 3-position to the 2-position, resulting in 2-phosphoglycerate.

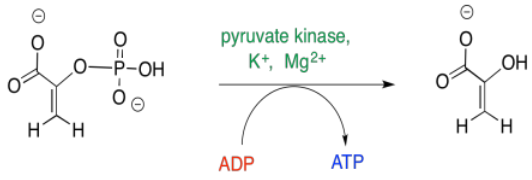


Subsequently, the 2-phosphoglycerate undergoes a dehydration, the loss of water. You might recall that dehydrations sometimes occur after aldol reactions: the O=C-CH-C-OH loses a proton at the alpha position and a hydroxide at the beta position to give the enone group, O=C-C=C, and water, HOH. That step is often driven by the conjugated system that results. In this case, the conjugated product is phosphoenolpyruvate.



2-phosphoglycerate (2-PG) phosphoenolpyruvate (PEP)

The final step in glycolysis is the loss of the phosphate group from phosphoenolpyruvate. This phosphate group is transferred to another molecule of ADP, forming ATP. The ATP can then be used to power processes elsewhere in the cell. Note that this is the second molecule of ATP produced during phase two. Since each molecule of glucose produces two three-carbon sugars that enter into phase two, a total of four molecules of ATP are produced per glucose. Remember, phase one required the consumption of two molecules of glucose, so this yield represents a doubling of the initial investment of ATP. It's like putting two dollars in the bank and getting four dollars back out.

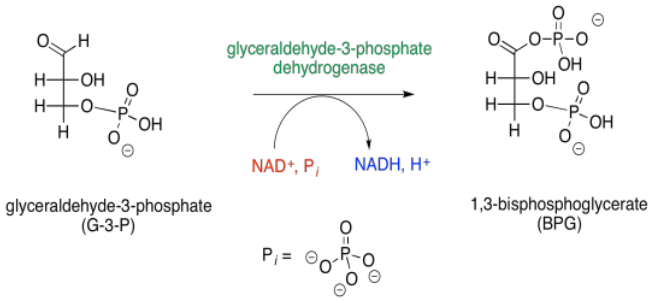


phosphoenolpyruvate (PEP) pyruvate

That's the end of glycolysis, but that's not the end of the story. So far, glucose has only been broken down to a three-carbon sugar. When we think of respiration, we think of glucose breaking down all the way to carbon dioxide. That part continues in the tricarboxylic acid cycle, or TCA cycle.

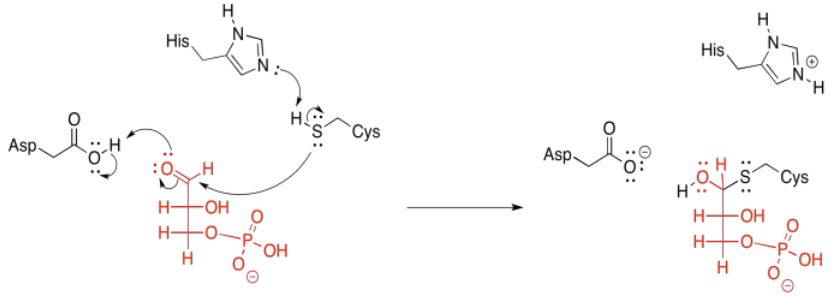
8.7: Catalysis of Phase Two

In phase two of glycolysis, glyceraldehyde-3-phosphate proceeds through an oxidation reaction, in which an aldehyde hydrogen is replaced by a phosphate group. If you are scratching your head, wondering how that reaction might happen, then that's a good thing. The hydrogen is not a good leaving group, and you haven't seen much precedent for this kind of reaction.



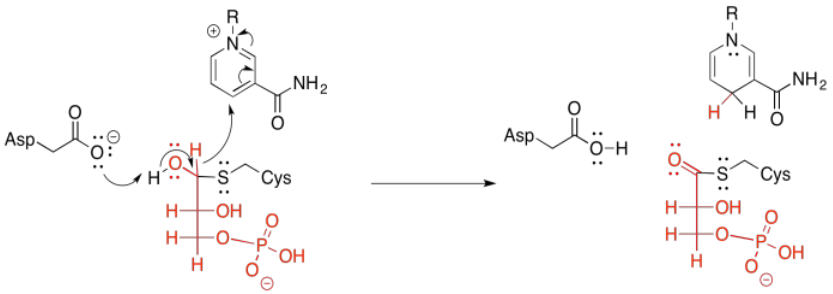
This step looks like a very good place for catalysis. The reaction doesn't look like it will work very well, and so we need an alternative, lower-energy pathway. At the very least, this is a good situation for the enzymatic strategy of approximation, in which two substrates are held near each other by their respective placements in the active site. Approximation is needed because of that poor hydride leaving group, H^-. It really can't be displaced from the molecule to become a hydride ion in free solution, because it isn't stable enough. It needs that NAD^+ acceptor to be waiting for it as it comes off the molecule of glyceraldehyde-3-phosphate.

But the hydride isn't displaced by the phosphate directly; there is an invisible step in between. A cysteine residue from the enzyme first donates to the carbonyl. Sulfur is a very good nucleophile for carbon electrophiles; sulfur is a little less electronegative and more polarizable than oxygen, so it can donate electrons relatively easily.



That donation results in the formation of a hemithioacetal. In addition, it tethers the glyceraldehyde molecule to the enzyme. This feature is an example of the group transfer strategy, in which the substrate becomes temporarily attached to the enzyme that is working on it. This group transfer might be explained as gaining an entropic edge to help get through an enthalpically difficult step. This next part may be a little bit tricky, so let's just tie the substrate down for a moment.

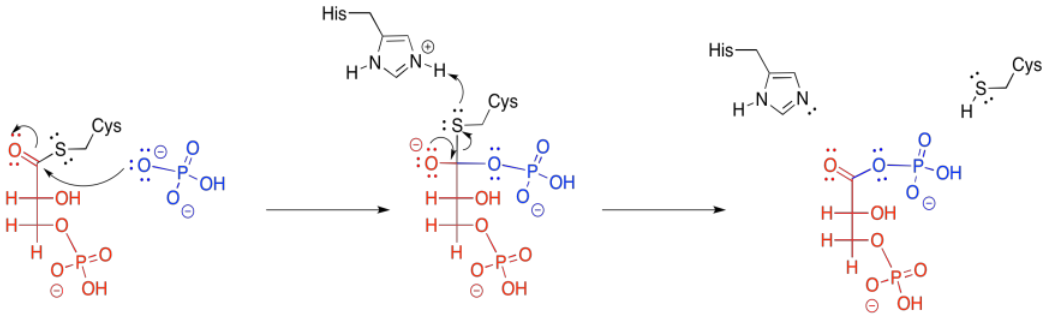
So, now we are ready to pi-donate from the tetrahedral intermediate, pushing the hydride onto the waiting NAD^+, like a fast pitch straight into the catcher's mitt.



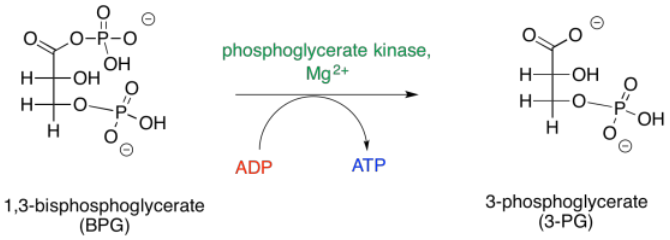
Of course, group transfer always relies on the substrate being cut from the enzyme again. Otherwise, the transfer would be an example of irreversible inhibition; the substrate molecule would be stuck in the enzyme, forever blocking its active site. The thing about sulfur, though, is that its polarizability makes it a pretty good leaving group. Remember, too, that thioesters are more reactive than regular esters. Thioesters sit higher on the ski hill illustrating the relative reactivity of carboxyloids. That means that the use of

a cysteine residue as the tethering group, rather than a lysine's nitrogen or a serine's oxygen, is particularly advantageous for the cleavage step.

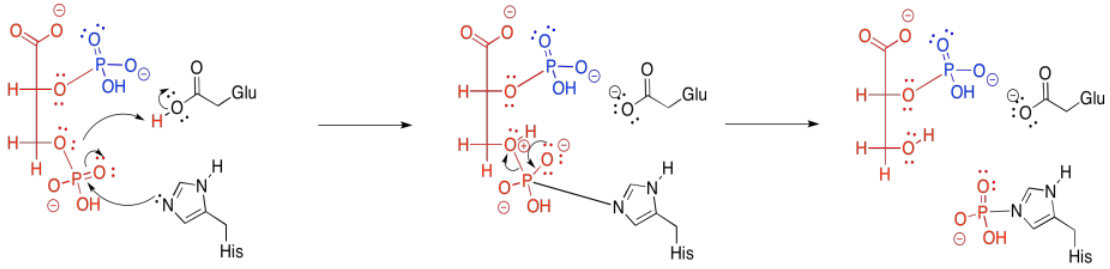
The cleavage step involves donation from an inorganic phosphate ion. The carbonyl opens up to give a tetrahedral intermediate, and when that intermediate collapses again, the cysteine is released.



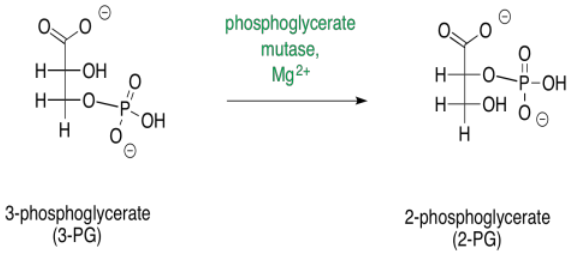
The second step of phase two looks a little simpler. It's just a displacement of a carboxylate leaving group from a phosphoanhydride.



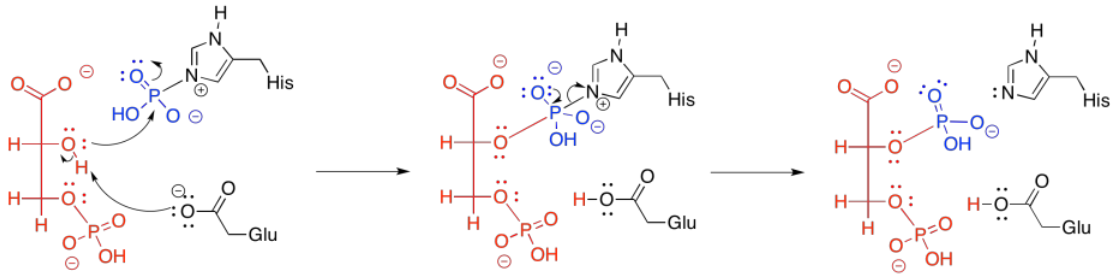
Remember, like the thioester it was formed from, this anhydride was high on the ski hill, because the carboxylate anion is a good leaving group. The phosphate donates to the phosphoryl group, resulting in a five-coordinate phosphorus. This intermediate collapses, ejecting the carboxylate leaving group.



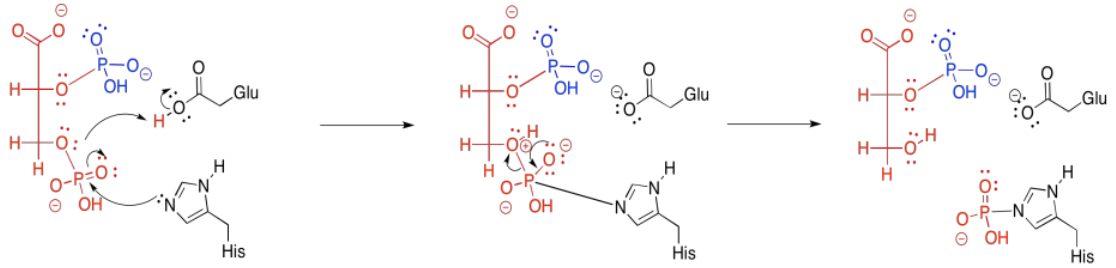
The third step also appears straightforward. It looks like the phosphate is just moving from one oxygen to another.



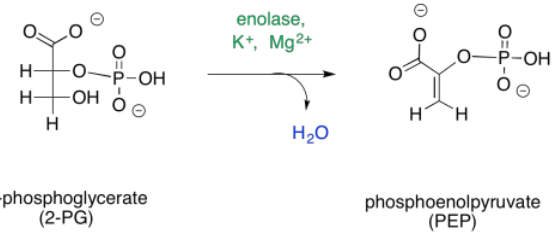
In practice, things are slightly more complicated. In animals, the phosphate that comes from the 3-position isn't the same as the phosphate that ends up at the 2-position. In other words, rather than just moving the phosphate from one place to another, a new phosphate is added before the old one is removed.



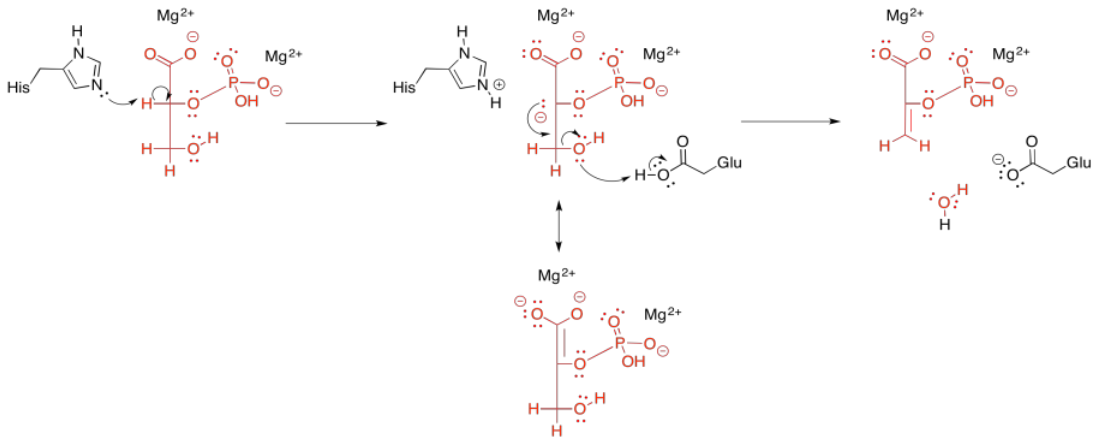
The new phosphate is delivered from a modified histidine residue in the anzyme. The same histidine can then pick up the old phosphate from the 3-position, which it will then hold onto, waiting to deliver it to the next substrate molecule that arrives in the enzyme.



The fourth step is, in principle, a simple dehydration.



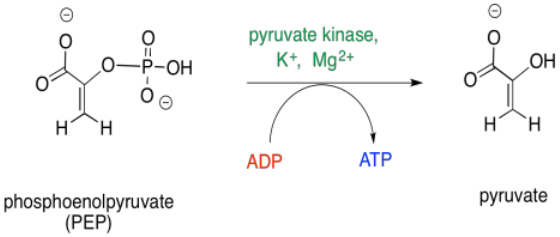
Once again, this step requires a cation to activate it. In some cases, two magnesium ions appear to be involved: one to bind the phosphate and one to bind the carboxylate. Other cases employ a magesium ion and a potassium ion.



Either way, coordination to a metal ion probably lowers the pKa of the alpha hydrogen. Instead of deprotonating to produce a tri-anion or tetra-anion (depending whether the phosphate is already singly deprotonated or doubly deprotonated), the metal-bound substrate will produce an anion with overall lower negative charge that we would have otherwise. The deprotonation seems to be carried out by a lysine in some enzymes and a histidine in others.

After that, the beta- hydroxy group is lost. It needs to pick up a proton to become water. That proton may be supplied by a nearby glutamate, which shuttles the proton from elsewhere.

The final step in glycolysis is another phosphate transfer.

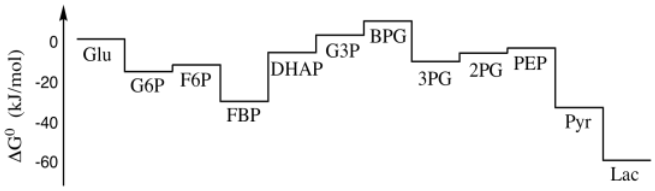


Once again, ADP is the nucelophile that displaces the leaving group from the phosphate electrophile. This time, the leaving group is an enolate anion. The reaction requires magnesium ions to hold the ADP in place.

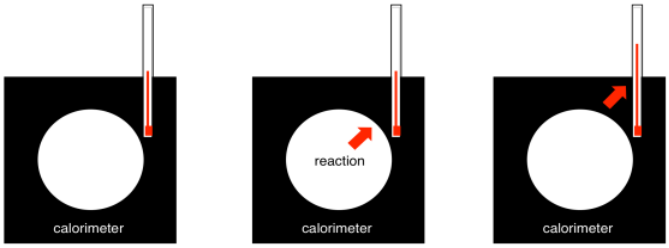
8.8: Thermodynamics of Glycolysis

Glycolysis is intimately linked to the release of energy in biological systems, and harnessing that energy to do work. That's what the field of thermodynamics is all about. In this section, we will take a very brief look at some of the energetic considerations of this pathway.

We have seen that glycolysis is a sequence of reactions leading from one intermediate compound in the pathway to the next. (To see that pathway again, click here.) Inevitably, there are energy changes associated with each of those reactions. Some of the reactions may be endothermic, others may be exothermic; some may be essentially irreversible, whereas others may occur in equilibrium. If we map these energy changes out from start to finish, we get a picture like the one below. It's a roller coaster, with lots of energetic drops but just as many hills, and it becomes difficult to think of glycolysis as a process that releases energy, except for the dramatic drop in the last couple of steps.



Where does a picture like this one come from? Well, it depicts a series of reactions, and the energy change associated with each reaction. We can determine the energy change associated with a specific reaction using calorimetry. A calorimeter is a well-insulated device in which we can perform a reaction. A thermometer tells us the temperature change as a result of the reaction. We can calibrate the device by releasing known amounts of heat and seeing how much its temperature rises. Consequently, we can also use that correlation backwards: given the temperature rise, we can deduce how much energy was released during a reaction.



Now, if enough people have studied this sort of thing for long enough, we can begin to compile a lot of data. Given enough data, you actually might not need to perform calorimetry to determine how much energy is involved in a reaction.

To illustrate why, consider one of the most common kinds of thermodynamic data you can find: heats of formation. The heat of formation of a compound is the energy involved when the compound is formed from the elements. So, for example, the heat of formation of methane would be the energy involved when hydrogen cas combines with carbon to form methane:

$$2\,H_2 + C \longrightarrow CH_4 \quad \Delta H = ??$$

It would be difficult to perform calorimetry in this case. First of all, there are just too many things that could happen if you managed to get hydrogen and carbon to combine; there are many other compounds made from hydrogen and carbon, so who knows what reaction would really occur?

But we find that heat of formation indirectly, using other data. We can burn methane:

$$2\,O_2 + CH_4 \longrightarrow CO_2 + 2\,H_2O \quad \Delta H = -802\ \frac{kJ}{mol}$$

We can burn hydrogen to get water:

$$H_2 + 0\cdot 5\,O_2 \longrightarrow H_2O \quad \Delta H = -285\cdot 8\ \frac{kJ}{mol}$$

We can burn carbon to get carbon dioxide:

$$O_2 + C \longrightarrow CO_2 \quad \Delta H = -393\cdot 5\ \frac{kJ}{mol}$$

Well, that just seems like a series of random facts, but equations of reaction are quite a bit like algebraic equations, and those reaction arrows are quite a bit like equals signs. If we keep that in mind, we can manipulate these equations to get useful information. For example, what would happen if we took the middle reaction and multiplied it by two?

$$2\,H_2 + O_2 \longrightarrow 2\,H_2O \;\; \Delta H = -571.6\,\frac{kJ}{mol}$$

Just as in algebra, if we multiply every term in an equation by the same factor, we end up with an equivalent equation. It's a perfectly legal operation. Note that if we multiple the equation by two, we also multiply the energy by two; it's part of the equation.

Now, you probably already know what happens if we consider one of these equations in reverse:

$$2\,CO_2 + 2\,H_2O \longrightarrow 2\,O_2 + CH_4 \;\; \Delta H = +802\,\frac{kJ}{mol}$$

If the reaction is exothermic in one direction, then it must be endothermic in the other. One way is downhill, so the other way is uphill.

Look what happens if we add these three reactions together in their current forms:

$$CO_2 + 2\,H_2O \longrightarrow 2\,O_2 + CH_4 \;\; \Delta H = +890.3\,\frac{kJ}{mol}$$

$$2\,H_2 + O_2 \longrightarrow 2\,H_2O \qquad \Delta H = -571.6\,\frac{kJ}{mol}$$

$$O_2 + C \longrightarrow CO_2 \qquad \Delta H = -393.5\,\frac{kJ}{mol}$$

$$CO_2 + 2\,H_2O + 2\,O_2 + 2\,H_2 + C \longrightarrow 2\,O_2 + CH_4 + 2\,H_2O + CO_2 \;\; \Delta H = +802\,\frac{kJ}{mol}$$

Several things cancel on the left and right, leaving:

$$2\,H_2 + C \longrightarrow CH_4 \;\; \Delta H = -74.8\,\frac{kJ}{mol}$$

What that means is that, if we have energetic information about some reactions, and we can combine the equations for those reactions to get a new equation of reaction, then we automatically get the energy associated with that new reaction.

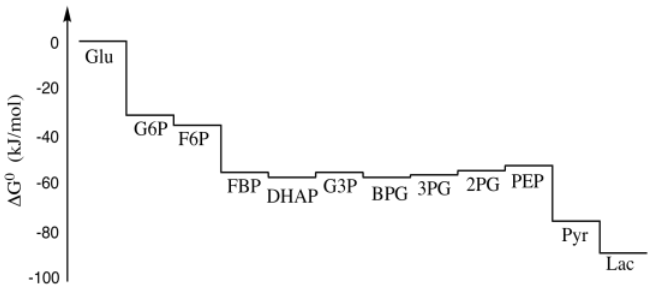
Essentially, if we want to know about the energetics of producing methane from carbon and hydrogen, then it doesn't matter *how* we get from the carbon and the hydrogen to the methane. We can first take the carbon and combine it with oxygen, not hydrogen, and make carbon dioxide. Then, we can take hydrogen and combine it with oxygen, not carbon, to make water. If, finally, we combine the water and the carbon dioxide we have made and produce methane, then the energy of that whole, roundabout process is the same as if we converted the carbon and the hydrogen directly into methane.

This idea illustrates something called Hess' Law. The overall energy required to get from one set of reactants to another set of products is always the same, regardless of the path taken. Hess' Law is true because energy is a "state function". If we know the state that something is currently in - for example, methane in the gas phase at a certain temperature and pressure - then we know its energy. It doesn't matter what has happened to it before, or how it got to its current state.

? Exercise 8.8.1

Problem GL9.1.

In the next section, we are going to see a slightly different picture of the energetic terrain of glycolysis. Rather than the roller coaster ride we saw before, we will find that glycolysis exists mostly on an energetic plain, with just a couple of steep drops. The reason for that has to do with the relative concentrations of the different species under cellular conditions.



8.9: Thermodynamics- The Role of Concentrations

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8.10: Gluconeogenesis

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8.11: Regulation

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8.12: Solutions for Selected Problems.

Bonds Broken:

$$C-C\ 6\times 80\frac{kcal}{mol}=480\frac{kcal}{mol}$$

$$C-H\ 16\times 100\frac{kcal}{mol}=1600\frac{kcal}{mol}$$

$$O=O\ 7\times 120\frac{kcal}{mol}=840\frac{kcal}{mol}$$

Total: 2,920 kcal/mol

Bonds Made:

$$C=O\ 14\times(-190\frac{kcal}{mol})=-2660\frac{kcal}{mol}$$

$$O-H\ 16\times(-110\frac{kcal}{mol})=-1760\frac{kcal}{mol}$$

Total: -4,420 kcal/mol

Overall: $1240-4420\frac{kcal}{mol}=-1500\frac{kcal}{mol}$

Bonds Broken:

$$C-C\ 7\times 80\frac{kcal}{mol}=560\frac{kcal}{mol}$$

$$C-H\ 18\times 100\frac{kcal}{mol}=1800\frac{kcal}{mol}$$

$$O=O\ 12.5\times 120\frac{kcal}{mol}=1500\frac{kcal}{mol}$$

Total: 3,860 kcal/mol

Bonds Made:

$$C=O\ 16\times(-190\frac{kcal}{mol})=-3040\frac{kcal}{mol}$$

$$O-H\ 18\times(-110\frac{kcal}{mol})=-1980\frac{kcal}{mol}$$

Total: -5,020 kcal/mol

Overall: $3860-5020\frac{kcal}{mol}=-1160\frac{kcal}{mol}$

Bonds Broken:

$$C-C\ 6\times 80\frac{kcal}{mol}=480\frac{kcal}{mol}$$

$$C-H\ 7\times 100\frac{kcal}{mol}=700\frac{kcal}{mol}$$

$$C-O\ 7\times 85\frac{kcal}{mol}=595\frac{kcal}{mol}$$

$$O-H\ 5\times 110\frac{kcal}{mol}=550\frac{kcal}{mol}$$

$$O=O\ 6\times 120\frac{kcal}{mol}=840\frac{kcal}{mol}$$

Total: 3,165 kcal/mol

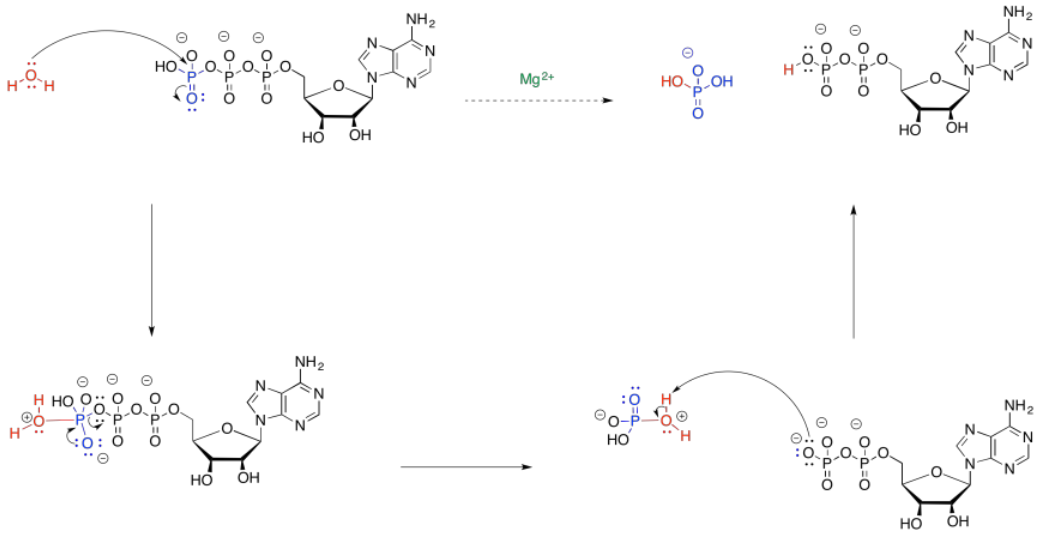
Bonds Made:

$$C=O\ 12\times(-190\frac{kcal}{mol})=-2280\frac{kcal}{mol}$$

$$O-H\ 12\times(-110\frac{kcal}{mol}=-1320\frac{kcal}{mol}$$

Total: -3,600 kcal/mol

Overall: $3165-3600\frac{kcal}{mol}=-435\frac{kcal}{mol}$



In the mechanism for hydrolysis, water acts as a nucleophile and ATP acts as an electrophile. That's a problem because ATP is negatively charged. It will not attract electrons very easily. By binding to magnesium ion (Mg^{2+}), the charge on the ATP will be lowered, accelerating the reaction with water.

$$glucose+2ATP\rightarrow 2G3P+2ADP$$

$$G3O+NAD^{+}+PO_4^{3-}+2ADP\rightarrow pyr+NADH+2ATP+H_2O$$

First we need to realise that one glucose gives rise to two molecules of G3P, so the second phase occurs twice for every glucose molecule consumed.

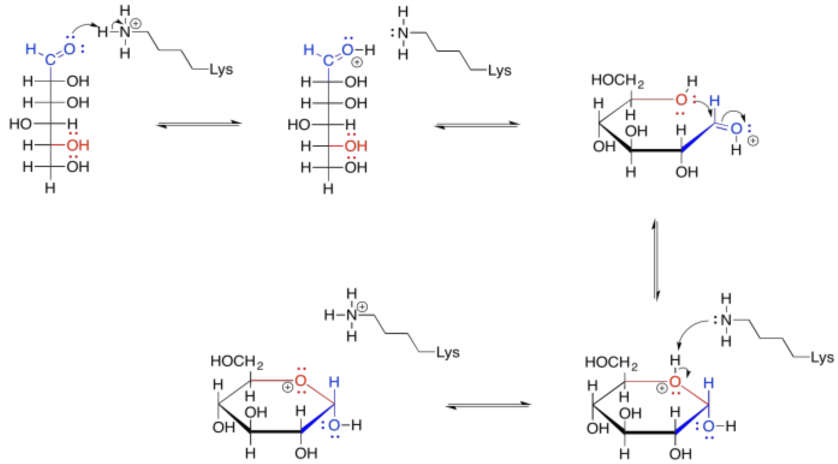
$$2G3P+2NAD^{+}+2PO_4^{3-}+4ADP\rightarrow 2pyr+2NADH+4ATP+2H_2O$$

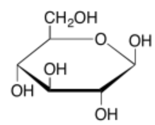
Adding the equations for the two phases together gives:

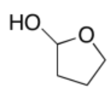
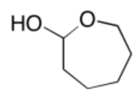
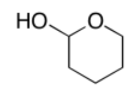
$$glucose+2ATP+2G3P+2NAD^{+}+2PO_4^{3-}+4ADP\rightarrow 2G3P+2ADP+2pyr+2NADH+4ATP+2H_2O$$

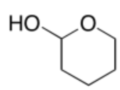
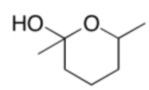
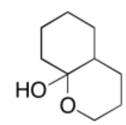
That equation can be simplified, because some things appear on both the left and the right. It's just like algebra.

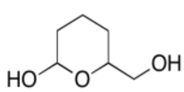
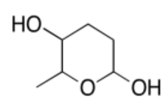
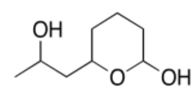
$$glucose+2NAD^{+}+2PO_4^{3-}+2ADP\rightarrow 2pyr+2NADH+2ATP+2H_2O$$

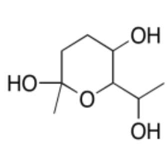
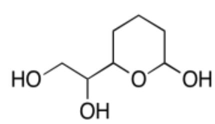
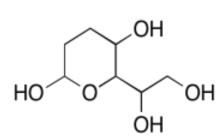


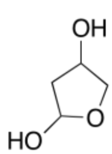
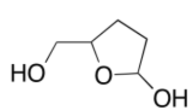
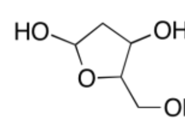


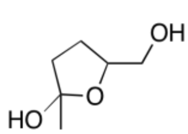
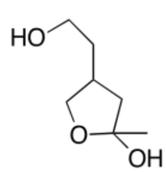
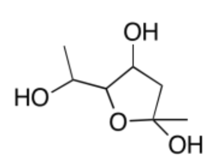
a)  b)  c) 

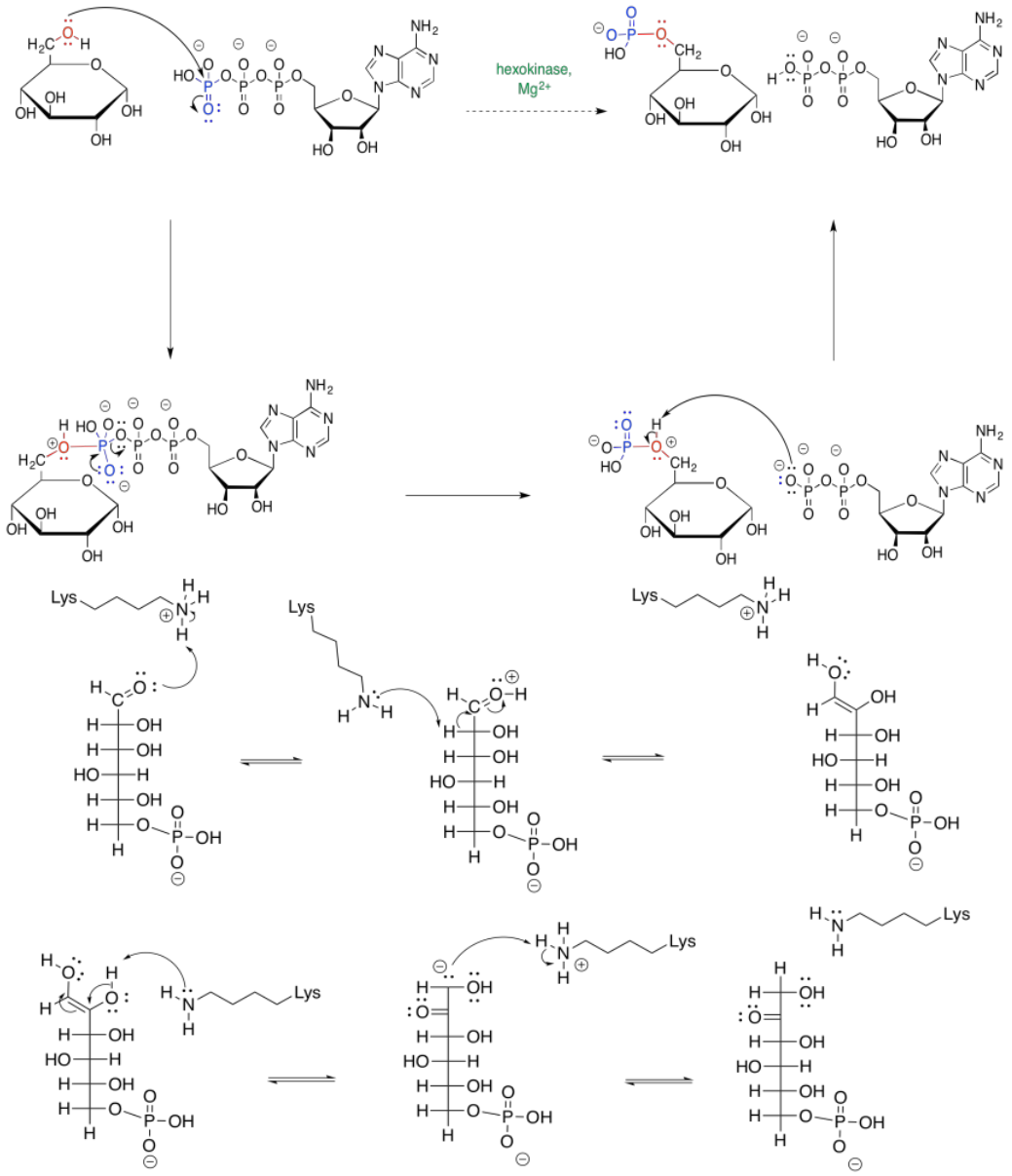
d)  e)  f) 

a)  b)  c) 

d)  e)  f) 

a)  b)  c) 

d)  e)  f) 



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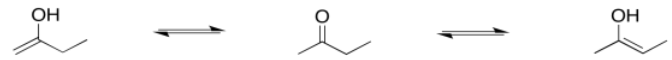

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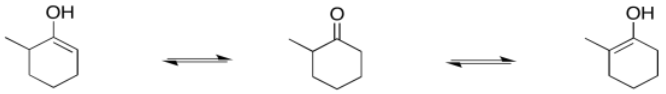

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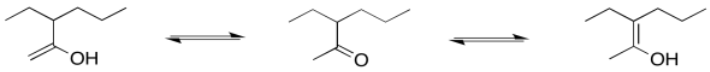

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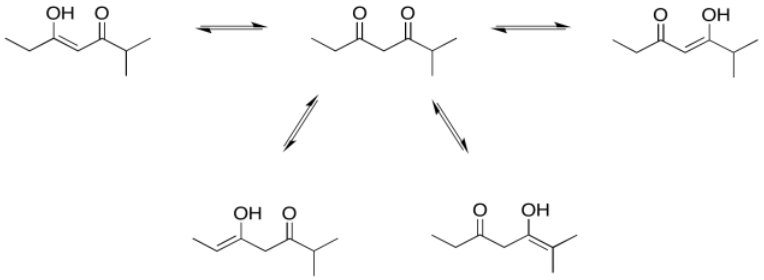

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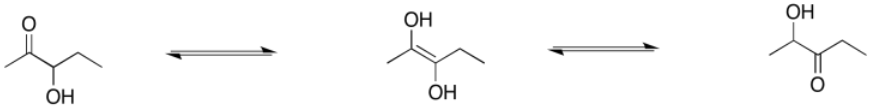

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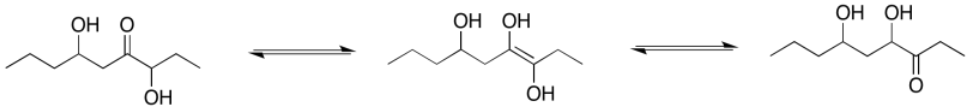

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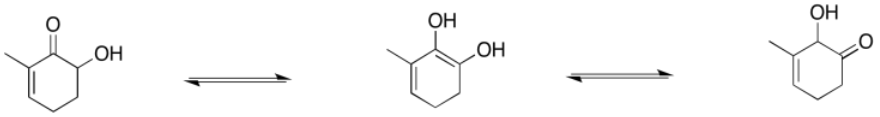

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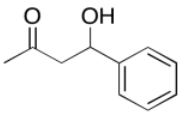

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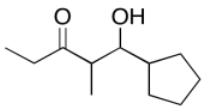

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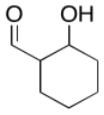

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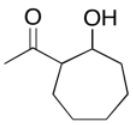

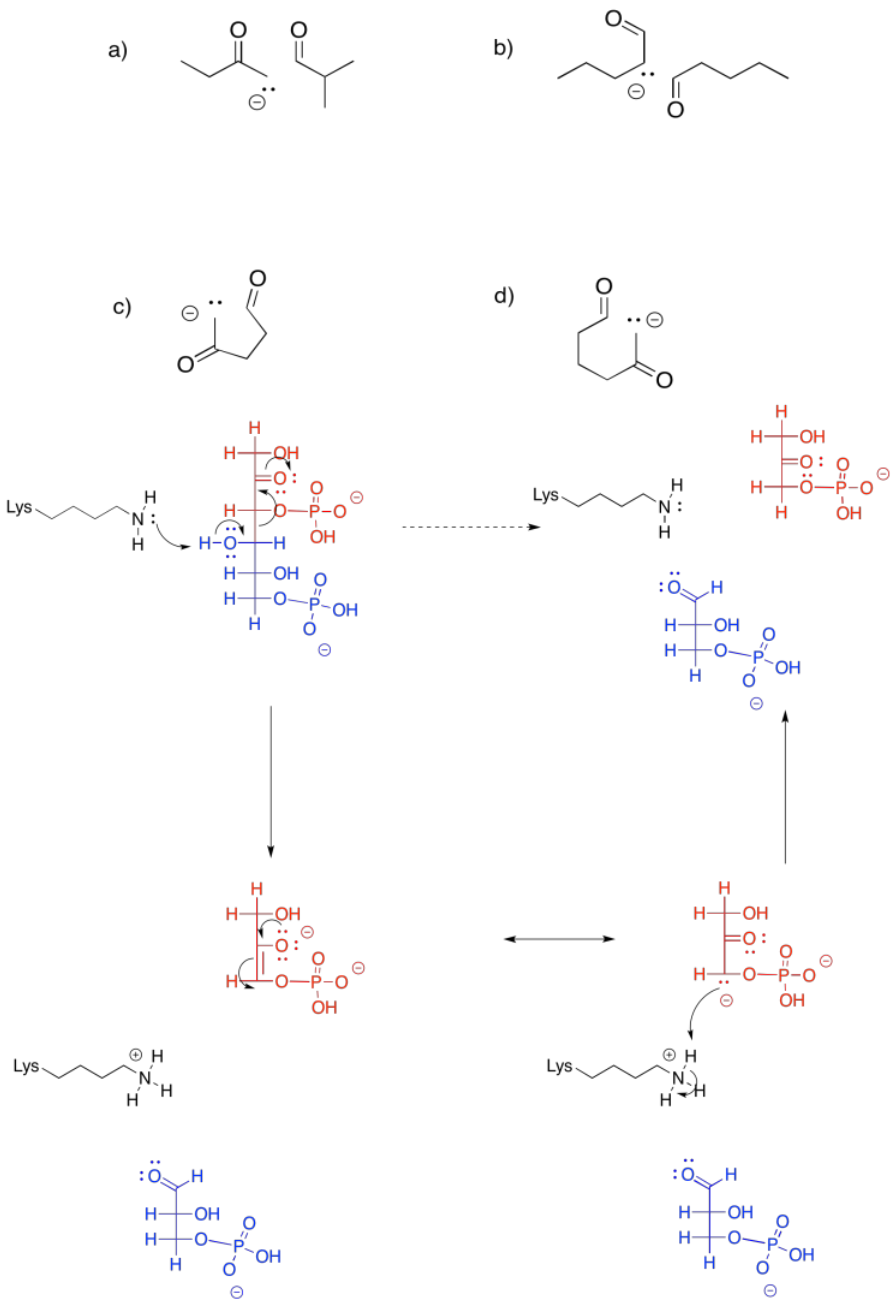
a)
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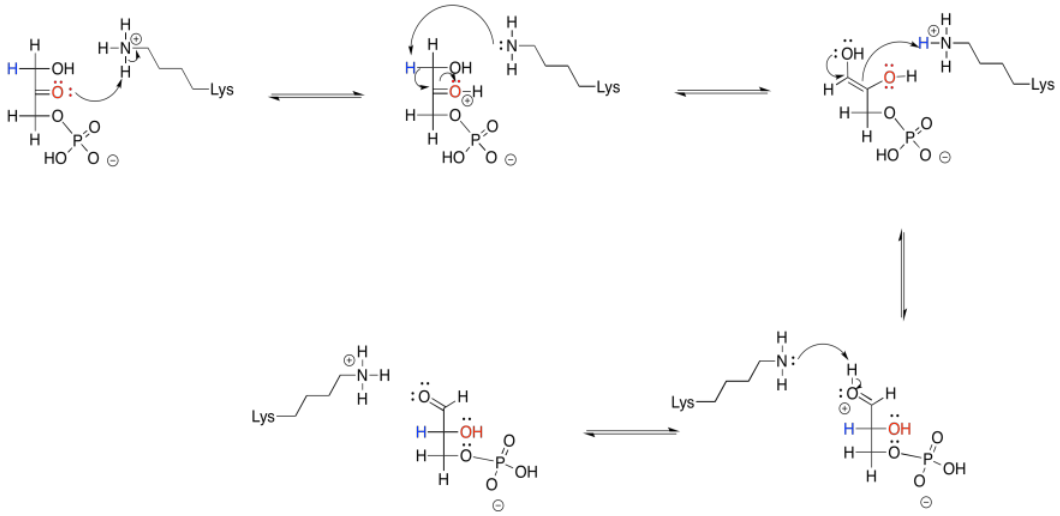
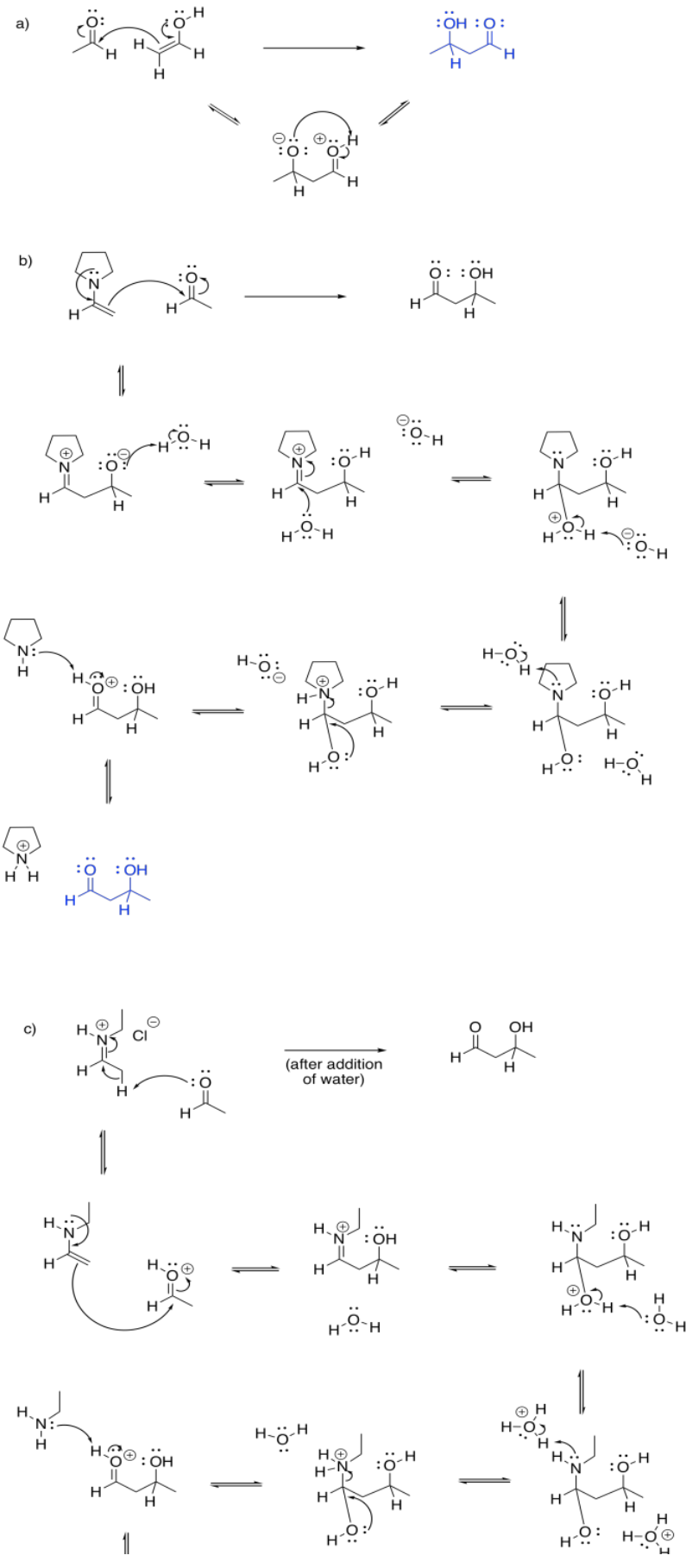
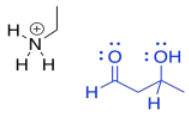
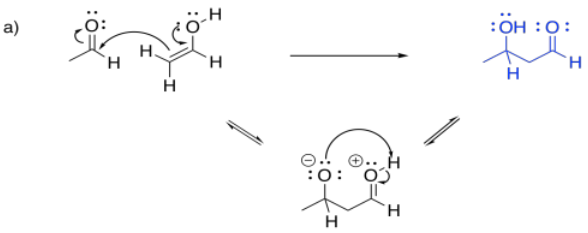
Lys







a)



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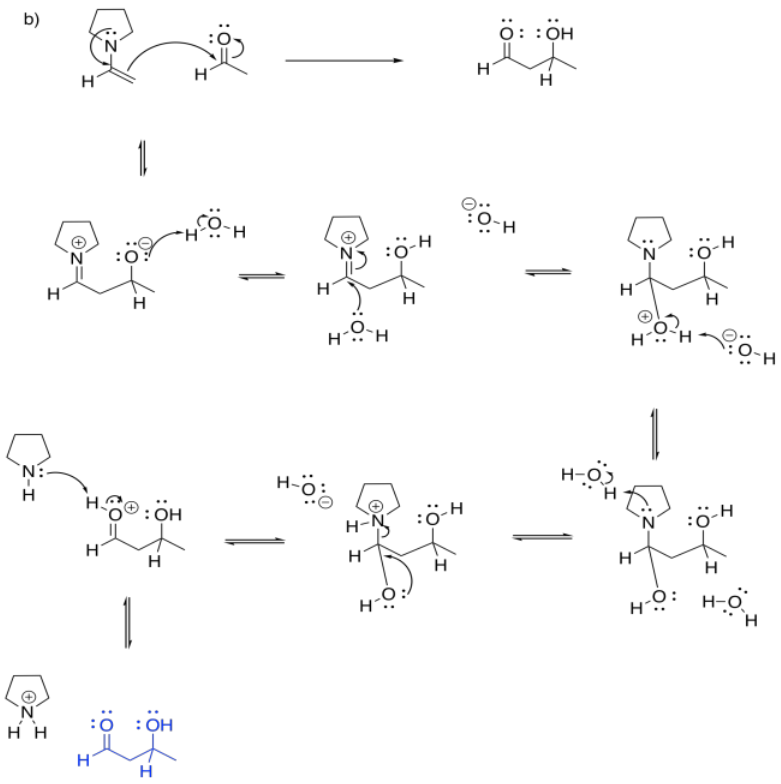

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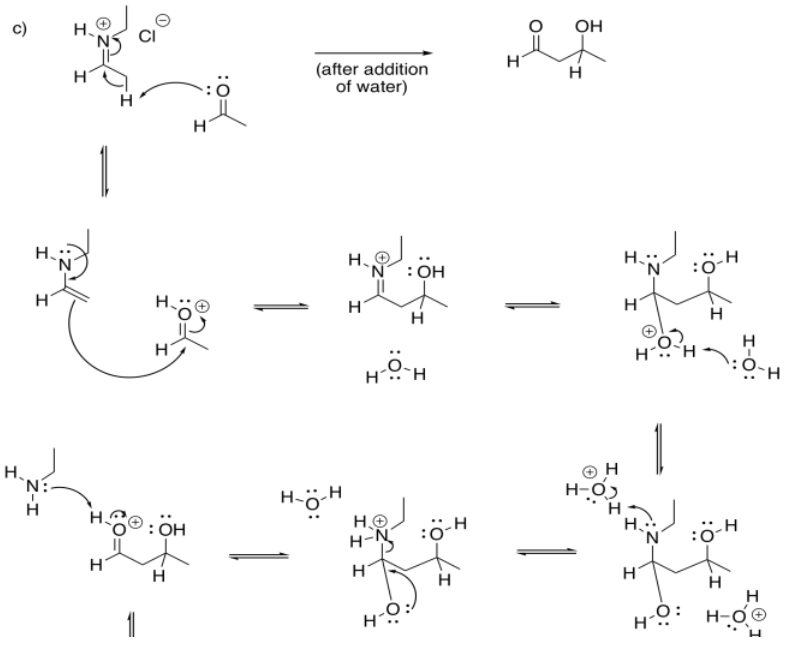
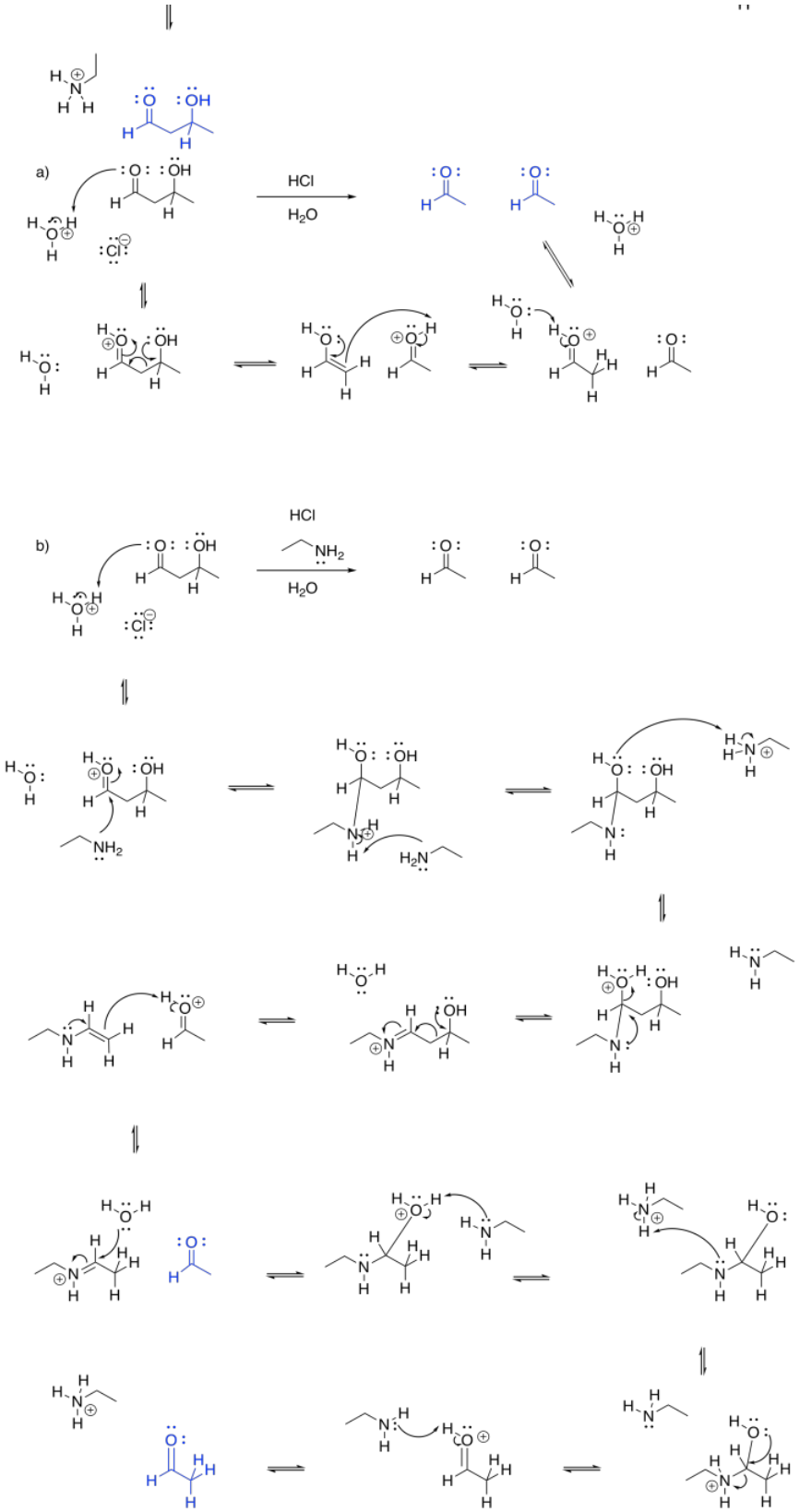




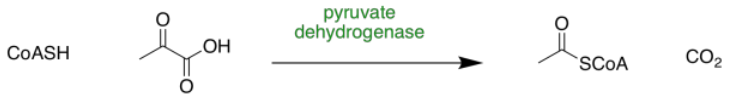
CHAPTER OVERVIEW

9: Mechanisms of the Tricarboxylic Acid Cycle

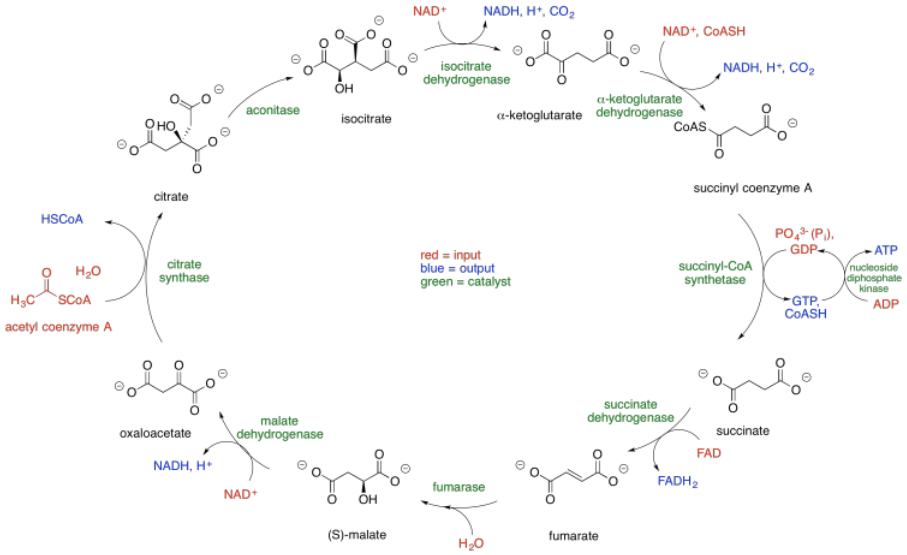
9.1: Overview of the TCA Cycle

The TCA cycle (**tri**carboxylic **a**cid cycle) is also called the citric acid cycle or, sometimes, the Krebs cycle. It takes up where glycolsis left off, improving the efficiency of respiration by extracting a little more energy to produce some more ATP.

We should start by looking at a map of the cycle. When we left off, glycolysis had reached its conclusion with the formation of pyruvate, a three-carbon compound. The pyruvate is converted into acetyl coenzyme A, an important metabolite involved in many processes.

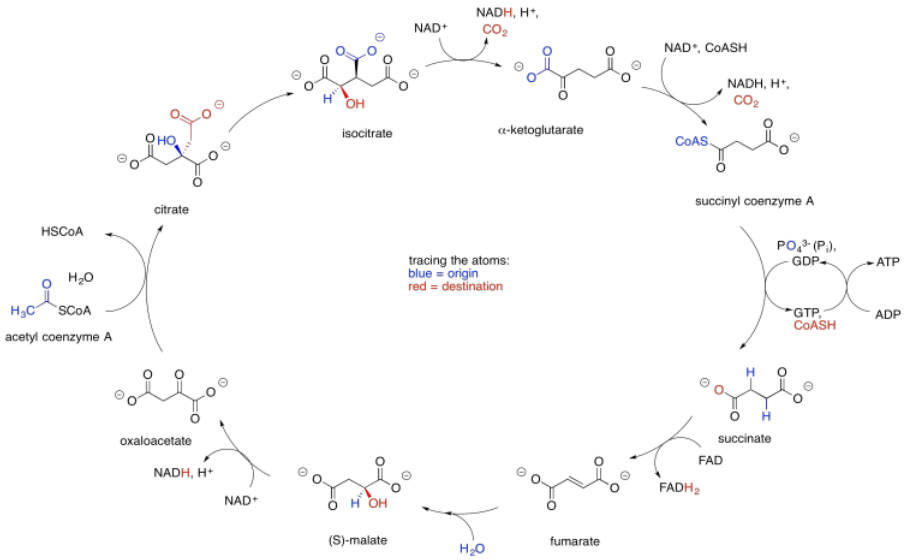


The acetyl coenzyme A is taken up into the citric acid cycle; you can think of it as the link between glycolysis and the TCA cycle. The cycle itself is shown below. In this map, compounds coming into the cycle are shown in red, compounds being produced are shown in blue, and the enzymes responsible for carrying out the various steps are shown in green.



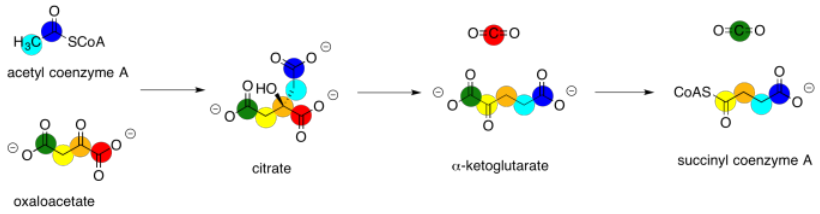
You can see that citric acid, or citrate anion, is the first-formed product once acetyl coenzyme A enters into the cycle. We can think of the oxaloacetate as a carrier that picks up the acetyl group from the acetylcoenzyme A, does some work, and is eventually regenerated. In reality, things are slightly more complicated, however.

It may be helpful to look at the TCA cycle in a slightly different way. We can take the same map and alter it so that it highlights the changes in the molecule at each stage of the cycle. In this map, each step is colour-coded so that you can follow where things are going during that step. For example, the acetyl coenzyme A is labelled in blue as it comes into the cycle; its destination within the citrate molecule is shown in red. In the second step, there is a hydroxyl group that shifts from one position to another. We can see where it starts out in blue and where it ends up in red.



Looking at the cycle in this way can help us to keep track of the changes at each stage of the cycle. That can be helpful as we try to analyse how each step occurs.

It can also be useful to label each carbon atom in those two beginning molecules, acetyl coenzyme A and oxaloacetate. When we do that, we get a sense of some overall changes occurring along the cycle. Specifically, there are a couple of molecules of carbon dioxide evolved along the way. The oxaloacetate picks up an acetyl group, growing from a four-carbon compound to a six-carbon compound. It later loses first one carbon and then a second, eventually becoming oxaloacetate again.



Where do these carbons come from? If you follow the cycle carefully, you will see that they actually come from two of the carbons in the original oxaloacetate molecule: one carbon from each end of the chain. Although the TCA cycle at first appears to involve the conversion of the acetyl group to two molecules of carbon dioxide -- an idea that seems consistent with the oxidation of glucose to carbon dioxide in respiration -- there is something more subtle happening here. The acetyl group is eventually becoming oxidised to carbon dioxide, but first it must be incorporated into the oxaloacetate molecule and sent through the TCA cycle a couple of times.

In the subsequent sections, we will take a closer look at the relationships between the compounds in the cycle before examining the mechanisms of the enzyme-catalysed reactions.

Exercise 9.1.1

If the conversion of oxaloacetate to citrate is Step 1 of the TCA cycle, which steps result in the loss of carbon dioxide?

Answer

Steps 3 and 4 (isocitrate to alpha-ketoglutarate and alpha-ketoglutarate to succinyl coenzyme A).

Exercise 9.1.2

Glycolysis and the TCA cycle are important metabolic processes central to the use of energy by the cell. If the conversion of oxaloacetate to citrate is Step 1 of the TCA cycle, which step is involved in ATP production?

Answer

Step 5 (succinyl coenzyme A to succinate).

Exercise 9.1.3

In addition to being useful cofactors for a number of processes, NADH and $FADH_2$ are employed in another metabolic process, oxidative phosphorylation, to make additional ATP. If the conversion of oxaloacetate to citrate is Step 1 of the TCA cycle, which steps are involved in NADH and $FADH_2$ production?

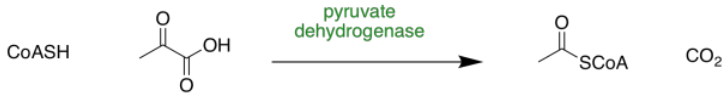
Answer

Steps 3 (isocitrate to alpha-ketoglutarate; NADH), 4 (alpha-ketoglutarate to succinyl coenzyme A; NADH), 6 (succinate to malate; $FADH_2$), and 8 (malate to oxaloacetate; NADH).

9.2: Transformations in the TCA Cycle

In this section, we will take a look at the individual steps that make up the TCA cycle. We will try to see how the molecules are changing, and relate those changes to standard events from organic reactivity.

The very first step that leads to the citric acid cycle is the the conversion of pyruvate to acetyl coenzyme A (or acetyl CoA).



Acetyl coenzyme A is a very important molecule in a wide range of biochemical reactions, in addition to its role in the citric acid cycle.

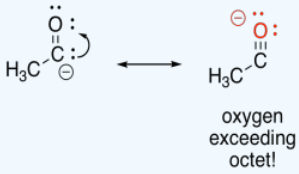
So, this is a really important transformation, yet this step poses a vexing problem. If you look at the reaction, you will see that one of the original three carbon atoms in pyruvate is lost as carbon dioxide. This is called a decarboxylation, and it is not uncommon in biological chemistry. A decarboxylation starts with a carboxylate or carboxylic acid group, which already contains a C=O bond as well as a C-O bond. A lone pair from the C-O oxygen donates to the carboxyl carbon, making the second C=O bond. That step displaces a leaving group from the other side of the carboxyl carbon. Most commonly, the leaving group needed for this step is a stable, enolate anion.

At first glance, things might seem to be OK for that to proceed in the pyruvate decomposition step, but there is a problem. The leaving group is not an enolate anion, and it isn't a particularly stable anion. The most stable carbon anions are resonance-delocalised, preferably over oxygen, as in an enolate or carbonate anion. The leaving group that we would have here, however, offers no such advantage.

Exercise 9.2.1

Show, with an additional resonance structure, why resonance delocalisation of the acyl anion is not possible.

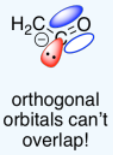
Answer



Exercise 9.2.2

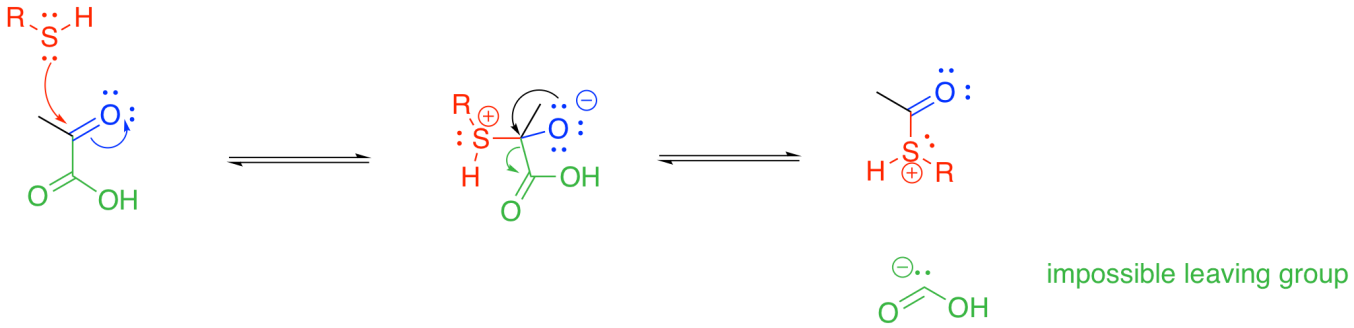
Show, using molecular orbital cartoons, why resonance delocalisation of the acyl anion is not possible.

Answer

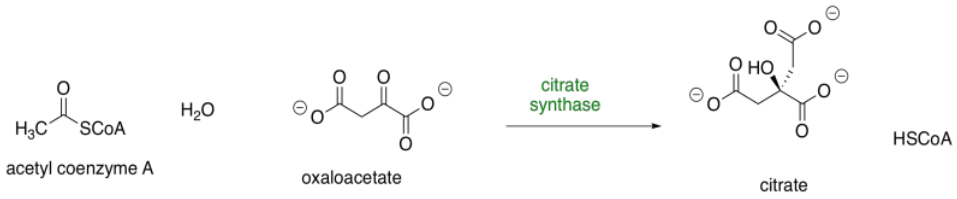


Something else is also happening in the pyruvate-to-acetyl CoA step. A thiolate group is also incorporated at this stage; in fact, this part brings in the coenzyme A. From that point of view, maybe this step is best thought of as a carboxylic substitution at the acyl group. Thiols can certainly displace leaving groups from carboxyloids.

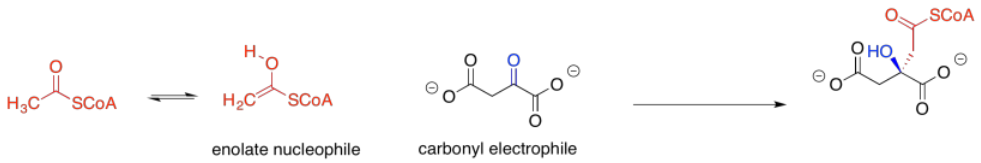
Unfortunately, we hit the same roadblock this way. We still need a carbonyl-based anion, and that isn't going to happen. Either way, the enzyme-catalysed strategy for this step must address stabilisation of that carbonyl fragment as an anion. That task is going to be accomplished through temporary attachment to an ylide, which we will see in the next section.



The TCA cycle really gets started with the addition of the acetyl CoA to oxaloacetate, forming citric acid. That step also results in displacement of the CoA thiol via hydrolysis.

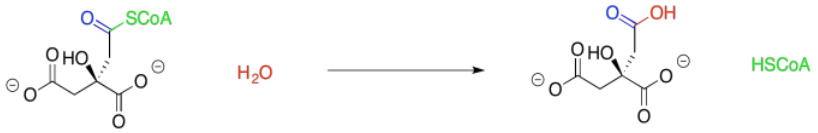


This citrate-forming step is a little easier to work through than that last one that we saw. The key is to recognise that the acetyl group, which contains a carbonyl and an alpha position, could easily tautomerize to form an enol. Viewed that way, the acetyl part of the acetyl CoA as a nucleophile, rather than an electrophile.

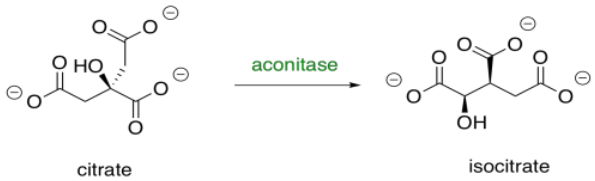


The best electrophile in the complementary molecule, the oxaloacetate, is the carbonyl of the ketone; remember, pi-donation, diminishes the electrophilicity of the carboxylate groups, to say nothing of the negative charge. So what we have here is a standard addition of a nucleophile to a carbonyl, with the latter forming a hydroxy group as it picks up a proton. With an enol or enolate nucleophile, it's an aldol reaction.

Furthermore, the displacement of the thiol by water seems pretty trivial. That's standard carboxyloid substitution.

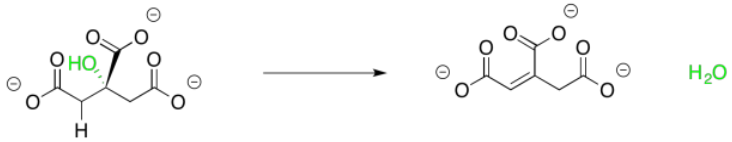


The subsequent conversion of citrate to isocitrate appears, at first, to be a little trickier. At one position, a hydroxy group is replaced by a hydrogen atom, whereas a hydroxy group replaces a hydrogen atom at another position.



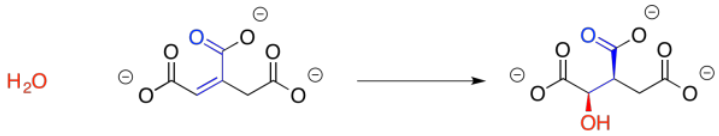
This one isn't terribly complicated either, though. It helps to see that the reaction is accomplished in two separate, and completely complementary, steps. You have seen the first one before in connection with aldol reactions. Sometimes an aldol reaction is followed by loss of a water molecule. The newly-made OH group picks up a proton from the neighbouring alpha position to form that water. Remember, the older term, "aldol condensation", refered to the formation of water, which would condense on the

glassware in which the reaction occurred. This step is often promoted by the presence of additional conjugation involving the new double bond and sometimes it is promoted by heat, but in this case it is carried out by an anzyme.



Note that we rotated around that middle bond of citrate, on the left, but it's still the same molecule.

We may not have considered the reversibility of this reaction before, but that's what we need to do now. The enone group, a carbonyl in conjugation with a C=C bond, is electrophilic at both the carbonyl carbon and the beta carbon. The water molecule could simply add back in where it used to be, making citrate again. There is another way to look at the electrophile, however, because there is another carbonyl at the other end of the double bond. Adding in that direction leads to isocitrate.

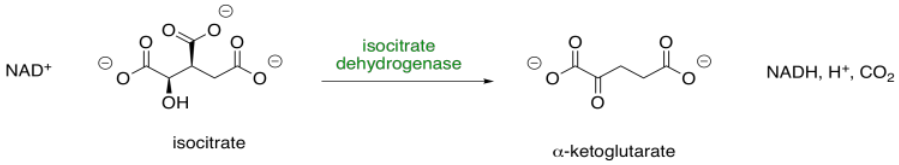


Exercise 9.2.3

Draw resonance structures that demonstrate the electrophilicity of the conjugated positions in the intermediate above.

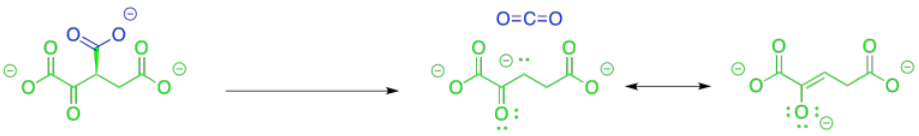
Answer

During the TCA cycle, two additional carbons are lost as carbon dioxide, as the six-carbon citrate makes its way back to the four-carbon oxaloacetate. The first one is lost in the conversion of isocitrate to alpha-ketoglutarate. Also in this step, a hydroxy group is converted into a carbonyl.



So, this step is another case of decarboxylation. We saw that event in the lead-in to the TCA cycle, formation of acetyl CoA. Just as we saw in that case, we need a stable leaving group for the carbon dioxide to leave behind, but it doesn't look like we have that here, either. Remember, it is best to have a resonance-stabilised carbon anion, but we don't have one.

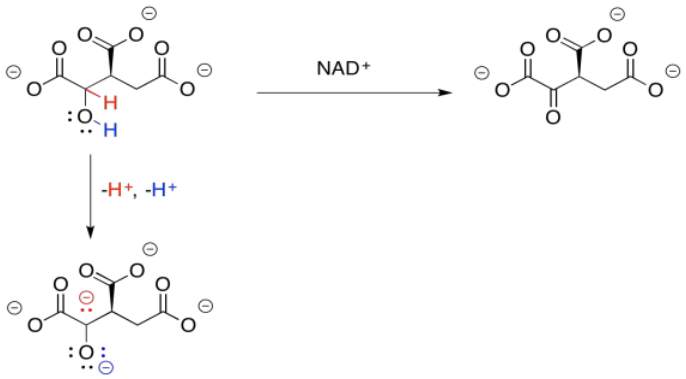
This time, the other half of the reaction could be very helpful. If that alcohol is coverted to a ketone, the problem of decarboxylation is solved because it would leave behind an enolate anion. The enolate anion is resonance-stabilised. That situation would be ideal for decarboxylation.



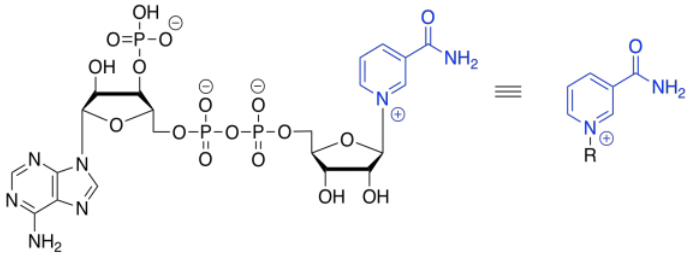
From the point of view of the kinds of reactions with which you are most familiar at this point, the more difficult part about this step is getting from the alcohol group to the ketone. That's a fairly common transformation, though, and in biology it is often

accomplished with the common cofactor, NAD^+.

Why do we need this cofactor? If you analyse the changes in the atoms from one structure to the next, you will notice that the conversion of the alcohol to a ketone requires the loss of two hydrogen atoms. A beginning student will often notice that fact and remove the protons in the best way that they know: as protons.

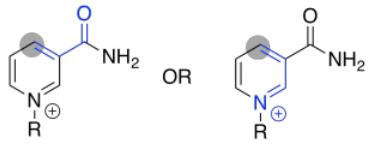


That will not work. If we just lose two protons, then we build up an additional 2- charge on the molecule. Electrons are very small, but they are very important, and they don't just disappear because it would make things more convenient. Now, there is a class of biological cofactors that will take care of this problem. These cofactors are biochemical oxidants, and NAD^+ is a member. It can accept two, and only two, electrons at a time. And that's exactly what we need.



NAD^+

NAD^+ can accept a pair of electrons because it is very electrophilic. That's partly because of the full positive charge. It also contains an electron-withdrawing carbonyl. These two factors combine to make this cofactor a good electrophile.



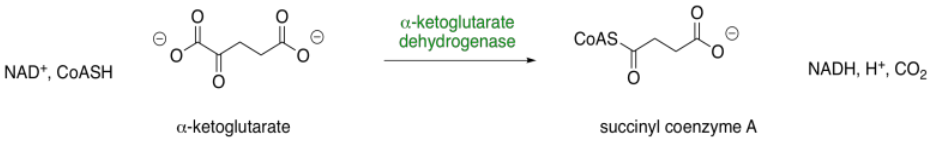
1,4-electophilic position

Exercise 9.2.4

Use resonance structures to confirm the electrophilicity of the indicated position.

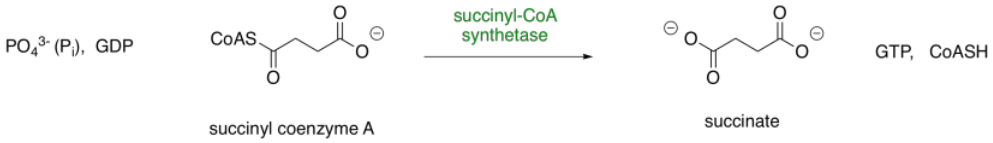
When NAD^+ accepts this electron pair, it becomes NADH, a biochemical reductant. It's worth looking at that for a moment because you have seen the sort of reaction that NADH can accomplish: the delivery of a hydride nucleophile (H^-) to a carbonyl electrophile. That would convert a ketone to an alcohol, for example. That's exactly the opposite of what we are doing here. Oxidation of the alcohol by NAD^+ is what's called the "microscopic reverse" of the hydride addition, or reduction, of the ketone to the alcohol. The reaction follows the same pathway, but in the opposite direction. Instead of NADH pushing a hydride ion onto an electrophilic carbonyl, the alcohol is pushing a hydride ion onto the electrophilic NAD^+.

The very next step of the TCA cycle is also a decarboxylation step.

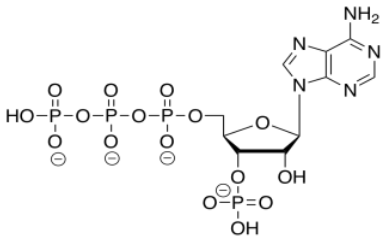


Once again, the major consideration here is the presence of a good leaving group. This time, the reaction looks an awful lot like that original step, the conversion of pyruvate to acetyl CoA. Decarboxylation will provide an anion that sits directly on the carbonyl carbon, rather than alpha to it. In fact, this problem will be solved in exactly the same way as in that first step. The pathway will involve temporary attachment of an ylide to stabilise the anion.

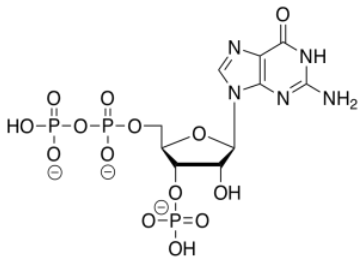
We now come to the ATP-producing step in the TCA cycle. Actually, ATP is not produced directly, but is coupled to a GTP-GDP cycle.



You recall that ATP is the triphosphate ester of the nucleotide, adenosine.



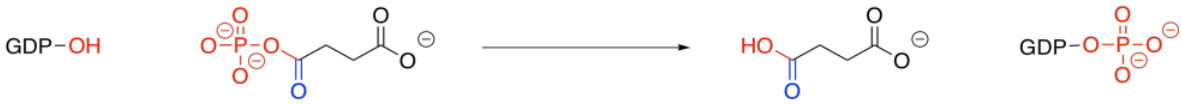
GDP is just the diphosphate ester of another nucleotide, guanosine.



At first glance, it looks like the GDP is just picking up another phosphate group from inorganic phosphate ion (P_i is a biochemistry shorthand for phosphate ion, whether it is present as PO_4^{3-}, HPO_4^{2-}, or $H_2PO_4^-$). For its part, the succinyl coenzyme A looks like it is simply getting hydrolysed: reacting directly with water to displace the thiol leaving group.

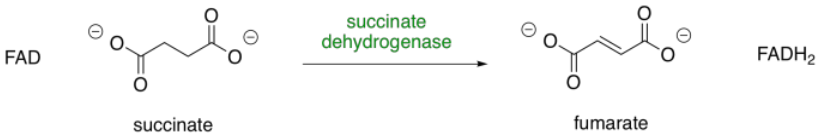
In reality, the succinyl CoA acts as a primer for the phosphate group, activating it as a more electrophilic phosphoanhydride. That step makes it easier for the GDP to donate to it as a nucleophile, leading to an additional phosphate connection.

The GDP simply displaces a carboxylate leaving group from the phosphoanhydride.



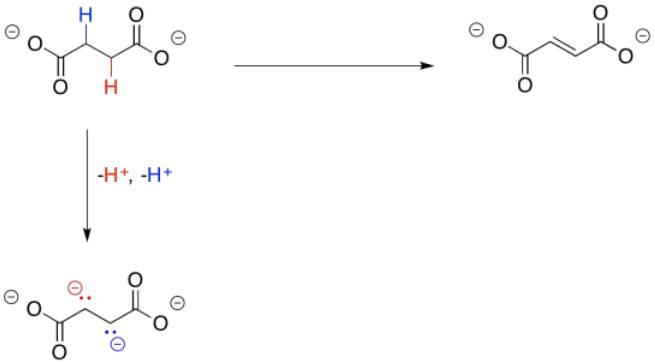
At this point, we have accomplished a lot in terms of the overall changes in the TCA cycle. We picked up a two-carbon piece in the form of an acyl group (CH_3CO). We have made a molecule of ATP. We have unloaded those two extra carbons as carbon dioxide and are back at a four-carbon diacid again; we have almost regenerated the oxaloacetate. We still have a couple of things to do in order to complete the cycle. We need to install another carbonyl in the four-carbon chain; that is, we need to add in an oxygen, somehow. On the way, we are going to produce some more NADH and $FADH_2$, which are also important in meeting the cell's energy needs, as well as its synthetic feedstock requirements.

To that end, succinate is first converted to fumarate. That's going to give the molecule an electrophilic position where it is needed, to allow the installation of that oxygen atom.

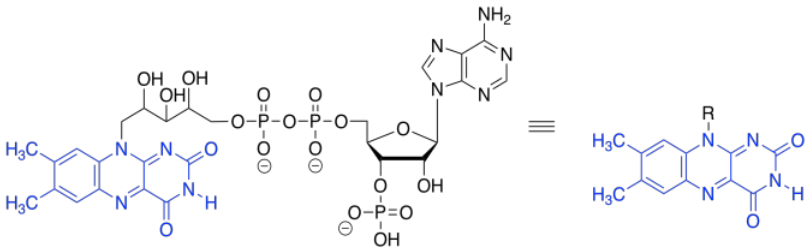


If you think about it, this step is similar to one you have seen before on this page. We need to make a double bond where there was previously a single bond. In order to do that, we need to lose two hydrogen atoms.

Losing two protons seems simple enough; that's especially true in this case, because each proton would be lost from an alpha position. Those alpha positions are ever-so-slightly acidic. However, that doesn't lead all the way to malate, because we still have two extra electrons to deal with.

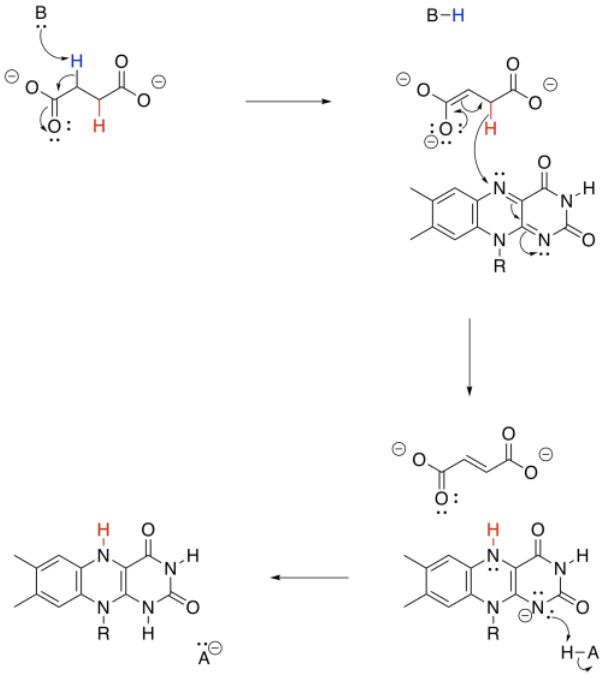


Again, we dealt with this problem earlier. All we needed was an oxidant, which would accept the two extra electrons. This time, instead of NAD^+, the process will make use of a molecule of FAD.



FAD

Just like the conversion of NAD^+ to NADH, the transformation of FAD to $FADH_2$ can absorb a hydride ion. That's a proton plus a lone pair.



Exercise 9.2.5

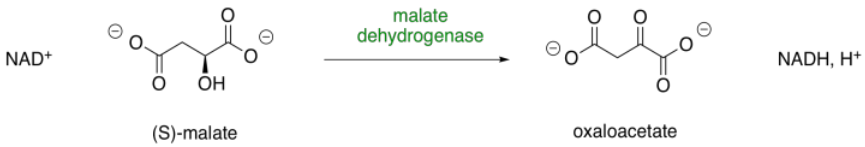
Overall, FAD takes up both a hydride (H^-) and a proton (H^+) in this step. We think of the hydride as adding to the nitrogen atom next to the benzene. Use resonance structures to show why that is probably the case.

We are almost there. Now, an oxygen atom is installed in the form of an OH group.

fumarate (S)-malate

Of course, at this point it seems pretty clear that that hydroxy group just comes from a 1,4-addition of water to the enone electrophile of the fumarate.

Finally, the resulting malate is converted back into oxaloacetate, completing the cycle. You have seen steps very similar to this one, earlier in the cycle. At this point we are ready to start the cycle again.



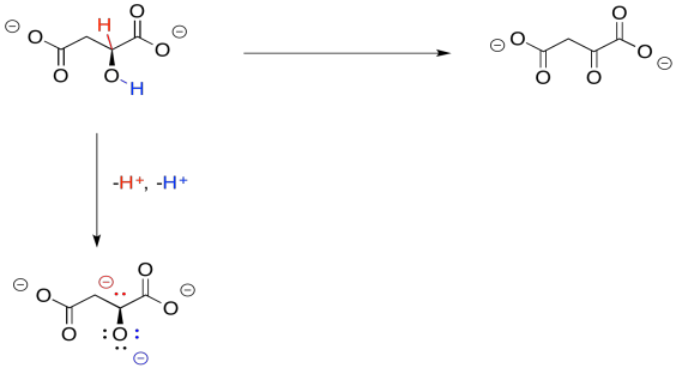
Exercise 9.2.6

Before reading further, explain the role of the NAD^+ in the final step of the TCA cycle.

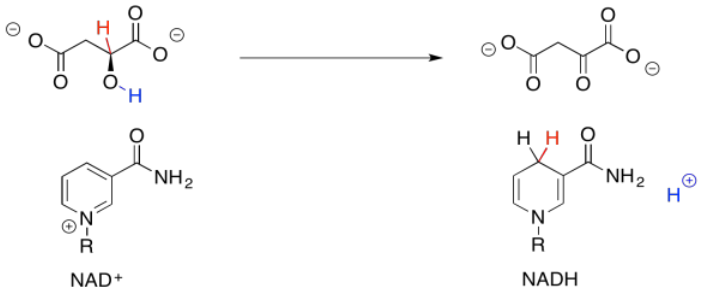
Exercise 9.2.7

The malate and oxaloacetate molecules in the above drawing are oriented in two different directions. Rotate the malate so that it more closely corresponds with the structure of the oxaloacetate.

So, if you couldn't remember where you have seen this sort of change before, take a closer look. The conversion of malate to oxaloacetate involves the loss of two hydrogen atoms. That's two protons plus two electrons.



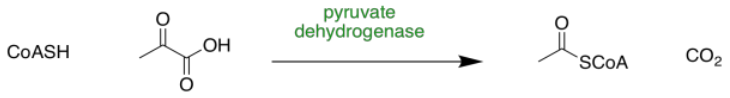
We can make this happen if we have an electron acceptor. A biochemical oxidant, such as NAD+, is a great candidate. It will accept a hydride ion from the malate, helping it on its way to oxaloacetate.



In the next section, we will take a closer look at the mechanisms that these compounds follow as they proceed through the TCA cycle.

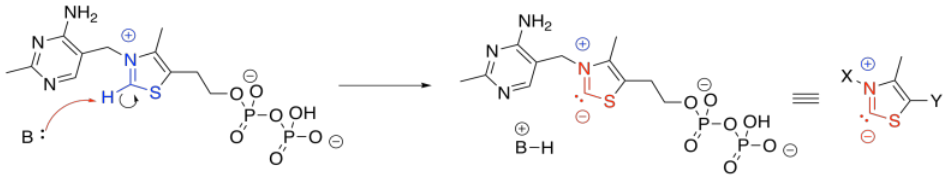
9.3: Catalysis in the TCA Cycle

The formation of acetyl coenzyme A (acetyl CoA or AcSCoA) is step zero of the TCA cycle. It is the connecting point between glycolysis and the TCA cycle.

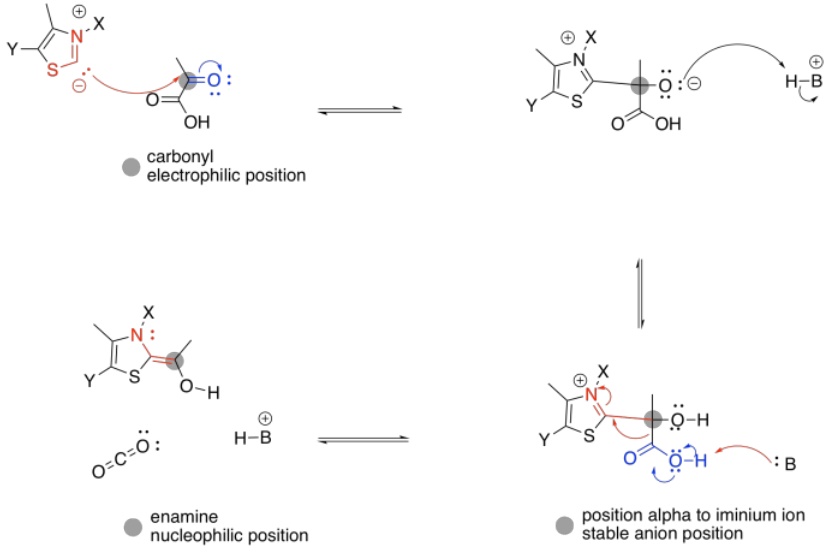


The sulfur in coenzyme A (CoASH) is a good nucleophile and the ketone in pyruvate is a good electrophile. Those factors should help these pieces to come together. The difficulty of this step, as we saw in the last section, is that we have no good leaving group.

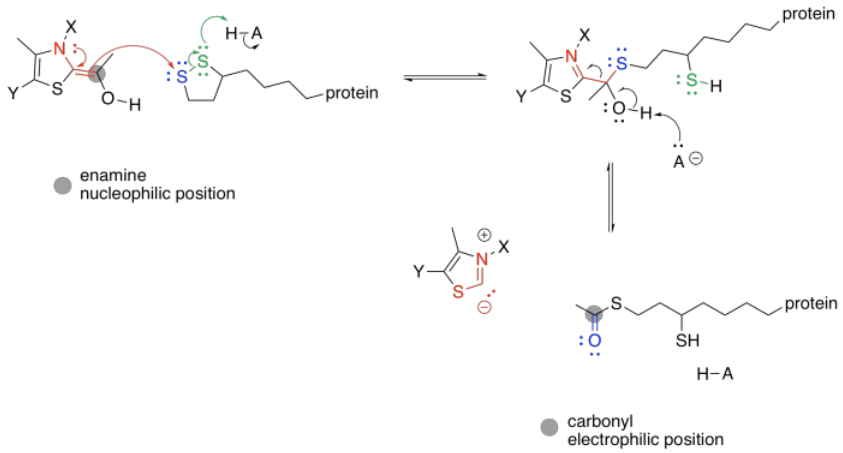
Nature's approach here is to do something we call an "umpolung" approach. Umpolung means reversing polarity. We will take that good electrophile and turn it into a good leaving group. We will make it into a stable anion. In pyruvate dehydrogenase, the enzyme that catalyses this step, the umpolung effect is achieved through the use of a thiamine pyrophosphate (TPP) ylide. An ylide ("ill-id") is just a compound that contains both a positive and negative charge on atoms that are right next to each other. It has a built-in nucleophilic part and electrophilic part, and they are in close proximity to each other.



The anionic position in the TPP ylide is nucleophilic. It can esily donate to that electrophilic position in pyruvate. You can see that happening in the left part of the picture above. After donation has taken place, on the right-hand side of the picture, that electrophilic carbon is no longer electrophilic. In fact, it is now found next to a C=N group. It is in an alpha position of an enamine. It is now a position of stable negative charge.



The enamine donates to the electrophilic disulfide of lipoic acid. Don't be too surprised; sulfur can be a good nucleophile, a good leaving group, or a good electrophile, depending on its bonding situation. In this case, one sulfur atom acts as an electrophile, and the adjacent sulfur atom acts as a leaving group.

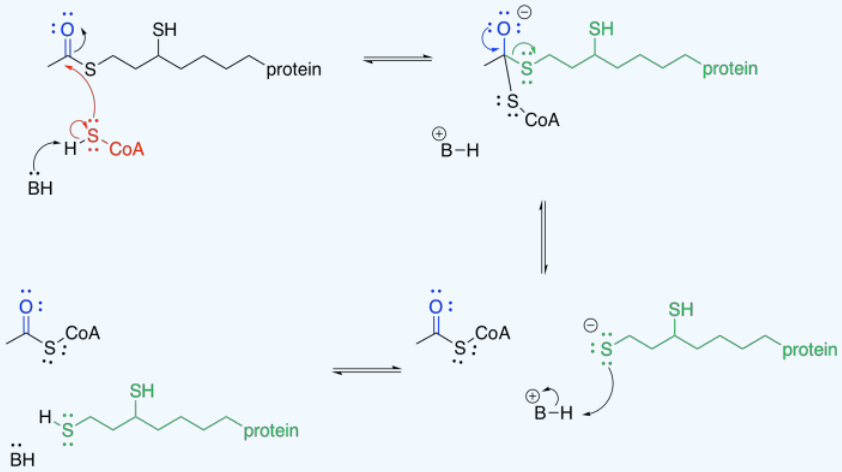


The TPP ylide is ejected via pi-donation. It is ready to be used again. At this point, the acyl group from the pyruvate has formed a thioester. Acetyl CoA is also a thioester, although it isn't the same one. An exchange of thiols accomplishes the conversion to acetyl CoA.

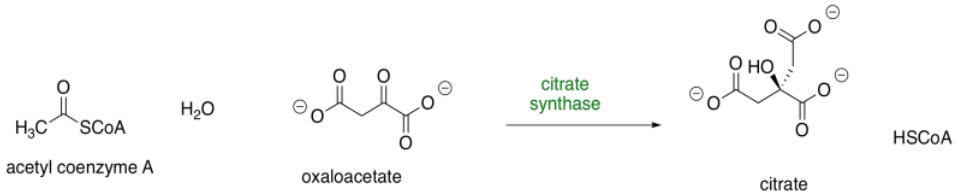
Exercise 9.3.1

Provide a mechanism for the conversion of one thioester into the other. Just use generic acids and bases, H-A and B.

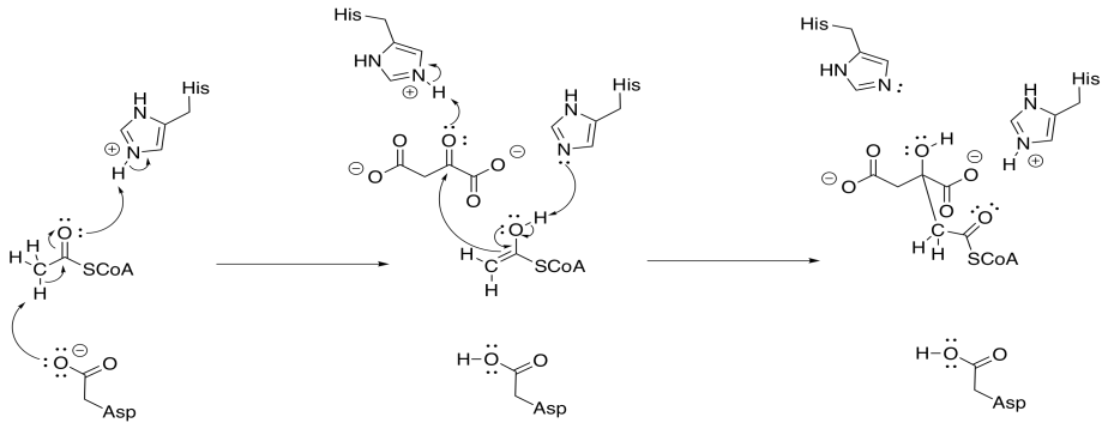
Answer



After formation of acetyl CoA, the new, two-carbon compound attaches to oxaloacetic acid, forming a six-carbon chain.



To accomplish that step, acetyl CoA is first converted into its nucleophilic enol form. The reaction is carried out by citrate synthase. A proton is effectively transferred from the alpha position to the carbonyl oxygen. In fact, a carboxylate group in the protein removes the alpha proton and a new proton is delivered to the oxygen by another residue.

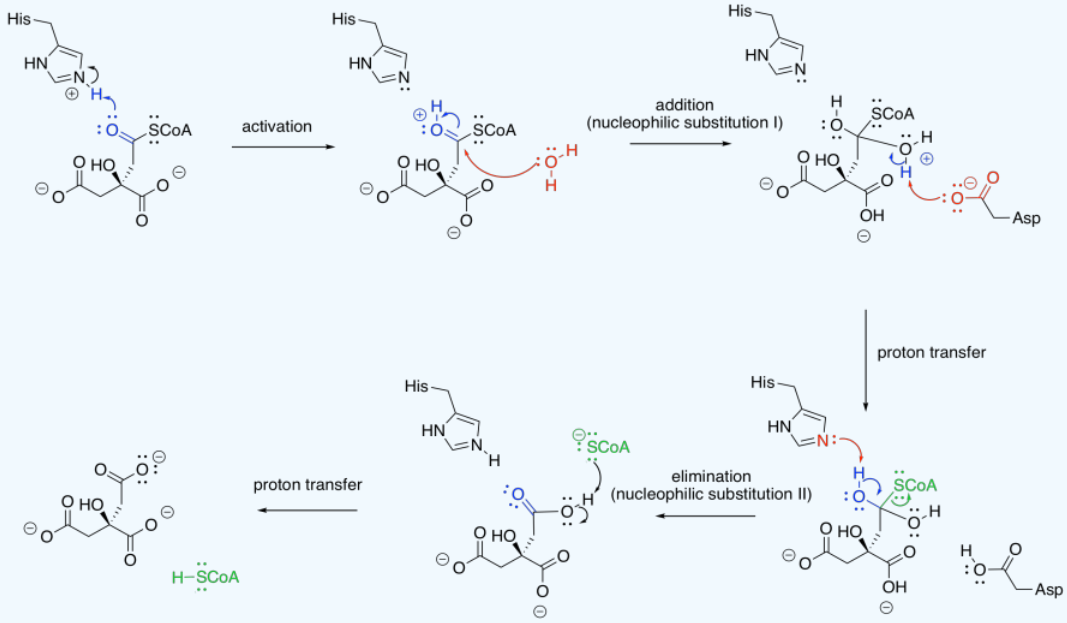


At that point, the nucleophilic enol donates to the electrophilic ketone of the oxaloacetic acid. Picking up a proton from a nearby residue completes this straightforward addition to a carbonyl.

Exercise 9.3.2

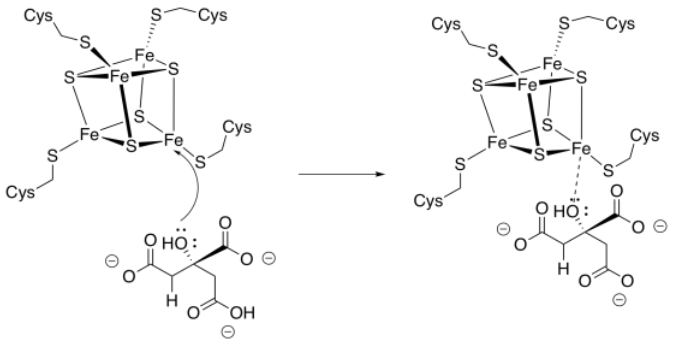
The next step is the hydrolysis of the thioester (O=C-SCoA) into a carboxylate ion (O=C-O$^-$). Provide a mechanism for this step. Use amino acid residues for acid and base steps.

Answer



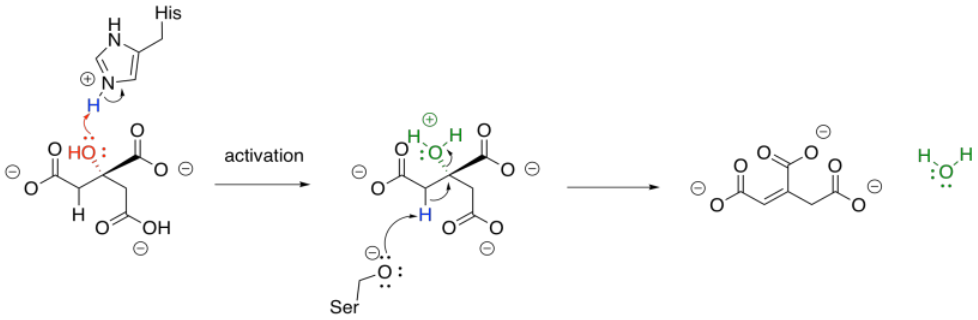
Aconitase carries out the next stage of the cycle, an isomerisation from citrate to isocitrate, in which a hydroxy group moves from one carbon to the next.

Aconitase is an unusual enzyme because it contains an iron-sulfur (FeS) cluster, a cubic group of four iron and four sulfur atoms, coordinated to a protein (usually through cysteine residues). Lots of enzymes contain FeS clusters, but usually they are concerned with shuttling individual electrons from one place to another. Aconitase doesn't do that, so why does it have its own FeS cluster?



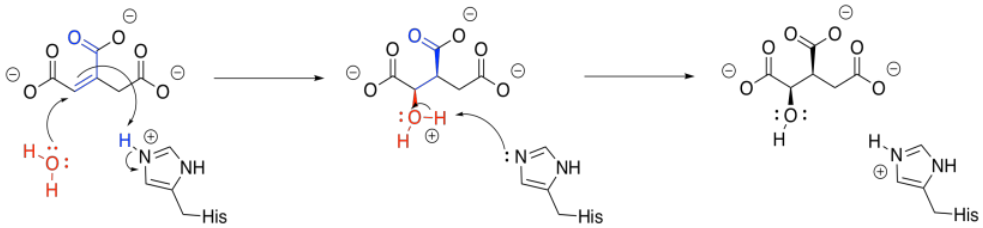
The isomerisation step occurs with specific stereochemistry, and it is believed that the FeS cluster plays a role in holding the molecule in a specific orientation while the reaction takes place. Usually, it is assumed that the hydroxy group coordinates with one of the iron atoms, but coordination by the carboxylates is also possible.

Once the citrate is in the proper position, the original hydroxy group is removed in a dehydration step. Here, the FeS cluster is left out of the picture to simplify things. The hydroxy group is protonated by a histidine residue, making a better leaving group, while a deprotonated serine residue pulls a proton from the nearby alpha position to complete the dehydration. It's unusual to see a deprotonated serine, but it is probably employed here because it is a very strong base. Other amino acids nearby probably play a role in stabilising that serine anion through intermolecular forces so that it can form more easily.

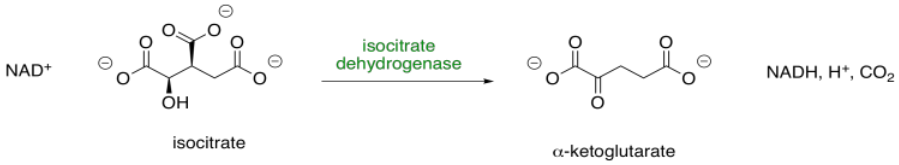


The sequence of some of these steps is not always clear, and sometimes appear to occur so quickly as to be simultaneous. That speed is made possible by the close proximity of the reactants in the active site of the protein. The step shown above is laid out as a separate activation step and deprotonation step in order to make the role of each amino acid very clear, but they don't necessarily happen one after the other like that.

Once the first water molecule is gone, we need to add the second to the other side of the new double bond. This step occurs via a 1,4-addition, and is still catalysed by aconitase. The 1,4-addition would result in an enolate anion, which would then be protonated. In the drawing, the steps are condensed, so the nearby histidine is already protonating that alpha position before the anion forms.

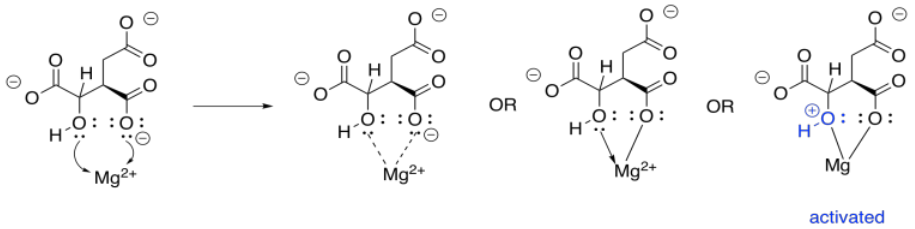


The isocitrate goes on to an oxidative decarboxylation step, carried out by isocitrate dehydrogenase.

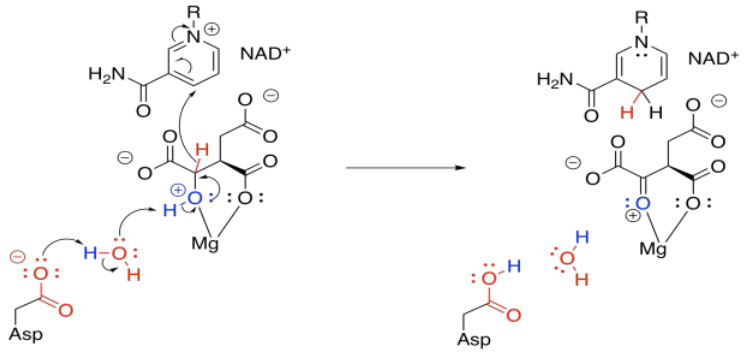


This enzyme requires a magnesium ion cofactor that binds and activates the isocitrate. There are always different ways to draw complexes like this. We can think of the isocitrate sort of sticking to the magnesium; we can think of it as forming one ionic bond

and one dative bond; and we can think of that dative bond as conferring a positive charge on the hydroxyl oxygen, which has donated a lone pair. That's a useful way to think about it this time, because we are going to remove that proton from the hydroxy group.



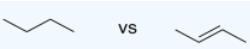
In this step, we face that problem of removing two protons and two electrons from the molecule, converting an alcohol to a ketone. Stated differently, we need to lose a proton (H^+) and a hydride ion (H^-). We need a base to remove the proton, and in this case a "relay" system is used, in which a protein residue is sitting a little too far away to pluck off that proton, so it takes one from a water, and the water takes one from the hydroxy group.

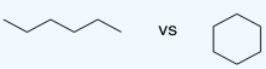


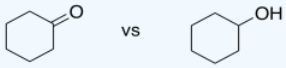
The hydride is delivered to NAD^+, a biochemical oxidising agent. It's frequently used to accept a pair of electrons in the form of a hydride ion. The NAD^+ is converted to NADH, and the NADH stores that electron pair for use in other processes.

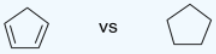
Exercise 9.3.3

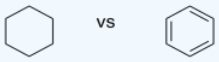
"Units of unsaturation" refer to how one molecule differs from another only by loss of groups of H_2 (or two hydrogen atoms, or two protons and two electrons). In each case, show how many protons and electrons are needed to convert one compound into the other.

a) 

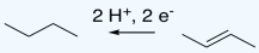
b) 

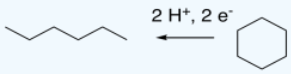
c) 

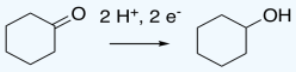
d) 

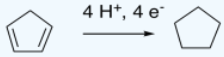
e) 

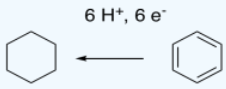
Answer

a) 

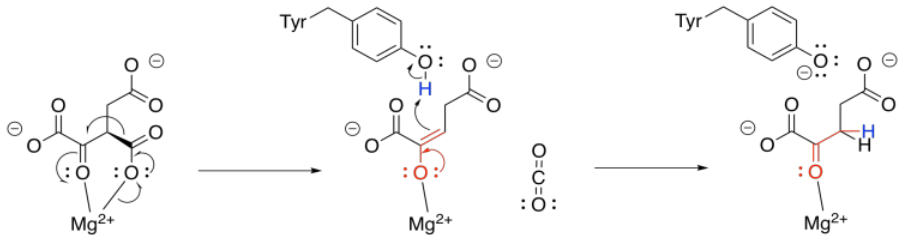
b) 

c) 

d) 

e) 

Now that the ketone has been formed, loss of carbon dioxide from the alpha position is relatively easy, because the CO_2 leaves behind a stable enolate anion. In this case, the enolate is further stabilised by the magnesium ion. The enolate is neutralised by picking up a proton from a nearby tyrosine. The compound that forms is called alpha-ketoglutarate.

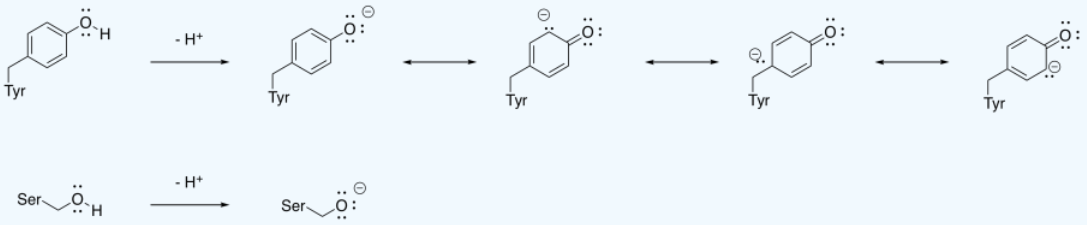


Exercise 9.3.4

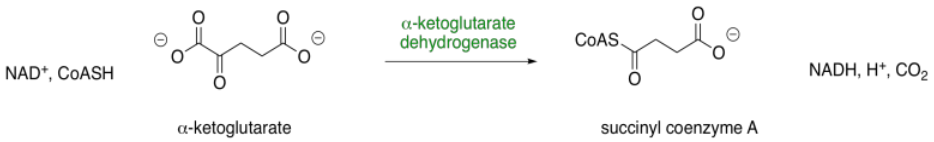
Explain why a tyrosine residue can be deprotonated very easily, but it is more difficult to remove a proton from a serine residue.

Answer

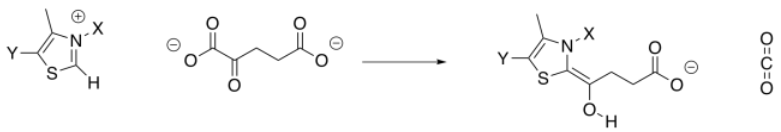
The anion that results from deprotonation of tyrosine is resonance-stabilised, but the anion that results from deprotonation of serine is not. The tyrosine anion is more stable compared to the serine anion and therefore the tyrosine anion forms more readily.



The alpha-ketoglutarate undergoes a second decarboxylation, carried out by alpha-ketoglutarate dehydrogenase. In the equation below, the carbon dioxide is lost from the left-hand side of the alpha-ketogllutarate molecule.



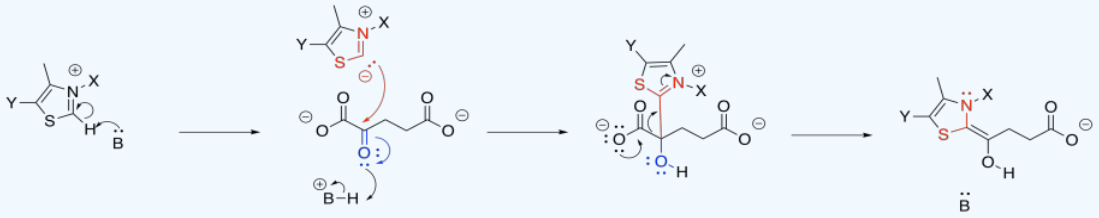
Decarboxylation requires a stable anion as a leaving group from the CO_2. In the case of isocitrate, that stable leaving group was provided by installing a carbonyl. The alpha-ketoglutarate already has a carbonyl, but it's in the wrong place. It's right next to the carboxylate group instead of one carbon over. This situation is similar to the one in which pyruvate was decarboxylated to form acetyl CoA, and it is solved in exactly the same way, using a TPP ylide. The TPP ylide installs an iminium group one carbon away from the carboxylate, meaning there is now an ability to stablise an anion at the right place.



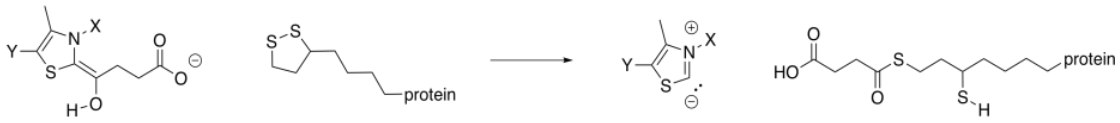
Exercise 9.3.5

Show the mechanism of TPP addition to alpha-ketoglutarate, and the subsequent decarboxylation. You can use generic B: and A-H as catalysts.

Answer



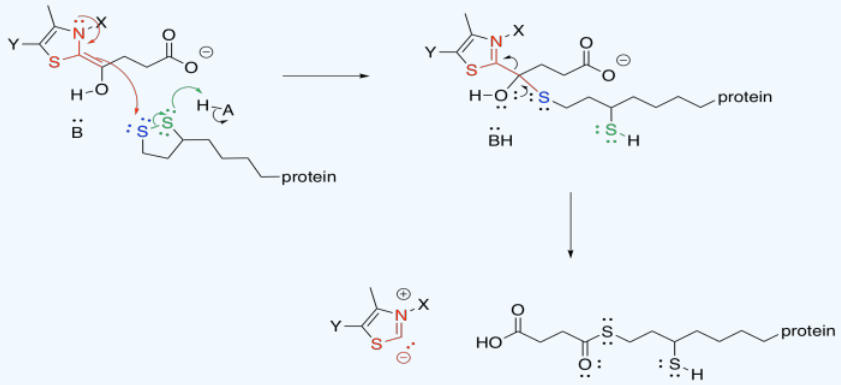
As in the case of pyruvate dehydrogenase, the TPP unit must be removed again. However, it is now part of a nucleophilic enamine group, and the obvious reaction partner for it is an electrophile. An electrophilic disulfide in lipoic acid is again used to reform the iminium group.



Exercise 9.3.6

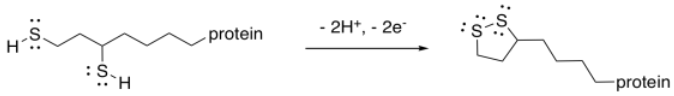
Show the mechanism of reaction with lipoic acid.

Answer

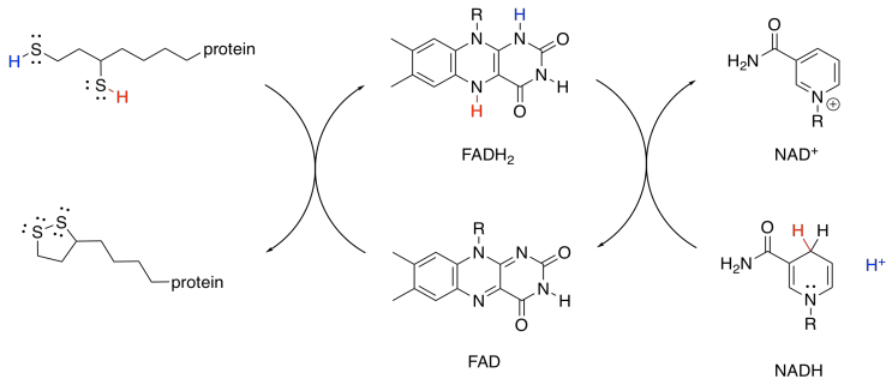


The ring-opened lipoic acid is traded for coenzyme A; that's just one sulfur nucleophile for one sulfur leaving group.

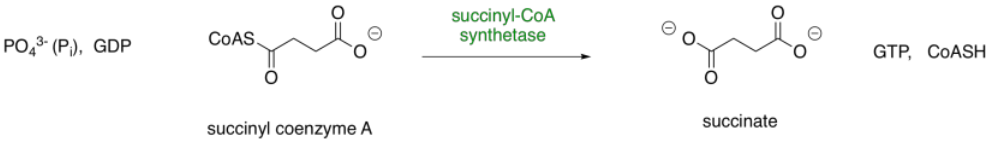
If you pay attention to the map of the citric acid cycle, you see that this step consumes another NAD^+ molecule, and results in another NADH. From the point of view of the main reactant that we are following through the cycle, we have nothing left to do. The alpha-ketoglutarate has been converted to succinyl coenzyme A, which is waiting for the next step. The NAD^+ is needed in a separate catalytic cycle, in which the ring-opened lipoic acid is closed again to form a new disulfide. The disulfide will be ready to react and keep the TCA cycle going.



This mechanism is actually a little bit complicated and requires shuttling of protons and electrons from one place to another. A second biochemical oxidising agent, FAD, acts as an intermediary that transports these pieces to the NAD^+.

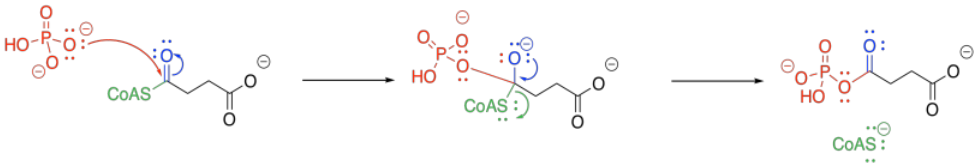


The ATP-forming step of the citric acid cycle takes up an inorganic phosphate and couples it to guanosine diphosphate; this step is carried out by succinyl coenzyme A synthetase. The guanosine diphosphate transfers the phosphate to an ADP in a separate cycle.

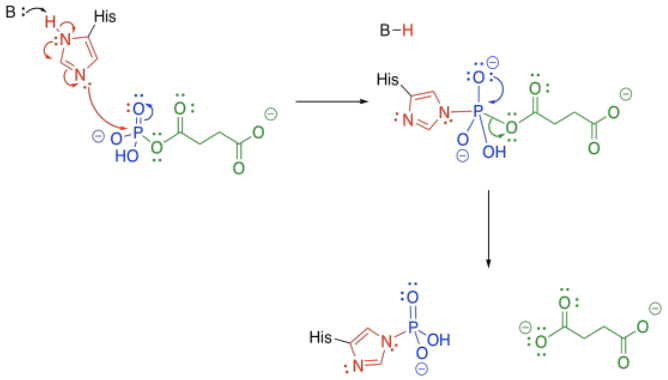


The trouble with phosphate-phosphate coupling is all of that negative charge, and no good leaving groups. Presumably, if we add another phosphate to a GDP or an ADP, we have displaced a hydroxide ion (HO^-) or, even worse, an oxide ion (O^{2-}). So, we need a work-around to take care of that problem.

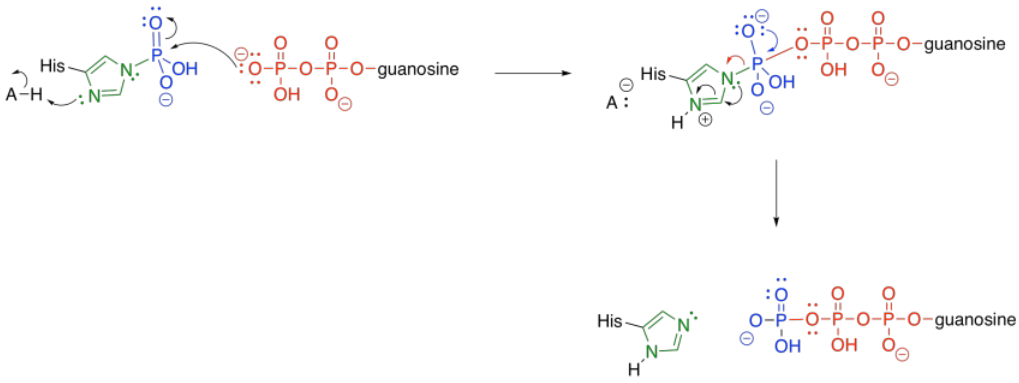
The negatively charged phosphate can certainly act as a nucleophile. It displaces CoASH from succinyl coenzyme A, forming an activated phosphoanhydride.



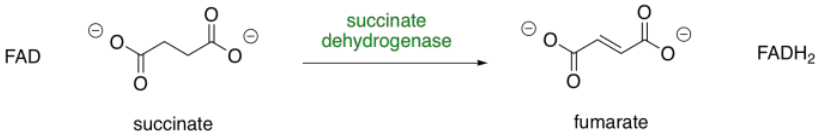
The phosphate group is transferred to a histidine. The histidine is nucleophilic, so it can donate to the phosphoanhydride group. An oxygen is lost from the phosphorus, forming a phosphonate group. The succinate is displaced as a leaving group, where it waits for the next part of the TCA cycle.



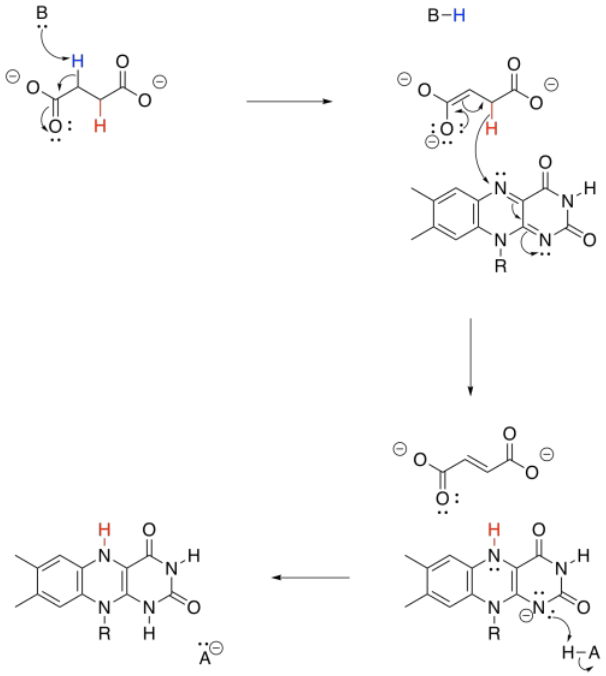
Meanwhile, the phosphate-histidine conjugate delivers the phosphonate group to guanosine diphosphate. The histidine is displaced as a leaving group, and is ready to start its cycle again.



At this point, just a few steps are needed to regenerate the oxaloacetate in order to start the TCA cycle over again. Some of those steps are still very important in terms of energy packaging for the cell. For example, the next step is catalysed by succinate dehydrogenase, which is an integral part of the oxidative phosphorylation complex in most species (that complex carries out the oxygen-consuming part of respiration).



By now, you may have noticed that a dehydrogenase makes use of those biochemical oxidants, FAD and NAD^+. This time, FAD is involved. Once again, two protons and two electrons need to be removed from succinate in order to form fumarate. And, once again, we can think about that as a proton and a hydride ion. A proton is removed from the alpha position, and the resulting enolate ion ejects a hydride onto the waiting FAD molecule.

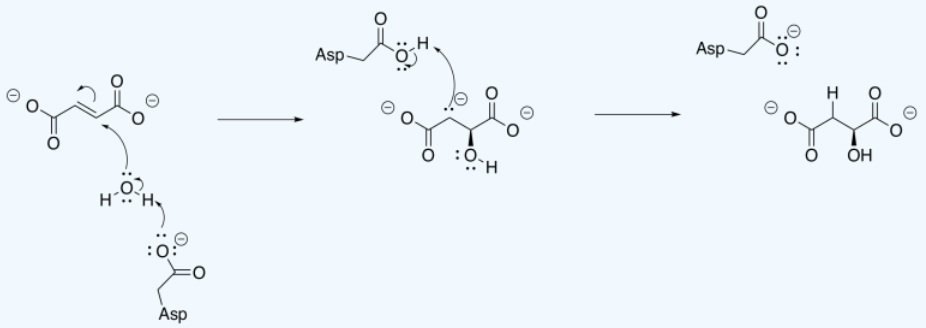


The conversion of fumarate to malate makes use of the enzyme, fumarase. The reaction is a hydration, similar to the one we saw carried out by aconitase. Note that a water molecule is added to one end of the double bond, which is electrophilic because it is conjugated with a carbonyl.

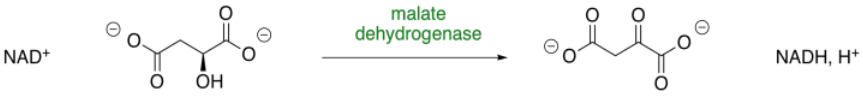
Exercise 9.3.7

Provide a mechanism for conversion of fumarate to malate.

Answer



Finally, malate is turned into oxaloacetate through the action of malate dehydrogenase. A NAD^+ cofactor is required for this step. Like some other steps we have seen before, this one involves the conversion of an alcohol group into a ketone group. It involves the loss of a proton and a hydride ion.

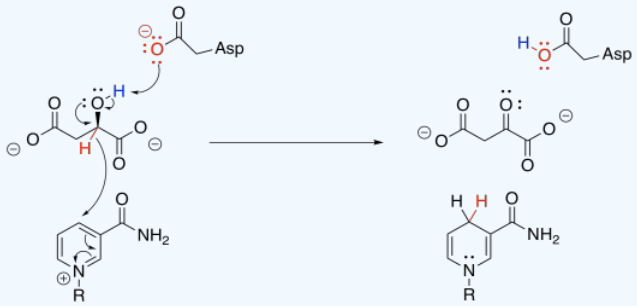


(S)-malate oxaloacetate

Exercise 9.3.8

Provide a mechanism for conversion of malate to oxaloacetate.

Answer



9.4: Solutions for Selected Problems

Exercise 9.1.1:

Steps 3 and 4 (isocitrate to alpha-ketoglutarate and alpha-ketoglutarate to succinyl coenzyme A).

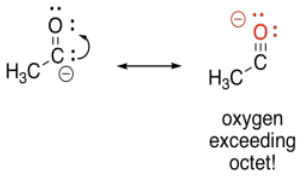
Exercise 9.1.2:

Step 5 (succinyl coenzyme A to succinate).

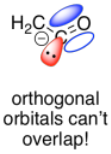
Exercise 9.1.3:

Steps 3 (isocitrate to alpha-ketoglutarate; NADH), 4 (alpha-ketoglutarate to succinyl coenzyme A; NADH), 6 (succinate to malate; $FADH_2$), and 8 (malate to oxaloacetate; NADH).

Exercise 9.2.1:

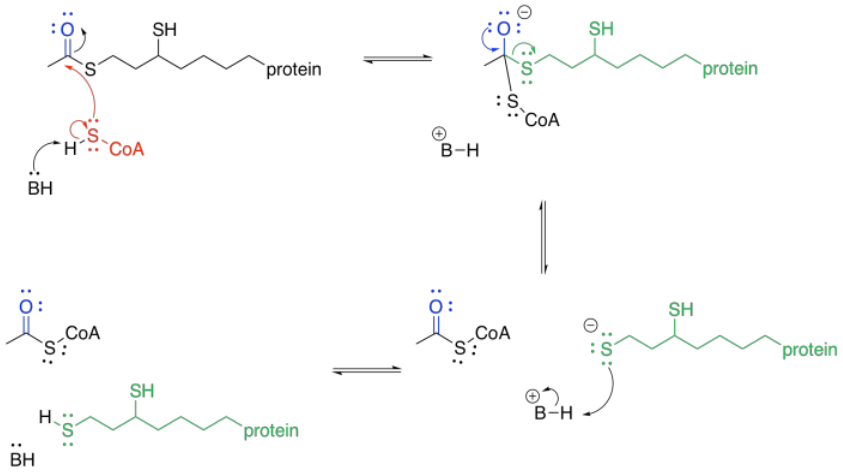


Exercise 9.2.2:

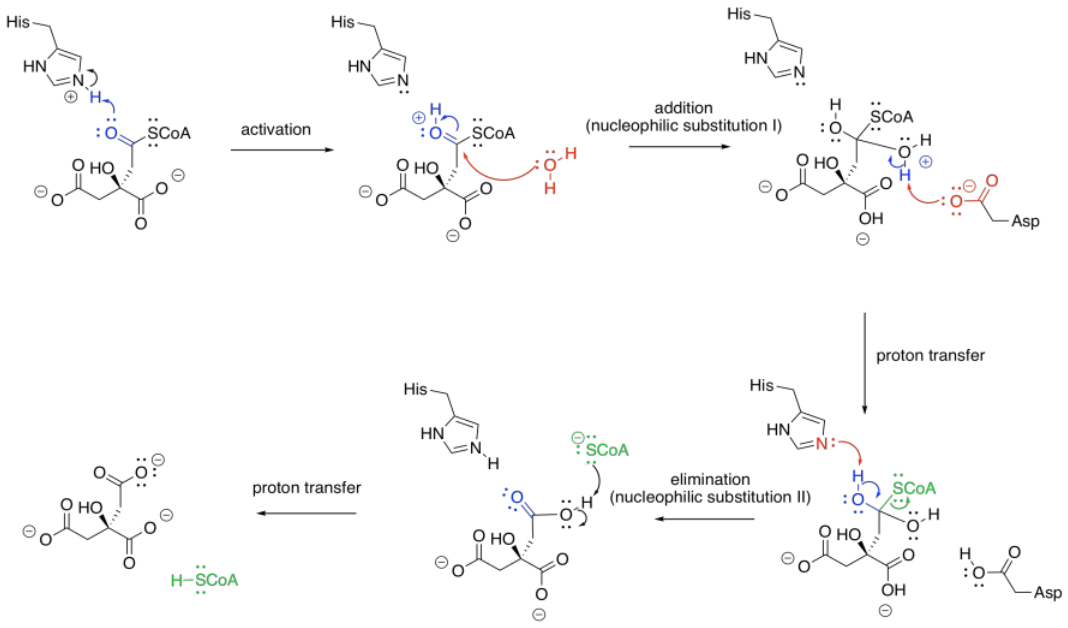


Exercise 9.2.3:

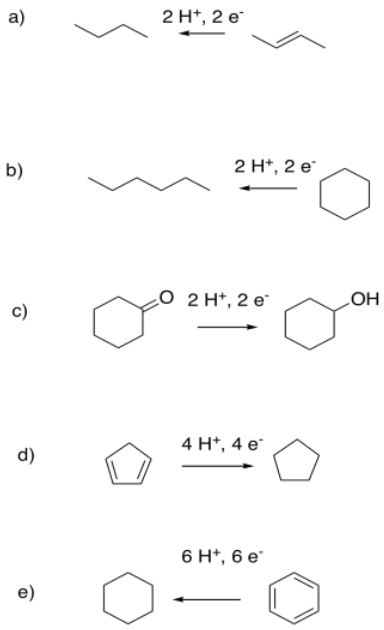
Exercise 9.3.1:



Exercise 9.3.2:

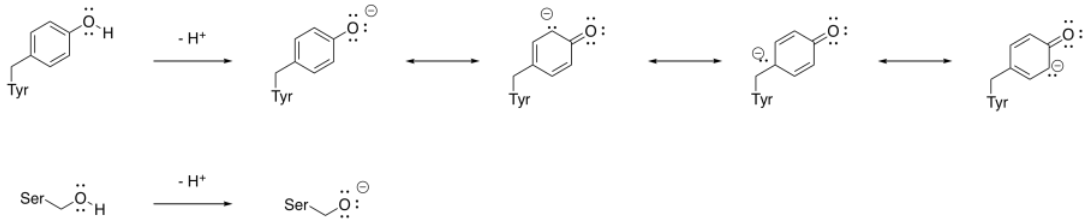


Exercise 9.3.3:

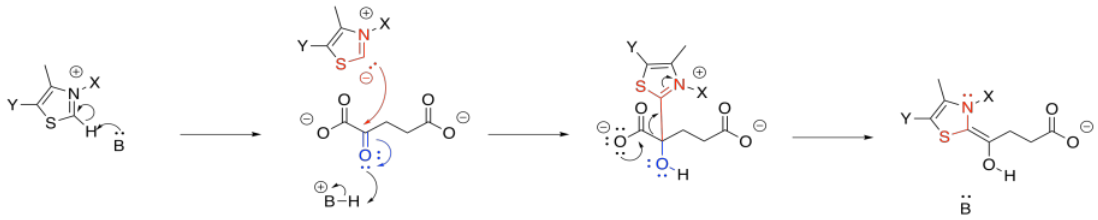


Exercise 9.3.4:

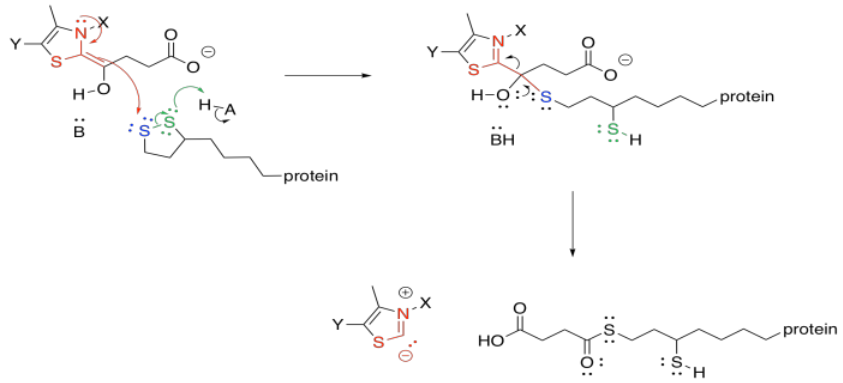
The anion that results from deprotonation of tyrosine is resonance-stabilised, but the anion that results from deprotonation of serine is not. The tyrosine anion is more stable compared to the serine anion and therefore the tyrosine anion forms more readily.



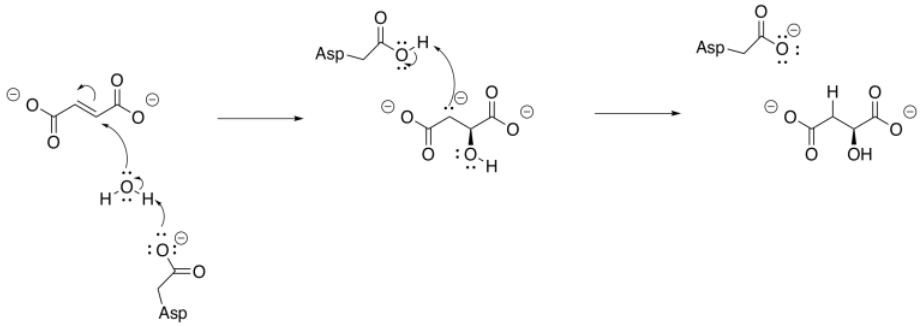
Exercise 9.3.5:



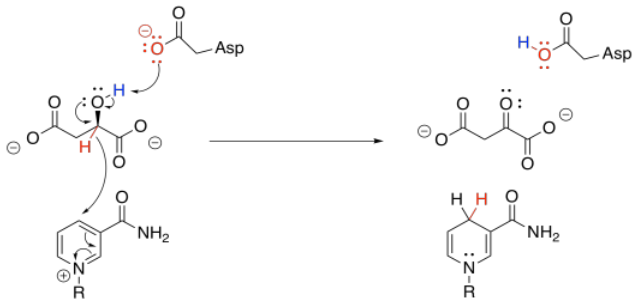
Exercise 9.3.6:



Exercise 9.3.7:



Exercise 9.3.8:

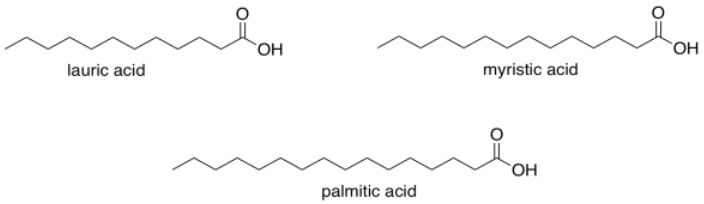


CHAPTER OVERVIEW

10: Fatty Acid Synthesis

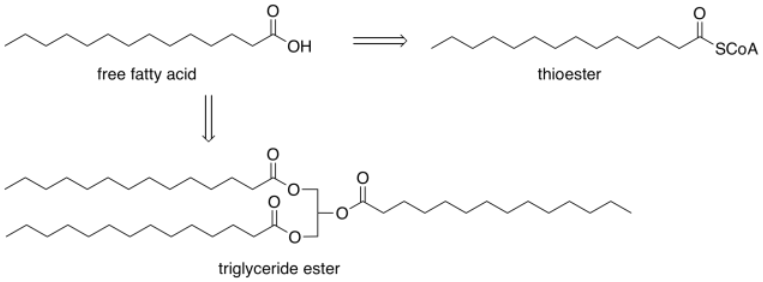
10.1: Overview of Fatty Acid Synthesis

Fatty acids are long-chain carboxylic acids. They are metabolically important because they can be used as high-energy fuel sources in the cell. Like gasoline, they contain long hydrocarbon chains, holding plenty of feedstocks for the formation of strong O-H and C=O bonds.



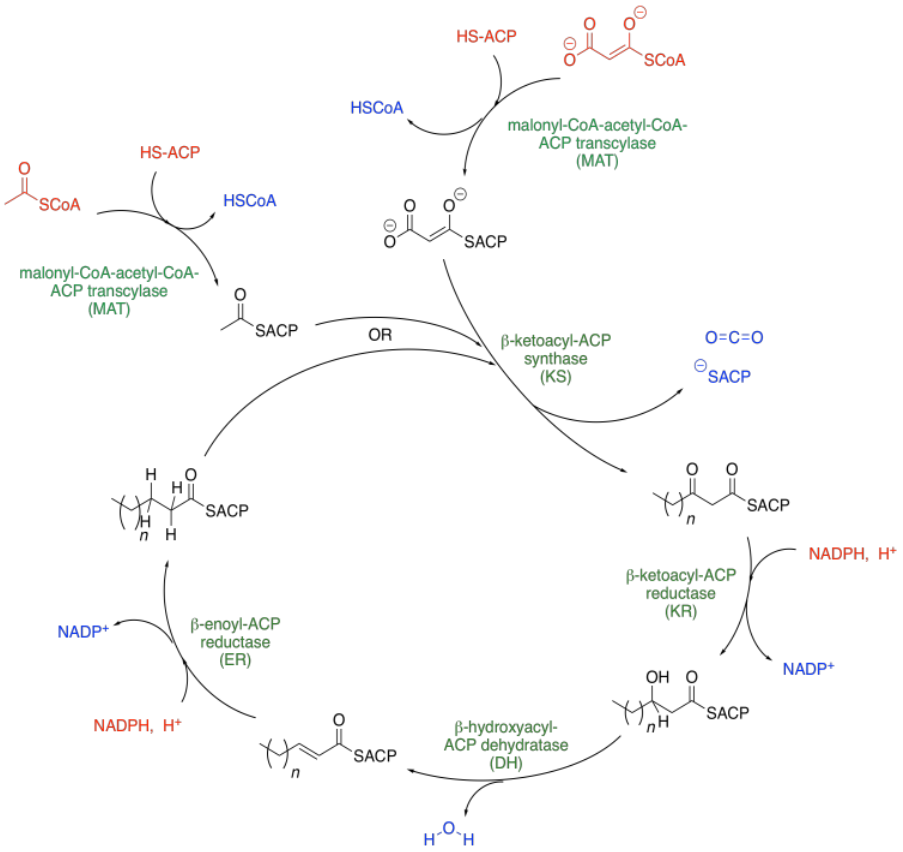
Here is a list of common fatty acids.

Fatty acids play a number of different roles, beyond serving as a fuel source. They can also be stored for the long term as triglycerides; we frequently see them modified in an ester form. These ester forms may be stored as fats, to be released when other energy stores are getting low, or they may be used to build cell membranes. For other purposes, they are modified into a thioester form. However, these modifications occur via carboxyloid substitutions that can be reversible. Hence, we can think of those other forms as pools of fatty acids because they can easily be converted into fatty acids if needed.



Where do fatty acids come from? Apart from a couple of them that we need to take in from certain foods, we can make them ourselves, if we have to, in our cells. So, we are going to take a look at the essential synthetic transformations that build up a fatty acid molecule from smaller molecules available in the cell.

The pathway for fatty acid biosynthesis is shown below. Inputs into the system are shown in red, outputs are shown in blue, and the enzymatic domains are shown in green. Interestingly, plants and bacteria use a separate enzyme for each of these steps, whereas fungi and animals employ a megasynthase, a giant enzyme that can perform all of the steps in sequence, like one big fatty acid factory.



The two units coming into the cycle are malonyl coenzyme A and acetyl coenzyme A. They join together to make a longer chain. The subscript *n* in the drawing is any even integer including zero. After the addition of the malonyl and acetyl thioesters at the top, we have a four carbon chain (n = 0). However, the product of the first cycle gets recycled and anothe rpair of carbons gets added, making a six-carbon chain, and so on.

In the following pages we'll develop some of the ideas about how all of this works from the molecular point of view.

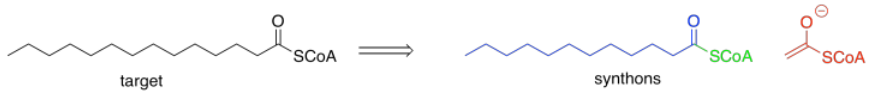
10.2: Transformations in Fatty Acid Synthesis

When we looked earlier at the citric acid cycle, we saw that acetyl coenzyme A, or AcCoA, was a key link between that process and glycolysis. This two-carbon remnant of glucose metabolism undergoes additional metabolic steps that harness energy in the form of ATP. But that's not the only purpose of AcCoA; it also serves as a building block for other compounds that are necessary for the survival of the cell or the organism.

Take myristic acid as an example, and think about how simple building blocks like AcCoA might be used to make it. AcCoA is a thioester, much like an ester but with a sulfur in place of one of the oxygen atoms. If we need to build myristic acid up from smaller pieces, we are going to need carbon-carbon bond-forming steps or *homologation* steps. You may not realise it, but there aren't an awful lot of those; their number just doesn't compare to the number of reactions that will simply switch out one heteroatom for another, such as an oxygen for a nitrogen. So, there may be a couple of choices, but not many.

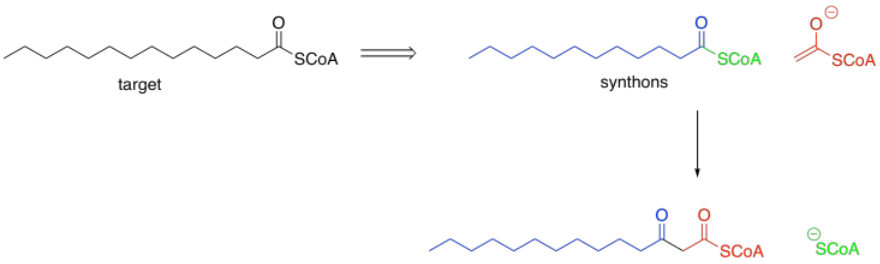
The obvious carbon-carbon bond-forming reaction to perform with an ester is a Claisen condensation. In a Claisen condensation, the leaving group attached to the carbonyl is replaced by an enolate nucleophile. If the enolate nucleophile comes from AcCoA, then two more carbons will be added to the structure of the electrophile. So, if we were going to add two carbons to something in order to get myristic acid, it should be something with twelve carbons, like lauric acid.

Remember, the open arrow (below) means "comes from", so this picture means the target compound, myristic acid thioester, could come from the two synthons on the right.



This isn't exactly how it happens in the cell, but there are a couple of complications in the actual biosynthesis and we will work our way up to them.

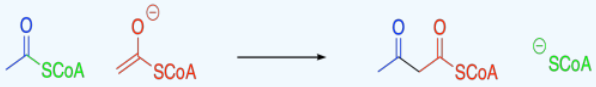
Retrosynthetically, we could think of myristic acid (or the corresponding thioester, easily hydrolysed to give the free fatty acid) as potentially being made from two simpler synthetic precursors: lauric acid (or its thioester) and the enolate ion of AcCoA. The AcCoA would add another two carbons to the chain of the lauric acid, making a fourteen-carbon chain.



? Exercise 10.2.1

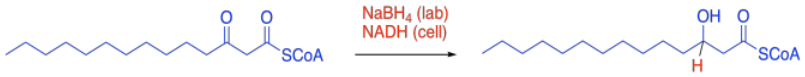
Show the product of a Claisen condensation between the enolate anion of acetyl CoA and another molecule of acetyl CoA.

Answer

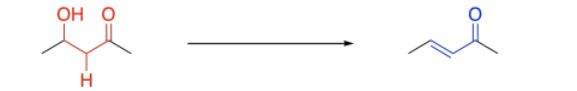


Where would the lauric acid come from? We will need to look further into that question, but you may already have thought of another problem that we need to solve, first: Although a Claisen condensation of lauric acid thioester and AcCoA enolate would result in a two-carbon chain extension, it would also bring an unwanted oxygen into the structure. There is a missing link between this structure and myristic acid. That oxygen needs to be replaced by a pair of hydrogens.

We can certainly get started by replacing one of the C=O bonds with a C-H bond. That should bring to mind a familiar carbonyl reaction. In the lab, we could use a hydride reagent, such as sodium borohydride (although we would have to worry about whether that thioester might react, too). In the cell, the equivalent reagent would be another hydride donor such as NADH.



That gets us part of the way there. How do we get rid of the other bond to oxygen? How do we add a second hydrogen? The first question might be answered by thinking about something else that might be familar: an aldol addition. The reason that might be relevant is that the compound now contains a beta-hydroxy carbonyl. We see something similar in an aldol addition. Aldol additions frequently result in beta-hydroxy carbonyl units. However, they sometimes proceed though a subsequent elimination reaction, the loss of water to give an enone ("een-own"). That variation is sometimes called an aldol condensation to distinguish the two outcomes, although the two terms are used loosely.



aldol addition pattern

aldol condensation pattern

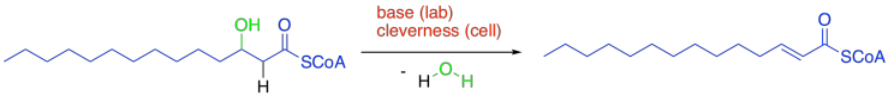
? Exercise 10.2.2

What is the driving force for the dehydration reaction (loss of water) after the initial aldol addition?

Answer

The product becomes conjugated. In general, the more conjugation there is in the product of an aldol addition, the more likely is a subsequent condensation (elimination or dehydration). However, other conditions can lead to the loss of water.

In laboratory chemistry, that condensation often results in the presence of strong base and high heat -- conditions that might be a little hard on a cell. We'll find that the reaction conditions are much milder in the cell.



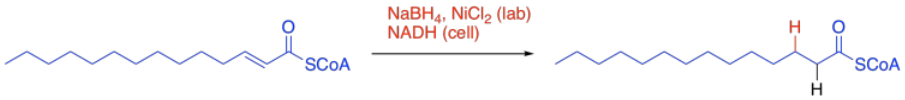
? Exercise 10.2.3

What thermodynamic factor leads increased heat to promote the dehydration reaction?

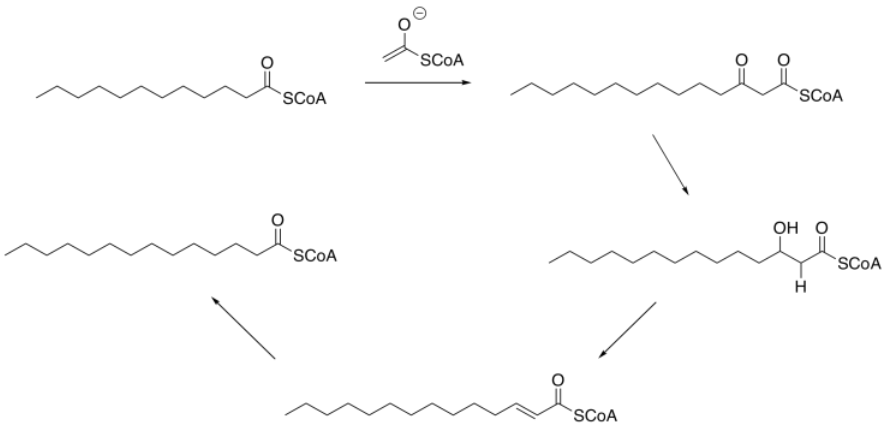
Answer

Entropy. The dehydration or elimination takes one molecule (the beta-hydroxy thioester) and converts it into two molecules (the water and the alpha,beta-unsaturated thioester. That change represents an increase in internal entropy. Because the entropy term in free energy is weighted by temperature ($\Delta G = \Delta H - T\Delta S$), it predominates as the temperature rises.

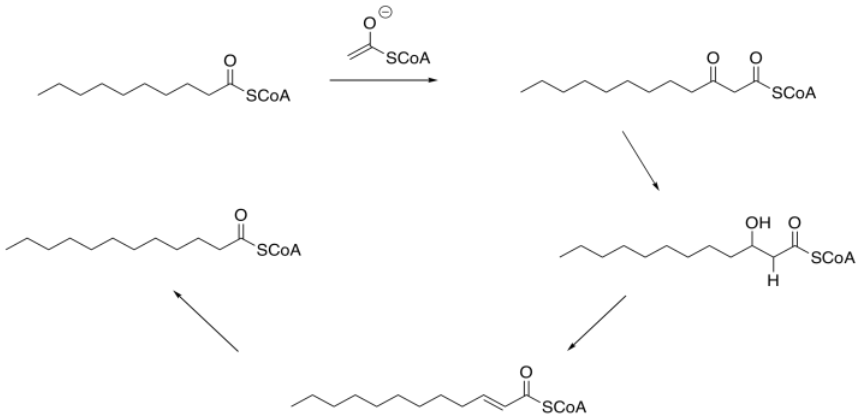
Now the problem of replacing that extra oxygen with two hydrogens is almost solved. The first hydrogen was added as a hydride, and that would work for the second one, too. This time, we need a 1,4-addition rather than a regular 1,2-addition. In the lab, that might be helped by adding a Lewis acid under the right conditions. In the cell, it might be aided by positioning of the hydride reducing agent in the right place in the enzyme, so that it delivers the hydride to the right place.



If we put all of those steps together, we can get from lauric acid thioester to myristic acid thioester in just a few steps.



Hold onto that thought, because we can use it again to make lauric acid from one that is two carbons shorter. In fact, we can keep repeating this cycle over and over until we work our way back to acetyl coenzyme A. Two molecules of AcCoA, one acting as the electrophile and the other as the enolate, could be used to make a four-carbon thioester. Adding another AcCoA would make a six-carbon thioester, and so on.



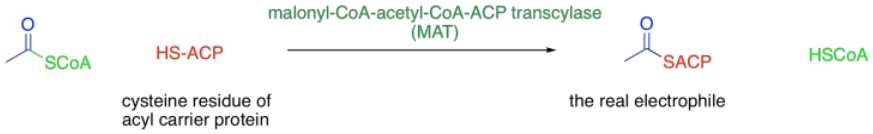
This dependence on a two-carbon building block is the reason for the vast preponderance of even-numbered carbon chains in natural fatty acids.

Next, we will take a look at how the cell actually shepherds these molecules through these kinds of reactions.

10.3: Catalysis in Fatty Acid Synthesis

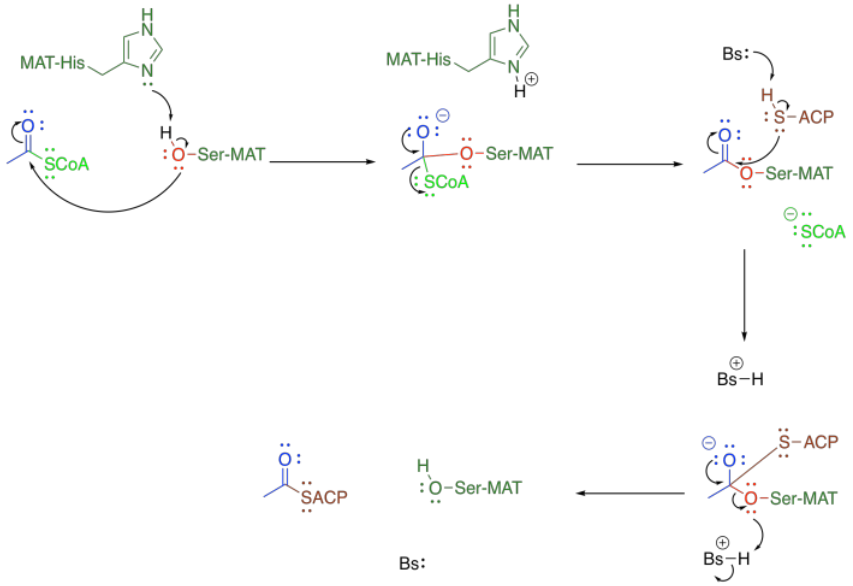
After the last page, we would have you believe that fatty acids are constructed from acetyl coenzyme A units, each acting as consecutive nucleophiles, building the structure two carbons at a time.

There are a number of aspects of the biosynthesis that we didn't consider in that synthetic overview, but we are going to add some extra levels of understanding now. The most obvious difference is that the biosynthesis does not even involve acetyl coenzyme A, although it does involve a related thioester. Prior to the reaction, the initial acetyl coenzyme A electrophile is attached to an acyl carrier protein (ACP) via a cysteine residue on the protein.



You can think of this as a regulatory step. The attachment of the acetyl group to the acyl carrier protein allows it to interact with the series of enzyme domains responsible for fatty acid biosynthesis.

This protein-attaching step is catalysed by malonyl-CoA-acetyl-CoA-ACP transcylase (everyone just calls it MAT). MAT uses a group transfer catalytic strategy, securing the acyl (or malonyl) group in place with a serine residue. The serine hydroxy group displaces the $CoAS^-$ thiolate from the acetyl, temporarily making it a regular ester. The serine is then displaced by a cysteine residue on the acyl carrier protein, or ACP. After that, the same sequence occurs with the malonyl group.



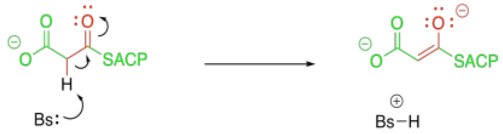
As in many such cases, the nucleophilicity of the key serine residue in MAT is enhanced through a hydrogen bond with a neighbouring histidine. This situation is pretty common in group transfer catalysis, especially in proteases. Frequently in these situations, a nearby aspartate or helps to in turn deprotonate the histidine (that's the so-called "catalytic triad" of ser-his-asp), but that part doesn't happen this time.

There is another big difference in the real biosynthetic route. In the Claisen condensation steps, the nucleophile does not really come from acetyl coenzyme A. Instead, it comes from malonyl coenzyme A. Acetyl coenzyme A and malonyl coenzyme A come together in a reaction catalysed by beta-ketoacyl-ACP synthase.

Notice that the malonyl group is also first attached to an acyl carrier protein, just like the acetyl group. That step is also carried out by MAT, and it happens in the same way.

What is the point of using malonate thioester instead of acetate thioester for one of the components? It doesn't look very efficient; a molecule of carbon dioxide is lost, rather than just the four-carbon product. There are a couple of possibilities to consider here.

First, the malonyl group is more acidic than the acetyl group, so it should be easier to convert into an enolate ion via removal of a proton.

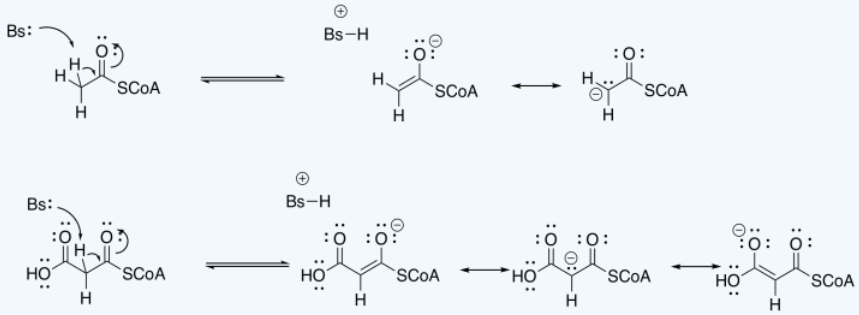


Exercise 10.3.1

Show why the malonyl ester would be deprotonated so much more easily than the acetyl ester.

Answer

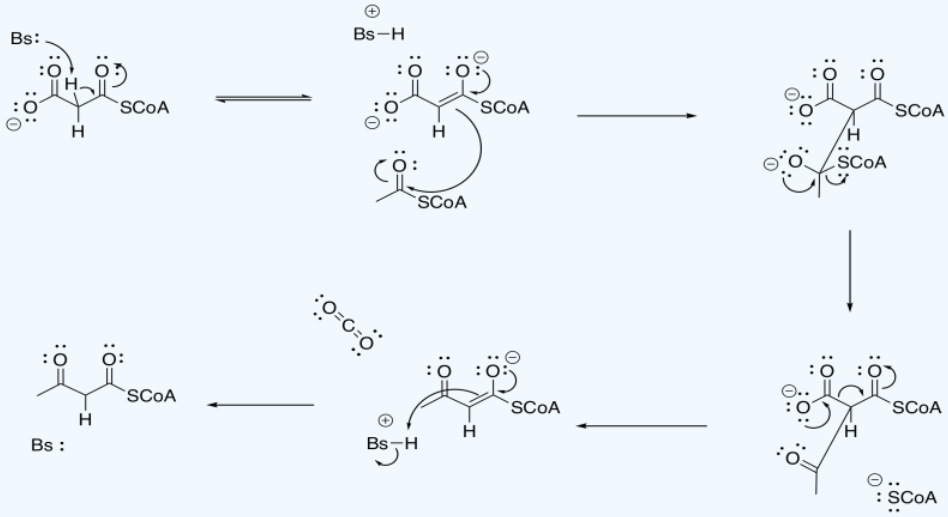
In the case of the malonyl enolate, there is additional delocalisation as demonstrated by resonance. This anion has extra stability.



Exercise 10.3.2

If the reaction did happen this way, there would still be an extra CO_2 in the structure after th Claisen reaction. Propose a mechanism for the Claisen reaction, and the loss of CO_2 from the product.

Answer

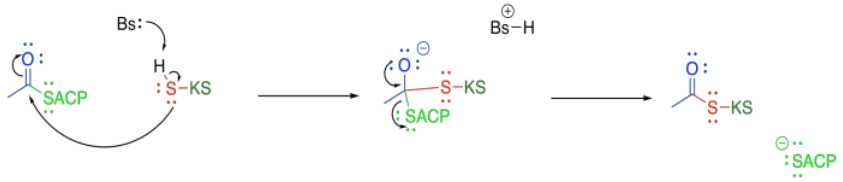


There are plenty of cases where this "malonate ester strategy" make reactions involving enolates much easier. Most biochemists think there is something different going on here, though. Rather than forming the enolate via proton removal, it is believed that the enolate forms via a decarboxylation reaction.

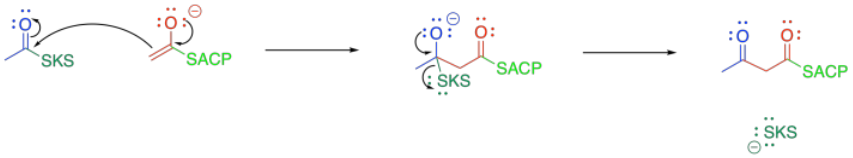
Decarboxylation reactions happen pretty easily if the CO_2 group is beta to another carbonyl. That's because of the relative stability of that enolate anion. This decarboxylation reaction, therefore, accomplishes two things at once: it gets rid of the extra carbon in the malonyl group, and it generates exactly the enolate needed for the Claisen condensation.

There is an additional reason why the pathway employs the malonyl group. The formation of carbon dioxide is exothermic because of the formation of a strong C=O bond, as well as being entropically favored. Those factors help make the decarboxylation a driving force for the reaction.

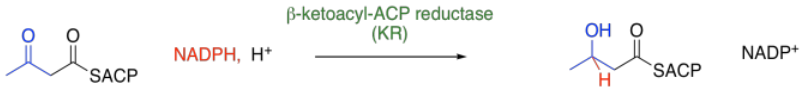
The beta-ketoacyl-ACP synthase (or KS) also uses a group transfer strategy to hold the acetyl group in place. This time, a cysteine residue on KS displaces the thiolate of the acyl carrier protein.



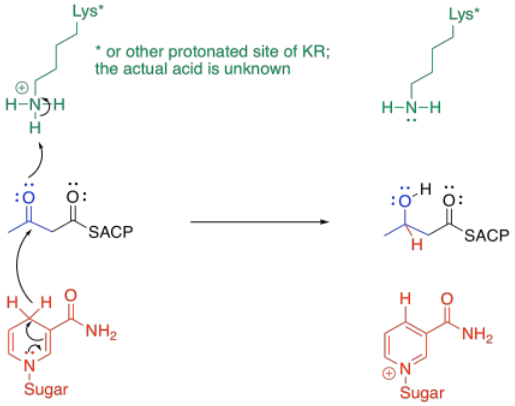
Once the acetyl group is tied down in the active site of KS, the malonyl-ACP enters the active site and undergoes decarboxylation, followed by Claisen condensation. The final part of the Claisen condensation releases the enzyme, completing the group transfer catalysis.



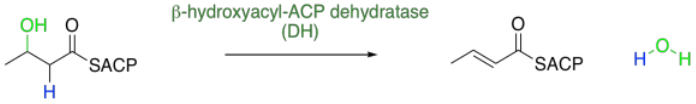
The subsequent steps aim to replace the beta-keto group with hydrogens. The first hydride is delivered with the help of beta-ketoacyl-ACP reductase, or KR.



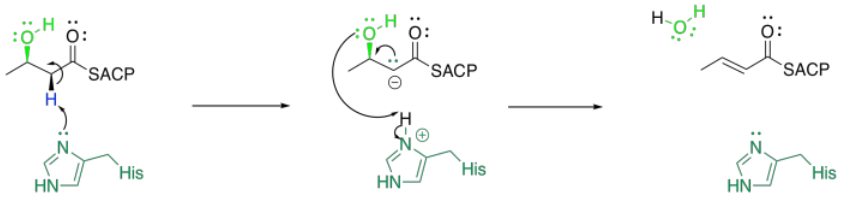
It's a pretty standard mechanism. Frequently in enzymatic reactions, the delivery of a proton happens almost at the same time as the delivery of a nucleophile to a carbonyl. In this case, the nucleophile is a hydride ion delivered by NADPH. The proton comes from some amino acid residue in a protonated state; lysine has been used in the illustration as an example.



Elimination of water is promoted by beta-hydroxyacyl-ACP dehydratase, or DH.

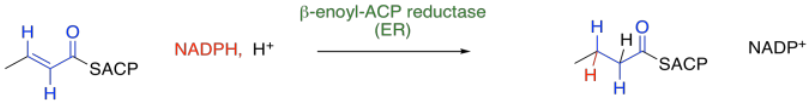


This looks like a tricky reaction. It depends once again on the ease of removing a proton from that alpha position. That's not terribly difficult, because a lone pair in the alpha position is stabilised by resonance. The other problem is pushing off the hydroxy group. That isn't a very good leaving group, so it poses some problem. However, it is thought that the histidine that deprotonates the alpha position then delivers the proton to the hydroxyl group. As a result, the hydroxyl group can leave as a water molecule.

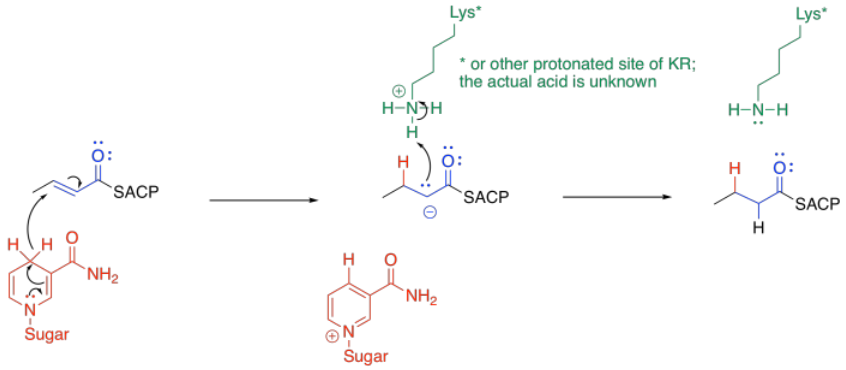


This pathway for an elimination reaction (the loss of a proton from one carbon and a leaving group from the next) is called an E1CB reaction. The CB in this acronym stands for the conjugate base that is formed after the deprotonation.

The final portion of the cycle is another hydride addition, this time carried out by beta-enoyl-ACP reductase (ER).



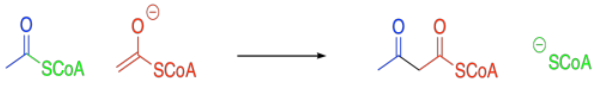
The mechanism is pretty similar to the first hydride addition. Once again, the exact nature of the proton donor is a little unclear, but the hydride donor is another NADPH molecule. This time, the NADPH must be positioned so that it delivers the hydride to the 1,4-position rather than to the carbonyl.



The final product of this cycle could be released or it could be sent back for another turn of the cycle, extending the fatty acid chain by two more carbons.

10.4: Solutions to Selected Problems

Exercise 10.2.1:



Exercise 10.2.2

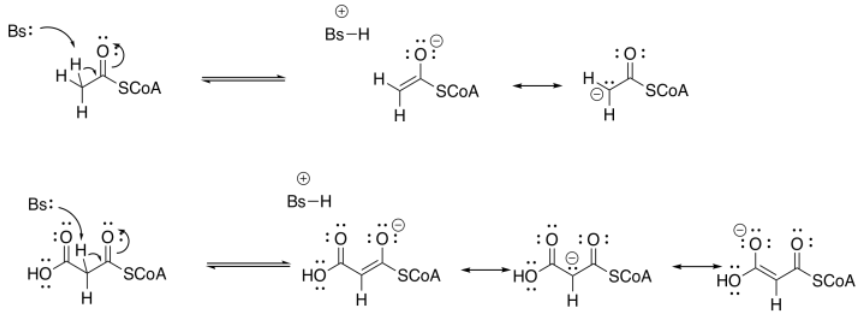
The product becomes conjugated. In general, the more conjugation there is in the product of an aldol addition, the more likely is a subsequent condensation (elimination or dehydration). However, other conditions can lead to the loss of water.

Exercise 10.2.3:

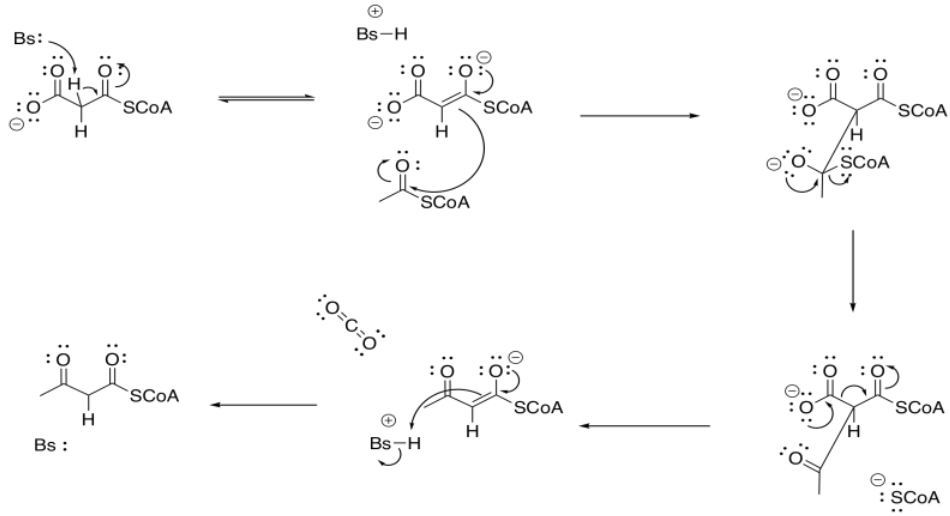
Entropy. The dehydration or elimination takes one molecule (the beta-hydroxy thioester) and converts it into two molecules (the water and the alpha,beta-unsaturated thioester. That change represents an increase in internal entropy. Because the entropy term in free energy is weighted by temperature ($\Delta G = \Delta H - T\Delta S$), it predominates as the temperature rises.

Exercise 10.3.1:

In the case of the malonyl enolate, there is additional delocalisation as demonstrated by resonance. This anion has extra stability.



Exercise 10.3.2:



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