ORGANIC CHEMISTRY II



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This text was compiled on 05/10/2026

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Licensing

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CHAPTER OVERVIEW

13: STRUCTURE AND SYNTHESIS OF ALCOHOLS

LEARNING OBJECTIVES

After reading this chapter and completing ALL the exercises, a student can be able to

- distinguish between alcohols, phenols, enols, and carboxylic acids - refer to section 13.1
- classify alcohols as primary, secondary, or tertiary - refer to section 13.2
- predict relative physical properties of alcohols, such as relative boiling points and solubility in a specified solvent - refer to section 13.3
- determine the structure of alcohols and phenols from spectroscopic data - refer to section 13.4
- predict the relative acidity of alcohols - refer to section 13.5
- use resonance to explain why phenols are more acidic than alcohols - refer to section 13.5
- specify the base needed to ionize an alcohol or phenol - refer to section 13.5
- predict the products and specify the reagents for alcohol and diol synthesis from alkyl halides, alkenes, and alkynes from the previous chapters - refer to section 13.6
- predict the products and specify the reagents to synthesize alcohols from the reduction of carbonyls - refer to section 13.7
- predict the products and specify the reagents to prepare Grignard and organolithium reagents - refer to section 13.8
- predict the products and specify the reagents for alcohol synthesis from organometallic reagents with aldehydes, ketones, esters, acyl halides, & epoxides - section 13.9
- distinguish between the structure and reactivity of thiols and sulfides - refer to section 13.10
- explain the commercial synthesis of alcohols - refer to section 13.11

Please note: IUPAC nomenclature and important common names of alcohols were explained in Chapter 3.

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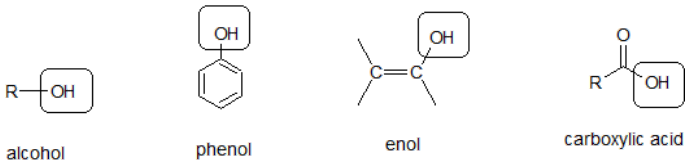
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13.1: INTRODUCTION TO STRUCTURE AND SYNTHESIS OF ALCOHOLS

INTRODUCTION

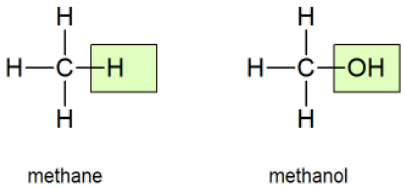
Alcohols, phenols, enols, and carboxylic acids all contain a hydroxyl group. However, the chemistry of these four different functional groups are different.



ALCOHOLS

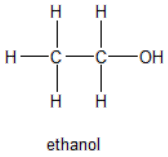
Molecules of alcohols contain one or more hydroxyl groups (OH groups) substituted for hydrogen atoms along the carbon chain.

The structure of the simplest alcohol, methanol (methyl alcohol), can be derived from that of methane by putting an OH in place of one of the H's:



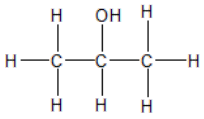
Methanol is also called wood alcohol because it can be obtained by heating wood in the absence of air, a process called **destructive distillation**. Methanol vapor given off when the wood is heated can be condensed to a liquid by cooling below its boiling point of 65°C. Methanol is highly toxic. In 1986, there were six deaths of residents of Peerless Lake, Alberta, brought about by drinking photocopier fluid which contained methanol (or methyl hydrate as it is often called in press reports). In 2000, more than 100 people died in El Salvador after black marketeers sold discarded liquor bottles that had been refilled with a methanol mixture. Indeed the problem has repeated itself globally and so often that in 2014 the World Health Organization released an information note warning of methanol poisoning outbreaks which "occur when methanol is added to illicitly- or informally-produced alcoholic drinks."

The second member of the alcohol family is ethanol (ethyl alcohol)— the substance we commonly call *alcohol*. Ethanol is also known as grain alcohol because it is obtained when grain or sugar ferments.



Fermentation refers to a chemical reaction which is speeded up by enzymes and occurs in the absence of air. (Enzymes, catalysts which occur naturally in yeasts and other living organisms, are discussed in more detail elsewhere.) Almost everyone is aware that the alcohol present in alcoholic beverages is ethanol (also called ethyl alcohol or grain alcohol). However, many people do not realize that in its pure state, or in solutions of high concentration, this substance is poisonous. In the laboratory one may find containers labeled "absolute ethanol," "95% ethanol" and "denatured ethanol." The acquisition of ethanol by laboratories, and its subsequent disposal, is carefully monitored by provincial authorities. On no account should one consider drinking laboratory ethanol, even after it has been diluted to a concentration equivalent to that found in beer. Denatured alcohol is ethanol to which appropriate quantities of poisonous or nauseating substances (such as methanol) have been added. Ethanol is used as a solvent, in some special fuels, in antifreeze, and to manufacture a number of other chemicals. You are probably most familiar with it as a component of alcoholic beverages. Ethanol makes up 3 to 6 percent of beer, 12 to 15 percent of most wines, and 49 to 59 percent of distilled liquor. (The "proof" of an alcoholic beverage is just twice the percentage of ethanol.) Alcohol's intoxicating effects are well known, and it is a mild depressant. Prolonged overuse can lead to liver damage.

A third commonly encountered alcohol, isopropyl alcohol ("rubbing alcohol" or 2-propanol), is also toxic. It has the ability to kill germs and has a temporary lubricating effect during the rubbing process. Unlike methanol, 2-propanol is not absorbed through the skin; therefore it poses less of a health hazard.

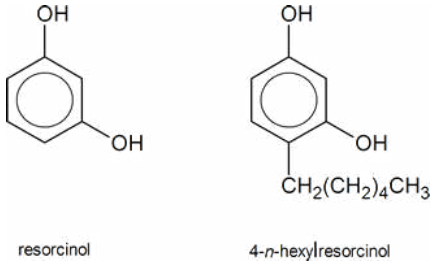


isopropanol

PHENOLS

A phenol is an organic compound in which a hydroxyl group is directly bonded to one of the carbon atoms of an aromatic ring. The chemical behavior of phenols is different in some respects from that of the alcohols, so it is sensible to treat them as a similar but characteristically distinct group.

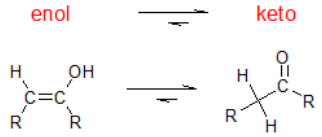
Until the late nineteenth century, a person undergoing surgery had to face the fact that he or she might suffer the consequences of what we now know to be bacterial infection, contracted during the course of the operation. The physicians of the time did not know that bacteria existed, and had no way to counter the problems that bacteria caused. In 1867, Joseph Lister, who had learned of the existence of bacteria as a result of research done by Louis Pasteur, began using solutions of phenol to clean wounds and surgical instruments. The phenol solution was an effective antiseptic, killing bacteria, and as a result, a patient's chances of surviving surgery improved greatly. Phenol itself was rather strong for these purposes—it burns healthy tissue—and substitutes were eventually found. One such substitute, used today in throat lozenges and mouthwashes, is 4-*n*-hexylresorcinol.



resorcinol 4-*n*-hexylresorcinol

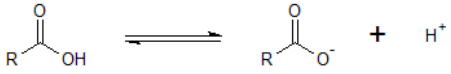
ENOLS

When a hydroxyl group is bonded to a vinyl carbon, the functional group is called an enol. As discussed in Chapter 10, alkyne hydration can result in enol formation. Enols undergo tautomerization to form ketones, In most cases, the keto-form is more stable and predominates the equilibrium. Phenol is an important exception to this trend.



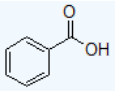
CARBOXYLIC ACIDS

In carboxylic acids, the hydroxyl group is bonded to a carbonyl carbon. As the name implies, this functional group is acidic and can readily donate the proton on the hydroxyl group.



Exercise

1. Classify the following compounds as alcohols, phenols, enols, or carboxylic acids. One compound can be classified by two of the options.

a) 

b) 

c) 

Answer

1.

a) carboxylic acid

b) phenol and enol

c) alcohol

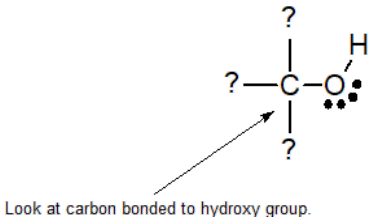
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13.2: CLASSIFICATION OF ALCOHOLS

Alcohol classification is an application of the neutral bonding patterns for organic compounds. Oxygen can only form two bonds. The alcohol functional group requires that one of these bonds form with hydrogen to create the hydroxyl group and the other bond needs to be with carbon to create an alcohol. All of the oxygen atoms of all the alcohols look the same, so a different distinction is needed. To classify alcohols, we look at the carbon atom bonded to the hydroxyl group.



methyl alcohol = no (0) other carbon atoms (CH_3OH)

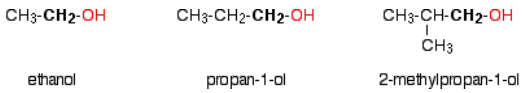
primary alcohols (1°) = 1 other carbon atoms

secondary alcohols (2°) = 2 other carbon atom

tertiary alcohols (3°) = 3 other carbon atoms

PRIMARY ALCOHOLS

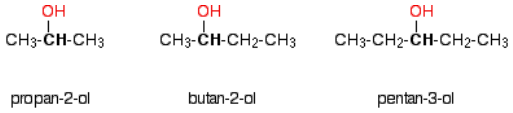
In a primary (1°) alcohol, the carbon which carries the -OH group is only attached to one alkyl group. Some examples of primary alcohols include:



Notice that it doesn't matter how complicated the attached alkyl group is. In each case there is only one linkage to an alkyl group from the CH_2 group holding the -OH group. There is an exception to this. Methanol, CH_3OH, is counted as a primary alcohol even though there are no alkyl groups attached to the carbon with the -OH group on it.

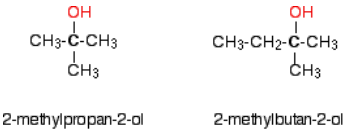
SECONDARY ALCOHOLS

In a secondary (2°) alcohol, the carbon with the -OH group attached is joined directly to two alkyl groups, which may be the same or different. Examples:



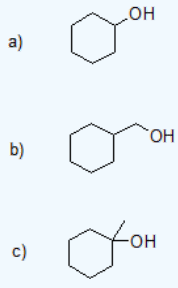
TERTIARY ALCOHOLS

In a tertiary (3°) alcohol, the carbon atom holding the -OH group is attached directly to three alkyl groups, which may be any combination of same or different. Examples:



Exercise

2. Classify the following alcohols as primary, secondary, or tertiary.



Answer

2.

a) secondary

b) primary

c) tertiary

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
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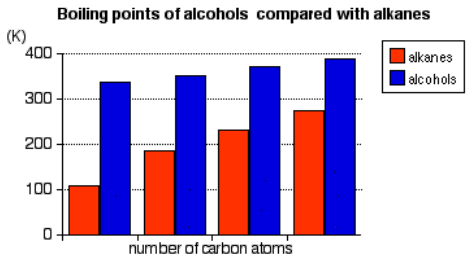
13.3: PHYSICAL PROPERTIES OF ALCOHOLS

BOILING POINTS

The chart below shows the boiling points of the following simple primary alcohols with up to 4 carbon atoms:

CH_3OH	CH_3CH_2OH	$CH_3CH_2CH_2OH$	$CH_3CH_2CH_2CH_2OH$
methanol	ethanol	propan-1-ol	butan-1-ol

These boiling points are compared with those of the equivalent alkanes (methane to butane) with the same number of carbon atoms.



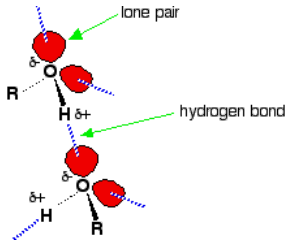
Notice that:

- The boiling points of the alcohols increase as the number of carbon atoms increases.

The patterns in boiling point reflect the patterns in intermolecular attractions.

HYDROGEN BONDING

Hydrogen bonding occurs between molecules in which a hydrogen atom is attached to a strongly electronegative element: fluorine, oxygen or nitrogen. In the case of alcohols, hydrogen bonds occur between the partially-positive hydrogen atoms and lone pairs on oxygen atoms of other molecules.



The hydrogen atoms are slightly positive because the bonding electrons are pulled toward the very electronegative oxygen atoms. In alkanes, the only intermolecular forces are van der Waals dispersion forces. Hydrogen bonds are much stronger than these, and therefore it takes more energy to separate alcohol molecules than it does to separate alkane molecules. This the main reason for higher boiling points in alcohols.

THE EFFECT OF VAN DER WAALS FORCES

- **Comparison between alkanes and alcohols**: Even without any hydrogen bonding or dipole-dipole interactions, the boiling point of the alcohol would be higher than the corresponding alkane with the same number of carbon atoms.

Compare ethane and ethanol:

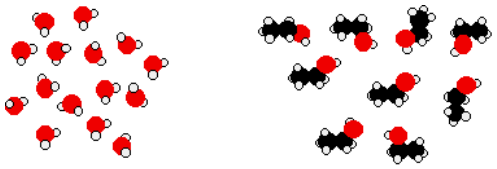


Ethanol is a longer molecule, and the oxygen atom brings with it an extra 8 electrons. Both of these increase the size of the van der Waals dispersion forces, and subsequently the boiling point. A more accurate measurement of the effect of the hydrogen bonding on boiling point would be a comparison of ethanol with propane rather than ethane. The lengths of the two molecules are more similar, and the number of electrons is exactly the same.

SOLUBILITY OF ALCOHOLS IN WATER

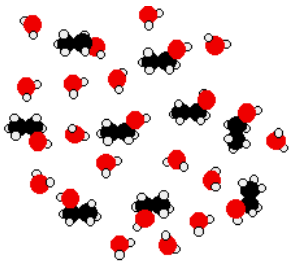
Small alcohols are completely soluble in water; mixing the two in any proportion generates a single solution. However, solubility decreases as the length of the hydrocarbon chain in the alcohol increases. At four carbon atoms and beyond, the decrease in solubility is noticeable; a two-layered substance may appear in a test tube when the two are mixed.

Consider ethanol as a typical small alcohol. In both pure water and pure ethanol the main intermolecular attractions are hydrogen bonds.



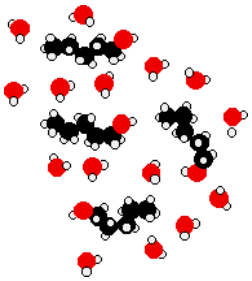
Both of these are held together mainly by hydrogen bonding.

In order to mix the two, the hydrogen bonds between water molecules and the hydrogen bonds between ethanol molecules must be broken. Energy is required for both of these processes. However, when the molecules are mixed, new hydrogen bonds are formed between water molecules and ethanol molecules.



New hydrogen bonds are set up between ethanol and water molecules.

The energy released when these new hydrogen bonds form approximately compensates for the energy needed to break the original interactions. In addition, there is an increase in the disorder of the system, an increase in entropy. This is another factor in deciding whether chemical processes occur. Consider a hypothetical situation involving 5-carbon alcohol molecules.

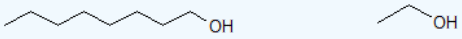


The hydrocarbon chains are forced between water molecules, breaking hydrogen bonds between those water molecules. The -OH ends of the alcohol molecules can form new hydrogen bonds with water molecules, but the hydrocarbon "tail" does not form hydrogen bonds. This means that many of the original hydrogen bonds being broken are never replaced by new ones.

In place of those original hydrogen bonds are merely van der Waals dispersion forces between the water and the hydrocarbon "tails." These attractions are much weaker, and unable to furnish enough energy to compensate for the broken hydrogen bonds. Even allowing for the increase in disorder, the process becomes less feasible. As the length of the alcohol increases, this situation becomes more pronounced, and thus the solubility decreases.

Exercise

Use 1-octanol and ethanol, shown below, to answer the following questions.



3. Which compound is more water soluble?
4. Which compound has the highest boiling point?

5. Explain why the answers above are not in conflict using your understanding of intermolecular forces, relative boiling points, and solubility.

Answer

3. ethanol

4. octanol

5. While both compounds exhibit H-bonding, the smaller, hydrophobic carbon chain of ethanol results in higher water solubility of ethanol while the longer carbon chain of octanol increases the surface area resulting in a higher boiling point.

CONTRIBUTORS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)
- John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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13.4: SPECTROSCOPY OF ALCOHOLS

INFRARED SPECTROSCOPY

If you look at an IR spectrum of 1-butanol, you will see:

- there are sp^3 C-H stretching and CH_2 bending modes at 2900 and 1500 cm^{-1}.
- there is a strong C-O stretching mode near 1000 cm^{-1}.
- there is a very large peak around 3400 cm^{-1}. O-H peaks are usually very broad like this one.

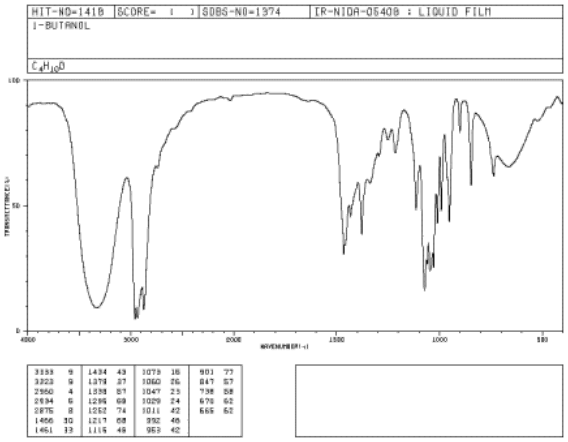


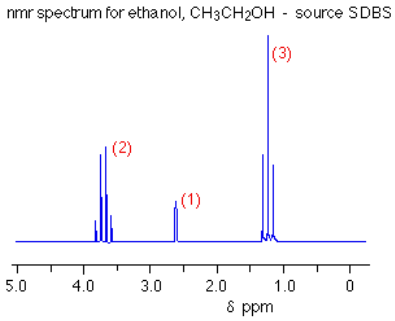
Figure IR8. IR spectrum of 1-butanol. Source: SDBSWeb : http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 14 July 2008)

Peak shapes are sometimes very useful in recognizing what kind of bond is present. The rounded shape of most O-H stretching modes occurs because of hydrogen bonding between different hydroxy groups. Because protons are shared to varying extent with neighboring oxygens, the covalent O-H bonds in a sample of alcohol all vibrate at slightly different frequencies and show up at slightly different positions in the IR spectrum. Instead of seeing one sharp peak, you see a whole lot of them all smeared out into one broad blob. Since C-H bonds don't hydrogen bond very well, you don't see that phenomenon in an ether, and an O-H peak is very easy to distinguish in the IR spectrum.

NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

ALCOHOLS

Where is the -O-H peak? This is very confusing! Different sources quote totally different chemical shifts for the hydrogen atom in the -OH group in alcohols - often inconsistently. For example:



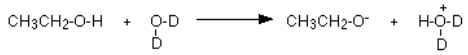
- The Nuffield Data Book quotes 2.0 - 4.0, but the Nuffield text book shows a peak at about 5.4.
- The OCR Data Sheet for use in their exams quotes 3.5 - 5.5.
- A reliable degree level organic chemistry text book quotes1.0 - 5.0, but then shows an NMR spectrum for ethanol with a peak at about 6.1.
- The SDBS database (used throughout this site) gives the -OH peak in ethanol at about 2.6.

The problem seems to be that the position of the -OH peak varies dramatically depending on the conditions - for example, what solvent is used, the concentration, and the purity of the alcohol - especially on whether or not it is totally dry.

A CLEVER WAY OF PICKING OUT THE -OH PEAK

If you measure an NMR spectrum for an alcohol like ethanol, and then add a few drops of deuterium oxide, D_2O, to the solution, allow it to settle and then re-measure the spectrum, the -OH peak disappears! By comparing the two spectra, you can tell immediately which peak was due to the -OH group.

The reason for the loss of the peak lies in the interaction between the deuterium oxide and the alcohol. All alcohols, such as ethanol, are very, very slightly acidic. The hydrogen on the -OH group transfers to one of the lone pairs on the oxygen of the water molecule. The fact that here we've got "heavy water" makes no difference to that.



The negative ion formed is most likely to bump into a simple deuterium oxide molecule to regenerate the alcohol - except that now the -OH group has turned into an -OD group.

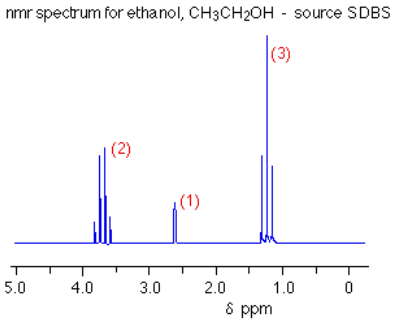


Deuterium atoms don't produce peaks in the same region of an NMR spectrum as ordinary hydrogen atoms, and so the peak disappears. You might wonder what happens to the positive ion in the first equation and the OD^- in the second one. These get lost into the normal equilibrium which exists wherever you have water molecules - heavy or otherwise.

$$2D_2O \rightleftharpoons D_3O^+ + OH^- \tag{13.4.1}$$

THE LACK OF SPLITTING WITH -OH GROUPS

Unless the alcohol is absolutely free of any water, the hydrogen on the -OH group and any hydrogens on the next door carbon don't interact to produce any splitting. The -OH peak is a singlet and you don't have to worry about its effect on the next door hydrogens.

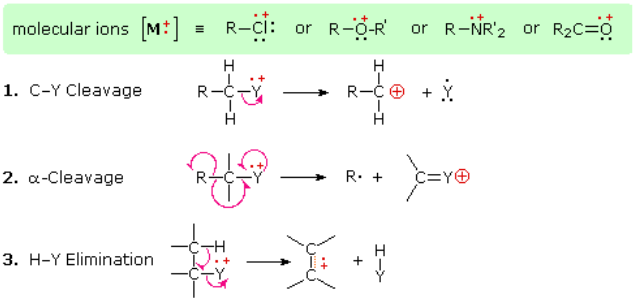


The left-hand cluster of peaks is due to the CH_2 group. It is a quartet because of the 3 hydrogens on the next door CH_3 group. You can ignore the effect of the -OH hydrogen. Similarly, the -OH peak in the middle of the spectrum is a singlet. It hasn't turned into a triplet because of the influence of the CH_2 group.

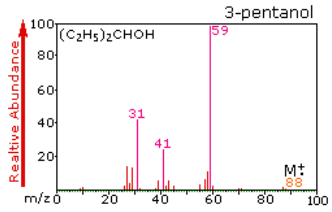
MASS SPECTRA FRAGMENTATION PATTERNS

The fragmentation of molecular ions into an assortment of fragment ions is a mixed blessing. The nature of the fragments often provides a clue to the molecular structure, but if the molecular ion has a lifetime of less than a few microseconds it will not survive long enough to be observed. Without a molecular ion peak as a reference, the difficulty of interpreting a mass spectrum increases markedly. Fortunately, most organic compounds give mass spectra that include a molecular ion, and those that do not often respond successfully to the use of milder ionization conditions. Among simple organic compounds, the most stable molecular ions are those from aromatic rings, other conjugated pi-electron systems and cycloalkanes. Alcohols, ethers and highly branched alkanes generally show the greatest tendency toward fragmentation.

The presence of a functional group, particularly one having a heteroatom Y with non-bonding valence electrons (Y = N, O, S, X etc.), can dramatically alter the fragmentation pattern of a compound. This influence is thought to occur because of a "localization" of the radical cation component of the molecular ion on the heteroatom. After all, it is easier to remove (ionize) a non-bonding electron than one that is part of a covalent bond. By localizing the reactive moiety, certain fragmentation processes will be favored. These are summarized in the following diagram, where the green shaded box at the top displays examples of such "localized" molecular ions. The first two fragmentation paths lead to even-electron ions, and the elimination (path #3) gives an odd-electron ion. Note the use of different curved arrows to show single electron shifts compared with electron pair shifts.

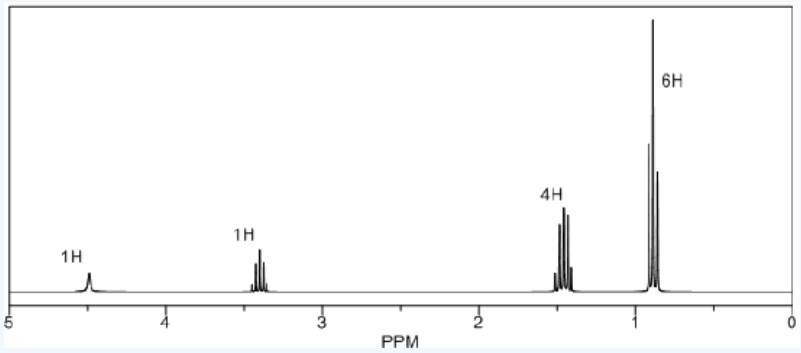


3-Pentanol shows three significant fragment ions. Alpha-fragmentation (loss of an ethyl radical) forms the m/z=59 base peak. Loss of water from this gives a m/z=41 fragment, and loss of ethene from m/z=59 gives a m/z=31 fragment.



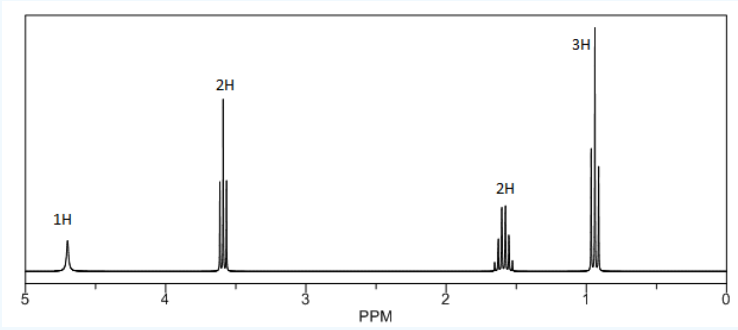
Exercise

6. From mass spectroscopy analysis it was determined that a compound has the general formula $C_5H_{12}O$. Given the following ^1H NMR spectrum, draw the structure. The integration values of each group of signals is given on the spectrum.



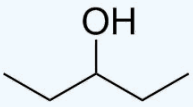
7. Given that alcohols are relatively acidic and the protons transfer in solution, what would you expect to happen to the NMR spectrum if D_2O was used as a solvent.

8. From mass spectroscopy analysis it was determined that a compound has the general formula $C3H_8O$. Given the following ^1H NMR spectrum, draw the structure. The integration values of each group of signals is given on the spectrum.



Answer

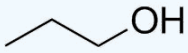
6.



7.

The alcohol proton signal's intensity in the ^{1}H NMR would be expected to diminish and likely disappear. This is due to the fact that NMR can only probe the spin changes of nuclei with an odd number of protons.

8.

1-propanol 

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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13.5: ACIDITY OF ALCOHOLS AND PHENOLS

OVERVIEW - AQUEOUS VS ORGANIC SOLVENTS

In aqueous solutions, phenols are weakly acidic and lower the pH of a solution. Sodium hydroxide can be used to fully deprotonate a phenol. Water soluble alcohols do not change the pH of the solution and are considered neutral. Aqueous solutions of sodium hydroxide can NOT deprotonate alcohols to a high enough concentration to be synthetically useful.

In solutions of organic solvents, more extreme reaction conditions can be created. Sodium metal can be added to an alcohol in an organic solvent system to fully deprotonate the alcohol to form alkoxide ions.

ACIDITY OF ALCOHOLS

Several important chemical reactions of alcohols involving the O-H bond or oxygen-hydrogen bond only and leave the carbon-oxygen bond intact. An important example is salt formation with acids and bases. Alcohols, like water, are both weak bases and weak acids. The acid ionization constant (Ka) of ethanol is about 10~18, slightly less than that of water. Ethanol can be converted to its conjugate base by the conjugate base of a weaker acid such as ammonia {Ka — 10~35), or hydrogen (Ka ~ 10-38). It is convenient to employ sodium metal or sodium hydride, which react vigorously but controllably with alcohols:

$$C_2H_5OH + Na^{\oplus}NH_2^{\ominus} \rightleftharpoons \underset{\text{sodium ethoxide}}{C_2H_5O^{\ominus}Na^{\oplus}} + NH_3$$
(sodium amide (sodamide))

$$2C_2H_5OH + 2Na \longrightarrow 2C_2H_5O^{\ominus}Na^{\oplus} + H_2$$

$$C_2H_5OH + Na^{\oplus}H^{\ominus} \longrightarrow C_2H_5O^{\ominus}Na^{\oplus} + H_2$$

The order of acidity of various liquid alcohols generally is water > primary > secondary > tertiary ROH. By this we mean that the equilibrium position for the proton-transfer reaction lies more on the side of ROH as R is changed from primary to secondary to tertiary; therefore, tert-butyl alcohol is considered less acidic than ethanol:

$$ROH + OH^- \rightleftharpoons RO^- + HOH \tag{13.5.1}$$

However, in the gas phase the order of acidity is reversed, and the equilibrium position for lies increasingly on the side of the alkoxide as R is changed from primary to secondary to tertiary, tert-butyl alcohol is therefore more acidic than ethanol in the gas phase. This seeming contradiction appears more reasonable when one considers what effect solvation (or the lack of it) has on equilibria. In solution, the larger alkoxide ions, probably are less well solvated than the smaller ions, because fewer solvent molecules can be accommodated around the negatively charged oxygen in the larger ions:

$CH_3O^{\ominus}$	$C_2H_5O^{\ominus}$	$(CH_3)_2CHO^{\ominus}$	$(CH_3)_3CO^{\ominus}$
methoxide	ethoxide	isopropoxide	*tert*-butoxide

Acidity of alcohols therefore decreases as the size of the conjugate base increases. However, “naked” gaseous ions are more stable the larger the associated R groups, probably because the larger R groups can stabilize the charge on the oxygen atom better than the smaller R groups. They do this by polarization of their bonding electrons, and the bigger the group, the more polarizable it is.

BASICITY OF ALCOHOLS

Alcohols are bases similar in strength to water and accept protons from strong acids. An example is the reaction of methanol with hydrogen bromide to give methyloxonium bromide, which is analogous to the formation of hydroxonium bromide with hydrogen bromide and water:

$$CH_3\ddot{O}H + HBr \rightleftharpoons \underset{\text{methyloxonium bromide}}{CH_3\overset{H}{\overset{|}{\ddot{O}}}H^{\oplus}} + Br^{\ominus}$$

$$H\ddot{O}H + HBr \rightleftharpoons \underset{\text{hydroxonium bromide}}{H\overset{H}{\overset{|}{\ddot{O}}}H^{\oplus}} + Br^{\ominus}$$

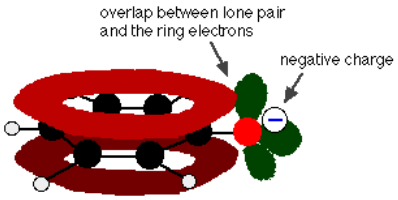
ACIDITY OF PHENOL

Compounds like alcohols and phenol which contain an -OH group attached to a hydrocarbon are very weak acids. Alcohols are so weakly acidic that, for normal lab purposes, their acidity can be virtually ignored. However, phenol is sufficiently acidic for it to have recognizably acidic properties - even if it is still a very weak acid. A hydrogen ion can break away from the -OH group and transfer to a base. For example, in solution in water:

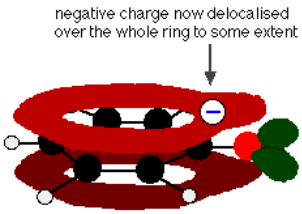


a **phenoxide** ion

Phenol is a very weak acid and the position of equilibrium lies well to the left. Phenol can lose a hydrogen ion because the phenoxide ion formed is stabilised to some extent. The negative charge on the oxygen atom is delocalised around the ring. The more stable the ion is, the more likely it is to form. One of the lone pairs on the oxygen atom overlaps with the delocalised electrons on the benzene ring.



This overlap leads to a delocalization which extends from the ring out over the oxygen atom. As a result, the negative charge is no longer entirely localized on the oxygen, but is spread out around the whole ion.



Spreading the charge around makes the ion more stable than it would be if all the charge remained on the oxygen. However, oxygen is the most electronegative element in the ion and the delocalized electrons will be drawn towards it. That means that there will still be a lot of charge around the oxygen which will tend to attract the hydrogen ion back again. That is why phenol is only a very weak acid.

Why is phenol a much stronger acid than cyclohexanol? To answer this question we must evaluate the manner in which an oxygen substituent interacts with the benzene ring. As noted in our earlier treatment of electrophilic aromatic substitution reactions, an oxygen substituent enhances the reactivity of the ring and favors electrophile attack at ortho and para sites. It was proposed that resonance delocalization of an oxygen non-bonded electron pair into the pi-electron system of the aromatic ring was responsible for this substituent effect. A similar set of resonance structures for the phenolate anion conjugate base appears below the phenol structures.

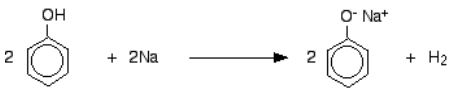
The resonance stabilization in these two cases is very different. An important principle of resonance is that charge separation diminishes the importance of canonical contributors to the resonance hybrid and reduces the overall stabilization. The contributing structures to the phenol hybrid all suffer charge separation, resulting in very modest stabilization of this compound. On the other hand, the phenolate anion is already charged, and the canonical contributors act to disperse the charge, resulting in a substantial stabilization of this species. The conjugate bases of simple alcohols are not stabilized by charge delocalization, so the acidity of these compounds is similar to that of water. An energy diagram showing the effect of resonance on cyclohexanol and phenol acidities is shown on the right. Since the resonance stabilization of the phenolate conjugate base is much greater than the stabilization of phenol itself, the acidity of phenol relative to cyclohexanol is increased. Supporting evidence that the phenolate negative charge is delocalized on the ortho and para carbons of the benzene ring comes from the influence of electron-withdrawing substituents at those sites.



sodium phenoxide

In this reaction, the hydrogen ion has been removed by the strongly basic hydroxide ion in the sodium hydroxide solution.

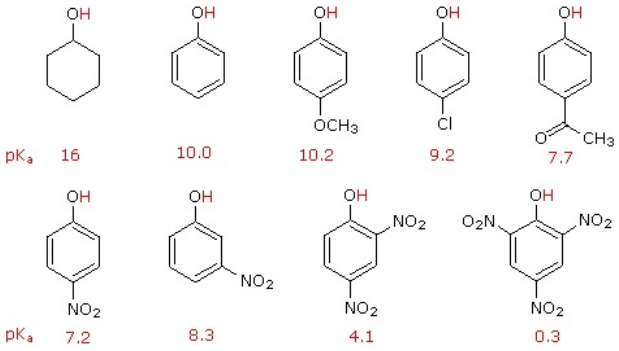
Acids react with the more reactive metals to give hydrogen gas. Phenol is no exception - the only difference is the slow reaction because phenol is such a weak acid. Phenol is warmed in a dry tube until it is molten, and a small piece of sodium added. There is some fizzing as hydrogen gas is given off. The mixture left in the tube will contain sodium phenoxide.

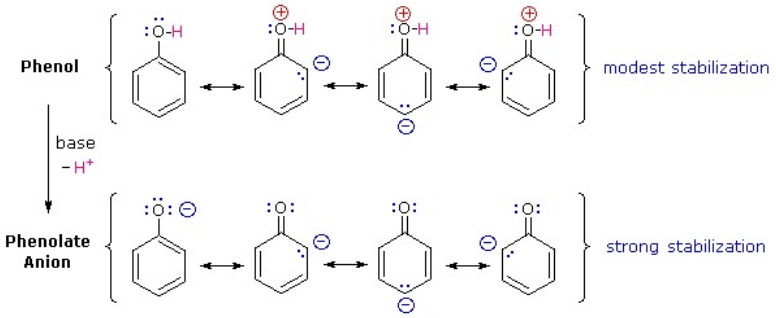


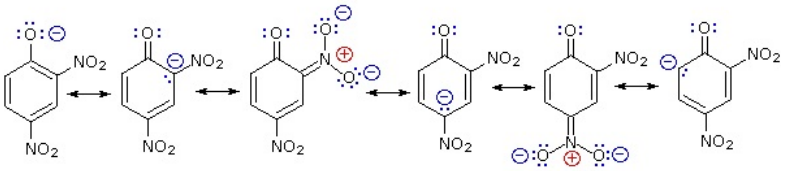
sodium phenoxide

ACIDITY OF SUBSTITUTED PHENOLS

Substitution of the hydroxyl hydrogen atom is even more facile with phenols, which are roughly a million times more acidic than equivalent alcohols. This phenolic acidity is further enhanced by electron-withdrawing substituents ortho and para to the hydroxyl group, as displayed in the following diagram. The alcohol cyclohexanol is shown for reference at the top left. It is noteworthy that the influence of a nitro substituent is over ten times stronger in the para-location than it is meta, despite the fact that the latter position is closer to the hydroxyl group. Furthermore additional nitro groups have an additive influence if they are positioned in ortho or para locations. The trinitro compound shown at the lower right is a very strong acid called picric acid.



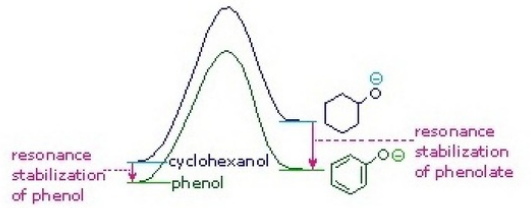




Resonance Stabilization of Phenolate by *ortho* and *para* Nitro Substituents

COMPARING THE ACIDITY OF ALCOHOLS WITH PHENOLS

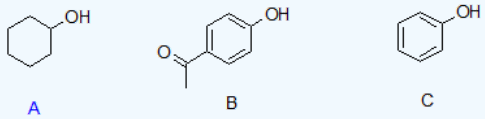
Why is phenol a much stronger acid than cyclohexanol? To answer this question we must evaluate the manner in which an oxygen substituent interacts with the benzene ring. As noted in our earlier treatment of electrophilic aromatic substitution reactions, an oxygen substituent enhances the reactivity of the ring and favors electrophile attack at ortho and para sites. It was proposed that resonance delocalization of an oxygen non-bonded electron pair into the pi-electron system of the aromatic ring was responsible for this substituent effect. Formulas illustrating this electron delocalization will be displayed when the "Resonance Structures" button beneath the previous diagram is clicked. A similar set of resonance structures for the phenolate anion conjugate base appears below the phenol structures.



The resonance stabilization in these two cases is very different. An important principle of resonance is that charge separation diminishes the importance of canonical contributors to the resonance hybrid and reduces the overall stabilization. The contributing structures to the phenol hybrid all suffer charge separation, resulting in very modest stabilization of this compound. On the other hand, the phenolate anion is already charged, and the canonical contributors act to disperse the charge, resulting in a substantial stabilization of this species. The conjugate bases of simple alcohols are not stabilized by charge delocalization, so the acidity of these compounds is similar to that of water. An energy diagram showing the effect of resonance on cyclohexanol and phenol acidities is shown on the right. Since the resonance stabilization of the phenolate conjugate base is much greater than the stabilization of phenol itself, the acidity of phenol relative to cyclohexanol is increased. Supporting evidence that the phenolate negative charge is delocalized on the ortho and para carbons of the benzene ring comes from the influence of electron-withdrawing substituents at those sites.

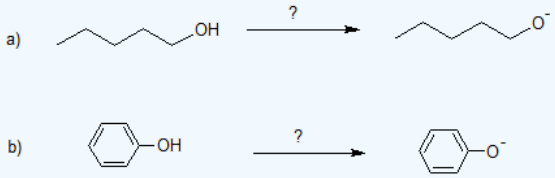
Exercise

9. Arrange the following compounds in order of decreasing acidity when they are in solution.



A B C

10. Specify the base needed to deprotonate each reactant.



Answer

9. B > C > A

10. a) Na or NaH or NNH_2

b) NaOH or KOH or LiOH

Contributors

- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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13.6: SYNTHESIS OF ALCOHOLS - REVIEW

ALCOHOLS ARE PREPARED BY S_N2 & S_N1 (SOLVOLYSIS) REACTIONS

Alkyl halides can be converted to alcohols by using S_N2 reactions with OH^- as a nucleophile. Substrates that undergo substitution by SN1 reaction can be converted to alcohols using water as the nucleophile (and it can even be the solvent). Recall that S_N1 reactions are promoted in polar, protic solvents.

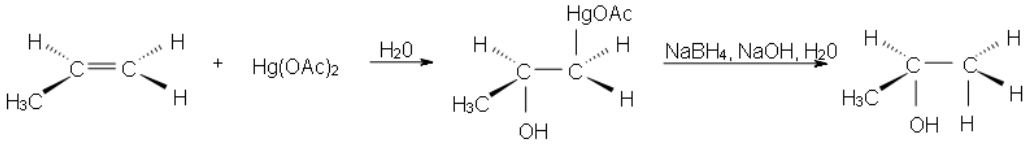
Example #1



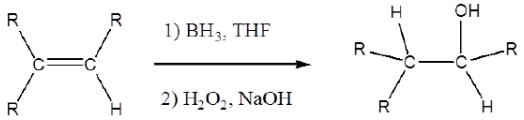
ALCOHOLS FROM ALKENES

Oxymercuration is a special electrophilic addition. It is anti-stereospecific and regioselective. Regioselectivity is a process in which the substituents choses one direction it prefers to be attached to over all the other possible directions. The good thing about this reaction is that there are no carbocation rearrangement due to stabilization of the reactive intermediate. Similar stabilization is also seen in bromination addition to alkenes.

Carbocation rearrangement is a process in which the carbocation intermediate can form a more stable ion. With carbocation rearrangement, the reaction would not be able to hydrate quickly under mild conditions and be produced in high yields. This reaction is very fast and proceeds with 90% yield.

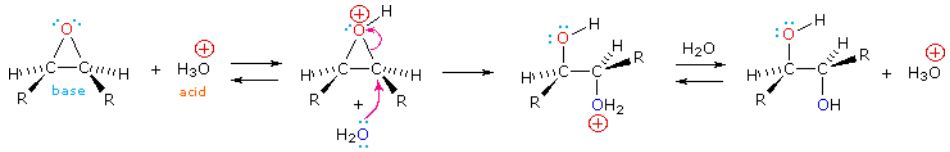


Hydroboration-Oxidation is a two step pathway used to produce alcohols. The reaction proceeds in an Anti-Markovnikov manner, where the hydrogen (from BH_3 or BHR_2) attaches to the more substituted carbon and the boron attaches to the least substituted carbon in the alkene bouble bond. Furthermore, the borane acts as a lewis acid by accepting two electrons in its empty p orbital from an alkene that is electron rich. This process allows boron to have an electron octet. A very interesting characteristic of this process is that it does not require any activation by a catalyst. The Hydroboration mechanism has the elements of both hydrogenation and electrophilic addition and it is a stereospecific (***syn addition),*** meaning that the hydroboration takes place on the same face of the double bond, this leads ***cis*** stereochemistry.

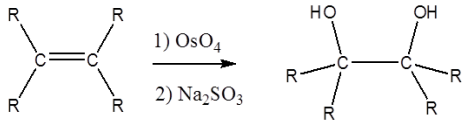


DIOLS FROM ALKENES

Epoxides may be cleaved by aqueous acid to give glycols that are often diastereomeric with those prepared by the syn-hydroxylation reaction described above. Proton transfer from the acid catalyst generates the conjugate acid of the epoxide, which is attacked by nucleophiles such as water in the same way that the cyclic bromonium ion described above undergoes reaction. The result is **anti-hydroxylation** of the double bond, in contrast to the syn-stereoselectivity of the earlier method. In the following equation this procedure is illustrated for a cis-disubstituted epoxide, which, of course, could be prepared from the corresponding cis-alkene. This hydration of an epoxide does not change the oxidation state of any atoms or groups.



Osmium tetroxide oxidizes alkenes to give glycols through syn addition. A glycol, also known as a vicinal diol, is a compound with two -OH groups on adjacent carbons.



The reaction with OsO_4 is a concerted process that has a cyclic intermediate and no rearrangements. Vicinal syn dihydroxylation complements the epoxide-hydrolysis sequence which constitutes an *anti* dihydroxylation of an alkene. When an alkene reacts with osmium tetroxide, stereocenters can form in the glycol product. Cis alkenes give meso products and trans alkenes give racemic mixtures.

CONTRIBUTORS AND ATTRIBUTIONS

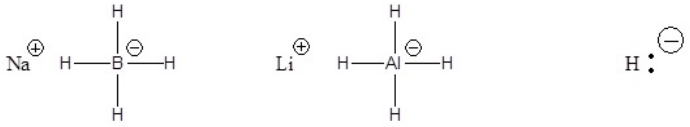
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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13.7: REDUCTION OF THE CARBONYL GROUP - SYNTHESIS OF 1º AND 2º ALCOHOLS

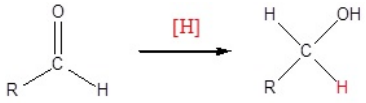
REDUCTION OF ALDEHYDES AND KETONES

The most common sources of the hydride nucleophile are lithium aluminum hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$). Note! The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-hydrogen bond. Because aluminum is less electronegative than boron, the Al-H bond in $LiAlH_4$ is more polar, thereby, making $LiAlH_4$ a stronger reducing agent.

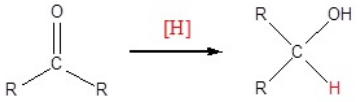


Sodium Borohydride **Lithium Aluminum Hydride** **Hydride Nucleophile**

Addition of a hydride anion ($H:^-$) to an aldehyde or ketone gives an alkoxide anion, which upon protonation yields the corresponding alcohol. Aldehydes produce 1º-alcohols and ketones produce 2º-alcohols.



Aldehyde **1° Alcohol**

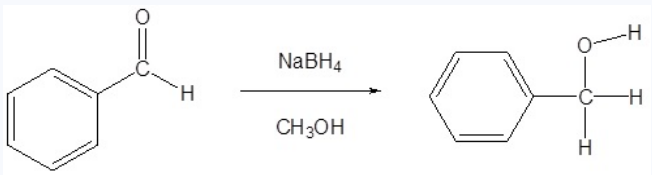


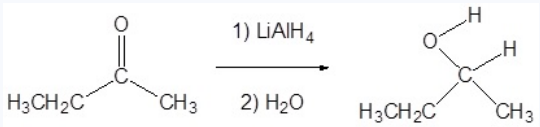
Ketone **2° Alcohol**

In metal hydrides reductions the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the sodium borohydride reduction the methanol solvent system achieves this hydrolysis automatically. In the lithium aluminum hydride reduction water is usually added in a second step. The lithium, sodium, boron and aluminum end up as soluble inorganic salts at the end of either reaction. Note! $LiAlH_4$ and $NaBH_4$ are both capable of reducing aldehydes and ketones to the corresponding 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. A carbonyl (aldehyde or ketone) plus two electrons and two protons becomes an alcohol.

Example 1

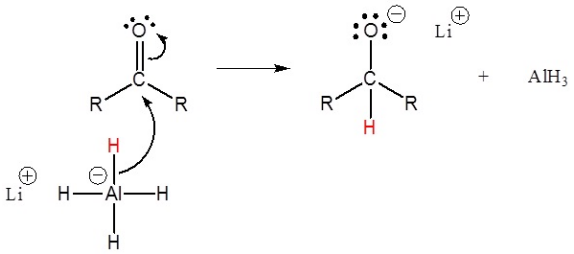




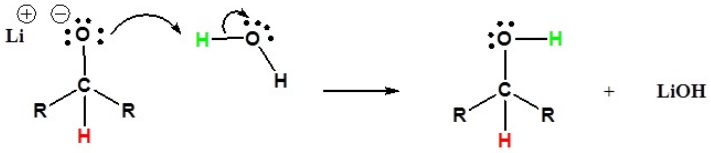
MECHANISM

This mechanism is for a $LiAlH_4$ reduction. The mechanism for a $NaBH_4$ reduction is the same except methanol is the proton source used in the second step.

1) Nucleopilic hydride anion reacts with the electrophilic carbonyl carbon forcing the pi electrons onto the electronegative oxygen atom.



2) The alkoxide is protonated.



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.

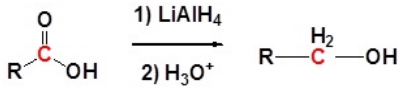
 CONADH2.png

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.

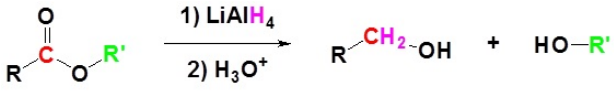
NADH is a common biological reducing agent. NADH is an acronym for nicotinamide adenine dinucleotide hydride. Insetad of an anionic donor that provides a hydride to a carbonyl, NADH is actually a neutral donor. It supplies a hydride to the carbonyl under very specific circumstances. In doing so, it forms a cation, NAD^+. However, NAD^+ is stabilized by the fact that its nicotinamide ring is aromatic; it was not aromatic in NADH.

REDUCTION OF CARBOXYLIC ACIDS AND ESTERS

Carboxylic acids can be converted to 1° alcohols using Lithium aluminum hydride ($LiAlH_4$). Note that $NaBH_4$ is not strong enough to convert carboxylic acids or esters to alcohols. An aldehyde is produced as an intermediate during this reaction, but it cannot be isolated because it is more reactive than the original carboxylic acid.



Esters can be converted to 1° alcohols using $LiAlH_4$, while sodium borohydride (***$NaBH_4$***) is not a strong enough reducing agent to perform this reaction.

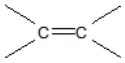
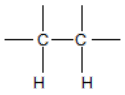


Ester **1° Alcohol**

REDUCTION REACTION SUMMARY

The table below summarize the reduction reactions covered so far in our text. It is important to distinguish between functional group reactivity as we add more multiple-step synthetic pathways.

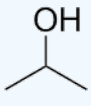
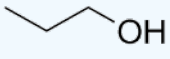
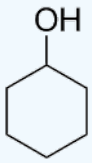
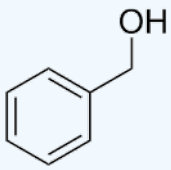
Reduction Reaction Summary

Reactant	Reduction Product with Specified Reagents H_2 with Pt, Pd or Ni	1) $NaBH_4$ 2) H_3O^+	1) $LiAlH_4$ 2) H_3O^+
	$RCH_2—OH$	$RCH_2—OH$	$RCH_2—OH$
	$RCH_2—OH$	$RCH_2—OH$	$RCH_2—OH$
	$RCH_2—OH$	$RCH_2—OH$	$RCH_2—OH$
	no rxn	no rxn	$RCH_2—OH$
	no rxn	no rxn	

Exercise

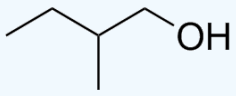
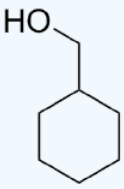
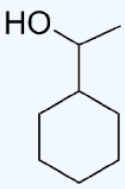
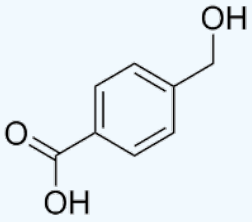
11.

Give the aldehyde, ketone, or carboxyllic acid (there can be multiple answers) that could be reduced to form the following alcohols.

(a)  (b)  (c)  (d) 

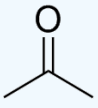
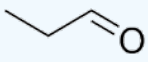
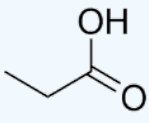
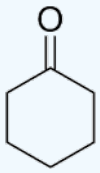
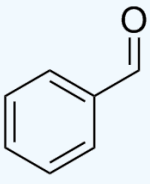
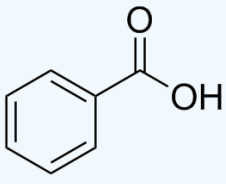
12.

Given the following alcohol, draw the structure from which it could be derived using only $NaBH_4$

(a)  (b)  (c)  (d) 

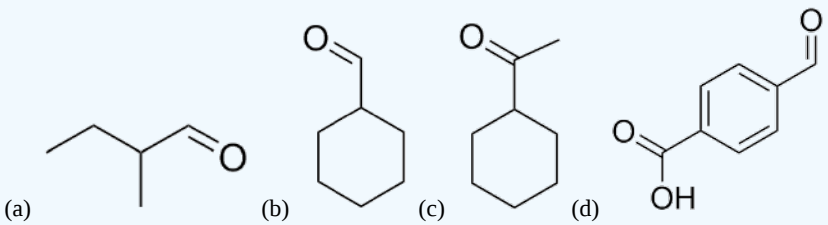
Answer

11.

(a)  (b)  or  (c)  (d)  or 

12.

Note, $NaBH_4$ is only a strong enough reducing agent to reduce ketones and aldehydes.



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

13.7: Reduction of the Carbonyl Group - Synthesis of 1º and 2º Alcohols is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

13.8: ORGANOMETALLIC REAGENTS

INTRODUCTION

A Grignard reagent has a formula **RMgX** where **X** is a halogen, and **R** is an alkyl or aryl (based on a benzene ring) group. For the purposes of this page, we shall take R to be an alkyl group. A typical Grignard reagent might be $\mathbf{CH_3CH_2MgBr}$. Organolithium reagents have the chemical formula RLi. A typical reagent might be $\mathbf{CH_3CH_2Li}$.

FORMATION OF ORGANOMETALLIC REAGENTS

Many organometallic reagents are commercially available, however, it is often necessary to make then. The following equations illustrate these reactions for the commonly used metals lithium and magnesium (R may be hydrogen or alkyl groups in any combination).

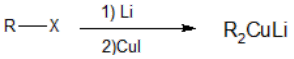
- **An Alkyl Lithium Reagent**

$$\mathbf{R_3C{-}X + 2\,Li \rightarrow R_3C{-}Li + LiX} \tag{13.8.1}$$

- **A Grignard Reagent**

$$\mathbf{R_3C{-}X + Mg \rightarrow R_3C{-}MgX} \tag{13.8.2}$$

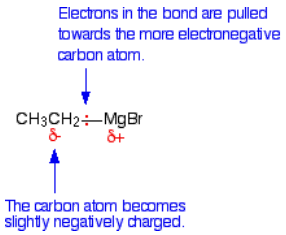
- **An Organocuprate Reagent**



Halide reactivity in these reactions increases in the order: Cl < Br < I and Fluorides are usually not used. The alkyl magnesium halides described in the second reaction are called Grignard Reagents after the French chemist, Victor Grignard, who discovered them and received the Nobel prize in 1912 for this work. The other metals mentioned above react in a similar manner, but Grignard and Alky Lithium Reagents most widely used. Although the formulas drawn here for the alkyl lithium and Grignard reagents reflect the stoichiometry of the reactions and are widely used in the chemical literature, they do not accurately depict the structural nature of these remarkable substances. Mixtures of polymeric and other associated and complexed species are in equilibrium under the conditions normally used for their preparation. Organocuprate reagents have limited reactivity and will be used for ketone synthesis.

ORGANOMETALLIC REAGENTS ARE STRONG NUCLEOPHILES

The bond between the carbon atom and the metal atom is polar. Therefore, organometallic reagents are strong nucleophiles. Using the Grignard reagent as an example, the carbon is more electronegative than magnesium, so the bonding pair of electrons is pulled towards the carbon creating a partial negative charge. Grignard reagents are strong nucleophiles. Nucleophilic carbon atoms are very useful in building carbon chains in multiple step systhesis.

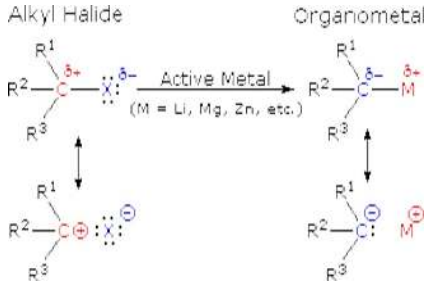


Grignard reactions create the possibility for substitution reactions at vinylic carbons. This reaction pathway is very useful since vinyl halides cannot react by the SN1 and SN2 mechanisms.

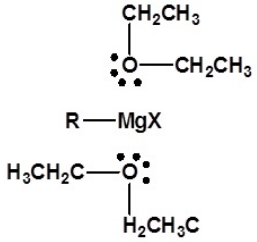
ORGANOMETALLIC REAGENTS AND PROTIC SOLVENTS (LIKE WATER)

Everything **must** be perfectly dry because organometallic reagents react with water (see below) or any protic solvent. Reactions using the Grignard reagent must use an ether as the solvent. Organolithium reactions also require aprotic solvents, but ethers are not required and alkanes can be used as solvents. The resulting reaction mixture is used directly for the next reaction. There are no separation and isolation procedures between reaction steps. Organometallic reagents react with water or any protic solvent to produce alkanes.

For this reason, everything has to be **very dry** during the preparation above. The term **dry** means that no water or other protonated solvents are present. There is still a **liquid** ether solvent.

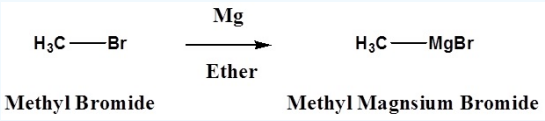


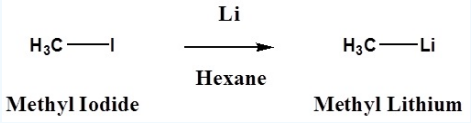
A suitable solvent must be used. For alkyl lithium formation pentane or hexane are usually used. Diethyl ether can also be used but the subsequent alkyl lithium reagent must be used immediately after preparation due to an interaction with the solvent. Ethyl ether or THF are essential for Grignard reagent formation. Lone pair electrons from two ether molecules form a complex with the magnesium in the Grignard reagent (As pictured below). This complex helps stabilize the organometallic and increases its ability to react.



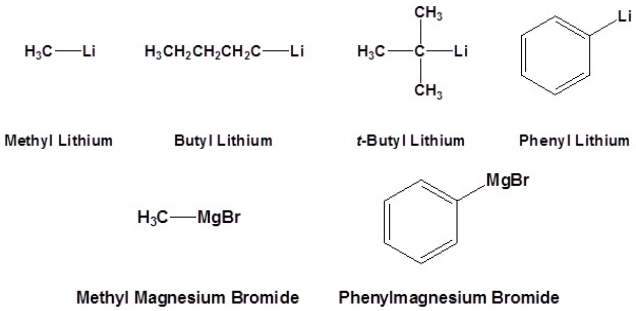
These reactions are obviously substitution reactions, but they cannot be classified as nucleophilic substitutions, as were the earlier reactions of alkyl halides. Because the functional carbon atom has been reduced, the polarity of the resulting functional group is inverted (an originally electrophilic carbon becomes nucleophilic). This change, shown below, makes alkyl lithium and Grignard reagents excellent nucleophiles and useful reactants in synthesis.

Example:





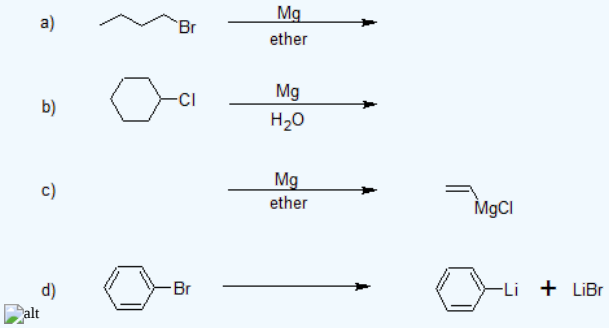
COMMON ORGANOMETALLIC REAGENTS



Exercises

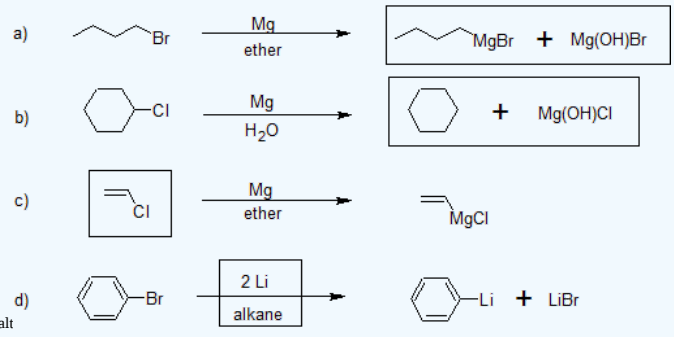
13.

Predict the product or specify the missing regent(s) in the reactions below.



Answer

13.

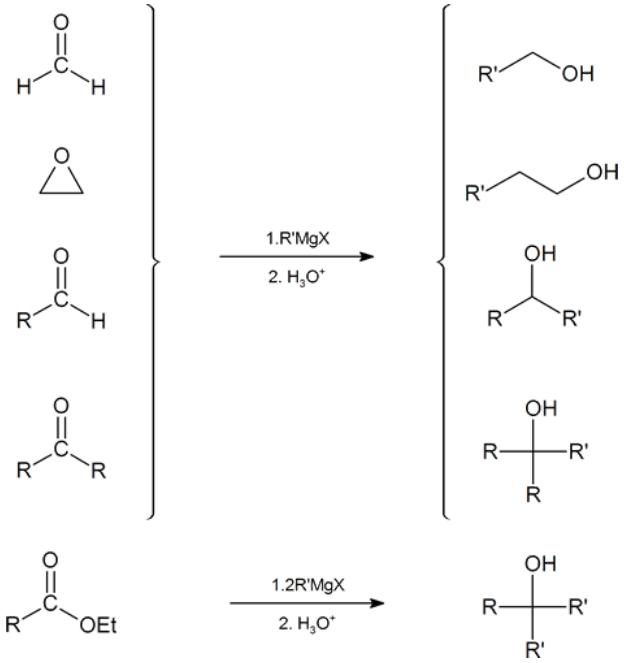


13.8: Organometallic Reagents is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

13.9: ORGANOMETALLIC REAGENTS IN ALCOHOL SYNTHESIS

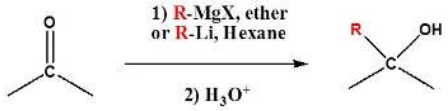
INTRODUCTION

The nucleophilic carbon atoms of organometallic reagents react with the electrophilic carbon atoms of aldehydes, ketones, acyl halides, esters, and epoxides to build larger carbon chains. In the process, an alcohol is formed. The ability to build larger organic molecules is an important and useful skill for multi-step synthesis. These various reaction pathways are summarized below showing the Grignard reagent.



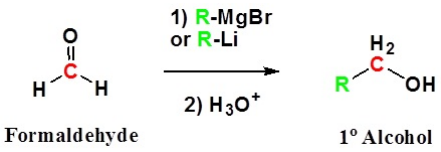
ORGANOMETALLIC REACTIONS WITH ALDEHYDES AND KETONES

Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. The basic reaction involves the nucleophilic reaction of the carbanionic carbon in the organometallic reagent with the electrophilic carbon in the carbonyl to form alcohols.

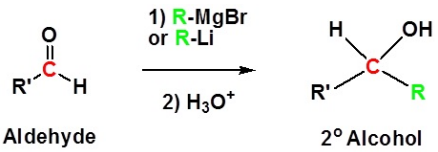


Both Grignard and Organolithium Reagents will perform these reactions.

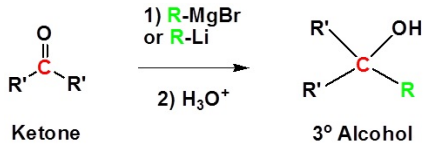
Addition to formaldehyde gives 1° alcohols.



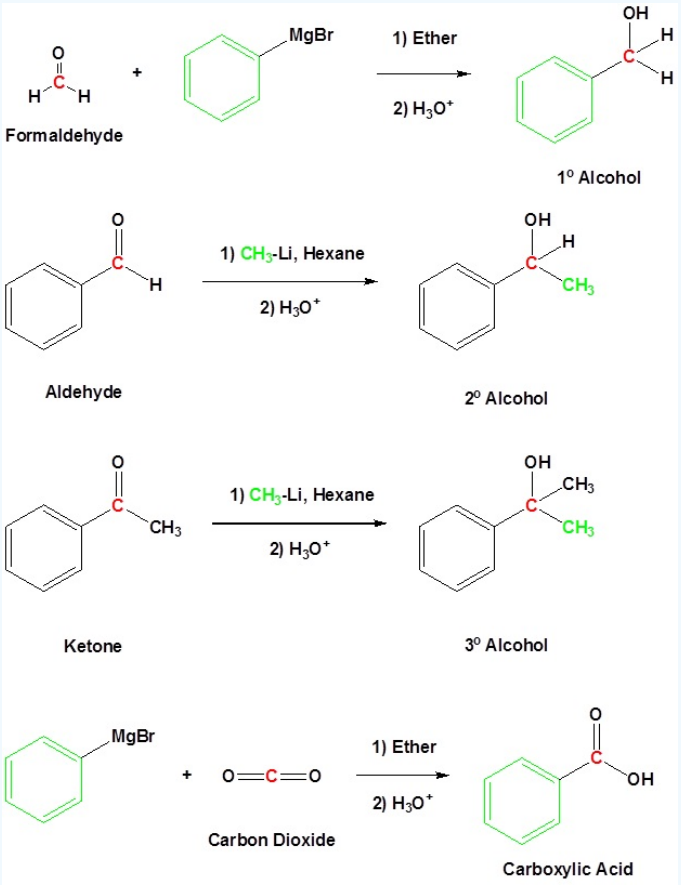
Addition to aldehydes gives 2° alcohols.



Addition to ketones gives 3° alcohols



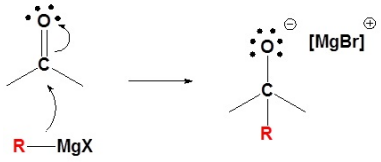
Examples



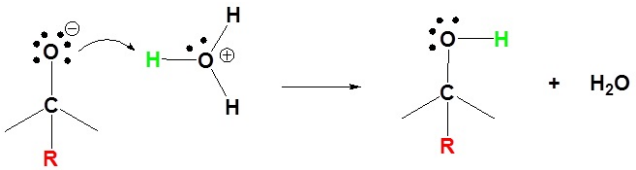
MECHANISM FOR THE ADDITION TO CARBONYLS

The mechanism for a Grignard agent is shown. The mechanism for an organolithium reagent is the same.

1) Nucleophilic reaction

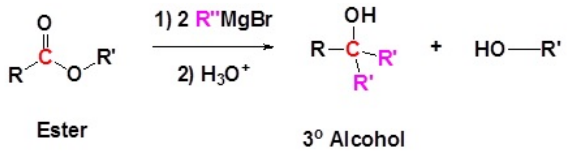


2) Protonation



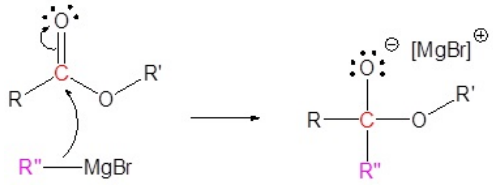
GRIGNARD REAGENTS CONVERT ESTERS TO 3° ALCOHOLS

After the first Grignard reaction, the carbonyl reforms creating a ketones which can then react with the Grignard. In effect, the Grignard reagent adds twice.

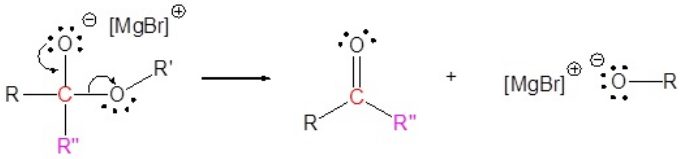


MECHANISM

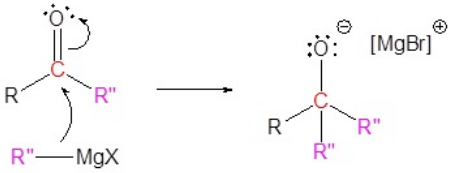
1) Nucleophilic reaction



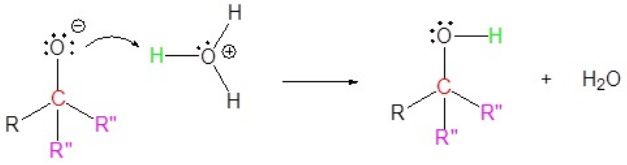
2) Carbonyl reforms with leaving group removal



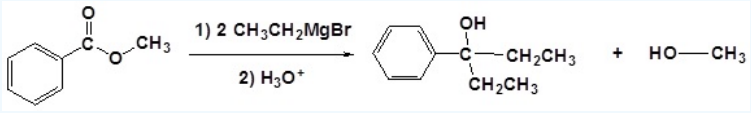
3) Nucleophilic reaction



4) Protonation

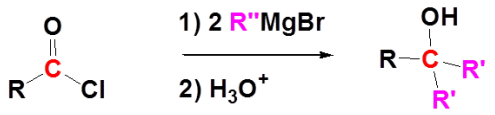


Example

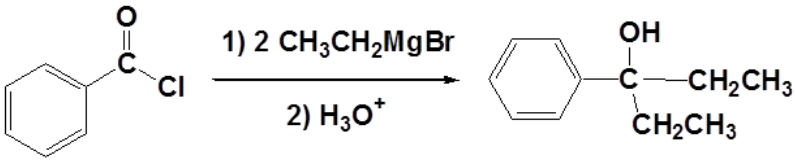


GRIGNARD REAGENTS CONVERT ACYL HALIDES TO 3° ALCOHOLS

Grignard reagents react with acyl halides similar to the reaction with esters. The first reaction produces a ketone which them undergoes a second reaction to form a tertiary alcohol following the analogous mechanism shown above for esters.

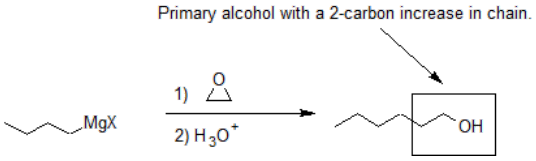


The reaction of benzoyl chloride with a Grignard reagent is shown below as an example.

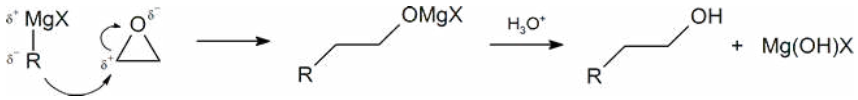


GRIGNARD REACTIONS WITH EPOXIDES

Another important route for producing an alcohol from a Grignard reagent involves the reaction of the Grignard reagent with ethylene oxide to produce a primary alcohol containing two more carbon atoms than the original Grignard reagent.

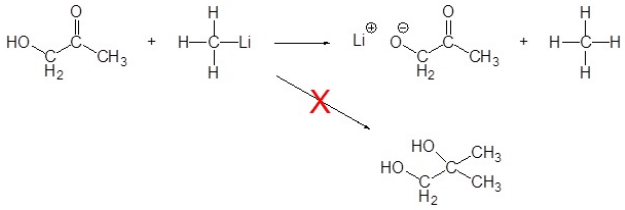


The first step of the mechanism is shown below. With the second step following the protonation step common to the other reaction pathways studied in this section.



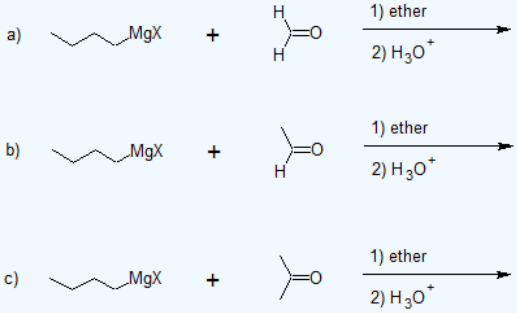
LIMITATION OF ORGANOMETALLIC REAGENTS

As discussed above, Grignard and organolithium reagents are powerful bases. Because of this they cannot be used as nucleophiles on compounds which contain acidic hydrogens. If they are used they will act as a base and deprotonate the acidic hydrogen rather than act as a nucleophile and attack the carbonyl. A partial list of functional groups which cannot be used are: alcohols, amides, 1° amines, 2° amines, carboxylic acids, and terminal alkynes.

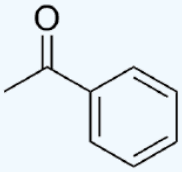


Exercises

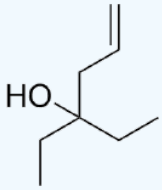
14. Predict the products of the reactions below.

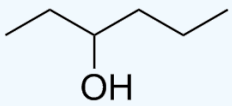


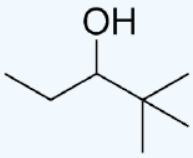
15. If allylmagnesium chloride were added to a solution of the following compound and then worked-up with acid, the product would contain a chiral center. Would the product be a racemic mixture or an enatiomerically pure product? Draw both enantiomers.

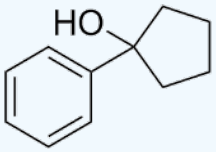


16. What combination of carbonyl compound and grignard (use MgBr) reagent would yield the following alcohols (after workup)?

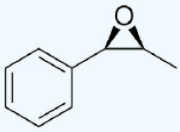
(a) 

(b) 

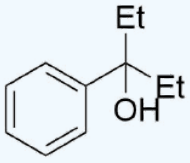
(c) 

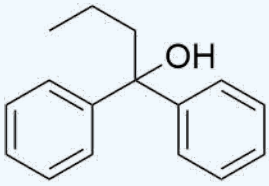
(d) 

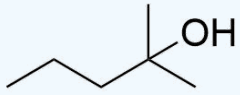
17. The following epoxide can be transformed into an alcohol using a grignard reagent, take for example allylmagnesium chloride. Draw the product of the treatment of this epoxide with this grignard after being worked up with H_2O. Note the stereochemistry and also remember that benzyllic carbons are good Sn2 electrophiles.



18. How might you prepare the following molecules from esters and Grignards?

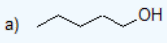
(a) 

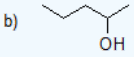
(b) 

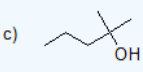
(c) 

Answer

14.

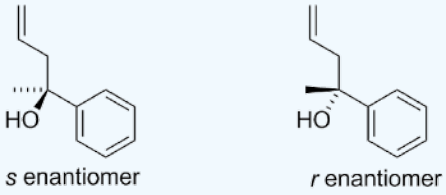
a) 

b) 

c) 

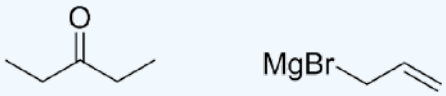
15.

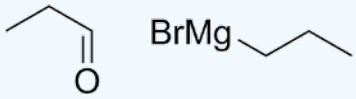
The result would be a racemic mixture of the following.

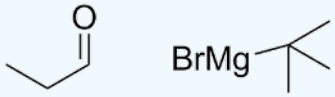


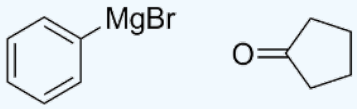
s enantiomer *r* enantiomer

16.

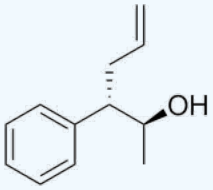
(a) 

(b) 

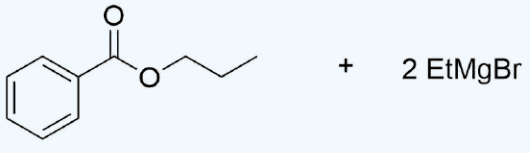
(c) 

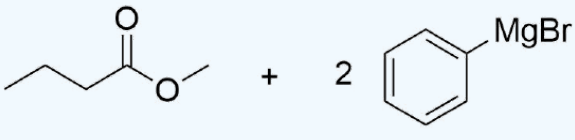
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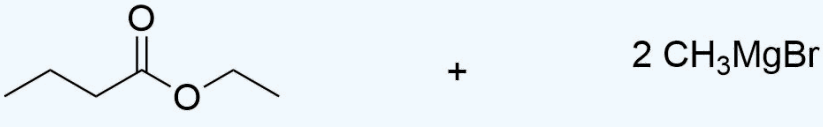
17.



18.

(a) 

(b) 

(c) 

CONTRIBUTORS AND ATTRIBUTIONS

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13.10: THIOLS (MERCAPTANS)

OBJECTIVES

After completing this section, you should be able to

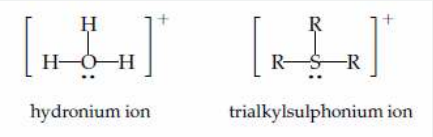
1. Nomenclature and Reactivity
   a. write the IUPAC name of a thiol, given its Kekulé, condensed or shorthand structure.
   b. draw the structure of a thiol, given its IUPAC name.
   c. write an equation to represent the formation of a thiol by the reaction of hydrosulfide anion with an alkyl halide.
   d. write an equation to illustrate the preparation of a thiol by the reaction of thiourea with an alkyl halide.
2. write an equation to show the interconversion between thiols and disulfides.
3. a. write the name of a sulfide, given its structure.
   b. draw the structure of a sulfide, given its name.
   c. write an equation showing how a sulfide may be prepared by the reaction of a thiolate anion on an alkyl halide.
   d. identify the product from the reaction of a given alkyl halide with a given thiolate anion.
   e. identify the reagents necessary to prepare a given sulfide.
   f. write an equation to illustrate the formation of a trialkylsulfonium salt from a sulfide and an alkyl halide.

KEY TERMS

- disulfide
- mercapto group
- (organic) sulfide
- sulfone
- sulfoxide
- thiol
- thiolate anion
- trialkylsulfonium ion (trialkylsulfonium salt)

STUDY NOTES

The chemistry of sulfur-containing organic compounds is often omitted from introductory organic chemistry courses. However, we have included a short section on these compounds, not for the sake of increasing the amount of material to be digested, but because much of the chemistry of these substances can be predicted from a knowledge of their oxygen-containing analogues. A thiol is a compound which contains an SH functional group. The -SH group itself is called a mercapto group. A disulfide is a compound containing an -S-S- linkage. (Organic) sulfides have the structure R-S-R′, and are therefore the sulfur analogues of ethers. The nomenclature of sulfides can be easily understood if one understands the nomenclature of the corresponding ethers. Notice that the term “thio” is also used in inorganic chemistry. For example, SO_4^{2-} is the sulfate ion; while $S_2O_3^{2-}$, in which one of the oxygen atoms of a sulfate ion has been replaced by a sulfur atom, is called thiosulfate. Thiolate anions, RS- , are analogous to alkoxy anions, RO- . Thiolate anions are better nucleophiles than are alkoxy anions (see Section 11.5, pages 389-394 of the textbook). If you have trouble understanding why trialkylsulfonium ions are formed, think of them as being somewhat similar to the hydronium ions that are formed by protonating water:



Later we shall see examples of tetraalkylammonium ions, R_4N^+, which again may be regarded as being similar to hydronium ions. sulfoxides and sulfones are obtained by oxidizing organic sulfides. You need not memorize the methods used to carry out these oxidations.

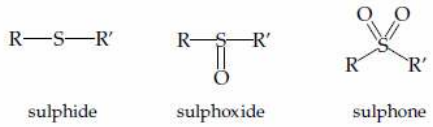


Table 18.1, below, provides a quick comparison of oxygen-containing and sulfur-containing organic compounds.

Oxygen-containing Compound	Sulphur Analogue
ether, R—O—R′	sulphide, R—S—R′
R—O—, alkoxy group	R—S—, alkylthio group
R—O⁻, alkoxy anion	R—S⁻, thiolate anion
alcohol, R—OH	thiol, R—SH
—OH, hydroxy group	—SH, mercapto group
R—O—O—R′, peroxide	R—S—S—R′, disulphide

Table 18.1 Comparison of compounds containing oxygen and sulphur

Note that when we name thiols, we include the "e" of the alkane name. Thus, CH_3CH_2SH is called "ethanethiol," not "ethanthiol."

OXIDATION STATES OF SULFUR COMPOUNDS

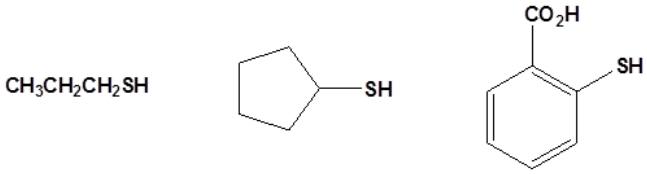
Oxygen assumes only two oxidation states in its organic compounds (–1 in peroxides and –2 in other compounds). Sulfur, on the other hand, is found in oxidation states ranging from –2 to +6, as shown in the following table (some simple inorganic compounds are displayed in orange).

Sulfur Oxidation States in Organic Compounds

-2	-1	0	+2	+4	+6
H_2S	R–S–S–R disulfides	S elemental	R–S(=O)–R sulfones	SO_2	SO_3
R–S–H thiols		R–S(=O)–R sulfoxides	R–S(=O)–OH sulfinic acids	R–S(=O)–OH sulfonic acids	R–O–S(=O)–O–R sulfate esters
R–S–R sulfides		R–S–OH sulfenic acids		R–O–S(=O)–O–R sulfite esters	
$R–S^{\oplus}(R)–R$ sulfonium ions					

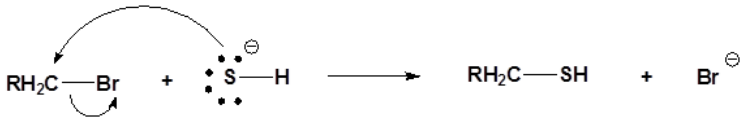
THIOLS

Thiols, which are also called mercaptans, are analogous to alcohols. They are named in a similar fashion as alcohols except the suffix *-thiol* is used in place of *-ol*. By itself the -SH group is called a mercapto group.

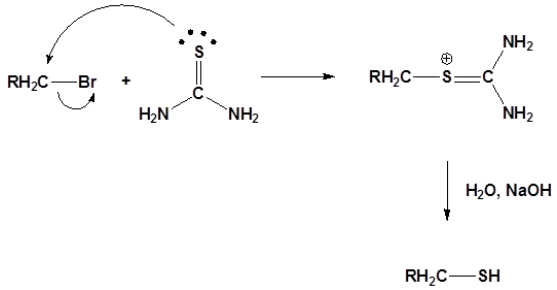


Propanethiol **Cyclopentanethiol** **o-Mercaptobenzoic acid**

Thiols are usually prepared by using the hydrosulfide anion (-SH) as a neucleophile in an S_N2 reaction with alkyl halides.

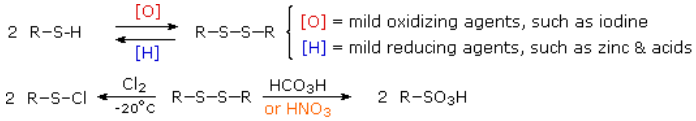


On problem with this reaction is that the thiol product can undergo a second S_N2 reaction with an additional alkyl halide to produce a sulfide side product. This problem can be solved by using thiourea, $(NH_2)_2C=S$, as the nucleophile. The reaction first produces an alkyl isothiourea salt and an intermediate. This salt is then hydrolyzed by a reaction with aqueous base.



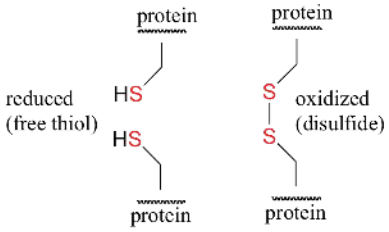
DISULFIDES

Oxidation of thiols and other sulfur compounds changes the oxidation state of sulfur rather than carbon. We see some representative sulfur oxidations in the following examples. In the first case, mild oxidation converts thiols to disufides. An equivalent oxidation of alcohols to peroxides is not normally observed. The reasons for this different behavior are not hard to identify. The S–S single bond is nearly twice as strong as the O–O bond in peroxides, and the O–H bond is more than 25 kcal/mole stronger than an S–H bond. Thus, thermodynamics favors disulfide formation over peroxide.



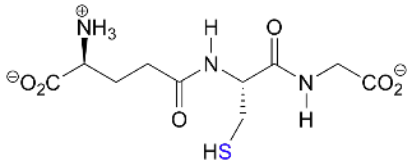
DISULFIDE BRIDGES IN PROTEINS

Disulfide (sulfur-sulfur) linkages between two cysteine residues are an integral component of the three-dimensional structure of many proteins. The interconversion between thiols and disulfide groups is a redox reaction: the thiol is the reduced state, and the disulfide is the oxidized state.



Notice that in the oxidized (disulfide) state, each sulfur atom has lost a bond to hydrogen and gained a bond to a sulfur - this is why the disulfide state is considered to be oxidized relative to the thiol state.

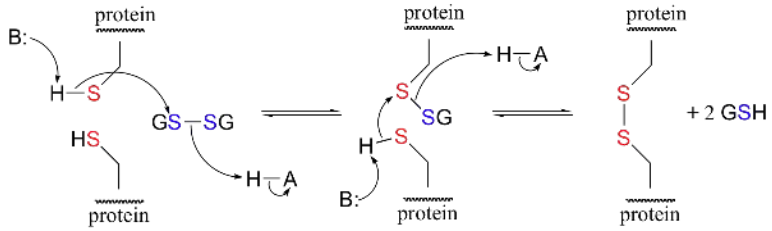
The redox agent that mediates the formation and degradation of disulfide bridges in most proteins is glutathione, a versatile coenzyme that we have met before in a different context (section 14.2A). Recall that the important functional group in glutathione is the thiol, highlighted in blue in the figure below. In its reduced (free thiol) form, glutathione is abbreviated 'GSH'.



Glutathione (GSH)

In its oxidized form, glutathione exists as a dimer of two molecules linked by a disulfide group, and is abbreviated 'GSSG'.

A new disulfide in a protein forms via a 'disulfide exchange' reaction with GSSH, a process that can be described as a combination of two S_N2-like attacks. The end result is that a new cysteine-cysteine disulfide forms at the expense of the disulfide in GSSG.

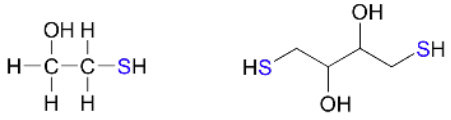


In its reduced (thiol) state, glutathione can reduce disulfides bridges in proteins through the reverse of the above reaction.

Disulfide bridges exist for the most part only in proteins that are located outside the cell. Inside the cell, cysteines are kept in their reduced (free thiol) state by a high intracellular concentration of GSH, which in turn is kept in a reduced state (ie. GSH rather than GSSG) by a flavin-dependent enzyme called glutathione reductase.

Disulfide bridges in proteins can also be directly reduced by another flavin-dependent enzyme called 'thioredoxin'. In both cases, NADPH is the ultimate electron donor, reducing FAD back to $FADH_2$ in each catalytic cycle.

In the biochemistry lab, proteins are often maintained in their reduced (free thiol) state by incubation in buffer containing an excess concentration of b-mercaptoethanol (BME) or dithiothreitol (DTT). These reducing agents function in a manner similar to that of GSH, except that DTT, because it has two thiol groups, forms an intramolecular disulfide in its oxidized form.



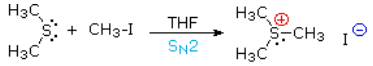
β-mercaptoethanol (BME) dithiothreitol (DTT)

SULFIDES

Sulfur analogs of ethers are called **sulfides**. The chemical behavior of sulfides contrasts with that of ethers in some important ways. Since hydrogen sulfide (H_2S) is a much stronger acid than water (by more than ten million fold), we expect, and find, thiols to be stronger acids than equivalent alcohols and phenols. Thiolate conjugate bases are easily formed, and have proven to be excellent nucleophiles in S_N2 reactions of alkyl halides and tosylates.

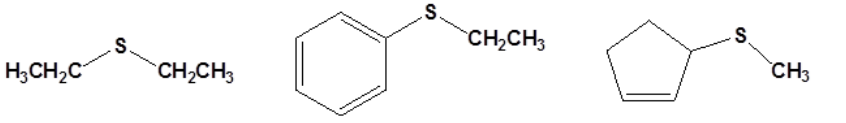
$$R\text{–}S^{(-)}\ Na^{(+)} + (CH_3)_2CH\text{–}Br \longrightarrow (CH_3)_2CH\text{–}S\text{–}R + Na^{(+)}\ Br^{(-)}$$

Although the basicity of ethers is roughly a hundred times greater than that of equivalent sulfides, the nucleophilicity of sulfur is much greater than that of oxygen, leading to a number of interesting and useful electrophilic substitutions of sulfur that are not normally observed for oxygen. Sulfides, for example, react with alkyl halides to give ternary sulfonium salts (equation # 1) in the same manner that 3º-amines are alkylated to quaternary ammonium salts. Although equivalent oxonium salts of ethers are known, they are only prepared under extreme conditions, and are exceptionally reactive.

1. 

dimethyl sulfide trimethylsulfonium iodide

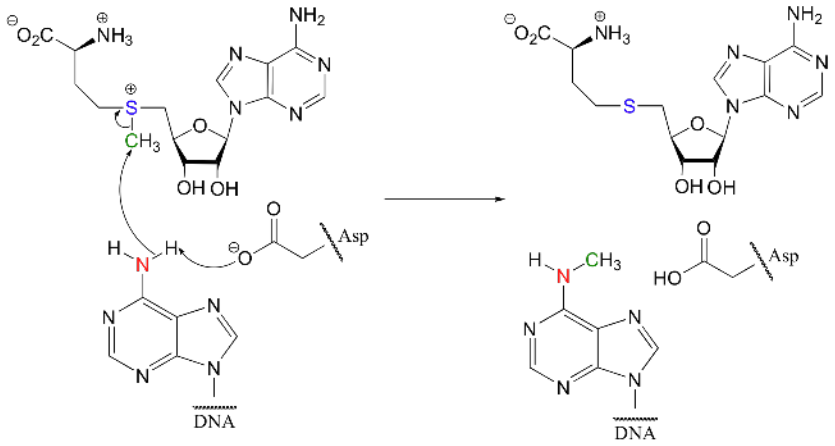
sulfides are named using the same rules as ethers except *sulfide* is used in the place of *ether*. For more complex substance alkylthio is used instead of alkoxy.



Diethyl sulfide **Ethyl phenyl sulfide** **3-(Methylthio)cyclopentene**

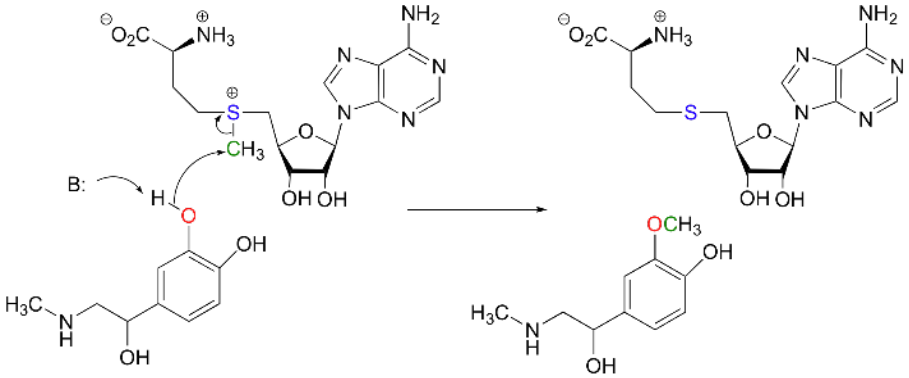
SAM METHYLTRANSFERASES

The most common example of sulfonium ions in a living organism is the reaction of S-Adenosylmethionine. Some of the most important examples of S_N2 reactions in biochemistry are those catalyzed by S-adenosyl methionine (SAM) – dependent methyltransferase enzymes. We have already seen, in chapter 6 and again in chapter 8, how a methyl group is transferred in an S_N2 reaction from SAM to the amine group on the nucleotide base adenosine:



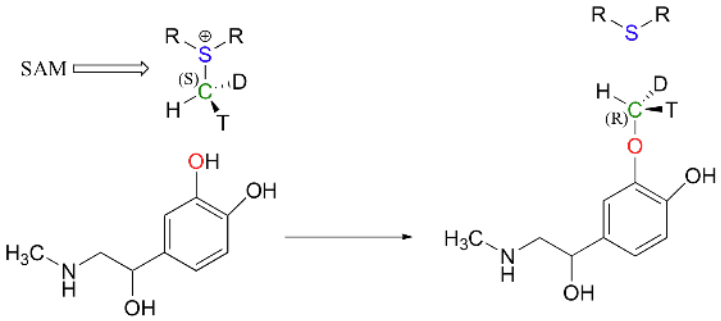
(*Nucleic Acids Res.* **2000**, *28*, 3950).

Another SAM-dependent methylation reaction is catalyzed by an enzyme called catechol-O-methyltransferase. The substrate here is epinephrine, also known as adrenaline.



Notice that in this example, the attacking nucleophile is an alcohol rather than an amine (that's why the enzyme is called an O-methyltransferase). In both cases, though, a basic amino acid side chain is positioned in the active site in just the right place to deprotonate the nucleophilic group as it attacks, increasing its nucleophilicity. The electrophile in both reactions is a methyl carbon, so there is little steric hindrance to slow down the nucleophilic attack. The methyl carbon is electrophilic because it is bonded to a positively-charged sulfur, which is a powerful electron withdrawing group. The positive charge on the sulfur also makes it an excellent leaving group, as the resulting product will be a neutral and very stable sulfide. All in all, in both reactions we have a reasonably good nucleophile, an electron-poor, unhindered electrophile, and an excellent leaving group.

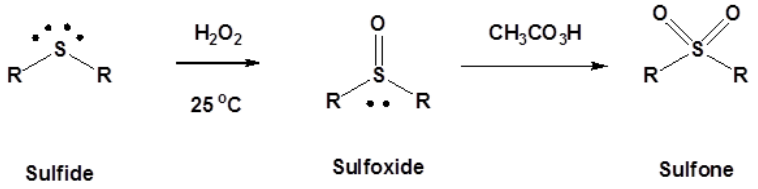
Because the electrophilic carbon in these reactions is a methyl carbon, a stepwise S_N1-like mechanism is extremely unlikely: a methyl carbocation is very high in energy and thus is not a reasonable intermediate to propose. We can confidently predict that this reaction is S_N2. Does this S_N2 reaction occur, as expected, with inversion of stereochemistry? Of course, the electrophilic methyl carbon in these reactions is achiral, so inversion is not apparent. To demonstrate inversion, the following experiment has been carried out with catechol-O-methyltransferase:



Here, the methyl group of SAM was made to be chiral by incorporating hydrogen isotopes tritium (^{3}H, T) and deuterium (^{2}H, D). The researchers determined that the reaction occurred with inversion of configuration, as expected for an S_N2 displacement (*J. Biol. Chem.*

1980, *255*, 9124).

Sulfides can be easily oxidized. Reacting a sulfide with hydrogen peroxide, H_2O_2, as room termpeature produces a sulfoxide (R_2SO). The oxidation can be continued by reaction with a peroxyacid to produce the sulfone (R_2SO_2)



A common example of a sulfoxide is the solvent dimethyl sulfoxide (DMSO). DMSO is polar aprotic solvent.

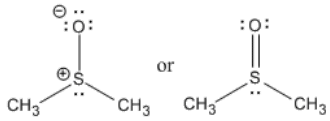


Figure AB16.3. DMSO is a very polar, aprotic solvent.

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

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13.11: COMMERCIALLY IMPORTANT ALCOHOLS

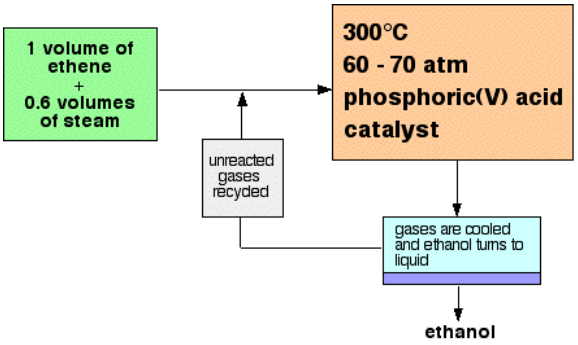
This page looks at the manufacture of alcohols by the direct hydration of alkenes, concentrating mainly on the hydration of ethene to make ethanol. It then compares that method with making ethanol by fermentation.

MANUFACTURING ALCOHOLS FROM ALKENES

Ethanol is manufactured by reacting ethene with steam. The catalyst used is solid silicon dioxide coated with phosphoric(V) acid. The reaction is reversible.

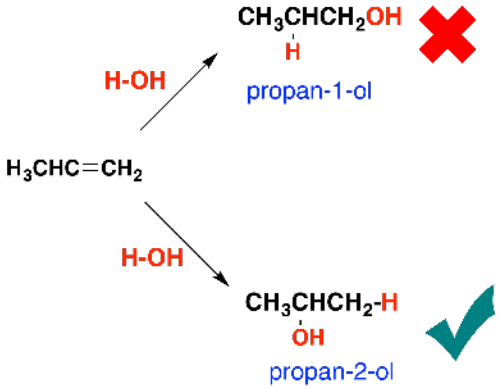
$$H_2C{=}CH_2(g) \;+\; H_2O(g) \xrightleftharpoons{H_3PO_4} CH_3CH_2OH(g)$$

Only 5% of the ethene is converted into ethanol at each pass through the reactor. By removing the ethanol from the equilibrium mixture and recycling the ethene, it is possible to achieve an overall 95% conversion. A flow scheme for the reaction looks like this:



THE MANUFACTURE OF OTHER ALCOHOLS FROM ALKENES

Some - but not all - other alcohols can be made by similar reactions. The catalyst used and the reaction conditions will vary from alcohol to alcohol. The reason that there is a problem with some alcohols is well illustrated with trying to make an alcohol from propene, $CH_3CH{=}CH_2$. In principle, there are two different alcohols which might be formed:



You might expect to get either propan-1-ol or propan-2-ol depending on which way around the water adds to the double bond. In practice what you get is propan-2-ol. If you add a molecule H-X across a carbon-carbon double bond, the hydrogen nearly always gets attached to the carbon with the most hydrogens on it already - in this case the CH_2 rather than the CH. The effect of this is that there are bound to be some alcohols which it is impossible to make by reacting alkenes with steam because the addition would be the wrong way around.

MAKING ETHANOL BY FERMENTATION

This method only applies to ethanol and you cannot make any other alcohol this way. The starting material for the process varies widely, but will normally be some form of starchy plant material such as maize (US: corn), wheat, barley or potatoes. Starch is a complex carbohydrate, and other carbohydrates can also be used - for example, in the lab sucrose (sugar) is normally used to produce ethanol. Industrially, this wouldn't make sense. It would be silly to refine sugar if all you were going to use it for was fermentation. There is no reason why you should not start from the original sugar cane, though.

The first step is to break complex carbohydrates into simpler ones. For example, if you were starting from starch in grains like wheat or barley, the grain is heated with hot water to extract the starch and then warmed with malt. Malt is germinated barley which contains

enzymes which break the starch into a simpler carbohydrate called maltose, $C_{12}H_{22}O_{11}$. Maltose has the same molecular formula as sucrose but contains two glucose units joined together, whereas sucrose contains one glucose and one fructose unit.

Yeast is then added and the mixture is kept warm (say 35°C) for perhaps several days until fermentation is complete. Air is kept out of the mixture to prevent oxidation of the ethanol produced to ethanoic acid (vinegar). Enzymes in the yeast first convert carbohydrates like maltose or sucrose into even simpler ones like glucose and fructose, both $C_6H_{12}O_6$, and then convert these in turn into ethanol and carbon dioxide. You can show these changes as simple chemical equations, but the biochemistry of the reactions is much, much more complicated than this suggests.

$$C_{12}H_{22}O_{11} + H_2O \longrightarrow 2C_6H_{12}O_6 \tag{13.11.1}$$

$$C_6H_{12}O_6 \longrightarrow 2CH_3CH_2OH + 2CO2 \tag{13.11.2}$$

Yeast is killed by ethanol concentrations in excess of about 15%, and that limits the purity of the ethanol that can be produced. The ethanol is separated from the mixture by fractional distillation to give 96% pure ethanol. For theoretical reasons (minimum boiling point azeotrope), it is impossible to remove the last 4% of water by fractional distillation.

Table 1.1.1: A comparison of fermentation with the direct hydration of ethene

	Fermentation	Hydration of ethene
Type of process	A batch process. Everything is put into a container and then left until fermentation is complete. That batch is then cleared out and a new reaction set up. This is inefficient.	A continuous flow process. A stream of reactants is passed continuously over a catalyst. This is a more efficient way of doing things.
Rate of reaction	Very slow.	Very rapid.
Quality of product	Produces very impure ethanol which needs further processing	Produces much purer ethanol.
Reaction conditions	Uses gentle temperatures and atmospheric pressure.	Uses high temperatures and pressures, needing lots of energy input.
Use of resources	Uses renewable resources based on plant material.	Uses finite resources based on crude oil.

CONTRIBUTORS

- Jim Clark (Chemguide.co.uk)

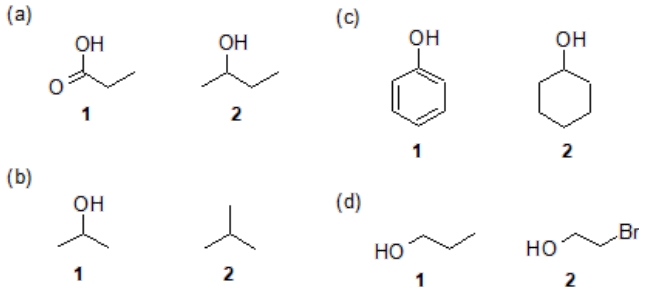
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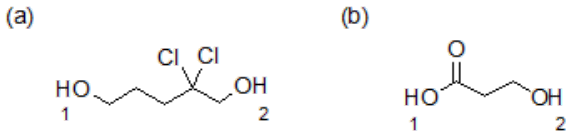
13.12: 13.12 ADDITIONAL EXERCISES

PHYSICAL PROPERTIES OF ALCOHOLS

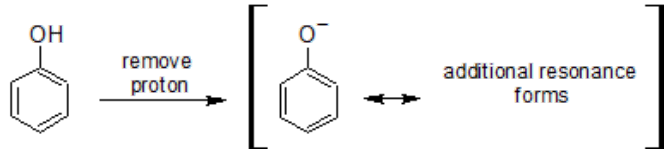
13-1 Identify which compound is more acidic. Explain your reasoning for each choice.



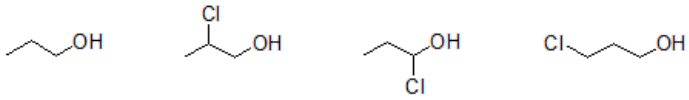
13-2 Identify which is the most acidic proton in the following compounds. Explain your reasoning for each choice.



13-3 Draw all possible resonance forms of the conjugate base of phenol.



13-4 List the following compounds in order from most to least acidic.



13-5 Predict which compound of each pair is more soluble in water and explain your reasoning.

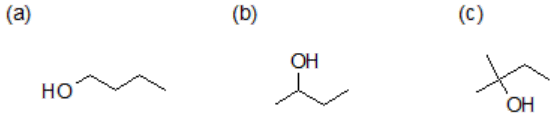
1. butan-1-ol or pentan-1-ol
2. phenol or cyclohexanol
3. octan-1,3-diol or octan-1-ol
4. 1-chlorohexane or hexan-1-ol

13-6 Predict which compound has the higher boiling point and explain your reasoning.

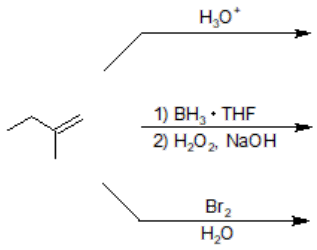
1. water or ethanol
2. butan-1-ol or octan-1-ol
3. hexan-2-ol or hexan-2-one

SYNTHESIS OF ALCOHOLS

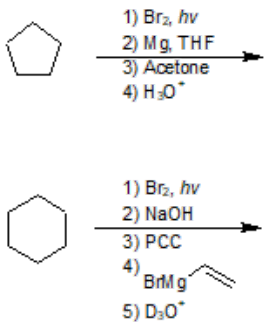
13-7 Show a possible way to synthesize the following alcohols.



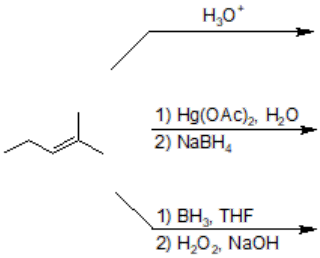
13-8 Give the product of each reaction.



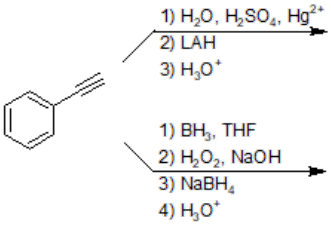
13-9 Give the product of each reaction.



13-10 Give the product of each reaction.

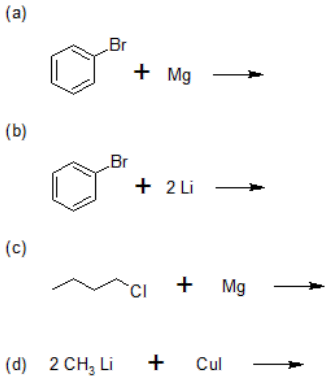


13-11 Give the product of each reaction.



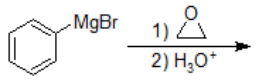
ORGANOMETALLIC REAGENTS FOR ALCOHOL SYNTHESIS

13-12 Draw the products of the following reactions.

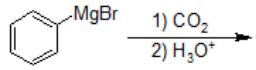


13-13 Draw the products of the following reactions.

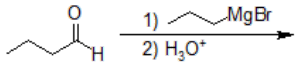
(a)



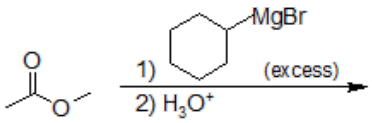
(b)



(c)

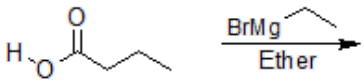


13-14 What is the final product of the following reaction.



13-15 Draw the mechanism for question **13-14**.

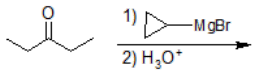
13-16 Identify the product of the following reaction and explain why that is the correct answer.



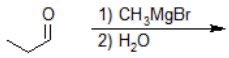
ADDITION OF ORGANOMETALLIC REAGENTS TO CARBONYL COMPOUNDS

13-17 Give the product(s) of the following reactions. Include stereochemistry when necessary.

(a)

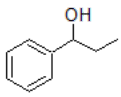


(b)



13-18 Show a possible carbonyl compound that was used to make the following alcohols through a Grignard reaction.

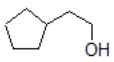
(a)



(b)

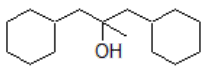


(c)

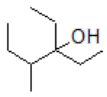


13-19 For the following compounds, identify the Grignard reagent used and the initial methyl ester compound.

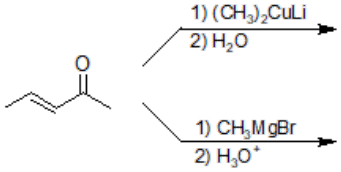
(a)



(b)



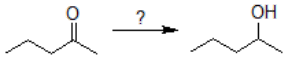
13-20 Give the products of the following reactions.



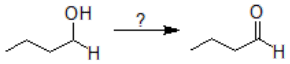
REDUCTION OF THE CARBONYL GROUP

13-21 Identify whether the initial compound is undergoing oxidation or reduction.

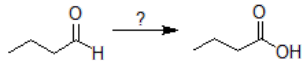
(a)



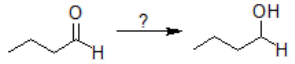
(b)



(c)

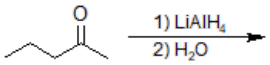


(d)

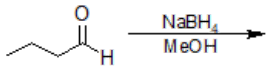


13-22 Give the product of each reaction.

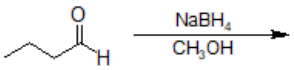
(a)

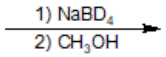


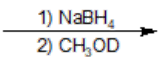
(b)



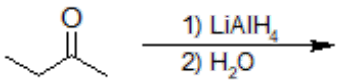
13-23 Give the product of each reaction (same starting molecule), making sure to specify where each proton ends up in the final product.



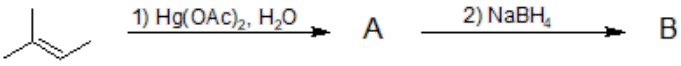




13-24 Give the mechanism for the following hydride reduction reaction.



13-25 Draw the structures for A and B.

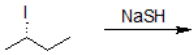


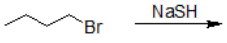
THIOLS (MERCAPTANS)

13-26 Name the following compounds following IUPAC nomenclature.

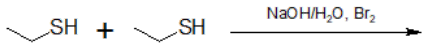


13-27 Identify the product of the following reaction. Include stereochemistry if appropriate.





13-28 Identify the product of the following reaction.



13.12: 13.12 Additional Exercises is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

13.13: SOLUTIONS TO ADDITIONAL EXERCISES

PHYSICAL PROPERTIES OF ALCOHOLS

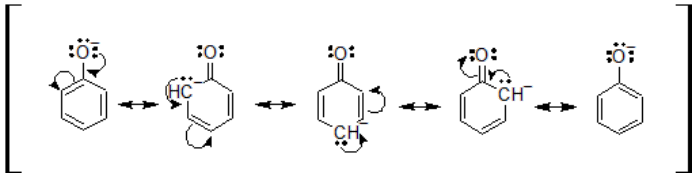
13-1

1. Compound 1 is more acidic than compound 2, since its conjugate base is stabilized by resonance.
2. Compound 1 is more acidic than compound 2 as the proton in question is bonded to a very electronegative atom (oxygen). When comparing the conjugate bases of both compounds, oxygen can stabilize a negative charge far better than the carbon atom of compound 2, allowing it to be a more stable conjugate base and stronger acid.
3. Compound 1 is more acidic than compound 2, since its conjugate base is stabilized by resonance.
4. Compound 2 is more acidic than compound 1. The halogen on compound 2 helps stabilize the negative charge of the conjugate base by withdrawing electron density through induction.

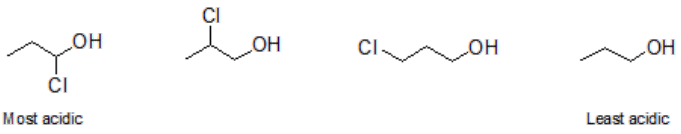
13-2

1. Proton 2 is more acidic than proton 1. The conjugate base formed by removing proton 2 is more stable than the conjugate base formed by removing proton 1, due to the strong induction effects by the halogens which withdraw electron density and stabilize the negative charge.
2. Proton 1 is more acidic than proton 2. The conjugate base formed by removing proton 1 is stabilized by resonance.

13-3 Resonance forms of the phenol conjugate base:



13-4



13-5

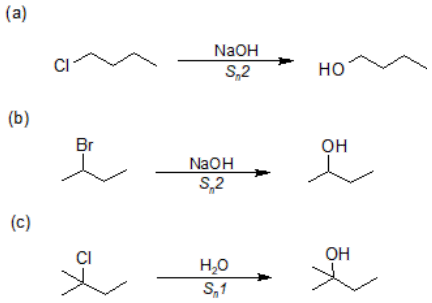
1. butan-1-ol is more soluble in water because it has a smaller hydrophobic region compared to pentan-1-ol, allowing butan-1-ol to interact with water better.
2. phenol is more soluble in water than cyclohexanol because of the more polar character of its ring. phenol is able to interact with water better than cyclohexanol due to the conjugated pi-system of electrons in its ring, which which gives it a more ionic character.
3. octan-1,3-diol is more soluble in water as it has two hydroxy groups, allowing it to form more hydrogen bonds and interact with water better than octan-1-ol.
4. hexan-1-ol is more soluble in water as it can hydrogen bond compared to alkyl halides, such as 1-chlorohexane, which are insoluble in water.

13-6

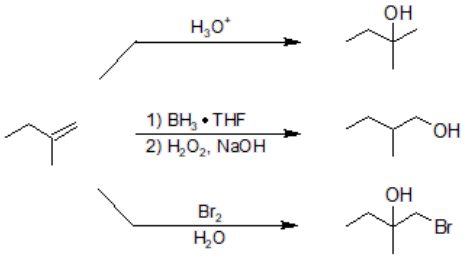
1. Water has a higher boiling point compared to ethanol as it participates in more hydrogen bonding with other water molecules, thus requiring more energy to break the intermolecular attractions between water molecules.
2. octan-1-ol has the higher boiling point compared to butan-1-ol. Both alcohols can H-bond, however the longer hydrophobic carbon chain tail of octan-1-ol experiences more van der Waal interactions compared to the shorter hydrophobic region of butan-1-ol leading to a higher boiling point.
3. Since hexan-1-ol can H-bond, it has a higher boiling point than hexan-2-one, which cannot H-bond.

SYNTHESIS OF ALCOHOLS

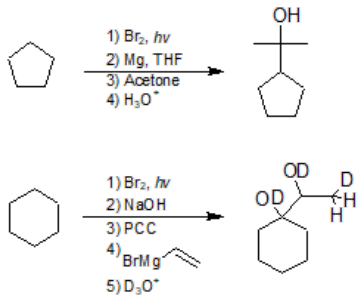
13-7



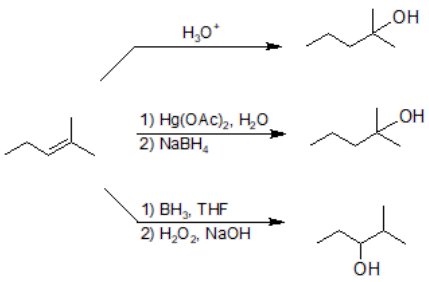
13-8



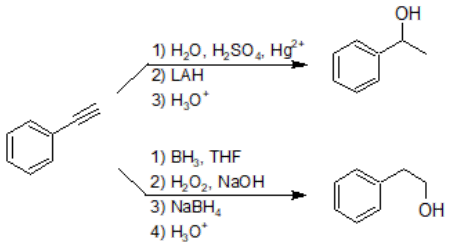
13-9



13-10



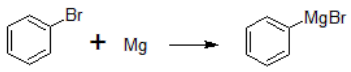
13-11



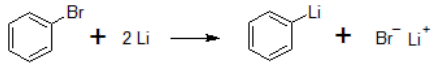
ORGANOMETALLIC REAGENTS FOR ALCOHOL SYNTHESIS

13-12

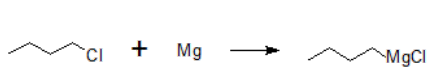
(a)



(b)



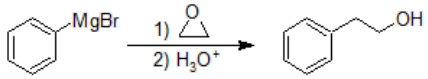
(c)



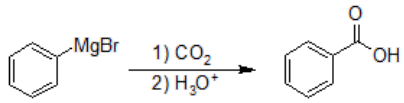
(d) $2\ CH_3Li + CuI \rightarrow (CH_3)_2CuLi + LiI$

13-13

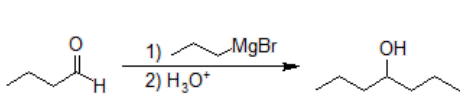
(a)



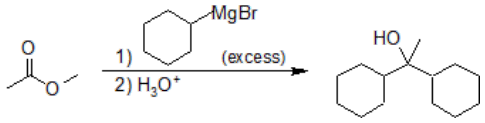
(b)



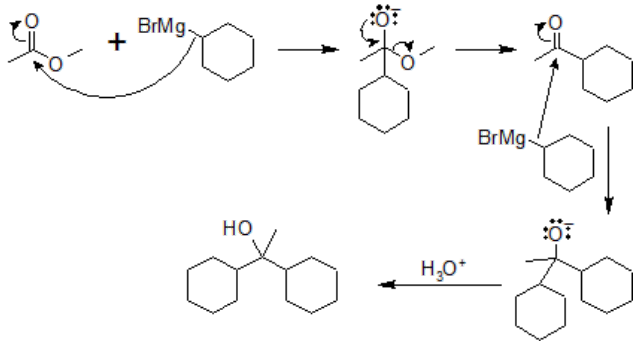
(c)



13-14

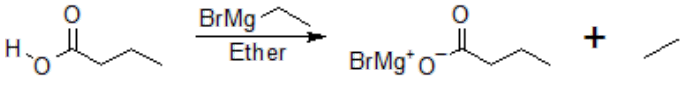


13-15



13-16

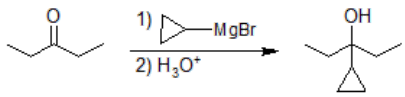
When you react an acid with an organometallic reagent, you will get a salt since organometallics are strong bases and will deprotonate the acid, before even getting a chance to attack the carbonyl carbon.



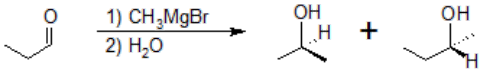
ADDITION OF ORGANOMETALLIC REAGENTS TO CARBONYL COMPOUNDS

13-17

(a)

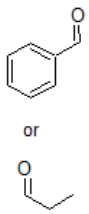


(b)

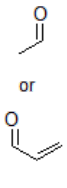


13-18

(a)



(b)

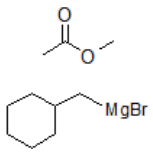


(c)

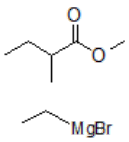


13-19

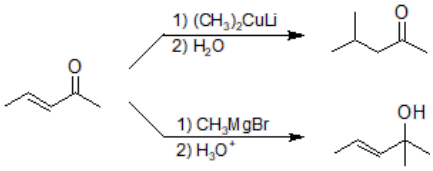
(a)



(b)



13-20



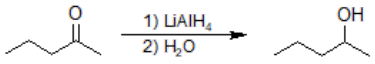
REDUCTION OF THE CARBONYL GROUP

13-21

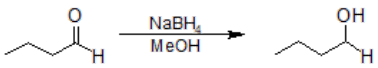
1. Reduction
2. Oxidation
3. Oxidation
4. Reduction

13-22

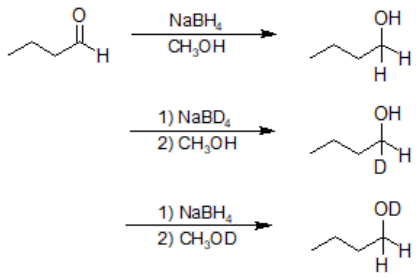
(a)



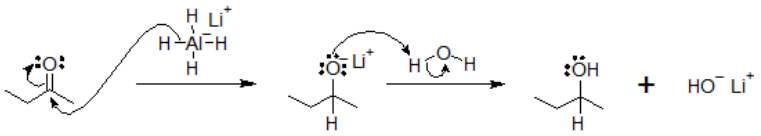
(b)



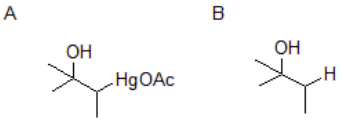
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13-24

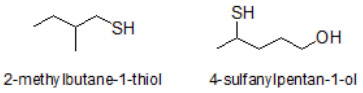


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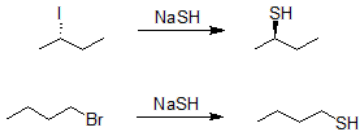


THIOLS (MERCAPTANS)

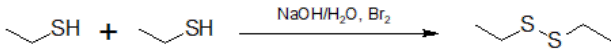
13-26



13-27



13-28



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CHAPTER OVERVIEW

14: REACTIONS OF ALCOHOLS

LEARNING OBJECTIVES

After reading this chapter and completing ALL the exercises, a student can be able to

- predict the products, specify the reagents, and determine the mechanism of the reactions of alcohols with

a. hydrohalic acids (refer to section 14.1)
b. phosphorous halides (refer to section 14.2)
c. thionyl chloride (refer to section 14.2)
d. carboxylic acids, acid chlorides, and tosyl choride (refer to section 14.3)
e. dehydrating reagents – H_2SO_4/heat or $POCl_3$/pyridine (refer to section 14.4)
f. oxidizing agents (refer to section 14.6)
g. sodium and potassium (refer to section 14.11)

- apply the most efficient and effective oxidizing agents (refer to section 14.6)
- determine the alcohol classification using laboratory experiments (refer to section 14.7)
- predict the products and specify the reagents of alcohol protecting group reactions (refer to section 14.9)
- predict the products and specify the reagents for diol cleavage reactions (refer to section 14.10)
- predict the products, specify the reagents for alkoxide ion reactions (refer to section 14.11)
- describe selected alcohol oxidation reactions in biology (refer to section 14.12)
- determine multiple-step synthetic pathways using alcohols (chapters 1-10 and 13-14)

14.1: Reactions of Alcohols with Hydrohalic Acids
14.2: Reactions with Phosphorus Halides and Thionyl Chloride
14.3: Alcohol conversion to Esters - Tosylate and Carboxylate
14.4: Dehydration Reactions of Alcohols
14.5: Oxidation States of Alcohols and Related Functional Groups
14.6: Oxidation Reactions of Alcohols
14.7: Determining Alcohol Classifications in the Lab - alternate reactions
14.8: Protection of Alcohols
14.9: Cleavage of Diols
14.10: Reactions of Alkoxides
14.11: Biological Oxidation - An Introduction
14.12: Additional Exercises
14.13: Solutions to Additional Exercises

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14.1: REACTIONS OF ALCOHOLS WITH HYDROHALIC ACIDS

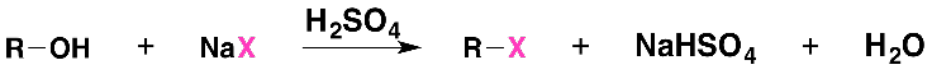
CONVERSION OF ALCOHOLS INTO ALKYL HALIDES

When alcohols react with a hydrogen halide, a substitution takes place producing an alkyl halide and water:

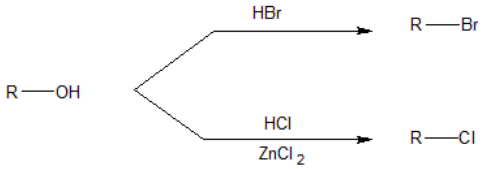


- The order of reactivity of alcohols is 3° > 2° > 1° methyl.
- The order of reactivity of the hydrogen halides is HI > HBr > HCl (HF is generally unreactive).

The reaction is acid catalyzed. Alcohols react with the strongly acidic hydrogen halides HCl, HBr, and HI, but they do not react with nonacidic NaCl, NaBr, or NaI. Primary and secondary alcohols can be converted to alkyl chlorides and bromides by allowing them to react with a mixture of a sodium halide and sulfuric acid:



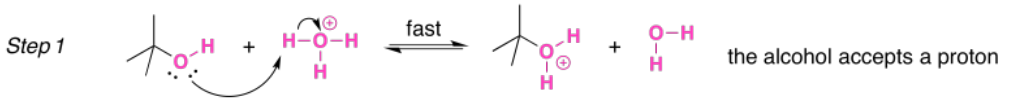
Because Cl- is a weaker nucleophile than Br-, the reaction with HCl requires a catalyst such as ZnCl2 as shown below.

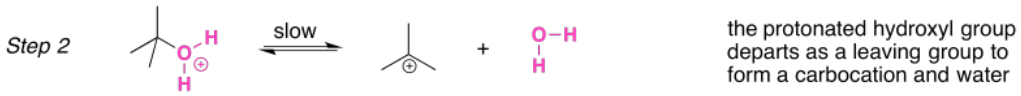


MECHANISMS OF THE REACTIONS OF ALCOHOLS WITH HX

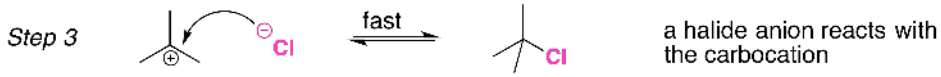
Secondary, tertiary, allylic, and benzylic alcohols appear to react by a mechanism that involves the formation of a carbocation, in an S_N1 reaction with the protonated alcohol acting as the substrate.

The S_N1 mechanism is illustrated by the reaction tert-butyl alcohol and aqueous hydrochloric acid (H_3O^+, Cl^-). The first two steps in this S_n1 substitution mechanism are protonation of the alcohol to form an oxonium ion. Although the oxonium ion is formed by protonation of the alcohol, it can also be viewed as a Lewis acid-base complex between the cation (R^+) and H_2O. Protonation of the alcohol converts a poor leaving group (OH-) to a good leaving group water, H_2O, which makes the dissociation step of the S_N1 mechanism more favorable.





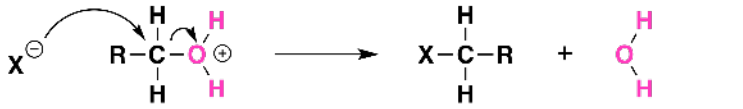
In step 3, the carbocation reacts with a nucleophile (a halide ion) to complete the substitution.



When we convert an alcohol to an alkyl halide, we carry out the reaction in the presence of acid and in the presence of halide ions, and not at elevated temperature. Halide ions are good nucleophiles (they are much stronger nucleophiles than water), and since halide ions are present in high concentration, most of the carbocations react with an electron pair of a halide ion to form a more stable species, the alkyl halide product. The overall result is an S_N1 reaction.

Not all acid-catalyzed conversions of alcohols to alkyl halides proceed through the formation of carbocations. Primary alcohols and methanol react to form alkyl halides under acidic conditions by an S_N2 mechanism.

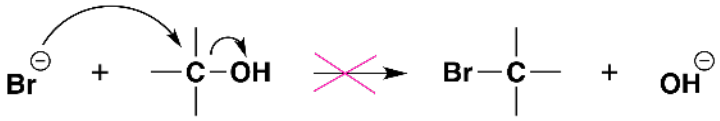
In these reactions the function of the acid is to produce a *protonated alcohol*. The halide ion then displaces a molecule of water (a good leaving group) from carbon; this produces an alkyl halide:



(protonated 1° alcohol or methanol)

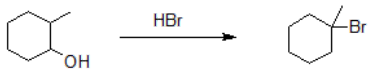
(A good leaving group)

Again, acid is required. Although halide ions (particularly iodide and bromide ions) are strong nucleophiles, they are not strong enough to carry out substitution reactions with alcohols themselves. Direct displacement of the hydroxyl group does not occur because the leaving group would have to be a strongly basic hydroxide ion:



We can see now why the reactions of alcohols with hydrogen halides are acid-promoted.

Carbocation rearrangements are extremely common in organic chemistry reactions are are defined as the movement of a carbocation from an unstable state to a more stable state through the use of various structural reorganizational "shifts" within the molecule. Once the carbocation has shifted over to a different carbon, we can say that there is a structural isomer of the initial molecule. However, this phenomenon is not as simple as it sounds.

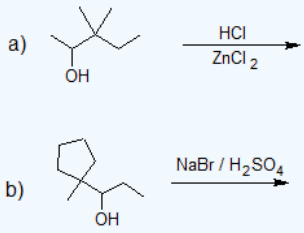


The carbocation intermediate undergoes a 1,2-hydride shift.

The most common methods for converting 1º- and 2º-alcohols to the corresponding chloro and bromo alkanes (*i.e.* replacement of the hydroxyl group) are treatments with thionyl chloride and phosphorus tribromide, respectively. These reagents are generally preferred over the use of concentrated HX due to the harsh acidity of these hydrohalic acids and the carbocation rearrangements associated with their use. The alcohol reactions with thionyl chloride or phosphorus tribromide are discussed in the next section.

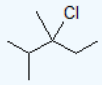
Exercises

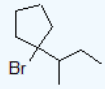
1. Predict the product of each reaction below.



Answer

1.

a) 

b) 

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

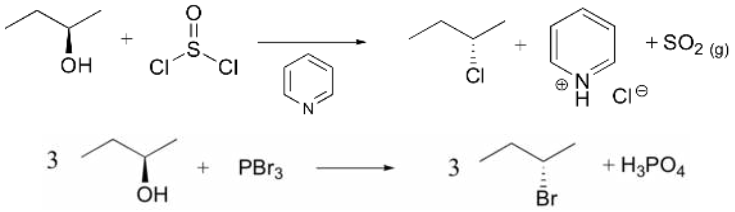
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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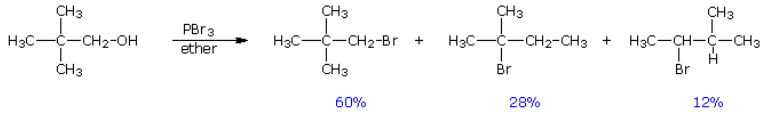
14.2: REACTIONS WITH PHOSPHORUS HALIDES AND THIONYL CHLORIDE

CARBOCATION CONTAINMENT

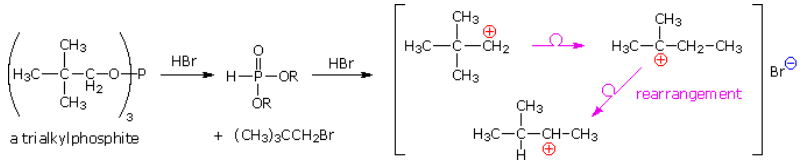
Synthetic organic chemists use phosphorus tribromide and thionyl chloride to convert an alcohol into a better leaving group without carbocation rearrangement.



Despite their general usefulness, phosphorous tribromide and thionyl chloride have shortcomings. Hindered 1º- and 2º-alcohols react sluggishly with the former, and may form rearrangement products, as noted in the following equation.

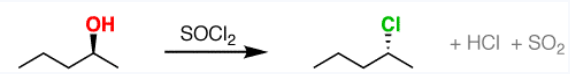


Below, an abbreviated mechanism for the reaction is displayed. The initially formed trialkylphosphite ester may be isolated if the HBr byproduct is scavenged by base. In the presence of HBr a series of acid-base and S_N2 reactions take place, along with the transient formation of carbocation intermediates. Rearrangement (pink arrows) of the carbocations leads to isomeric products.



Reaction of thionyl chloride with chiral 2º-alcohols has been observed to proceed with either inversion or retention. In the presence of a base such as pyridine, the intermediate chlorosulfite ester reacts to form an "pyridinium" salt, which undergoes a relatively clean S_N2 reaction to the inverted chloride. In ether and similar solvents the chlorosulfite reacts with retention of configuration, presumably by way of a tight or intimate ion pair. This is classified as an $\mathbf{S_Ni}$ reaction (nucleophilic substitution internal). The carbocation partner in the ion pair may also rearrange. These reactions are illustrated by the following equations. An alternative explanation for the retention of configuration, involving an initial solvent molecule displacement of the chlorosulfite group (as SO_2 and chloride anion), followed by chloride ion displacement of the solvent moiety, has been suggested. In this case, two inversions lead to retention.

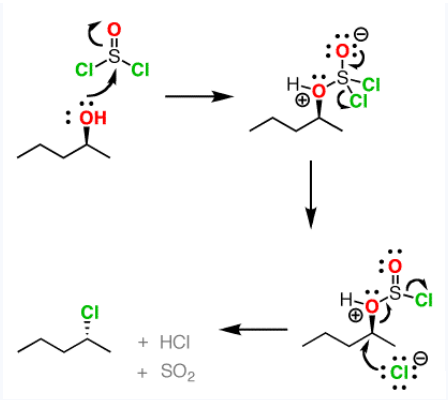
Example: Conversion of Alcohols to Alkyl Chlorides



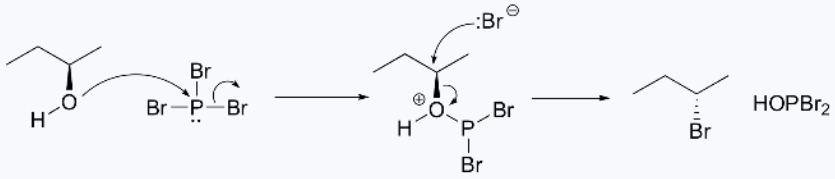
There's one important thing to note here: see the stereochemistry? It's been inverted.*(white lie alert – see below) That's an important difference between $SOCl_2$ and tosyl chloirde, TsCl, which leaves the stereochemistry alone. The TsCl reaction is studied in section 12.3.

MECHANISMS

Since the reaction proceeds through a backside S_N2 reaction, there is inversion of configuration at the carbon



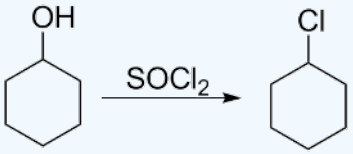
The PBr_3 reaction is thought to involve two successive S_N2-like steps:



Notice that these reactions result in inversion of stereochemistry in the resulting alkyl halide.

Exercises

2. Draw the mechanism of the reaction of thinoylchloride with cyclohexanol, given below.

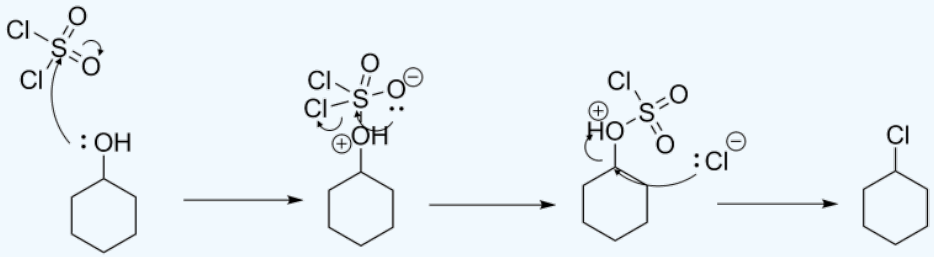


3. Draw the expected product of the reaction of cylohexanol with the following reagents.

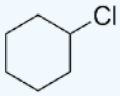
(a) $SOCl_2$ (b) PBr_3

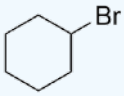
Answer

2.



3.

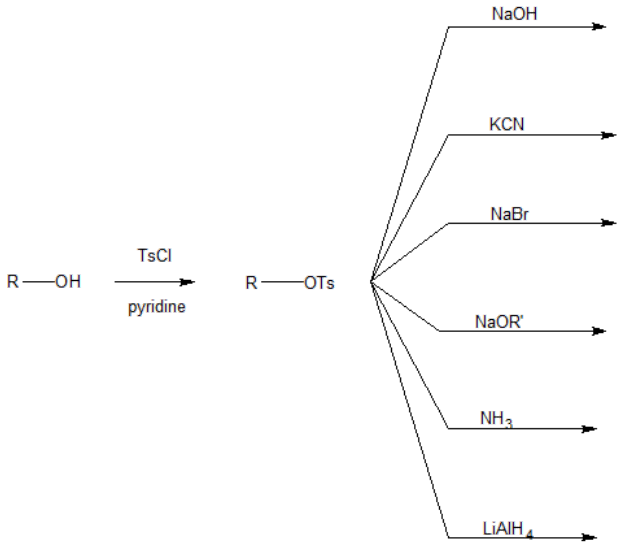
(a) 

(b) 

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14.3: ALCOHOL CONVERSION TO ESTERS - TOSYLATE AND CARBOXYLATE

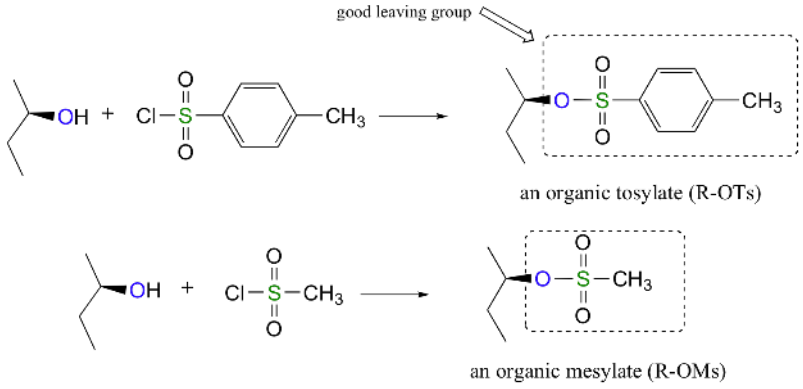
The poor leaving group of alcohols can be overcome by converting the hydroxyl group to a tosylate ester, an excellent leaving group. The tosylate ester undergoes subsequent reactions (typically S_N1 or S_N2) as part of a multiple step synthesis.



The synthesis of carboxylate esters (the other ester) is commonly the final step of a synthetic pathway.

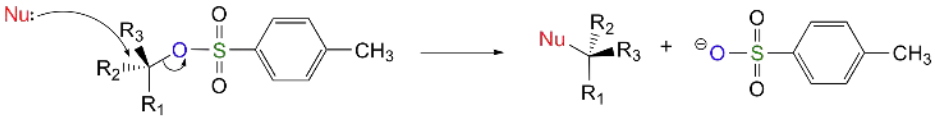
Tosylate Ester Formation

We can transform an alcohol group into a sulfonic ester using *para*-toluene sulfonyl chloride (Ts-Cl) or methanesulfonyl chloride (Ms-Cl), creating what is termed an organic **tosylate** or **mesylate:**

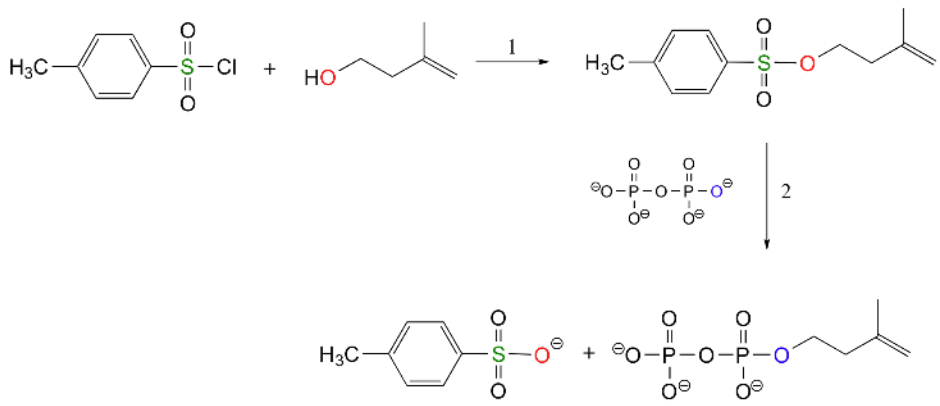


Notice that unlike the halogenation reactions of alcohols with thionyl chloride or phosphorous tribromide, conversion of an alcohol to a tosylate or mesylate proceeds with retention of configuration at the electrophilic carbon.

Tosylate/mesylate groups are excellent leaving groups in nucleophilic substitution reactions, due to resonance delocalization of the developing negative charge on the leaving oxygen.



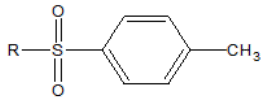
The laboratory synthesis of isopentenyl diphosphate - the 'building block' molecule used by nature for the construction of isoprenoid molecules such as cholesterol and b-carotene - was accomplished by first converting the alcohol into an organic tosylate (step 1), then displacing the tosylate group with an inorganic pyrophosphate nucleophile (step 2) (*J. Org. Chem* **1986**, *51*, 4768).



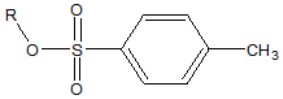
The major reactive species of tosylate chemistry are summarized below.

Tosyl Groups

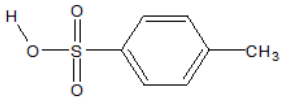
Ts
tosyl group



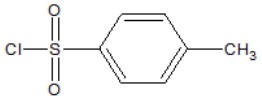
ROTs
tosylate ester



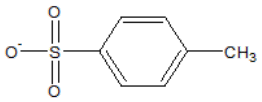
TsOH or p-TSA
tosic acid



TsCl
tosyl chloride

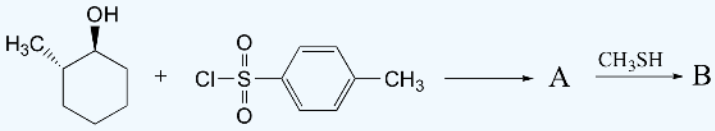


$^{-}$OTs
tosylate ion



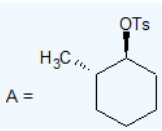
Exercise

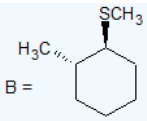
4. Predict the structures of A and B in the following reaction.



Answer

4.

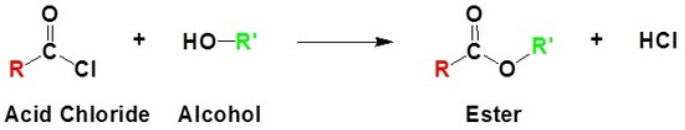






CONVERSION OF ALCOHOLS INTO ESTERS

Acid chlorides react with alcohols to form esters

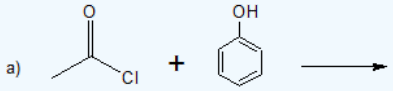


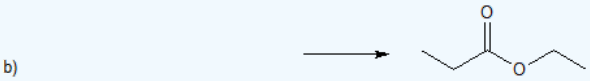
Example 14.3.1



Exercise

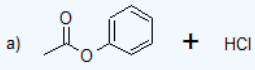
5. Predict the products or specify the reagents for the following reactions.

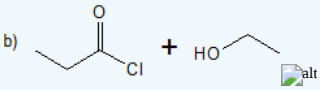




Answer

5.





CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

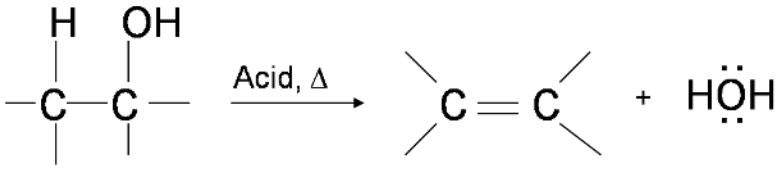
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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14.4: DEHYDRATION REACTIONS OF ALCOHOLS

DEHYDRATION OF ALCOHOLS TO YIELD ALKENES

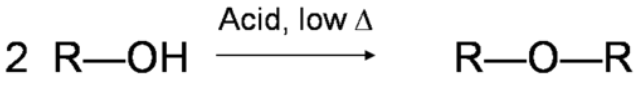
One way to synthesize alkenes is by dehydration of alcohols, a process in which alcohols undergo E1 or E2 mechanisms to lose water and form a double bond. The dehydration reaction of alcohols to generate alkene proceeds by heating the alcohols in the presence of a strong acid, such as sulfuric or phosphoric acid, at high temperatures.



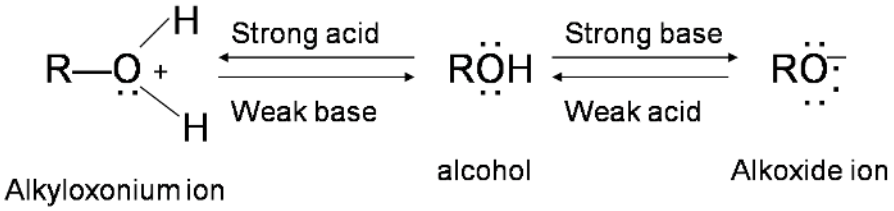
The required range of reaction temperature decreases with increasing substitution of the hydroxy-containing carbon:

- 1° alcohols: 170° - 180°C
- 2° alcohols: 100°– 140 °C
- 3° alcohols: 25°– 80°C

If the reaction is not sufficiently heated, the alcohols do not dehydrate to form alkenes, but react with one another to form ethers (e.g., the Williamson Ether Synthesis).



Alcohols are amphoteric; they can act as both acid or base. The lone pair of electrons on oxygen atom makes the –OH group weakly basic. Oxygen can donate two electrons to an electron-deficient proton. Thus, in the presence of a strong acid, R—OH acts as a base and protonates into the very acidic alkyloxonium ion +OH2 (The pKa value of a tertiary protonated alcohol can go as low as -3.8). This basic characteristic of alcohol is essential for its dehydration reaction with an acid to form alkenes.



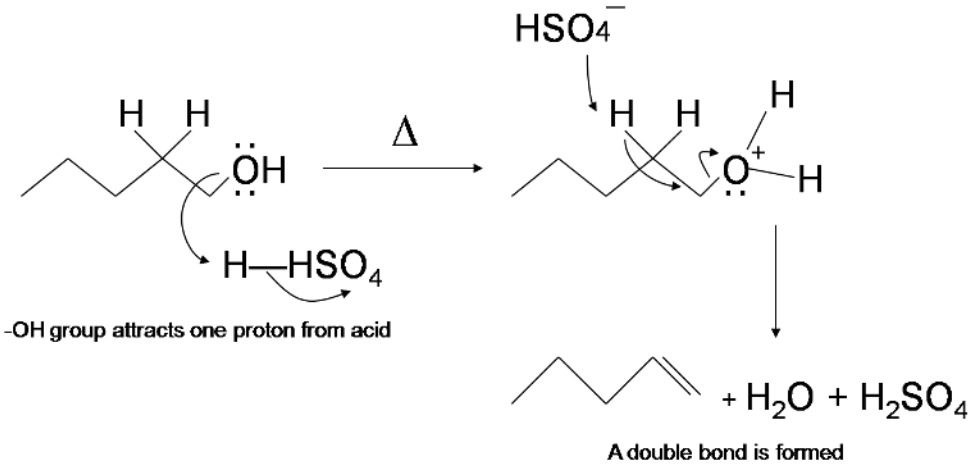
MECHANISM FOR THE DEHYDRATION OF ALCOHOL INTO ALKENE

Different types of alcohols may dehydrate through a slightly different mechanism pathway. However, the general idea behind each dehydration reaction is that the –OH group in the alcohol donates two electrons to H^+ from the acid reagent, forming an alkyloxonium ion. This ion acts as a very good leaving group which leaves to form a carbocation. The deprotonated acid (the base) then reacts with the hydrogen adjacent to the carbocation and form a double bond.

Primary alcohols undergo bimolecular elimination (E2 mechanism) while secondary and tertiary alcohols undergo unimolecular elimination (E1 mechanism). The relative reactivity of alcohols in dehydration reactions is ranked as follows:

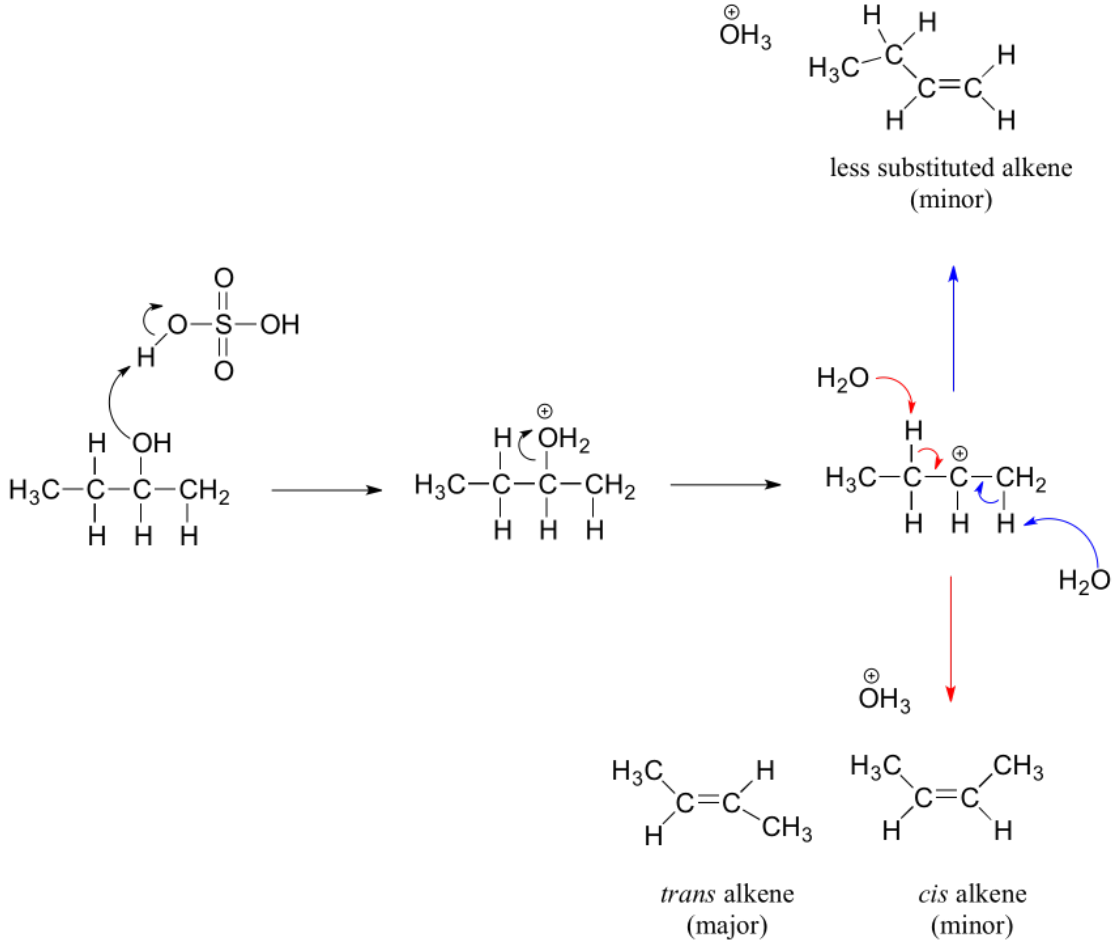
Methanol < *primary* < *secondary* < *tertiary*

Primary alcohols dehydrate through the E2 mechanism. The hydroxyl oxygen donates two electrons to a proton from sulfuric acid (H_2SO_4), forming an alkyloxonium ion. Then the conjugate base, HSO_4^-, reacts with one of the adjacent (beta) hydrogen atoms while the alkyloxonium ion leaves in a concerted process, forming a double bond.



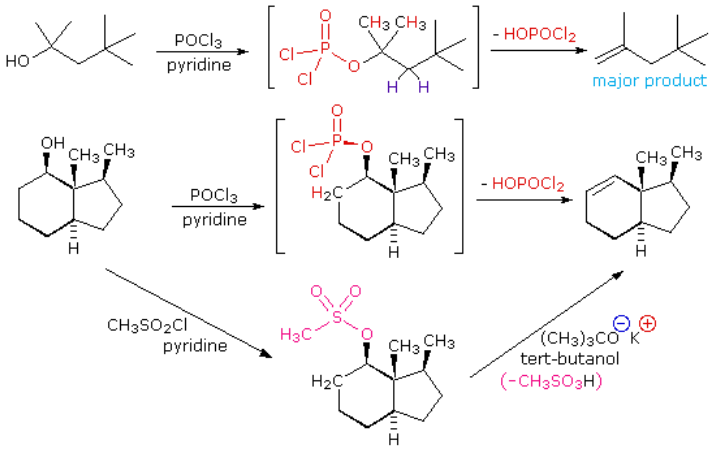
Secondary and tertiary alcohols dehydrate through the E1 mechanism. Similarly to the reaction above, secondary and tertiary –OH protonate to form alkyloxonium ions. However, in this case the ion leaves first and forms a carbocation as the reaction intermediate. The water molecule (which is a stronger base than the HSO_4^- ion) then abstracts a proton from an adjacent carbon to form a double bond. Notice in the mechanism below that the alkene formed depends on which proton is abstracted: the red arrows show formation of the more substituted 2-butene, while the blue arrows show formation of the less substituted 1-butene. Recall that according to Zaitsev's Rule, the more substituted alkenes are formed preferentially because they are more stable than less substituted alkenes. Additinally, trans alkenes are more stable than cis alkenes and are also the major product formed. For the example below, the trans diastereomer of the 2-butene product is most abundant.

DEHYDRATION REACTION OF SECONDARY ALCOHOL



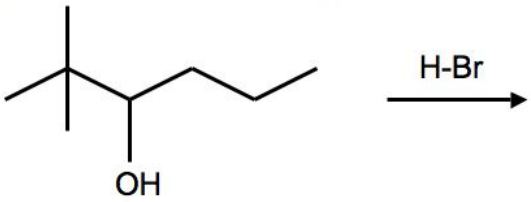
The dehydration mechanism for a tertiary alcohol is analogous to that shown above for a secondary alcohol.

The E2 elimination of 3º-alcohols under relatively non-acidic conditions may be accomplished by treatment with phosphorous oxychloride ($POCl_3$) in pyridine. This procedure is also effective with hindered 2º-alcohols, but for unhindered and 1º-alcohols an S_N2 chloride ion substitution of the chlorophosphate intermediate competes with elimination. Examples of these and related reactions are given in the following figure. The first equation shows the dehydration of a 3º-alcohol. The predominance of the non-Zaitsev product (less substituted double bond) is presumed due to steric hindrance of the methylene group hydrogen atoms, which interferes with the approach of base at that site. The second example shows two elimination procedures applied to the same 2º-alcohol. The first uses the single step POCl3 method, which works well in this case because SN2 substitution is retarded by steric hindrance. The second method is another example in which an intermediate sulfonate ester confers halogen-like reactivity on an alcohol. In every case the anionic leaving group is the conjugate base of a strong acid.

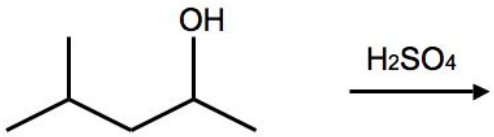


PRACTICE PROBLEMS (AKA EXERCISES)

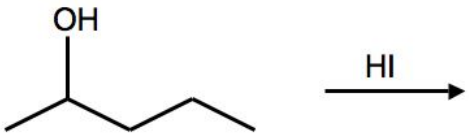
1) Please show the arrow pushing mechanism and the major final product:



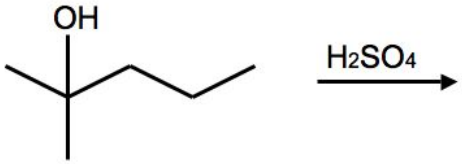
2) Please show the mechanism with **hydride shift** and show the final product:



3) Show both major and minor products of the given reaction:

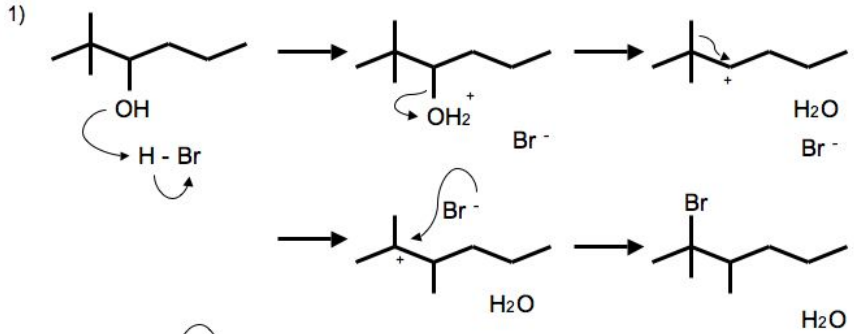


4) Show both major and minor products of the given reaction:

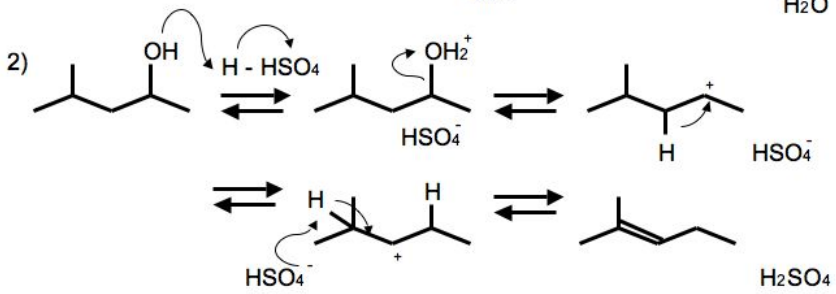


Answers to Practice Problems:

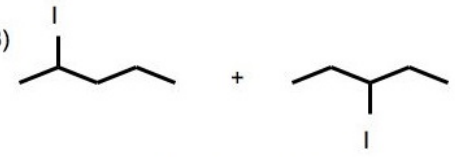
1)



2)



3)

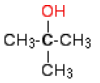


Equal amounts

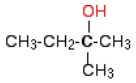
4)



Major product Minor product



2-methylpropan-2-ol

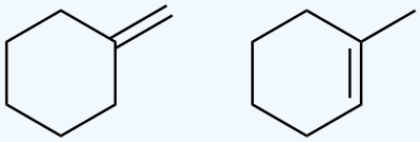


2-methylbutan-2-ol

Exercises

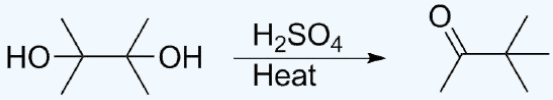
6. Starting with cyclohexanol, describe how you would prepare cyclohexene.

7. In the dehydration of 1-methylcyclohexanol, which product is favored?



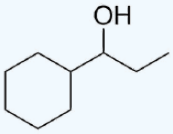
8.

In the dehydration of this diol the resulting product is a ketone. Draw the mechanism of its formation. (Hint a rearrangement occurs)



9.

Draw an arrow pushing mechanism for the acid catalyzed dehydration of the following alcohol, make sure to draw both potential mechanisms. Assume no rearrangement for the first two product mechanisms. Which of these two would likely be the major product? If there was a rearrangement, draw the expected major product.



Answer

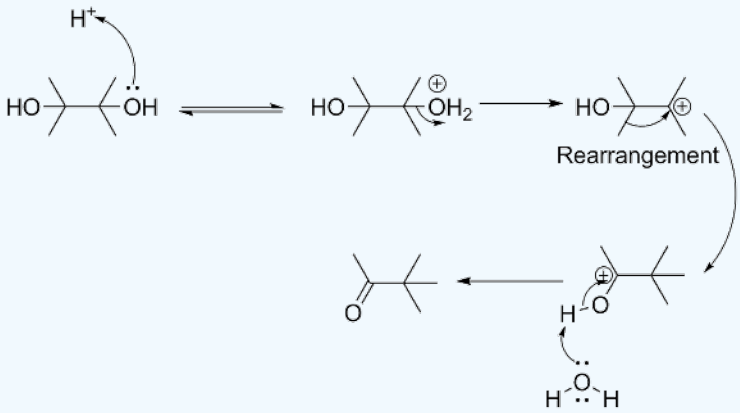
6. H_2SO_4 with heat since there are no concerns about C+ rearrangement

7. The more substituted alkene is favored, as more substituted alkenes are relatively lower in energy.



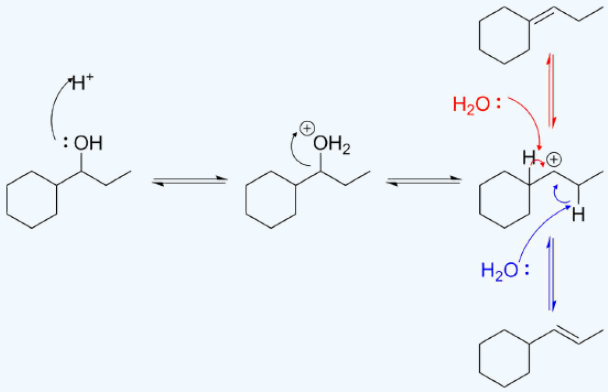
8.

This reaction is known as the Pinacol rearrangement.



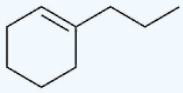
Note how the carbocation after the rearrangement is resonance stabilized by the oxygen

9. Note: While the mechanism is instructive for the first part of the this answer. The carbocation rearrangement would occur and determine the major and minor products as explained in the second part of this answer.



The major product of this mechanism would be the more highly substituted alkene, or the product formed from the red arrows.

Note: With the secondary carbocation adjacent a tertiary carbon center, a 1,2 hydride shift (rearrangement) would occur to form a tertiary carbocation and vcompound below would be the major product. The minor product being the same product as the one formed from the red arrows.



CONTRIBUTORS AND ATTRIBUTIONS

- Jeffrey Ma

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14.5: OXIDATION STATES OF ALCOHOLS AND RELATED FUNCTIONAL GROUPS

INTRODUCTION

You are undoubtedly already familiar with the general idea of oxidation and reduction: you learned in general chemistry that when a compound or atom is oxidized it loses electrons, and when it is reduced it gains electrons. You also know that oxidation and reduction reactions occur in pairs: if one species is oxidized, another must be reduced at the same time - thus the term 'redox reaction'.

Most of the redox reactions you have seen previously in general chemistry probably involved the flow of electrons from one metal to another, such as the reaction between copper ion in solution and metallic zinc:

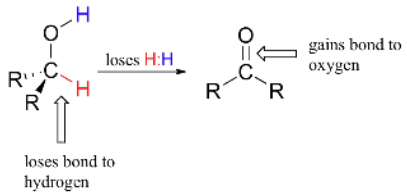
$$Cu^{+2}_{(aq)} + Zn_{(s)} \rightarrow Cu_{(s)} + Zn^{+2}_{(aq)} \tag{16.1.1}$$

In organic chemistry, redox reactions look a little different. Electrons in an organic redox reaction often are transferred in the form of a hydride ion - a proton and two electrons. Because they occur in conjunction with the transfer of a proton, these are commonly referred to as **hydrogenation** and **dehydrogenation** reactions: a hydride plus a proton adds up to a hydrogen (H_2) molecule. Be careful - do not confuse the terms **hydrogenation** and **dehydrogenation** with **hydration** and **dehydration** - the latter refer to the gain and loss of a *water* molecule (and are *not* redox reactions), while the former refer to the gain and loss of a *hydrogen* molecule.

OXIDATION AND REDUCTION - THE ORGANIC CHEMISTRY VIEW

When a carbon atom in an organic compound loses a bond to hydrogen and gains a new bond to a heteroatom (or to another carbon), we say the compound has been dehydrogenated, or oxidized. A very common biochemical example is the oxidation of an alcohol to a ketone or aldehyde:

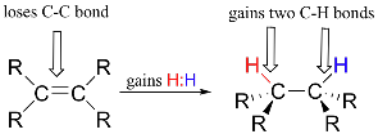
Dehydrogenation (oxidation) of an alcohol



When a carbon atom loses a bond to hydrogen and gains a bond to a heteroatom (or to another carbon atom), it is considered to be an oxidative process because hydrogen, of all the elements, is the least electronegative. Thus, in the process of dehydrogenation the carbon atom undergoes an overall loss of electron density - and loss of electrons is oxidation.

Conversely, when a carbon atom in an organic compound gains a bond to hydrogen and loses a bond to a heteroatom (or to another carbon atom), we say that the compound has been hydrogenated, or reduced. The hydrogenation of a ketone to an alcohol, for example, is overall the reverse of the alcohol dehydrogenation shown above. Illustrated below is another common possibility, the hydrogenation (reduction) of an alkene to an alkane.

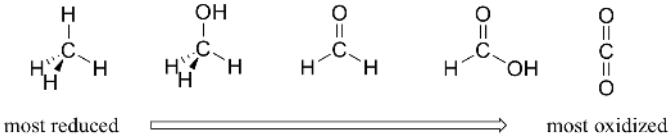
Hydrogenation (reduction) of an alkene



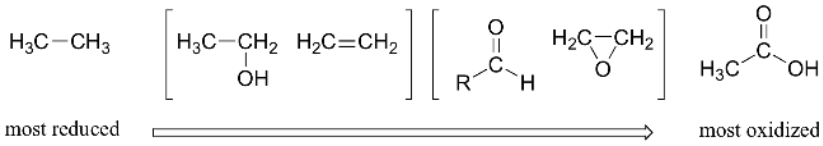
Hydrogenation results in *higher* electron density on a carbon atom(s), and thus we consider process to be one of reduction of the organic molecule.

Notice that neither hydrogenation nor dehydrogenation involves the gain or loss of an oxygen *atom*. Reactions which *do* involve gain or loss of one or more oxygen atoms are usually referred to as 'oxygenase' and 'reductase' reactions.

For the most part, when talking about redox reactions in organic chemistry we are dealing with a small set of very recognizable functional group transformations. It is therefore very worthwhile to become familiar with the idea of 'oxidation states' as applied to organic functional groups. By comparing the relative number of bonds to hydrogen atoms, we can order the familiar functional groups according to oxidation state. We'll take a series of single carbon compounds as an example. Methane, with four carbon-hydrogen bonds, is highly reduced. Next in the series is methanol (one less carbon-hydrogen bond, one more carbon-oxygen bond), followed by formaldehyde, formate, and finally carbon dioxide at the highly oxidized end of the group.



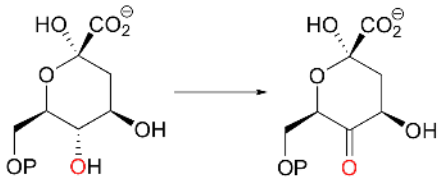
This pattern holds true for the relevant functional groups on organic molecules with two or more carbon atoms:



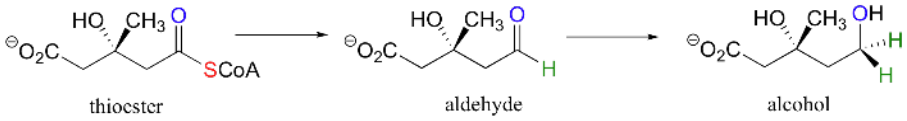
Alkanes are highly reduced, while alcohols - as well as alkenes, ethers, amines, sulfides, and phosphate esters - are one step up on the oxidation scale, followed by aldehydes/ketones/imines and epoxides, and finally by carboxylic acid derivatives (carbon dioxide, at the top of the oxidation list, is specific to the single carbon series).

Notice that in the series of two-carbon compounds above, ethanol and ethene are considered to be in the same oxidation state. You know already that alcohols and alkenes are interconverted by way of addition or elimination of water. When an alcohol is dehydrated to form an alkene, one of the two carbons loses a C-H bond and gains a C-C bond, and thus is oxidized. However, the other carbon loses a C-O bond and gains a C-C bond, and thus is considered to be reduced. Overall, therefore, there is no change to the oxidation state of the molecule.

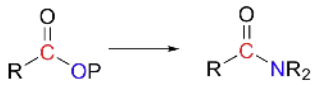
You should learn to recognize when a reaction involves a change in oxidation state in an organic reactant. Looking at the following transformation, for example, you should be able to quickly recognize that it is an oxidation: an alcohol functional group is converted to a ketone, which is one step up on the oxidation ladder.



Likewise, this next reaction involves the transformation of a carboxylic acid derivative (a thioester) first to an aldehyde, then to an alcohol: this is a *double* reduction, as the substrate loses two bonds to heteroatoms and gains two bonds to hydrogens.



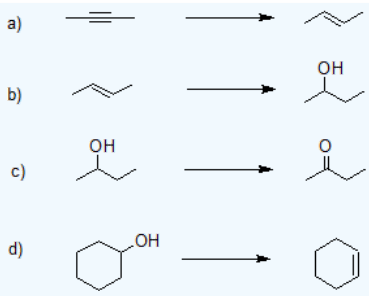
An acyl transfer reaction (for example the conversion of an acyl phosphate to an amide) is *not* considered to be a redox reaction - the oxidation state of the organic molecule is does not change as substrate is converted to product, because a bond to one heteroatom (oxygen) has simply been traded for a bond to another heteroatom (nitrogen).



It is important to be able to recognize when an organic molecule is being oxidized or reduced, because this information tells you to look for the participation of a corresponding redox agent that is being reduced or oxidized- remember, oxidation and reduction always occur in tandem! We will soon learn in detail about the most important biochemical and laboratory redox agents.

Exercises

10. Indicate whether the following reactions are oxidations [O], reductions [H], hydrations, or dehydrations.



Answer

10.

a) reduction

b) hydration

c) oxidation

d) dehydration

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

14.5: Oxidation States of Alcohols and Related Functional Groups is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

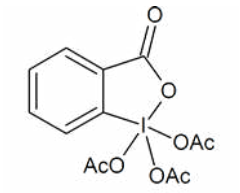
14.6: OXIDATION REACTIONS OF ALCOHOLS

OXIDIZING AGENTS

The oxidizing agent commonly shown is a solution of sodium or potassium dichromate(VI) acidified with dilute sulfuric acid. If oxidation occurs, the orange solution containing the dichromate(VI) ions is reduced to a green solution containing chromium(III) ions. The electron-half-equation for this reaction is

$$Cr_2O_7^{2-} + 14H^+ + 6e^- \rightarrow 2Cr^{3+} + 7H_2O \tag{17.7.1}$$

- $K_2C_r2O_7$ potassium dichromate
- CrO_3 Chromium Trioxide
- Pyridinium chlorochromate (PCC) is a milder version of chromic acid that is suitable for converting a primary alcohol into an aldehyde without oxidizing it all the way to a carboxylic acid. This reagent is being replaced in laboratories by Dess-Martin periodinane (DMP), which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous reaction conditions. DMP is named after Daniel Dess and James Martin, who developed it in 1983. Both reagents are used along with H_2SO_4, H_2O



Dess–Martin periodinane (DMP)

PRIMARY ALCOHOLS

Primary alcohols can be oxidized to either aldehydes or carboxylic acids depending on the reaction conditions. In the case of the formation of carboxylic acids, the alcohol is first oxidized to an aldehyde which is then oxidized further to the acid.

FULL OXIDATION TO CARBOXYLIC ACIDS

You need to use an excess of the oxidizing agent and make sure that the aldehyde formed as the half-way product stays in the mixture. The alcohol is heated under reflux with an excess of the oxidizing agent. When the reaction is complete, the carboxylic acid is distilled off. The full equation for the oxidation of ethanol to ethanoic acid is:

$$3CH_3CH_2OH + 2Cr_2O_7^{2-} + 16H+ \rightarrow 3CH_3COOH + 4Cr^{3+} + 11H_2O \tag{17.7.1}$$

The more usual simplified version looks like this:

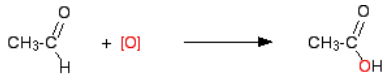
$$CH_3CH_2OH + 2[O] \rightarrow CH_3COOH + H_2O \tag{17.7.2}$$

Alternatively, you could write separate equations for the two stages of the reaction - the formation of ethanal and then its subsequent oxidation.

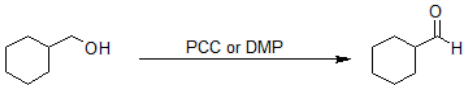
$$CH_3CH_2OH + [O] \rightarrow CH_3CHO + H_2O \tag{17.7.3}$$

$$CH_3CHO + [O] \rightarrow CH_3COOH \tag{17.7.4}$$

This is what is happening in the second stage:



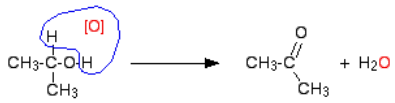
PARTIAL OXIDATION TO CARBOXYLIC ACIDS



SECONDARY ALCOHOLS

Secondary alcohols are oxidized to ketones - and that's it. For example, if you heat the secondary alcohol propan-2-ol with sodium or potassium dichromate(VI) solution acidified with dilute sulfuric acid, you get propanone formed. Playing around with the reaction

conditions makes no difference whatsoever to the product. Using the simple version of the equation and showing the relationship between the structures:

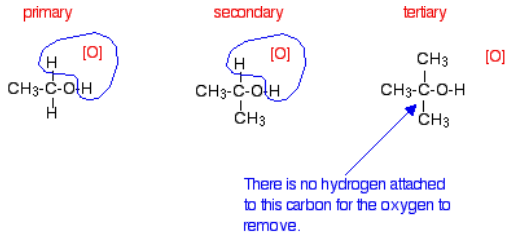


If you look back at the second stage of the primary alcohol reaction, you will see that an oxygen "slotted in" between the carbon and the hydrogen in the aldehyde group to produce the carboxylic acid. In this case, there is no such hydrogen - and the reaction has nowhere further to go.

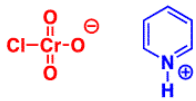
TERTIARY ALCOHOLS

Tertiary alcohols are not oxidized by acidified sodium or potassium dichromate(VI) solution - there is no reaction whatsoever. If you look at what is happening with primary and secondary alcohols, you will see that the oxidizing agent is removing the hydrogen from the -OH group, and a hydrogen from the carbon atom attached to the -OH. Tertiary alcohols don't have a hydrogen atom attached to that carbon.

You need to be able to remove those two particular hydrogen atoms in order to set up the carbon-oxygen double bond.



OXIDATION OF PRIMARY ALCOHOLS BY PCC - A CLOSER LOOK



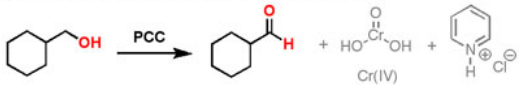
PCC (Pyridinium Chlorochromate)

Pyridinium chlorochromate (PCC) is a milder version of chromic acid.

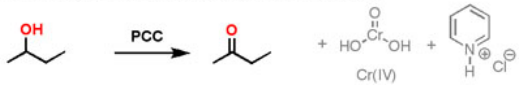
PCC oxidizes alcohols one rung up the oxidation ladder, from primary alcohols to aldehydes and from secondary alcohols to ketones. Unlike chromic acid, PCC will not oxidize aldehydes to carboxylic acids. Similar to or the same as: CrO_3 and pyridine (the Collins reagent) will also oxidize primary alcohols to aldehydes. Here are two examples of PCC in action.

- If you add one equivalent of PCC to either of these alcohols, you obtain the oxidized version. The byproducts (featured in grey) are Cr(IV) as well as pyridinium hydrochloride.
- One has to be careful with the amount of water present in the reaction. If water were present, it can ad to the aldehyde to make the hydrate, which could be further oxidized by a second equivalent of PCC were it present. This is not a concern with ketones, since there is no H directly bonded to C.

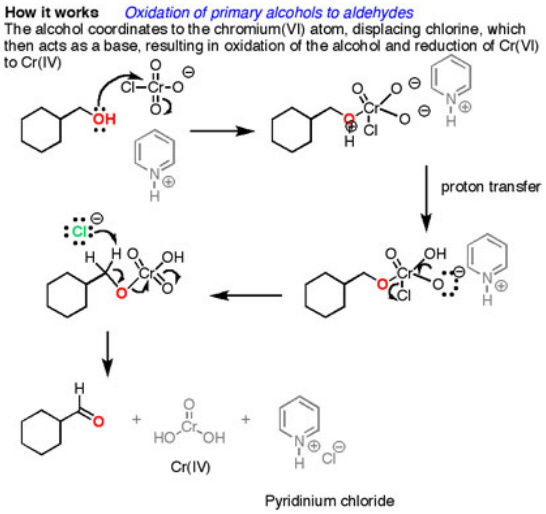
Example 1: Oxidation of primary alcohols to aldehydes



Example 2: Oxidation of secondary alcohols to ketones



How does it work? Oxidation reactions of this sort are actually a kind of elimination reaction. We're going from a carbon-oxygen single bond to a carbon-oxygen double bond. The elimination reaction can occur because we're putting a good leaving group on the oxygen, namely the chromium, which will be displaced when the neighboring C-H bond is broken with a base.

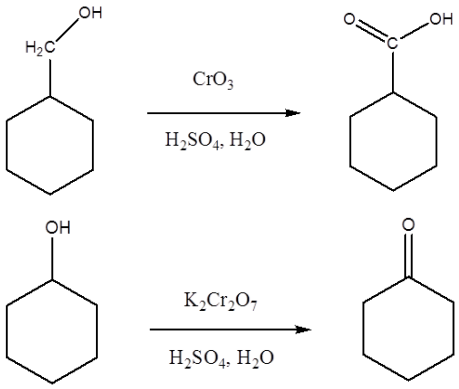


In the first step, the oxygen on the chromium reacts with the alcohol hydroxy group to form the Cr-O bond. Secondly, a proton on the (now positive) OH is transferred to one of the oxygens of the chromium, possibly through the intermediacy of the pyridinium salt. A chloride ion is then displaced, in a reaction reminiscent of a 1,2 elimination reaction, to form what is known as a chromate ester.

The C-O double bond is formed when a base removes the proton on the carbon adjacent to the oxygen. [aside: I've drawn the base as Cl^- although there are certainly other species which could also act as bases here (such as an alcohol). It is also possible for pyridine to be used as the base here, although only very low concentrations of the deprotonated form will be present under these acidic conditions.] The electrons from the C-H bond move to form the C-O bond, and in the process break the O-Cr bond, and Cr(VI) becomes Cr(IV) in the process (drawn here as O=Cr(OH)2).

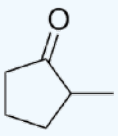
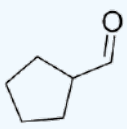
Real life notes: If you end up using PCC in the lab, don't forget to add molecular sieves or Celite or some other solid to the bottom of the flask, because otherwise you get a nasty brown tar that is a real major pain to clean up. The toxicity and mess associated with chromium has spurred the development of other alternatives like TPAP, IBX, DMP, and a host of other neat reagents you generally don't learn about until grad school.

EXAMPLES



Exercises

11. Draw the alcohol that the following ketones/aldehydes would have resulted from if oxidized. What oxidant could be used?

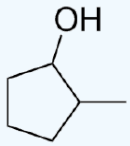
(a)  (b) 

12. Show the products of the oxidation of 1-propanol and 2-propanol with chromic acid in aqueous solution.

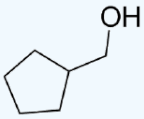
Answer

11. Any oxidant capable of oxidizing an alcohol to a ketone would work, such as the Jones reagent (CrO_3, H_2SO_4, H_2O), PCC, or Dess-Martin periodinane.

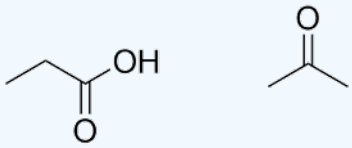
(a)



(b) Since this is a primary alcohol, there are some precautions necessary to avoid formation of the carboxyllic acid. Milder oxidants such as the Dess-Martin periodinane, and also PCC (there is no water to form the carboxyllic acid) would work.



12. The answers are correlated with the question.



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

James Ashenhurst (MasterOrganicChemistry.com)

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14.7: DETERMINING ALCOHOL CLASSIFICATIONS IN THE LAB - ALTERNATE REACTIONS

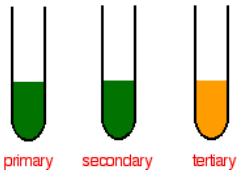
USING ALCOHOL REACTIVITY TO DISTINGUISH BETWEEN CLASSIFICATIONS

The presence of an alcohol can be determined with test reagents that react with the -OH group. The initial test to identify alcohols is to take the neutral liquid, free of water and add solid phosphorus(V) chloride. A a burst of acidic steamy hydrogen chloride fumes indicate the presence of an alcohol. Subsequent tests are needed to distinguish between alcohol classifications.

DETERMINING THE TERTIARY ALCOHOL

A few drops of the alcohol are added to a test tube containing potassium dichromate(VI) solution acidified with dilute sulfuric acid. The tube is warmed in a hot water bath.

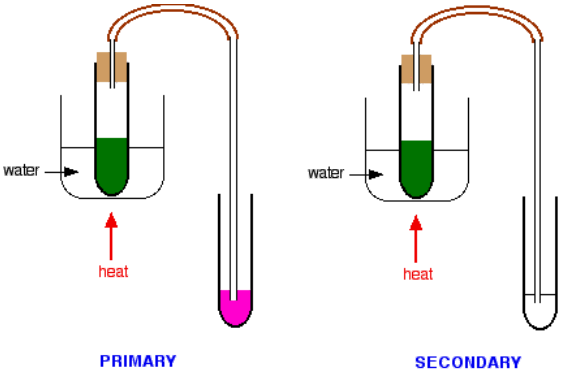
After heating, the following colors are observed:



In the case of a primary or secondary alcohols, the orange solution turns green. The Schiff's test will need to be performed to distinguish between the primary and secondary alcohols. With a tertiary alcohol, there is no color change.

SCHIFF'S REAGENT - DISTINGUISHING BETWEEN THE PRIMARY AND SECONDARY ALCOHOLS

Schiff's reagent is a fuchsian dye decolorized by passing sulfur dioxide through it. In the presence of even small amounts of an aldehyde, it turns bright magenta. It must, however, be used absolutely cold, because ketones react with it very slowly to give the same color. Heat obviously causes a faster color change, but is potentially confusing because of the competing ketone reaction. While warming the reaction mixture in the hot water bath, pass any vapors produced through some Schiff's reagent.



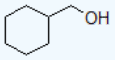
- If the Schiff's reagent quickly becomes magenta, then an aldehyde was produced from a primary alcohol.
- If there is no color change in the Schiff's reagent, or only a trace of pink color within a minute or so, then no aldehyde was produced and a primary alcohol is not present.

A secondary alcohol is identified by the color change with the acidified potassium dichromate(VI) solution and the absence of a color change with the Schiff's reagent might.

Exercise

13. The chromic acid oxidation test and Schiff's test are performed on the three alcohols shown below. Describe the expected test results.

a) 

b) 

c) 

Answer

13.

a) The chromic acid solution turns green, but the Schiff's reagent remains colorless.

b) The chromic acid solution turns green, and the Schiff's reagent turns magenta.

c) The chromic acid solution remains orance, and the Schiffs reagent remains colorless.

CONTRIBUTORS

- Jim Clark (Chemguide.co.uk)

14.7: Determining Alcohol Classifications in the Lab - alternate reactions is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

14.8: PROTECTION OF ALCOHOLS

INTRODUCTION

Often during the synthesis of complex molecules, one functional group in a molecule interferes with an intended reaction on a second functional group on the same molecule. An excellent example is the fact that a Grignard reagent can't be prepared from halo alcohol because the C-Mg bond is not compatible with the acidic -OH group.

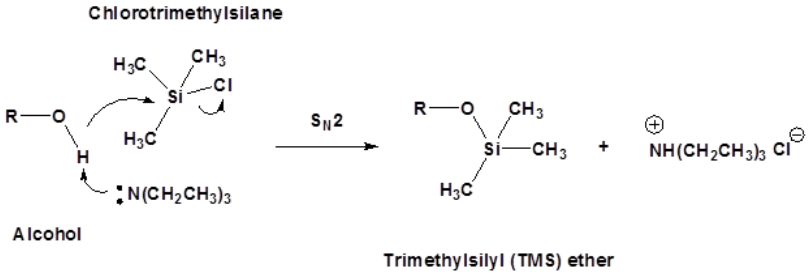
When situations like this occurs, chemists circumvent the problem by protecting the interfering functional group.

Functional group protection involves three steps:

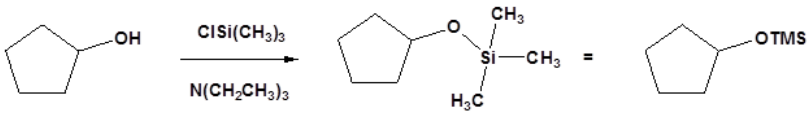
1. Blocking the interfering functionality by introducing a protecting group.
2. Performing the intended reaction.
3. Removing the protecting group and reforming the original functional group.

There are several methods for protecting an alcohol, however, the most common is the reaction with a chlorotrialkylsilane, Cl-SiR_3 This reactions forms a trialkylsilyl ether, R'-O-SiR_3. Chlorotrimethylsilane is often used in conjuction with a base, such as triethylamine, The base helps to form the alkoxide anion and remove the HCl produced by the reaction.

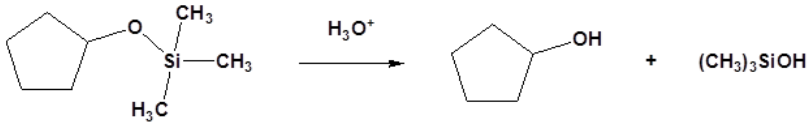
GENERAL REACTION



EXAMPLE

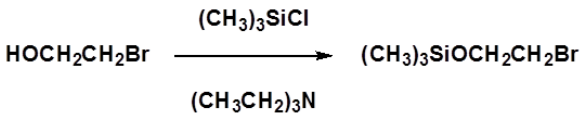


The silyl ether protecting group can be removed by reaction with an aqueous acid or the fluoride ion.

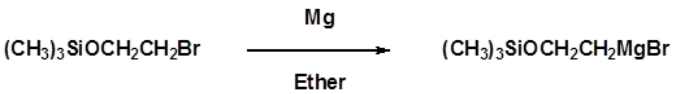


By utilizing a protecting group a Grignad reagent can be formed and reacted on a halo alcohol.

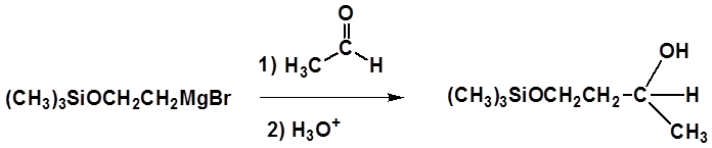
1) Protect the Alcohol



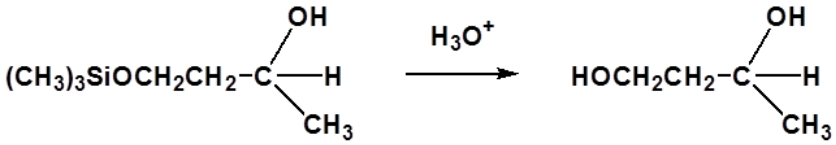
2) Form the Grignard Reagent



3) Perform the Grignard Reaction

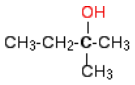


4) Deprotection





2-methylpropan-2-ol



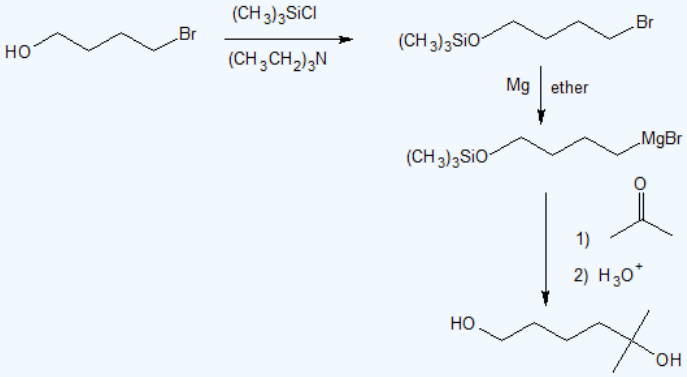
2-methylbutan-2-ol

Exercise

14. Propose a multiple-step synthesis to transform 4-bromo-1-butanol into 5-methylhexane-1,5-diol.

Answer

14.



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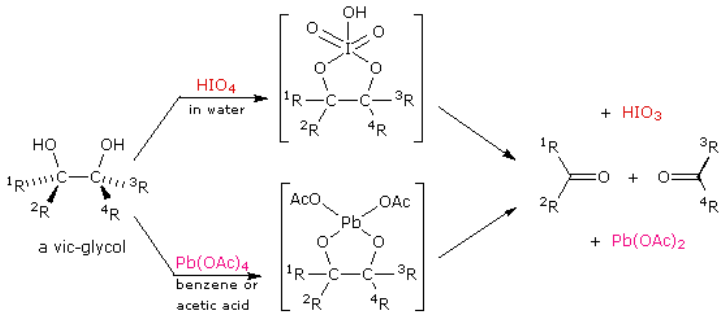
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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14.9: CLEAVAGE OF DIOLS

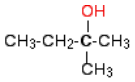
GLYCOL CLEAVAGE

The vicinal glycols prepared by alkene hydroxylation (reaction with osmium tetroxide or permanganate) are cleaved to aldehydes and ketones in high yield by the action of **lead tetraacetate** ($Pb(OAc)_4$) or **periodic acid** (HIO_4). This oxidative cleavage of a carbon-carbon single bond provides a two-step, high-yield alternative to ozonolysis, that is often preferred for small scale work involving precious compounds. A general equation for these oxidations is shown below. As a rule, cis-glycols react more rapidly than trans-glycols, and there is evidence for the intermediacy of heterocyclic intermediates (as shown), although their formation is not necessary for reaction to occur.





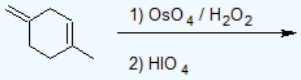
2-methylpropan-2-ol



2-methylbutan-2-ol

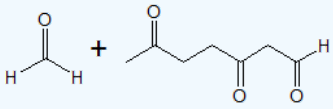
Exercise

15. Predict the product of the reaction below.



Answer

15.



CONTRIBUTORS AND ATTRIBUTIONS

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

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14.10: REACTIONS OF ALKOXIDES

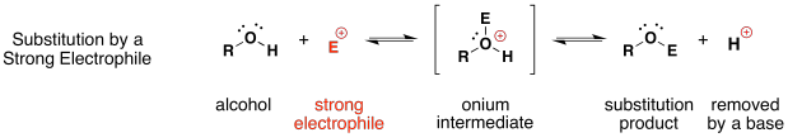
INTRODUCTION

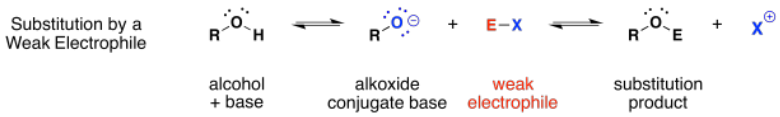
The hydrogen atom of a hydroxyl group is ionizable and can be replaced by other substituents as illustrated in the reactions below. The first reaction shows simple alcohols with sodium (and sodium hydride). The second reaction shows the isotopic exchange that occurs when mixing an alcohol with deuterium oxide (heavy water). This exchange, which is catalyzed by acid or base, is rapid under normal conditions because it is difficult to avoid traces of these catalysts in most experimental systems.

$$2\ R{-}O{-}H + 2\ Na \longrightarrow 2\ R{-}O^{(-)}Na^{(+)} + H_2$$

$$R{-}O{-}H + D_2O \rightleftharpoons R{-}O{-}D + D{-}O{-}H$$

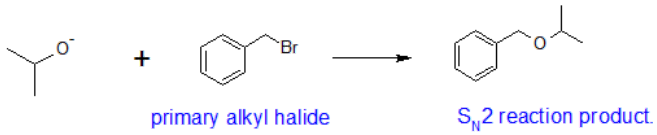
The mechanism by which these substitution reactions proceed is straightforward. The oxygen atom of an alcohol is nucleophilic; therefore, it is prone to react with electrophiles. The resulting "onium" intermediate then loses a proton to a base, forming the substitution product. If a strong electrophile is not present, then the nucleophilicity of the oxygen may be enhanced by conversion to its conjugate base (an alkoxide). This powerful nucleophile then reacts with weak electrophiles. These two variations of the substitution mechanism are illustrated in the following diagram.

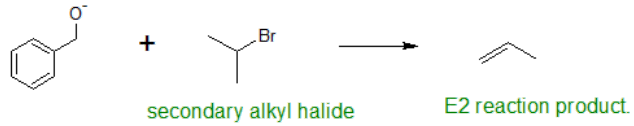




WILLIAMSON ETHER SYNTHESIS

Alkyl substitution of the hydroxyl group creates ethers. This reaction provides examples of both strong electrophilic substitution (first equation below) and weak electrophilic substitution (second equation). The latter S_N2 reaction is known as the **Williamson ether synthesis** and is generally only used with 1º alkyl halide reactants because the strong alkoxide base leads to E2 elimination with 2º and 3º alkyl halides.



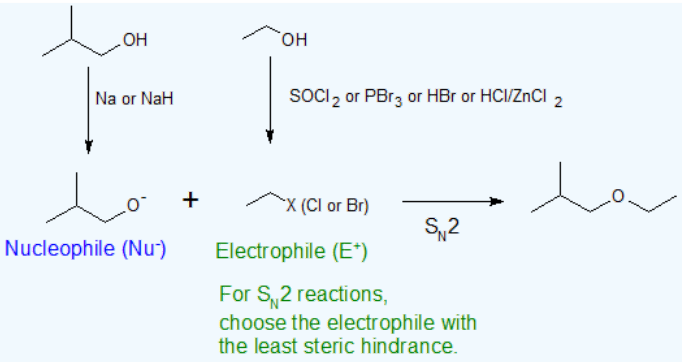


Exercise

16. Show how you would use the Williamson Ether synthesis to make 1-ethoxy-2-methylpropane from isobutyl alcohol and ethanol.

Answer

16.



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14.11: BIOLOGICAL OXIDATION - AN INTRODUCTION

FOUNDATION

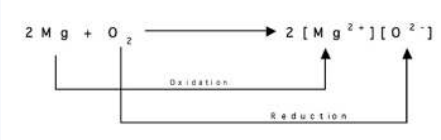
All reactions which involve electron flow are considered oxidation-reduction reactions. The basic definition can be defined as: One reactant is oxidized (loses electrons), while another is reduced (gains electrons). A couple of basic oxidation-reduction or "redox" example's are given here.

Example 1

The reaction of magnesium metal with oxygen, involves the oxidation of magnesium

$$2Mg(s) + O_2(g) \rightarrow 2MgO(s) \tag{14.11.1}$$

Since the magnesium solid is oxidized, we expect to see a loss of electrons. Similarly, since oxygen must therefore be reduced, we should see a gain of electrons.



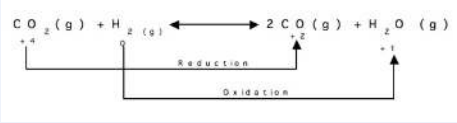
As the magnesium is oxidized there is a loss of 2 electrons while simultaneously, oxygen gains those two electrons. Another example of a redox reaction is with the two gasses CO_2 and H_2. This redox reaction also demonstrates the importance of implementing "oxidation numbers" in the methodology of redox reactions, allowing for the determination of which reactant is being reduced and which reactant is being oxidized.

Example 2

The reaction of carbon dioxide gas with hydrogen gas, involving the oxidation of hydrogen

$$CO_2(g) + H_2(g) \rightarrow 2CO(g) + H_2O(g) \tag{14.11.2}$$

Since the hydrogen gas is being oxidized (reductant), we expect to see an overall loss of electrons for the resulting molecule. Similarly, we expect to see a gain in the overall number of electrons for the resulting molecule of the oxidant (CO_2).



Here it is possible to infer that the carbon of CO_2 is being reduced by review of its unique oxidation number. Such that, C (of CO_2) goes from an oxidation number of +4 to C (of CO) having an oxidation number of +2, representing a loss of two electrons. Similarly, H_2 is noted as going from an oxidation number of 0 to +1, or gaining one electron in a reduction process. For more information on oxidation numbers, review the following link: Oxidation-Reduction Reactions

A BASIC BIOLOGICAL MODEL

The flow of electrons is a vital process that provides the necessary energy for the survival of all organisms. The primary source of energy that drives the electron flow in nearly all of these organisms is the radiant energy of the sun, in the form of electromagnetic radiation or Light. Through a series of nuclear reactions, the sun is able to generate thermal energy (which we can feel as warmth) from electromagnetic radiation (which we perceive as light). However, the particular wavelength of the electromagnetic spectrum we are able to detect with the human eye is only between 400 and 700 nm in wavelength. It should therefore be noted that the visible part of the electromagnetic spectrum is actually a small percentage of the whole; where a much greater percentage remains undetectable for the human eye.

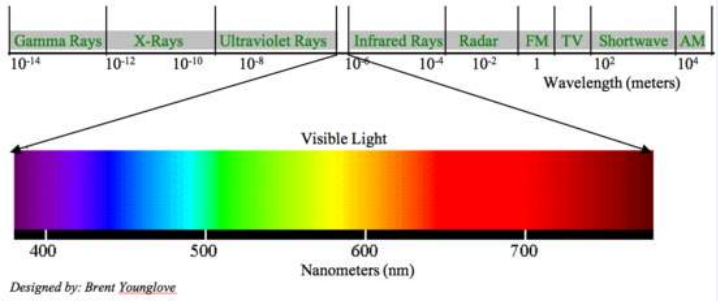


Figure 1: The electromagnetic spectrum with an emphasis on the visible light region

In physics, the use of the term "light" refers to electromagnetic radiation of any wavelength, independent of its detectability for the human eye. For plants, the upper and lower ends of the visible spectrum are the wavelengths that help drive the process of splitting water (H_2O) during photosynthesis, to release its electrons for the biological reduction of carbon dioxide (CO_2) and the release of diatomic oxygen (O_2) to the atmosphere. It is through the process of photosynthesis that plants are able to use the energy from light to convert carbon dioxide and water into the chemical energy storage form called glucose.

Plants represent one of the most basic examples of biological oxidation and reduction. The chemical conversion of carbon dioxide and water into sugar (glucose) and oxygen is a light-driven reduction process:

$$6CO_2 + 6H_2O \rightarrow C_6H_{12}O_6 + 6O_2 \tag{14.11.3}$$

The process by which non photosynthetic organisms and cells obtain energy, is through the consumption of the energy rich products of photosynthesis. By oxidizing these products, electrons are passed along to make the products carbon dioxide, and water, in an environmental recycling process. The process of oxidizing glucose and atmospheric oxygen allowed energy to be captured for use by the organism that consumes these products of the plant. The following reaction represents this process:

$$C_6H_{12}O_6 + O_2 \rightarrow 6CO_2 + 6H_2O + Energy \tag{14.11.4}$$

It is therefore through this process that heterotrophs (most generally "animals" which consume other organisms obtain energy) and autotrophs (plants which are able to produce their own energy) participate in an environmental cycle of exchanging carbon dioxide and water to produce energy containing glucose for organismal oxidation and energy production, and subsequently allowing the regeneration of the byproducts carbon dioxide and water, to begin the cycle again. Therefore, these two groups of organisms have been allowed to diverge interdependently through this natural life cycle.

PHYSICAL CHEMISTRY'S UNDERSTANDING

Biological oxidation-reduction reactions, or simply *biological oxidations* utilize multiple stages or processes of oxidation to produce large amounts of Gibbs energy, which is used to synthesize the energy unit called adenosine triphosphate or ATP. To efficiently produce ATP, the process of glycolysis must be near an abundance of oxygen. Since glycolysis by nature is not an efficient process, if it lacks sufficient amounts of oxygen the end product pyruvate, is reduced to lactate with NADH as the reducing agent. However, in a more favorable aerobic process, the degradation of glucose through glycolysis proceeds with two additional processes known as the *citric acid cycle* and the terminal *respiratory chain;* yielding the end products carbon dioxide and water, which we exhale with each breath.



Figure 2: The three main processes for the breakdown of glucose into carbon dioxide and water

The products NADH and $FADH_2$ formed during glycolysis and the citric acid cycle are able to reduce molecular oxygen (O_2) thereby releasing large amounts of Gibbs energy used to make ATP. The process by which electrons are transferred from NADH or $FADH_2$ to O_2 by a series of electron transfer carriers, is known as *oxidative phosphorylation*. It is through this process that ATP is able to form as a result of the transfer of electrons.

Thee specific examples of redox reactions that are used in biological processes, involving the transfer of electrons and hydrogen ions as follows. During some biological oxidation reactions, there is a simultaneous transfer of hydrogen ions with electrons (1). In other instances, hydrogen ions may be lost by the substance being oxidized while transferring only its electrons to the substance being reduced (2). A third type of biological oxidation might involve only a transfer of electrons (3). It should be noted that biological oxidation rarely proceeds in a direct manner, and generally involves complex mechanisms of several enzymes. The outline below recaps the three processes of biological oxidation stated above, in descending order.

Table 1: Transfer of hydrogen ions and electrons for the general reaction scheme of A + B with intermediate stage shown

Reactants	Intermediate Stage	Products
$AH_2 + B$	$[A + 2H^+ + 2e^- + B]$	$A + BH_2$
$AH_2 + B$	$[A + 2H^+ + 2e^- + B]$	$A + B^{2-} + 2H^+$
$A^{2-} + B$	$[A + 2e^- + B]$	$A + B^{2-}$

In the last stage of the metabolic process (the terminal respiratory chain), the sequence by which electrons are carried is determined by relative redox potentials. The carrier molecules used to transfer electrons in this stage are called cytochromes, which are an electron-carrying protein containing a heme group. The iron atom of each cytochrome molecule can exist either in the oxidized (Fe^{3+}) or reduced (Fe^{2+}) form. Within the terminal respiratory chain, each carrier molecule alternates between the reduced state and the oxidized state, with molecular oxygen as the final electron acceptor at the end.



Figure 3. The terminal respitory chain showing electron transport and phosphorylation. Electrons from the citric acid cycle are transferred from one carrier to another, where each carrier alternates between the reduced and oxidized state. Molecular oxygen represents the final electron acceptor.

It is through the knowledge of redox potentials, that the knowledge of biological processes can be further expanded. The standard reduction potential is denoted as $E^{o'}$ and is often based on the hydrogen electrode scale of pH 7, rather than pH 0, a common reference point for listed values. Moreover, the superscript symbol (^{o}) denotes standard-state conditions, while the adjacent superscript symbol (') denotes the pH scale of 7 for biochemical processes.

It therefore becomes possible to trace the energy transfer in cells back to the fundamental flow of electrons from one particular molecule to another. Where this electron flow occurs via the physics principle of higher potential to lower potential; similar to a ball rolling down a hill, as opposed to the opposite direction. All of these reactions involving electron flow can be attributed to the basic definition of the oxidation-reduction pathway stated above.

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1. Chang, Raymond. *PHYSICAL CHEMISTRY for the Chemical and Biological Sciences* . 3rd. Sausalito, CA: University Science Books , 373-389. Print.
2. Nelson, David, and Michael Cox. *LEHNINGER PRINCIPLES OF BIOCHEMISTRY* . 5th . New York, NY: Freeman and Company, 22. Print.

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- Brent Younglove (Hope)

DS — DekiScript —
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14.12: ADDITIONAL EXERCISES

14-1 What is the IUPAC name for the product of the following reaction?



a) 1-(3-methylcyclopentyl)ethan-1-ol

b) (3-methylcyclopentyl)acetaldehyde

c) 1-(3-methylcyclopentyl)ethan-1-one

d) 1-(3-methylcyclopentyl)ethane-1,2-diol

14-2 Convert 3-chlorocyclohexanol to the following products. Any of these products can be used as the reactant in any subsequent part.

(a) 3-chlorocyclohexane

(b) 3-chlorocyclohexyl tosylate

(c) 3-chlorohexanone

d) sodium 3-chlorocyclohexan-1-olate

(e) 3-chloro-1-methylcyclohexanol

(f) 1-bromo-3-chlorocyclohexane

(g) 3-chlorocyclohexyl acetate

(h) 1-chloro-3-ethoxycyclohexane

14-3 Show how you would synthesis the chloride, bromide, and iodide from the corresponding alcohols

(a) 1-halopentane (halo=chloro, bromo, iodo)

(b) halocyclobutane

(c) 1-halo-1-ethylcyclopentane

(d) 1-halo-2-propylcyclopentane

14-4 Predict the major products of the following reactions. Clearly indicate stereochemistry where appropriate.

(a) (R)-pentan-2-ol + TsCl in pyridine

(b) (R)-2-pentyl tosylate + NaBr

(c) cyclopentanol + CrO3/H2SO4

(d) 2-cyclopenttylethanol +CrO3.pyridine.HCl

(e) 2-cyclopenttylethanol+ CrO3/H2SO4

(f) 1-propanol + HCl/ZnCl2

(g) 2-methylpropan-2-ol +HBr

(h) ethanol + CH3MgCl

(i) potassium *tert*-butoxide + ethyl iodide

(j) tert-butyl tosylate + sodium ethoxide

(k) 1-methylcyclohexanol + H2SO4/heat

(l) product from (k) + OsO4/H2O2, then HIO4

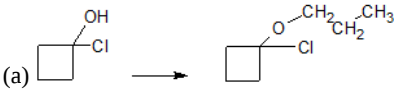
(m) sodium cyclohexoxide + 1-iodopropane

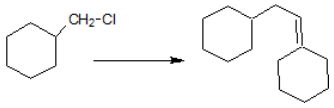
(n) sodium ethoxide + isopropyl tosylate

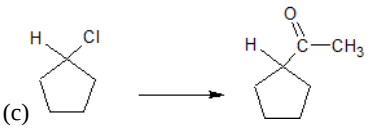
(o) cyclopentylmethanol + DMSO+ oxalyl chloride

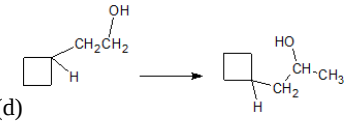
(p) cyclopropanol + DMP reagent

14-5 Propose an efficient synthesis for each of the following transformation

(a) 

(b) 

(c) 

(d) 

14-6 Predict the major products of sulfuric acid catalyzed dehydration

(a) butan-1-ol

(b) 2-methyl-3-pentanol

(c) cyclohexanol

(d) 1-cyclopentylethanol

(d) cyclohexylmethanol

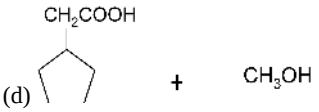
(e) 2-methylcyclohexanol

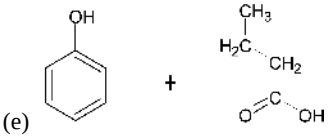
14-7 Predict the products of the following ester synthesis reactions

(a) $CH_3CH_2COOH + CH_3CH_2CH_2OH$

(b) $CH_3CH_2OH + HNO_3$

(c) $CH_3OH + H_3PO_4$

(d) 

(e) 

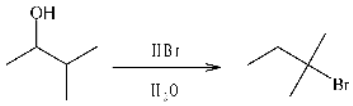
14-8 Show how you would convert (R)-2-pentanol to:

(a) (S)-2-chloropentane

(b) (R)-2-bromopentane

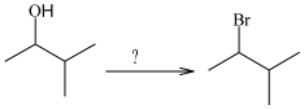
(c) (S)-2-pentanol

14-9 When 3-methyl-2-butanol reacts with concentrated aqueous HBr, the major product is 2-bromo-2-methylbutane



a) Propose a plausible mechanism for the above reaction

b) Show how you would convert 3-methyl-2-butanol into 2-bromo-3-methylbutane:



14-10 Predict the major products when trans-2-ethylcyclopentanol reacts with the following reagents. Include stereochemistry if necessary.

(a) PBr_3

(b) $SOCl_2$

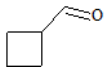
(c) Lucas reagent

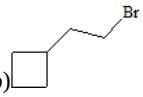
(d) concentrated HBr

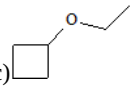
(e) TsCl/py then NaCN

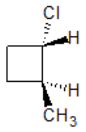
(f)TsCl/py then NaOEt

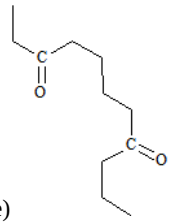
14-11 Using an alcohol of your choice, show how you would synthesis each following compound.

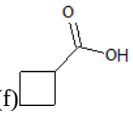
(a) 

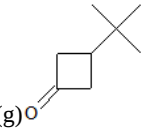
(b) 

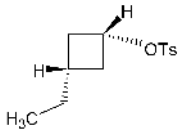
(c) 

(d) 

(e) 

(f) 

(g) 

(h) 

14-12 Describe chemical tests that can be used to distinguish the following pairs of compounds. Include the reagents, reaction conditions, observations, and chemical equations in your answers.

(a) 2-propanol and 2-methyl-2-propanol

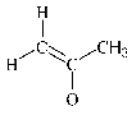
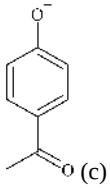
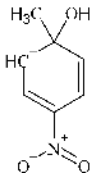
(b) 1-propanol and 2-propanol

(c) cyclopentanol and cyclopentene

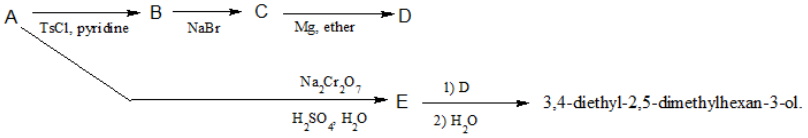
(d) cyclopentanol and 1-cyclopentylethanone

(e) cyclopentanone and 1-methylcyclopentanol

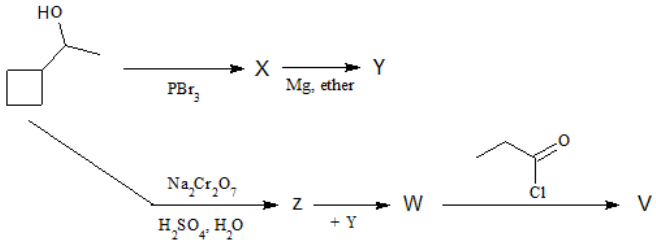
14-13 Draw important resonance structures for the following compounds

(a)  (b)  (c) 

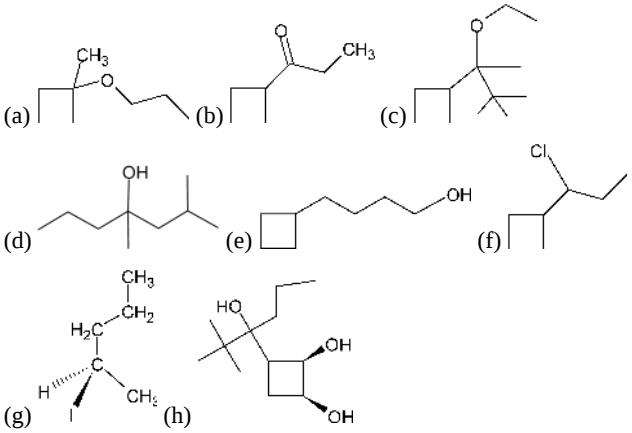
14-14 The following sequence of reaction transforms alcohol A to 3,4-diethyl-2,5-dimethylhexan-3-ol. Propose structure for compounds A, B, C, D, and E.



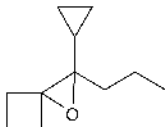
14-15 Consider the following transformation. Identify the structures of compound X, Y, Z, W, and V.



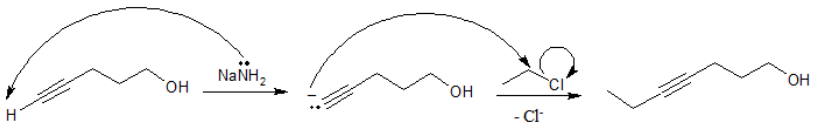
14-16 Show how each of the following compounds can be synthesized. You might use any alcohol containing five or fewer carbon atoms as your starting materials.



14-17 Show how you would synthesize the following compound. Only use alcohols containing four or fewer carbons as your organic materials. You might use any necessary solvents and inorganic reagents.



14-18



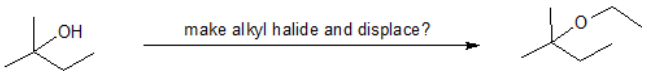
a) The above transformation does not work because of a common conceptual error. What is the conceptual error implicit in this transformation?

b) Show how you could accomplish the transformation in good yield?

14-19 X and Y are constitutional isomers of molecular formula C3H6O. Given the following results with four chemical test, propose structures and assign IUPAC names for X and Y.

	$SOCl_2$	**$K_2Cr_2O_7$**	**Br_2 (liquid)**	**Tollens' reagent**
Compound X	No Rxn	Orange -> Green	No Rxn	No Rxn
Compound Y	Bubbles	Orange -> Green	Decolorize	Grey precipitate of Silver

14-20 The Williamson ether synthesis converts an alkyl halide or tosylate to an ether. Would the following synthesis be possible? If not, explain why not and show an alternative synthesis that would be more likely to work.

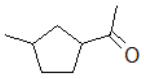


14.12: Additional Exercises is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

14.13: SOLUTIONS TO ADDITIONAL EXERCISES

14-1

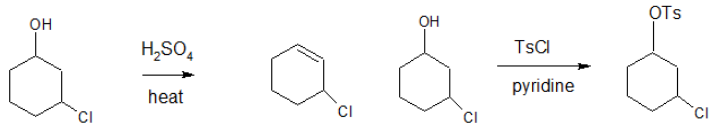
C.



1-(3-methylcyclopentyl)ethan-1-one

14-2

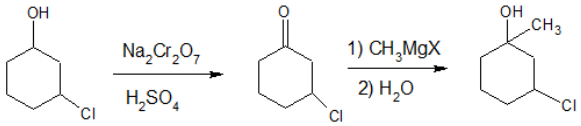
(a) (b)



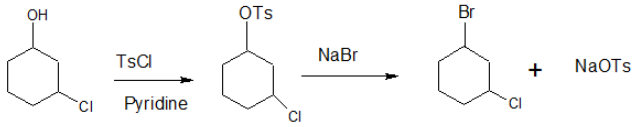
(c) (d)



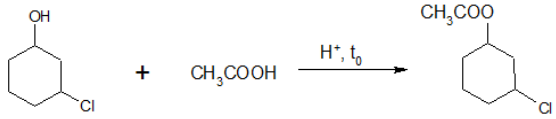
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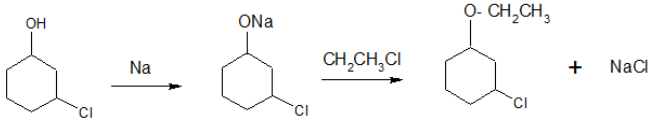
(f)



(g)

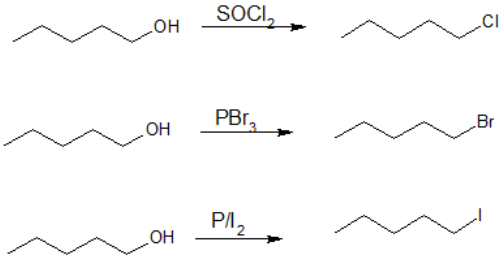


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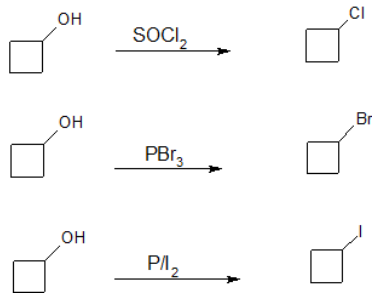


14-3

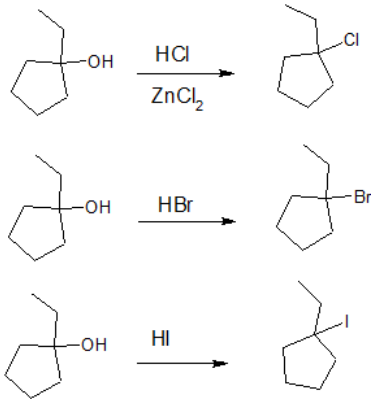
(a)



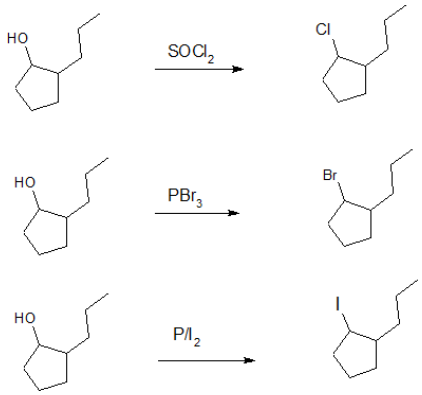
(b)


OH
SOCl2
Cl
OH
PBr3
Br
OH
PI2
I

(c)

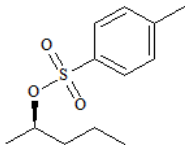

OH
HCl
ZnCl2
Cl
OH
HBr
Br
OH
HI
I

(d)

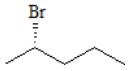

HO
SOCl2
Cl
HO
PBr3
Br
HO
PI2
I

14-4

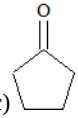
(a)

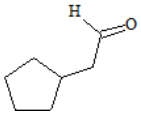

O
O
S
O

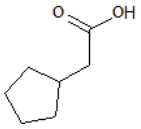
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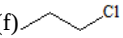

Br

(c)

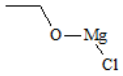

O

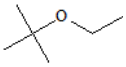
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(e) 

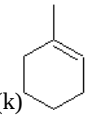
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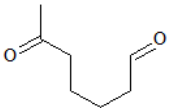
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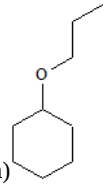
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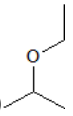
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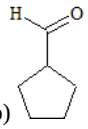
(j) 

(k) 

(l) 

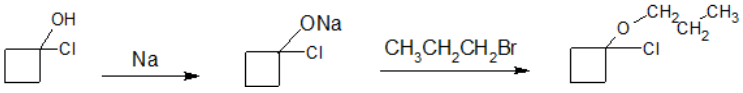
(m) 

(n) 

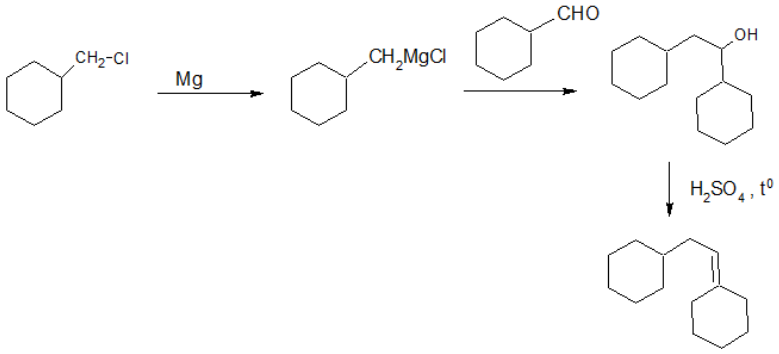
(o) 

(p) 

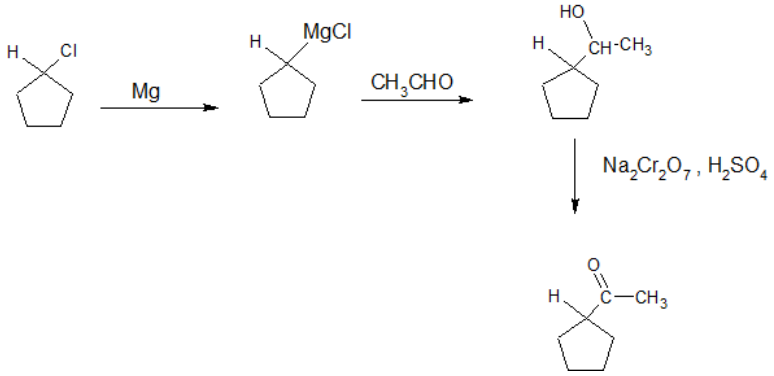
14-5

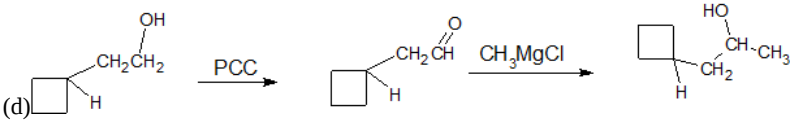
(a) 

(b)



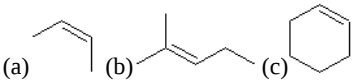
(c)



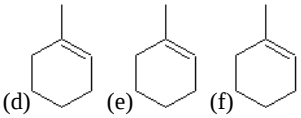


(d)

14-6



(a) (b) (c)

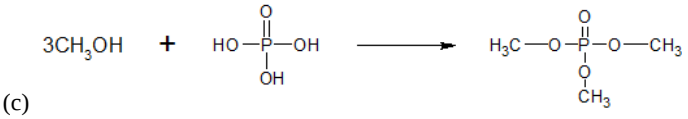


(d) (e) (f)

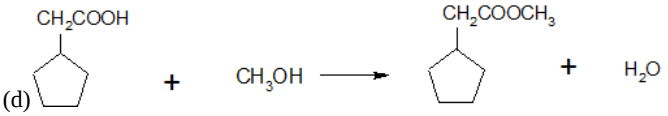
14-7

(a) $CH_3CH_2COOH + CH_3CH_2CH_2OH \longrightarrow CH_3CH_2COOCH_2CH_2CH_3$

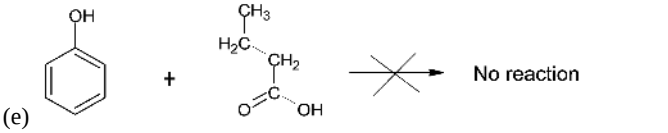
(b) $HNO_3 + CH_3CH_2OH \longrightarrow CH_3CH_2ONO_2 + H_2O$



(c)



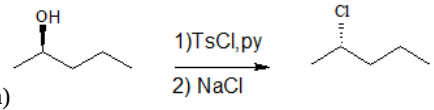
(d)



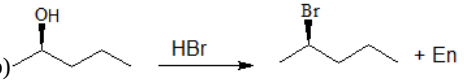
(e)

14-8

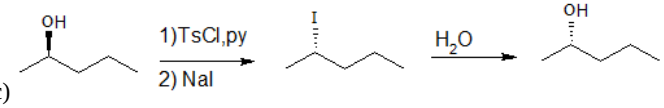
(a)



(b)

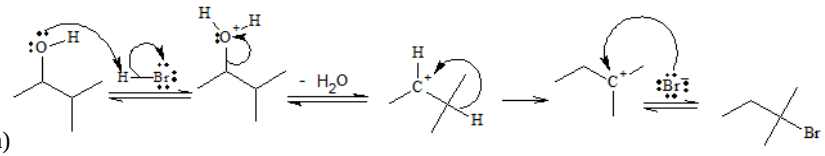


(c)

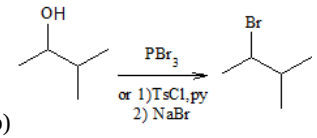


14-9

(a)

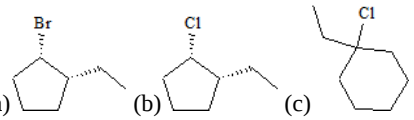


(b)

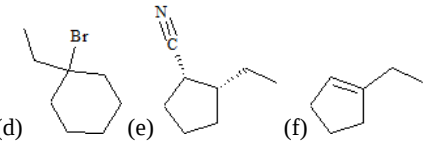


14-10

(a) (b) (c)

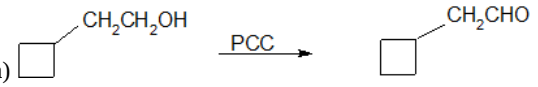


(d) (e) (f)

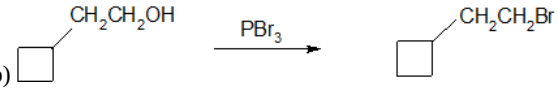


14-11

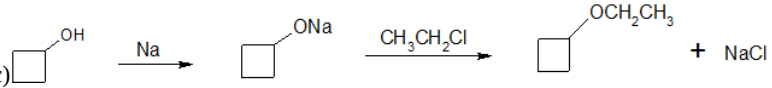
(a)



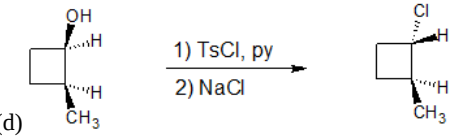
(b)



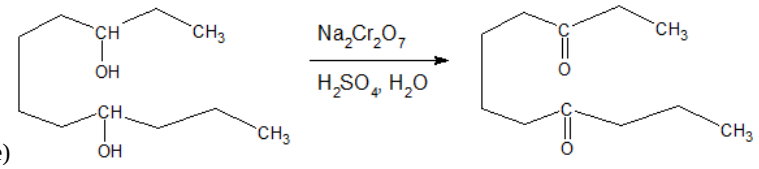
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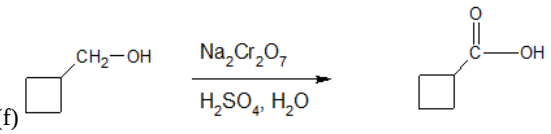


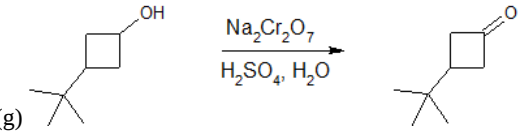
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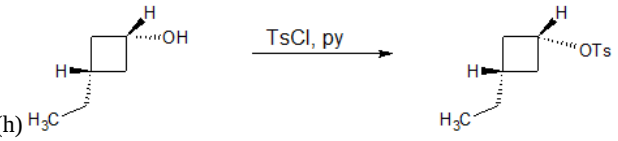


(e)



(f) 

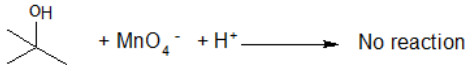
(g) 

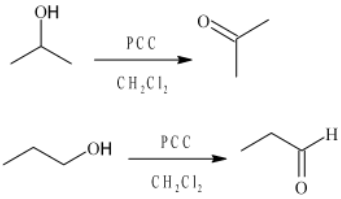
(h) 

14-12

(a) We can use potassium permanganate solution to distinguish between 2-propanol and 2-methyl-2-propanol. In acidic condition, KMnO4 oxidizes 2-propanol into acetone which forms the MnO2 brown precipitate and vanishes KMnO4 purple. As tertiary alcohol cannot be oxidized, 2-methyl-2-propanol remains purple.



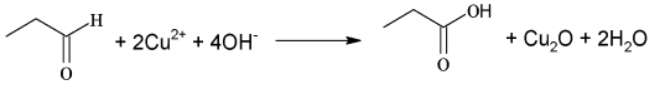


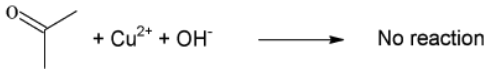


(b) 1-propanol and 2-propanol first need to be oxidized into propanal and acetone respectively.

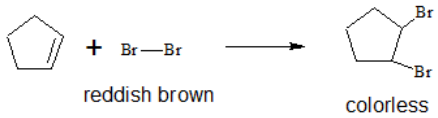
Note: we use pyridinium chlorochromate (PCC) in methylene chloride CH2Cl2 to produce aldehyde without further oxidation.

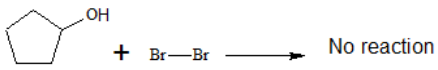
Fehling's test then can be used to determine the presence of an aldehyde. Propanal reacts with Fehling's reagent (Cu2+ in basic solution), forming a brick-red precipitate Cu2O, while acetone cannot react to Fehling's solution, remaining a deep transparent blue color.





(c) We can use Bromine test to distinguished between cyclopentanol and cyclopentene. Bromine reacts rapidly with cyclopentene, in which the reddish brown color disappears quickly without forming HBr gas bubble. Cyclopentanol does not react with bromine.

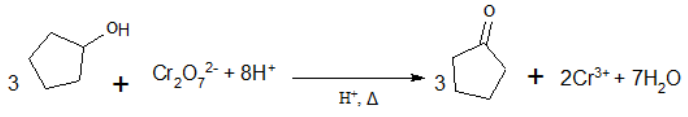


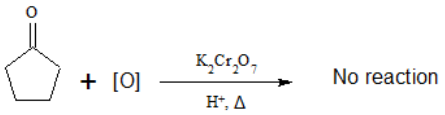


(d) Besides KMnO4, K2Cr2O7 in acidic condition is another oxidizing agent that can be used to distinguish between cyclopentanol and cyclopentanone. Acidified K2Cr2O7 oxidizes cyclopentanol into cyclopentanone. Evidence for the reaction is the orange solution

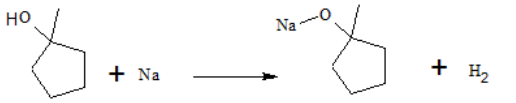
(Cr2O72-) turns green solution (Cr3+).

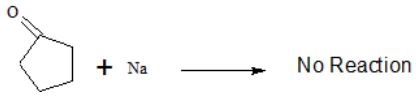
1-cyclopentylethanone cannot be oxidized, remaining the orange solution.





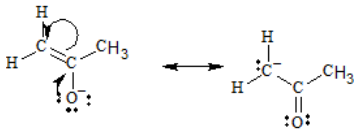
(e) Sodium metal can be used to distinguish between cyclopentanone and 1-methylcyclopentanol. 1-methylcyclopentanol reacts with Na, forming sodium 1-methylcyclopentanolate and releasing H2 bubbles. Cyclopentanone does not react with sodium metal.



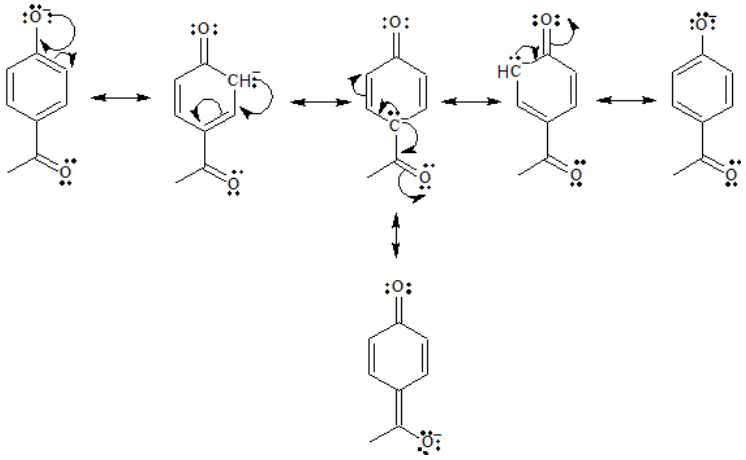


14-13

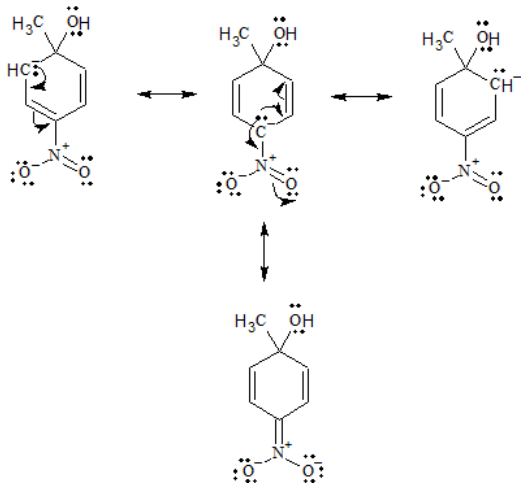
(a)



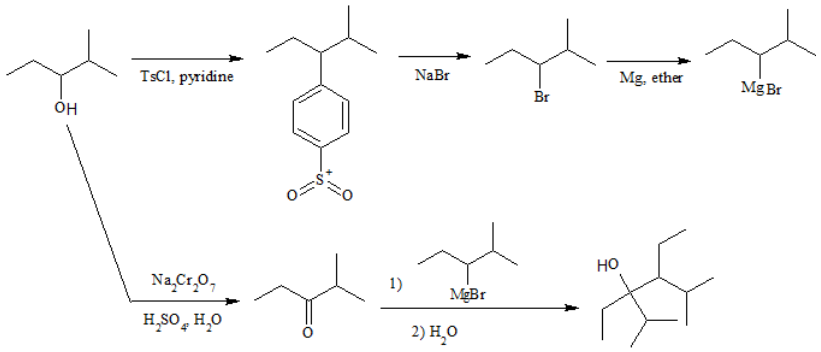
(b)



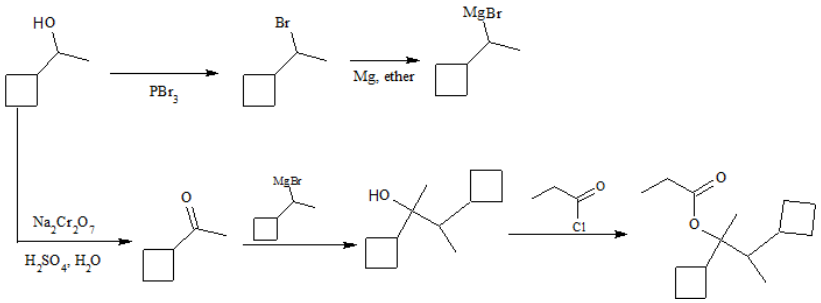
(c)



14-14

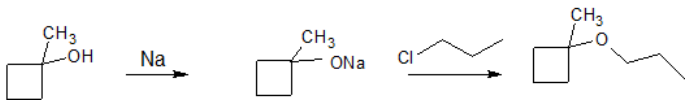


14-15

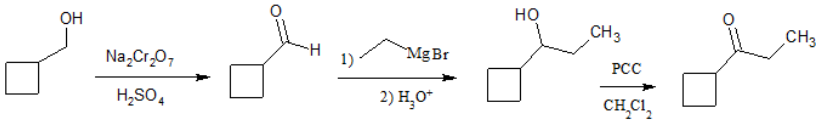


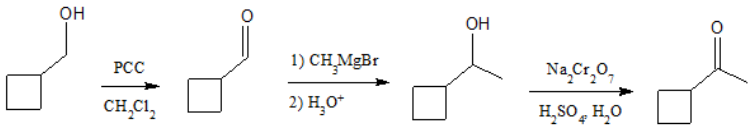
14-16

(a)

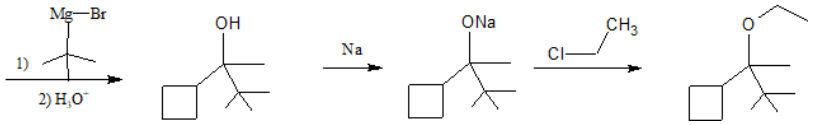


(b)

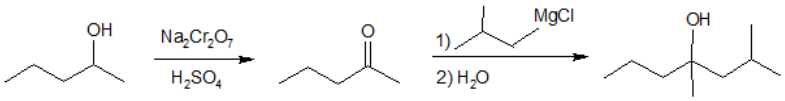



OH
PCC
CH_2Cl_2
O
1) CH_3MgBr
2) H_3O^+
OH
$Na_2Cr_2O_7$
H_2SO_4, H_2O
O

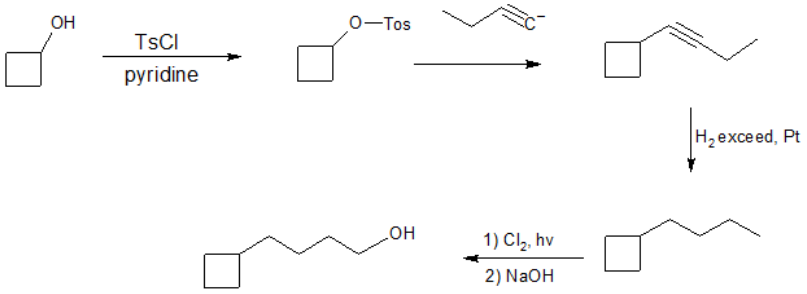
(c)


Mg—Br
1)
2) H_3O^-
OH
Na
ONa
Cl
CH_3
O

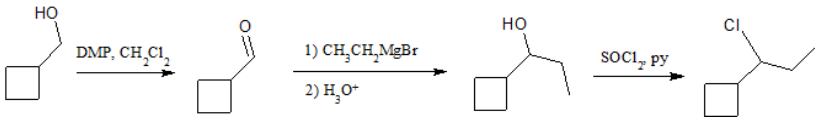
(d)


OH
$Na_2Cr_2O_7$
H_2SO_4
O
1)
MgCl
2) H_2O
OH

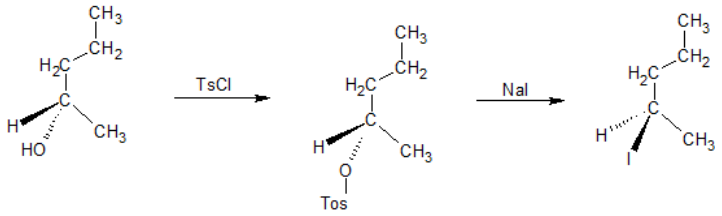
(e)


OH
TsCl
pyridine
O—Tos
C^-
H_2 exceed, Pt
OH
1) Cl_2, hv
2) NaOH

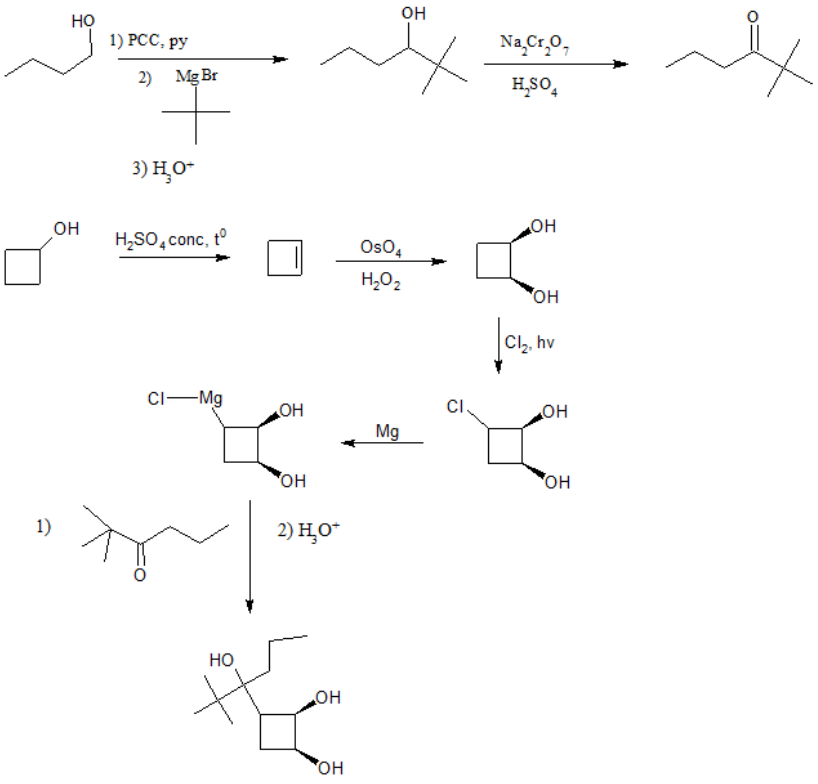
(f)


HO
DMP, CH_2Cl_2
O
1) CH_3CH_2MgBr
2) H_3O^+
HO
$SOCl_2$, py
Cl

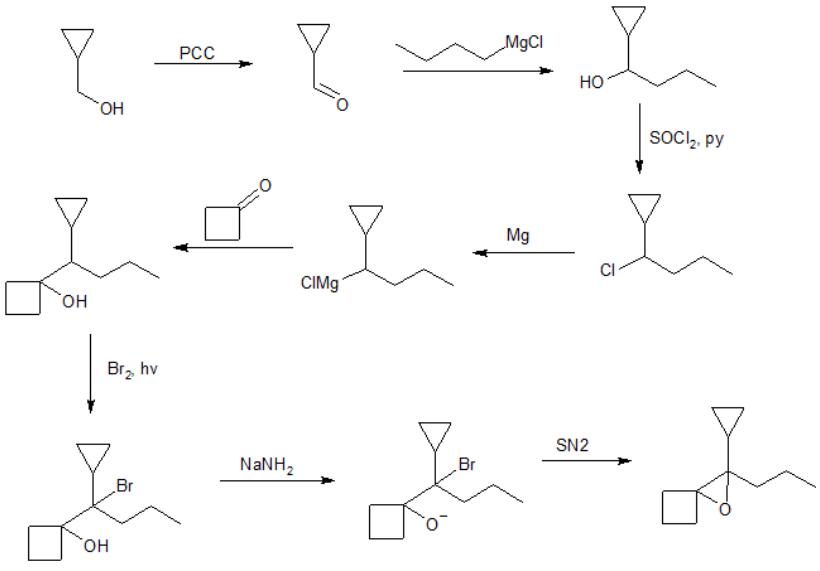
(g)


CH_3
CH_2
H_2C
C
H
HO
CH_3
TsCl
CH_3
CH_2
H_2C
C
H
CH_3
O
Tos
NaI
CH_3
CH_2
H_2C
C
H
I
CH_3

(h)


HO
1) PCC, py
2) MgBr
3) H3O+
OH
Na2Cr2O7
H2SO4
O
OH
H2SO4 conc, t0
OsO4
H2O2
OH
OH
Cl2, hv
Cl
Mg
OH
OH
Cl
Mg
OH
OH
1)
O
2) H3O+
HO
OH
OH

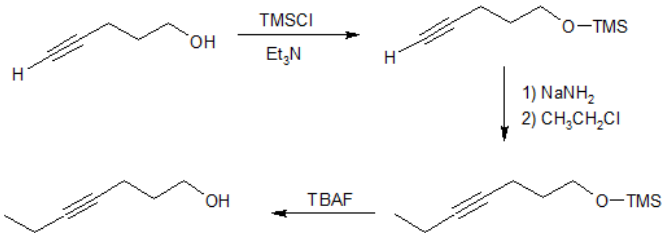
14-17


PCC
O
MgCl
HO
SOCl2, py
Cl
Mg
ClMg
O
OH
Br2, hv
Br
OH
NaNH2
Br
O−
SN2
O
OH
Na2Cr2O7
H2SO4
O
OH
SOCl2
py
Cl
+ Mg
MgCl

14-18

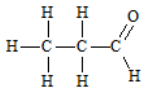
a) Alcohol functional group typically has pKa of 16 while the pKa of a terminal alkyne is usually about 25. The strong base NaNH2 would deprotonate the stronger acid, which in this case is the terminal alkyne. The resulting alkoxide then react with the alkyl halide CH3CH2Cl

b)



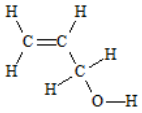
14-19

Compound X



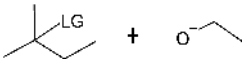
propanal

Compound Y

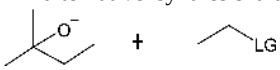


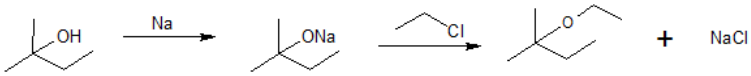
prop-2-en-1-ol

14-20

Williamson ether synthesis is an SN2 reaction, which favors strong nucleophile and a primary substrate for back-side attack. Since a tertiary alcohol is given, the resulting alkyl halide is also tertiary, which is sterically hindered for SN2 reaction to occur. 

The alkoxide then would function as a base, and an elimination reaction would happen instead of SN2 reaction.

An alternative synthesis that is more likely to occur involving the reaction between a tertiary alkoxide and a primary alkyl halide: 



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CHAPTER OVERVIEW

15: ETHERS, EPOXIDES AND THIOETHERS

LEARNING OBJECTIVES

After reading this chapter and completing ALL the exercises, a student can be able to

- predict relative boiling points and solubilities of ethers (refer to section 15.1)
- explain how ether solvents stabilize electrophilic reagents (refer to section 15.1)
- determine the structures of ethers from their spectra, and explain their characteristic absorptions and fragmentations (refer to section 15.2)
- devise efficient laboratory synthesis of ethers and epoxides, including:

a) Williamson ether synthesis (refer to section 15.3)

b) alkoximercuration-demercuration (refer to section 15.4)

c) peroxyacid epoxidation (refer to Chapter 9 section 12)

d) base-promoted cyclization of halohydrins (refer to section 15.7)

- predict the products or reactions of ethers and epoxides, including:

a) acidic cleavage of ethers (refer to section 15.5)

b) opening of epoxides (refer to section 15.8)

c) reactions of epoxides with organometallic reagents (refer to section 15.10)

- explain how Crown ethers solvate metal cations (refer to section 15.10)
- explain the reaction of epoxy monomers to form the adhesive resin (refer to section 15.11)
- describe the structure and reactive of sulfides (refer to section 15.12)
- use your knowledge of chemical reactivity to propose mechanisms and products for similar reactions you have never seen before (chapters to date)
- propose multiple-step syntheses using all of the reactions studied through this chapter (chapters to date)

Please note: IUPAC nomenclature and important common names of alcohols were explained in Chapter 3.

15.1: Physical Properties of Ethers
15.2: Spectroscopy of Ethers
15.3: The Williamson Ether Synthesis
15.4: Alkoxymercuration-Demercuration Synthesis of Ethers
15.5: Acidic Cleavage of Ethers
15.6: Autoxidation of Ethers
15.7: Synthesis of Epoxides
15.8: Opening of Epoxides
15.9: Reactions of Epoxides with Grignard and Organolithium Reagents
15.10: Crown Ethers
15.11: Epoxy Resins - The Advent of Modern Glues
15.12: Thioethers (Sulfides) and Silyl Ethers
15.13: Additional Exercises
15.14: Solutions to Additional Exercises

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15.1: PHYSICAL PROPERTIES OF ETHERS

COMPARISONS OF PHYSICAL PROPERTIES OF ALCOHOLS AND ETHERS

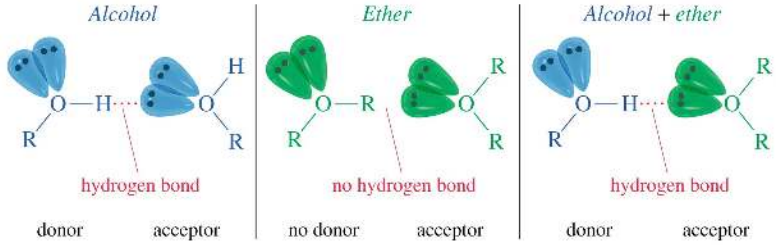
Ether molecules have no hydrogen atom on the oxygen atom (that is, no OH group). Therefore there is no intermolecular hydrogen bonding between ether molecules, and ethers therefore have quite low boiling points for a given molar mass. Ether molecules do have an oxygen atom, however, and engage in hydrogen bonding with water molecules. Consequently, an ether has about the same solubility in water as the alcohol that is isomeric with it. For example, dimethyl ether and ethanol (both having the molecular formula C_2H_6O) are completely soluble in water, whereas diethyl ether and 1-butanol (both $C_4H_{10}O$) are barely soluble in water (8 g/100 mL of water). Indeed, ethers have boiling points about the same as those of alkanes of comparable molar mass and much lower than those of the corresponding alcohols as shown in the table below.

Table. Comparison of Boiling Points of Alkanes, Alcohols, and Ethers

Condensed Structural Formula	Name	Molar Mass	Boiling Point (°C)	Intermolecular Hydrogen Bonding in Pure Liquid?
$CH_3CH_2CH_3$	propane	44	–42	no
CH_3OCH_3	dimethyl ether	46	–25	no
CH_3CH_2OH	ethyl alcohol	46	78	yes
$CH_3CH_2CH_2CH_2CH_3$	pentane	72	36	no
$CH_3CH_2OCH_2CH_3$	diethyl ether	74	35	no
$CH_3CH_2CH_2CH_2OH$	butyl alcohol	74	117	yes

ETHERS ARE GOOD SOLVENTS FOR MANY ORGANIC REACTIONS

Ethers can only accept H-bonds, while alcohols are both H-bond donors and acceptors. The ability of ethers to accept H-bonds combined with the London forces of the alkyl groups bonded to the oxygen allows ethers to be excellent solvents for a wide range of organic compounds. The low chemical reactivity of ethers also makes ethers a preferred solvent for many organic reactions. Additionally, the high volatility of ethers allows for their evaporation when isolating reaction products.



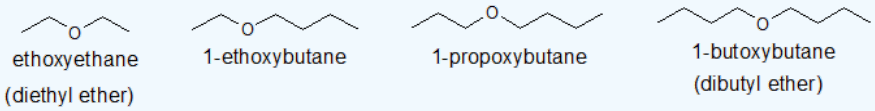
Exercise

1. Draw the bond-line structures and arrange the following ethers in order of increasing boiling point: 1-propoxybutane, diethyl ether, 1-ethoxybutane, dibutyl ether.

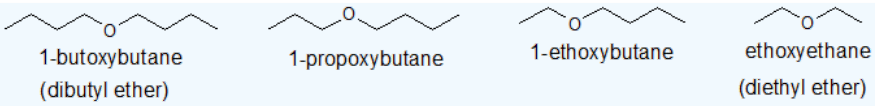
2. Arrange the following ethers in order of increasing water solubility: 1-propoxybutane, diethyl ether, 1-ethoxybutane, dibutyl ether.

Answer

1.



2.



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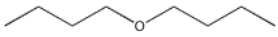
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

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15.2: SPECTROSCOPY OF ETHERS

INFRARED SPECTROSCOPY

Oxygen forms two bonds. An oxygen atom could be found in between two carbons, as in dibutyl ether.



dibutyl ether or butyl ether

If you look at an IR spectrum of dibutyl ether, you will see:

- there are the usual sp^3 C-H stretching and CH_2 bending modes at 2900 and 1500 cm^{-1}.
- there is a strong peak near 1000 cm^{-1}. This peak is due to the C-O stretching vibration.

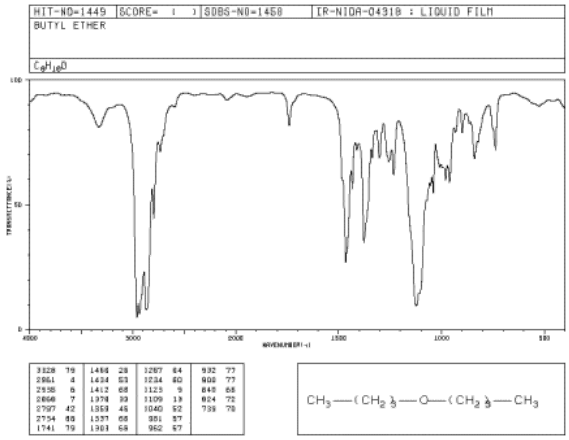
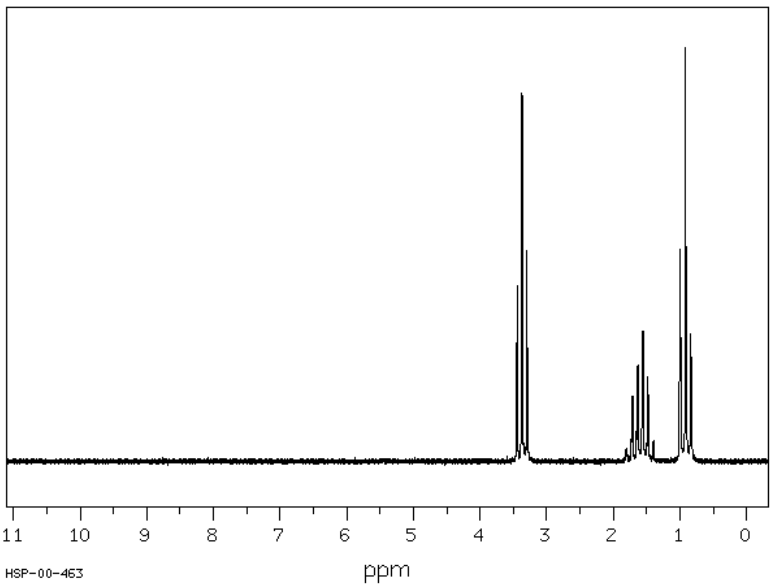


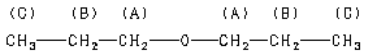
Figure IR. IR spectrum of dibutyl ether. Source: SDBSWeb: http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 14 July 2008)

NMR SPECTROSCOPY

- Hydrogens on carbon adjacent to the ether show up in the region of 3.4-4.5 ppm.
- Similar peaks in epoxides are shifted to a slightly higher field than other ethers. Hydrogens on carbons in and epoxide show up at 2.5 to 3.5 ppm.

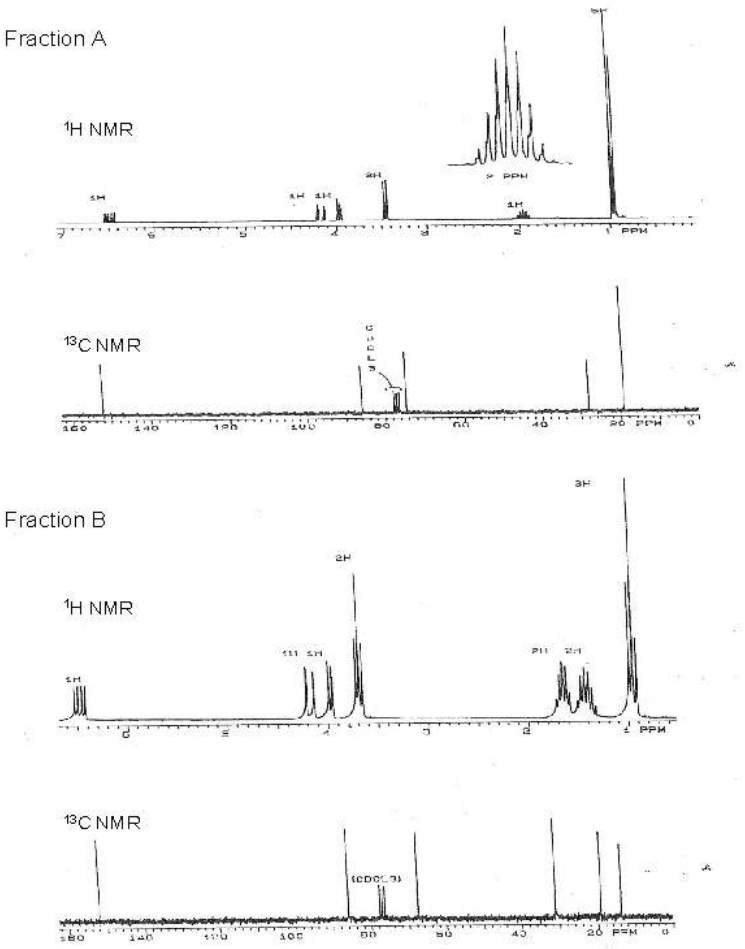
The 1H NMR spectrum of dipropyl ether shows three signals with the triplet at 3.37 ppm assigned to the -CH_2- beside the ether and the other two signals upfield (1.59 and 0.93 ppm). Notice the protons closer to the electron withdrawing oxygen atom are further downfield indicating some deshielding. Protons at (A) and (C) are each coupled to two equivalent (B) protons. So, each of these signals appears as a triplet. The (B) protons in turn are coupled to a set of two and three equivalent protons and you would therefore formally expect a quartet of triplets. However, because the coupling constants are very similar, the signal appears as a sextet. Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 28 June 2017)





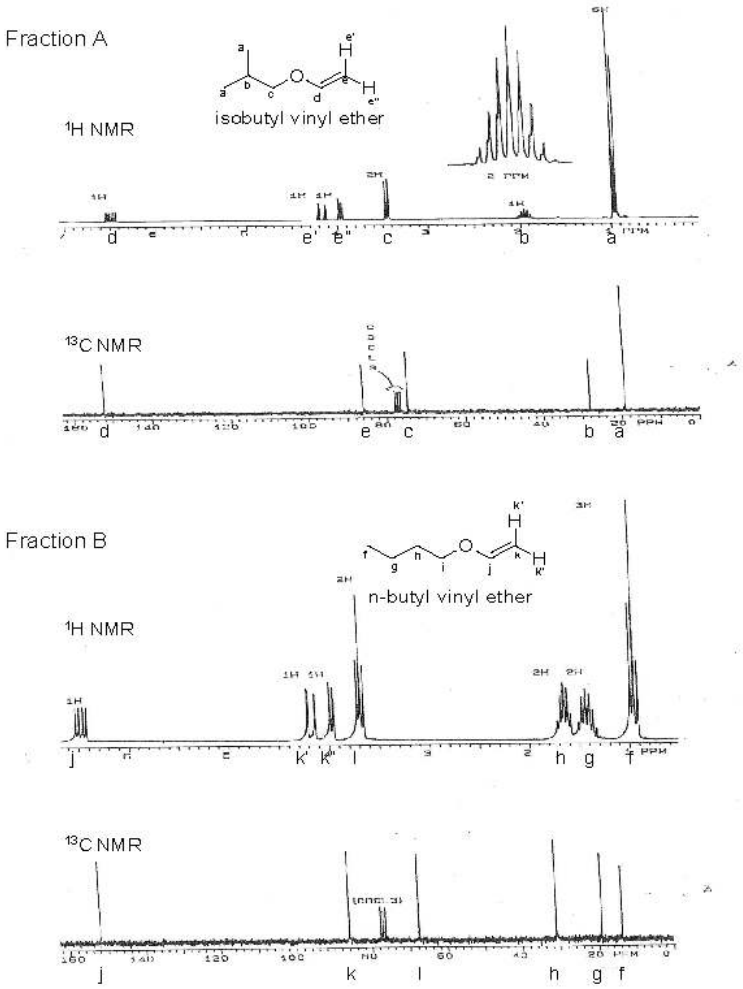
Exercise

2. A mixture of ethers was separated into two fractions: A and B. Elemental analysis reveals that the fractions are structural isomers: 72% C, 12% H, and 16% O. The IR spectra for both fractions show a couple weak bands near 3050 cm^{-1}, several stronger bands around 2950 cm^{-1}, and a strong, sharp band near 1204 cm^{-1}. The proton and ^{13}C NMR spectra for each fraction are shown below. Give the common name and draw the bond-line structure for each fraction and correlate the NMR signals with their respective atoms.



Answer

2.



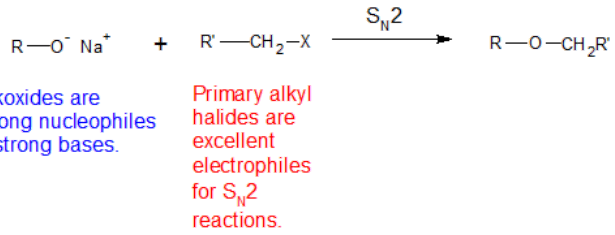
CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

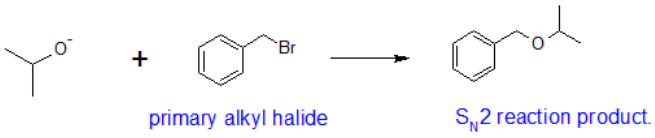
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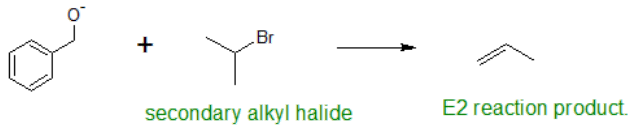
15.3: THE WILLIAMSON ETHER SYNTHESIS

One important procedure, known as the Williamson Ether Synthesis, proceeds by an S_N2 reaction of an alkoxide nucleophile with an alkyl halide. There are four reaction pathways possible between an alkoxide and alkyl halide: S_N2, S_N1, E2, and E1. To maximize the amount of ether produced by the S_N2 mechanism, use a 1º alkyl halide as the electrophile because the strong alkoxide base leads to E2 elimination with 2º and 3º alkyl halides.



The reactions below show how alkoxide and alkyl halide structure can influence the products when applied to an unsymmetrical ether. Two different combinations of reactants are possible. Of these one is usually better than the other for ether synthesis. The first reaction gives a better and cleaner yield of benzyl isopropyl ether, while the second reaction generates considerable elimination product.

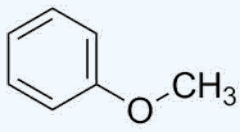


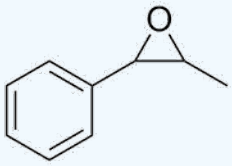


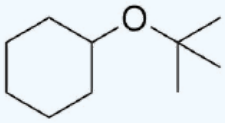
Exercises

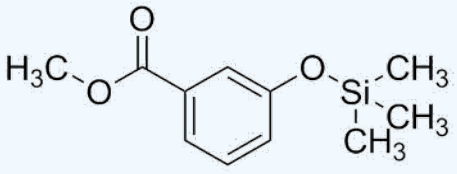
3. When preparing ethers using the Williamson ether synthesis, what factors are important when considering the nucleophile and the electrophile?

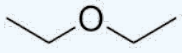
4. How would you synthesize the following ethers? Keep in mind there are multiple ways. The Williamson ether synthesis, alkoxymercuration of alkenes, and also the acid catalyzed substitution.

(a) 

(b) 

(c) 

(d) 

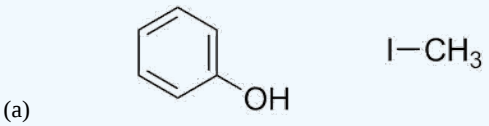
(e) 

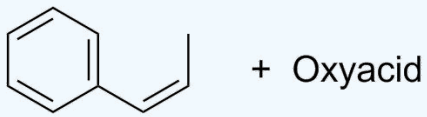
5. Draw the electron arrow pushing mechanism for the formation of diethyl ether in the previous problem.

Answer

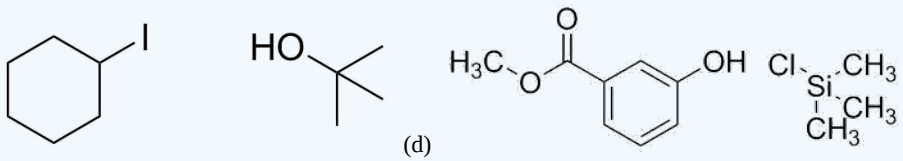
3. The nucleophile ideally should be very basic, yet not sterically hindered. This will minimize any elimination reactions. The electrophile should have the characteristics of a good S_N2 electrophile, preferably primary to minimize any elimination reactions.

4. The Williamson ether syntheses require added catalytic base. Also, most of the halides can be interchanged, say for example for a -Br or a -Cl. Although, typically -I is the best leaving group.

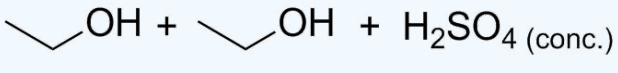
(a) 

(b) 

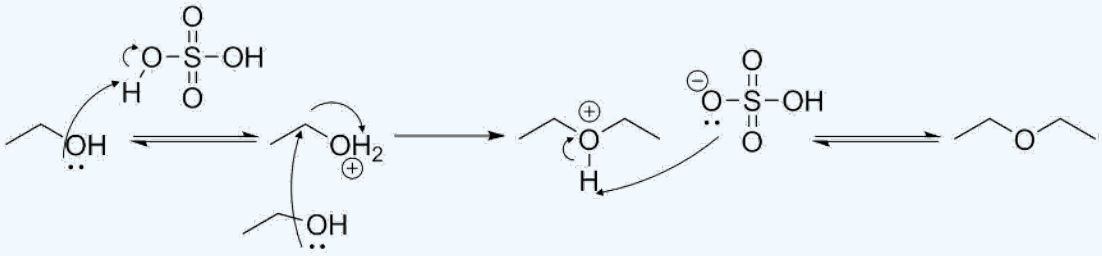
(c)

(d) 

Note, there is only one ether (also called a silyl ether, and often used as an alcohol protecting group.) The other group is an ester.

(e) 

5.

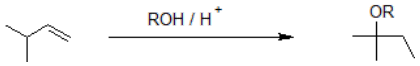


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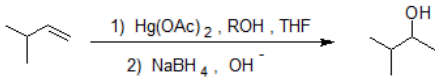
15.4: ALKOXYMERCURATION-DEMERCURATION SYNTHESIS OF ETHERS

INTRODUCTION

Acid-catalyzed ether synthesis from alkenes is limited by carbocation stability. Carbocation rearrangement can occur to form a more stable ion as shown in the example below.



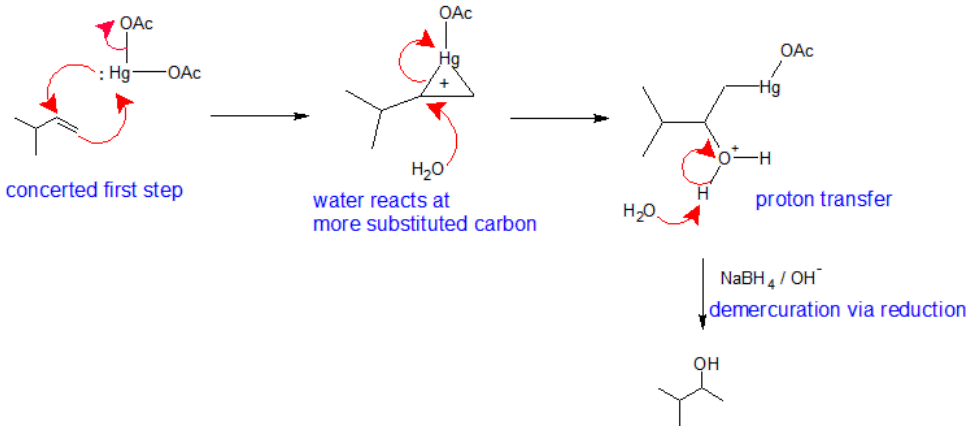
Acid-catalyzed ether synthesis using the alkoxymercuration-demercuration reaction pathway reliably produces the Markovnikov product **without** carbocation rearrangment as shown in the example below.



Alkoxymercuration-demercuration is a two step pathway used to produce ethers that proceeds in a Markovnikov manner and is stereospecific (***anti addition).*** The two steps of alkoxymerecuration-demercuraton take place on opposite faces of the double bond creating ***trans*** stereochemistry.

ALKOXYMERCURATION-DEMERCURATION MECHANISM

This reaction follows electrophilic addition mechanism we have learned. The major difference is that a mercurium ion bridge stabilizes the carbocation intermediate so that it cannot rearrange. Metals are electropositive. Mercury carries a partial positive charge in the acetate complex and is the electrophile. During the first step of this mechanism, the pi electrons form a bond to mercury while the lone pair on the mercury simultaneously bonds to the other vinyl carbon creating a mercurium ion bridge. The mercurium ion forms in conjunction with the loss of an acetate ion. The mercurium ion stabilizes the carbocation so that it does not rearrange. In the second step of this mechanism, an alcohol molecule reacts with the most substituted carbon to open the mercurium ion bridge. The third step of this mechanism is a proton transfer to a solvent alcohol molecule to neutralize the addition product. The fourth step of the reaction pathway is the reduction of the organomercury intermediate with sodium borohydride under basic conditions. The mechanism of the fourth step is beyond the scope of first year organic chemistry.



Notice that overall, the alkoxymercuration - demercuration mechanism follows Markovnikov's regioselectivity with the OR group attached to the most substituted carbon and the H attached to the least substituted carbon. The reaction is useful, because strong acids are not required and carbocation rearrangements are avoided because no discreet carbocation intermediate forms.

Exercise

6. Show how 3-methyl-2-isopropoxypentane may be synthesized by

a) Williamson ether synthesis

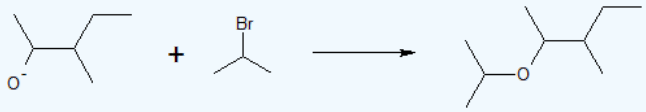
b) Alkoxymercuration-demercuration

c) Which synthesis is better? Why?

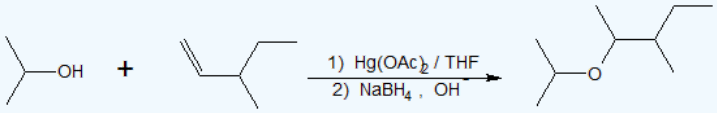
Answer

6.

a)



b)



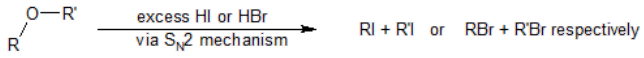
c) The alkoxymercuration-demercuration is more effective because the Williamson Synthesis would use a bulky base and secondary alkyl halide. These reactants would favor the elimination mechanism. Additionally, the alkene can under go carbocation rearrangement, so the mercurium ion stabilization of the reactive intermediate is needed.

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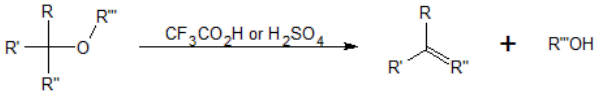
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15.5: ACIDIC CLEAVAGE OF ETHERS

The most common reaction of ethers is cleavage of the C–O bond by strong acids. This may occur by S_N1 or E1 mechanisms for 3º-alkyl groups or by an S_N2 mechanism for 1º-alkyl groups.

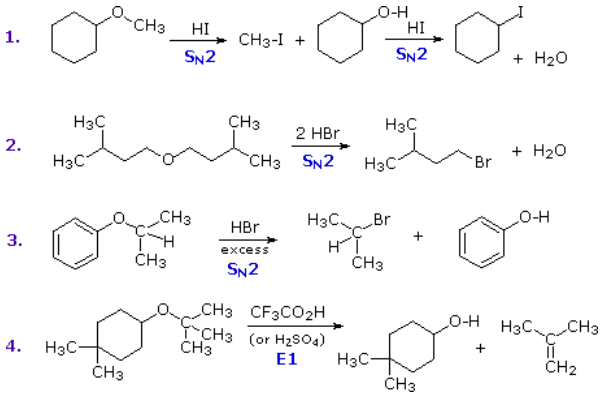


R groups need to be primary or unhindered secondary.



A bulky R group will favor an elimination reaction.

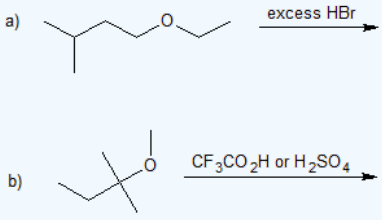
Some examples are shown in the following diagram. The conjugate acid of the ether is an intermediate in all these reactions, just as conjugate acids were intermediates in certain alcohol reactions.



The first two reactions proceed by a sequence of S_N2 steps in which the iodide or bromide anion displaces an alcohol in the first step, and then converts the conjugate acid of that alcohol to an alkyl halide in the second. Since S_N2 reactions are favored at least hindered sites, the methyl group in example #1 is cleaved first. The 2º-alkyl group in example #3 is probably cleaved by an S_N2 mechanism, but the S_N1 alternative cannot be ruled out. The phenol formed in this reaction does not react further, since S_N2, S_N1 and E1 reactions do not take place on aromatic rings. The last example shows the cleavage of a 3º-alkyl group by a strong acid. Acids having poorly nucleophilic conjugate bases are often chosen for this purpose so that E1 products are favored.

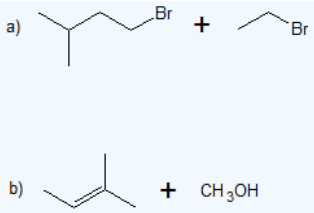
Exercise

7. Draw the bond-line structures of the product(s) for each reaction below.



Answer

7.

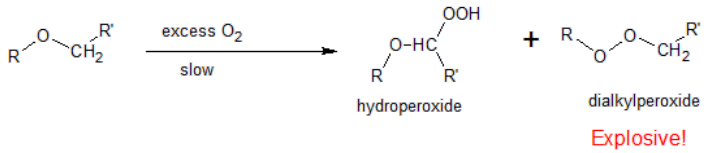


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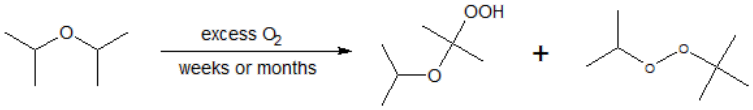
15.6: AUTOXIDATION OF ETHERS

Over time ethers that are exposed to air will autoxidize to peroxides which are potentially explosive. The general reaction is shown below.



Explosive!

For example, diisopropyl ether will autoxidize to the products shown in the reaction below.



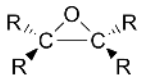
How to avoid explosions.

1. buy ether in small quantities
2. keep containers tightly sealed
3. use opened containers promptly
4. discard suspect containers

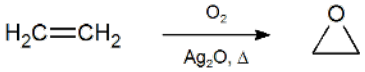
15.6: Autoxidation of Ethers is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

15.7: SYNTHESIS OF EPOXIDES

Epoxides (also known as **oxiranes**) are three-membered ring structures in which one of the vertices is an oxygen and the other two are carbons.



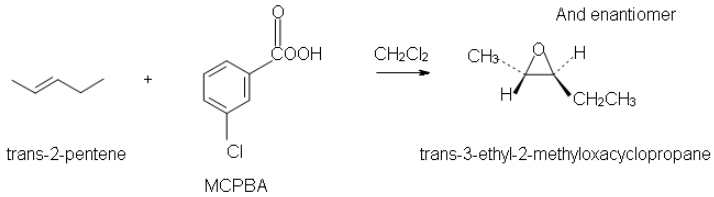
The most important and simplest epoxide is ethylene oxide which is prepared on an industrial scale by catalytic oxidation of ethylene by air.



Ethylene oxide is used as an important chemical feedstock in the manufacturing of ethylene glycol, which is used as antifreeze, liquid coolant and solvent. In turn, ethylene glycol is used in the production of polyester and polyethylene terephthalate (PET) the raw material for plastic bottles.

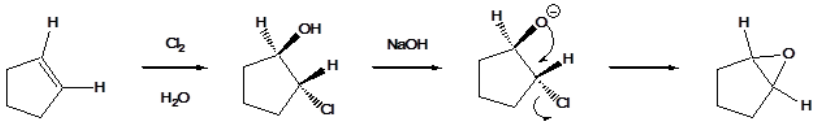
PEROXYACID REACTIONS WITH ALKENES

Oxacyclopropane synthesis by peroxycarboxylic acid requires an alkene and a peroxycarboxylic acid as well as an appropriate solvent. The peroxycarboxylic acid has the unique property of having an electropositive oxygen atom on the COOH group. The reaction is initiated by the electrophilic oxygen atom reacting with the nucleophilic carbon-carbon double bond. The mechanism involves a concerted reaction with a four-part, circular transition state. The result is that the originally electropositive oxygen atom ends up in the oxacyclopropane ring and the COOH group becomes COH.



INTRAMOLECULAR WILLIAMSON ETHER SYNTHESIS VIA HALOHYDRINS

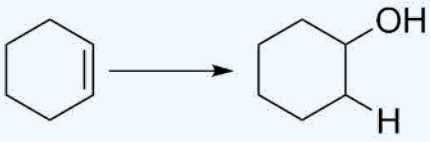
Epoxides can also be synthesized by the treatment of a halohydrin with a base. This causes an intramolecular Williamson ether synthesis.



Exercise

8. What reagents would you use to perform the following transformations?

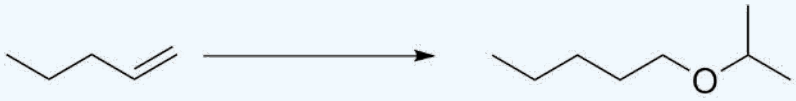
(a)



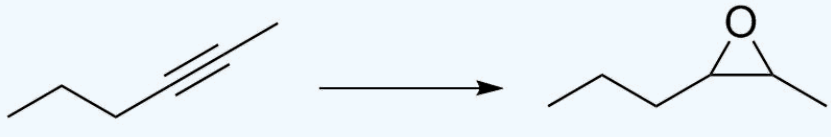
(b)



(c)



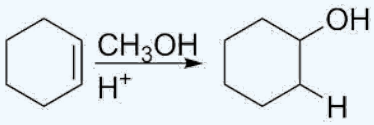
(d)



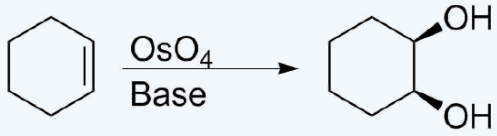
Answer

8.

(a)

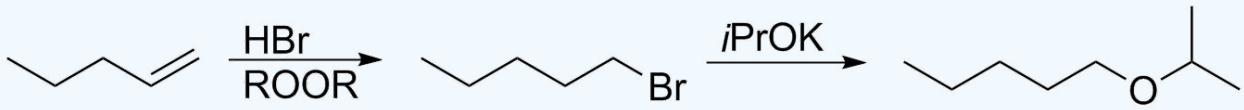


(b)



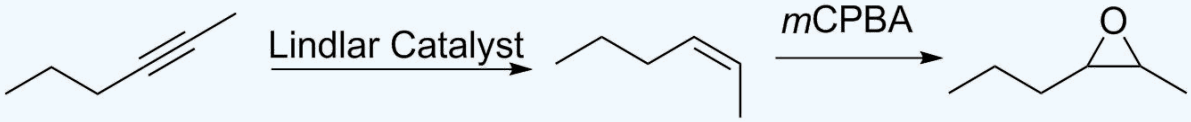
Note the cis addition

(c)



An oxidation to an alcohol through hydroboration, and subsequent substitution with 2-bromopropane could also work, but this route provides the least likelihood of an elimination reaction occurring.

(d)



Lindlar's catalyst reduces alkynes to cis/Z alkenes. This stereochemistry is retained after epoxidation.

CONTRIBUTORS AND ATTRIBUTIONS

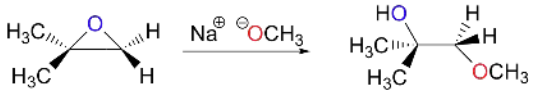
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15.8: OPENING OF EPOXIDES

EPOXIDE RING-OPENING REACTIONS - S_N1 VS. S_N2, REGIOSELECTIVITY, AND STEREOSELECTIVITY

The ring-opening reactions of epoxides provide an excellent review of the differences between S_N1 and S_N2 reactions. Both mechanisms are good examples of **regioselective reactions**. In a regioselective reaction, two (or more) different constitutional isomers are possible as products, but one is formed preferentially (or sometimes exclusively). Ring-opening reactions can proceed by either S_N2 or S_N1 mechanisms, depending on the nature of the epoxide and on the reaction conditions. For the S_N1 mechanism, the stability of the charged intermediate determines the regioselectivity. For the concerted S_N2 mechanism, sterics are the dominating consideration. If the epoxide is asymmetric, the structure of the product will vary according to which mechanism dominates. When an asymmetric epoxide undergoes solvolysis in basic methanol, ring-opening occurs by an S_N2 mechanism, and the *less* substituted carbon is the site of nucleophilic reaction, leading to what we will refer to as product B:

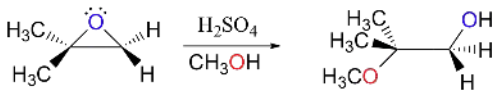
basic ring-opening:



product **B**

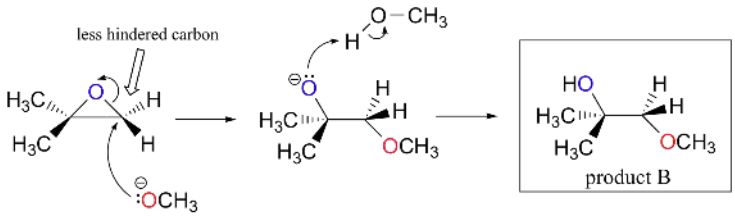
Conversely, when solvolysis occurs in acidic methanol, the reaction occurs by a mechanism with substantial S_N1 character, and the *more* substituted carbon is the site of reaction. As a result, product A predominates.

acidic ring-opening:



product **A**

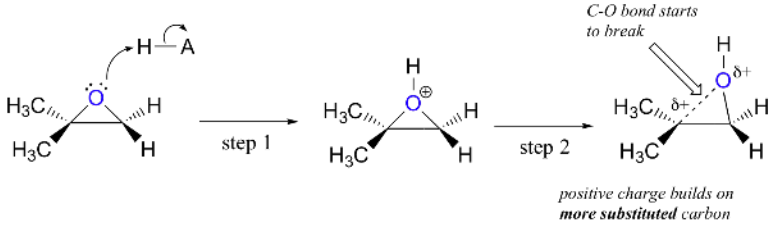
Let us examine the basic, S_N2 case first. The leaving group is an alkoxide anion, because there is no acid available to protonate the oxygen prior to ring opening. An alkoxide is a poor leaving group, and thus the ring is unlikely to open without a 'push' from the nucleophile.



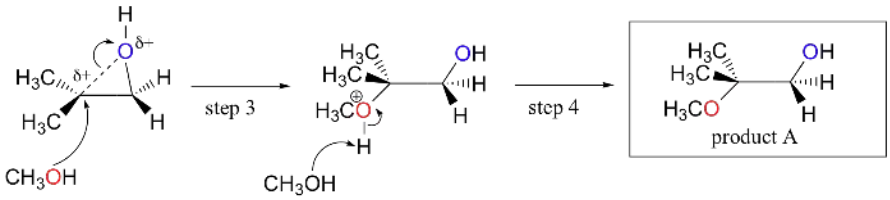
The nucleophile itself is a potent, deprotonated, negatively charged methoxide ion. When a nucleophilic substitution reaction involves a poor leaving group and a powerful nucleophile, it is very likely to proceed by an S_N2 mechanism.

What about the electrophile? There are two electrophilic carbons in the epoxide, but the best target for the nucleophile in an S_N2 reaction is the carbon that is *least hindered*. This accounts for the observed regiochemical outcome. Like in other S_N2 reactions, bimolecular, nucleophilic substitution reactions take place from the backside, resulting in inversion at the electrophilic carbon.

The acid-catalyzed epoxide ring-opening reaction mechanism is analogous to the formation of the bromonium ion in halogenation of alkenes and mercurium ion formation in oxymercuration/demercuratioin or alkoxymercuration/demercuration. First, the oxygen is protonated, creating a good leaving group (step 1 below) . Then the carbon-oxygen bond begins to break (step 2) and positive charge begins to build up on the more substituted carbon (recall carbocation stability).



Unlike in an S_N2 reaction, the nucleophile reacts with the electrophilic carbon (step 3) before a complete carbocation intermediate has a chance to form.

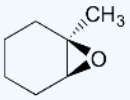


The reaction takes place preferentially from the backside (like in an S_N2 reaction) because the carbon-oxygen bond is still to some degree in place, and the oxygen blocks reaction from the front side. Notice, however, how the regiochemical outcome is different from the base-catalyzed reaction: in the acid-catalyzed process, the nucleophile reacts with the more substituted carbon because this carbon that holds a greater degree of positive charge.

Example

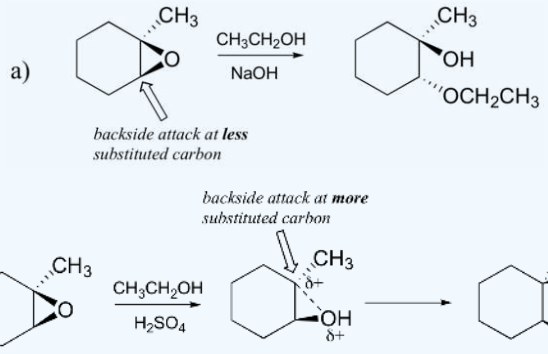
Predict the major product(s) of the ring opening reaction that occurs when the epoxide shown below is treated with:

a. ethanol and a small amount of sodium hydroxide
b. ethanol and a small amount of sulfuric acid



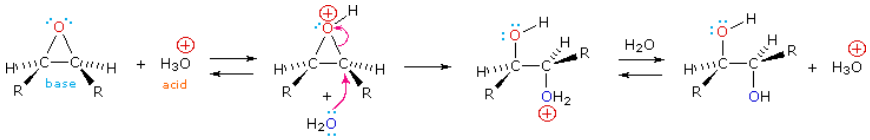
*Hint: be sure to consider both regiochemistry **and** stereochemistry!*

Answer



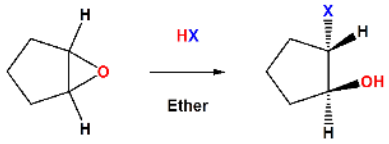
ANTI DIHYDROXYLATION

Epoxides may be cleaved by aqueous acid to give glycols that are often diastereomeric with those prepared by the syn-hydroxylation reaction. Proton transfer from the acid catalyst generates the conjugate acid of the epoxide, which is attacked by nucleophiles such as water in the same way that the cyclic bromonium ion described above undergoes reaction. The result is **anti-hydroxylation** of the double bond. In the following equation this procedure is illustrated for a cis-disubstituted epoxide, which can be prepared from the corresponding cis-alkene. This hydration of an epoxide does not change the oxidation state of any atoms or groups.



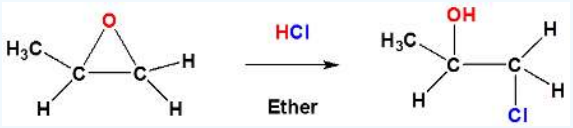
ADDITION OF HX

Epoxides can also be opened by other anhydrous acids (HX) to form a trans halohydrin. When both the epoxide carbons are either primary or secondary the halogen anion will react with the less substituted carbon and an S_N2 like reaction. However, if one of the epoxide carbons is tertiary, the halogen anion will primarily react with the tertiary carbon in a S_N1 like reaction.

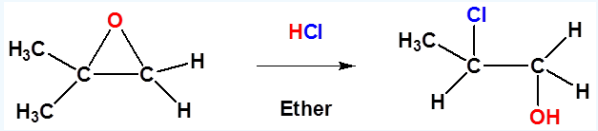


Example

In the first example, the epoxide is formed by a secondary and primary carbon. The reaction with the Cl^- nucleophile proceeds via the S_N2 mechanism and reacts with the least substituted carbon.

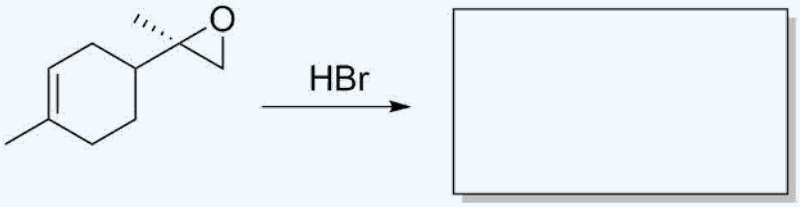


In the second example, the epoxide is formed by a tertiary and primary carbon. The reaction with Cl^- nucleophile proceeds via the S_N1 like mechanism and reacts with the most substituted carbon because it carries the greater partial positive charge.

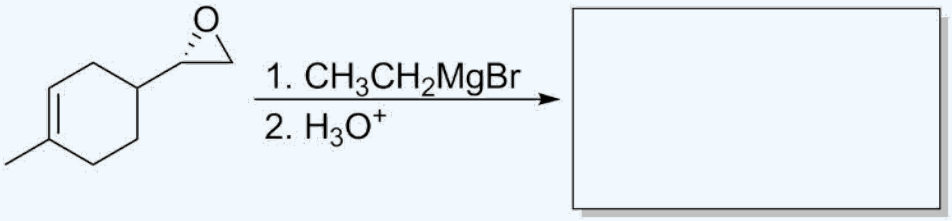


Exercise

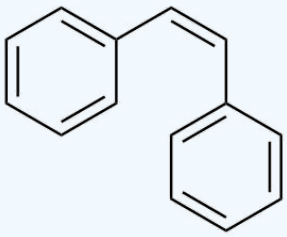
9. Given the following, predict the product assuming only the epoxide is affected. (Remember stereochemistry)



10. Predict the product of the following, similar to above but a different nucleophile is used and not in acidic conditions. (Remember stereochemistry)

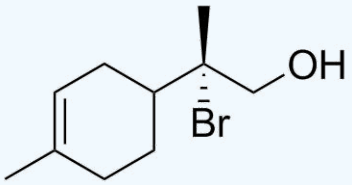


11. Epoxides are often very useful reagents to use in synthesis when the desired product is a single stereoisomer. If the following alkene were reacted with an oxyacid to form an epoxide, would the result be a enantiomerically pure? If not, what would it be?



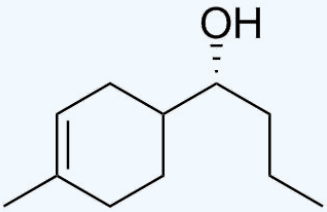
Answer

9.



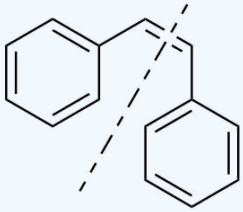
Note that the stereochemistry has been inverted

10.

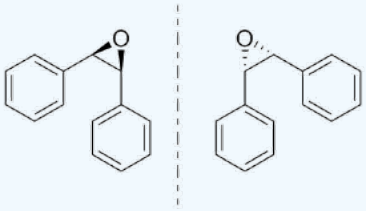


11.

First, look at the symmetry of the alkene. There is a mirror plane, shown here.



Then, think about the mechanism of epoxidation with an oxyacid, take for example *m*CPBA. The mechanism is concerted, so the original *cis* stereochemistry is not changed. This leads to "two" epoxides.



However, these two mirror images are actually identical due to the mirror plane of the *cis* geometry. It is a meso compound, so the final result is a single stereoisomer, but not a single enantiomer.

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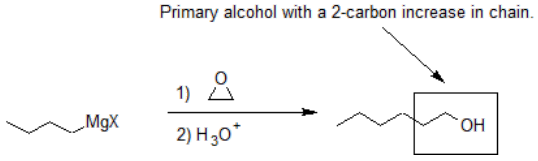
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
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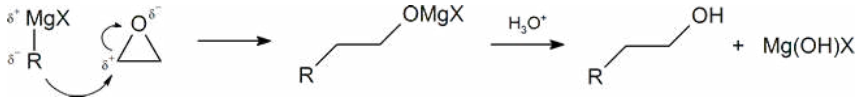
15.9: REACTIONS OF EPOXIDES WITH GRIGNARD AND ORGANOLITHIUM REAGENTS

GRIGNARD REACTIONS WITH EPOXIDES

Grignard reactions with ethylene oxide produce a primary alcohol containing two more carbon atoms than the original Grignard reagent.

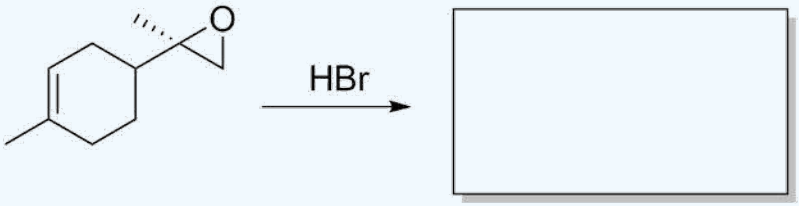


The first step of the mechanism is shown below. With the second step following the protonation step common to the other reaction pathways studied in this section. This reaction follows the same S_N2 mechanism as the opening of epoxide rings under basic conditions since Grignard reagents are both strong nucleophiles and strong bases.

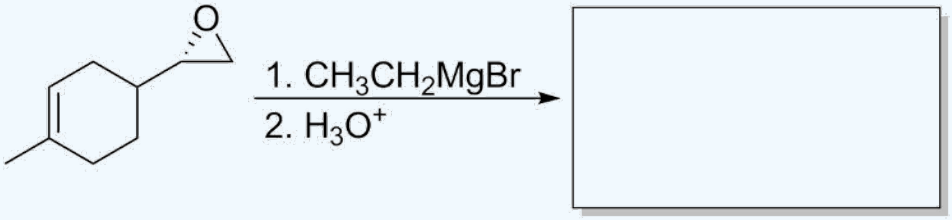


Exercise

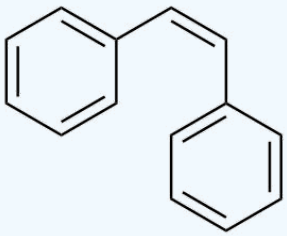
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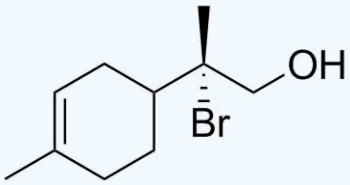


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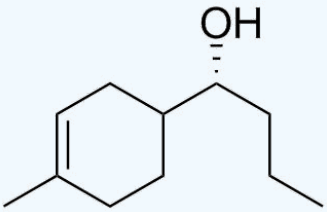
Answer

12.



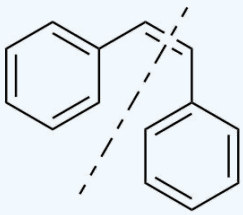
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13.

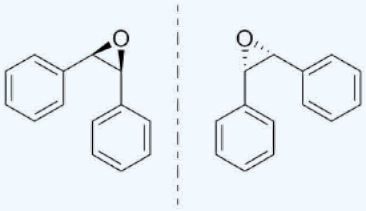


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15.10: CROWN ETHERS

A “crown ether ” is a cyclic ether containing several (i.e., 4, 5, 6 or more) oxygen atoms. It is possible to dissolve ionic compounds in organic solvents using crown ethers. Cyclic polyether with four or more oxygen atoms separated by two or three carbon atoms. All crown ethers have a central cavity that can accommodate a metal ion coordinated to the ring of oxygen atoms., cyclic compounds with the general formula $(OCH_2CH_2)_n$. Crown ethers are named using both the total number of atoms in the ring and the number of oxygen atoms. Thus 18-crown-6 is an 18-membered ring with six oxygen atoms (part (a) in Figure 18.7.1). The cavity in the center of the crown ether molecule is lined with oxygen atoms and is large enough to be occupied by a cation, such as K^+. The cation is stabilized by interacting with lone pairs of electrons on the surrounding oxygen atoms. Thus crown ethers solvate cations inside a hydrophilic cavity, whereas the outer shell, consisting of C–H bonds, is hydrophobic. Crown ethers are useful for dissolving ionic substances such as $KMnO_4$ in organic solvents such as isopropanol $[(CH_3)_2CHOH]$ (Figure 18.7.1). The availability of crown ethers with cavities of different sizes allows specific cations to be solvated with a high degree of selectivity.

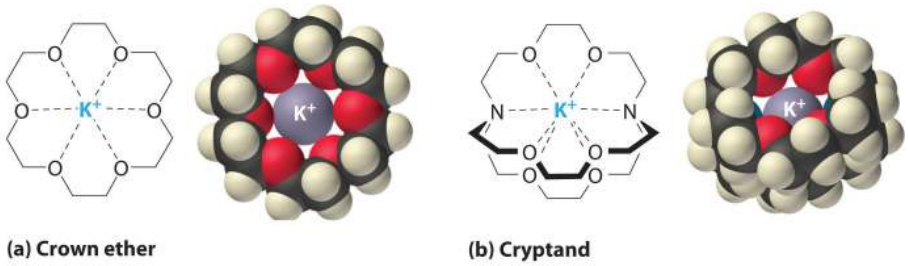


Figure: 1 Crown Ethers and Cryptands (a) The potassium complex of the crown ether 18-crown-6. Note how the cation is nestled within the central cavity of the molecule and interacts with lone pairs of electrons on the oxygen atoms. (b) The potassium complex of 2,2,2-cryptand, showing how the cation is almost hidden by the cryptand. Cryptands solvate cations via lone pairs of electrons on both oxygen and nitrogen atoms.



Figure 2: Effect of a Crown Ether on the Solubility of KMnO4 in Benzene*. Normally which is intensely purple, is completely insoluble in benzene which has a relatively low dielectric constant. In the presence of a small amount of crown ether, KMnO4 dissolves in benzene as shown by the reddish purple color caused by the permanganate ions in solution.*

Cryptands (from the Greek *kryptós*, meaning “hidden”) are compounds that can completely surround a cation with lone pairs of electrons on oxygen and nitrogen atoms (Figure 18.7.1b). The number in the name of the cryptand is the number of oxygen atoms in each strand of the molecule. Like crown ethers, cryptands can be used to prepare solutions of ionic compounds in solvents that are otherwise too nonpolar to dissolve them.

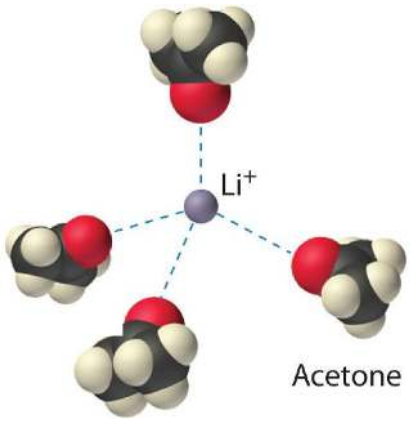


Figure 18.7.3: Ion–Dipole Interactions in the Solvation of Li^+ Ions by Acetone, a Polar Solvent

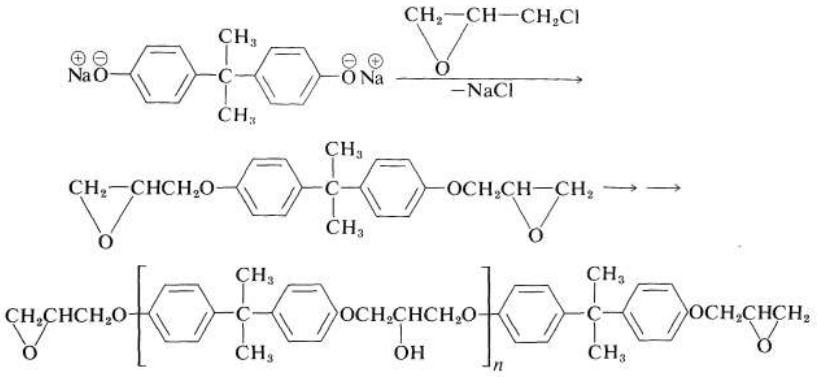
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15.11: EPOXY RESINS - THE ADVENT OF MODERN GLUES

A very useful group of adhesives and plastics is based on condensation polymers of bisphenol A and chloromethyloxacyclopropane (epichlorohydrin). The first step in the formation of epoxy resins is to form a prepolymer by condensation polymerization of the sodium salt of bisphenol A with the epoxide:



The formation of a prepolymer involves two different kinds of reactions. One is an S_N2-type displacement, and the other is oxide-ring opening of the product by attack of more bisphenol A. Usually, for practical purposes the degree of polymerization n of the prepolymer is small (5 to 12 units).

The epoxy prepolymer can be cured, that is, converted to a three-dimensional network, in several different ways. A trifunctional amine, such as $NH_2CH_2CH_2NHCH_2CH_2NH_2$, can be mixed in and will extend the chain of the polymer and form cross-links by reacting with the oxide rings:



Alternatively, a polybasic acid anhydride can be used to link the chains through combination with secondary alcohol functions and then the oxide rings.

CONTRIBUTORS AND ATTRIBUTIONS

- John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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15.12: THIOETHERS (SULFIDES) AND SILYL ETHERS

Thiols and sulfides are the "sulfur equivalent" of alcohols and ethers. You can replace the oxygen atom of an alcohol with a sulfur atom to make a thiol; similarly, you can replace the oxygen atom in an ether with S to make the corresponding alkyl sulfide. This is because thiols contain the C-S-H functional group, while sulfides contain the C-S-C group.

OXIDATION STATES OF SULFUR COMPOUNDS

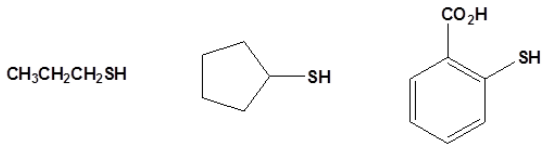
Oxygen assumes only two oxidation states in its organic compounds (–1 in peroxides and –2 in other compounds). Sulfur, on the other hand, is found in oxidation states ranging from –2 to +6, as shown in the following table (some simple inorganic compounds are displayed in orange).

Sulfur Oxidation States in Organic Compounds

-2	-1	0	+2	+4	+6
H_2S R–S–H thiols R–S–R sulfides R–S(⊕)(R)–R sulfonium ions	R–S–S–R disulfides	S elemental R–S(=O)–R sulfoxides R–S–OH sulfenic acids	R–S(=O)(=O)–R sulfones R–S(=O)–OH sulfinic acids	SO_2 R–S(=O)(=O)–OH sulfonic acids R-O–S(=O)(=O)–O-R sulfite esters	SO_3 R-O–S(=O)(=O)–O-R sulfate esters

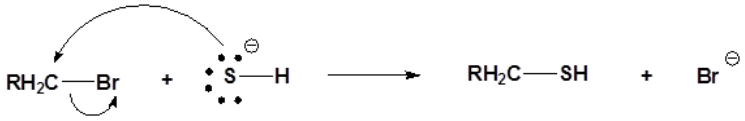
THIOLS

Thiols are often called “mercaptans,” a reference to the Latin term mercurium captans(capturing mercury), since the -SH group forms strong bonds with mercury and its ions. Thiols are analogous to alcohols. They are named in a similar fashion as alcohols except the suffix -thiol is used in place of -ol. By itself the -SH group is called a mercapto group.

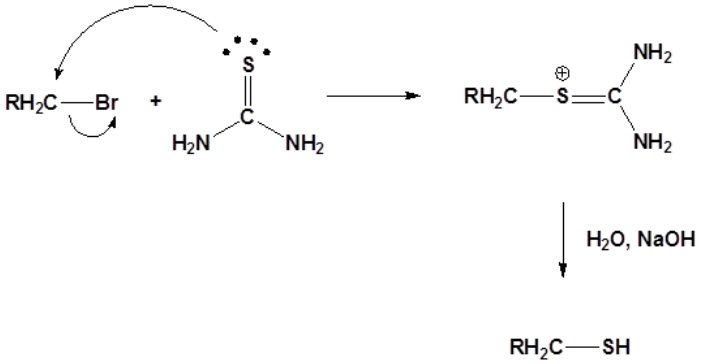


Propanethiol Cyclopentanethiol o-Mercaptobenzoic acid

Thiols are usually prepared by using the hydrosulfide anion (-SH) as a nucleophile in an S_N2 reaction with alkyl halides.

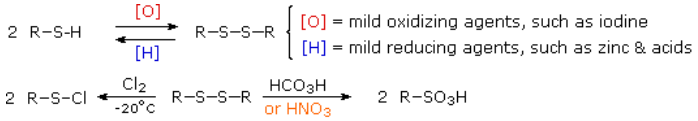


On problem with this reaction is that the thiol product can undergo a second S_N2 reaction with an additional alkyl halide to produce a sulfide side product. This problem can be solved by using thiourea, $(NH_2)_2C=S$, as the nucleophile. The reaction first produces an alkyl isothiourea salt and an intermediate. This salt is then hydrolyzed by a reaction with aqueous base.



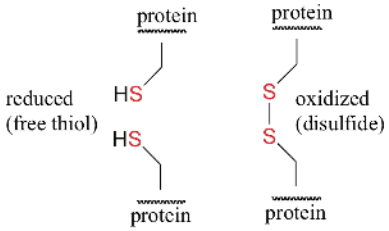
DISULFIDES

Oxidation of thiols and other sulfur compounds changes the oxidation state of sulfur rather than carbon. We see some representative sulfur oxidations in the following examples. In the first case, mild oxidation converts thiols to disufides. An equivalent oxidation of alcohols to peroxides is not normally observed. The reasons for this different behavior are not hard to identify. The S–S single bond is nearly twice as strong as the O–O bond in peroxides, and the O–H bond is more than 25 kcal/mole stronger than an S–H bond. Thus, thermodynamics favors disulfide formation over peroxide.

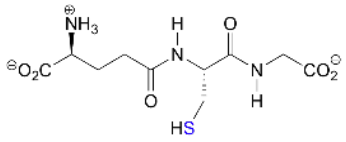


DISULFIDE BRIDGES IN PROTEINS

Disulfide (sulfur-sulfur) linkages between two cysteine residues are an integral component of the three-dimensional structure of many proteins. The interconversion between thiols and disulfide groups is a redox reaction: the thiol is the reduced state, and the disulfide is the oxidized state.



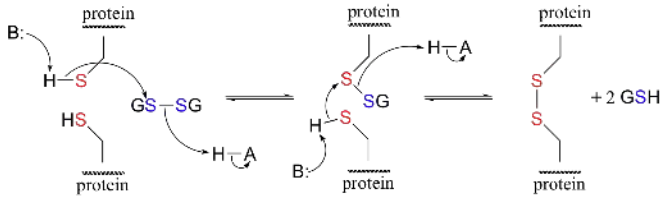
Notice that in the oxidized (disulfide) state, each sulfur atom has lost a bond to hydrogen and gained a bond to a sulfur - this is why the disulfide state is considered to be oxidized relative to the thiol state. The redox agent that mediates the formation and degradation of disulfide bridges in most proteins is glutathione, a versatile coenzyme that we have met before in a different context (section 14.2A). Recall that the important functional group in glutathione is the thiol, highlighted in blue in the figure below. In its reduced (free thiol) form, glutathione is abbreviated 'GSH'.



Glutathione (GSH)

In its oxidized form, glutathione exists as a dimer of two molecules linked by a disulfide group, and is abbreviated 'GSSG'.

A new disulfide in a protein forms via a 'disulfide exchange' reaction with GSSH, a process that can be described as a combination of two S_N2-like attacks. The end result is that a new cysteine-cysteine disulfide forms at the expense of the disulfide in GSSG.

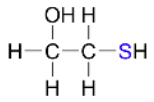


In its reduced (thiol) state, glutathione can reduce disulfides bridges in proteins through the reverse of the above reaction.

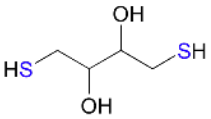
Disulfide bridges exist for the most part only in proteins that are located outside the cell. Inside the cell, cysteines are kept in their reduced (free thiol) state by a high intracellular concentration of GSH, which in turn is kept in a reduced state (ie. GSH rather than GSSG) by a flavin-dependent enzyme called glutathione reductase.

Disulfide bridges in proteins can also be directly reduced by another flavin-dependent enzyme called 'thioredoxin'. In both cases, NADPH is the ultimate electron donor, reducing FAD back to $FADH_2$ in each catalytic cycle.

In the biochemistry lab, proteins are often maintained in their reduced (free thiol) state by incubation in buffer containing an excess concentration of b-mercaptoethanol (BME) or dithiothreitol (DTT). These reducing agents function in a manner similar to that of GSH, except that DTT, because it has two thiol groups, forms an intramolecular disulfide in its oxidized form.



β-mercaptoethanol
(BME)



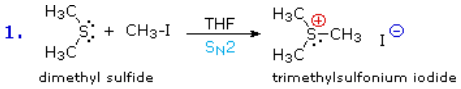
dithiothreitol
(DTT)

SULFIDES

Sulfur analogs of ethers are called **sulfides**. Sulfides are less common than thiols as naturally occurring compounds. However, sulfides—especially disulfides (C-S-S-C)—have important biological functions, mainly in reducing agents (antioxidants). The chemical behavior of sulfides contrasts with that of ethers in some important ways. Since hydrogen sulfide (H_2S) is a much stronger acid than water (by more than ten million fold), we expect, and find, thiols to be stronger acids than equivalent alcohols and phenols. Thiolate conjugate bases are easily formed, and have proven to be excellent nucleophiles in S_N2 reactions of alkyl halides and tosylates.

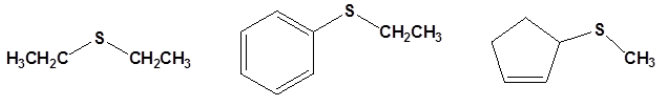
$$R\text{–}S^{(-)}\ Na^{(+)} + (CH_3)_2CH\text{–}Br \longrightarrow (CH_3)_2CH\text{–}S\text{–}R + Na^{(+)}\ Br^{(-)}$$

Although the basicity of ethers is roughly a hundred times greater than that of equivalent sulfides, the nucleophilicity of sulfur is much greater than that of oxygen, leading to a number of interesting and useful electrophilic substitutions of sulfur that are not normally observed for oxygen. Sulfides, for example, react with alkyl halides to give ternary sulfonium salts (equation # 1) in the same manner that 3º-amines are alkylated to quaternary ammonium salts. Although equivalent oxonium salts of ethers are known, they are only prepared under extreme conditions, and are exceptionally reactive.



1. dimethyl sulfide + CH_3-I —THF, S_N2→ trimethylsulfonium iodide

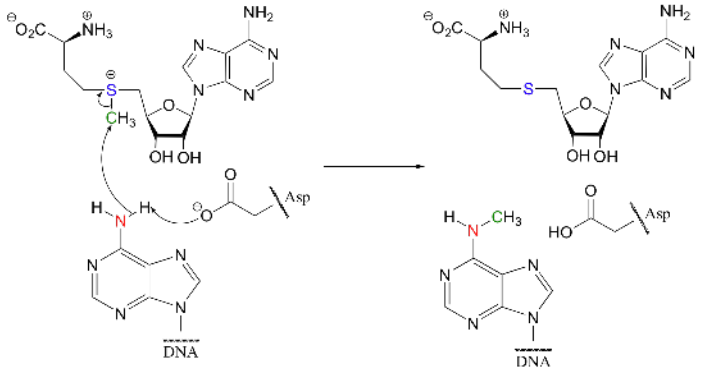
sulfides are named using the same rules as ethers except *sulfide* is used in the place of *ether*. For more complex substance alkylthio is used instead of alkoxy.



Diethyl sulfide **Ethyl phenyl sulfide** **3-(Methylthio)cyclopentene**

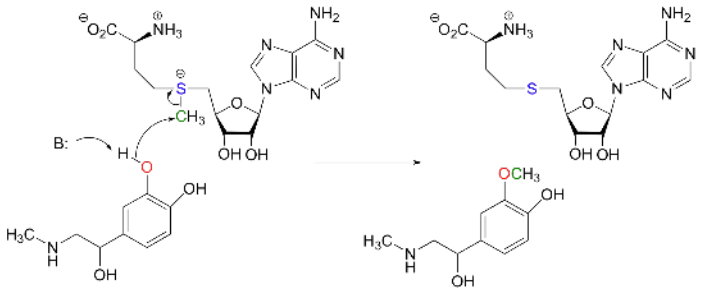
SAM METHYLTRANSFERASES

The most common example of sulfonium ions in a living organism is the reaction of S-Adenosylmethionine. Some of the most important examples of S_N2 reactions in biochemistry are those catalyzed by S-adenosyl methionine (SAM) – dependent methyltransferase enzymes. We have already seen, in chapter 6 and again in chapter 8, how a methyl group is transferred in an S_N2 reaction from SAM to the amine group on the nucleotide base adenosine:



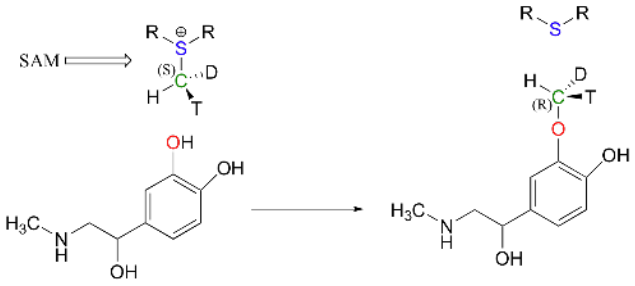
(*Nucleic Acids Res.* **2000**, *28*, 3950).

Another SAM-dependent methylation reaction is catalyzed by an enzyme called catechol-O-methyltransferase. The substrate here is epinephrine, also known as adrenaline.



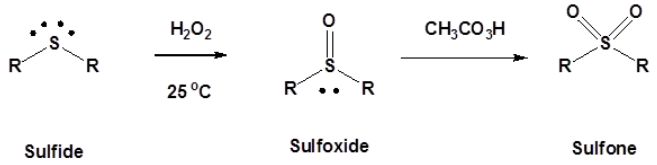
Notice that in this example, the attacking nucleophile is an alcohol rather than an amine (that's why the enzyme is called an O-methyltransferase). In both cases, though, a basic amino acid side chain is positioned in the active site in just the right place to deprotonate the nucleophilic group as it attacks, increasing its nucleophilicity. The electrophile in both reactions is a methyl carbon, so there is little steric hindrance to slow down the nucleophilic attack. The methyl carbon is electrophilic because it is bonded to a positively-charged sulfur, which is a powerful electron withdrawing group. The positive charge on the sulfur also makes it an excellent leaving group, as the resulting product will be a neutral and very stable sulfide. All in all, in both reactions we have a reasonably good nucleophile, an electron-poor, unhindered electrophile, and an excellent leaving group.

Because the electrophilic carbon in these reactions is a methyl carbon, a stepwise S_N1-like mechanism is extremely unlikely: a methyl carbocation is very high in energy and thus is not a reasonable intermediate to propose. We can confidently predict that this reaction is S_N2. Does this S_N2 reaction occur, as expected, with inversion of stereochemistry? Of course, the electrophilic methyl carbon in these reactions is achiral, so inversion is not apparent. To demonstrate inversion, the following experiment has been carried out with catechol-O-methyltransferase:



Here, the methyl group of SAM was made to be chiral by incorporating hydrogen isotopes tritium (^{3}H, T) and deuterium (^{2}H, D). The researchers determined that the reaction occurred with inversion of configuration, as expected for an S_N2 displacement (*J. Biol. Chem.* **1980,** *255,* 9124).

Sulfides can be easily oxidized. Reacting a sulfide with hydrogen peroxide, H_2O_2, as room termpeature produces a sulfoxide (R_2SO). The oxidation can be continued by reaction with a peroxyacid to produce the sulfone (R_2SO_2)



A common example of a sulfoxide is the solvent dimethyl sulfoxide (DMSO). DMSO is polar aprotic solvent.

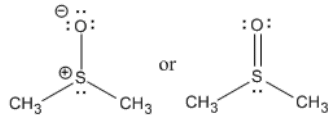


Figure AB16.3. DMSO is a very polar, aprotic solvent.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

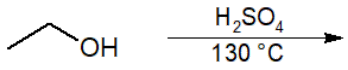
- Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

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15.13: ADDITIONAL EXERCISES

Industrial Synthesis of Ethers using Bimolecular Condensation

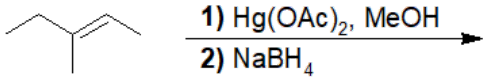
15-1 Give the final product of the following reaction.



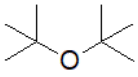
15-2 Draw the mechanism for the reaction in the previous problem, **15-1**.

Synthesis of Ethers by Alkoxymercuration-Demercuration

15-3 Predict the product of the following reaction and give its correct IUPAC nomenclature.



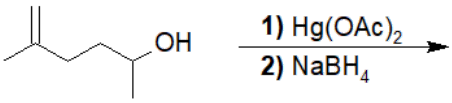
15-4 Propose a route of synthesis (that includes an alkoxymercuration-demercuration reaction) for the following ether starting with a carbon molecule containing no more than 3 carbons.



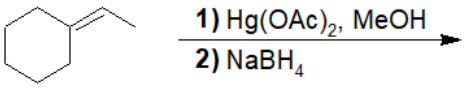
2-*tert*-butoxy-2-methylpropane

15-5 Predict the products of the following reactions.

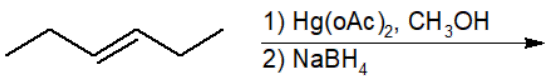
a)



b)

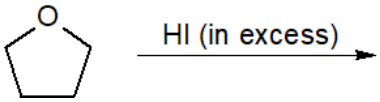


15-6 Give the final product for the following reaction.



Cleavage of Ethers

15-7 Choose the correct IUPAC name for the product of the following reaction.



a) Butan-1-ol

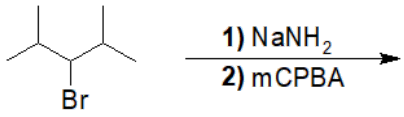
b) 1-iodobutane

c) 1,4-diiodobutane

d) 2-iodooxolane

Synthesis of Epoxides

15-8 Choose the correct IUPAC nomenclature of the product of the following reaction and provide its structure.



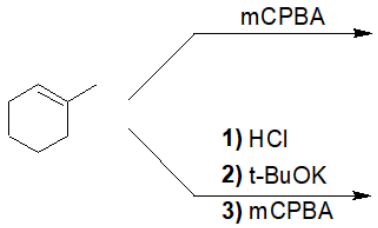
a) 2,2-dimethyl-3-(propan-2-yl)oxirane

b) 2,4-dimethylpentan-2-ol

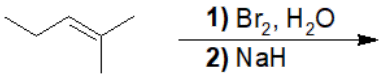
c) 2,4-dimethylpent-2-en-3-ol

d) 2-methyl-2-(2-methylpropyl)oxirane

15-9 Predict the products of the following reactions.

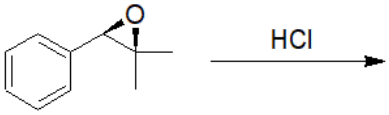


15-10 Predict the product of the following reaction. Be sure to include proper stereochemistry.

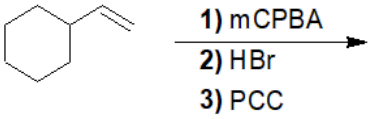


Reactions of Epoxides

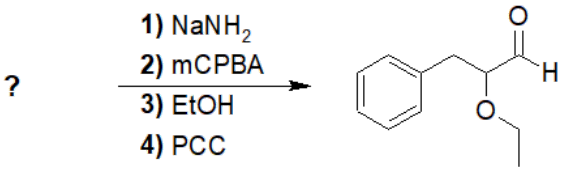
15-11 Provide the structure of the product of the following reaction. Be sure to include proper stereochemistry.



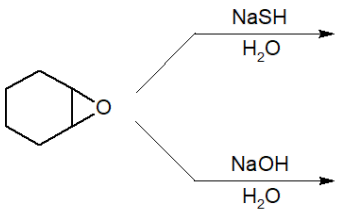
15-12 Predict the product of the following reaction.



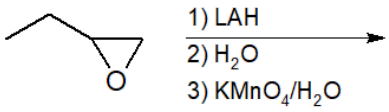
15-13 Suggest the structure of the starting brominated molecule that was used in the following reaction to make the final product.



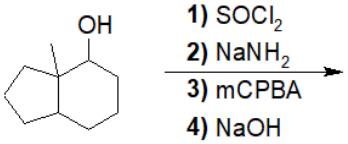
15-14 Provide the final products of the following reactions.



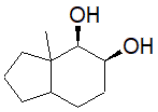
15-15 Provide the final product of the following reaction.



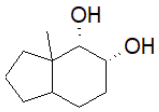
15-16 Choose the correct product of the following reaction.



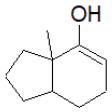
a)



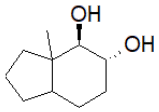
b)



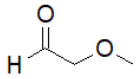
c)



d)



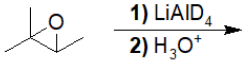
15-17 Suggest a route of synthesis (that includes an epoxide intermediate) for the following compound, starting with ethane and using any other necessary reagents.



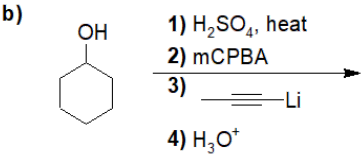
methoxyacetaldehyde

15-18 Predict the products of the following reactions. Be sure to include stereochemistry where applicable.

a)

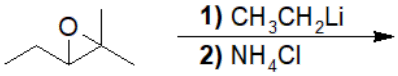


b)

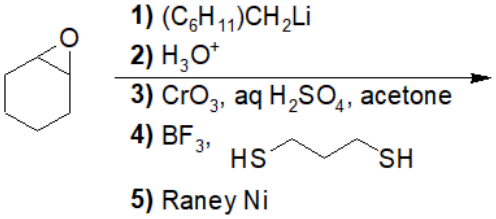


Reactions of Epoxides with Grignard and Organolithium Reagents

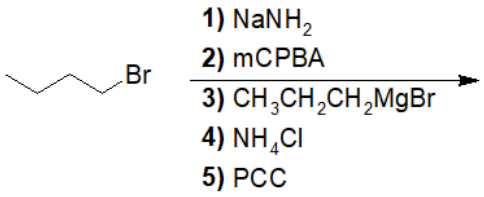
15-19 Predict the product of the following reaction and give the proper IUPAC nomenclature.



15-20 Predict the product of the following reaction.



15-21 Choose the correct IUPAC nomenclature of a product of the following reaction.



a) heptan-4-one

b) heptan-3-one

c) 3-aminoheptan-3-ol

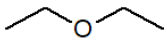
d) (3Z)-hept-3-en-3-ol

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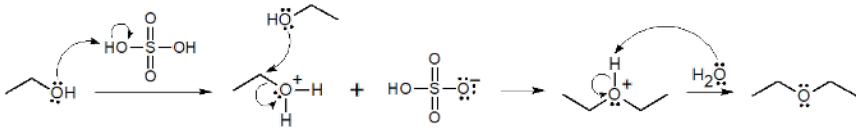
15.14: SOLUTIONS TO ADDITIONAL EXERCISES

Industrial Synthesis of Ethers using Bimolecular Condensation

15-1:

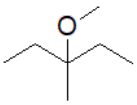


15-2:



Synthesis of Ethers by Alkoxymercuration-Demercuration

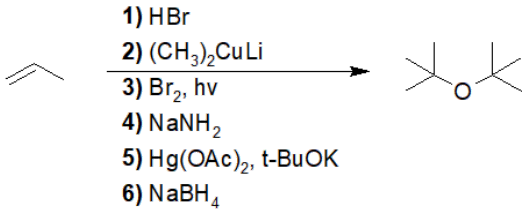
15-3:



3-methoxy-3-methylpentane

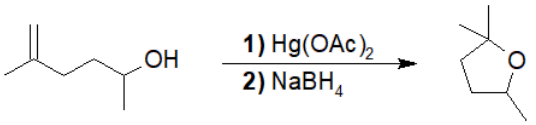
15-4:

Possible route of synthesis:

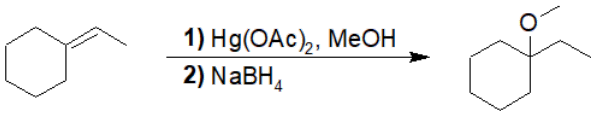


15-5:

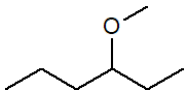
a)



b)



15-6:



Cleavage of Ethers

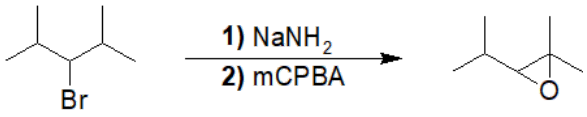
15-7:

Answer: C

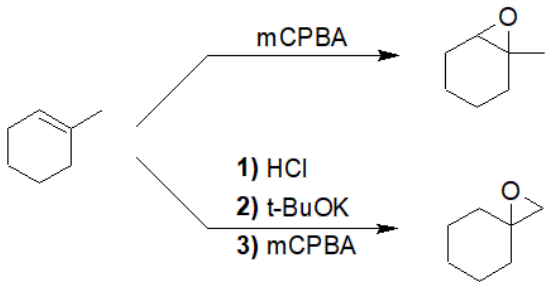
Synthesis of Epoxides

15-8:

Answer: A



15-9:

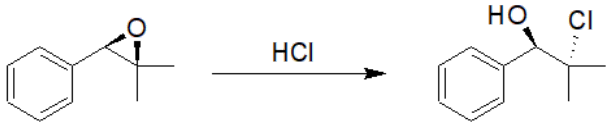


15-10:

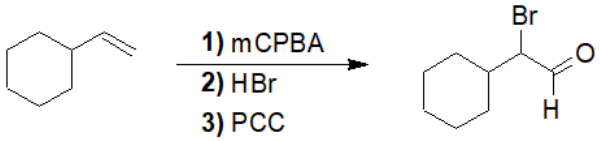


Reactions of Epoxides

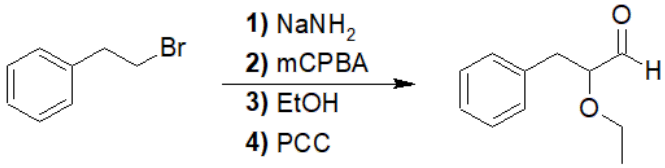
15-11:



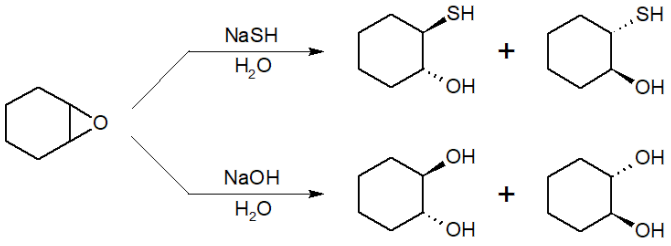
15-12:



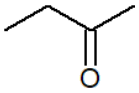
15-13:



15-14:



15-15:

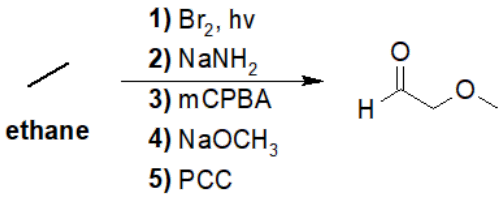


15-16:

Answer: D

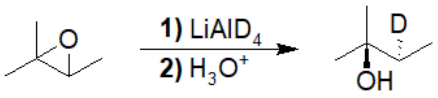
15-17:

Possible route of synthesis:

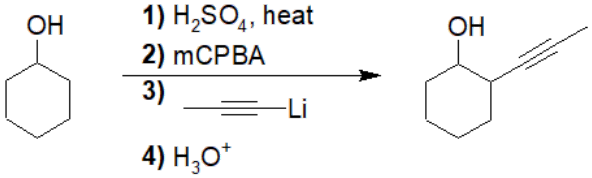


15-18:

a)

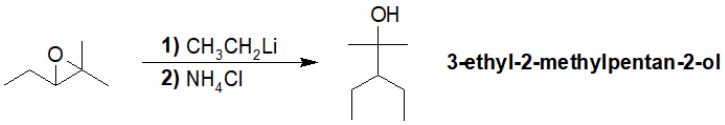


b)

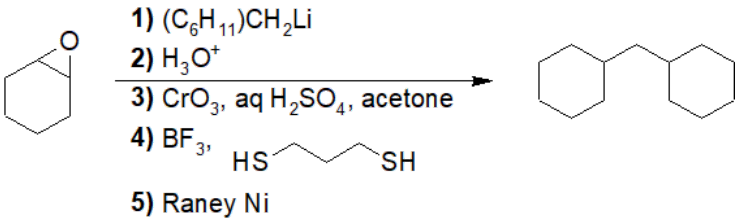


Reactions of Epoxides with Grignard and Organolithium Reagents

15-19:



15-20:



15-21:

Answer: B

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CHAPTER OVERVIEW

16: CONJUGATED SYSTEMS, ORBITAL SYMMETRY, AND ULTRAVIOLET SPECTROSCOPY

LEARNING OBJECTIVES

After reading this chapter and completing ALL the exercises, a student can be able to

- construct & interpret MO diagrams of ethene, butadiene and allylic systems (refer to section 16.1)
- recognize reactions that are enhanced by resonance stabilization of the allylic intermediate (refer to section 16.2)
- predict the products and specify the reagents for electrophilic addition reactions (EAR) of conjugated dienes (refer to section 16.3)
- specify reaction conditions to promote thermodynamic or kinetic control of the reaction mechanism; correlate these conditions to reaction energy diagrams (section 16.4)
- predict the products and specify the reagents for bimolecular substitution reactions (S_N2) of allylic halides (refer to section 16.5)
- predict the products of Diels-Alder reactions with stereochemistry, including the orientation of cycloaddition with asymmetrical reagents (refer to sections 16.6 and 16.7)
- develop mechanisms to explain the observed products of 1,2- & 1,4- addition reactions, including the resonance forms of the stabilized intermediates (refer to section 16.6)
- use MO theory to predict whether cycloaddition reactions will be thermally or photochemically allowed (refer to section 16.6 and 16.7)
- recognize the effect of conjugation on UV absorption (refer to section 16.9 and 16.10)
- use Beer's Law in UV absorption calculations (refer to section 16.9 and 16.10)
- explain how light, the conjugation of double bonds, and the stereochemistry of double bonds contribute to visualizing color

16.1: Stability of Conjugated Dienes - Molecular Orbital Theory
16.2: Allylic Cations
16.3: Electrophilic Additions to Conjugated Dienes
16.4: Kinetic versus Thermodynamic Control
16.5: SN2 Reactions of Allylic Halides and Tosylates
16.6: The Diels-Alder (4 + 2) Cycloaddition Reaction
16.7: Diels-Alder Stereochemistry
16.8: Diene Polymers - Natural and Synthetic Rubbers
16.9: Structure Determination in Conjugated Systems - Ultraviolet Spectroscopy
16.10: Interpreting Ultraviolet Spectra - The Effect of Conjugation
16.11: Conjugation, Color, and the Chemistry of Vision
16.12: Additional Exercises
16.13: Solutions to Additional Exercises

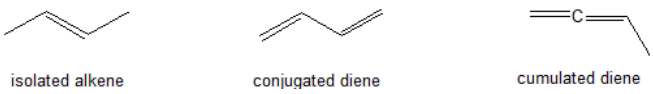
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16: Conjugated Systems, Orbital Symmetry, and Ultraviolet Spectroscopy is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

16.1: STABILITY OF CONJUGATED DIENES - MOLECULAR ORBITAL THEORY

INTRODUCTION

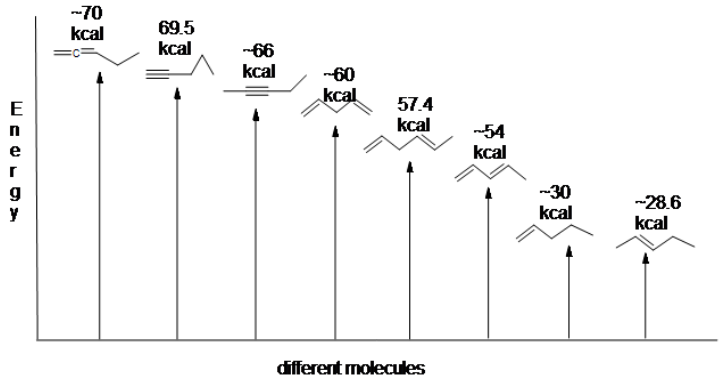
Conjugated dienes are characterized by alternating carbon-carbon double bonds separated by carbon-carbon single bonds. Cumulated dienes are characterized by adjacent carbon-carbon double bonds. While conjugated dienes are energetically more stable than isolated double bonds. Cumulated double bonds are unstable. The chemistry of cumulated double bonds can be explored in advance organic chemistry courses. The chemistry of isolated alkenes is covered in Chapters 8 and 9 of this LibreText. The chemistry of conjugated double bonds is the focus of this chapter.



CONJUGATED DIENE STABILITY

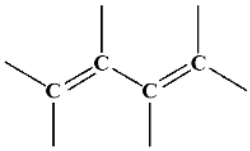
Conjugated dienes are more stable than non conjugated dienes (both isolated and cumulated) due to factors such as delocalization of charge through resonance and hybridization energy. This stability can be seen in the differences in the energies of hydrogenation between isolated and conjugated alkenes. Since the higher the heat of hydrogenation the less stable the compound, it is shown below that conjugated dienes (~54 kcal) have a lower heat of hydrogenation than their isolated (~60 kcal) and cumulated diene (~70 kcal) counterparts.

Here is an energy diagram comparing different types of bonds with their heats of hydrogenation to show relative stability of each molecule:

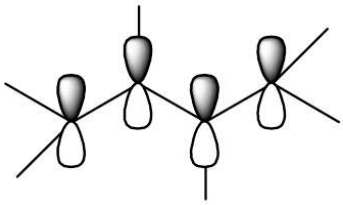


STABILITY OF CONJUGATED DIENES - THE RESONANCE EXPLANATION

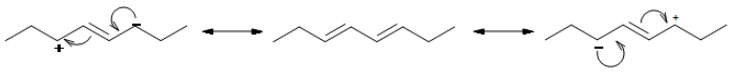
Conjugated double bonds are separated by a single bond. 1,3-dienes are an excellent example of a conjugated system. Each carbon in 1,3 dienes is sp^2 hybridized and therefore has one *p* orbital. The four *p* orbitals in 1,3-butadiene overlap to form a conjugated system.



1,3-Diene

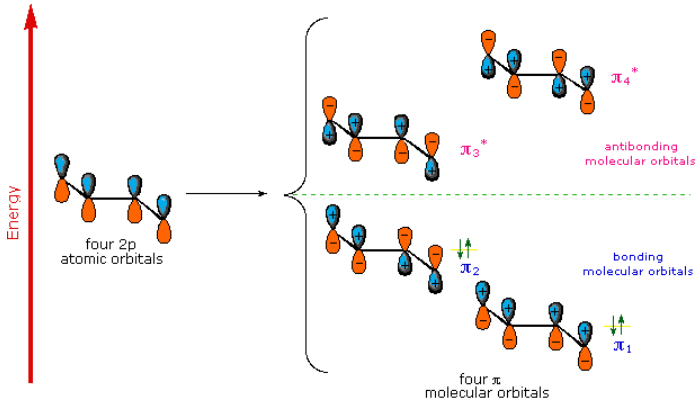


The resonance structure shown below gives a good understanding of how the pi electrons are delocalized across the four carbons in this conjugated diene. This delocalization of electrons stablizes the conjugated diene:



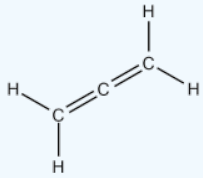
STABILITY OF CONJUGATED DIENES - THE MOLECULAR ORBITALS EXPLANATION

A molecular orbital model for 1,3-butadiene is shown below. Note that the lobes of the four p-orbital components in each pi-orbital are colored differently and carry a plus or minus sign. This distinction refers to different phases, defined by the mathematical wave equations for such orbitals. Regions in which adjacent orbital lobes undergo a phase change are called **nodes**. Orbital electron density is zero in such regions. Thus a single p-orbital has a node at the nucleus, and all the pi-orbitals shown here have a nodal plane that is defined by the atoms of the diene. This is the only nodal surface in the lowest energy pi-orbital, π_1. Higher energy pi-orbitals have an increasing number of nodes. Since 1,3-butadiene has four pi electrons. The two bonding molecular orbitals are filled to explain the measurable stability of conjugated double bonds.



Exercise

1. The heat of hydrogenation for allene is about 300 kJ/mol. Order a conjugated diene, a non-conjugated diene, and allene in increasing stability.



Allene

Answer

1. allene < non-conjugated diene < conjugated diene (most stable)

CONTRIBUTORS AND ATTRIBUTIONS

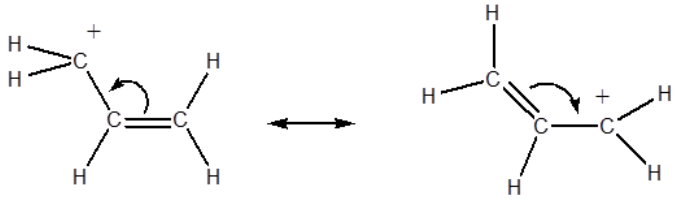
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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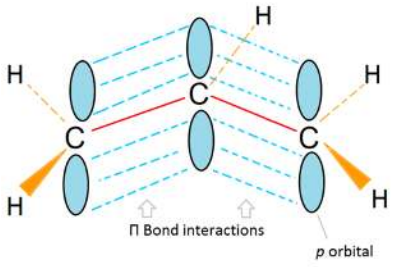
16.2: ALLYLIC CATIONS

RESONANCE AND ALLYLIC CARBOCATION STABILITY

Conjugation occurs when p orbital on three or more adjacent atoms can overlap. Conjugation tends to stabilize molecules. Allylic carbocations are a common conjugated system. The resonance structures below help explain the stability of allylic carbocations. The true structure of the conjugated allyl carbocation is a hybrid of of the two resonance structure so the positive charge is delocalized over the two terminal carbons. This delocalization stablizes the allyl carbocation making it more stable than a normal primary carbocation.



The positive charge of a carbocation is contained in a p orbital of a sp^2 hybridized carbon. This allows for overlap with double bonds. The positive charge is more stable because it is spread over 2 carbons.



MOLECULAR ORBITALS AND ALLYLIC CARBOCATION STABILITY

The stability of the carbocation of propene is due to a conjugated π electron system. A "double bond" doesn't really exist. Instead, it is a group of 3 adjacent, overlapping, non-hybridized *p* orbitals we call a **conjugated π electron system**. You can clearly see the interactions between all three of the *p* orbitals from the three carbons resulting in a really stable cation. It all comes down to where the location of the electron-deficient carbon is.

Molecular orbital descriptions can explain allylic stability in yet another way using 2-propenyl. Fig.6

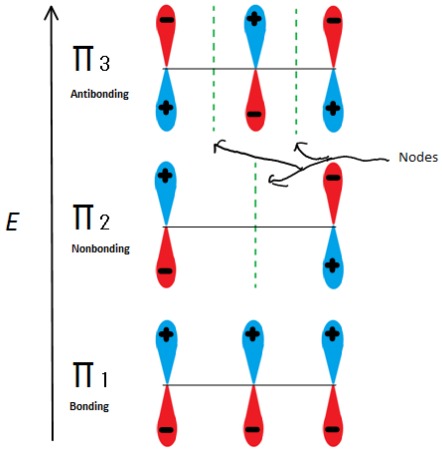


Figure: The 3 possible Molecular orbitals of 2-propenyl

If we just take the π molecular orbital and not any of the s, we get three of them. π_1 is bonding with no nodes, π_2 is nonbonding (In other words, the same energy as a regular *p*-orbital) with a node, and π_3 is antibonding with 2 nodes (none of the orbitals are interacting). The first two electrons will go into the π_1 molecular orbital, regardless of whether it is a cation, radical, or anion. If it is a radical or anion, the next electron goes into the π_2 molecular orbital. The last anion electron goes into the nonbonding orbital also. So no matter what kind of carbon center exists, no electron will ever go into the antibonding orbital.

The Bonding orbitals are the lowest energy orbitals and are favorable, which is why they are filled first. Even though the nonbonding orbitals can be filled, the overall energy of the system is still lower and more stable due to the filled bonding molecular orbitals.

This figure also shows that π_2 is the only molecular orbital where the electrion differs, and it is also where a single node passes through the middle. Because of this, the charges of the molecule are mainly on the two terminal carbons and not the middle carbon.

This molecular orbital description can also illustrate the stability of allylic carbon centers in figure 7.

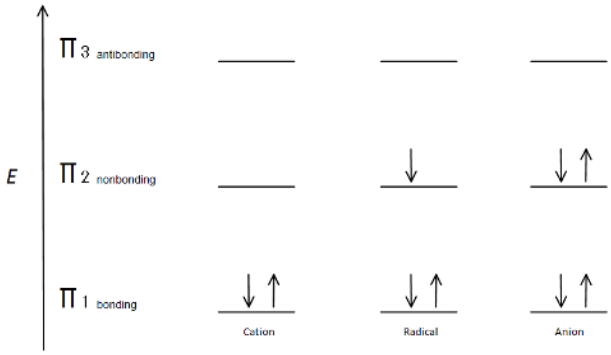
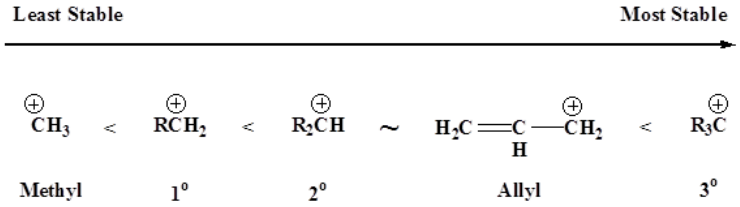


Figure: Diagram showing how the electrons fill based on the Aufbau principle.

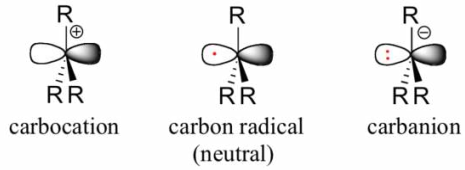
The π bonding orbital is lower in energy than the nonbonding *p* orbital. Since every carbon center shown has two electrons in the lower energy, bonding π orbitals, the energy of each system is lowered overall (and thus more stable), regardless of cation, radical, or anion.

RELATIVE STABILITIES OF CARBOCATIONS

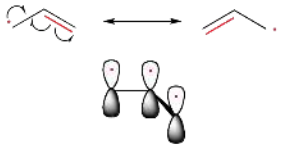


ALLYLIC RADICALS

As organic chemists, we are particularly interested in radical intermediates in which the unpaired electron resides on a carbon atom. Experimental evidence indicates that the three bonds in a carbon radical have trigonal planar geometry, and therefore the carbon is considered to be sp^2-hybridized with the unpaired electron occupying the perpendicular, unhybridized $2p_z$orbital. Contrast this picture with carbocation and carbanion intermediates, which are both also trigonal planar but whose $2p_z$ orbitals contain zero or two electrons, respectively.



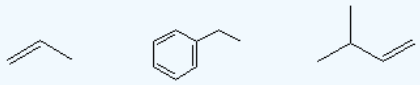
The trend in the stability of carbon radicals parallels that of carbocations (section 8.4B): tertiary radicals, for example, are more stable than secondary radicals, followed by primary and methyl radicals. This should make intuitive sense, because radicals, like carbocations, can be considered to be electron deficient, and thus are stabilized by the electron-donating effects of nearby alkyl groups. Benzylic and allylic radicals are more stable than alkyl radicals due to resonance effects - an unpaired electron can be delocalized over a system of conjugated pi bonds. An allylic radical, for example, can be pictured as a system of three parallel $2p_z$ orbitals sharing three electrons.



This can also explain why allylic radicals are much more stable than secondary or even tertiary carbocations. This is all due to the positioning of the pi orbitals and ability for overlap to occur to strengthen the single bond between the two double bonds.

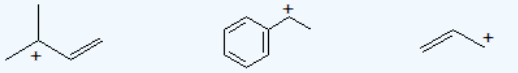
Exercise

2. Draw the bond-line structure for the most stable carbocation that can be formed from each hydrocarbon below. Arrange the carbocations in order of decreasing stability.



Answer

2. Carbocations in order of decreasing stability.



tertiary allylic | secondary benzylic | primary allylic

CONTRIBUTORS AND ATTRIBUTIONS

- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)
- Jeffrey Hu

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16.3: ELECTROPHILIC ADDITIONS TO CONJUGATED DIENES

OBJECTIVES

- After completing this section, you should be able to
- write an equation for the addition of one or two mole equivalents of a halogen or a hydrogen halide to a nonconjugated diene.
- write an equation for the addition of one or two mole equivalents of a halogen or a hydrogen halide to a conjugated diene.
- write the mechanism for the addition of one mole equivalent of hydrogen halide to a conjugated diene, and hence account for the formation of 1,2- and 1,4-addition products.
- explain the stability of allylic carbocations in terms of resonance.
- draw the resonance contributors for a given allylic carbocation.
- predict the products formed from the reaction of a given conjugated diene with one mole equivalent of halogen or hydrogen halide.
- predict which of the possible 1,2- and 1,4-addition products is likely to predominate when one mole equivalent of a hydrogen halide is reacted with a given conjugated diene.
- use the concept of carbocation stability to explain the ratio of the products obtained when a given conjugated diene is reacted with one mole equivalent of hydrogen halide.

KEY TERMS

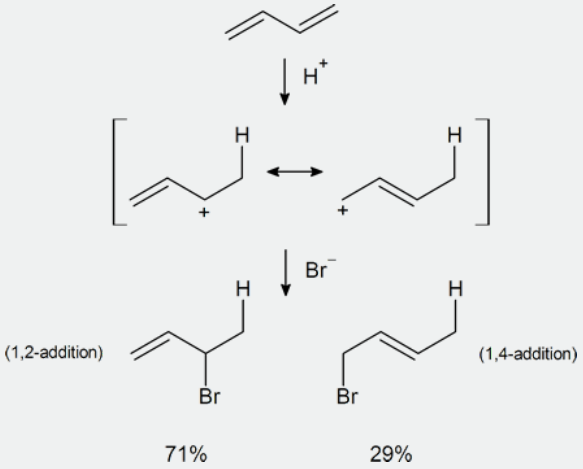
- Make certain that you can define, and use in context, the key terms below.
- 1,2-addition
- 1,4-addition

STUDY NOTES

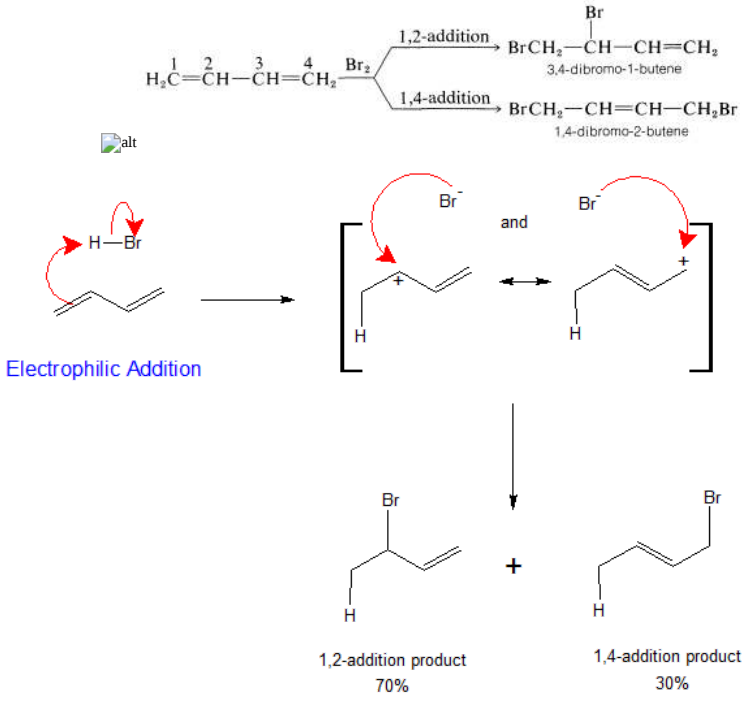
Notice that the numbers used in the expressions 1,2-addition and 1,4-addition do *not* refer to the positions of the carbon atoms in the diene molecule. Here, 1,2 indicates two neighbouring carbon atoms, while 1,4 indicates two carbon atoms which are separated in the carbon chain by two additional carbon atoms. Thus in 1,2- and 1,4-additions to 2,4-hexadiene, the additions actually occur at carbons 2 and 3, and 2 and 5, respectively.

The term “monoadduct” should be interpreted as meaning the product or products formed when one mole of reagent adds to one mole of substrate. In the objectives above, this process is referred to as the addition of one mole equivalent (or one mol equiv).

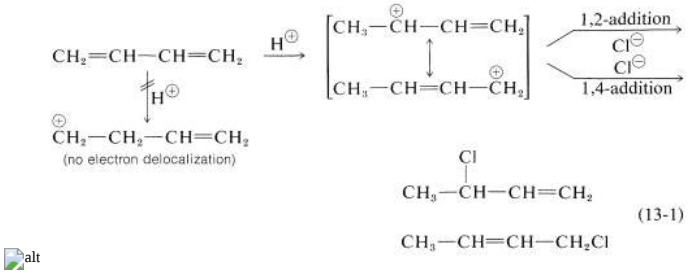
In Section 7.9 we saw that electrophilic addition to a simple alkene would follow Markovnikov’s rule, where the stability of the carbocation intermediate would increase: primary < secondary < tertiary. With conjugated dienes the allylic carbocation intermediately generated has different resonance forms. The following scheme represents the mechanism for the addition of HBr to 1,3-butadiene (at 0°C). Note the resonance contributors for the allylic carbocation intermediate and that the product resulting from the secondary cation is generated in higher yield than from the primary cation as you might expect from our discussions until now. However, in the next section you will see that the resulting product ratio can be drastically affected by a number of reaction conditions, including temperature.



The reactions of 1,3-butadiene are reasonably typical of conjugated dienes. The compound undergoes the usual reactions of alkenes, such as catalytic hydrogenation or radical and polar additions, but it does so *more readily* than most alkenes or dienes that have isolated double bonds. Furthermore, the products frequently are those of 1,2 *and* **1,4 addition:**



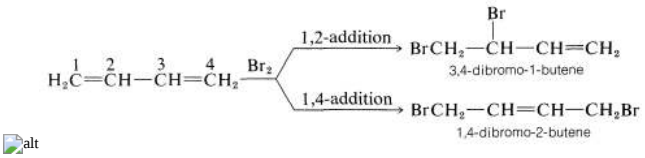
Formation of both 1,2- and 1,4-addition products occurs not only with halogens, but also with other electrophiles such as the hydrogen halides. The mechanistic course of the reaction of 1,3-butadiene with hydrogen chloride is shown in Equation 13-1. The first step, as with alkenes, is formation of a carbocation. However, with 1,3-butadiene, if the proton is added to C1C1 (but not C2C2), the resulting cation has a substantial delocalization energy, with the charge distributed over two carbons (review Sections 6-5 and 6-5C if this is not clear to you). Attack of Cl⊖Cl⊖ as a nucleophile at one or the other of the positive carbons yields the 1,2- or the 1,4- addition product:



An important feature of reactions in which 1,2 and 1,4 additions occur in competition with one another is that the ratio of the products can depend on the temperature, the solvent, and also on the *total time of reaction*.

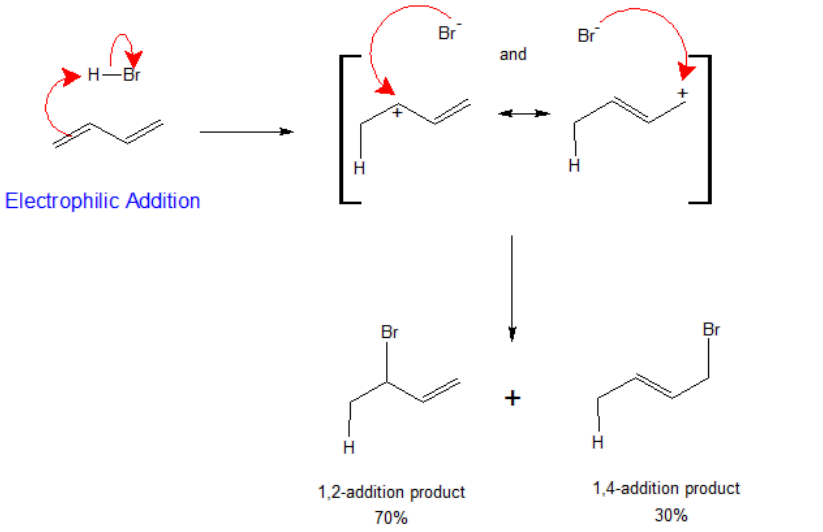
DIRECT VS CONJUGATE ADDITION

The description of direct versus conjugate addition uses numbers localized within the conjugate system and have nothing to do with the numbering system used to determine the IUPAC name for a conjugated diene. The reactions of 1,3-butadiene are reasonably typical of conjugated dienes and illustrate the difference in the numbering system to describe the reaction versus the IUPAC nomenclature numbers.



MECHANISM FOR THE ELECTROPHILIC ADDITION TO CONJUGATE DIENES

The mechanism below explains the formation and distribution of addition products to conjugated dienes using 1,3-butadiene as an example. The first step, as with isolated alkenes, is the formation of a carbocation. For 1,3-butadiene, the proton is added to form the allylic, resonance stabilized carbocation intermediate. The resulting cation has a substantial delocalization energy, with the charge distributed over two carbons. The nucleophile reacts with both carbons, but favors the carbon bearing the larger partial positive charge. The reaction yields both the 1,2- or the 1,4- addition products. The more stable the intermediate produces the greater the percentage of the final products as shown in the mechanism below.



Formation of both 1,2- and 1,4-addition products occurs not only with hydrohalic acids, but with halogens, catalytic hydrogenation or radical, and other polar additions associated with the electrophilic addition reactions of isolated alkenes.

In a tertiary (3°) alcohol, the carbon atom holding the -OH group is attached directly to three alkyl groups, which may be any combination of same or different. Examples:

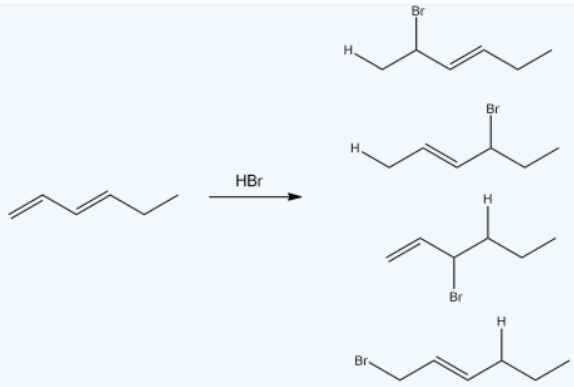
Exercise

3. Give the 1,2 and the 1,4 products of the addition of one equivalent of HBr to 1,3-hexa-diene.

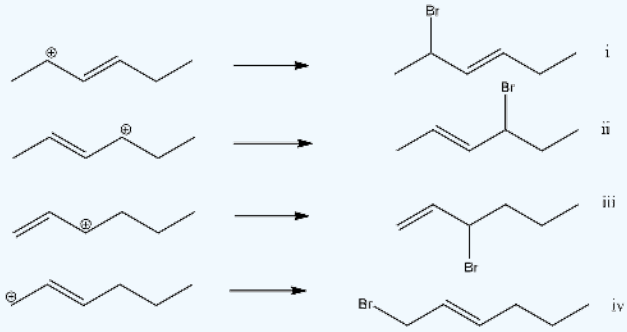
4. Look at the previous addition reaction of HBr with a diene. Consider the transition states, predict which of them would be the major products and which will be the minor.

Answer

3.



4. The products i-iii all show a secondary cation intermediate which is more stable than primary. Therefore those would be major products and the iv product would be the minor product.



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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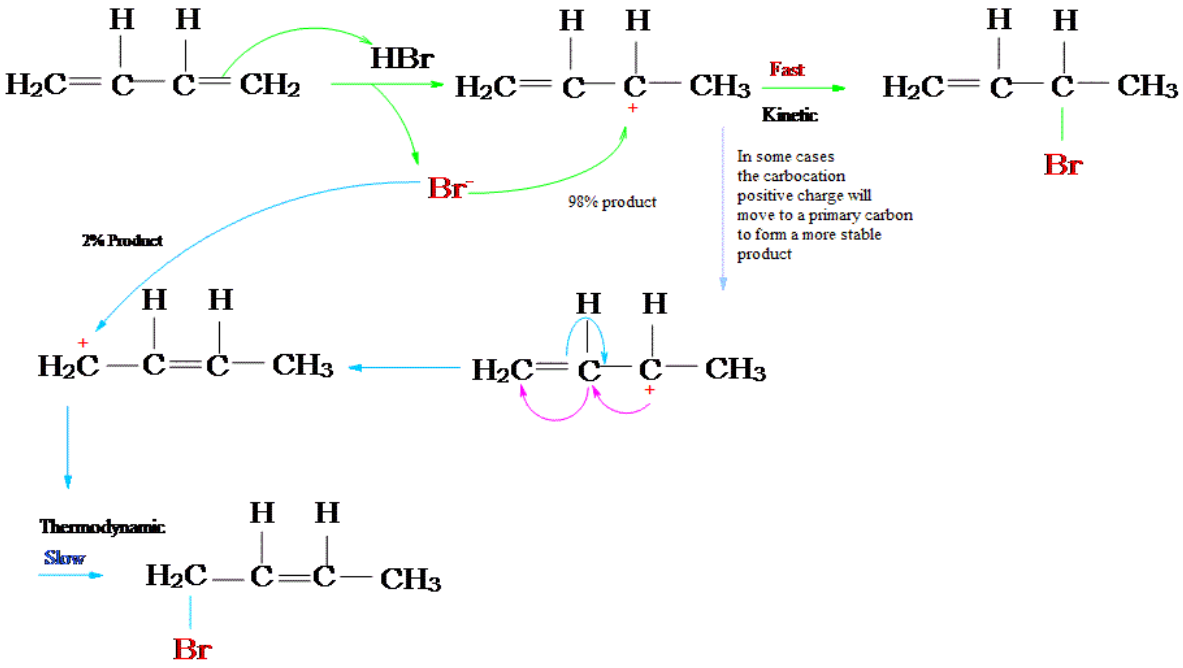
16.4: KINETIC VERSUS THERMODYNAMIC CONTROL

THERMODYNAMIC VS KINETIC CONTROL

Upon electrophilic addition, the conjugated diene forms a mixture of two products—the kinetic product and the thermodynamic product—whose ratio is determined by the conditions of the reaction. A reaction yielding more thermodynamic product is under thermodynamic control, and likewise, a reaction that yields more kinetic product is under kinetic control. The reaction of one equivalent of hydrogen bromide with 1,3-butadiene gives different ratios of products under different reaction conditions to illustrate the difference between thermodynamic and kinetic control.

The green mechanism arrows show the formation of the kinetically favored 1,2-addition product. As shown in the reaction energy diagram below the reaction, the 1,2-addition reaction has a smaller activation energy and faster reaction rate. This faster reaction rate is what led to the term "kinetic control". This reaction is favored by low temperatures where the activation energy becomes the primary barrier to chemical reactivity.

The blue mechanism arrows show the formation of the 1,4-addition product, the thermodynamically favored product. As shown in the reaction energy diagram below the reaction, the product of the 1,4-addition reaction is lower in potential energy. Its formation is favored by reactions at high temperatures where there is adequate thermodynamic energy to overcome all of the activation energy barriers. This reaction is favored by elevated temperatures which led to the term "thermodynamic control".



Reaction Energy Diagram for 1,3-butadiene + HBr

The table below summarizes the empirically derived reactivity patterns for conjugated dienes at four different reaction conditions. Becoming familiar with the reactivity data and patterns in this table helps us build wisdom for determining the optimum reaction conditions when competing mechanisms are possible.

Table : Conjugated Dienes: Kinetic vs. Thermodynamic Conditions

Temperature	Kinetic or Thermodynamically Controlled	Speed of Reaction	1,2-adduct : 1,4-adduct Ratio
-15 °C	Kinetic	Fast	70:30
0 °C	Kinetic	Fast	60:40
40 °C	Thermodynamic	Slow	15:85
60 °C	Thermodynamic	Slow	10:90

A Warning: Not every reaction has different thermodynamic and kinetic products!

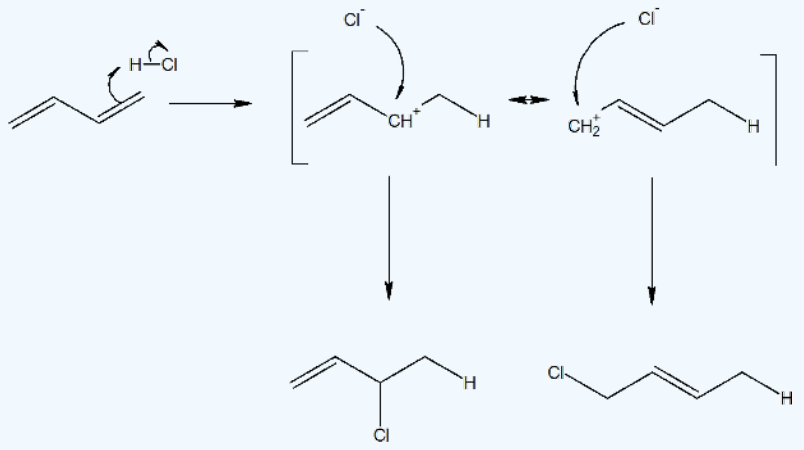
Note that not every reaction has an energy profile diagram like Figure **16.4.1**, and not every reaction has different thermodynamic and kinetic products! If the transition states leading to the formation of **C** (e.g., T_{C1}, *and* T_{C2}) were to be higher in energy than that leading to **B** (e.g., T_{B1}, *and* T_{B2}), then **B** would simultaneously be both the thermodynamic and kinetic product. There are plenty of reactions in which the more stable product (*thermodynamic*) is also formed faster (*kinetic*).

Exercise

5. Consider the reaction with 1,3-buta-diene reacting with HCl. Propose a mechanism for the reaction.

Answer

5.



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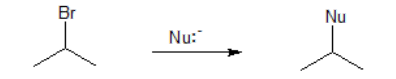
- Orthocresol (@chemistry StackExchange)
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Natasha Singh

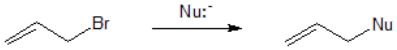
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16.5: SN2 REACTIONS OF ALLYLIC HALIDES AND TOSYLATES

S_N2 REACTIONS OF ALLYLIC HALIDES AND TOSYLATES

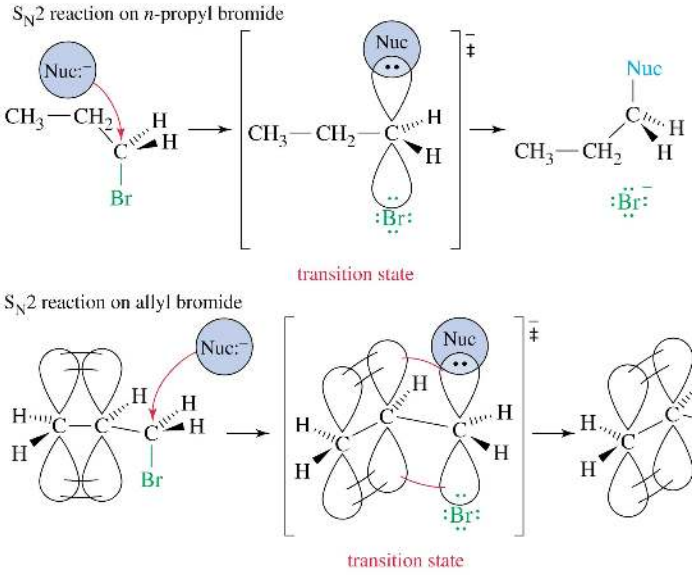
Allylic halides and tosylates are excellent electrophiles for bimolecular nucleophilic substitution reactions (S_N2).





Faster reaction rate because of resonance stabilized transition state through hyperconjugation between the p orbitals of the pi bond system and the orbital of the nucleophile.

They exhibit faster S_N2 reactivity than secondary alkyl halides because the bimolecular transition state is stabilized by hyperconjugation between the orbital of the nucleophile and the conjugated pi bond of the allylic group as shown in the diagram below.

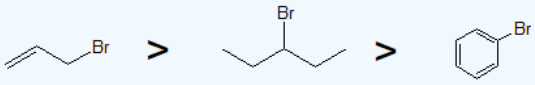


Exercise

6. Arrange the compounds 3-bromopentane, bromobenzene, and 3-bromo-1-propene in order of decreasing S_N2 reactivity using their bond-line structures.

Answer

6.



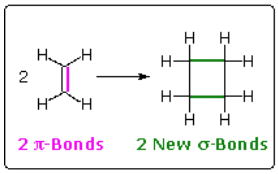
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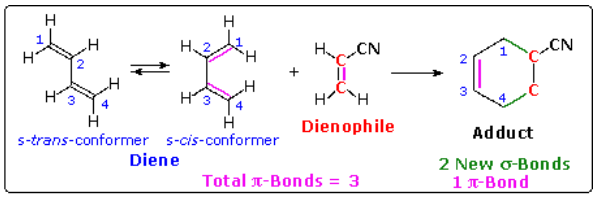
16.6: THE DIELS-ALDER (4 + 2) CYCLOADDITION REACTION

THE DIELS-ALDER (4+2) CYCLOADDITION REACTION

A cycloaddition reaction is the concerted bonding together of two independent pi-electron systems to form a new ring of atoms. When this occurs, two pi-bonds are converted to two sigma-bonds, the simplest example being the hypothetical combination of two ethene molecules to give cyclobutane. This does not occur under normal conditions, but the cycloaddition of 1,3-butadiene to cyanoethene (acrylonitrile) does, and this is an example of the Diels-Alder reaction. The following diagram illustrates two cycloadditions, and introduces several terms that are useful in discussing reactions of this kind.



A [2+2] Cycloaddition



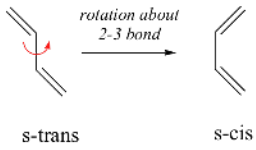
A [4+2] Cycloaddition

In the hypothetical ethylene dimerization on the left, each reactant molecule has a pi-bond (colored orange) occupied by two electrons. The cycloaddition converts these pi-bonds into new sigma-bonds (colored green), and this transformation is then designated a [2+2] cycloaddition, to enumerate the reactant pi-electrons that change their bonding location.

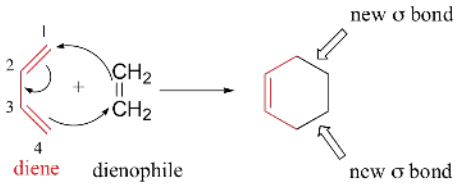
The Diels-Alder reaction is an important and widely used method for making six-membered rings, as shown on the right. The reactants used in such reactions are a conjugated diene, simply referred to as the **diene**, and a double or triple bond co-reactant called the **dienophile**, because it combines with (has an affinity for) the diene. The Diels-Alder cycloaddition is classified as a [4+2] process because the diene has four pi-electrons that shift position in the reaction and the dienophile has two.

DIELS-ALDER MECHANISM

The Diels-Alder reaction is a single step process, so the diene component must adopt an s-cisconformation in order for the end carbon atoms (#1 & #4) to bond simultaneously to the dienophile. For many acyclic dienes the s-trans conformer is more stable than the s-cis conformer (due to steric crowding of the end groups), but the two are generally in rapid equilibrium, permitting the use of all but the most hindered dienes as reactants in Diels-Alder reactions. In order for a Diels-Alder reaction to occur, the diene molecule must adopt what is called the **s-cis conformation**:

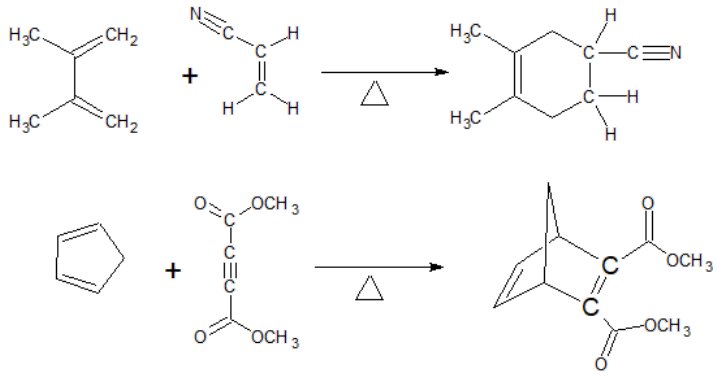


In its usual form, the diene component is electron rich, and the best dienophiles are electron poor due to electron withdrawing substituents such as CN, C=O & NO_2. The initial bonding interaction reflects this electron imbalance, with the two new sigma-bonds being formed simultaneously, but not necessarily at equal rates. Essentially, this process involves overlap of the 2p orbitals on carbons 1 and 4 of the diene with the two 2p orbitals on the sp^2-hybridized carbons of the dienophile. Both of these new overlaps form new sigma bonds, and a new pi bond is formed between carbon 2 and 3 of the diene.



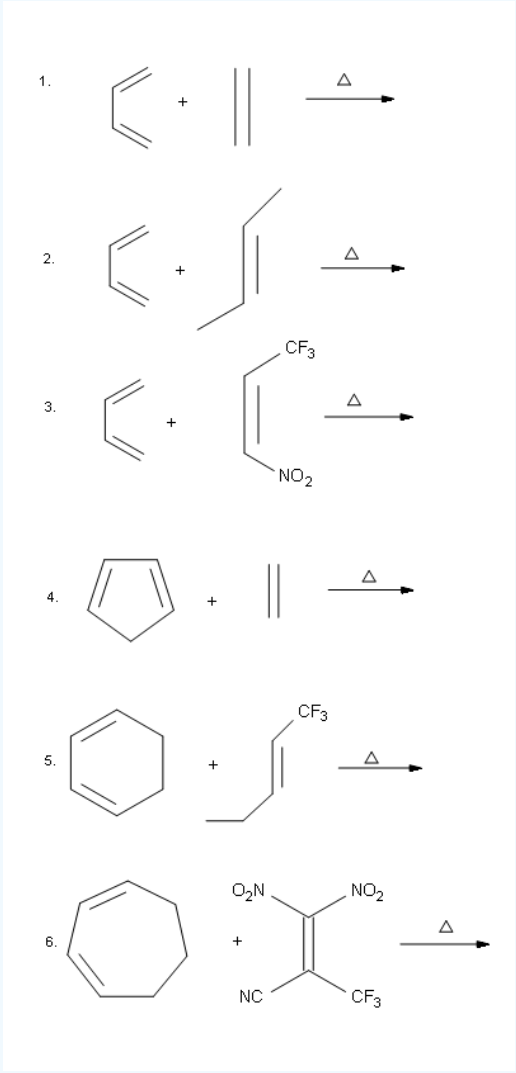
One of the most important things to understand about this process is that it is *concerted* – all of the electron rearrangement takes place at once, with no carbocation intermediates.

Since the diene takes the role of the nucleophile, electron donating group increase the reactivity of the diene. While the dienophile takes the role of the electrophile, electronwithdrawing groups increase the reactivity of the dienophile. The reactions below are examples of the Diels-Alder reaction.



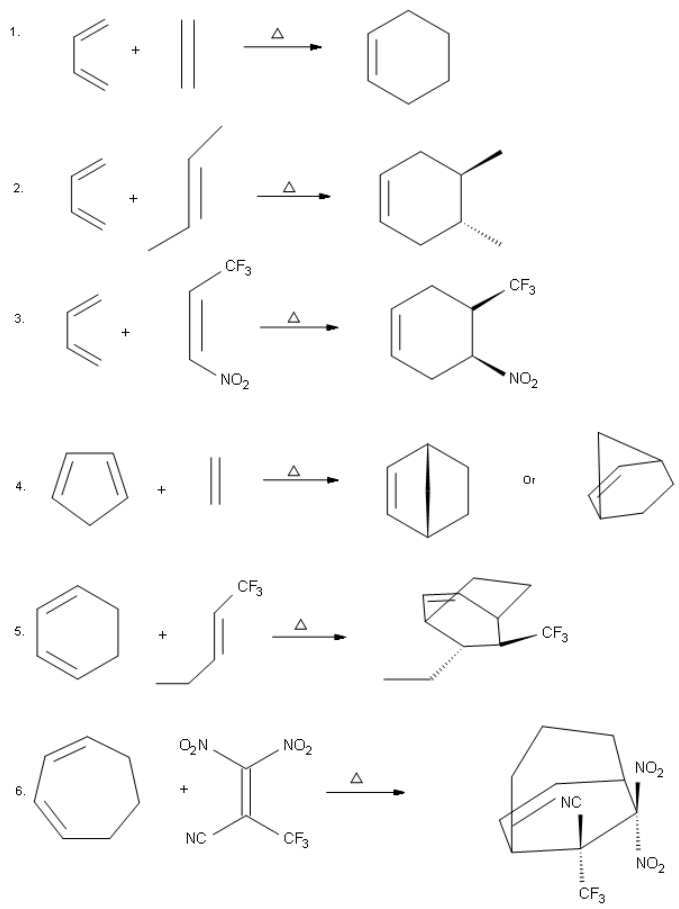
Exercise

7. Draw the bond-line structures for the reactions below.



Answer

7.



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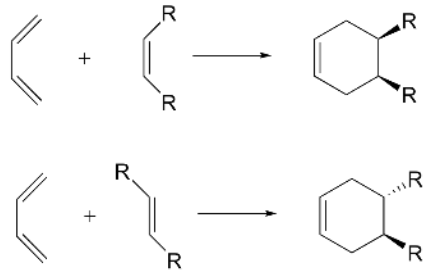
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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Amar Patel (UCD)

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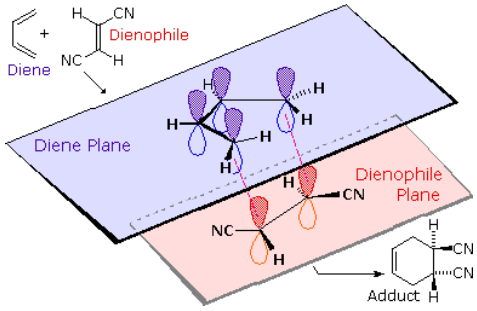
16.7: DIELS-ALDER STEREOCHEMISTRY

DIELS-ALDER REACTIONS ARE STEREOSPECIFIC

The Diels-Alder reaction is enormously useful for synthetic organic chemists, not only because ring-forming reactions are useful in general but also because in many cases two new stereocenters are formed, and the reaction is inherently stereospecific. A *cis* dienophile will generate a ring with *cis* substitution, while a *trans* dienophile will generate a ring with *trans* substitution:

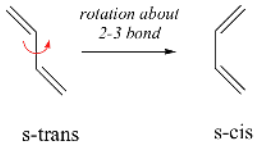


We noted earlier that addition reactions of alkenes often exhibited stereoselectivity, in that the reagent elements in some cases added syn and in other cases anti to the the plane of the double bond. Both reactants in the Diels-Alder reaction may demonstrate stereoisomerism, and when they do it is found that the relative configurations of the reactants are preserved in the product (the adduct). The following drawing illustrates this fact for the reaction of 1,3-butadiene with (E)-dicyanoethene. The trans relationship of the cyano groups in the dienophile is preserved in the six-membered ring of the adduct. Likewise, if the terminal carbons of the diene bear substituents, their relative configuration will be retained in the adduct. Using the earlier terminology, we could say that bonding to both the diene and the dienophile is syn. An alternative description, however, refers to the planar nature of both reactants and terms the bonding in each case to be **suprafacial** (i.e. to or from the same face of each plane). This stereospecificity also confirms the synchronous nature of the 1,4-bonding that takes place.

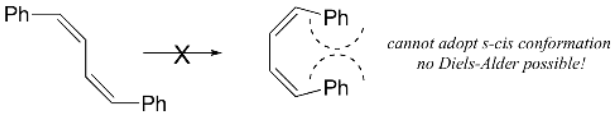


DIENE SUBSTITUENTS AND DIELS-ALDER REACTIVITY

In order for a Diels-Alder reaction to occur, the diene molecule must adopt what is called the **s-cis conformation**:

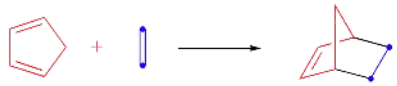


The s-cis conformation is higher in energy than the s-trans conformation, due to steric hindrance. For some dienes, extreme steric hindrance causes the s-cis conformation to be highly strained, and for this reason such dienes do not readily undergo Diels-Alder reactions.

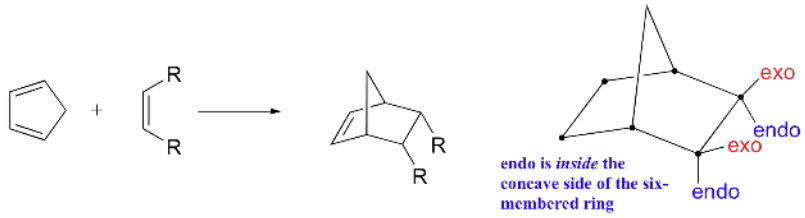


BICYCLIC RING FORMATION AND THE EXO- AND ENDO- POSITIONS

Cyclic dienes that are 'locked' in the s-cis conformation are especially reactive. The result of a Diels-Alder reaction involving a cyclic diene is a **bicyclic** structure:

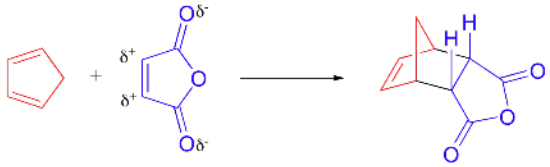


Here, we see another element of stereopecificity: Diels-Alder reactions with cyclic dienes favor the formation of bicyclic structures in which substituents are in the **endo position**.



The endo position on a bicyclic structure refers to the position that is *inside* the concave shape of the larger (six-membered) ring. As you might predict, the **exo position** refers to the *outside* position.

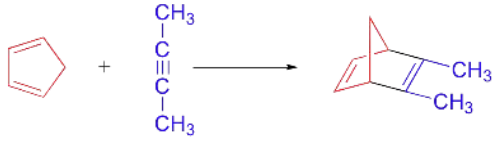
The rate at which a Diels-Alder reaction takes place depends on electronic as well as steric factors. A particularly rapid Diels-Alder reaction takes place between cyclopentadiene and maleic anhydride.



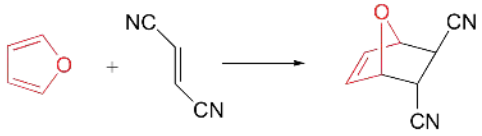
We already know that cyclopentadiene is a good diene because of its inherent s-cis conformation. Maleic anhydride is also a very good dienophile, because the electron-withdrawing effect of the carbonyl groups causes the two alkene carbons to be electron-poor, and thus a good target for reaction with the pi electrons in the diene.

In general, Diels-Alder reactions proceed fastest with electron-donating groups on the diene (eg. alkyl groups) and electron-withdrawing groups on the dienophile.

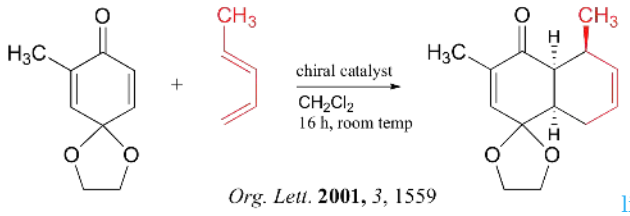
Alkynes can also serve as dienophiles in Diels-Alder reactions:



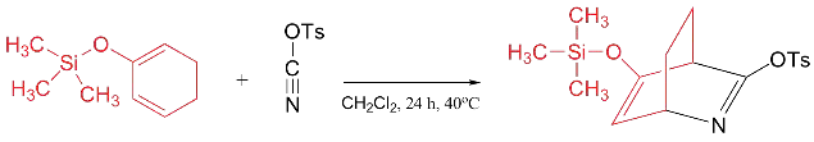
Below are three examples of Diels-Alder reactions that have been reported in recent years:



J. Med. Chem. **2008,** *51*, 424 link



Org. Lett. **2001,** *3*, 1559 link



J. Org. Chem. **2003,** *68,* 8256 link

OTHER PERICYCLIC REACTIONS

The Diels-Alder reaction is just one example of a **pericyclic** reaction: this is a general term that refers to concerted rearrangements that proceed though cyclic transition states. Two well-studied intramolecular pericyclic reactions are known as the Cope rearrangement . . .

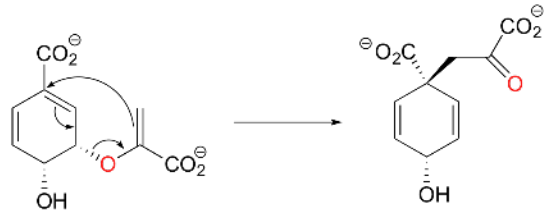


. . .and the Claisen rearrangement (when an oxygen is involved):



Notice that the both of these reactions require compounds in which two double bonds are separated by three single bonds.

Pericyclic reactions are rare in biological chemistry, but here is one example: the Claisen rearrangement catalyzed by chorismate mutase in the aromatic amino acid biosynthetic pathway.



chorismate prephenate

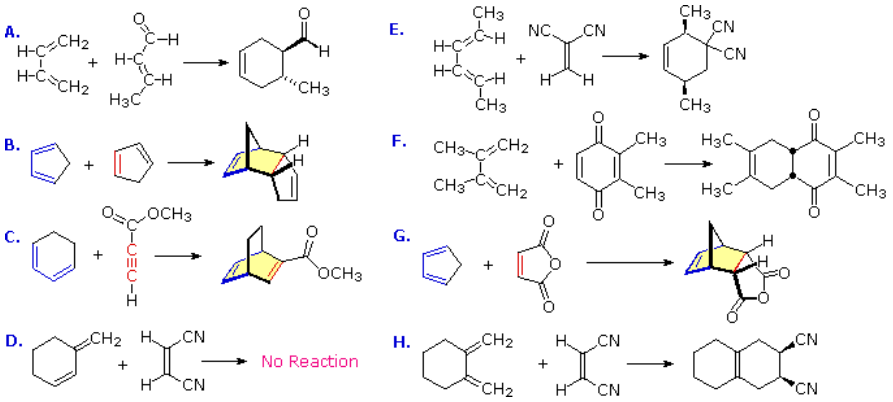
The study of pericyclic reactions is an area of physical organic chemistry that blossomed in the mid-1960s, due mainly to the work of R.B. Woodward, Roald Hoffman, and Kenichi Fukui. The **Woodward-Hoffman rules** for pericyclic reactions (and a simplified version introduced by Fukui) use molecular orbital theory to explain why some pericyclic processes take place and others do not. A full discussion is beyond the scope of this text, but if you go on to study organic chemistry at the advanced undergraduate or graduate level you are sure to be introduced to this fascinating area of inquiry.

DIELS-ALDER REACTION SUMMARY

The essential characteristics of the Diels-Alder cycloaddition reaction may be summarized as follows:

1. The reaction always creates a new six-membered ring. When intramolecular, another ring may also be formed.
2. The diene component must be able to assume a s-cis conformation.
3. Electron withdrawing groups on the dienophile facilitate reaction.
4. Electron donating groups on the diene facilitate reaction.
5. Steric hindrance at the bonding sites may inhibit or prevent reaction.
6. The reaction is stereospecific with respect to substituent configuration in both the dienophile and the diene.

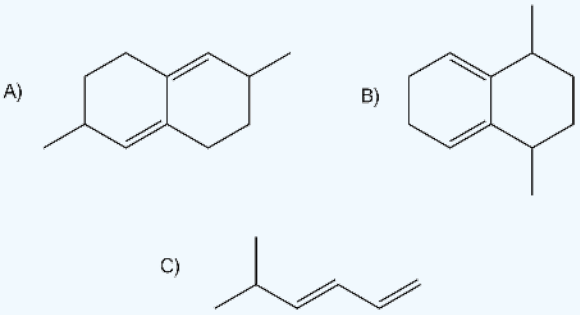
These features are illustrated by the following eight examples, one of which does not give a Diels-Alder cycloaddition.



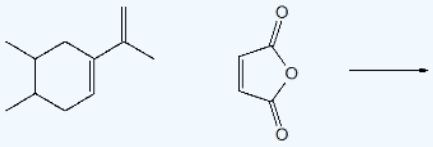
There is no reaction in example **D** because this diene cannot adopt an s-cis orientation. In examples **B, C, F, G & H** at least one of the reactants is cyclic so that the product has more than one ring, but the newly formed ring is always six-membered. In example **B** the the same cyclic compound acts as both the diene colored blue) and the dienophile (colored red). The adduct has three rings, two of which are the five-membered rings present in the reactant, and the third is the new six-membered ring (shaded light yellow). Example **C** has an alkyne as a dienophile (colored red), so the adduct retains a double bond at that location. This double bond could still serve as a dienophile, but in the present case the diene is sufficiently hindered to retard a second cycloaddition. The quinone dienophile in reaction **F** has two dienophilic double bonds. However, the double bond with two methyl substituents is less reactive than the unsubstituted dienophile due in part to the electron donating properties of the methyl groups and in part to steric hindrance. The stereospecificity of the Diels-Alder reaction is demonstrated by examples **A, E & H**. In **A & H** the stereogenic centers lie on the dienophile, whereas in **E** these centers are on the diene. In all cases the configuration of the reactant is preserved in the adduct.

Exercise

8. Of the following dienes, which are S-trans and which are s-cis? Of those that are s-trans, are they able to rotate to become s-cis?



9. Predict the product of the following reaction.



Answer

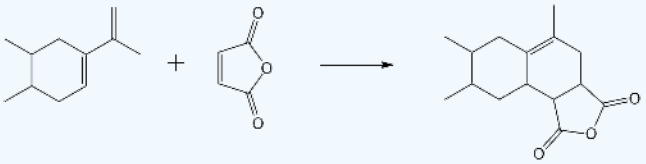
8.

A) s-trans, unable to rotate to become s-cis

B) s-cis

C) s-trans, can rotate to become s-cis.

9.



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

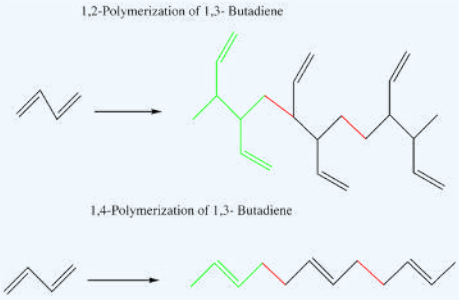
16.7: Diels-Alder Stereochemistry is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

16.8: DIENE POLYMERS - NATURAL AND SYNTHETIC RUBBERS

Conjugated dienes (alkenes with two double bonds and a single bond in between) can be polymerized to form important compounds like rubber. This takes place, in different forms, both in nature and in the laboratory. Interactions between double bonds on multiple chains leads to cross-linkage which creates elasticity within the compound.

POLYMERIZATION OF 1,3-BUTADIENE

For rubber compounds to be synthesized, 1,3-butadiene must be polymerized. Below is a simple illustration of how this compound is formed into a chain. The 1,4 polymerization is much more useful to polymerization reactions.



Above, the green structures represent the base units of the polymers that are synthesized and the red represents the bonds between these units which form these polymers. Whether the 1,3 product or the 1,4 product is formed depends on whether the reaction is thermally or kinetically controlled.

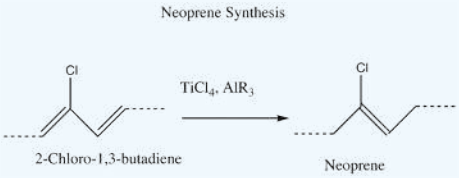
NATURAL RUBBER

Natural rubber is an addition polymer that is obtained as a milky white fluid known as latex from a tropical rubber tree. Natural rubber is from the monomer isoprene (2-methyl-1,3-butadiene), which is a conjugated diene hydrocarbon as mentioned above. In natural rubber, most of the double fonds formed in the polymer chain have the Z configuration, resulting in natural rubber's elastomer qualities.

Charles Goodyear accidentally discovered that by mixing sulfur and rubber, the properties of the rubber improved in being tougher, resistant to heat and cold, and increased in elasticity. This process was later called vulcanization after the Roman god of fire. Vulcanization causes shorter chains to cross link through the sulfur to longer chains. The development of vulcanized rubber for automobile tires greatly aided this industry.

SYNTHETIC RUBBER

The most important synthetic rubber is Neoprene which is produced by the polymerization of 2-chloro-1,3-butadiene.



In this illustration, the dashed lines represent repetition of the same base units, so both the products and reactants are polymers. The reaction proceeds with a mechanism similar to the Friedel-Crafts mechanism. Cross-linkage between the chlorine atom of one chain and the double bond of another contributes to the overall elasticity of neoprene. This cross-linkage occurs as the chains lie next to each other at random angles, and the attractions between double bonds prevent them from sliding back and forth.

OUTSIDE LINKS

- "Dienes," http://en.Wikipedia.org/wiki/Diene
- "Rubber," http://en.Wikipedia.org/wiki/Rubber
- "Neoprene," en.Wikipedia.org/wiki/Neoprene

REFERENCES

1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. New York: W. H. Freeman & Company, 2007.
2. Buehr, Walter. Rubber: Natural and Synthetic. Morrow, 1964.

Exercise

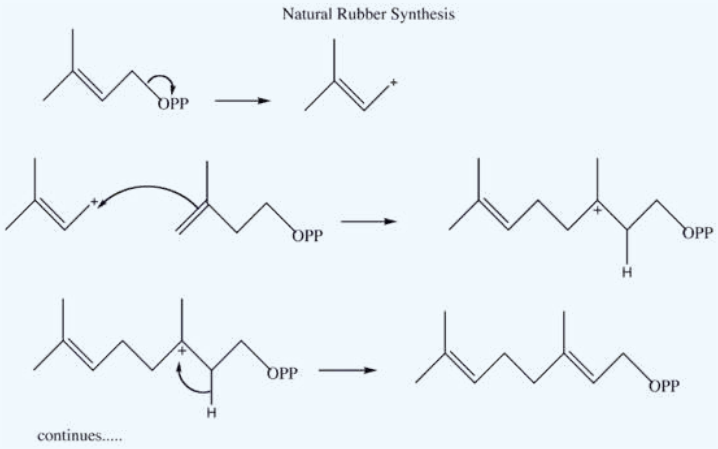
10. Draw out the mechanism for the natural synthesis of rubber from 3-methyl-3-butenyl pyrophosphate and 2-methyl-1,3-butadiene. Show the movement of electrons with arrows.

11. Draw a segment for the polymer that may be made from 2-*tert*-butyl-1,3-butadiene.

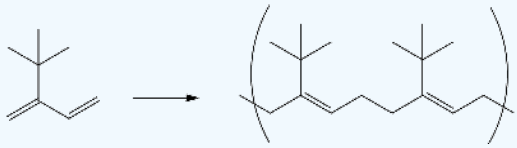
12. Propose the mechanism for the acid catalyzed polymerization of 2-methyl-1,3-butadiene.

Answer

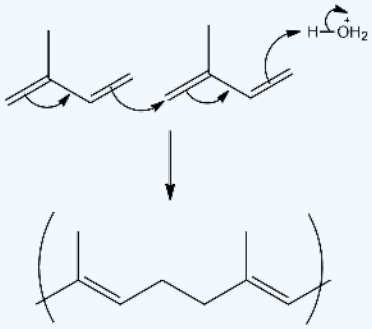
10.



11.



12. The initial step is an addition of a hydrogen from the acid, followed by the polymerization.



CONTRIBUTORS AND ATTRIBUTIONS

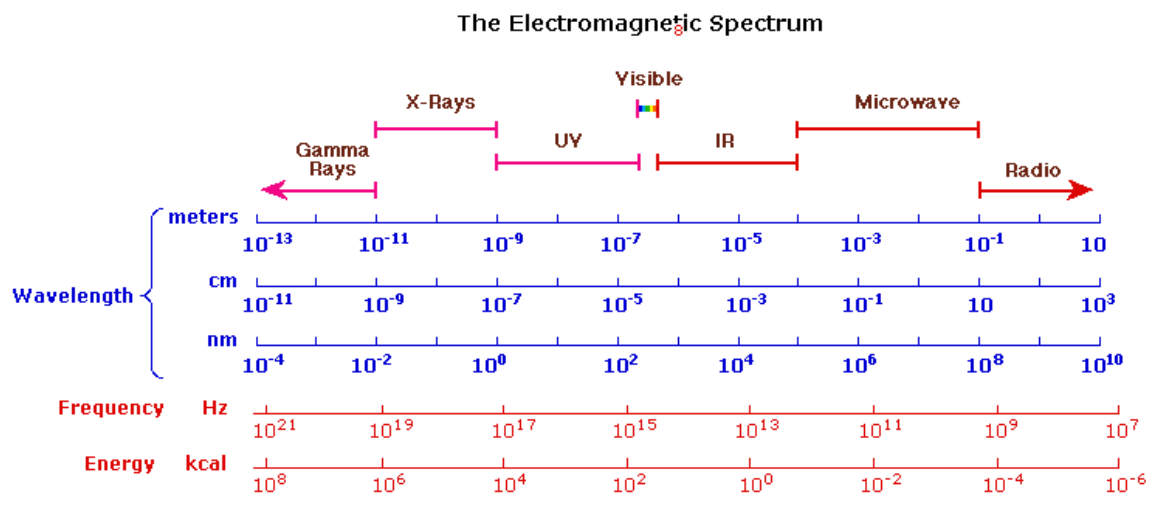
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
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16.9: STRUCTURE DETERMINATION IN CONJUGATED SYSTEMS - ULTRAVIOLET SPECTROSCOPY

THE ELECTROMAGNETIC SPECTRUM

The visible spectrum constitutes but a small part of the total radiation spectrum. Most of the radiation that surrounds us cannot be seen, but can be detected by dedicated sensing instruments. This **electromagnetic spectrum** ranges from very short wavelengths (including gamma and x-rays) to very long wavelengths (including microwaves and broadcast radio waves). The following chart displays many of the important regions of this spectrum, and demonstrates the inverse relationship between wavelength and frequency (shown in the top equation below the chart).

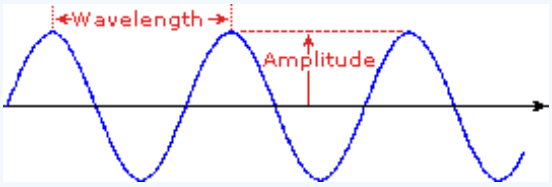


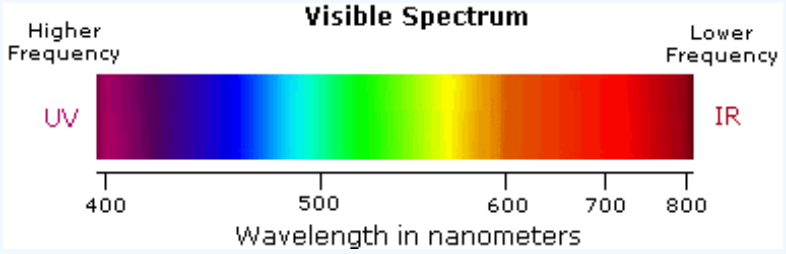
The energy associated with a given segment of the spectrum is proportional to its frequency. The bottom equation describes this relationship, which provides the energy carried by a photon of a given wavelength of radiation.

$\upsilon = c/\lambda$ υ=frequency, λ=wavelength, c=velocity of light ($c = 3 \cdot 10^{10}$ cm/sec)

$\Delta E = h\upsilon$ E=energy, υ=frequency, h=Planck's constant ($h = 6.6 \cdot 10^{-27}$ erg sec)

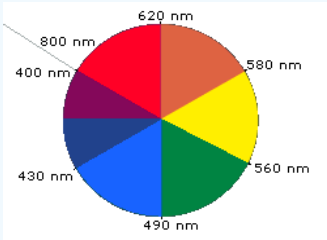
To obtain specific frequency, wavelength and energy values use this calculator.





- **Indigo:** 420 - 440 nm
- **Green:** 490 - 570 nm
- **Orange:** 585 - 620 nm
- **Red:** 620 - 780 nm

When white light passes through or is reflected by a colored substance, a characteristic portion of the mixed wavelengths is absorbed. The remaining light will then assume the complementary color to the wavelength(s) absorbed. This relationship is demonstrated by the color wheel shown below. Here, complementary colors are diametrically opposite each other. Thus, absorption of 420-430 nm light renders a substance yellow, and absorption of 500-520 nm light makes it red. Green is unique in that it can be created by absoption close to 400 nm as well as absorption near 800 nm.

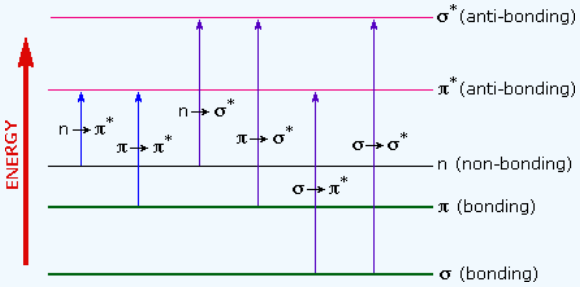


Early humans valued colored pigments, and used them for decorative purposes. Many of these were inorganic minerals, but several important organic dyes were also known. These included the crimson pigment, kermesic acid, the blue dye, indigo, and the yellow saffron pigment, crocetin. A rare dibromo-indigo derivative, punicin, was used to color the robes of the royal and wealthy. The deep orange hydrocarbon carotene is widely distributed in plants, but is not sufficiently stable to be used as permanent pigment, other than for food coloring. A common feature of all these colored compounds, displayed below, is a system of **extensively conjugated π-electrons**.

UV-VISIBLE ABSORPTION SPECTRA

To understand why some compounds are colored and others are not, and to determine the relationship of conjugation to color, we must make accurate measurements of light absorption at different wavelengths in and near the visible part of the spectrum. Commercial optical spectrometers enable such experiments to be conducted with ease, and usually survey both the near ultraviolet and visible portions of the spectrum.

The visible region of the spectrum comprises photon energies of 36 to 72 kcal/mole, and the near ultraviolet region, out to 200 nm, extends this energy range to 143 kcal/mole. Ultraviolet radiation having wavelengths less than 200 nm is difficult to handle, and is seldom used as a routine tool for structural analysis.



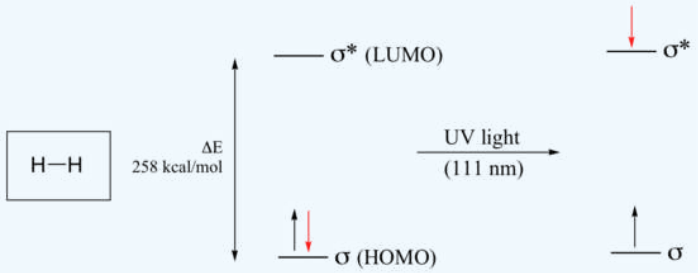
The energies noted above are sufficient to promote or excite a molecular electron to a higher energy orbital. Consequently, absorption spectroscopy carried out in this region is sometimes called "electronic spectroscopy". A diagram showing the various kinds of electronic excitation that may occur in organic molecules is shown on the left. Of the six transitions outlined, only the two lowest energy ones (left-most, colored blue) are achieved by the energies available in the 200 to 800 nm spectrum. As a rule, energetically favored electron promotion will be from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO), and the resulting species is called an **excited state**.

When sample molecules are exposed to light having an energy that matches a possible electronic transition within the molecule, some of the light energy will be absorbed as the electron is promoted to a higher energy orbital. An optical spectrometer records the wavelengths at which absorption occurs, together with the degree of absorption at each wavelength. The resulting spectrum is presented as a graph of absorbance (A) versus wavelength, as in the isoprene spectrum shown below. Since isoprene is colorless, it does not absorb in the visible part of the spectrum and this region is not displayed on the graph. **Absorbance** usually ranges from 0 (no absorption) to 2 (99% absorption), and is precisely defined in context with spectrometer operation.

ELECTRONIC TRANSITIONS

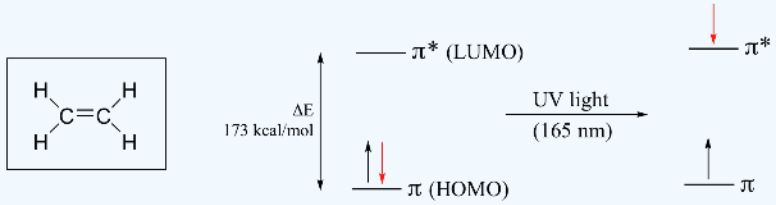
Let's take as our first example the simple case of molecular hydrogen, H_2. As you may recall from section 2.1A, the molecular orbital picture for the hydrogen molecule consists of one bonding σ MO, and a higher energy antibonding σ* MO. When the molecule is in the

ground state, both electrons are paired in the lower-energy bonding orbital – this is the Highest Occupied Molecular Orbital (HOMO). The antibonding σ* orbital, in turn, is the Lowest Unoccupied Molecular Orbital (LUMO).



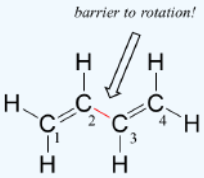
If the molecule is exposed to light of a wavelength with energy equal to **ΔE**, the HOMO-LUMO energy gap, this wavelength will be absorbed and the energy used to bump one of the electrons from the HOMO to the LUMO – in other words, from the σ to the σ* orbital. This is referred to as a **σ - σ* transition**. **ΔE** for this electronic transition is 258 kcal/mol, corresponding to light with a wavelength of 111 nm.

When a double-bonded molecule such as ethene (common name ethylene) absorbs light, it undergoes a **π - π* transition.** Because π-π* energy gaps are narrower than σ - σ* gaps, ethene absorbs light at 165 nm - a longer wavelength than molecular hydrogen.



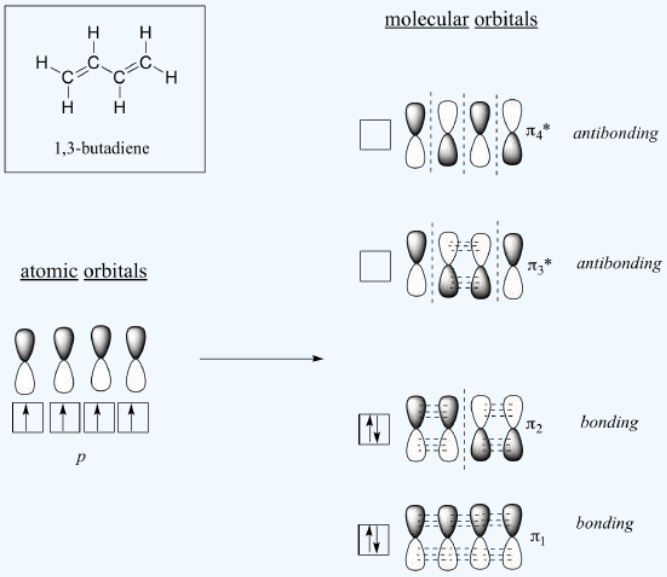
The electronic transitions of both molecular hydrogen and ethene are too energetic to be accurately recorded by standard UV spectrophotometers, which generally have a range of 220 – 700 nm. Where UV-vis spectroscopy becomes useful to most organic and biological chemists is in the study of molecules with conjugated pi systems. In these groups, the energy gap for π -π* transitions is smaller than for isolated double bonds, and thus the wavelength absorbed is longer. Molecules or parts of molecules that absorb light strongly in the UV-vis region are called **chromophores**.

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



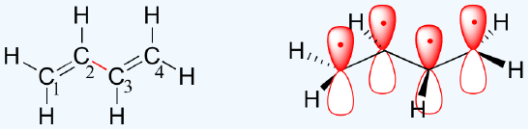
Experimentally, however, it is observed that there is a significant barrier to rotation about the C_2-C_3 bond, and that the entire molecule is planar. In addition, the C_2-C_3 bond is 148 pm long, shorter than a typical carbon-carbon single bond (about 154 pm), though longer than a typical double bond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

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



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

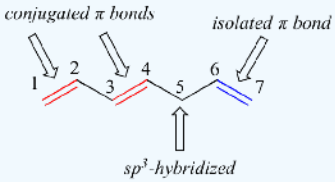
By the *aufbau* principle, the four electrons from the isolated $2p_z$ atomic orbitals are placed in the bonding pi_1 and pi_2 MO's. Because pi_1 includes constructive interaction between C_2 and C_3, there is a degree, in the 1,3-butadiene molecule, of pi-bonding interaction between these two carbons,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



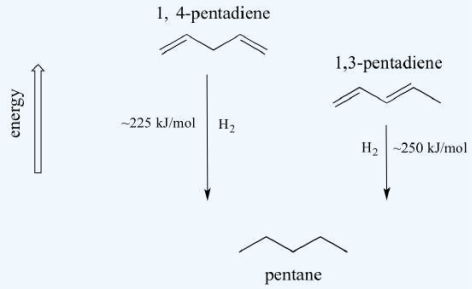
1,3-butadiene

space-filling view

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

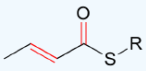


A very important concept to keep in mind is that *there is an inherent thermodynamic stability associated with conjugation.* This stability can be measured experimentally by comparing the **heat of hydrogenation** of two different dienes. (Hydrogenation is a reaction type that we will learn much more about in chapter 15: essentially, it is the process of adding a hydrogen molecule - two protons and two electrons - to a p bond). When the two *conjugated* double bonds of 1,3-pentadiene are 'hydrogenated' to produce pentane, about 225 kJ is released per mole of pentane formed. Compare that to the approximately 250 kJ/mol released when the two *isolated* double bonds in 1,4-pentadiene are hydrogenated, also forming pentane.

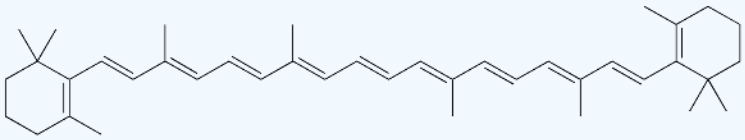


The conjugated diene is lower in energy: in other words, it is more stable. In general, conjugated pi bonds are more stable than isolated pi bonds.

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



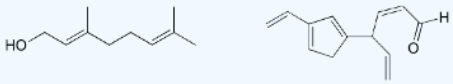
In molecules with extended pi systems, the HOMO-LUMO energy gap becomes so small that absorption occurs in the visible rather then the UV region of the electromagnetic spectrum. Beta-carotene, with its system of 11 conjugated double bonds, absorbs light with wavelengths in the blue region of the visible spectrum while allowing other visible wavelengths – mainly those in the red-yellow region - to be transmitted. This is why carrots are orange.



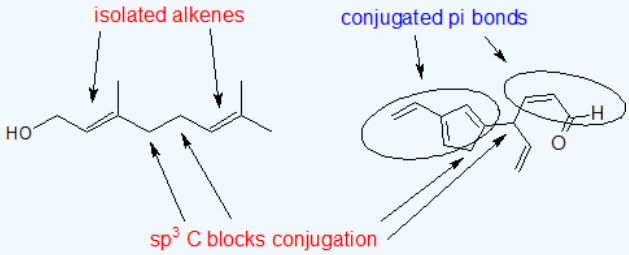
β-carotene

EXAMPLE 1

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

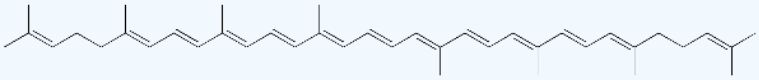


Solution: Look for sp^3 hybridized carbons to find disruptions in conjugation.



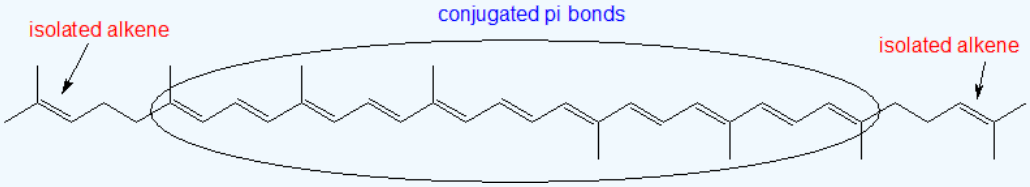
EXAMPLE 2

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



lycopene

Solution: There are 11 conjugated pi bonds for a total of 22 pi electrons and 2 isolated pi bonds.



Exercise

13. What is the energy range for 300 nm to 500 nm in the ultraviolet spectrum? How does this compare to energy values from NMR and IR spectroscopy?

Answer

13.

$E = hc/\lambda$

$E = (6.62 \times 10^{-34}\ \text{Js})(3.00 \times 10^{8}\ \text{m/s})/(3.00 \times 10^{-7}\ \text{m})$

$E = 6.62 \times 10^{-19}\ \text{J}$

The range of 3.972×10^{-19} to 6.62×10^{-19} joules. This energy range is greater in energy than the in NMR and IR.

CONTRIBUTORS

- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

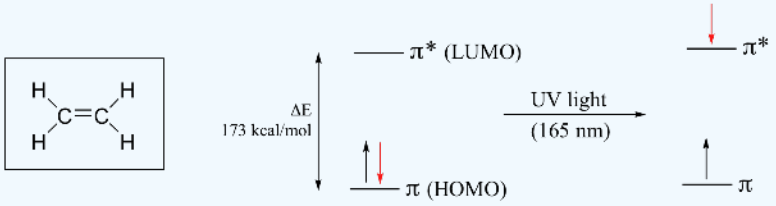
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16.10: INTERPRETING ULTRAVIOLET SPECTRA - THE EFFECT OF CONJUGATION

UV SPECTROSCOPY AND PI ELECTRON TRANSITIONS BETWEEN THE HOMO AND LUMO

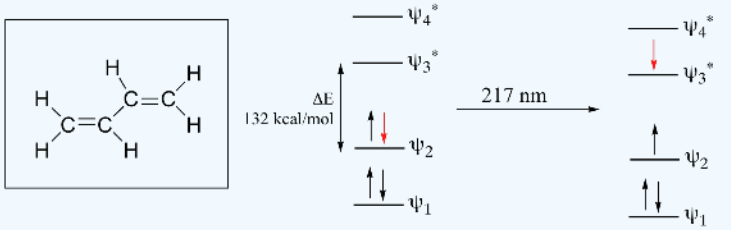
The ultraviolet absorption maximum of a conjugated molecule is dependent upon the extent of conjugation. As the conjugation increases, the Molecular Orbital energy decreases so that the pi electron transitions occur in the UV and visible regions of the electromagnetic spectrum. Molecules or parts of molecules that absorb light strongly in the UV-vis region are called **chromophores**.

When a double-bonded molecule such as ethene (common name ethylene) absorbs light, it undergoes a **π - π* transition.** Because π-π* energy gaps are narrower than σ - σ* gaps, ethene absorbs light at 165 nm - a longer wavelength than molecular hydrogen.



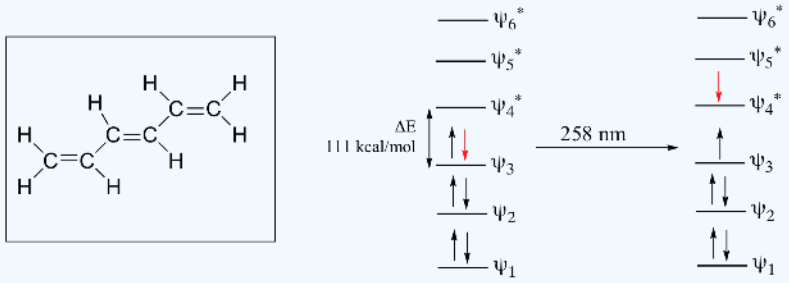
The electronic transitions of both molecular hydrogen and ethene are too energetic to be accurately recorded by standard UV spectrophotometers, which generally have a range of 220 – 700 nm. Where UV-vis spectroscopy becomes useful to most organic and biological chemists is in the study of molecules with conjugated pi systems. In these groups, the energy gap for π -π* transitions is smaller than for isolated double bonds, and thus the wavelength absorbed is longer.

Let's revisit the MO picture for 1,3-butadiene, the simplest conjugated system. Recall that we can draw a diagram showing the four pi MO's that result from combining the four $2p_z$ atomic orbitals. The lower two orbitals are bonding, while the upper two are anti-bonding.

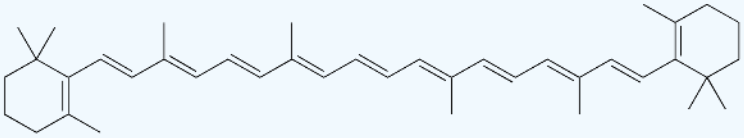


Comparing this MO picture to that of ethene, our isolated pi-bond example, we see that the HOMO-LUMO energy gap is indeed smaller for the conjugated system. 1,3-butadiene absorbs UV light with a wavelength of 217 nm.

As conjugated pi systems become larger, the energy gap for a π - π* transition becomes increasingly narrow, and the wavelength of light absorbed correspondingly becomes longer. The absorbance due to the π - π* transition in 1,3,5-hexatriene, for example, occurs at 258 nm, corresponding to a **Δ**E of 111 kcal/mol.

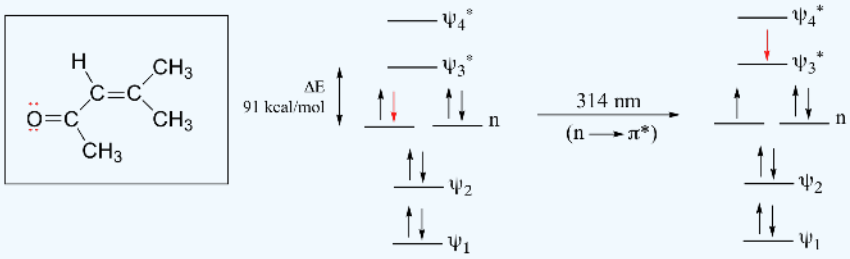


In molecules with extended pi systems, the HOMO-LUMO energy gap becomes so small that absorption occurs in the visible rather then the UV region of the electromagnetic spectrum. Beta-carotene, with its system of 11 conjugated double bonds, absorbs light with wavelengths in the blue region of the visible spectrum while allowing other visible wavelengths – mainly those in the red-yellow region - to be transmitted. This is why carrots are orange.



β-carotene

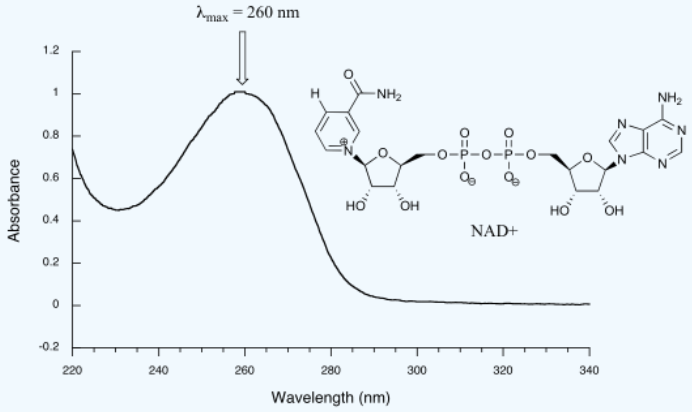
The conjugated pi system in 4-methyl-3-penten-2-one gives rise to a strong UV absorbance at 236 nm due to a π - π* transition. However, this molecule also absorbs at 314 nm. This second absorbance is due to the transition of a non-bonding (lone pair) electron on the oxygen up to a π* antibonding MO:



This is referred to as an **n - π* transition**. The nonbonding (n) MO's are higher in energy than the highest bonding p orbitals, so the energy gap for an n - π* transition is smaller that that of a π - π* transition – and thus the n - π* peak is at a longer wavelength. In general, n - π* transitions are weaker (less light absorbed) than those due to π - π* transitions.

LOOKING AT UV-VIS SPECTRA

We have been talking in general terms about how molecules absorb UV and visible light – now let's look at some actual examples of data from a UV-vis absorbance spectrophotometer. The basic setup is the same as for IR spectroscopy: radiation with a range of wavelengths is directed through a sample of interest, and a detector records which wavelengths were absorbed and to what extent the absorption occurred. Below is the absorbance spectrum of an important biological molecule called nicotinamide adenine dinucleotide, abbreviated NAD^+ (we'll learn what it does in section 16.4) This compound absorbs light in the UV range due to the presence of conjugated pi-bonding systems.



You'll notice that this UV spectrum is much simpler than the IR spectra we saw earlier: this one has only one peak, although many molecules have more than one. Notice also that the convention in UV-vis spectroscopy is to show the baseline at the bottom of the graph with the peaks pointing up. Wavelength values on the x-axis are generally measured in nanometers (nm) rather than in cm^{-1} as is the convention in IR spectroscopy.

Peaks in UV spectra tend to be quite broad, often spanning well over 20 nm at half-maximal height. Typically, there are two things that we look for and record from a UV-Vis spectrum.. The first is $\lambda_{max,}$ which is the wavelength at maximal light absorbance. As you can see, NAD^+ has $\lambda_{max,}$ = 260 nm. We also want to record how much light is absorbed at $\lambda_{max.}$ Here we use a unitless number called **absorbance**, abbreviated 'A'. This contains the same information as the 'percent transmittance' number used in IR spectroscopy, just expressed in slightly different terms. To calculate absorbance at a given wavelength, the computer in the spectrophotometer simply takes the intensity of light at that wavelength *before* it passes through the sample (I_0), divides this value by the intensity of the same wavelength *after* it passes through the sample (I), then takes the $\log_{10}$ of that number:

$A = \log I_0/I$

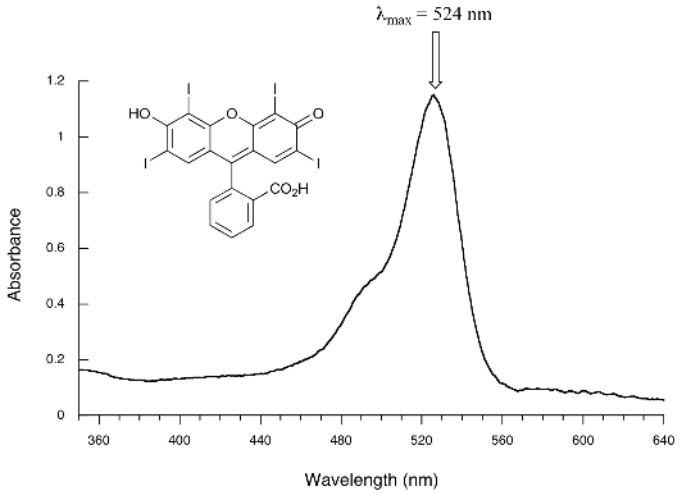
You can see that the absorbance value at 260 nm (A_{260}) is about 1.0 in this spectrum.

Exercise

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

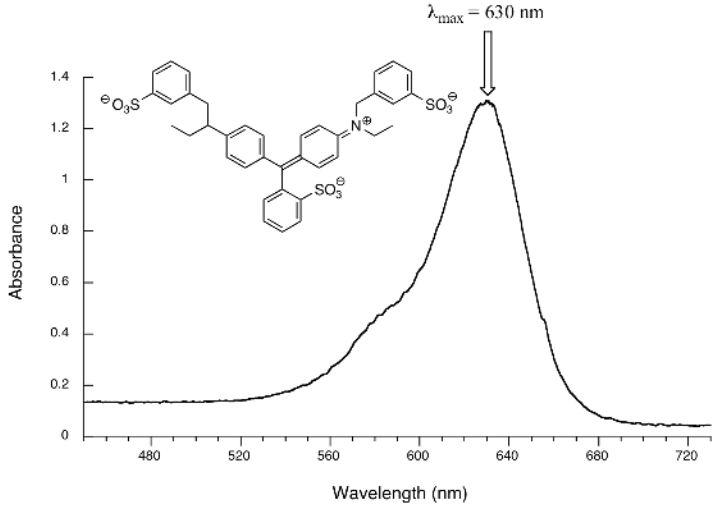
Solution

Here is the absorbance spectrum of the common food coloring Red #3:



Here, we see that the extended system of conjugated pi bonds causes the molecule to absorb light in the visible range. Because the λ_{max} of 524 nm falls within the green region of the spectrum, the compound appears red to our eyes.

Now, take a look at the spectrum of another food coloring, Blue #1:



Here, maximum absorbance is at 630 nm, in the orange range of the visible spectrum, and the compound appears blue.

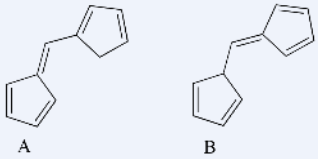
Exercise

15. How large is the π - π* transition in 4-methyl-3-penten-2-one?

Solution

Exercise

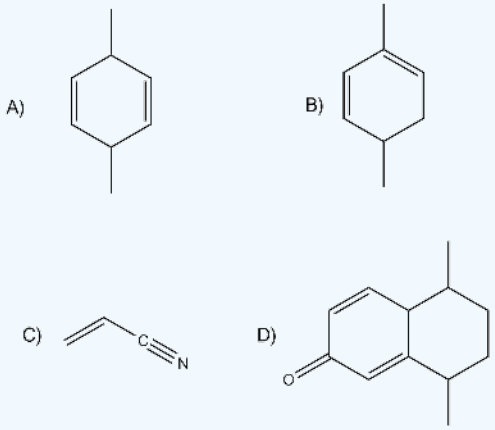
16. Which of the following molecules would you expect absorb at a longer wavelength in the UV region of the electromagnetic spectrum? Explain your answer.



Solution

Exercise

17. Which of the following would show UV absorptions in the 200-300 nm range?



Answer

17. B would be the only one to show in that range.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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16.11: CONJUGATION, COLOR, AND THE CHEMISTRY OF VISION

INTRODUCTION

Light is one of the most important resources for civilization, it provides energy as it pass along by the sun. Light influence our everyday live. Living organisms sense light from the environment by photoreceptors. Light, as waves carry energy, contains energy by different wavelength. In vision, light is the stimulus input. Light energy goes into the eye and stimulates its photoreceptors.

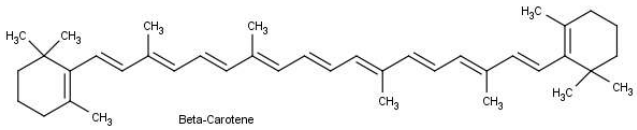
PHYSICAL CHARACTERISTICS OF LIGHT

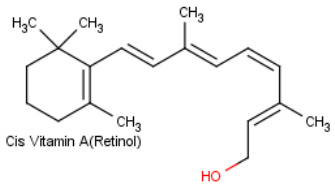
File:EM spectrum.svg[1]

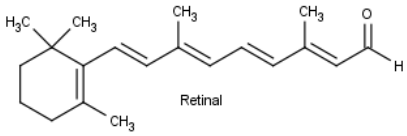
The energy of light can be determined from its wavelength. The energy of light increases from long wavelength to short wavelength. The visible spectrum ranges from 400 nm to 700 nm.

ENERGY CONVERTING CHEMICALS

Light energy can convert chemical to other forms. Vitamin A, also known as retinol, anti-dry eye vitamins, is a required nutrition for human health. The predecessor of vitamin A is present in the variety of plant carotene. Vitamin A is critical for vision because it is needed by the retina of eye. Retinol can be convert to retinal, and retinal is a chemical necessary for rhodopsin. As light enters the eye, the 11-*cis*-retinal is isomerized to the all-"trans" form.

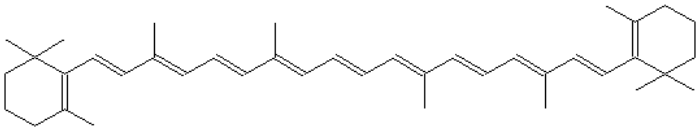






COLORED MOLECULES

The conjugated double bonds in beta-carotene produce the orange color in carrots. The conjugated double bonds in lycopene produce the red color in tomatoes.



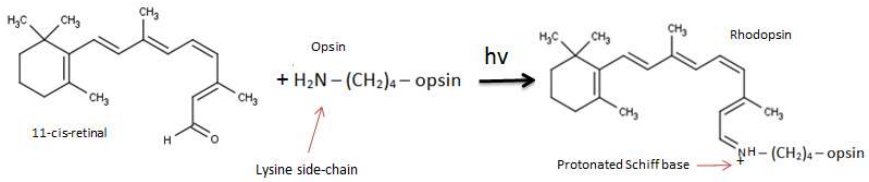
ß carotene



lycopene

MECHANISM OF VISION

We now know in rhodopsin, there is protein and retinal. The large protein is called opsin. Opsin does not absorb visible light, but when it bonded with 11-cis-retinal by its lysine side-chain to from rhodopsin, the new molecule has a very broad absorption band in the visible region of the spectrum.[2][3]

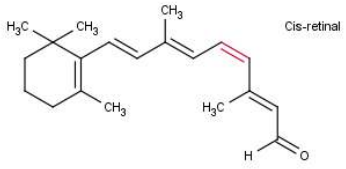


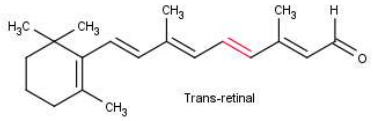
The reaction above shows Lysine side-chain from the opsin react with 11-cis-retinal when stimulated. By removing the oxygen atom form the retinal and two hydrogen atom form the free amino group of the lysine, the linkage show on the picture above is formed, and it is called Schiff base.

SIGNAL TRANSDUCTION PATHWAY

In human eyes, rod and cones react to light stimulation, and a series of chemical reactions happen in cells. These cells receive light, and pass on signals to other receiver cells. This chain of process is class signal transduction pathway. Signal transduction pathway is a mechanism that describe the ways cells react and response to stimulation.

The molecule cis-retinal can absorb light at a specific wavelength. When visible light hits the cis-retinal, the cis-retinal undergoes an isomerization, or change in molecular arrangement, to all-trans-retinal. The new form of trans-retinal does not fit as well into the protein, and so a series of geometry changes in the protein begins. The resulting complex is referred to a bathrhodopsin (there are other intermediates in this process, but we'll ignore them for now).





As the protein changes its geometry, it initiates a cascade of biochemical reactions that results in changes in charge so that a large potential difference builds up across the plasma membrane. This potential difference is passed along to an adjoining nerve cell as an electrical impulse. The nerve cell carries this impulse to the brain, where the visual information is interpreted.

REFERENCES

1. Biochemistry, L. Stryer (W.H. Freeman and Co, San Francisco, 1975).
2. *The Cambridge Guide to the Material World*, Rodney Cotterill (Cambridge University Press, Cambridge, 1985)

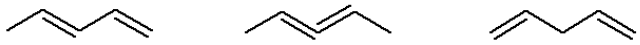
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16.12: ADDITIONAL EXERCISES

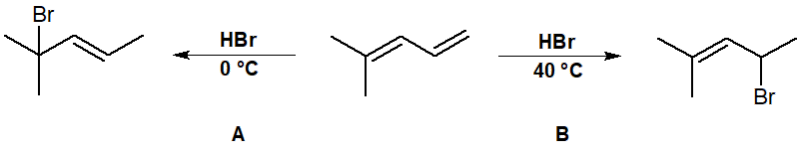
General Review

16-1 Identify which of the following dienes are isolated, conjugated, or cumulated.

a) b) c)



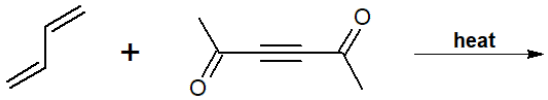
16-2 Identify which pathway gives the thermodynamic or the kinetic product and provide a reason for your answer.



16-3 Draw the resonance structures of the following molecule.

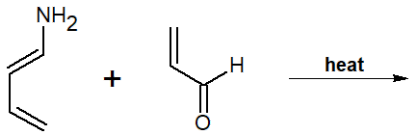


16-4 Provide the final product of the following reaction.



16-5 Predict the final product for the following reactions.

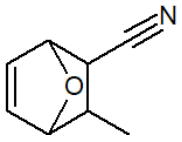
a)



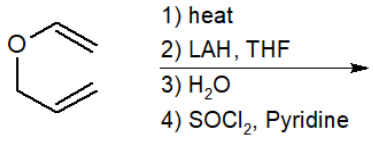
b)



16-6 For the following compound, predict which bonds could be broken to give the most probable Diels-Alder dienes that reacted to make the compound. Provide the resulting dienes from the prediction.

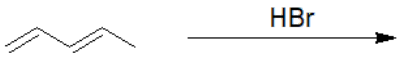


16-7 Give the final product of the following reaction chain..



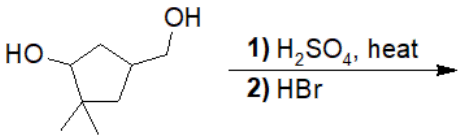
1,2- and 1,4-Addition to Conjugated Dienes

16-8 Predict all possible products of the following reaction.



16-9 Identify the kinetic and thermodynamic products of the previous problem, **16-8**.

16-10 Predict the kinetic product(s) of the following reaction and provide proper IUPAC nomenclature.

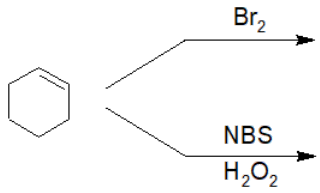


Allylic Radicals

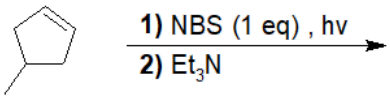
16-11 Draw arrows to show the movement of electrons in the following allylic radical.



16-12 Show the products of the following reactions.



16-13 Choose the correct answer of the following reaction.



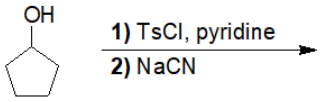
a) **b)** **c)** **d)**



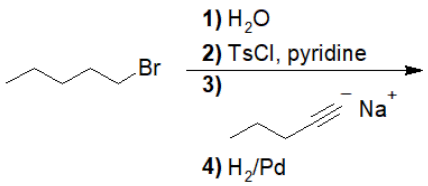
S_N2 Displacement Reactions of Allylic Halides and Tosylates

16-14 Predict the products of the following reactions.

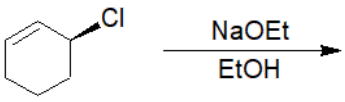
a)



b)



16-15 Choose the correct IUPAC nomenclature of the product of the following reaction and provide its structure.



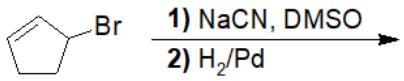
a) (3R)-3-ethoxycyclohex-1-ene

b) (3S)-3-ethoxycyclohex-1-ene

c) ethoxycyclohexane

d) cyclohexa-1,3-diene

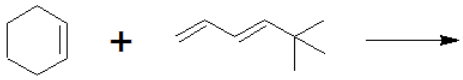
16-16 Predict the product of the following reaction.



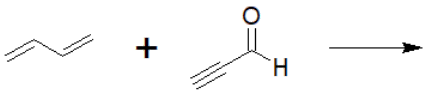
Diels-Alder Reactions

16-17 Predict the products of the following Diels-Alder reactions.

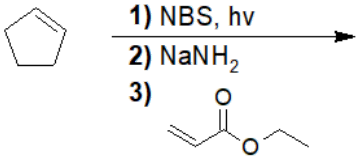
a)



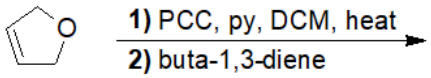
b)



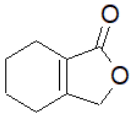
16-18 Predict the product of the following reaction.



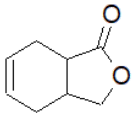
16-19 Choose the correct answer.



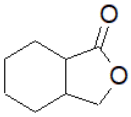
a)



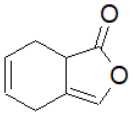
b)



c)



d)



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16.13: SOLUTIONS TO ADDITIONAL EXERCISES

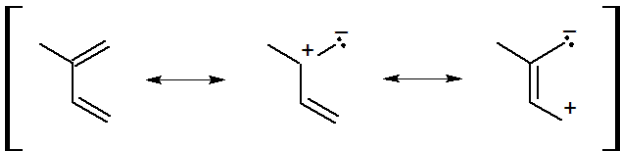
General Review

16-1

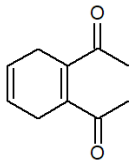
1. Conjugated
2. Cumulated
3. Isolated

16-2 Pathway A leads to the kinetic product. Since the intermediate formed during this pathway is the most stable intermediate, it forms the fastest and will always give the kinetic product. Pathway B forms the thermodynamic product, which is the most stable final product.

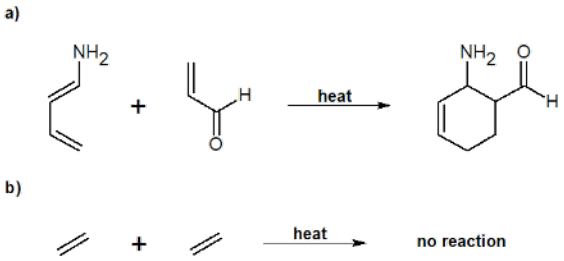
16-3



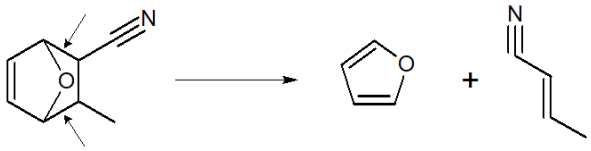
16-4



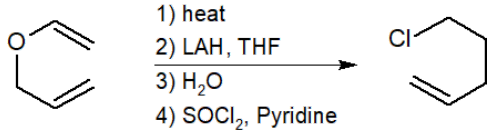
16-5



16-6

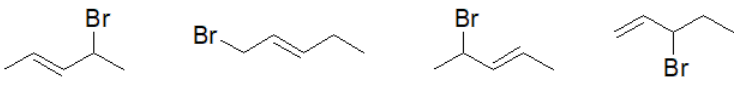


16-7



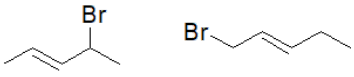
1,2- and 1,4-Addition to Conjugated Dienes

16-8:



16-9:

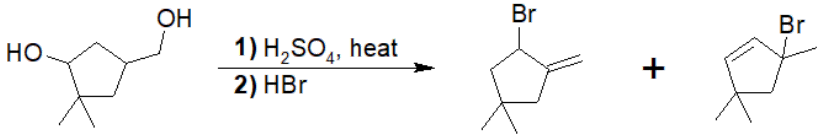
Thermodynamic:



Kinetic:

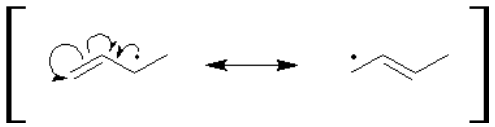


16-10:

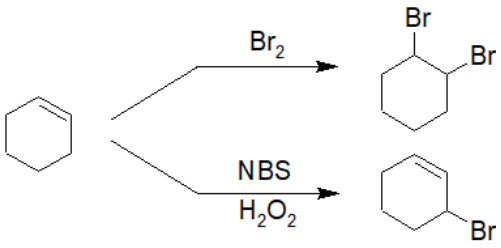


Allylic Radicals

16-11:



16-12:

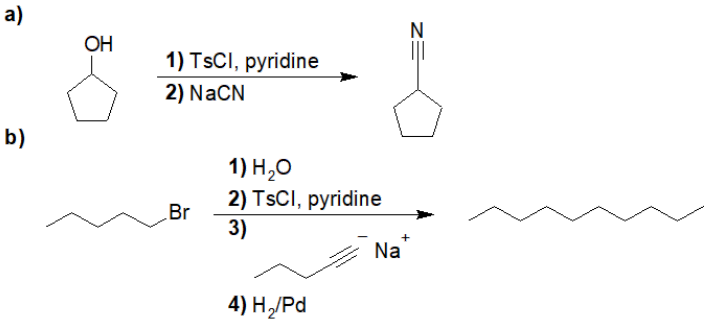


16-13:

Answer: C

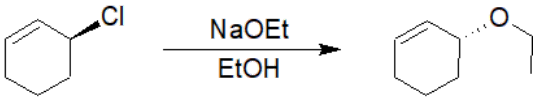
S_N2 Displacement Reactions of Allylic Halides and Tosylates

16-14:

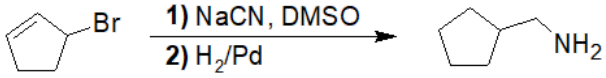


16-15:

Answer:



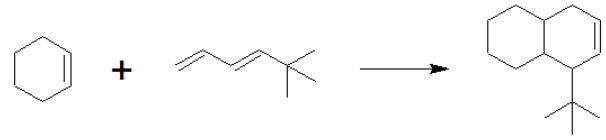
16-16:



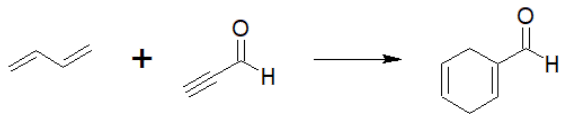
Diels-Alder Reactions

16-17:

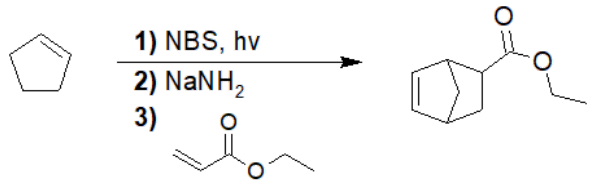
a)



b)



16-18:



16-19:

Answer: B

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CHAPTER OVERVIEW

17: AROMATIC COMPOUNDS

After reading this chapter and completing ALL the exercises, a student can be able to

- summarize the discovery of the structure of benzene (refer to section 17.1)
- predict the physical properties of aromatic compounds using IMFs (refer to section 17.2)
- apply resonance and MO Theory to the structure of benzene (refer to section 17.3)
- apply MO Theory to cyclobutadiene (refer to section 17.4)
- apply resonance to aromatic compounds and ions (refer to sections 17.5 and 17.6)
- use Hückel's rule to predict whether a given cyclic compound or ion is aromatic, antiaromatic or nonaromatic (refer to sections 17.5 and 17.6)
- for heterocycles, determine whether the lone pairs of the heteroatoms occupy p orbitals or sp^2 orbitals (refer to sections 17.5 and 17.7)
- for heterocyclic amines, and predict whether the nitrogen atom is weakly or strongly basic (refer to sections 17.5 and 17.7)
- use Huckel's Rule to prdict whether polycyclic aromatic hydrocarbons are aromatic (refer to setions 17.5 and 17.8)
- use IR, NMR, UV and mass spectra to determine the structures of aromatic compounds (refer to section 17.9)
- given an aromatic compound, predict the important features of its spectra (refer to section 17.9)

Please note: IUPAC nomenclature and important common names of alcohols were explained in Chapter 3.

17.1: Introduction- The Discovery of Benzene

17.2: The Structure and Properties of Benzene and its Derivatives

17.3: Resonance and the Molecular Orbitals of Benzene

17.4: The Molecular Orbital Picture of Cyclobutadiene

17.5: Aromaticity and Huckel's Rule

17.6: Aromatic Ions - a closer look

17.7: Heterocyclic Aromatic Compounds - a closer look

17.8: Polycyclic Aromatic Hydrocarbons

17.9: Spectroscopy of Aromatic Compounds

17.10: Additional Exercises

17.11: Solutions to Additional Exercises

Template:HideTOC

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17.1: INTRODUCTION- THE DISCOVERY OF BENZENE

THE 100 YEAR MYSTERY OF BENZENE

It took humans over 100 years to determine and confirm the structure of benzene. Why did it take so long? Why was there such a curiosity? The 1:1 ratio of carbon to hydrogen in the empirical formula and low chemical reactivity of benzene were a paradox to chemists in the early 1800's.

In 1825, Michael Faraday isolated an oily residue of gas lamps. Faraday called this liquid "bicarburet of hydrogen" and measured the boiling point to be 80°C. Additionally, Faraday determined the empirical formula to be CH. About nine years later, Eilhard Mitscherlich synthesized the same compound from benzoic acid and lime (CaO).

During the mid to late 1800's, several possible structures (shown below) were proposed for benzene.



It was not until the 1930's that Kekule's structure was confirmed by X-ray and electron diffraction. During the end of Kekule's career he revealed that the structure came to him in a vision after enjoying a glass or two of wine by the fire in his favorite chair. His inspiration for the structure of benzene was derived from an ouroboros in the flames.



17.1: Introduction- The Discovery of Benzene is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

17.2: THE STRUCTURE AND PROPERTIES OF BENZENE AND ITS DERIVATIVES

BENZENE

Benzene, C_6H_6, is the simplest member of a large family of hydrocarbons, called aromatic hydrocarbons. These compounds contain ring structures and exhibit bonding that must be described using the resonance hybrid concept of valence bond theory or the delocalization concept of molecular orbital theory. (To review these concepts, refer to the earlier chapters on chemical bonding). The resonance structures for benzene, C_6H_6, are:

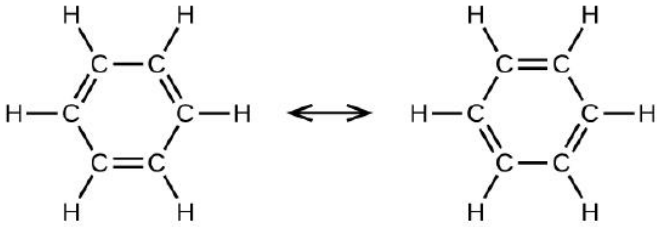


Figure **17.2.10**.

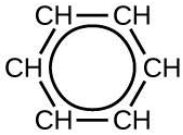
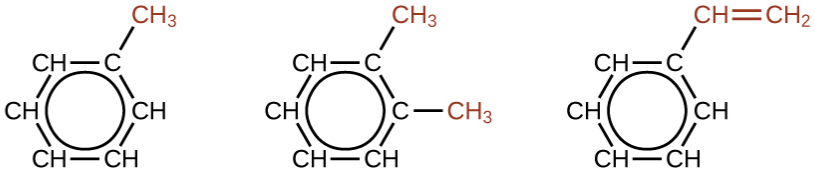


Figure : This diagram shows the unique bonding structure of benzene.

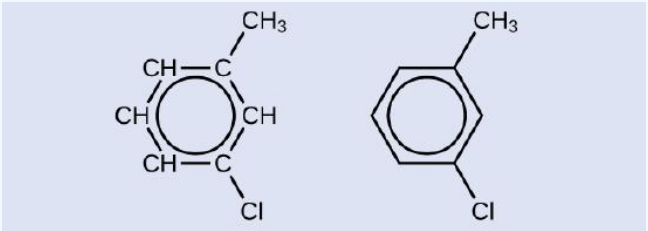
There are many derivatives of benzene. The hydrogen atoms can be replaced by many different substituents. Aromatic compounds more readily undergo substitution reactions than addition reactions; replacement of one of the hydrogen atoms with another substituent will leave the delocalized double bonds intact. The following are typical examples of substituted benzene derivatives:



Toluene and xylene are important solvents and raw materials in the chemical industry. Styrene is used to produce the polymer polystyrene.

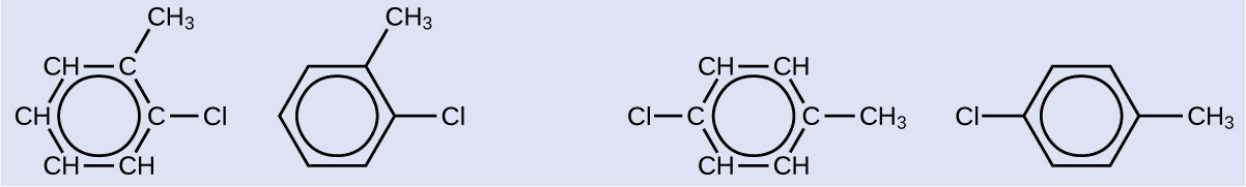
Example: Structure of Aromatic Hydrocarbons

One possible isomer created by a substitution reaction that replaces a hydrogen atom attached to the aromatic ring of toluene with a chlorine atom is shown here. Draw two other possible isomers in which the chlorine atom replaces a different hydrogen atom attached to the aromatic ring:



Solution

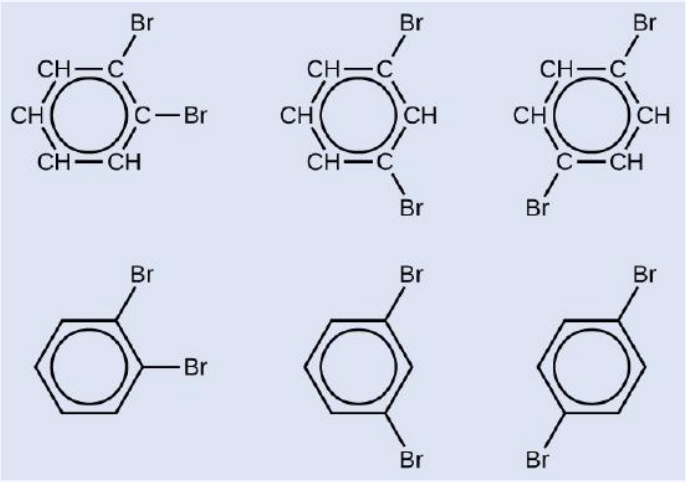
Since the six-carbon ring with alternating double bonds is necessary for the molecule to be classified as aromatic, appropriate isomers can be produced only by changing the positions of the chloro-substituent relative to the methyl-substituent:



Exercise

1. Draw three isomers of a six-membered aromatic ring compound substituted with two bromine atoms.

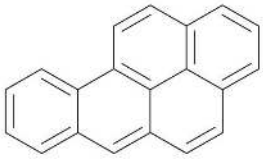
Answer



LARGER ARENES

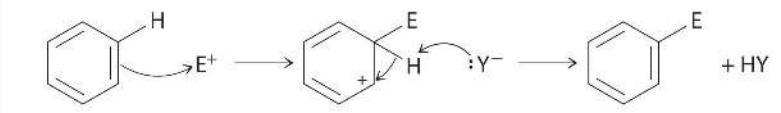
Most arenes that contain a single six-membered ring are volatile liquids, such as benzene and the xylenes, although some arenes with substituents on the ring are solids at room temperature. In the gas phase, the dipole moment of benzene is zero, but the presence of electronegative or electropositive substituents can result in a net dipole moment that increases intermolecular attractive forces and raises the melting and boiling points. For example, 1,4-dichlorobenzene, a compound used as an alternative to naphthalene in the production of mothballs, has a melting point of 52.7°C, which is considerably greater than the melting point of benzene (5.5°C).

Certain aromatic hydrocarbons, such as benzene and benz[a]pyrene, are potent liver toxins and carcinogens. In 1775, a British physician, Percival Pott, described the high incidence of cancer of the scrotum among small boys used as chimney sweeps and attributed it to their exposure to soot. His conclusions were correct: benz[a]pyrene, a component of chimney soot, charcoal-grilled meats, and cigarette smoke, was the first chemical carcinogen to be identified.



Benz[a]pyrene

Although arenes are usually drawn with three C=C bonds, benzene is about 150 kJ/mol more stable than would be expected if it contained three double bonds. This increased stability is due to the delocalization of the π electron density over all the atoms of the ring. Compared with alkenes, arenes are poor nucleophiles. Consequently, they do not undergo addition reactions like alkenes; instead, they undergo a variety of electrophilic aromatic substitution reactions that involve the replacement of –H on the arene by a group –E, such as $–NO_2$, $–SO_3H$, a halogen, or an alkyl group, in a two-step process. The first step involves addition of the electrophile (E) to the π system of benzene, forming a carbocation. In the second step, a proton is lost from the adjacent carbon on the ring:



The carbocation formed in the first step is stabilized by resonance.

> *Arenes undergo substitution reactions rather than elimination because of increased stability arising from delocalization of their π electron density.*

Many substituted arenes have potent biological activity. Some examples include common drugs and antibiotics such as aspirin and ibuprofen, illicit drugs such as amphetamines and peyote, the amino acid phenylalanine, and hormones such as adrenaline as shown below.

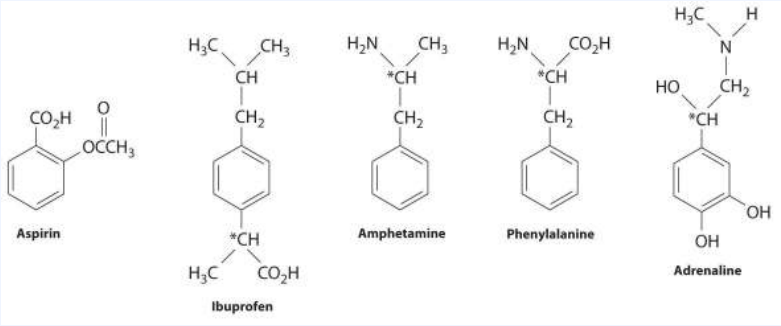


Figure: Biologically Active Substituted Arenes; Chiral centers are indicated with an asterisk.

Aspirin (antifever activity), ibuprofen (antifever and anti-inflammatory activity), and amphetamine (stimulant) have pharmacological effects. Phenylalanine is an amino acid. Adrenaline is a hormone that elicits the “fight or flight” response to stress.

PHYSICAL PROPERTIES

The physical properties of aromatic compounds are similar to other hydrocarbons. As hydrocarbons, the dominant IMF is the London Dispersion Force. This relatively weak IMF results in more volatile compounds which led to the term "aromatic". Chemists can frequently recognize the presence of an aromatic compound by simply smelling its aroma.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Paul Flowers (University of North Carolina - Pembroke), Klaus Theopold (University of Delaware) and Richard Langley (Stephen F. Austin State University) with contributing authors. Textbook content produced by OpenStax College is licensed under a Creative Commons Attribution License 4.0 license. Download for free at http://cnx.org/contents/85abf193-2bd...a7ac8df6@9.110).

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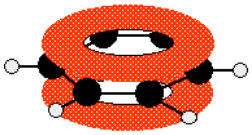
17.3: RESONANCE AND THE MOLECULAR ORBITALS OF BENZENE

BENZENE STRUCTURE

Among the many distinctive features of benzene, its aromaticity is the major contributor to why it is so unreactive. This section will try to clarify the theory of aromaticity and why aromaticity gives unique qualities that make these conjugated alkenes inert to compounds such as Br_2 and even hydrochloric acid. It will also go into detail about the unusually large resonance energy due to the six conjugated carbons of benzene.



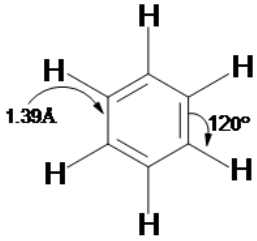
The delocalization of the p-orbital carbons on the sp^2 hybridized carbons is what gives the aromatic qualities of benzene.



This diagram shows one of the molecular orbitals containing two of the delocalized electrons, which may be found anywhere within the two "doughnuts". The other molecular orbitals are almost never drawn.

- Benzene (C_6H_6) is a planar molecule containing a ring of six carbon atoms, each with a hydrogen atom attached.
- The six carbon atoms form a perfectly regular hexagon. All of the carbon-carbon bonds have exactly the same lengths - somewhere between single and double bonds.
- There are delocalized electrons above and below the plane of the ring, which makes benzene particularly stable.
- Benzene resists addition reactions because those reactions would involve breaking the delocalization and losing that stability.

Because of the aromaticity of benzene, the resulting molecule is planar in shape with each C-C bond being 1.39 Å in length and each bond angle being 120°. You might ask yourselves how it's possible to have all of the bonds to be the same length if the ring is conjugated with both single (1.47 Å) and double (1.34 Å), but it is important to note that there are no distinct single or double bonds within the benzene. Rather, the delocalization of the ring makes each count as one and a half bonds between the carbons which makes sense because experimentally we find that the actual bond length is somewhere in between a single and double bond. Finally, there are a total of six p-orbital electrons that form the stabilizing electron clouds above and below the aromatic ring.

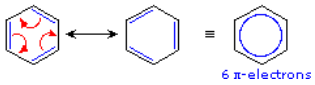


If benzene is forced to react by increasing the temperature and/or by addition of a catalyst, It undergoes **substitution reactions** rather than the addition reactions that are typical of alkenes. This further confirms the previous indication that the six-carbon benzene core is unusually stable to chemical modification. The conceptual contradiction presented by a high degree of unsaturation (low H:C ratio) and high chemical stability for benzene and related compounds remained an unsolved puzzle for many years. Eventually, the presently accepted structure of a regular-hexagonal, planar ring of carbons was adopted, and the exceptional thermodynamic and chemical stability of this system was attributed to resonance stabilization of a conjugated cyclic triene.

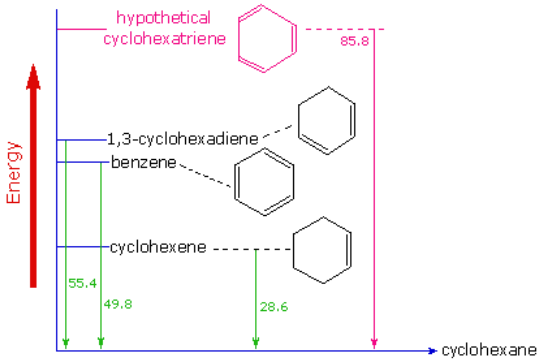
THE HIGH STABILITY OF BENZENE

Here, two structurally and energetically equivalent electronic structures for a stable compound are written, but no single structure provides an accurate or even an adequate representation of the true molecule. The six-membered ring in benzene is a perfect hexagon (all carbon-carbon bonds have an identical length of 1.40 Å). The cyclohexatriene contributors would be expected to show alternating bond lengths, the double bonds being shorter (1.34 Å) than the single bonds (1.54 Å). An alternative representation for benzene (circle within a hexagon)

emphasizes the pi-electron delocalization in this molecule, and has the advantage of being a single diagram. In cases such as these, the electron delocalization described by resonance enhances the stability of the molecules, and compounds composed of such molecules often show exceptional stability and related properties.



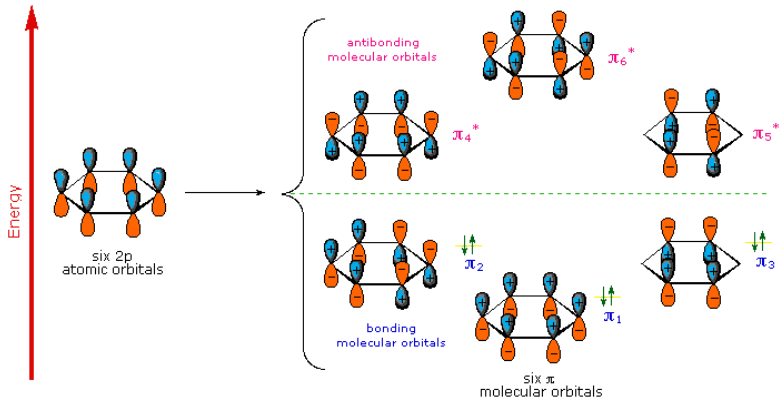
Evidence for the enhanced thermodynamic stability of benzene was obtained from measurements of the heat released when double bonds in a six-carbon ring are hydrogenated (hydrogen is added catalytically) to give cyclohexane as a common product. In the following diagram cyclohexane represents a low-energy reference point. Addition of hydrogen to cyclohexene produces cyclohexane and releases heat amounting to 28.6 kcal per mole. If we take this value to represent the energy cost of introducing one double bond into a six-carbon ring, we would expect a cyclohexadiene to release 57.2 kcal per mole on complete hydrogenation, and 1,3,5-cyclohexatriene to release 85.8 kcal per mole. These **heats of hydrogenation** would reflect the relative thermodynamic stability of the compounds. In practice, 1,3-cyclohexadiene is slightly more stable than expected, by about 2 kcal, presumably due to conjugation of the double bonds. **Benzene, however, is an extraordinary 36 kcal/mole more stable than expected**. This sort of stability enhancement is now accepted as a characteristic of all aromatic compounds.



A molecular orbital description of benzene provides a more satisfying and more general treatment of "aromaticity". We know that benzene has a planar hexagonal structure in which all the carbon atoms are sp^2 hybridized, and all the carbon-carbon bonds are equal in length. As shown below, the remaining cyclic array of six p-orbitals (one on each carbon) overlap to generate six molecular orbitals, three bonding and three antibonding. The plus and minus signs shown in the diagram do not represent electrostatic charge, but refer to phase signs in the equations that describe these orbitals (in the diagram the phases are also color coded). When the phases correspond, the orbitals overlap to generate a common region of like phase, with those orbitals having the greatest overlap (e.g. π_1) being lowest in energy. The remaining carbon valence electrons then occupy these molecular orbitals in pairs, resulting in a fully occupied (6 electrons) set of bonding molecular orbitals. It is this completely filled set of bonding orbitals, or **closed shell**, that gives the benzene ring its thermodynamic and chemical stability, just as a filled valence shell octet confers stability on the inert gases.

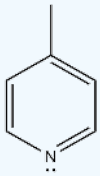
THE MOLECULAR ORBITALS OF BENZENE

Since benzene has six pi electrons, all of the bonding MOs are filled which indicates a highly stable molecule.



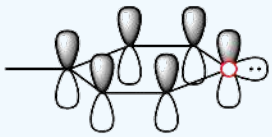
Exercise

2. The molecule shown, *p*-methylpyridine, has similar properties to benzene (flat, 120° bond angles). Draw the pi-orbitals for this compound.



Answer

2. The nitrogen has a lone pair of electrons perpendicular to the ring.



O =N

CONTRIBUTORS AND ATTRIBUTIONS

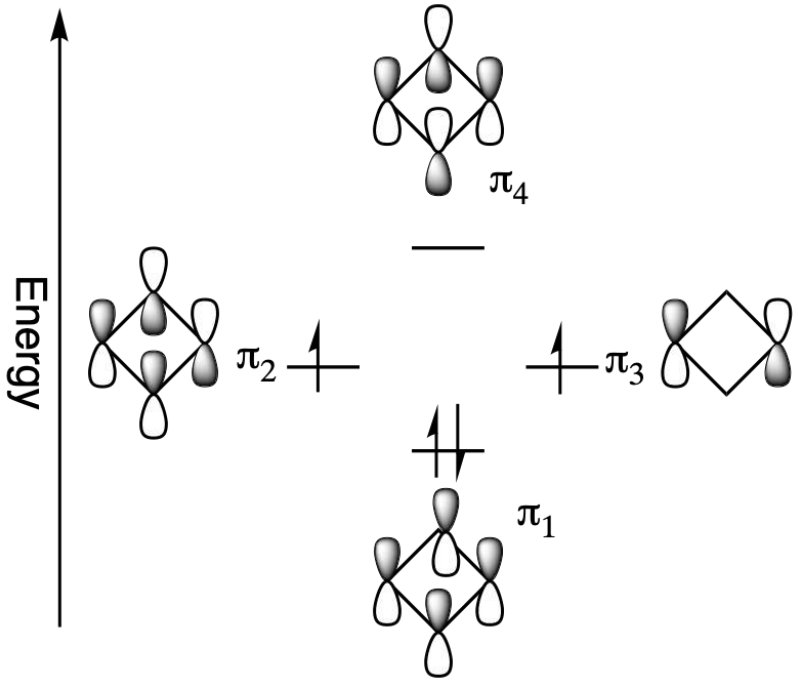
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
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17.4: THE MOLECULAR ORBITAL PICTURE OF CYCLOBUTADIENE

MOLECULAR ORBITAL DIAGRAM FOR CYCLOBUTADIENE

Cyclobutadiene is so unstable that its physical properties have not been reliably measured. The diagram below helps explain why cyclobutadiene is very unstable. With four pi electrons, both non-bonding Molecular Orbitals are singly occupied. Cyclobutadiene is so unstable relative to cyclobutane, that it is described as "antiaromatic". This term will be further explored in the next section.



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17.5: AROMATICITY AND HUCKEL'S RULE

In 1931, German chemist and physicist Erich Hückel proposed a theory to help determine if a planar ring molecule would have aromatic properties. His rule states that if a cyclic, planar molecule has 4n+2 π electrons, it is considered aromatic. This rule would come to be known as Hückel's Rule.

HUCKEL'S RULE: AROMATIC, ANTIAROMATIC, AND NONAROMATIC

Huckel's Rule is a set of algorithms that combine the number of π electrons (N) and the physical structure of the ring system to determine whether the molecule is aromatic, antiaromatic, or nonaromatic.

The number of π electrons in an **aromatic** system can be determined by the following algorithm:

$$N = 4n + 2 \tag{17.5.1}$$

where n is an integer.

The number of π electrons in an **antiaromatic** system can be determined by the following algorithm:

$$N = 4n \tag{17.5.2}$$

where n is an integer.

If a compound does not have a continuous ring of conjugated p orbitals in a planar conformation, then it is nonaromatic.

Huckel's Rule is a useful first step in evaluating the potential for a ringed molecule to be aromatic. The planar requirement of the ring may require further investigation.

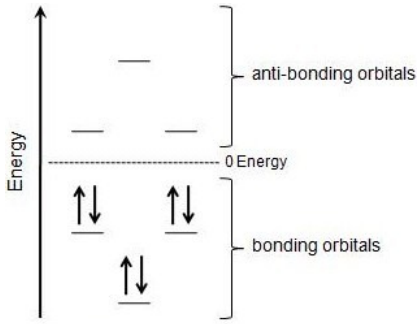
Four Criteria for Aromaticity

When deciding if a compound is aromatic, go through the following checklist. If the compound does not meet all the following criteria, it is likely not aromatic.

1. The molecule is cyclic (a ring of atoms)
2. The molecule is planar (all atoms in the molecule lie in the same plane)
3. The molecule is fully conjugated (p orbitals at every atom in the ring)
4. The molecule has 4n+2 π electrons (n=0 or any positive integer)

WHY 4N+2 π ELECTRONS?

According to Hückel's Molecular Orbital Theory, a compound is particularly stable if all of its bonding molecular orbitals are filled with paired electrons. This is true of aromatic compounds, meaning they are quite stable. With aromatic compounds, 2 electrons fill the lowest energy molecular orbital, and 4 electrons fill each subsequent energy level (the number of subsequent energy levels is denoted by n), leaving all bonding orbitals filled and no anti-bonding orbitals occupied. This gives a total of 4n+2 π electrons. You can see how this works with the molecular orbital diagram for the aromatic compound, benzene, below. Benzene has 6 π electrons. Its first 2 π electrons fill the lowest energy orbital, and it has 4 π electrons remaining. These 4 fill in the orbitals of the succeeding energy level. Notice how all of its bonding orbitals are filled, but none of the anti-bonding orbitals have any electrons.



molecular orbital diagram for benzene

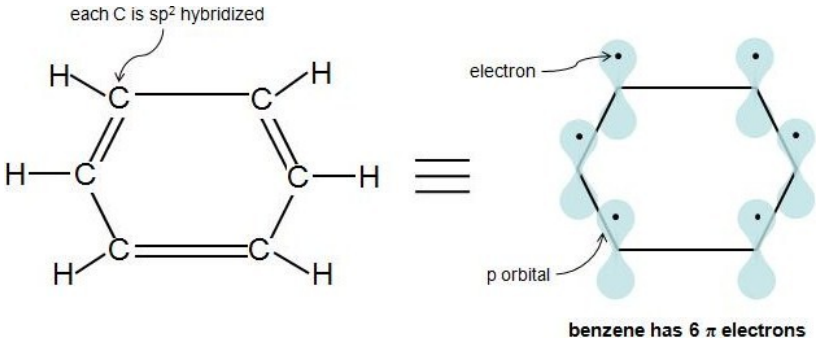
To apply the 4n+2 rule, first count the number of π electrons in the molecule. Then, set this number equal to $4n + 2$ and solve for n. If is 0 or any positive integer (1, 2, 3,...), the rule has been met. For example, benzene has six π electrons:

$$4n + 2 = 6$$
$$4n = 4$$
$$n = 1$$

For benzene, we find that $n = 1$, which is a positive integer, so the rule is met.

HOW CAN YOU TELL WHICH ELECTRONS ARE π ELECTRONS?

Perhaps the toughest part of Hückel's Rule is figuring out which electrons in the compound are actually π electrons. Once this is figured out, the rule is quite straightforward. π electrons lie in p orbitals and sp^2 hybridized atoms have 1 p orbital each. So if every carbon atom in the cyclic compound is sp^2 hybridized, this means the molecule is fully conjugated (has 1 p orbital at each atom), and the electrons in these p orbitals are the π electrons. A simple way to know if an atom is sp^2 hybridized is to see if it has 3 attached atoms and no lone pairs of electrons. This video provides a very nice tutorial on how to determine an atom's hybridization. In a cyclic hydrocarbon compound with alternating single and double bonds, each carbon is attached to 1 hydrogen and 2 other carbons. Therefore, each carbon is sp^2 hybridized and has a p orbital. Let's look at our previous example, benzene:

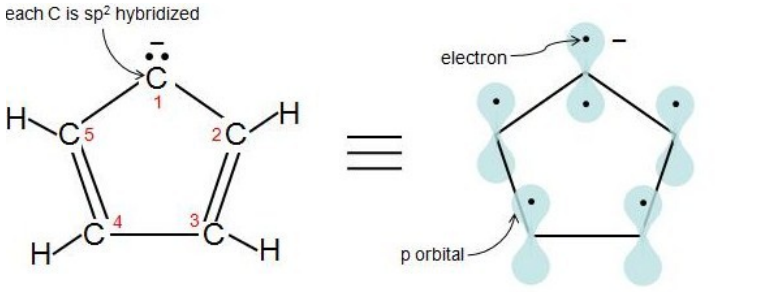


benzene has 6 π electrons

Each double bond (π bond) always contributes 2 π electrons. Benzene has 3 double bonds, so it has 6 π electrons.

AROMATIC IONS

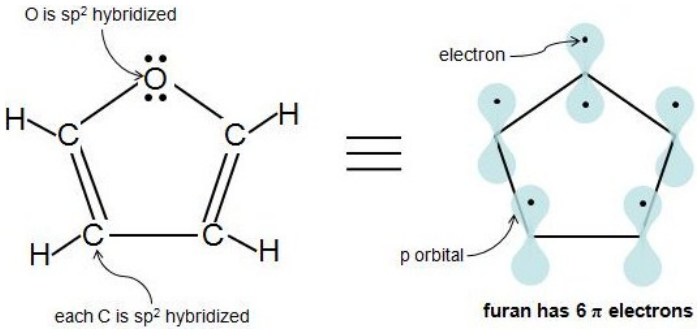
Hückel's Rule also applies to ions. As long as a compound has 4n+2 π electrons, it does not matter if the molecule is neutral or has a charge. For example, cyclopentadienyl anion is an aromatic ion. How do we know that it is fully conjugated? That is, how do we know that each atom in this molecule has 1 p orbital? Let's look at the following figure. Carbons 2-5 are sp^2 hybridized because they have 3 attached atoms and have no lone electron pairs. What about carbon 1? Another simple rule to determine if an atom is sp^2 hybridized is if an atom has 1 or more lone pairs and is attached to an sp^2 hybridized atom, then that atom is sp^2 hybridized also. This video explains the rule very clearly. Therefore, carbon 1 has a p orbital. Cyclopentadienyl anion has 6 π electrons and fulfills the 4n+2 rule.



cyclopentadienyl anion has 6 π electrons

HETEROCYCLIC AROMATIC COMPOUNDS

So far, you have encountered many carbon homocyclic rings, but compounds with elements other than carbon in the ring can also be aromatic, as long as they fulfill the criteria for aromaticity. These molecules are called heterocyclic compounds because they contain 1 or more different atoms other than carbon in the ring. A common example is furan, which contains an oxygen atom. We know that all carbons in furan are sp^2 hybridized. But is the oxygen atom sp^2 hybridized? The oxygen has at least 1 lone electron pair and is attached to an sp^2 hybridized atom, so it is sp^2 hybridized as well. Notice how oxygen has 2 lone pairs of electrons. How many of those electrons are π electrons? An sp^2 hybridized atom only has 1 p orbital, which can only hold 2 electrons, so we know that 1 electron pair is in the p orbital, while the other pair is in an sp^2 orbital. So, only 1 of oxygen's 2 lone electron pairs are π electrons. Furan has 6 π electrons and fulfills the 4n+2 rule.



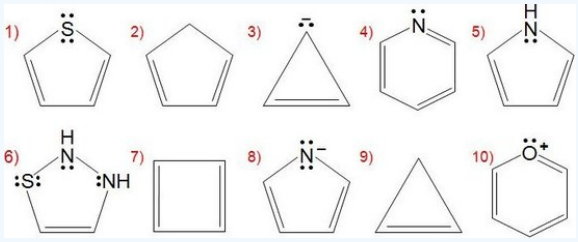
A Common Misconception

A very common misconception is that hybridization can be used to predict the geometry, or that hybridization somehow involves an energy cost associated with 'promoting' electrons into the hybrid orbitals. **This is entirely wrong.** Hybridization is always determined by geometry. You can only assign hybridization states to an atom if you already know its geometry, based on some experimental or theoretical evidence. The geometry of the oxygen in furan is trigonal planar and therefore the hybridization must be sp^2.

The *specific* rule is that if you have an sp^2 conjugated system, the lone pair will be involved ***if it makes the system more stable.*** In this case, conferring Hückel $4n + 2$ aromaticity. For furan with *two* lone pairs on the oxygen atom, if we count electrons from the carbon atoms, we have 4 (one per carbon). So adding two electrons from one of the lone pairs will give 6 = 4(1)+2, so Hückel rule is applicable and furan is aromatic.

Exercise

3. Using the criteria for aromaticity, determine if the following molecules are aromatic:



Answer

3.

Cpd 1: Aromatic - only 1 of S's lone pairs counts as π electrons, so there are 6 π electrons, n=1 Not aromatic - not fully conjugated, top C is sp^3 hybridized

Cpd 2: Not aromatic - top C is sp^2 hybridized, but there are 4 π electrons, n=1/2

Cpd 3: Aromatic - N is using its 1 p orbital for the electrons in the double bond, so its lone pair of electrons are not π electrons, there are 6 π electrons, n=1

Cpd 4: Aromatic - there are 6 π electrons, n=1

Cpd 5: Aromatic - there are 6 π electrons, n=1 because the N assumes sp^2 hybridization.

Cpd 6: Not aromatic - all atoms are sp^2 hybridized, but only 1 of S's lone pairs counts as π electrons, so there 8 π electrons, n=1.5

Cpd 7: Not aromatic - there are 4 π electrons, n=1/2

Cpd 8: Aromatic - only 1 of N's lone pairs counts as π electrons, so there are 6 π electrons, n=1

Cpd 9: Not aromatic - not fully conjugated, top C is sp^3 hybridized

Cpd 10: Aromatic - O is using its 1 p orbital for the elections in the double bond, so its lone pair of electrons are not π electrons, there are 6 π electrons, n=1

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CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- bon and Geoff Hutchison from Chemistry StackExchange

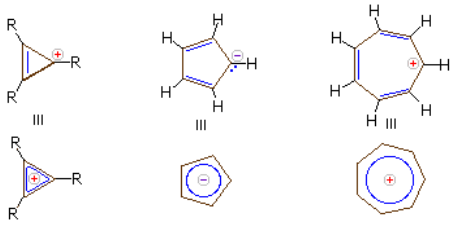
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17.6: AROMATIC IONS - A CLOSER LOOK

Cyclic anions and cations can be aromatic if they follow Huckel's Rule. Since aromatic ions have increased stability, it is important to recognize their formation when predicting reaction products.

CHARGED AROMATIC COMPOUNDS

Carbanions and carbocations may also show aromatic stabilization. Some examples are:

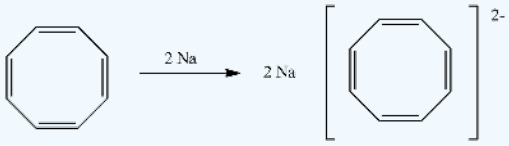


The three-membered ring cation has 2 π-electrons and is surprisingly stable, considering its ring strain. Cyclopentadiene is as acidic as ethanol, reflecting the stability of its 6 π-electron conjugate base. Salts of cycloheptatrienyl cation (tropylium ion) are stable in water solution, again reflecting the stability of this 6 π-electron cation.

Exercise

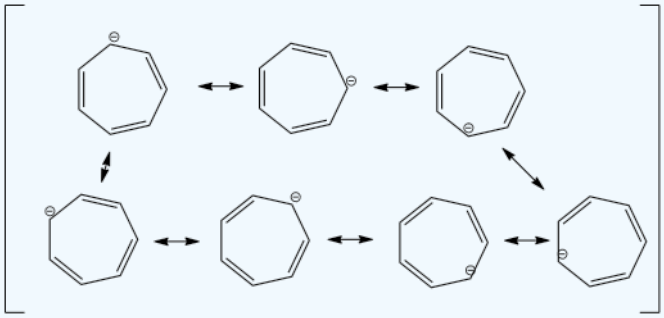
4. Draw the resonance structures for cycloheptatriene anion. Are all bonds equivalent? How many lines (signals) would you see in a H^1 C^{13} NMR?

5. The following reaction occurs readily. Propose a reason why this occurs?



Answer

4. All protons and carbons are the same, so therefore each spectrum will only have one signal each.



5. The ring becomes aromatic with the addition of two electrons. Thereby obeying the 4n+2 rule.

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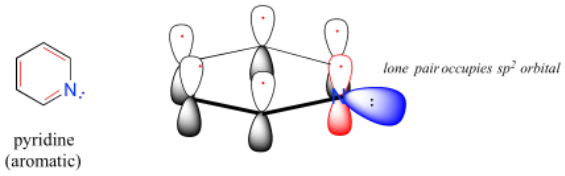
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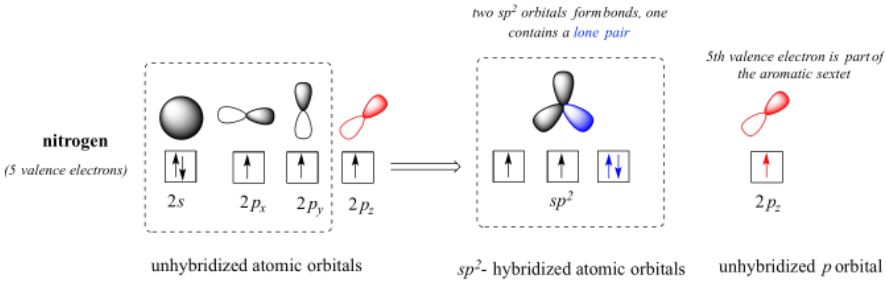
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17.7: HETEROCYCLIC AROMATIC COMPOUNDS - A CLOSER LOOK

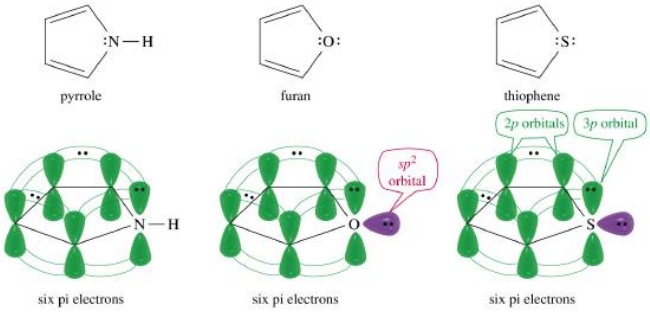
AROMATIC HETEROCYCLES

While benzene is the archetypical aromatic compound, many unsaturated cyclic compounds have exceptional properties that we now consider characteristic of "aromatic" systems. The aromatic heterocycle pyridine is similar to benzene, and is often used as a weak base for scavenging protons. In the bonding picture for pyridine, the nitrogen is sp^2-hybridized, with two of the three sp^2 orbitals forming sigma overlaps with the sp^2 orbitals of neighboring carbon atoms, and the third nitrogen sp^2 orbital containing the lone pair. The unhybridized p orbital contains a single electron, which is part of the 6 pi-electron system delocalized around the ring.

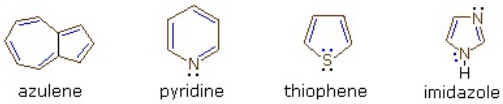




Pyrrole, furan, and thiophene have heterocyclic five-membered rings, in which the heteroatom has at least one pair of non-bonding valence shell electrons. By hybridizing this heteroatom to a sp^2 state, a p-orbital occupied by a pair of electrons and oriented parallel to the carbon p-orbitals is created. The resulting planar ring meets the first requirement for aromaticity, and the π-system is occupied by 6 electrons, 4 from the two double bonds and 2 from the heteroatom, thus satisfying the Hückel Rule.



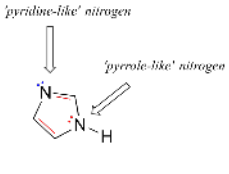
Four additional examples of heterocyclic aromatic compounds are shown below.



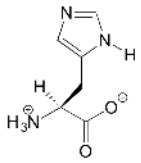
The first example is azulene, a blue-colored 10 π-electron aromatic hydrocarbon isomeric with naphthalene. The second and third compounds are heterocycles having aromatic properties. Pyridine has a benzene-like six-membered ring incorporating one nitrogen atom. The non-bonding electron pair on the nitrogen is not part of the aromatic π-electron sextet, and may bond to a proton or other electrophile without disrupting the aromatic system. In the case of thiophene, a sulfur analog of furan, one of the sulfur electron pairs (colored blue) participates in the aromatic ring π-electron conjugation. The last compound is imidazole, a heterocycle having two nitrogen atoms. Note that only one of the nitrogen non-bonding electron pairs is used for the aromatic π-electron sextet. The other electron pair is weakly basic and behaves similarly to the electron pair in pyridine.

THE TWO NITROGENS OF IMIDAZOLE

Imidazole is another important example of an aromatic heterocycle found in biomolecules - the side chain of the amino acid histidine contains an imidazole ring. In imidazole, one nitrogen is 'pyrrole-like' (the lone pair contributes to the aromatic sextet) and one nitrogen is 'pyridine-like' (the lone pair is located in an sp^2 orbital, and is *not* part of the aromatic sextet). The diagram below shows how the lone pair electrons on the nitrogen atoms differ.



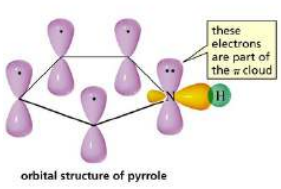
imidazole

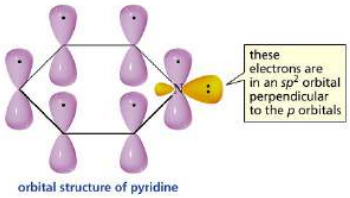


histidine

BASICITY VERSUS AROMATICITY

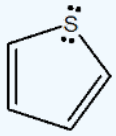
When the nitrogen atom of an aromatic heterocycle contains a pi bond, then the lone pair occupies an sp^2 orbital and is available to react as a weak base. We can view these nitrogens as being "pyridine like". When the nitrogen atom of an aromatic heterocycle has single bonds only, then the nitrogen is still sp^2 hybridized, but the lone pair occupies the unhybridized p orbital to create aromaticity. This lone pair is part of the conjugated pi electron system and is not available to react as a weak base.



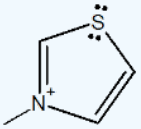


Exercise

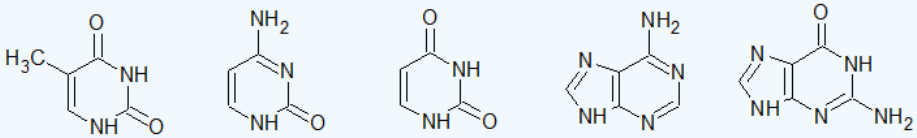
6. Draw the orbitals of thiophene to show that is aromatic.



7. The following ring is called a thiazolium ring. Describe how it is aromatic.

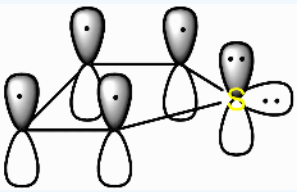


8. The nitrogenous bases for the nucleotides of DNA and RNA are shown below. Determine which nitrogen atoms are weak bases and which nitrogen atoms have lone pairs contributing to the aromaticity of the compound.

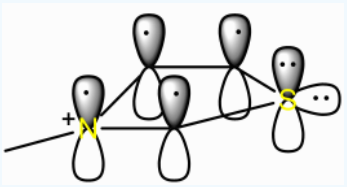


Answer

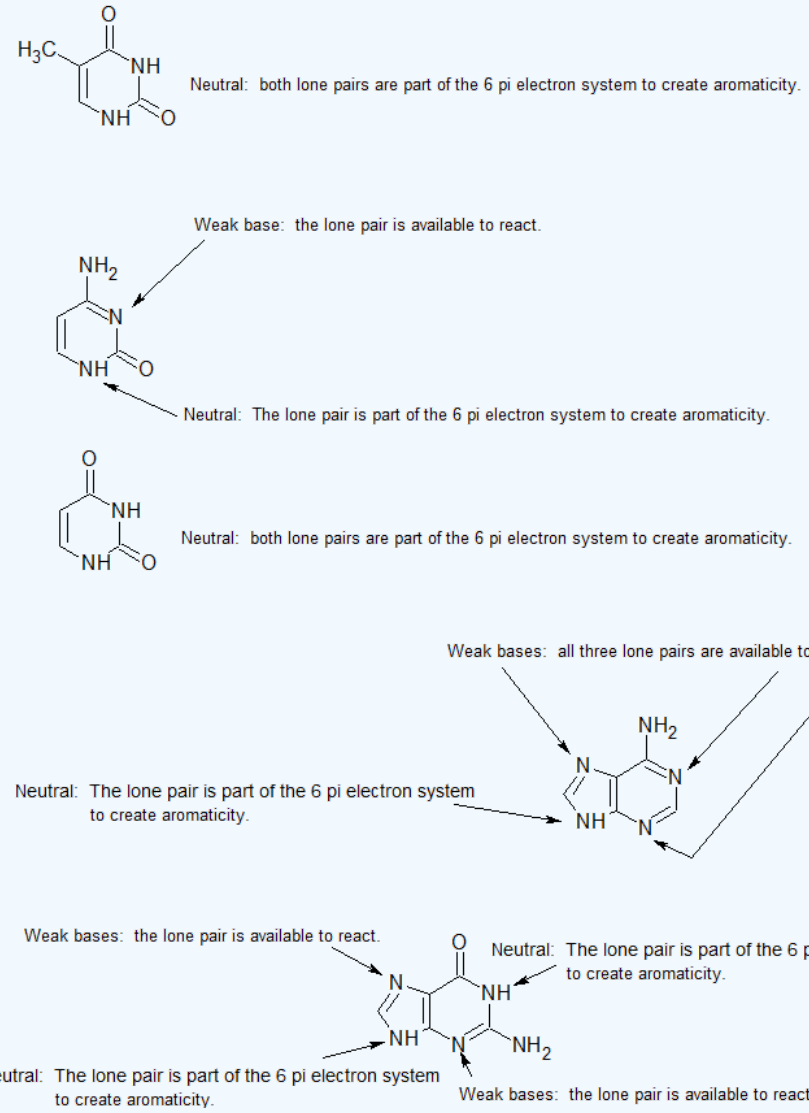
6. This drawing shows it has 6 electrons in the pi-orbital.



7. Similar to the last question, the drawing shows that there is only 6 electrons in the pi-system.



8.



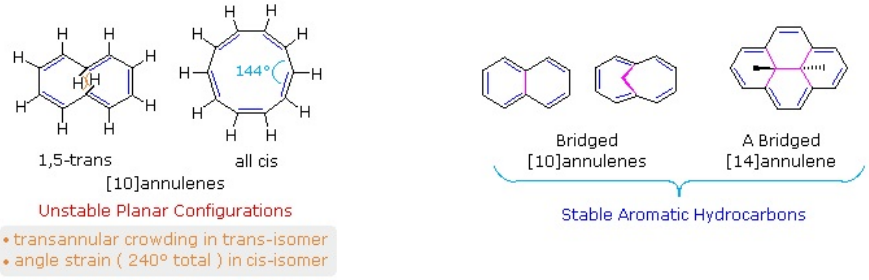
CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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17.8: POLYCYCLIC AROMATIC HYDROCARBONS

AROMATIC COMPOUND WITH A SINGLE RING



AROMATIC COMPOUNDS WITH MORE THAN ONE RING

Benzene rings may be joined together (fused) to give larger polycyclic aromatic compounds. A few examples are drawn below, together with the approved numbering scheme for substituted derivatives. The peripheral carbon atoms (numbered in all but the last three examples) are all bonded to hydrogen atoms. Unlike benzene, all the C-C bond lengths in these fused ring aromatics are not the same, and there is some localization of the pi-electrons.

The six benzene rings in coronene are fused in a planar ring; whereas the six rings in hexahelicene are not joined in a larger ring, but assume a helical turn, due to the crowding together of the terminal ring atoms. This helical configuration renders the hexahelicene molecule chiral, and it has been resolved into stable enantiomers.

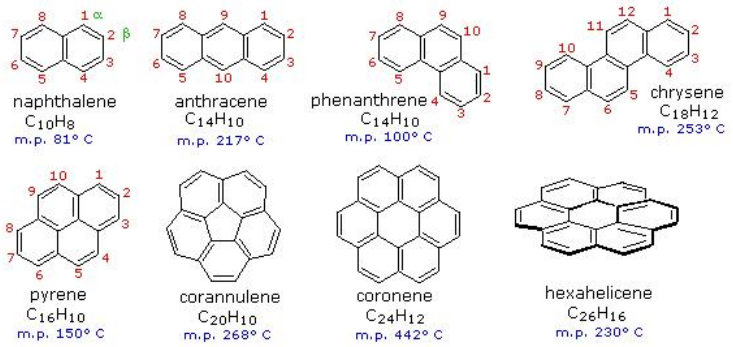
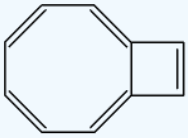


Figure 2: Examples of Polycyclic Aromatic Hydrocarbons (PAHs).

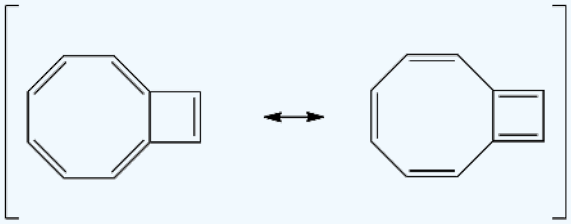
Exercise

9. This is an isomer of naphthalene. Is it aromatic? Draw a resonance structure for it.



Answer

9. Yes, it is aromatic. 4n+2 pi-electrons.



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- Prof. Steven Farmer (Sonoma State University)
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17.9: SPECTROSCOPY OF AROMATIC COMPOUNDS

THE CHEMICAL SHIFTS OF AROMATIC PROTONS

Some protons resonate much further downfield than can be accounted for simply by the deshielding effect of nearby electronegative atoms. Vinylic protons (those directly bonded to an alkene carbon) and aromatic (benzylic) protons are dramatic examples.



We'll consider the aromatic proton first. Recall that in benzene and many other aromatic structures, a sextet of pelectrons is delocalized around the ring. When the molecule is exposed to B_0, these pelectrons begin to circulate in a **ring current**, generating their own induced magnetic field that opposes B_0. In this case, however, the induced field of the pelectrons does not shield the benzylic protons from B_0 as you might expect– rather, it causes the protons to experience a *stronger* magnetic field in the direction of B_0 – in other words, it *adds* to B_0 rather than subtracting from it.

To understand how this happens, we need to understand the concept of **diamagnetic anisotropy** (anisotropy means `non-uniformity`). So far, we have been picturing magnetic fields as being oriented in a uniform direction. This is only true over a small area. If we step back and take a wider view, however, we see that the lines of force in a magnetic field are actually anisotropic. They start in the 'north' direction, then loop around like a snake biting its own tail.



If we are at point A in the figure above, we feel a magnetic field pointing in a northerly direction. If we are at point B, however, we feel a field pointing to the south.

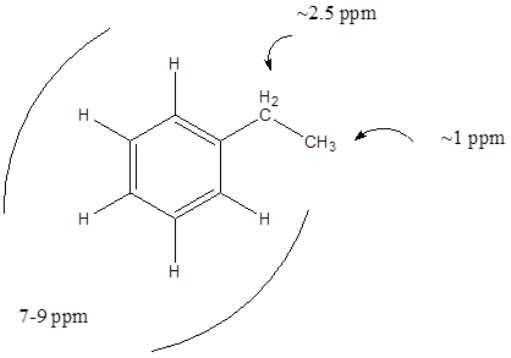
In the induced field generated by the aromatic ring current, the benzylic protons are at the equivalent of ‘point B’ – this means that the induced current in this region of space is oriented in the *same* direction as B_0.



In total, the benzylic protons are subjected to three magnetic fields: the applied field (B_0) and the induced field from the pelectrons pointing in one direction, and the induced field of the non-aromatic electrons pointing in the opposite (shielding) direction. The end result is that benzylic protons, due to the anisotropy of the induced field generated by the ring current, appear to be highly deshielded. Their chemical shift is far downfield, in the 6.5-8 ppm region.

CHARACTERISTIC NMR ABSORPTION OF BENZENE DERIVATIVES

Hydrogens directly attached to an arene ring show up about 7-9 PPM in the NMR. **This is called the aromatic region.** Hydrogen environments directly bonded to an arene ring show up about 2.5 PPM.



CHARATERISTIC IR ABSORPTION OF BENZENE DERIVATIVES

Arenes have absorption bands in the 650-900 cm^{-1} region due to bending of the C–H bond out of the plane of the ring. The exact placement of these absorptions can indicate the pattern of substitution on a benzene ring. However, this is beyond the scope of introductory organic chemistry. Arenes also possess a characteristic absorption at about 3030-3100 cm^{-1} as a result of the aromatic C–H stretch. It is somewhat higher than the alkyl C–H stretch (2850–2960 cm^{-1}), but falls in the same region as olefinic compounds. Two bands (1500 and 1660 cm^{-1}) caused by C=C in plane vibrations are the most useful for characterization as they are intense and are likely observed.

In aromatic compounds, each band in the spectrum can be assigned:

- C–H stretch from 3100-3000 cm^{-1}
- overtones, weak, from 2000-1665 cm^{-1}
- C–C stretch (in-ring) from 1600-1585 cm^{-1}
- C–C stretch (in-ring) from 1500-1400 cm^{-1}
- C–H "oop" from 900-675 cm^{-1}

Note that this is at slightly higher frequency than is the –C–H stretch in alkanes. This is a very useful tool for interpreting IR spectra. Only alkenes and aromatics show a C–H stretch slightly higher than 3000 cm^{-1}.

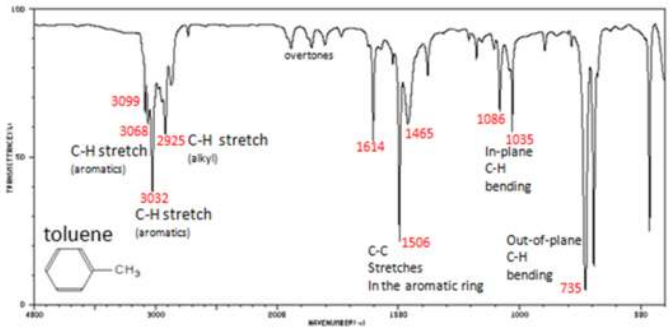
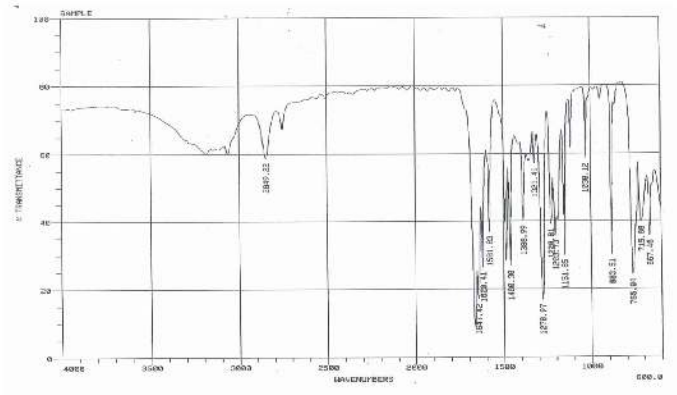


Figure. Infrared Spectrum of Toluene

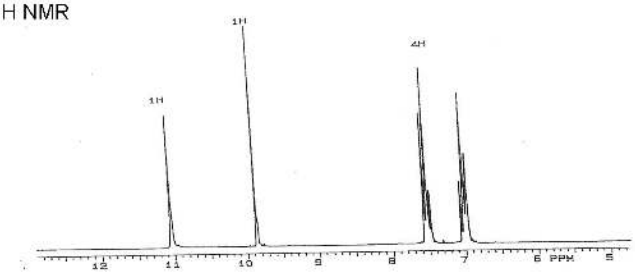
Exercise

10. A straw-colored oily liquid with a bitter almond odor and burning nut-like taste was isolated from the exudate of the castor sacs of mature North American beavers. The oily is slightly soluble in water with a boiling point of 197ºC. Elemental analysis results are as follows: 68.84% C, 4.96% H, and 26.20% O. Name, draw the bond-line structure, and correlate the structure with the IR, ^{1}H NMR, and ^{13}C NMR spectral data below.

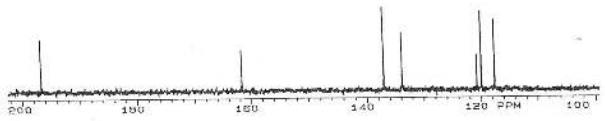
IR Spectrum



^{1}H NMR

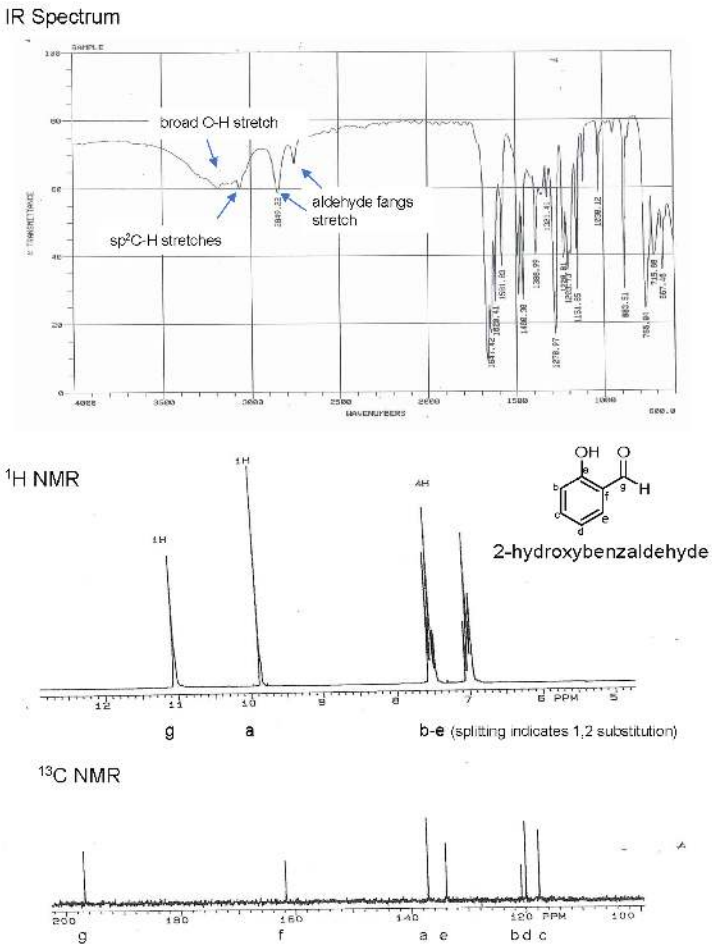


^{13}C NMR



Answer

10.



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- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
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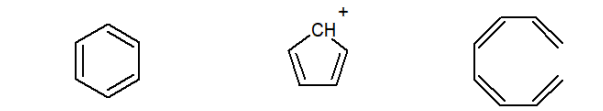
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17.10: ADDITIONAL EXERCISES

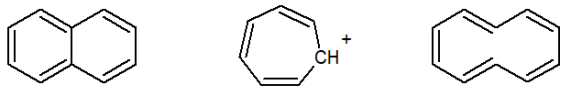
General Review

17-1 State whether the following molecules are aromatic, antiaromatic or nonaromatic.

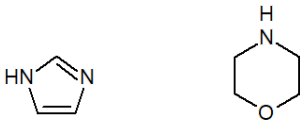
a) b) c)



d) e) f)

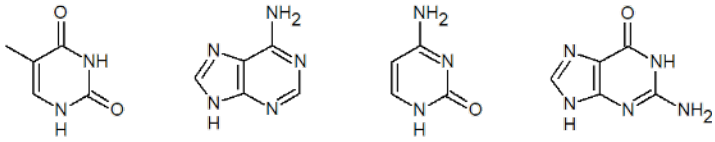


17-2 Predict which of the following nitrogen-containing heterocycles is more acidic than the other. Provide a reason for your choices.



A **B**

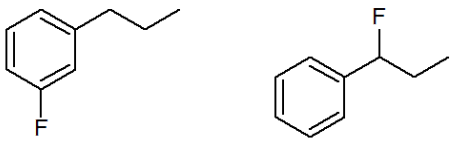
17-3 For the following bases of DNA, identify the heterocyclic compound that makes up the core structure of each one - purine or pyrimidine?



Thymine **Adenine** **Cytosine** **Guanine**

17-4 Provide the proper IUPAC names for the following compounds.

A **B**



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17.11: SOLUTIONS TO ADDITIONAL EXERCISES

General Review

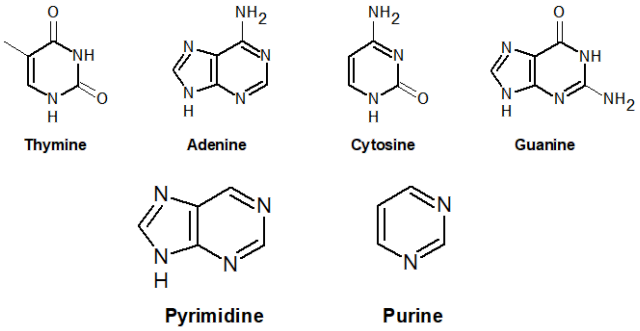
17-1

1. Aromatic
2. Antiaromatic
3. Nonaromatic
4. Aromatic
5. Aromatic
6. Nonaromatic

17-2

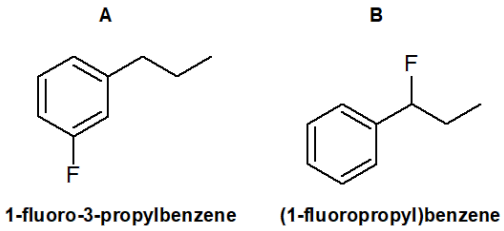
Compound A will be more acidic than compound B due to the aromaticity of its conjugate base. When compound A loses its proton, the new lone pair of electrons can delocalize with the double bonds in the ring, whereas when compound B is deprotonated, its new lone pair of electrons is localized on the nitrogen. Compound B is the stronger base.

17-3



Thymine and Cytosine are derivatives of purine. Adenine and Guanine are derivatives of pyrimidine.

17-4



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CHAPTER OVERVIEW

18: REACTIONS OF AROMATIC COMPOUNDS

LEARNING OBJECTIVES

After reading this chapter and completing ALL the exercises, a student can be able to

- propose mechanisms for Electrophilic Aromatic Substitution Reactions (EAS): halogenation, nitration, sulfonation, and Friedel-Crafts Alkylation & Acylation (sections 18.1 to 18.5)
- predict products and specify reagents for Electrophilic Aromatic Substitution Reactions (EAS): halogenation, nitration, sulfonation, and Friedel-Crafts Alkylation & Acylation (sections 18.1 to 18.5)
- draw resonance structures of the sigma complexes resulting from EAS rxns of substituted aromatic rings (sections 18.1 to 18.5)
- draw reaction energy diagrams for EAS reactions (sections 18.1 to 18.5)
- explain why substituents are activating or deactivating and o,p-directors or m-directors (section 18.6)
- list the major substituents in their EAS activation “pecking order” (section 18.6)
- predict the products of side chain reactions: oxidation of catechols and alkyl substituents, bromination of benzylic carbons, S_N1 and S_N2 rxns at the benzylic carbon, reduction of carbonyls, and reduction of nitro groups (sections 18.7 and 18.12)
- design multiple step syntheses that use substituent effects to create the desired isomers of multi-substituted aromatic compounds (sections 18.8 and 18.9)
- predict the products of Nucleophilic Aromatic Substitution Reactions (NAS): addition-elimination and elimination-addition (benzyne) (sections 18.10 and 18.11)
- propose mechanisms for Nucleophilic Aromatic Substitution Reactions (NAS): addition-elimination and elimination-addition (benzyne) (sections 18.10 and 18.11)

18.1: Electrophilic Aromatic Substitution (EAS)
18.2: Halogenation of Benzene (an EAS Reaction)
18.3: Nitration of Benzene (an EAS Reaction)
18.4: Sulfonation of Benzene (an EAS Reaction)
18.5: Alkylation and Acylation of Benzene - The Friedel-Crafts EAS Reactions
18.6: Substituent Effects on the EAS Reaction
18.7: Side-Chain Reactions of Benzene Derivatives
18.8: Synthetic Strategies for Di-substituted Benzenes
18.9: Trisubstituted Benzenes - Effects of Multiple Substituents
18.10: Nucleophilic Aromatic Substitution - The Addition-Elimantion Mechanism
18.11: NAS Reactions - the Elimination-Addition (Benzyne) Mechanism
18.12: Reduction of Aromatic Compounds
18.13: Additional Exercises
18.14: Solutions to Additional Exercises

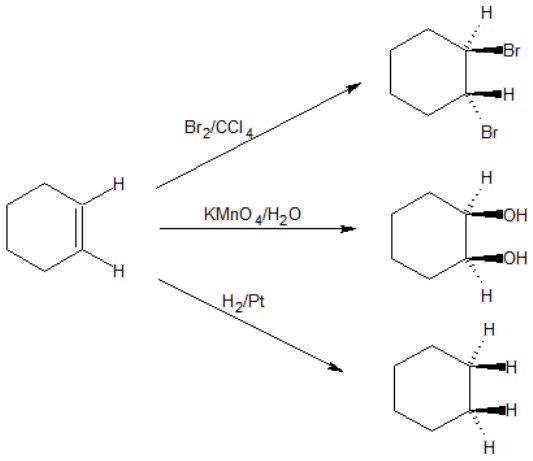
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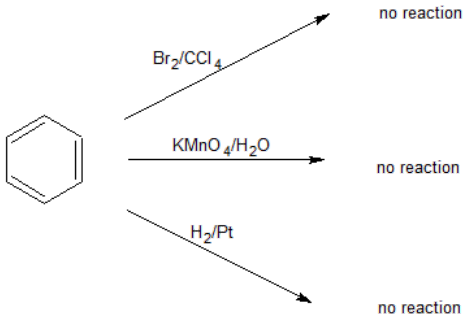
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18.1: ELECTROPHILIC AROMATIC SUBSTITUTION (EAS)

BENZENE AND ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS

While it took chemists many years to determine the structure of benzene and its derivatives, chemists recognized this class of compounds by their distinct aromas and low reactivity compared to isolated alkenes.





With the stability created by the conjugated pi electron system, the lack of chemical reactivity is not surprising. However, over time chemists found ways to catalyze reactions of benzene and its derivatives. With its strong electronic character, benzene is inherently electrophilic. The majority of the reactions for benzene are Electrophilic Aromatic Substitution reactions. One of the benzene hydrogen atoms can be substituted for a different group with electrophilic properties followed by restoration of the stable aromatic ring.

EXAMPLES OF ELECTOPHILIC AROMATIC SUBSTITUTION (EAS)

Many substitution reactions of benzene have been observed, the five most useful are listed below (chlorination and bromination are the most common halogenation reactions). Since the reagents and conditions employed in these reactions are electrophilic, these reactions are commonly referred to as **Electrophilic Aromatic Substitution**. The catalysts and co-reagents serve to generate the strong electrophilic species needed to effect the initial step of the substitution. The specific electrophile believed to function in each type of reaction is listed in the right hand column.

Reaction Type	Typical Equation				Electrophile $E^{(+)}$
Halogenation:	C_6H_6	+ Cl_2 & heat $FeCl_3$ catalyst	⟶	C_6H_5Cl + HCl Chlorobenzene	$Cl^{(+)}$ or $Br^{(+)}$
Nitration:	C_6H_6	+ HNO_3 & heat H_2SO_4 catalyst	⟶	$C_6H_5NO_2$ + H_2O Nitrobenzene	$NO_2^{(+)}$
Sulfonation:	C_6H_6	+ H_2SO_4 + SO_3 & heat	⟶	$C_6H_5SO_3H$ + H_2O Benzenesulfonic acid	$SO_3H^{(+)}$
Alkylation: Friedel-Crafts	C_6H_6	+ R-Cl & heat $AlCl_3$ catalyst	⟶	C_6H_5-R + HCl An Arene	$R^{(+)}$
Acylation: Friedel-Crafts	C_6H_6	+ RCOCl & heat $AlCl_3$ catalyst	⟶	C_6H_5COR + HCl An Aryl Ketone	$RCO^{(+)}$

GENERAL MECHANISM

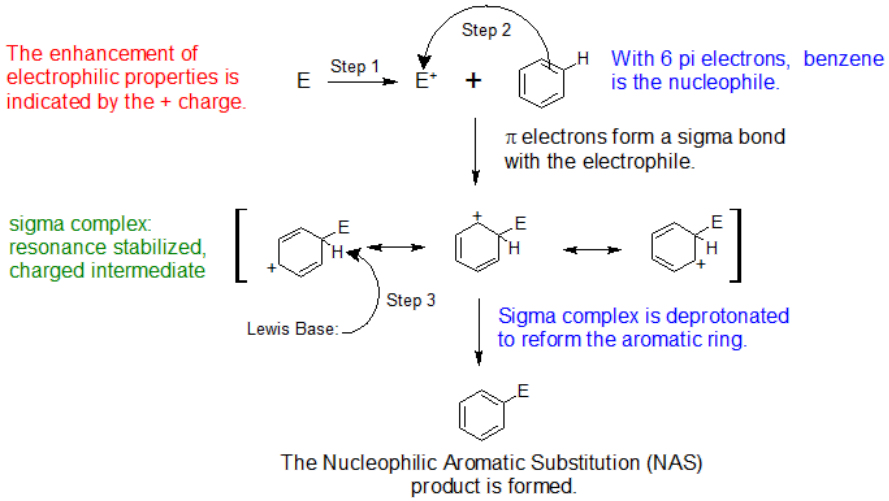
Electrophilic Aromatic Substitution (EAS) reactions include the same three mechanistic steps. Step 1 is needed to create a strong enough Electrophile to create reactivity with the pi electrons of benzene. Because the sigma complex is resonance stabilized, carbocation rearrangement is not a consideration for this intermediate.

Step 1: Formation of a Strong Electrophile

Step 2: Benzene pi electrons form a sigma bond with the Strong Electrophile to create the "sigma complex", a resonance stabilized, charged intermediate

Step 3: Deprotonation of the sigma complex to reform the aromatic ring

The generic mechanism shared by all EAS reactions is shown below.



ACTIVATING AND DEACTIVATION GROUPS

As we study the EAS reactions, we will learn that some substituents increase the reactivity of the benzene ring for EAS reactions and are called "activating groups". Other substituents decrease the reactivity of the benzene ring for EAS reactions and are called "deactivating groups". These groups can be recognized by their effects on the stability of the sigma complex.

CONTRIBUTORS AND ATTRIBUTIONS

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

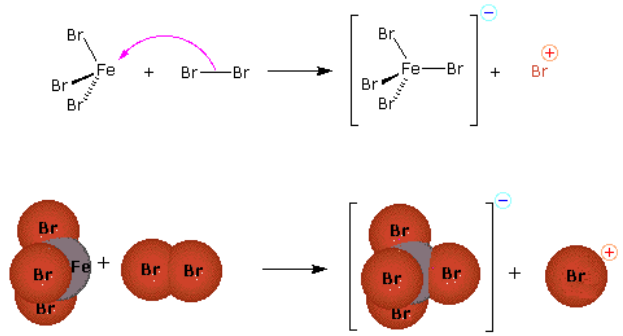
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18.2: HALOGENATION OF BENZENE (AN EAS REACTION)

A MECHANISM FOR HALOGENATION OF BENZENE

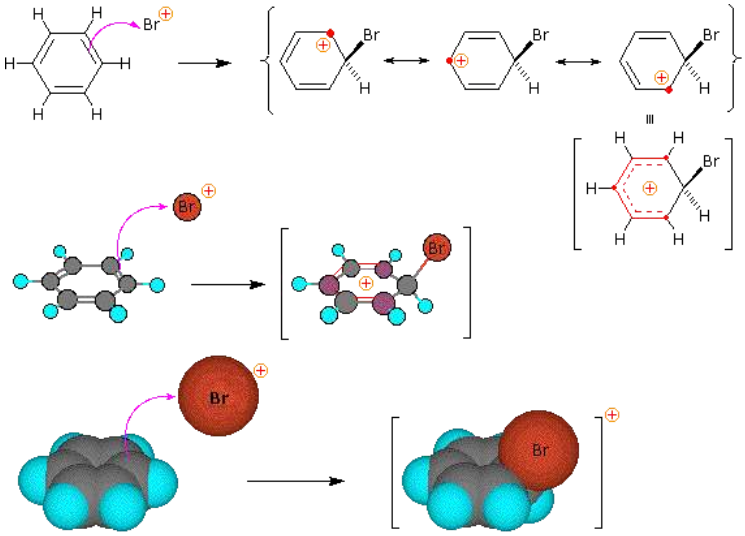
A three-step mechanism is common for many electrophilic aromatic substitution reactions. In the first step, a strong electrophile is created to entice the pi electrons of the aromatic ring to react. In the second, slow or rate-determining step a pair of pi electrons from the benzene form a sigma-bond with the electrophile generating a positively charged sigma complex (**the benzenonium intermediate for halogenation)**. In the third, fast step, a proton is removed from the sigma complex producing a halogenated benzene ring. The steps are illustrated below.

Step 1: Formation of a strong electrophile, in this case an electrophilic bromine cation.

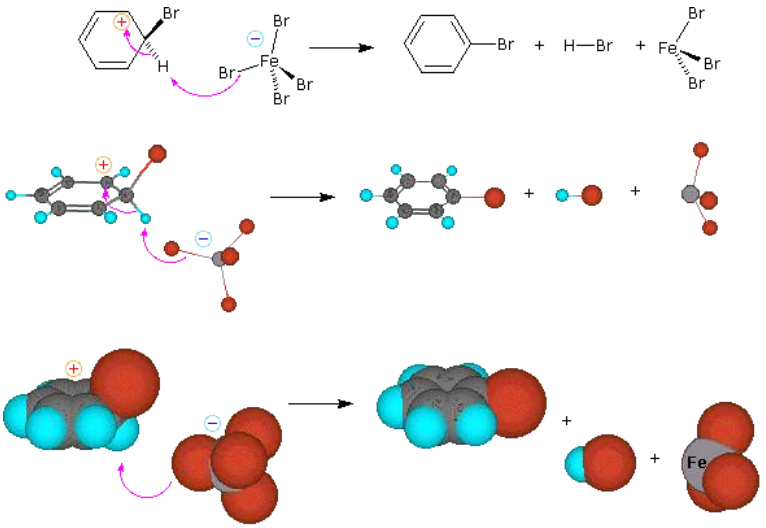


Ferric bromide and other Lewis acids enhance the electrophilic strength of bromine by forming a complex anion, in this case $FeBr_4^{\ominus}$. At the same time, this complexation creates the strongly electrophilic bromine cation, which reacts with nucleophiles.

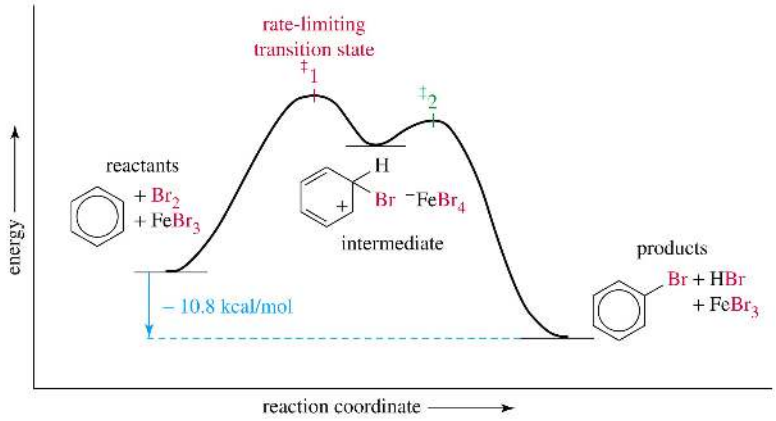
Step 2: Pi electrons of benzene react with the bromine cation to form the sigma comoplex, resonance stabilized benzenonium intermediate. This step is the rate determining step.



Step 3: Deprotonation of the benzenonium intermediate (sigma complex) to restore aromaticity.

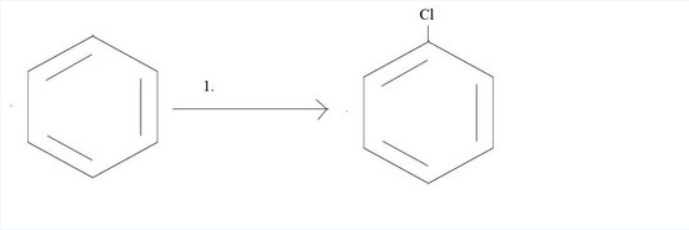


The reaction energy diagram below shows Steps 2 and 3 of the mechanism since these steps involve benzene.

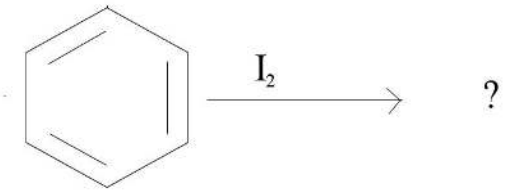


Exercises

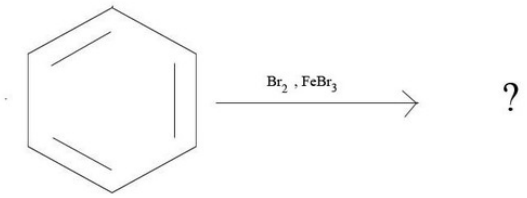
1. What reagents would you need to get the given product?



2. What product would result from the given reagents?



3. What is the major product given the reagents below?



4. Draw the formatin of Cl^+ from $AlCl_3$ and Cl_2

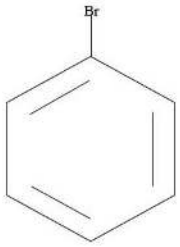
5. Draw the mechanism of the reaction between Cl^+ and a benzene.

Answer

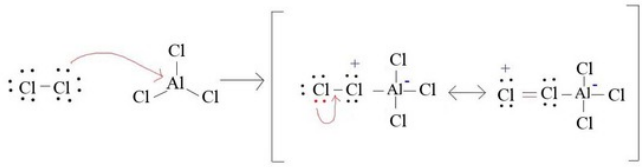
1. Cl_2 and $AlCl_3$ or Cl_2 and $FeCl_3$

2. No Reaction

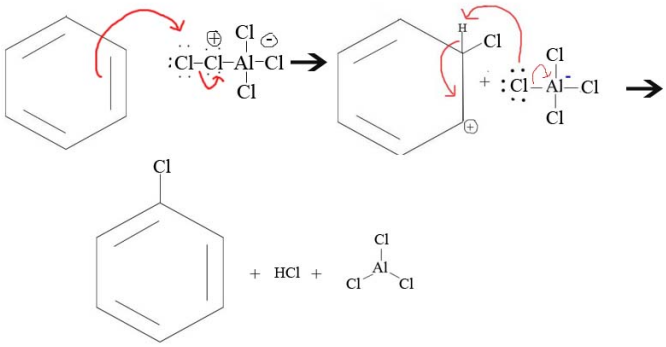
3.



4.



5.



CONTRIBUTORS AND ATTRIBUTIONS

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- Prof. Steven Farmer (Sonoma State University)
- Catherine Nguyen
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

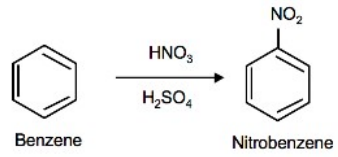
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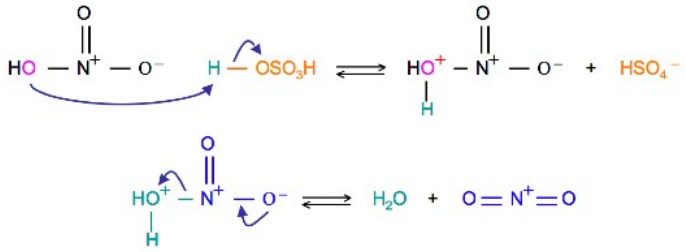
18.3: NITRATION OF BENZENE (AN EAS REACTION)

NITRATION OF BENZENE

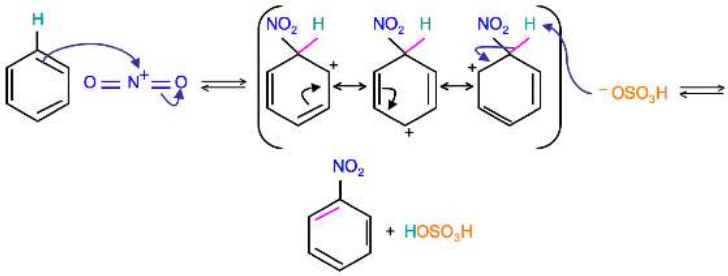
Sulfuric acid catalyzes the nitration of benzene. It is important to note the chemical formula for the nitrate group bonded to benzene is -NO_2. The chemical formula and name are assigned from an organic chemistry perspective which does not align with the inorganic perspective.



Step 1: Nitric acid (HNO_3) is protonated by sulfuric acid which causes the loss of a water molecule and formation of a nitronium ion, a strong electrophile.



Steps 2 and 3: Two pi electrons from benzene form a sigma bond with the nitronium ion to create the sigma complex. Bisulfate deprotonates the sigma complex to restore the aromatic ring as shown below.

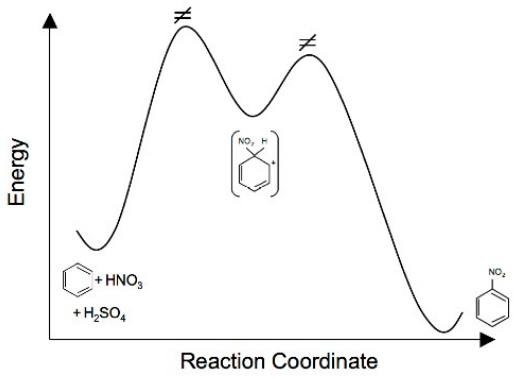


Exercise

6. Draw an energy diagram for the nitration of benzene. Draw the intermediates, starting materials, and products. Label the transition states.

Answer

6.



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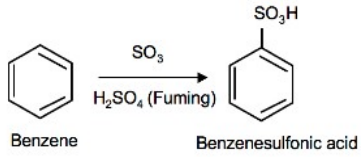
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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Catherine Nguyen

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18.4: SULFONATION OF BENZENE (AN EAS REACTION)

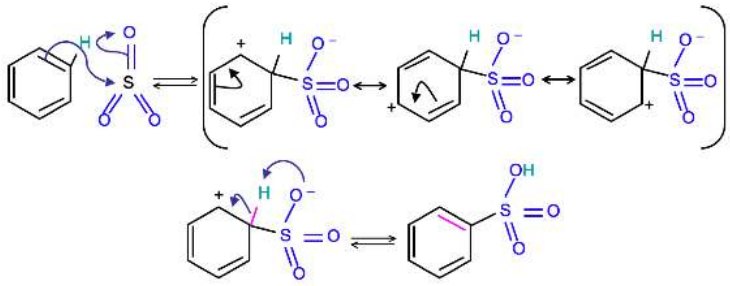
SULFONATION OF BENZENE

Sulfonation is a reversible reaction that produces benzenesulfonic acid by adding sulfur trioxide and fuming sulfuric acid. It is important to note that the chemical formula of the sulfonic group is $-SO_3H$. The reaction is reversed by adding hot aqueous acid to benzenesulfonic acid to produce benzene.



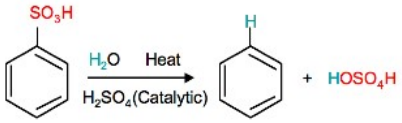
MECHANISM

To produce benzenesulfonic acid from benzene, fuming sulfuric acid and sulfur trioxide are added. Fuming sulfuric acid, also refered to as *oleum*, is a concentrated solution of dissolved sulfur trioxide in sulfuric acid. The sulfur in sulfur trioxide is electrophilic because the oxygens pull electrons away from it because oxygen is very electronegative. The benzene reacts with the sulfur of sulfur trixoxide to form the sigma complex. A subsequent proton transfer occurs to produce benzenesulfonic acid. All three steps are shown together in the mechanism below.

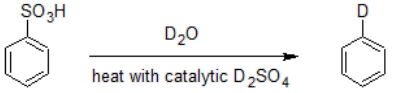


REVERSE SULFONATION

Sulfonation of benzene is a reversible reaction. Sulfur trioxide readily reacts with water to produce sulfuric acid and heat. Therefore, by adding heat to benzenesulfonic acid in diluted aqueous sulfuric acid the reaction is reversed.



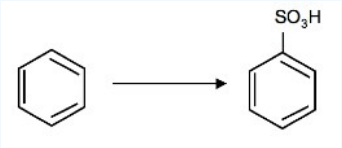
The reversibility of the sulfonation reaction creates an opportunity to prepare deuterated benzene. Isotopically labeled reagents can be useful in determining reaction mechanisms since the C-D bond is stronger than the C-H bond.



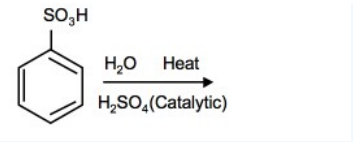
Excess D_2O can produce fully duterated benzene, C_6D_6.

Exercise

7. What is/are the required reagent(s)for the following reaction:



8. What is the product of the following reaction:



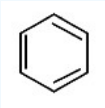
9. Why is it important that the nitration of benzene by nitric acid occurs in sulfuric acid?

10. Write a detailed mechanism for the sulfonation of benzene, including all resonance forms.

Answer

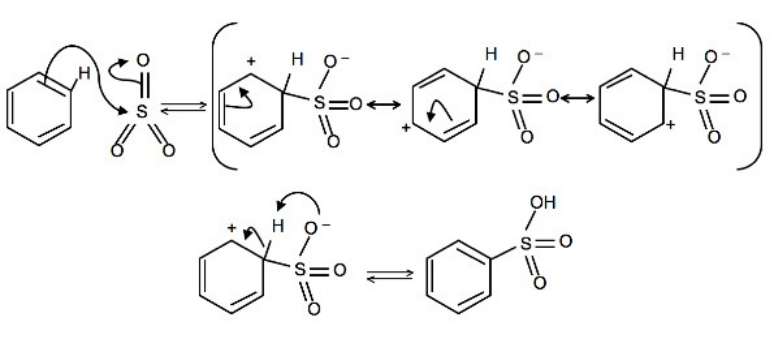
7. SO_3 and H_2SO_4 (fuming)

8.



9. Sulfuric acid is needed in order for a good electrophile to form. Sulfuric acid protonates nitric acid to form the nitronium ion (water molecule is lost). The nitronium ion is a very good electrophile and is open to attack by benzene. Without sulfuric acid the reaction would not occur.

10.



CONTRIBUTORS AND ATTRIBUTIONS

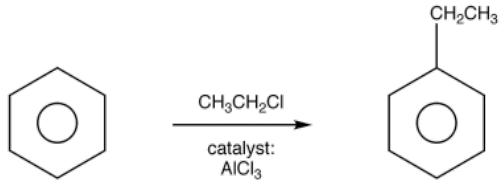
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- Catherine Nguyen

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18.5: ALKYLATION AND ACYLATION OF BENZENE - THE FRIEDEL-CRAFTS EAS REACTIONS

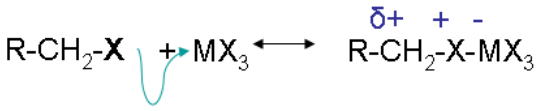
FRIEDEL-CRAFTS ALKYLATION

The Fridedel-Crafts Alkylation reaction froms alkyl benzenes from alkyl halides. The usefulness of this reaction is limited, because it can be difficult to stop the reaction at a single alkylation. Additionally, a carbocation intermediate is produced in Step 1 which brings the potential for carbocation rearrangements (ominous theme music).

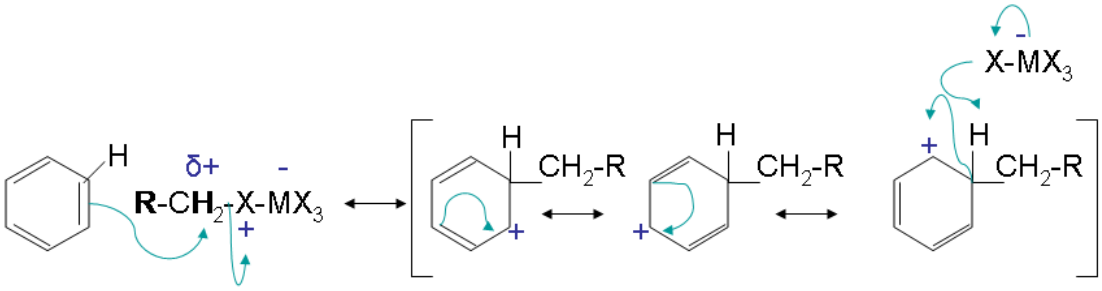


The mechanism takes place as follows:

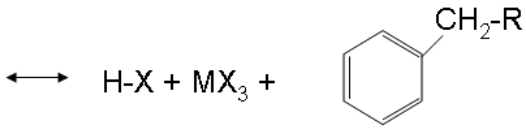
Step 1: A carbocation is created to form the electrophile. This steps activates the haloalkane. Secondary and tertiary halides only form the free carbocation in this step.



Step 2: The pi electrons from benzene react with the electrophile to form the resonance stabilized alkylbenzenium ion.



Step 3: Any Lewis Base reacts picks up the hydrogen from the allkylbenzenium ion to reform the aromatic ring.

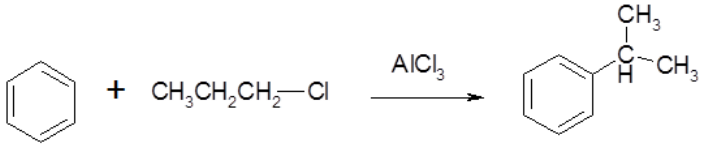


The finish step shown above is the two products.

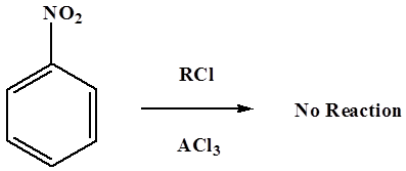
The reactivity of haloalkanes increases as you move up the periodic table and increase polarity. This means that an RF haloalkane is most reactive followed by RCl then RBr and finally RI. This means that the Lewis acids used as catalysts in Friedel-Crafts Alkylation reactions tend have similar halogen combinations such as BF_3, $SbCl_5$, $AlCl_3$, $SbCl_5$, and $AlBr_3$, all of which are commonly used in these reactions.

SOME LIMITATIONS OF FRIEDEL-CRAFTS ALKYLATION

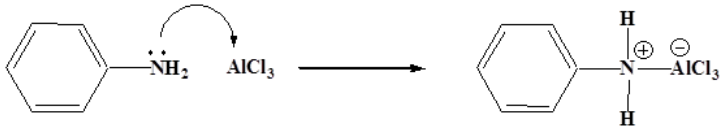
There are possibilities of carbocation rearrangements when you are trying to add a carbon chain greater than two carbons. The rearrangements occur due to hydride shifts and methyl shifts. For example, the product of a Friedel-Crafts Alkylation will show an iso rearrangement when adding a three carbon chain as a substituent. One way to resolve these problems is through Friedel-Crafts Acylation.



Also, the reaction will only work if the ring you are adding a substituent to is not deactivated. Friedel-Crafts fails when used with compounds such as nitrobenzene and other strong deactivating systems.

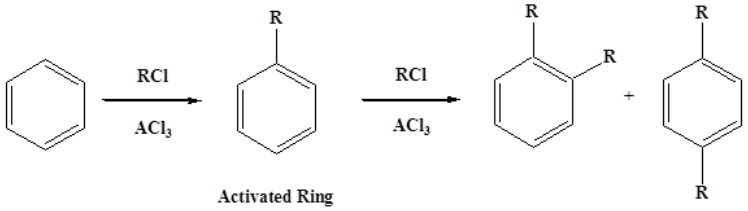


Friedel-Crafts reactions cannot be preformed then the aromatic ring contains a NH_2, NHR, or NR_2 substituent. The lone pair electrons on the amines react with the Lewis acid $AlCl_3$. This places a positive charge next to the benzene ring, which is so strongly activating that the Friedel-Crafts reaction cannot occur.



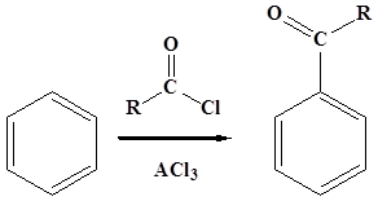
The positive charge strongly deactivates the benzene ring

Lastly, Friedel-Crafts alkylation can undergo polyalkylation. The reaction adds an electron donating alkyl group, which activates the benzene ring to further alkylation.



Activated Ring

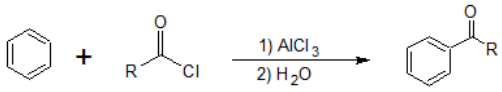
This problem does not occur during Friedel-Crafts Acylation because an acyl group is deactivating. The prevents further acylations.



Dectivated Ring

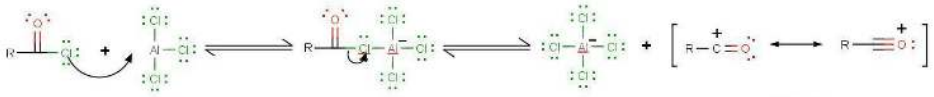
FRIEDEL-CRAFTS ACYLATION

There is an additional reaction step for Fridel-Crafts Acylation. The acyl group of the product complexes with the aluminum chloride. Water is added to isolate the acyl benzene final product.



1st Reaction

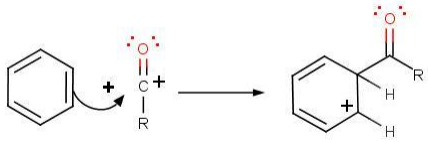
Mechanism Step 1: Acylium ion formation



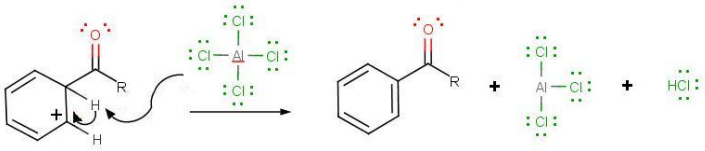
Acyl Chloride

Acylium Ion (Resonance Stabilized)

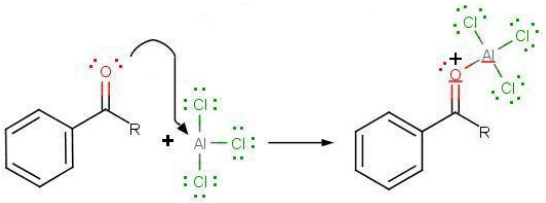
Mechanism Step 2: Pi electrons of benzene react with the acylium ion to form the sigma complex, resonance stabilized acylbenzenium intermediate:



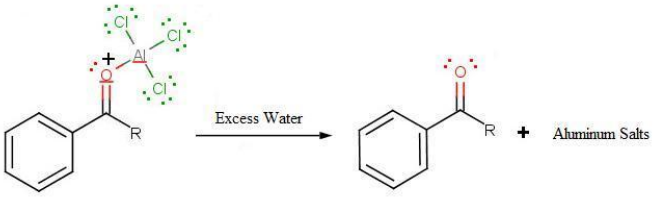
Mechanism Step 3: Deprotonation of the sigma comlex to restore aromaticity.



During the third step, $AlCl_4$ returns to remove a proton from the benzene ring, which enables the ring to return to aromaticity. In doing so, the original $AlCl_3$ is regenerated for use again, along with HCl. Most importantly, we have the first part of the final product of the reaction, which is a ketone. The product forms a complex with aluminum chloride as shown below.



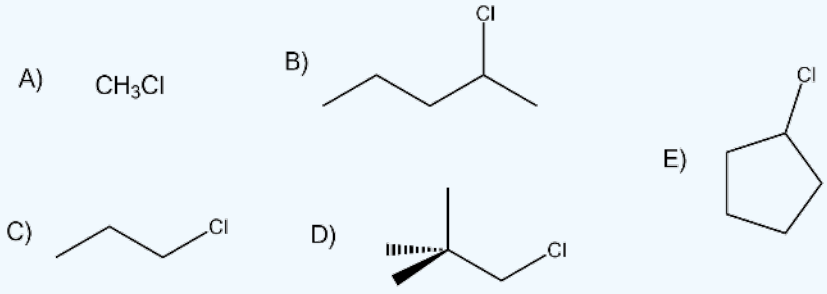
2nd Reaction: Water is added to liberate the final product as the acylbenzene:



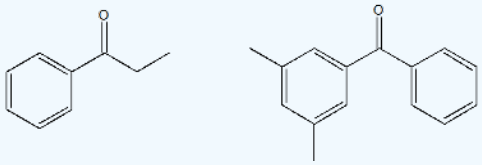
Friedel-Crafts Acylations offer several synthetic advantages over Friedel-Crafts Alkylation. These advantages provide greater control over the production of reaction products. The acylium ion is stabilized by resonance, so no carbocation rearrangement occurs. Additionally, acyl groups are deactivating with for EAS reactions, so the product does not undergo further reactions. However, Friedel-Crafts Acylations do not work with nitrobenzenes or other deactivated benzene rings. The concept of deactivated will be more fully explored in the next two sections of this chapter.

Exercise

11. Which of the following will NOT undergo a rearrangement in a Friedel-Crafts reaction?



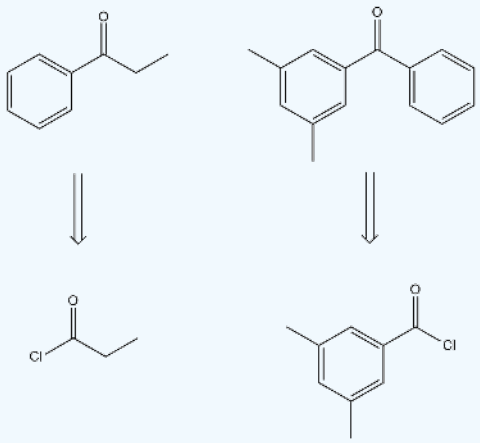
12. Suggest an acyl chloride that was used to make the following compounds:



Answer

11. A, B, and E will not undergo a rearrangement.

12.



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

18.5: Alkylation and Acylation of Benzene - The Friedel-Crafts EAS Reactions is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

18.6: SUBSTITUENT EFFECTS ON THE EAS REACTION

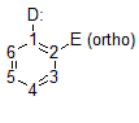
IMPORTANT NOTE:

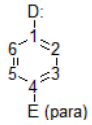
Recognizing substituents as Electron Donating or Withdrawing is a useful skill for evaluating reaction mechanisms. For Electrophilic Aromatic Substitution (EAS) reactions, the rate determining step is the formation of a positively charged sigma complex. In future reactions, the intermediate may have a negative charge. While the electron donating and withdrawing properties of a substituent are inherent within the substituent, their effect on the stability of an intermediate and the reaction rate depends on the charge of the intermediate.

SUBSTITUENTS AND THEIR DIRECTING EFFECTS IN EAS REACTIONS

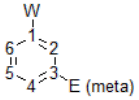
Electron donating groups (D) direct the reaction to the ortho- or para-position, which means the electrophile substitutes for the hydrogen on carbon 2 or carbon 4 relative to the donating group. The withdrawing group directs the reaction to the meta position, which means the electrophile substitutes for the hydrogen on carbon 3 relative to the withdrawing group. The halogens are an exception to this pattern. The halogens are a deactivating group that direct ortho or para substitution.

Donating groups direct the Electrophile (E) to the ortho- and para-positions.





Withdrawing groups direct the Electrophile (E) to the meta-postion.



Examples of electron donating groups in the relative order from the most activating group to the least activating:

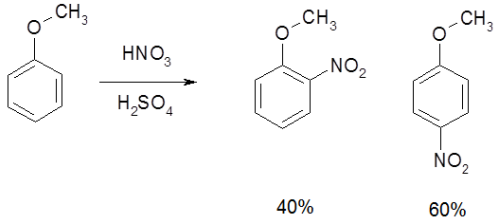
$-NH_2$, $-NR_2$ > -OH, -OR> -NHCOR> $-CH_3$ and other alkyl groups with R as alkyl groups (C_nH_{2n+1})

Examples of electron withdraing groups in the relative order from the most deactivating to the least deactivating:

$-NO_2$, $-CF_3$> -COR, -CN, $-CO_2R$, $-SO_3H$ > Halogens with R as alkyl groups (C_nH_{2n+1})

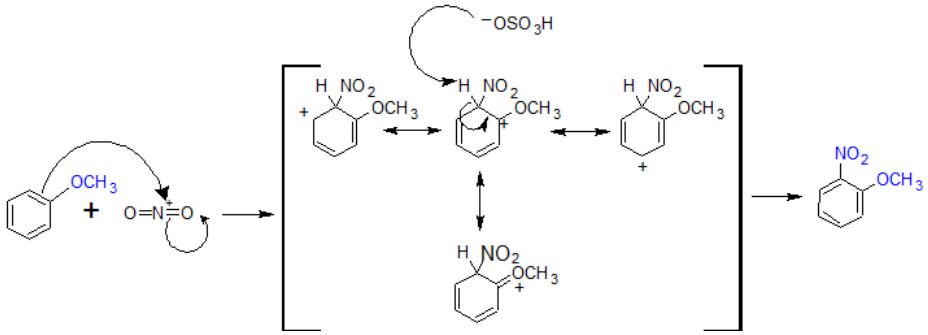
ORTHO-, PARA-DIRECTORS VIA RESONANCE

Groups that donate electrons through resonance are ortho-, para-directors for EAS reactions. Methoxybenzene (anisole) will be used to demonstrate the ortho-, para-direction of substituents that stabilize the sigma complex through resonance. The nitronium ion ($O=N^+=O$) will be used to represent the Electrophile (E+).

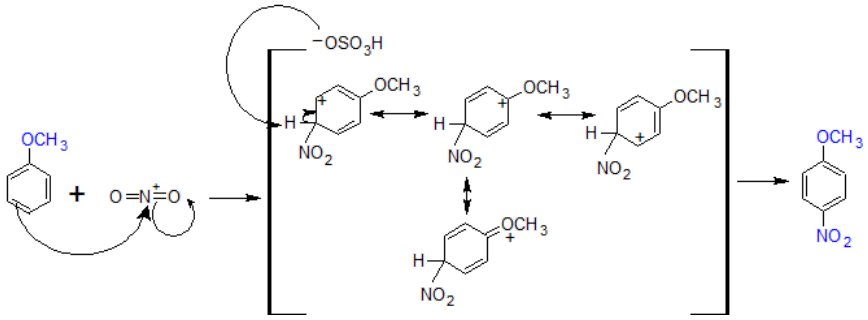


The ortho- and para-directed mechanisms for the nitration of anisole are shown below. When the nitro group adds at the ortho or para position, the stability of the sigma complex is increased by the presence of a fourth resonance form . The greater the stability of the sigma complex causes the ortho and para products for form faster than meta. Generally, the para-product is favored over the ortho-product because of steric effects even though there are two ortho- positions.

Mechanism for ortho-directed product formation

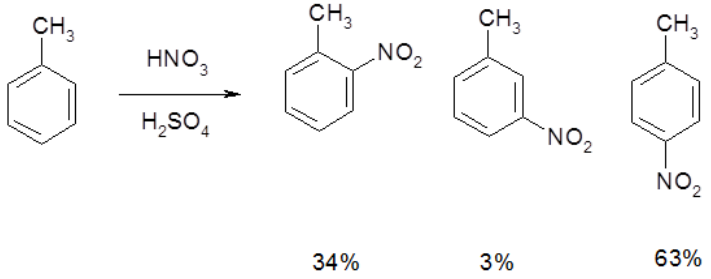


Mechanism for para-directed product formation



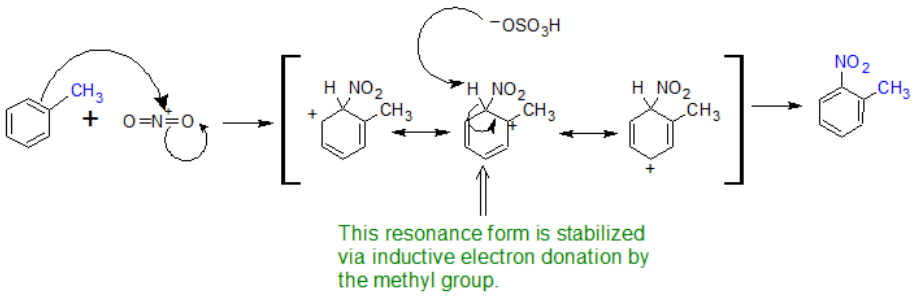
ORTHO-, PARA-DIRECTORS VIA INDUCTION

Alkyl groups are ortho-, para-directors for EAS reactions. Toluene will be used to demonstrate the ortho-, para-direction of substituents that stabilize the sigma complex through induction. The nitronium ion ($O=N^+=O$) will be used to represent the Electrophile (E^+). Since the inductive effect is weaker than resonance, we can see that a small percentage of the meta product is also isolated.

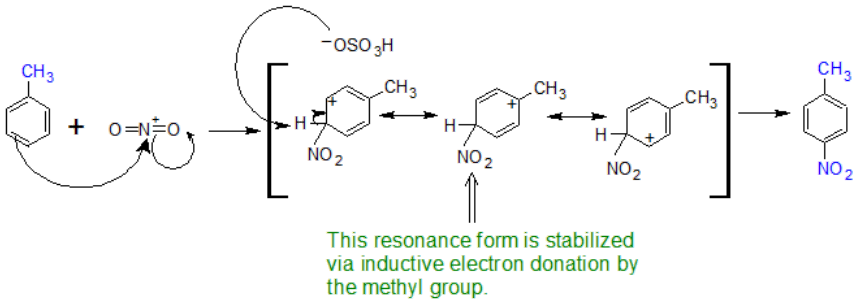


Looking at the stability of the resonance structures of the sigma complex in the reaction mechanism for nitration of toluene explains why the ortho- and para- substitutions are the major products. When the nitro group adds at the ortho or para position, the methyl group stabilizes the transition state through induction electron donation which favors the formation of the ortho- and para- products. As seen with the resonance directed products, the para product is favored because of steric effects even though there are two ortho- positions.

Mechanism for ortho-directed product formation



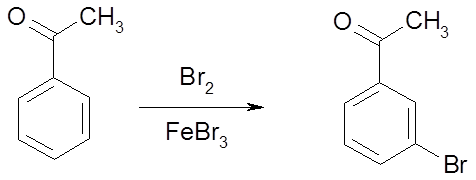
Mechanism for para-directed product formation



META DIRECTORS - THE ELECTRON WITHDRAWING GROUPS

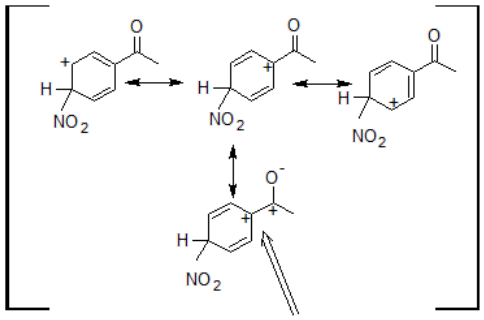
Electron withdrawing groups destabilize the sigma complex and deactivate benzene rings to EAS reactions. For electron withdrawing groups, all of the sigma complexes are destabilized. The meta-position is the least destabilized and produces the largest percentage of the reaction products.

Acetophenone will be used to demonstrate the reactivity of meta-directors using the sigma complexes below. Acyl groups are resonance deactivators.



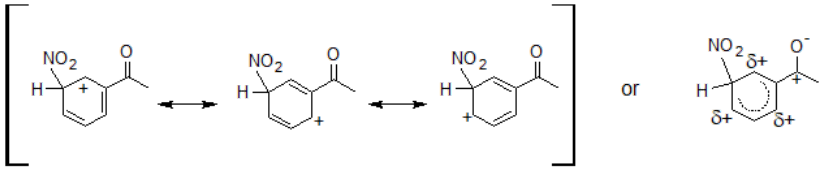
72%

Ortho and para reactions produce a resonance structure that places the arenium cation next to an additional cation at the carbonyl carbon. This close proximity of partial positive charges destabilizes the sigma complex and slows down ortho and para reaction.



para-(shown) and ortho-directors destabilize the sigma complex by forcing two partial positive charges into close proximity.

By default the meta product forms faster because the destabilizing effects are reduced through greater physical separation of the partial positive charges.



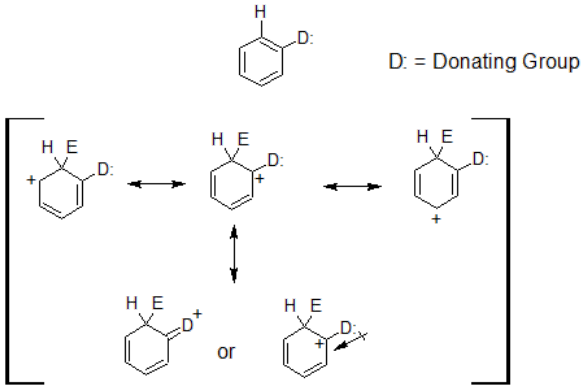
Meta-directors reduce destabilization of the sigma complex.

SUBSTITUENTS AND ELECTROPHILIC AROMATIC SUBSTITUTION (EAS) REACTION RATES

Since sigma complex formation is the rate determining step of EAS reactions, benzene derivatives are divided into two groups based on how the substituent stabilizes or destabilizes the positively charged sigma complex. The EAS reaction of a substituted ring with an activating group is faster than benzene. On the other hand, a substituted ring with a deactivated group is slower than benzene. Activating groups speed up the EAS reaction by either resonance or inductive electron donation (typically R groups). For resonance, unpaired electrons can be donated to stabilize the positive charge of the sigma complex in the transition state. Stabilizing the intermediate, speeds up the reaction by lowering the activating energy. Inductive electron donation by R groups is an analogous, yet weaker effect than resonance. Inductive electron donation helps to stabilize the sigma complex and speed up (activate) the reaction. Deactivating groups withdraw the electrons away from the carbocation of the sigma complex causing destabilization and increasing the activation energy which slows down (deactivates) the reaction.

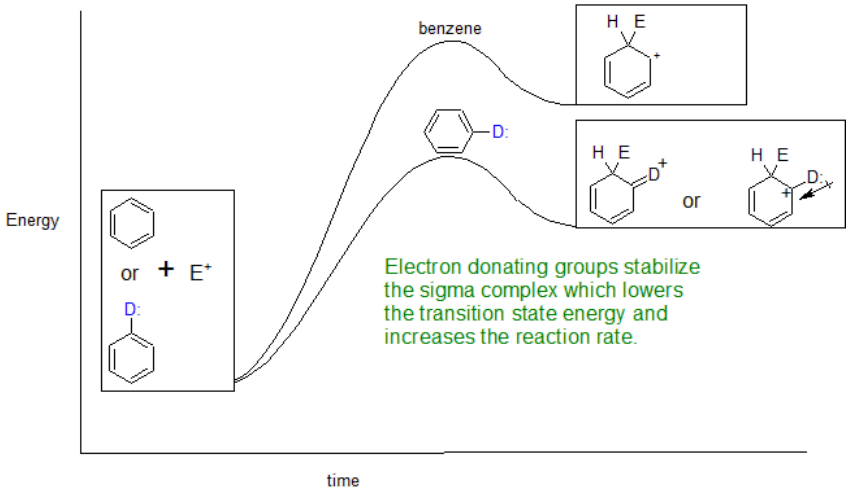
- **Activated rings**: the substituents on the ring **donate** electrons and increase EAS reaction rates
  - Examples of electron donating groups in the relative order from the most activating group to the least activating:

    $-NH_2$, $-NR_2$ > -OH, -OR> -NHCOR> $-CH_3$ and other alkyl groups with R as alkyl groups (C_nH_{2n+1})



The electron donating group (D:) activates the ring with an additional resonance form or inductive donation effect to stabilize the + charge of the sigma complex.

The reaction energy diagram illustrating the substituent effect of electron donating groups (D:) on EAS reaction rates is shown below.



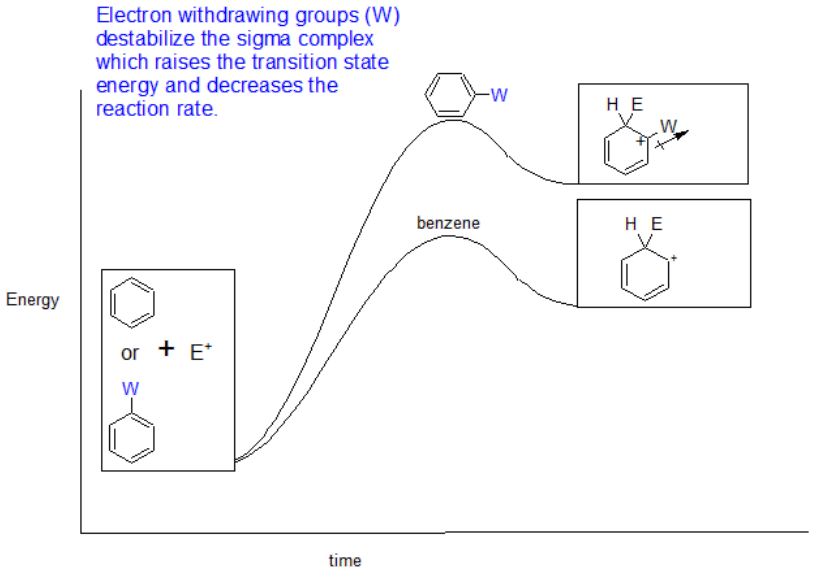
- **Deactivated rings**: the substituents on the ring **withdraw** electrons and decrease EAS reaction rates
  - Examples of electron withdraing groups in the relative order from the most deactivating to the least deactivating:

$-NO_2$, $-CF_3$> -COR, -CN, $-CO_2R$, $-SO_3H$ > Halogens with R as alkyl groups (C_nH_{2n+1})



The electron withdrawing group (W) deactivates the ring by destabilizing the sigma complex. Note the proximity of the + and δ+ charges.

The reaction energy diagram illustrating the substituent effect of electron withdrawing groups (W) on EAS reaction rate is shown below.



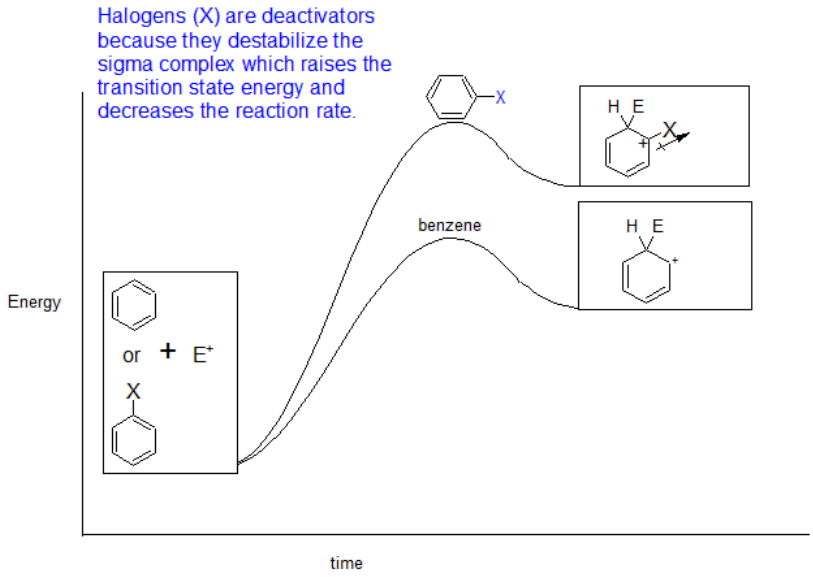
- **The Halogen Paradox: Deactivators that are ortho, para-directors**

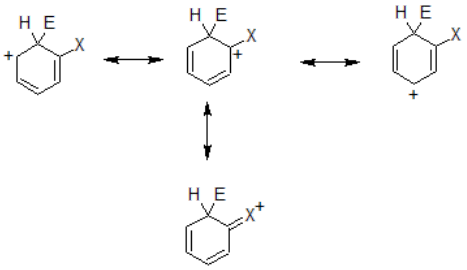
Halogens deactivate rings to subsequent EAS reactions. The order of reactivity of the benzene rings toward the electrophilic substitution when it is substituted with a halogen groups, follows the order of electronegativity.

$$F > Cl > Br > I$$

The ring that is substituted with the most electronegative halogen is the most reactive ring (less deactivating substituent) and the ring that is substituted with the least electronegatvie halogen is the least reactive ring (more deactivating substituent). The size of the halogen also effects the reactivity of the benzene ring - as the size of the halogen increases, the reactivity of the ring decreases.

However, the lone pair electrons on the halogen atoms are still available for resonance delocalization in the sigma complex causing ortho-, para-direction of the electrophile. The reaction energy diagram below resolves these contradictory aspects of EAS reactions of halogenated benzene derivatives.





Halogens (X) are o-, p-directors because they create an addition resonance form in the sigma complex.

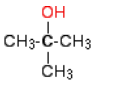
REFERENCES

1. Schore, N.E. and P.C. Vollhardt. 2007. *Organic Chemistry, structure and function*, 5th ed. New York,NY: W.H. Freeman and Company.
2. Fryhle, C.B. and G. Solomons. 2008. *Organic Chemistry*, 9th ed.Danvers,MA: Wiley.

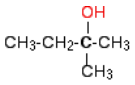
OUTSIDE LINKS

- http://en.Wikipedia.org/wiki/Activating_group
- http://en.Wikipedia.org/wiki/Deactivating_group
- http://www.columbia.edu/itc/chemistry/c3045/client_edit/ppt/PDF/12_12_14.pdf

In a tertiary (3°) alcohol, the carbon atom holding the -OH group is attached directly to three alkyl groups, which may be any combination of same or different. Examples:



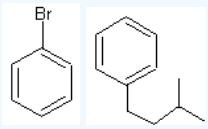
2-methylpropan-2-ol



2-methylbutan-2-ol

Exercises

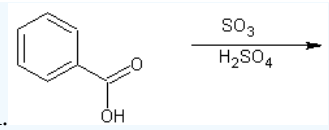
13. Predict the direction of the electrophile substition on these rings:



14. Which nitration product is going to form faster?

nitration of aniline or nitration of nitrobenzene?

15. Predict the product of the following two sulfonation reactions:

A. 

16. Classify these two groups as activating or deactivating groups:

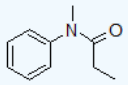
A. alcohol

B. ester

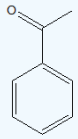
17. By which effect does trichloride effect a monosubstituted ring?

18. Trichloromethylbenzene has a strong concentration of electrons at the methyl substituent. Comparing this compound with toluene, which is more reactive toward electrophilic substitution?

19. The following compound is less reactive towards electrophilic substitution than aniline? Explain.



20. Consider the intermediates of the following molecule during an electrophilic substitution. Draw resonance structures for ortho, meta, and para reactions.

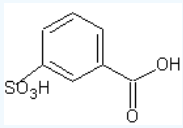


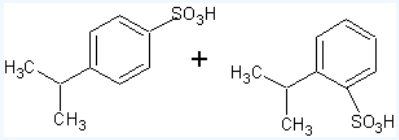
Answer

13. The first substitution is going to be ortho and/or para substitution since we have a halogen subtituent. The second substition is going to be ortho and/or para substitution also since we have an alkyl substituent.

14. The nitration of aniline is going to be faster than the nitration of nitrobenzene, since the aniline is a ring with NH_2 substituent and nitrobenzene is a ring with NO_2 substiuent. As described above $NH_2$is an activating group which speeds up the reaction and NO_2 is deactivating group that slows down the reaction.

15.

A. the product is 

B. the product is 

16.

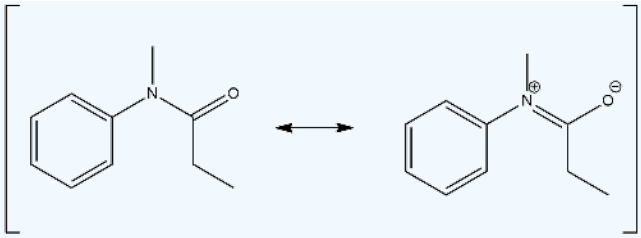
A. alcohol is an activating group.

B. ester is a deactivating group.

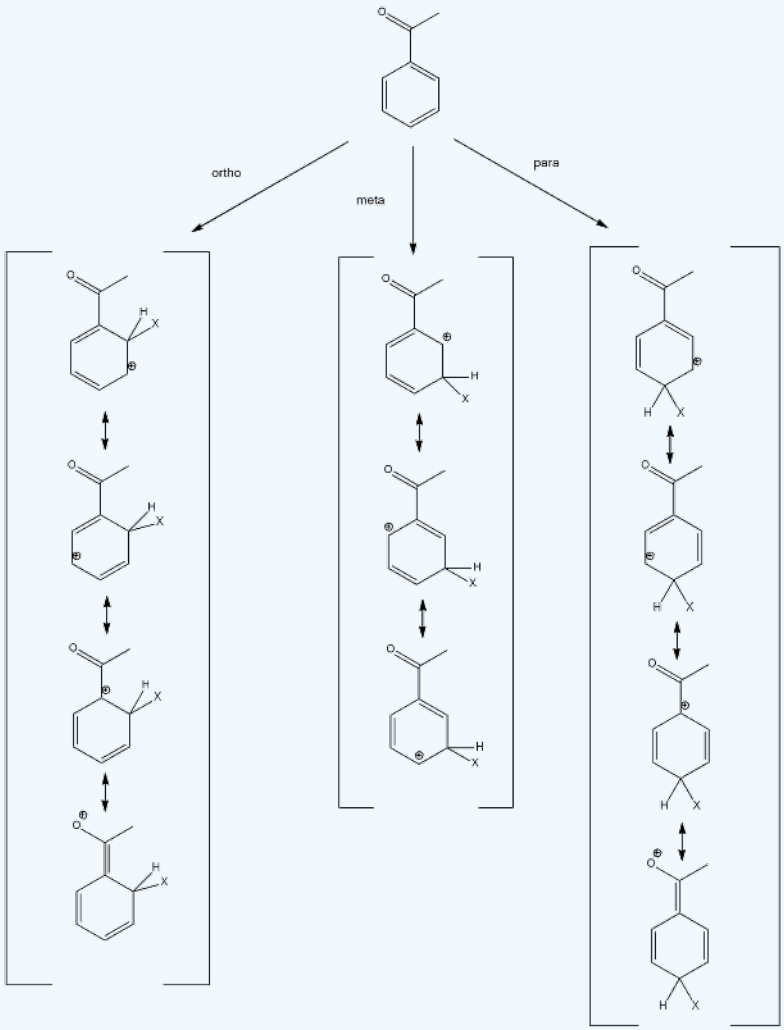
17. Trichloride deactivate a monosubstitued ring by inductive effect.

18. The trichloromethyl group is an electron donor into the benzene ring, therefore making it more stable and therefore more reactive compared to electrophilic substitution.

19. As seen in resonance the electron density is also localized off of the ring, thereby deactivating it compared to aniline.



20.



16.6 TRISUBSTITUTED BEN

EXERCISES

QUESTIONS

Q16.5.1

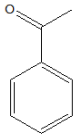
(Trichlorometyl)benzene has a strong concentration of electrons at the methyl substituent. Comparing this toluene, which is more reactive toward electrophilic substitution?

Q16.5.2

The following compound is less reactive towards electrophilic substitution than aniline? Explain.

Q16.5.3

Consider the intermediates of the following molecule during an electrophilic substitution. Draw resonance structures for ortho, meta, and para attacks.



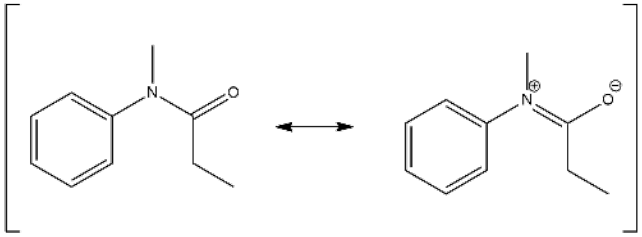
SOLUTIONS

S16.5.1

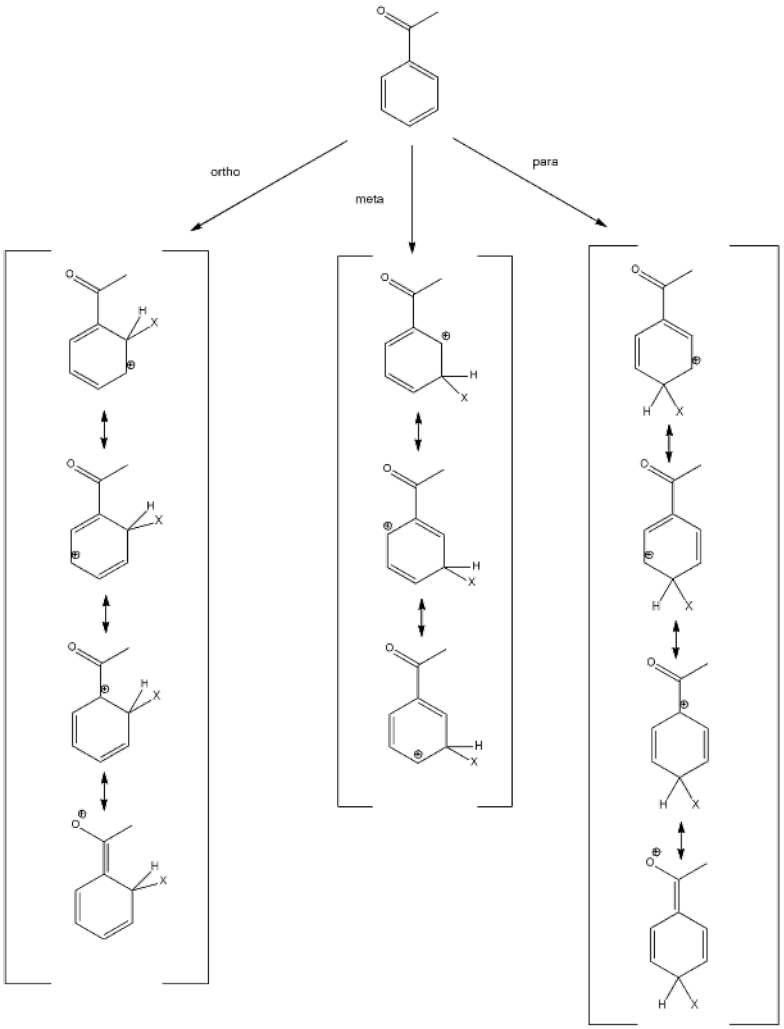
The trichloromethyl group is an electron donor into the benzene ring, therefore making it more stable and therefore more reactive compared to electrophilic substitution.

S16.5.2

As seen in resonance the electron density is also localized off of the ring, thereby deactivating it compared to aniline.



S16.5.3



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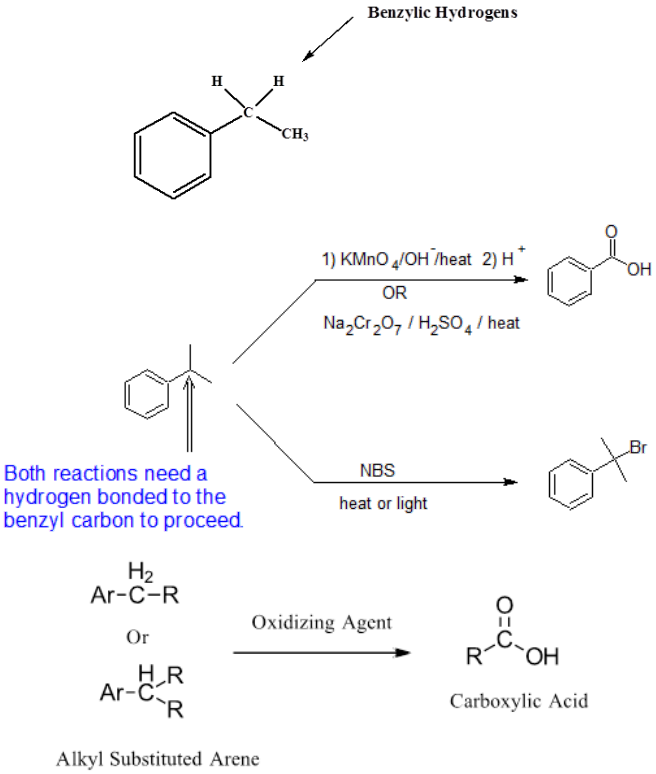
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Lana Alawwad (UCD)

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18.7: SIDE-CHAIN REACTIONS OF BENZENE DERIVATIVES

OXIDATION OF ALKYL SIDE CHAINS

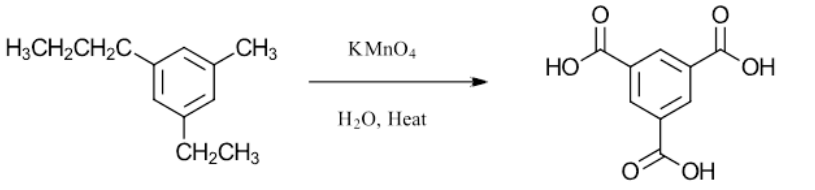
There is another reaction which occurs at the atom directly attached to an aromatic ring. This is known as "side chain oxidation." When a compound which has an alkyl group directly attached to an aryl group is treated with a strong oxidizing agent like potassium permanganate ($KMnO_4$) or Jones Reagent (CrO_3/H_2SO_4), the benzylic carbon is oxidized to a carboxylic acid group which remains attached to the aryl group. Any other carbon-carbon bonds in the alkyl group are broken. For the oxidation reaction, the number of carbon atoms in the alkyl side chain does not matter, However, the benzylic carbon must have at least one benzylic hydrogen attached. Thus, tertiary carbons attached to an aromatic ring are not affected by these reactions. It should be noted that during this reaction an ortho/para directing alkyl group is converted to a meta directing carboxylic.

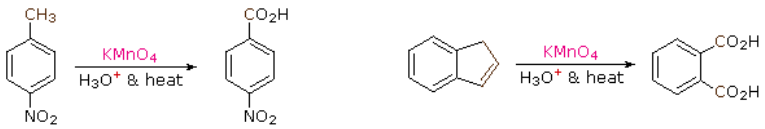


Add tertiary no reaction

Two other examples of this reaction are given below, and illustrate its usefulness in preparing substituted benzoic acids.

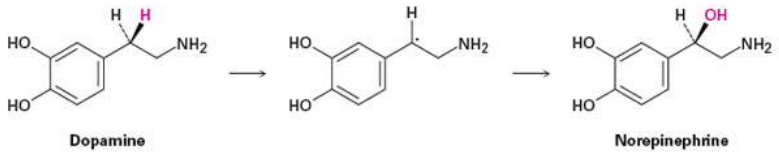
Add straing chain and tertirary.

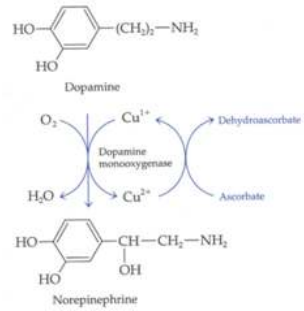




The mechanism of this reaction is obscure, but the fact that it specifically requires that there be a benzylic C-H bond suggests that breaking this bond is essential. Any intermediate that might be formed by breaking this bond will be stabilized by resonance with the aryl group, which provides an explanation for the specificity of attack at the benzylic position. Such reactions also occur in a biological context. Enzymes oxidize alkyl side chains on aromatic rings as part of making such compounds soluble enough to be eliminated.

ANALOGOUS SIDE-CHAIN OXIDATIONS OCCUR IN VARIOUS BIOSYNTHETIC PATHWAYS. THE NEUROTRANSMITTER NOREPINEPHRINE, FOR INSTANCE, IS BIOSYNTHESIZED FROM DOPAMINE BY A BENZYLIC HYDROXYLATION REACTION. THE PROCESS IS CATALYZED BY THE COPPER-CONTAINING ENZYME DOPAMINE -MONOOXYGENASE AND OCCURS BY A RADICAL MECHANISM. A COPPER–OXYGEN SPECIES IN THE ENZYME FIRST ABSTRACTS THE *PRO*-R BENZYLIC HYDROGEN TO GIVE A RADICAL, AND A HYDROXYL IS THEN TRANSFERRED FROM COPPER TO CARBON.





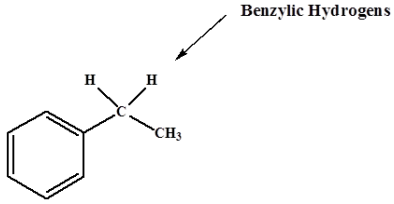
BROMINATION OF THE BENZYLIC CARBON

The bromination reaction is the N-bromosuccinamide (NBS) radical, substitution reaction previously studied. As with the oxidation reaction, one benzylic hydrogen is needed so that it can be substituted with bromine. Examples of both reactions are shown below.

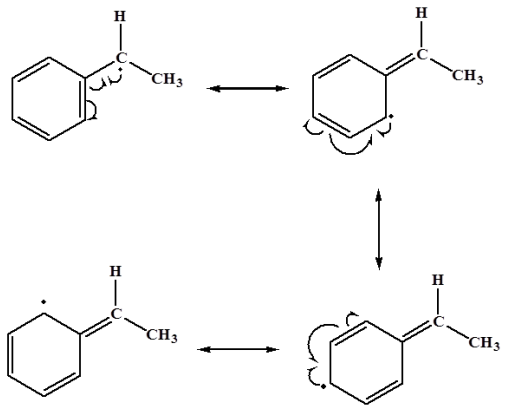
The brominating reagent, N-bromosuccinimide (NBS), has proven useful for achieving allylic or benzylic substitution in CCl_4 solution at temperatures below its boiling point (77 ºC). One such application is shown in the second equation. the allylic bromination with NBS is analagous to the alkane halogenation reaction (Section 10.3) since it also occurs as a radical chain reaction. The NBS serves as the source for the bromine, which is used in the initiation step to create a bromine radical that then abstracts a proton from the allylic position in the propagation step. The radical created then reacts with the NBS to to become bromiated and the cycle continues until it is terminated.

The predominance of allylic substitution over other positions comes down to bond dissociation energies. The relative bond dissociation energies are shown in the table at the top of this section. The C-H bond that we are focusing on as the point of difference for each of the energies shows that the allylic C-H bond has a strength of about 88 kcal/mol. This means that the allylic radical created is more stable than a typical alkyl radical with the same substitution by about 9 kcal/mol. Therefore, this radical is the most likely one to form and thus react.

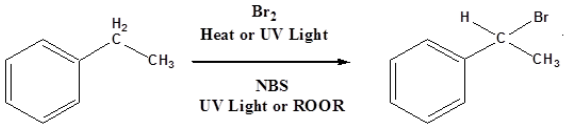
The benzylic C-H bonds weaker than most sp^3 hybridized C-H. This is because the radical formed from homolysis is resonance stabilized.



Resonance stabilization of the benzylic radical

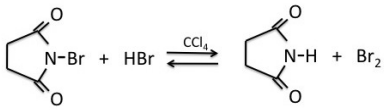


Because of the weak C-H bonds, benzylic hydrogens can form benzylic halides under radical conditions.



NBS AS A BROMINE SOURCE

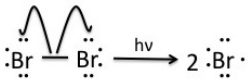
NBS (N-bromosuccinimide) is the most commonly used reagent to produce low concentrations of bromine. When suspended in tetrachloride (CCl_4), NBS reacts with trace amounts of HBr to produce a low enough concentration of bromine to facilitate the allylic bromination reaction.



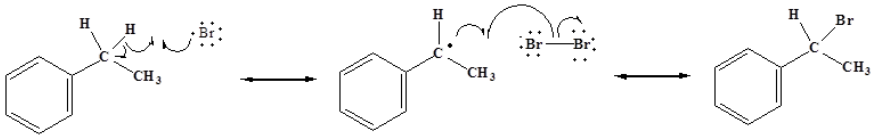
ALLYLIC BROMINATION MECHANISM

Step 1: Initiation

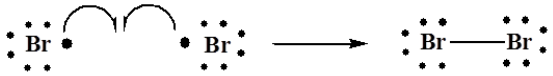
Once the pre-initiation step involving NBS produces small quantities of Br_2, the bromine molecules are homolytically cleaved by light to produce bromine radicals.



Step 2 and 3: Propagation

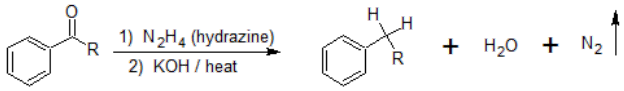


Step 4: Termination



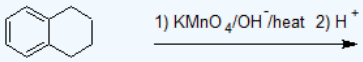
ACYL SIDE CHAIN REDUCTIONS

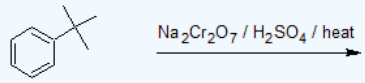
Since there are several limitations to the Friedel-Crafts alkylation that are not observed with the Friedel-Crafts acylation, reduction of the acyl side chain to an alkyl side chain is a useful reaction for multiple step synthesis. The Wolff-Kishner reaction reduces the carbon groups (aldehydes and ketones) to alkanes and is not limited to acyl groups bonded to benzene rings. This acyl reduction reaction is also useful because acyl groups are deactivating, meta-directors, and alkyl groups are activating, ortho-, para-directors which adds flexibility to multiple step synthesis strategies.

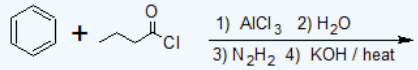


Exercise

21. Draw the bond-line structures for the product(s) of the following reactions.

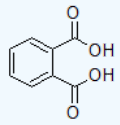
a) 

b) 

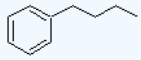
c) 

Answer

21.

a) 

b) No reaction because there are no benzylic hydrogens.

c) 

This compond cannot be synthesized by
F-C Alkylation because of carbocation rearrangment.

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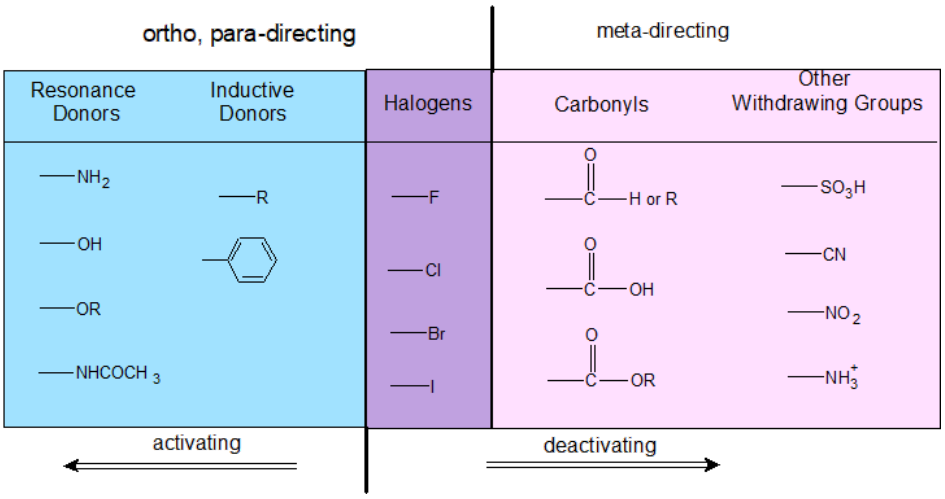
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
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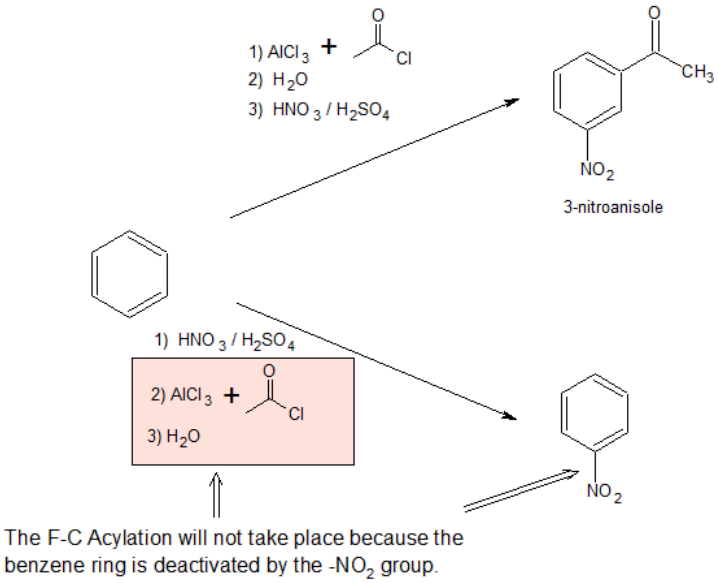
18.8: SYNTHETIC STRATEGIES FOR DI-SUBSTITUTED BENZENES

SYNTHETIC CONSIDERATIONS

To develop multiple step syntheses for di-substituted benzene derivatives, the regiochemistry of the substituents will determine the order of the reactions. The directing effects of the benzene substituents are summarized below.

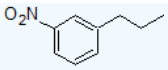


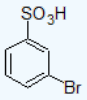
The limitations of the Friedel-Crafts reactions must also be considered. Friedel-Crafts alkylation and acylation reactions can only occur on benzene rings or benzene rings with ortho-, para-directors (activated rings or rings with halogens). Even though both acyl and nitro groups are meta-directors, benzene would need to be acylated before it is nitrated. To synthesize 3-nitroanisole [1-(3-nitrophenyl)ethan-1-one], the top reaction sequence is needed. The bottom reaction sequence will not produce the desired product as shown in the two synthetic pathways below.

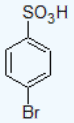


Exercise

22. Starting with benzene and using any synthetic reagents, propose a multiple step synthesis for each of the following compounds.

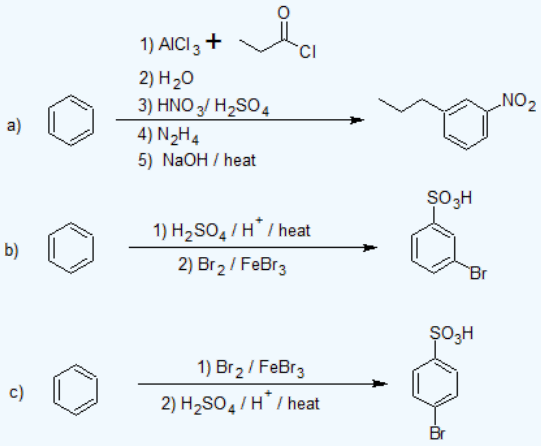
a) 

b) 

c) 

Answer

22.



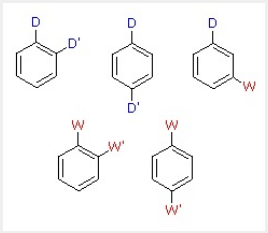
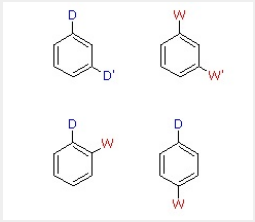
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18.9: TRISUBSTITUTED BENZENES - EFFECTS OF MULTIPLE SUBSTITUENTS

ORIENTATIONAL INTERACTION OF SUBSTITUENTS

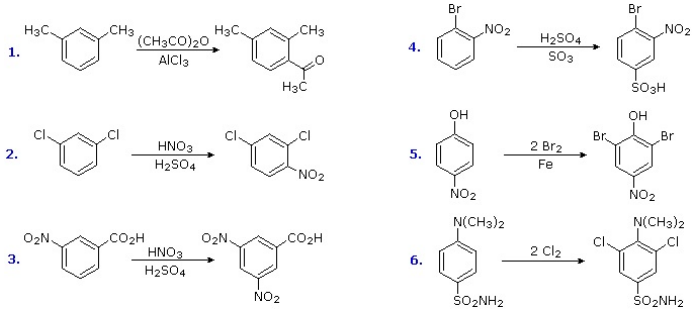
When a benzene ring has two substituent groups, each exerts an influence on subsequent substitution reactions. The activation or deactivation of the ring can be predicted more or less by the sum of the individual effects of these substituents. The site at which a new substituent is introduced depends on the orientation of the existing groups and their individual directing effects. We can identify two general behavior categories, as shown in the following table. Thus, the groups may be oriented in such a manner that their directing influences act in concert, reinforcing the outcome; or are opposed (antagonistic) to each other. Note that the orientations in each category change depending on whether the groups have similar or opposite individual directing effects.

Antagonistic or Non-Cooperative	Reinforcing or Cooperative
	

D = Electron Donating Group (ortho/para-directing)
W = Electron Withdrawing Group (meta-directing)

REINFORCING OR COOPERATIVE SUBSTITUTIONS

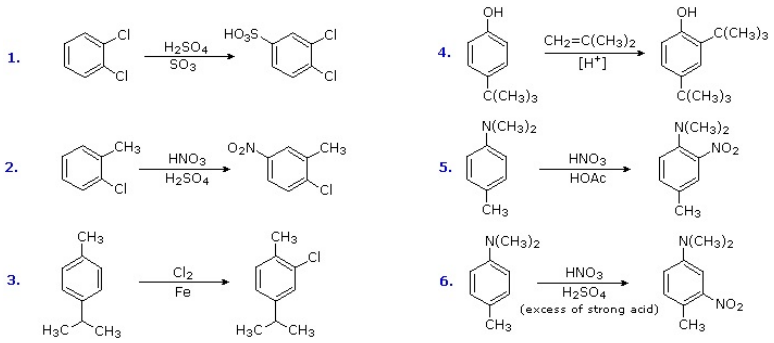
The products from substitution reactions of compounds having a reinforcing orientation of substituents are easier to predict than those having antagonistic substituents. For example, the six equations shown below are all examples of reinforcing or cooperative directing effects operating in the expected manner. Symmetry, as in the first two cases, makes it easy to predict the site at which substitution is likely to occur. Note that if two different sites are favored, substitution will usually occur at the one that is least hindered by ortho groups.



The first three examples have two similar directing groups in a meta-relationship to each other. In examples 4 through 6, oppositely directing groups have an ortho or para-relationship. The major products of electrophilic substitution, as shown, are the sum of the individual group effects. The strongly activating hydroxyl (–OH) and amino ($–NH_2$) substituents favor dihalogenation in examples 5 and six.

ANTAGONISTIC OR NON-COOPERATIVE SUBSTITUTIONS

Substitution reactions of compounds having an antagonistic orientation of substituents require a more careful analysis. If the substituents are identical, as in example 1 below, the symmetry of the molecule will again simplify the decision. When one substituent has a pair of non-bonding electrons available for adjacent charge stabilization, it will normally exert the product determining influence, examples 2, 4 & 5, even though it may be overall deactivating (case 2). Case 3 reflects a combination of steric hindrance and the superior innate stabilizing ability of methyl groups relative to other alkyl substituents. Example 6 is interesting in that it demonstrates the conversion of an activating ortho/para-directing group into a deactivating meta-directing "onium" cation [$–NH(CH_3)_2^{(+)}$] in a strong acid environment.



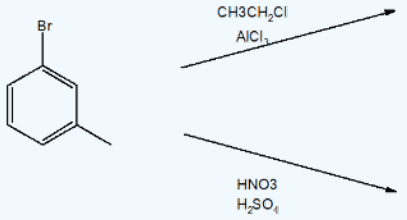
In a tertiary (3°) alcohol, the carbon atom holding the -OH group is attached directly to three alkyl groups, which may be any combination of same or different. Examples:

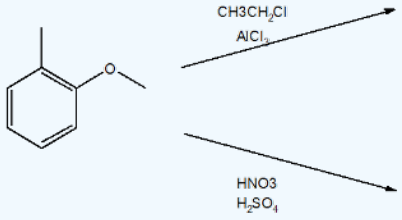


2-methylpropan-2-ol 2-methylbutan-2-ol

Exercise

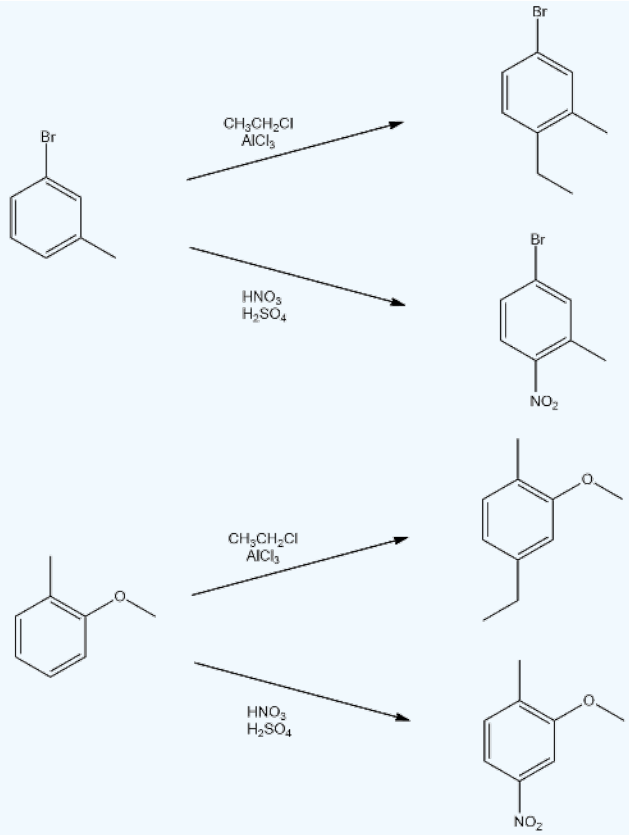
23. Predict the products of the following reactions:





Answer

23.



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- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
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18.10: NUCLEOPHILIC AROMATIC SUBSTITUTION - THE ADDITION-ELIMANTION MECHANISM

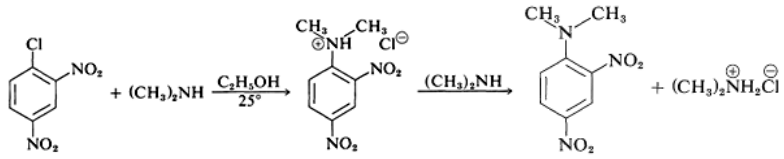
A NUCLEOPHILIC AROMATIC DISPLACEMENT REACTIONS OF ARYL HALIDES

The carbon-halogen bonds of aryl halides are like those of alkenyl halides in being much stronger than those of alkyl halides. The simple aryl halides generally are resistant to reaction with nucleophiles in either S_N1 or S_N2 reactions. However, this low reactivity can be changed dramatically by changes in the reaction conditions and the structure of the aryl halide. In fact, nucleophilic displacement becomes quite rapid

a. when the aryl halide is activated by substitution with strongly electron-attracting groups such as $N0_2$, and
b. when very strongly basic nucleophilic reagents are used.

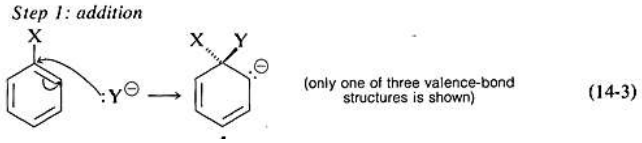
ADDITION-ELIMINATION MECHANISM OF NUCLEOPHILIC SUBSTITUTION OF ARYL HALIDES

Although the simple aryl halides are inert to the usual nucleophilic reagents, considerable activation is produced by strongly electron-attracting substituents provided these are located in either the ortho or para positions, or both. For example, the displacement of chloride ion from 1-chloro-2,4-dinitrobenzene by dimethylamine occurs readily in ethanol solution at room temperature. Under the same conditions chlorobenzene completely fails to react; thus the activating influence of the two nitro groups amounts to a factor of at least 108:

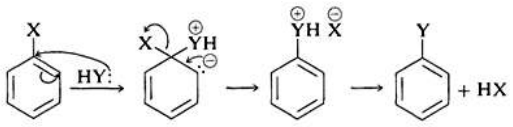


In general, the reactions of activated aryl halides closely resemble the S_N2-displacement reactions of aliphatic halides. The same nucleophilic reagents are effective (e.g., CH_3O^-, HO^-, and RNH_2); the reactions are second order overall (first order in halide and first order in nucleophile); and for a given halide the stronger the nucleophile, the faster the reaction. However, there must be more than a subtle difference in mechanism because an aryl halide is unable, to pass through the same type of transition state as an alkyl halide in S_N2 displacements.

The generally accepted mechanism of nucleophilic aromatic substitution of aryl halides carrying activating groups involves two steps that are closely analogous to those described for alkenyl and alkynyl halides. The first step involves the nucleophile $Y:^-$ reacting with the carbon bearing the halogen substituent to form an intermediate carbanion (Equation 14-3). The aromatic system is destroyed on forming the anion, and the carbon at the reaction site changes from planar (sp^2 bonds) to tetrahedral (sp^3 bonds).

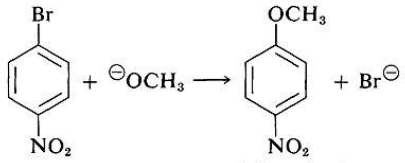


In the second step, loss of an anion, X^- or Y^-, regenerates an aromatic system. If X^- is lost, the overall reaction is nucleophilic displacement of X by Y. In the case of a neutral nucleophilic reagent, Y or HY, the reaction sequence would be the same except for the necessary adjustments in the charge of the intermediate:



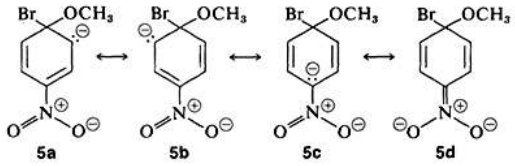
Why is this reaction pathway generally unfavorable for the simple aryl halides? The answer is that the anionic intermediate is too high in energy to be formed at any practical rate. Not only has the anion lost the aromatic stabilization of the benzene ring, but its formation results in transfer of negative charge to the ring carbons, which themselves are not very electronegative:

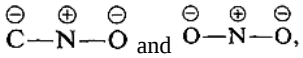
However, when strongly electron-attracting groups are located on the ring at the ortho-para positions, the intermediate anion is stabilized by delocalization of electrons from the ring carbons to more favorable locations on the substituent groups. As an example, consider the displacement of bromine by $^-OCH_3$ in the reaction of 4-bromonitrobenzene and methoxide ion:



4-nitromethoxybenzene

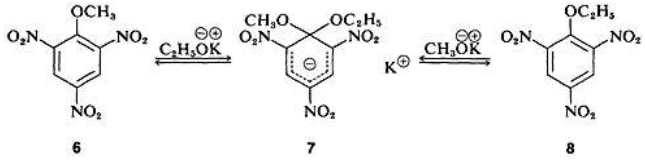
The anionic intermediate formed by addition of methoxide ion to the aryl halide can be described by the valence-bond structures 5a-5d. Of these structures 5d is especially important because the charge is transferred from the ring carbons to the electronegative oxygen of the nitro substituent:



Substituents in the meta positions have much less effect on the reactivity of an aryl halide because delocalization of electrons to the substituent is not possible. No formulas can be written analogous to 5c and 5d in which the negative charges are both on atoms next to positive nitrogen,  and ,

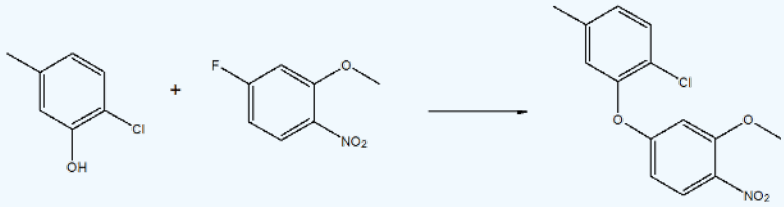


In a few instances, stable compounds resembling the postulated reaction intermediate have been isolated. One classic example is the complex 7 (isolated by J. Meisenheimer), which is the product of the reaction of either the methyl aryl ether 6 with potassium ethoxide, or the ethyl aryl ether 8 and potassium methoxide:



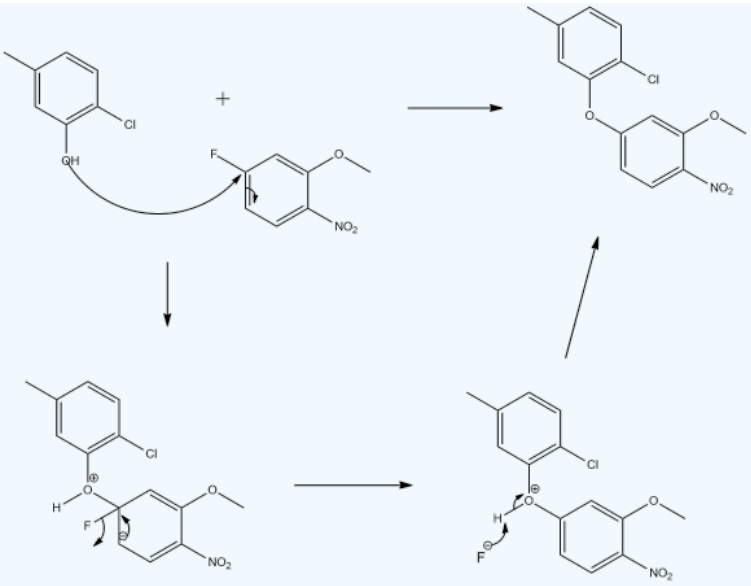
Exercise

24. Propose a mechanism for the following reaction:



Answer

24.



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

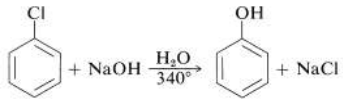
John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

18.10: Nucleophilic Aromatic Substitution - The Addition-Elimantion Mechanism is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

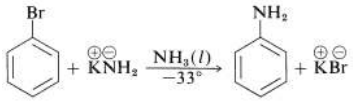
18.11: NAS REACTIONS - THE ELIMINATION-ADDITION (BENZYNE) MECHANISM

ELIMINATION-ADDITION MECHANISM OF NUCLEOPHILIC AROMATIC SUBSTITUTION VIA BENZYNE (ARYNES)

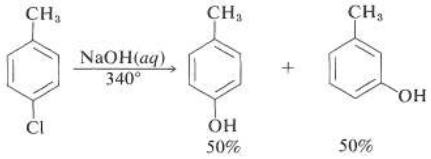
The reactivities of aryl halides, such as the halobenzenes, are exceedingly low toward nucleophilic reagents that normally effect displacements with alkyl halides and activated aryl halides. Substitutions do occur under forcing conditions of either high temperatures or very strong bases. For example, chlorobenzene reacts with sodium hydroxide solution at temperatures around **340°** and this reaction was once an important commercial process for the production of benzenol (phenol):



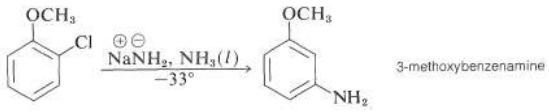
In addition, aryl chlorides, bromides, and iodides can be converted to areneamines **$ArNH_2$** by the conjugate bases of amines. In fact, the reaction of potassium amide with bromobenzene is extremely rapid, even at temperatures as low as **−33°** with liquid ammonia as solvent:



However, displacement reactions of this type differ from the previously discussed displacements of activated aryl halides in that rearrangement often occurs. That is, *the entering group does not always occupy the same position on the ring as that vacated by the halogen substituent*. For example, the hydrolysis of 4-chloromethylbenzene at **340°** gives an equimolar mixture of 3- and 4-methylbenzenols:

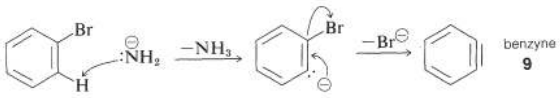


Even more striking is the exclusive formation of 3-methoxybenzenamine in the amination of 2-chloromethoxybenzene. Notice that this result is a violation of the principle of least structural change (Section 1-1H):



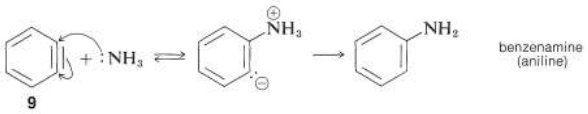
The mechanism of this type of reaction has been studied extensively, and much evidence has accumulated in support of a stepwise process, which proceeds first by base-catalyzed *elimination* of hydrogen halide (**HX**) from the aryl halide - as illustrated below for the amination of bromobenzene:

Elimination

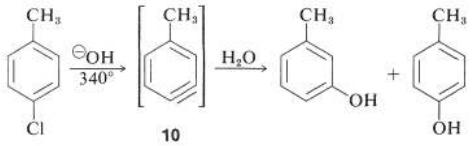


The product of the elimination reaction is a highly reactive intermediate **9** called **benzyne**, or **dehydrobenzene**, which differs from benzene in having two less hydrogen and an extra bond between two ortho carbons. Benzyne reacts rapidly with any available nucleophile, in this case the solvent, ammonia, to give an addition product:

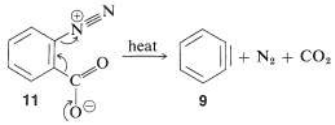
Addition



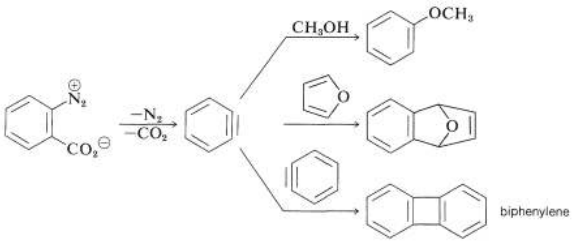
The rearrangements in these reactions result from the reaction of the nucleophile at one or the other of the carbons of the extra bond in the intermediate. With benzyne the symmetry is such that no rearrangement would be detected. With substituted benzynes isomeric products may result. Thus 4-methylbenzyne, **10**, from the reaction of hydroxide ion with 4-chloro-1-methylbenzene gives both 3- and 4-methylbenzenols:



In the foregoing benzyne reactions the base that produces the benzyne in the elimination step is derived from the nucleophile that adds in the addition step. This need not always be so, depending on the reaction conditions. In fact, the synthetic utility of aryne reactions depends in large part of the success with which the aryne can be generated by one reagent but captured by another. One such method will be discussed in Section 14-10C and involves organometallic compounds derived from aryl halides. Another method is to generate the aryne by thermal decomposition of a 1,2-disubstituted arene compound such as **11**, in which both substituents are leaving groups - one leaving with an electron pair, the other leaving without:



When **11** decomposes in the presence of an added nucleophile, the benzyne intermediate is trapped by the nucleophile as it is formed. Or, if a conjugated diene is present, benzyne will react with it by a [4 + 2] cycloaddition. In the absence of other compounds with which it can react, benzyne will undergo [2 + 2] cycloaddition to itself:

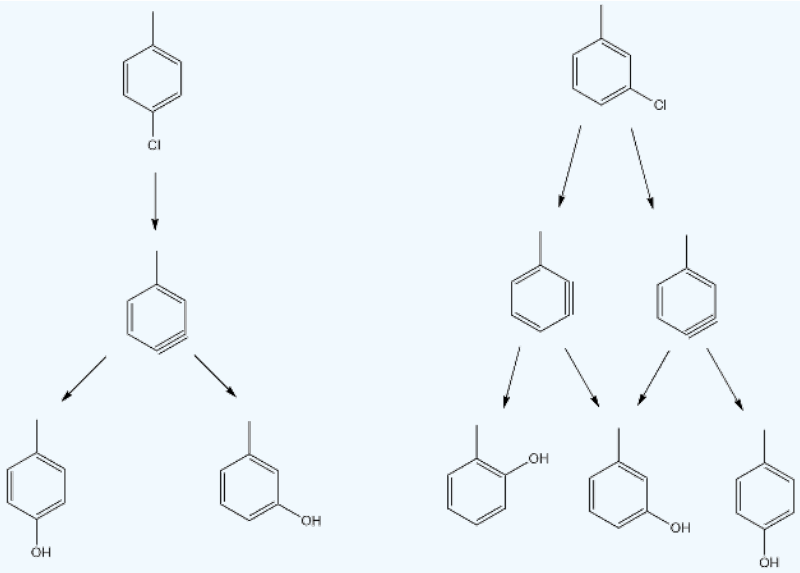


Exercise

25. When *p*-chlorotoluene is reacted with NaOH, two products are seen. While when *m*-chlorotoluene is reacted with NaOH, three products are seen. Explain this.

Answer

25. You need to look at the benzyne intermediates. The para substituted only allows for two products, while the para produces two different alkynes which give three different products.



CONTRIBUTORS AND ATTRIBUTIONS

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- Prof. Steven Farmer (Sonoma State University)

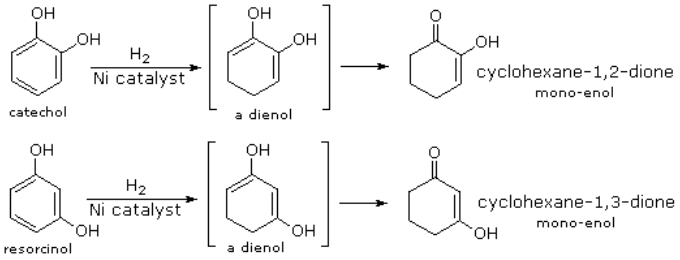
John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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18.12: REDUCTION OF AROMATIC COMPOUNDS

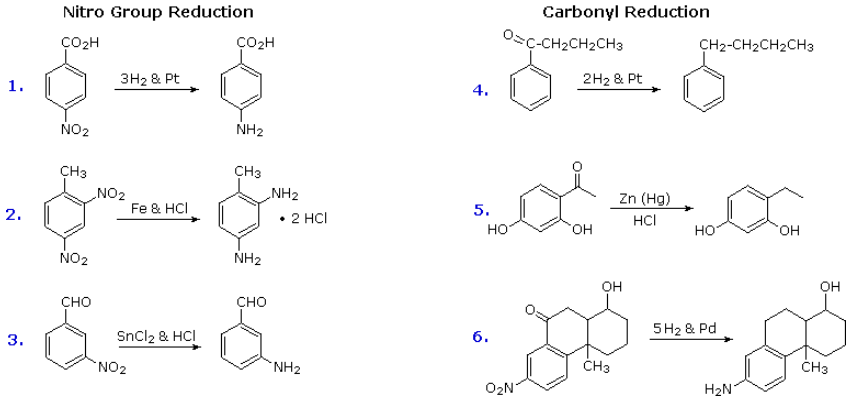
REDUCTION OF AROMATIC COMPOUNDS

Although it does so less readily than simple alkenes or dienes, benzene adds hydrogen at high pressure in the presence of Pt, Pd or Ni catalysts. The product is cyclohexane and the heat of reaction provides evidence of benzene's thermodynamic stability. Substituted benzene rings may also be reduced in this fashion, and hydroxy-substituted compounds, such as phenol, catechol and resorcinol, give carbonyl products resulting from the fast ketonization of intermediate enols. Nickel catalysts are often used for this purpose, as noted in the following equations.



REDUCTION OF NITRO GROUPS AND ARYL KETONES SUBSTITUENTS ON BENZENE RINGS

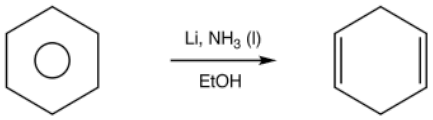
Electrophilic nitration and Friedel-Crafts acylation reactions introduce deactivating, meta-directing substituents on an aromatic ring. The attached atoms are in a high oxidation state, and their reduction converts these electron withdrawing functions into electron donating amino and alkyl groups. Reduction is easily achieved either by catalytic hydrogenation (H_2 + catalyst), or with reducing metals in acid. Examples of these reductions are shown here, equation 6 demonstrating the simultaneous reduction of both functions. Note that the butylbenzene product in equation 4 cannot be generated by direct Friedel-Crafts alkylation due to carbocation rearrangement. The zinc used in ketone reductions, such as 5, is usually activated by alloying with mercury (a process known as amalgamation).



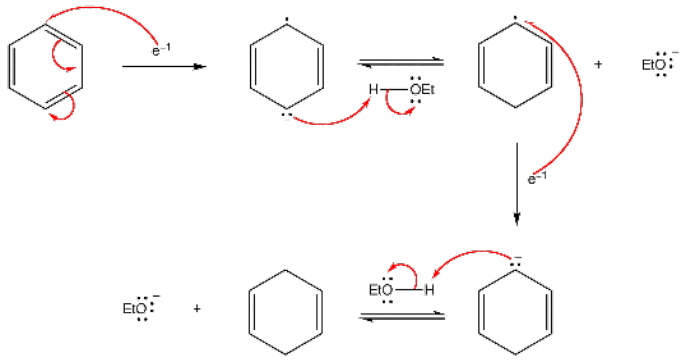
Several alternative methods for reducing nitro groups to amines are known. These include zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution. The procedures described above are sufficient for most cases.

THE BIRCH REDUCTION

Another way of adding hydrogen to the benzene ring is by treatment with the electron rich solution of alkali metals, usually lithium or sodium, in liquid ammonia. See examples of this reaction, which is called the **Birch Reduction.** The Birch reduction is the dissolving-metal reduction of aromatic rings in the presence of an alcohol.

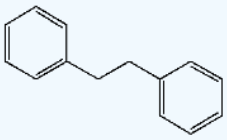


MECHANISM:



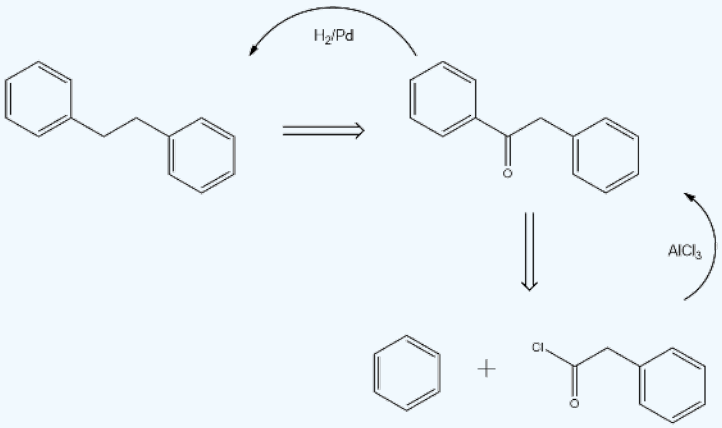
Exercise

26. How would you make the following from benzene and an acid chloride?



Answer

26.



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Mario Morataya (UCD)
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

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18.13: ADDITIONAL EXERCISES

18-1 Draw the resonance structures for benzaldehyde to show the electron-withdrawing group.

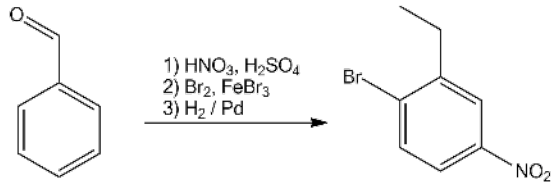
18-2 Draw the resonance structures for methoxybenzene to show the electron-donating group.

18-3 How would make the following compounds from benzene?

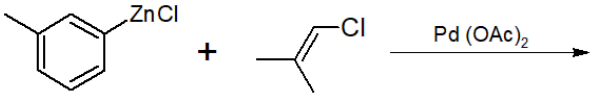
A) *m*-bromonitrobenzene

B) *m*-bromoethylbenzene

18-4 There is something wrong with the following reaction, what is it?



18-5 Choose the correct answer.



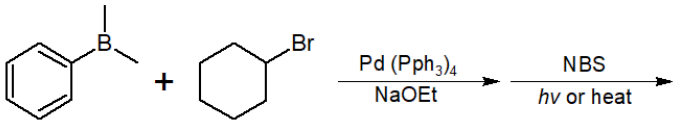
a) 1-methyl-3-(2-methylprop-1-en-1-yl)benzene

b) 2-chloro-4-methyl-1-(2-methylprop-1-en-1-yl)benzene

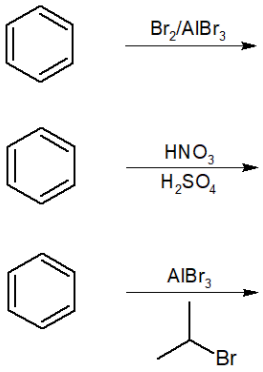
c) 1-chloro-3-(2-methylprop-1-en-1-yl)benzene

d) 1-(1-chloroethenyl)-3-methylbenzene

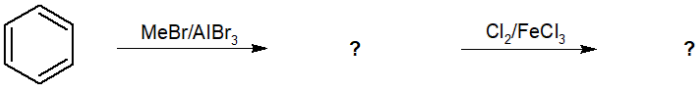
18-6 Predict the final product of the following reaction chain.



18-7 Provide the final product for the following reactions.

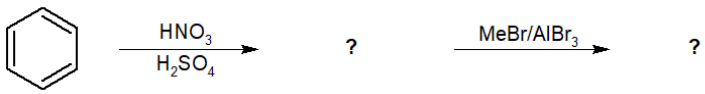


18-8 For the following reaction chain, provide the intermediate and final product(s).



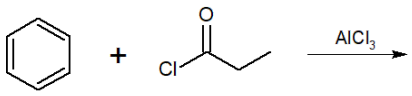
18-9 Give the IUPAC name for the final product(s) of the previous problem, **18-8**.

18-10 For the following reaction chain, provide the intermediate and final product(s).

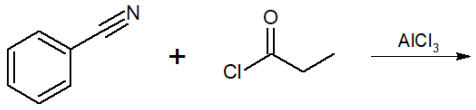


18-11 Give the final product of the following reactions.

a)

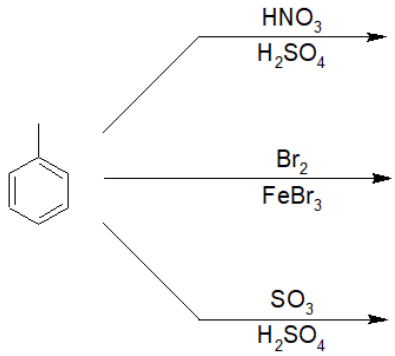


b)

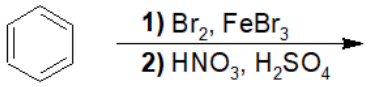


Halogenation, Nitration, and Sulfonation of Benzene

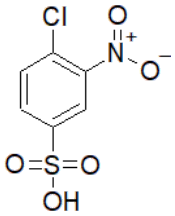
18-12 Predict the products of the following reactions.



18-13 Give the IUPAC nomenclature and structure of the product of the following reaction.



18-14 Choose the correct answer that describes the best route of synthesis of the following molecule.



a) Chlorination, sulfonation, nitration

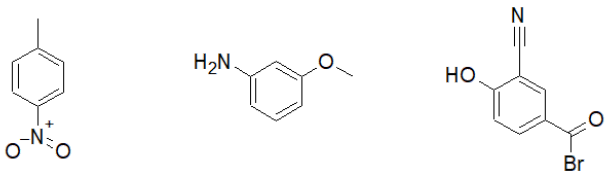
b) Sulfonation, nitration, chlorination

c) Nitration, sulfonation, chlorination

Activating, Ortho-, Para-Directing Substituents

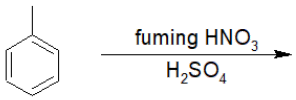
18-15 For the following compounds, point to the position(s) on the ring that are most likely to have a substituent added.

a) **b)** **c)**

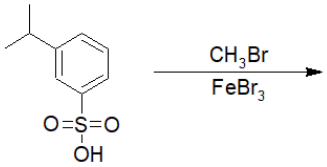


18-16 Predict the major product of the following reactions.

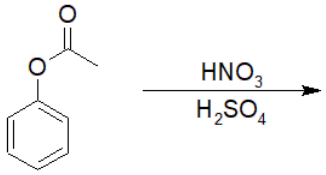
a)



b)



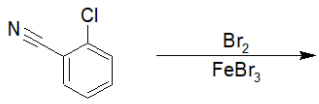
18-17 Provide the correct IUPAC nomenclature and structure of the product of the following reaction.



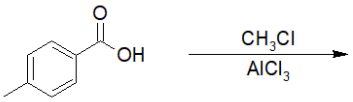
Deactivating, Meta-Directing Substituents

18-18 Predict the products of the following reactions.

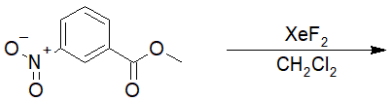
a)



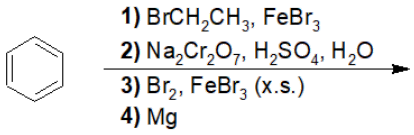
b)



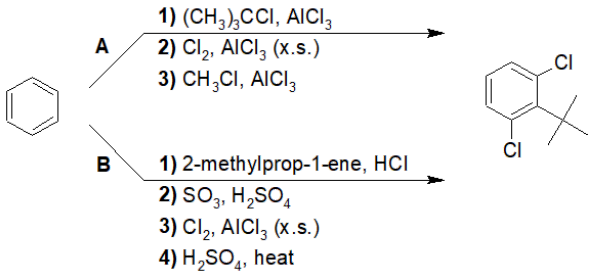
c)



18-19 Predict the product of the following reaction.



18-20 Choose the pathway that will lead to the product formed on the right.



Halogen Substitutes: Deactivating, but Ortho, Para-Directing

18-21 Choose the correct IUPAC nomenclature of one of the products of the following reaction.



a) 3-bromobenzene-1-sulfonic acid

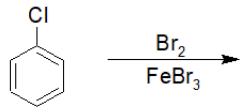
b) 4-bromobenzene-1-sulfonic acid

c) 5-bromobenzene-1,3-disulfonic acid

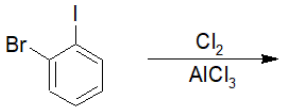
d) 4-bromophenyl hydrogen sulfate

18-22 Predict the products of the following reactions.

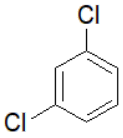
a)



b)



18-23 Propose a route of synthesis for the following compound, starting with chlorobenzene (assume any desired intermediate compounds can be isolated for use in subsequent steps).

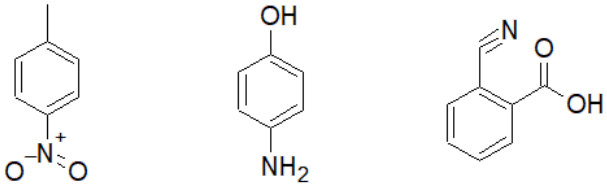


1,3-dichlorobenzene

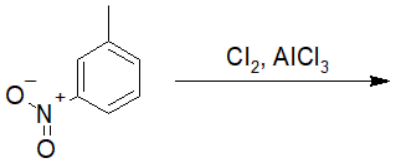
Effects of Multiple Substituents on Electrophilic Aromatic Substitution

18-24 For the following compounds, identify which substituent is the stronger activating group and predict the position(s) of a subsequent electrophilic aromatic substitution.

a) **b)** **c)**

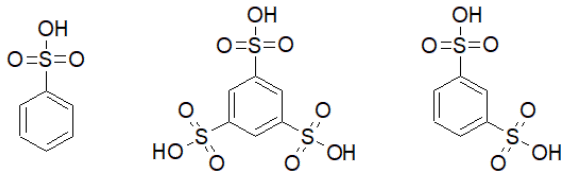


18-25 Predict all possible singly chlorinated products of the following reaction.

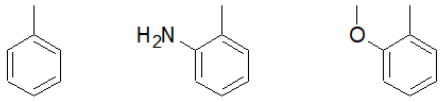


18-26 Rank the following compounds in order from slowest to fastest to go through an electrophilic aromatic substituent reaction.

a)



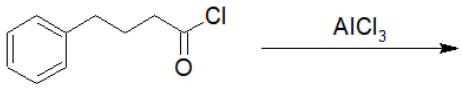
b)



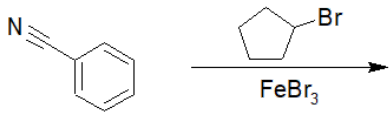
Friedel-Crafts Alkylation/Acylation

18-27 Predict the products of the following reactions.

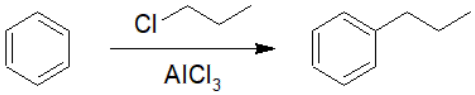
a)



b)

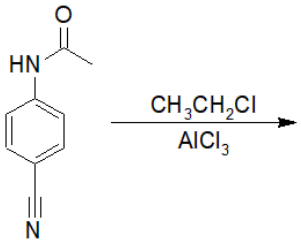


18-28 Explain whether or not the following reaction is the best way to synthesize propylbenzene and if not, propose a better route of synthesis.



propylbenzene

18-29 Choose the correct answer and if a product is formed, provide the structure of the product.



a) No reaction

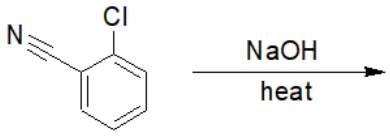
b) 4-amino-2-methylbenzonitrile

c) 4-amino-2-ethylbenzonitrile

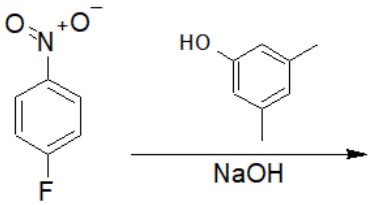
d) N-(4-cyano-2-ethylphenyl)acetamide

Nucleophilic Aromatic Substitution

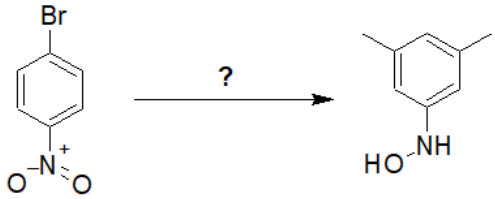
18-30 Predict the product of the following reaction and provide the correct IUPAC nomenclature.



18-31 Predict the product of the following reaction.

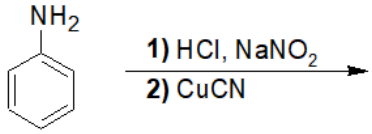


18-32 Suggest a route of synthesis to make *N*-hydroxy-3,5-dimethylaniline from 1-bromo-4-nitrobenzene.

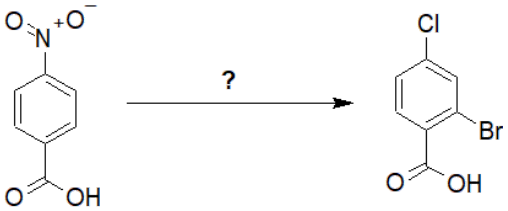


Aromatic Substitutions Using Organometallic Reagents

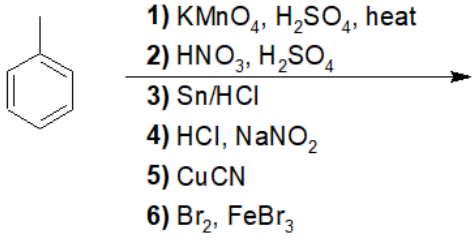
18-33 Provide the structure and IUPAC nomenclature of the product of the following reaction.



18-34 Suggest a route of synthesis to make 2-bromo-4-chlorobenzoic acid from 4-nitrobenzoic acid.



18-35 Choose the correct IUPAC nomenclature for the product of the following reaction.



a) 2-bromo-5-nitrobenzoic acid

b) 2-bromo-5-cyanobenzoic acid

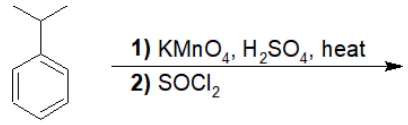
c) 3-cyano-5-nitrobenzoyl bromide

d) 3-bromo-5-cyanobenzoic acid

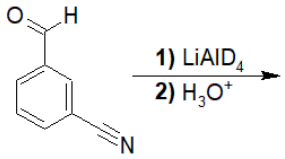
Side-Chain Reactions of Benzene Derivatives

18-36 Predict the products of the following reactions.

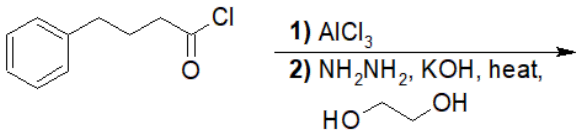
a)



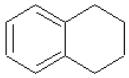
b)



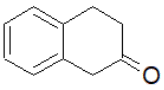
18-37 Choose the correct structure of the product of the following reaction.



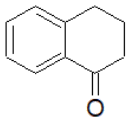
a)



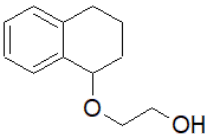
b)



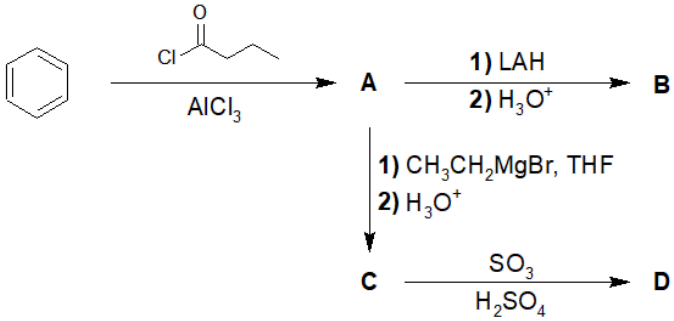
c)



d)



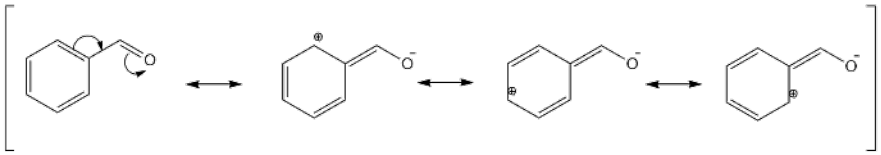
18-38 Provide the intermediate and final products of the following reactions.



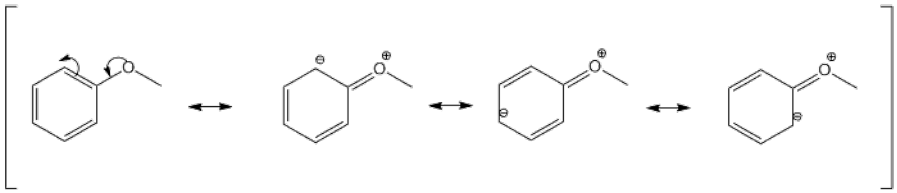
18.13: Additional Exercises is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

18.14: SOLUTIONS TO ADDITIONAL EXERCISES

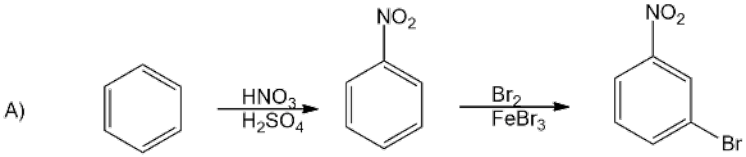
18-1

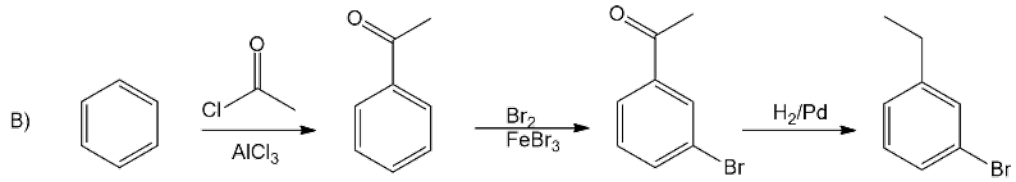


18-2



18-3 This is just one possible way to synthesize it.

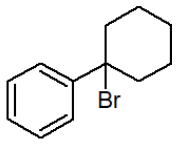




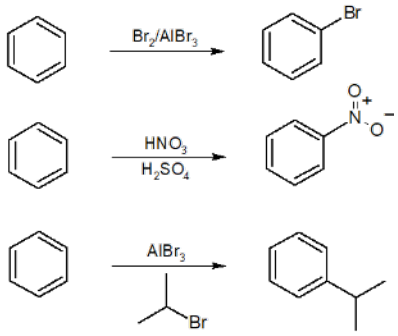
18-4 The bromine should be in the meta position. Right now it is in the ortho position, from perhaps having the ethyl group present first and then the having it substituted there. BUT the ethyl group is last to form, and the aldehyde and nitro groups would both encourage a meta substitution.

18-5 Answer: A

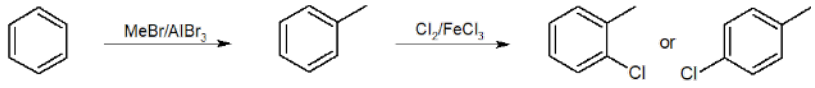
18-6



18-7

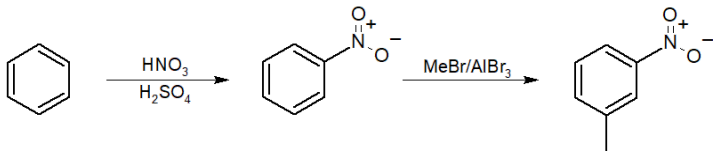


18-8

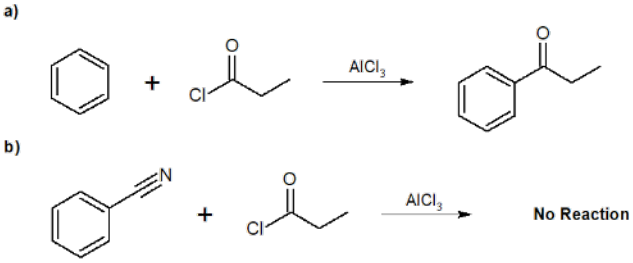


18-9 1-chloro-2-methylbenzene and 1-chloro-4-methylbenzene

18-10

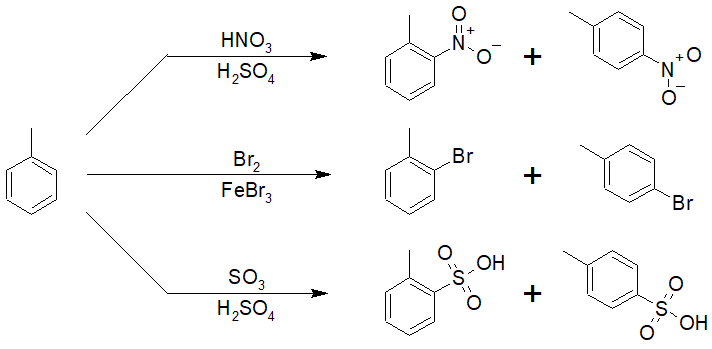


18-11

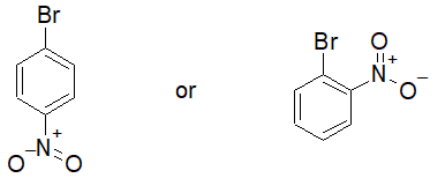


Halogenation, Nitration, and Sulfonation of Benzene

18-12:



18-13:



1-bromo-4-nitrobenzene **1-bromo-2-nitrobenzene**

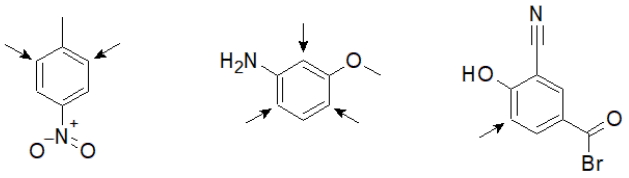
18-14:

Answer: A

Activating, Ortho-, Para-Directing Substituents

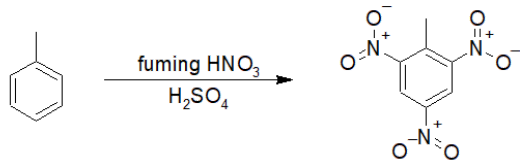
18-15:

a) b) c)

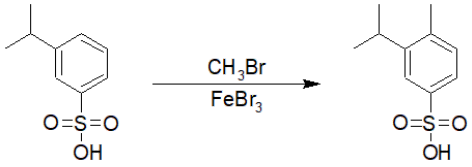


18-16:

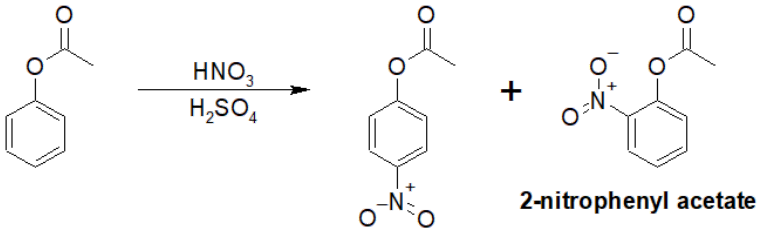
a)



b)



18-17:



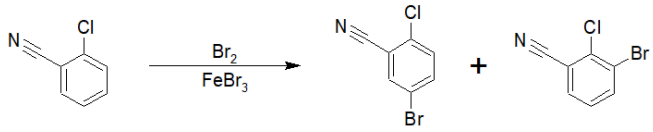
4-nitrophenyl acetate

2-nitrophenyl acetate

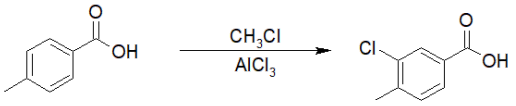
Deactivating, Meta-Directing Substituents

18-18:

a)

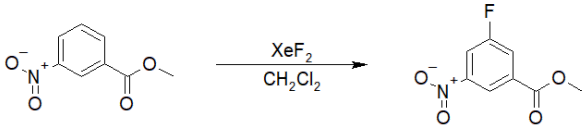


b)

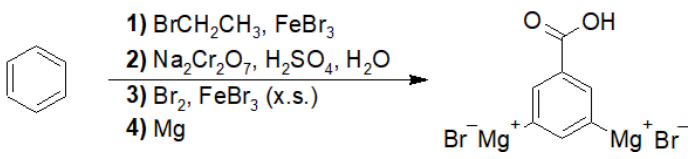


can also have a dichlorinated product

c)



18-19:



18-20:

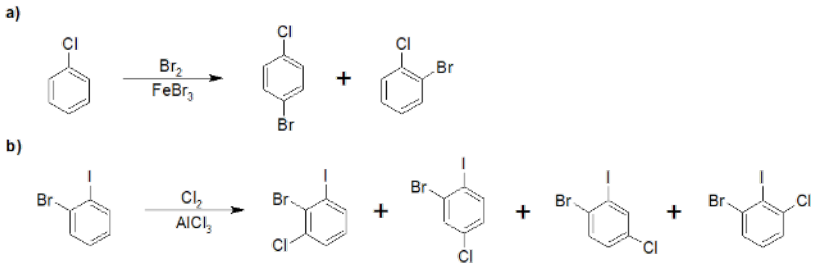
Answer: B

Halogen Substitutes: Deactivating, but Ortho, Para-Directing

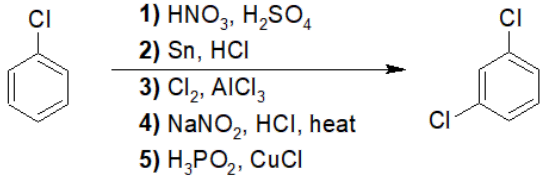
18-21:

Answer: B

18-22:

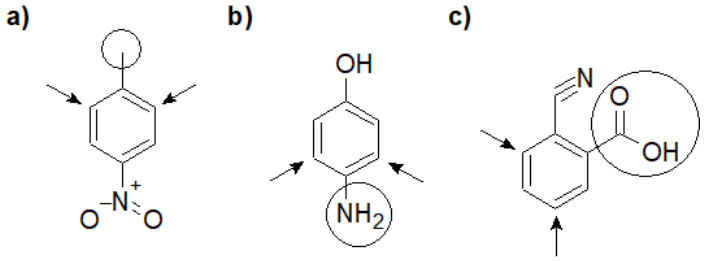


18-23:

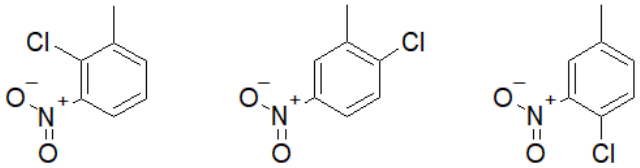


Effects of Multiple Substituents on Electrophilic Aromatic Substitution

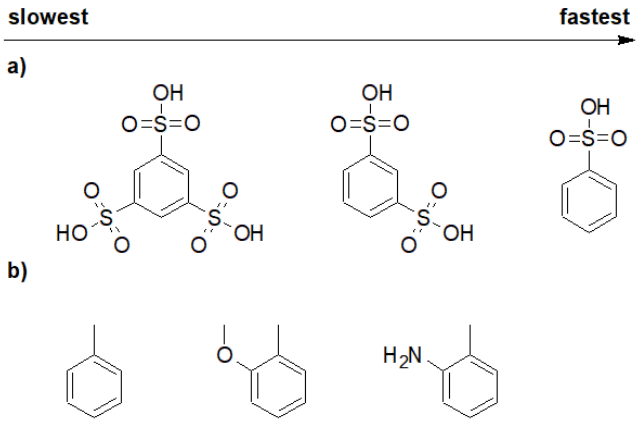
18-24:



18-25:

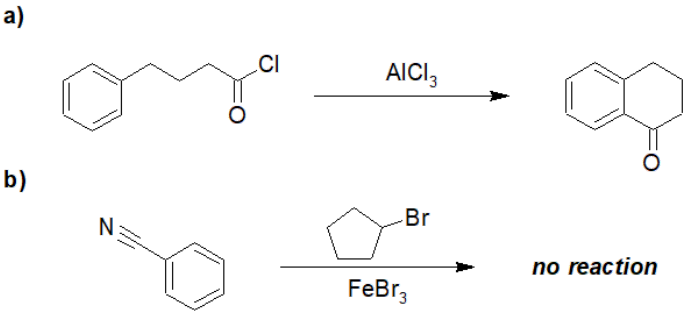


18-26:



Friedel-Crafts Alkylation/Acylation

18-27:

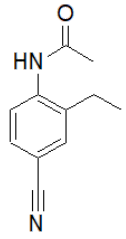


18-28:

Friedel-Crafts alkylation using 1-chloropropane is not the best way to synthesize propylbenzene. You will end up with (propan-2-yl)benzene as your main product due to a hydride shift occurring during an intermediate step. A better route of synthesis may be Friedel-Crafts acylation using propanoyl chloride to make 1-phenylpropan-1-one, followed by a Clemmensen reduction to obtain the final product.

18-29:

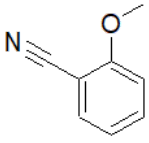
Answer: D



***N*-(4-cyano-2-ethylphenyl)acetamide**

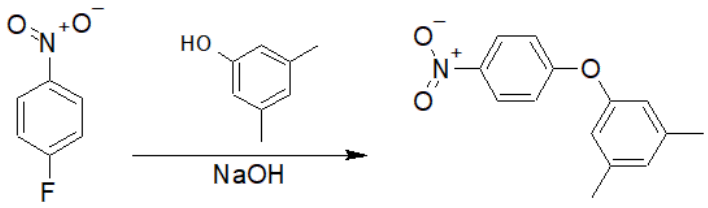
Nucleophilic Aromatic Substitution

18-30:



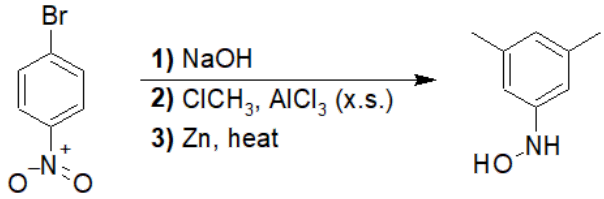
2-methoxybenzonitrile

18-31:



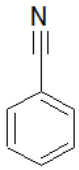
18-32:

Possible route of synthesis:



Aromatic Substitutions Using Organometallic Reagents

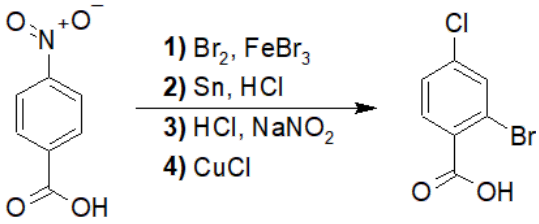
18-33:



benzonitrile

18-34:

Possible route of synthesis:



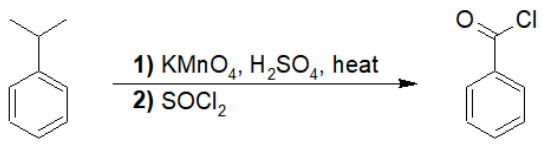
18-35:

Answer: D

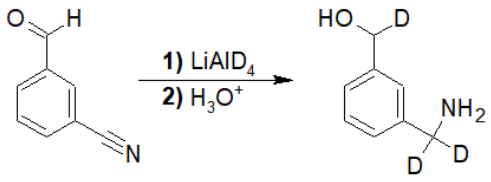
Side-Chain Reactions of Benzene Derivatives

18-36:

a)



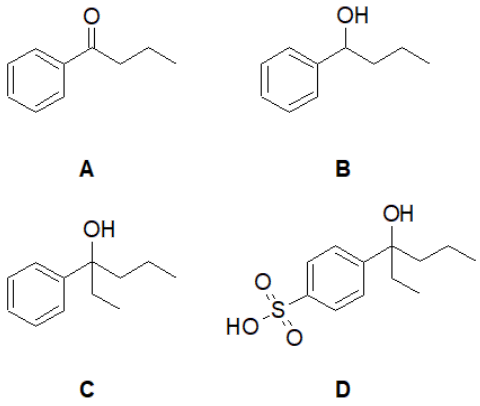
b)



18-37:

Answer: A

18-38:



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CHAPTER OVERVIEW

19: KETONES AND ALDEHYDES

After reading this chapter and completing ALL the exercises, a student can be able to

- describe the structure and physical properties of aldehydes and ketones (section 19.1)
- determine the structure of aldehydes and ketones from their elemental analysis and spectral data (MS, IR ^{1}H NMR & ^{13}C NMR) (section 19.2)
- predict the products and specify the reagents to synthesize aldehydes and ketones for reactions studied to date (section 19.3)
- predict the products and specify the reagents to synthesize aldehydes and ketones for new reactions (section 19.4)
- write the general mechanism for nucleophilic addition reactions with aldehydes and ketones (sections 19.5 to 19.11, 19.13, & 19.15)
- predict the relative reactivity of carbonyl compounds to nucleophilic addition reactions (sections 19.5 to 19.13, & 19.15)
- predict the relative equilibrium constant & rates of hydration for aldehydes and ketones (section 19.6)
- show the general mechanism for the Wittig reaction (section 19.13)
- predict the products and specify the reagents for oxidation and reduction reactions of aldehydes and ketones (section 19.14 and 19.15)
- combine the reactions studied to date to develop efficient and effective multiple-step synthesis including the use of acetals/ketals as protecting groups (sect 19.12)

Please note: IUPAC nomenclature and important common names of aldehydes and ketones were explained in Chapter 3.

19.1: Carbonyl Compound Structure and Properties
19.2: Spectroscopy of Ketones and Aldehydes
19.3: Review of Ketone and Aldehyde Synthesis
19.4: 19.4 New Synthesis of Aldehydes and Ketones
19.5: Nucleophilic Addition Reactions of Ketones and Aldehydes
19.6: Nucleophilic Addition of Water (Hydration)
19.7: Nucleophilic Addition of Cyanide and Acetylide
19.8: Nucleophilic Addition of Grignards
19.9: Nucelophilic Addition of Amines (Imine and Enamine Formation)
19.10: Nucleophilic Addition of Hydrazine (Wolff-Kishner Reaction)
19.11: Nucelophilic Addition of Alcohols (Acetal Formation)
19.12: Acetals as Protecting Groups
19.13: Nucelophilic Addition of Phosphorus Ylides (The Wittig Reaction)
19.14: Oxidation of Aldehydes
19.15: Reductions of Ketones and Aldehydes
19.16: Additional Exercises
19.17: Solutions to Additional Exercises

Template:HideTOC

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19.1: CARBONYL COMPOUND STRUCTURE AND PROPERTIES

THE CARBONYLS: THE ALDEHYES AND KETONES

While there are several functional groups that include a carbonyl structural feature, the term "carbonyls" is used to describe aldehydes and ketones.



the carbonyl structural feature

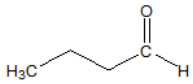
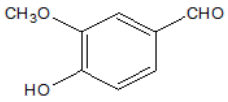
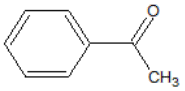
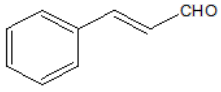
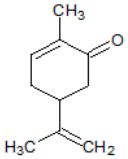


aldehyde



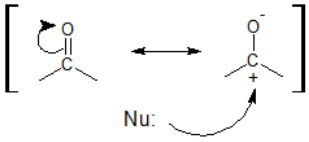
ketone

Aldehydes and ketones share a great deal of chemical reactivity so it makes sense to talk about these two functional groups within the same chapter. Aldehydes and ketones are both polar molecules that are H-bond acceptors. Following the "4 to 6 Rule", aldehydes and ketones with short carbon chains are soluble in water. Aldehydes and ketones are typically liquids with densities of approximately 0.8 g/mL. Aldehydes and ketones are prevalent in common household substances as shown in the table below.

Compound	Structure	Odor	Uses
Butyraldehyde		buttery	foods
Vanillin		vanilla	foods & perfumes
Acetophenone		pistachio	ice cream
Trans-Cinnamaldehyde		cinnamon & drugs	candy, food,
(-) carvone		spearmint	candy & food
(+) carvone seed		caraway	food

ALDEHYDES AND KETONES ARE ELECTROPHILES

The carbon of the carbonyl group is electrophilic because of resonance as shown below.



The δ+ and trigonal planar molecular shape make carbonyl carbons good electrophiles.

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19.2: SPECTROSCOPY OF KETONES AND ALDEHYDES

IR SPECTRA

The carbonyl stretching vibration band C=O of saturated aliphatic ketones appears:

C=O stretch

- aliphatic ketones 1715 cm^{-1}
- alpha, beta-unsaturated ketones 1685-1666 cm^{-1}

Figure 8. shows the spectrum of 2-butanone. This is a saturated ketone, and the C=O band appears at 1715.

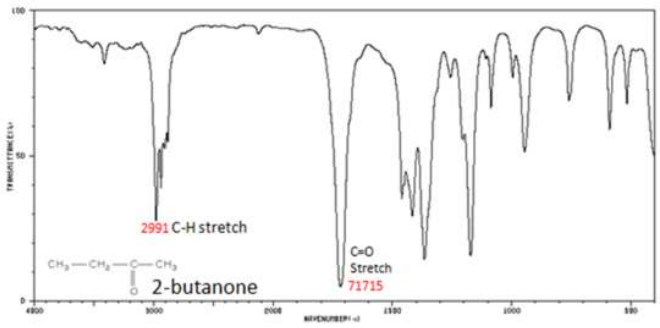


Figure 8. Infrared Spectrum of 2-Butanone

If a compound is suspected to be an aldehyde, a peak always appears around 2720 cm^{-1} which often appears as a shoulder-type peak just to the right of the alkyl C–H stretches.

H–C=O stretch 2830-2695 cm^{-1}

C=O stretch

- aliphatic aldehydes 1740-1720 cm^{-1}
- alpha, beta-unsaturated aldehydes 1710-1685 cm^{-1}

Figure 9. shows the spectrum of butyraldehyde.

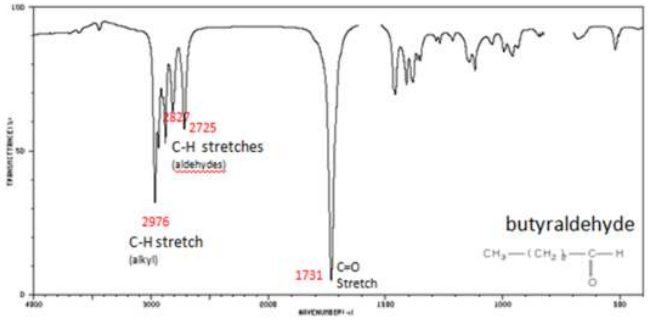
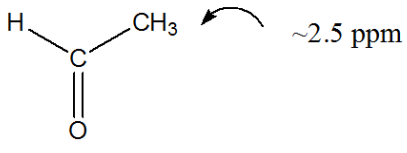


Figure 9. Infrared Spectrum of Butyraldehyde

NMR SPECTRA

Hydrogens attached to carbon adjacent to the sp^2 hybridized carbon in aldehydes and ketones usually show up 2.0-2.5 ppm.

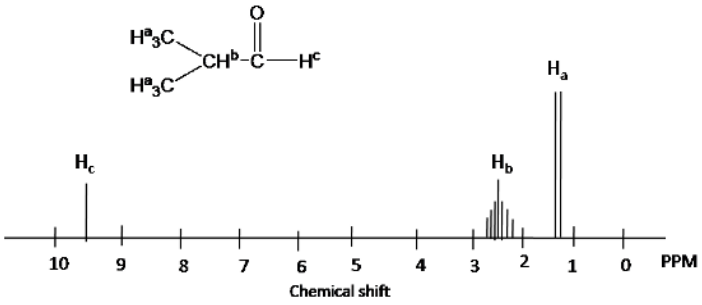


.

Aldehyde hydrogens are highly deshielded and appear far downfield as 9-10 ppm.

Chemical shift of each protons is predicted by ^1H chemical shift ranges (H_a): chemical shift of methyl groups (1.1 ppm). (H_b) The chemical shift of the -CH- group move downfield due to effect an adjacent aldehyde group: (2.4 ppm). The chemical shift of aldehyde hydrogen is

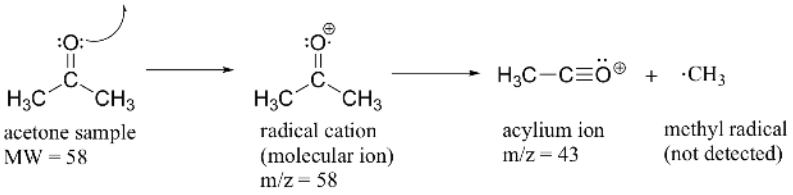
highly deshielded (9.6 ppm).



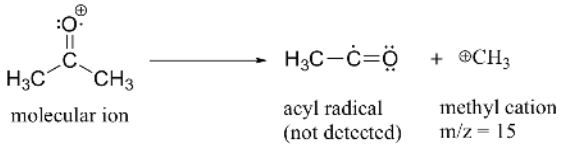
4) Splitting pattern is determined by (N+1) rule: Ha is split into two peaks by H_b(#of proton=1). H_b has the septet pattern by H_a (#of proton=6). H_c has one peak.(Note that H_c has doublet pattern by H_b due to vicinal proton-proton coupling.)

MASS SPECTRA

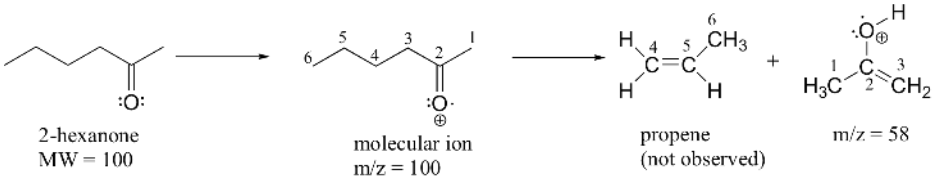
Much of the utility in electron-ionization MS comes from the fact that the radical cations generated in the electron-bombardment process tend to fragment in predictable ways. Detailed analysis of the typical fragmentation patterns of different functional groups is beyond the scope of this text, but it is worthwhile to see a few representative examples, even if we don't attempt to understand the exact process by which the fragmentation occurs. We saw, for example, that the base peak in the mass spectrum of acetone is m/z = 43. This is the result of cleavage at the 'alpha' position - in other words, at the carbon-carbon bond adjacent to the carbonyl. Alpha cleavage results in the formation of an acylium ion (which accounts for the base peak at m/z = 43) and a methyl radical, which is neutral and therefore not detected.



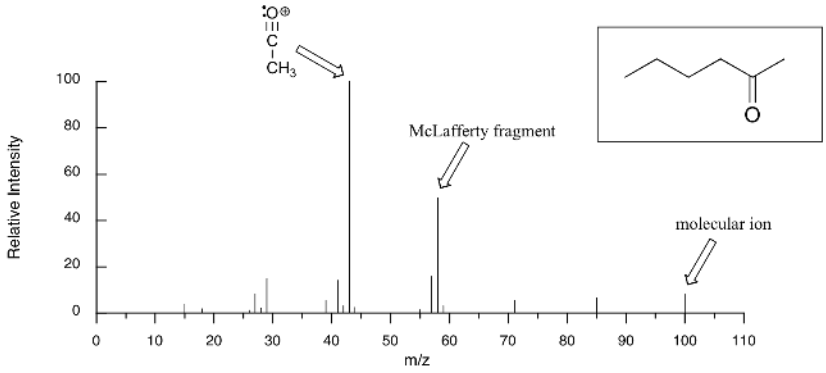
After the parent peak and the base peak, the next largest peak, at a relative abundance of 23%, is at m/z = 15. This, as you might expect, is the result of formation of a methyl cation, in addition to an acyl radical (which is neutral and not detected).



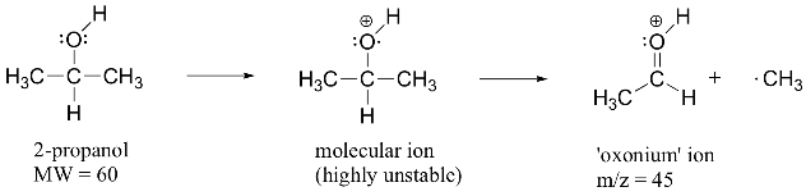
A common fragmentation pattern for larger carbonyl compounds is called the **McLafferty rearrangement**:

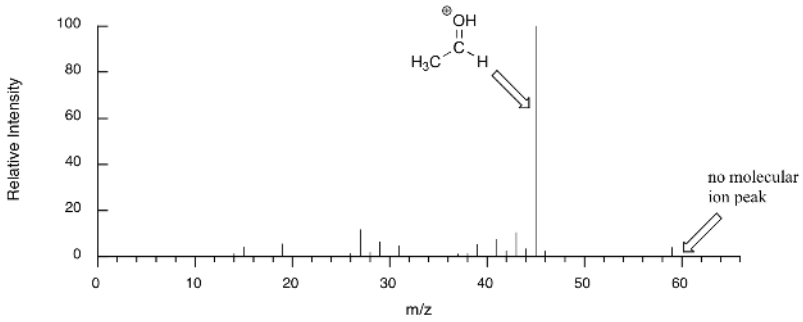


The mass spectrum of 2-hexanone shows a 'McLafferty fragment' at m/z = 58, while the propene fragment is not observed because it is a neutral species (remember, only cationic fragments are observed in MS). The base peak in this spectrum is again an acylium ion.



When alcohols are subjected to electron ionization MS, the molecular ion is highly unstable and thus a parent peak is often not detected. Often the base peak is from an ‘oxonium’ ion.



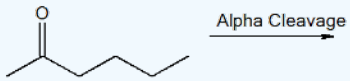


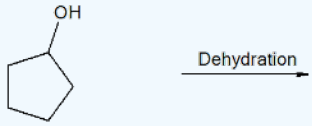
Other functional groups have predictable fragmentation patterns as well. By carefully analyzing the fragmentation information that a mass spectrum provides, a knowledgeable spectrometrist can often ‘put the puzzle together’ and make some very confident predictions about the structure of the starting sample.

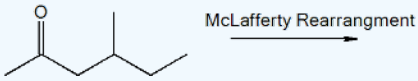
Click here for examples of compounds listed by functional group, which demonstrate patterns which can be seen in mass spectra of compounds ionized by electron impact ionization.

Exercise

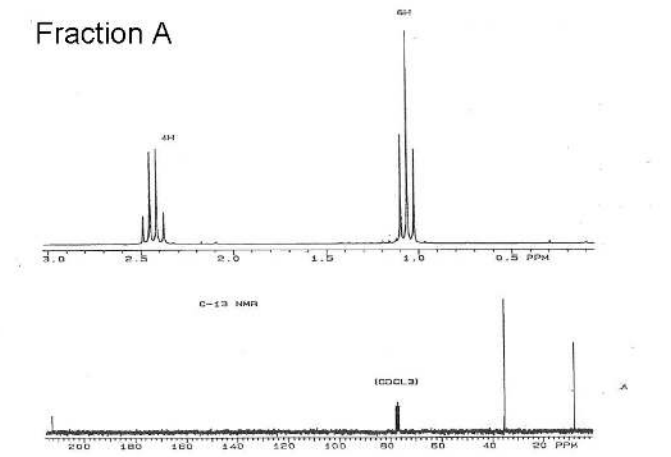
1. a) What are the masses of all the components in the following fragmentation reactions?

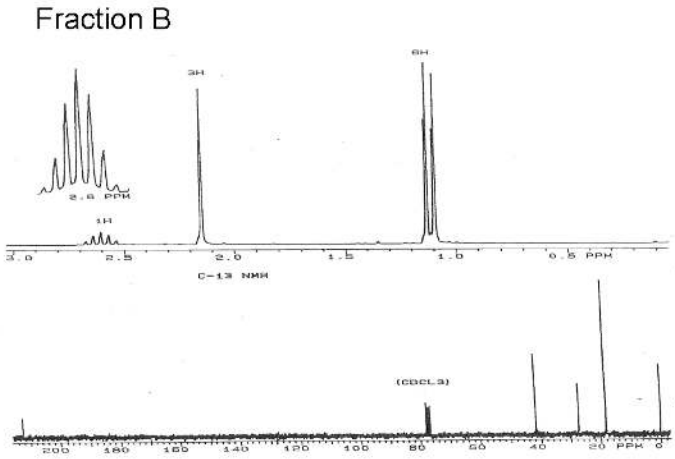


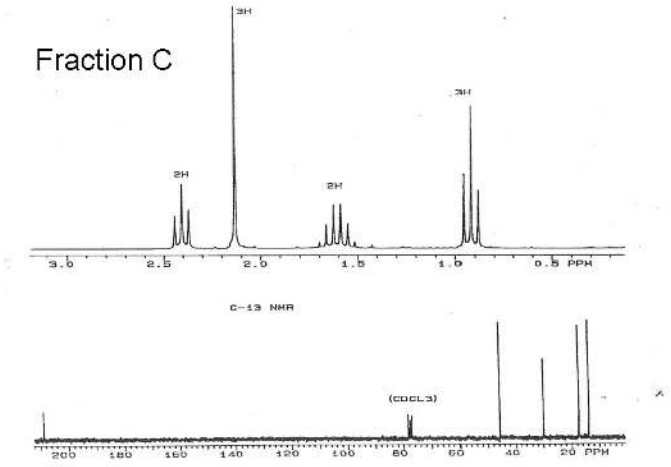




b) A mixture was separated into three fractions: A, B, and C. Elemental analysis reveals that the fractions are structural isomers with the following composition: 69.72% C, 11.70% H, and 18.58% O. The IR spectra for all fractions show several moderate bands around 2950 cm^{-1}, and a strong band near 1700 cm^{-1}. The proton and ^{13}C NMR spectra for each fraction are shown below. Give the common name and draw the bond-line structure for each fraction and correlate the NMR signals with their respective atoms.

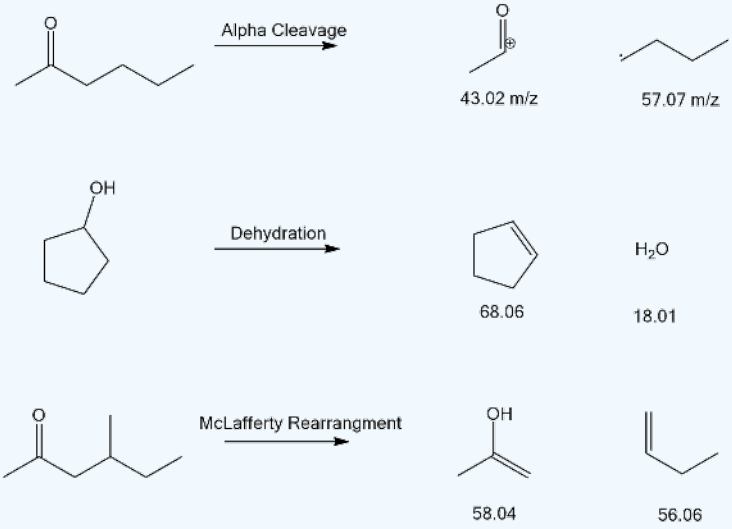

Fraction A
6H
4H
3.0
2.5
2.0
1.5
1.0
0.5 PPM
C-13 NMR
(CDCL3)
200
180
160
140
120
100
80
60
40
20 PPM


Fraction B
6H
3H
2.6 PPM
1H
3.0
2.5
2.0
1.5
1.0
0.5 PPM
C-13 NMR
(CDCL3)
200
180
160
140
120
100
80
60
40
20 PPM

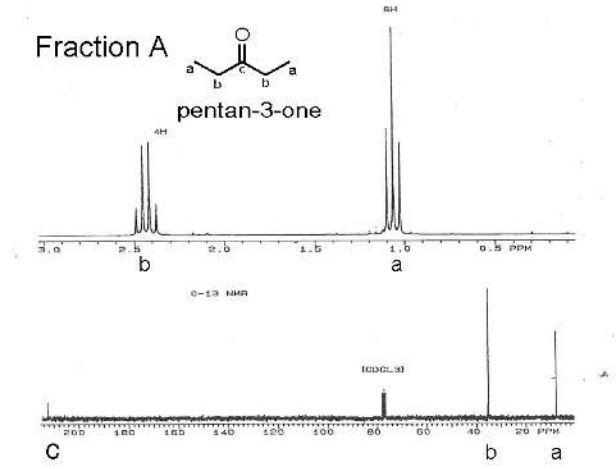

Fraction C
3H
3H
2H
2H
3.0
2.5
2.0
1.5
1.0
0.5 PPM
C-13 NMR
(CDCL3)
200
180
160
140
120
100
80
60
40
20 PPM

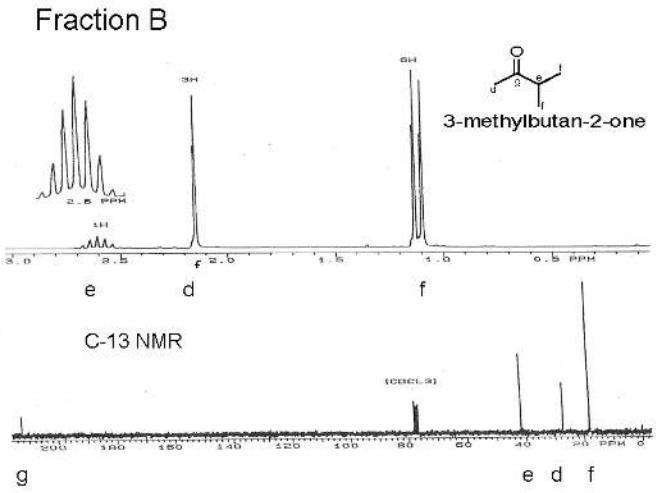
Answer

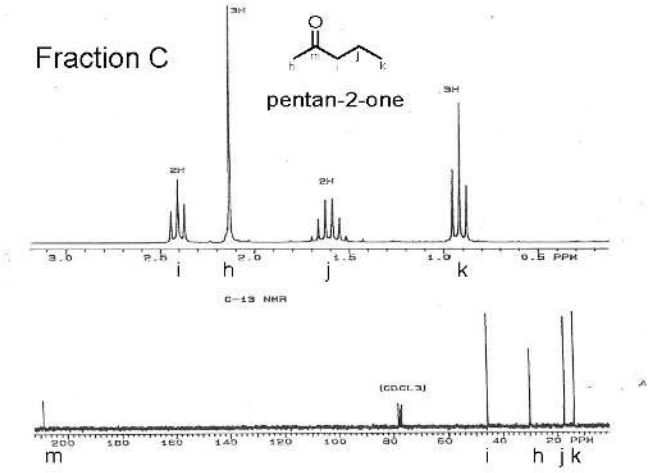
1. a)


Alpha Cleavage
43.02 m/z
57.07 m/z
OH
Dehydration
68.06
H_2O
18.01
McLafferty Rearrangment
OH
58.04
56.06

b)


Fraction A
pentan-3-one
6H
4H
b
a
C-13 NMR
(CDCL3)
c
b
a


Fraction B
3-methylbutan-2-one
3H
6H
1H
e
d
f
C-13 NMR
(CDCL3)
g
e
d
f


Fraction C
pentan-2-one
3H
2H
2H
3H
i
h
j
k
C-13 NMR
(CDCL3)
m
i
h
j
k

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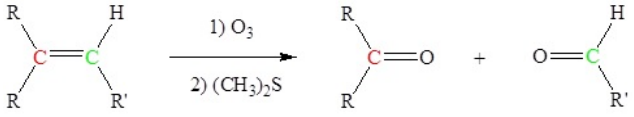
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

19.2: Spectroscopy of Ketones and Aldehydes is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

19.3: REVIEW OF KETONE AND ALDEHYDE SYNTHESIS

So far this text has discussed aldehyde and ketone synthesis from the ozolysis of alkenes, hydration of alkynes, oxidation of alcohols, and Friedel-Crafts acylation of benzene rings.

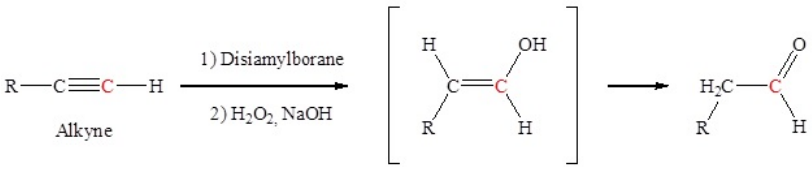
ALKENES CAN BE CLEAVED USING OZONE (O_3) TO FORM ALDEHYDES AND/OR KETONES



Alkene

HYDRATION OF AN ALKYNE TO FORM ALDEHYDES

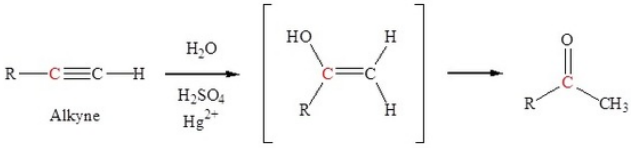
Anti-Markovnikov addition of a hydroxyl group to an alkyne forms an aldehyde. The addition of a hydroxyl group to an alkyne causes tautomerization which subsequently forms a carbonyl.



Alkyne

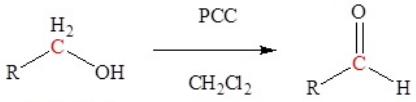
HYDRATION OF AN ALKYNE TO FORM KETONES

The addition of a hydroxyl group to an alkyne causes tautomerization which subsequently forms a carbonyl. Markovnikov addition of a hydroxyl group to an alkyne forms a ketone.



Alkyne

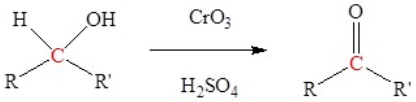
OXIDATION OF 1^O ALCOHOLS WITH PCC TO FORM ALDEHYDES



1° Alcohol

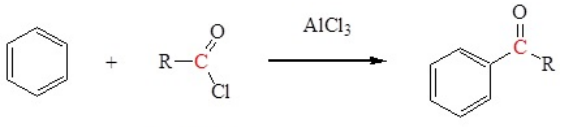
OXIDATION OF 2^O ALCOHOLS TO FORM KETONES

Typically uses Jones reagent (CrO_3 in H_2SO_4) but many other reagents can be used



2° Alcohol

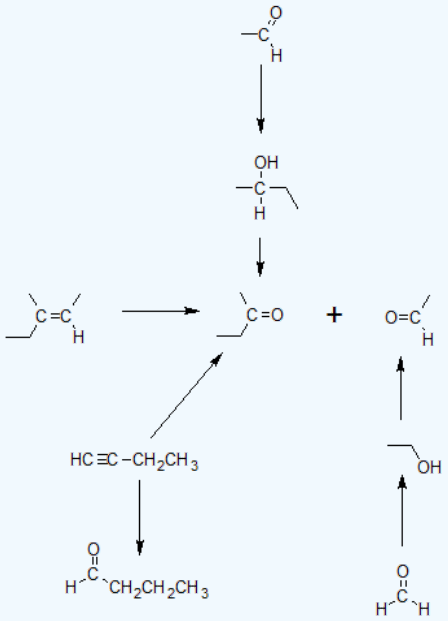
FRIEDEL-CRAFTS ACYLATION TO FORM A KETONE



Acid Chloride

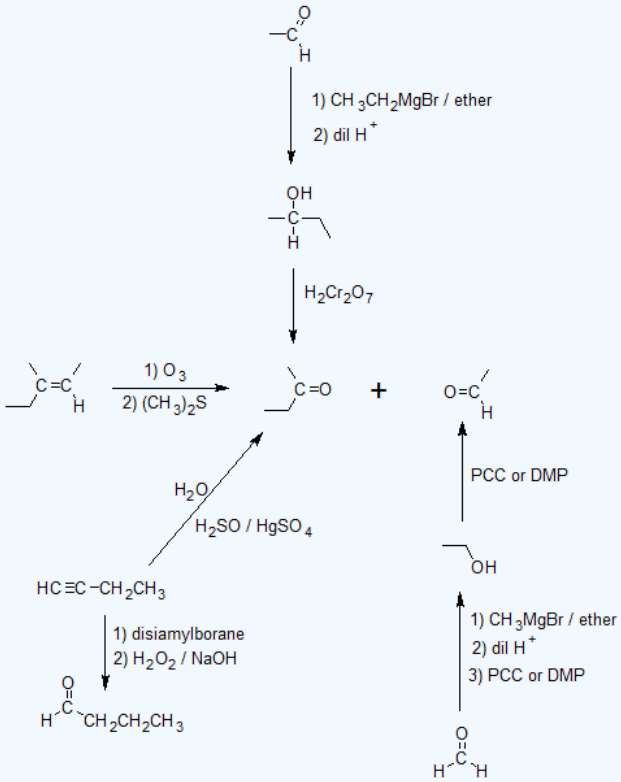
Exercise

2. Specify the reagents to complete the reaction map below.



Answer

2.



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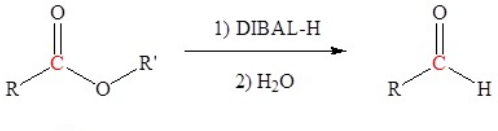
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
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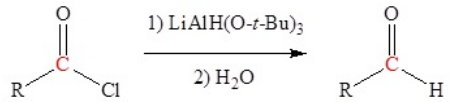
19.4: 19.4 NEW SYNTHESIS OF ALDEHYDES AND KETONES

ESTER, ACID CHLORIDE, AND NITRILE REDUCTION TO FORM ALDEHYDES

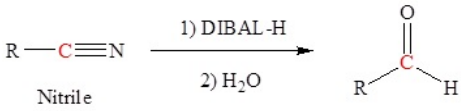
The reduction of esters, acid chlorides, and nitriles require reducing agents that are derivatives of lithium aluminum hydride ($LiAlH_4$). For esters and nitriles, $LiAlH_4$ is modified into the organometallic reagent diisobutyl aluminum hydride which can be represented as DIBAL or DIBAL-H or DIBAH or DIBALH. To reduce acid chlorides, t-butoxide groups are combined with $LiAlH_4$ to form lithium tritert-butoxy aluminum hydride.



Ester



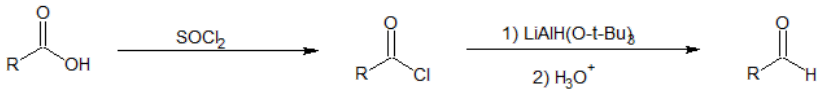
Acid Chloride



Nitrile

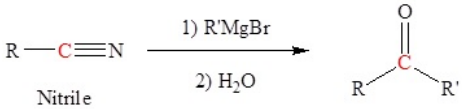
CARBOXYLIC ACIDS CAN BE CONVERTED TO ALDEHYDES

Carboxylic acids cannot be reduced directly to aldehydes. Carboxylic acids can be converted to acid chlorides using thionyl chloride which can then be reduced to aldehydes using $LiAlH(O\text{-}t\text{-}Bu)_3$.



GRIGNARD REAGENTS REACT WITH NITRILES TO FORM KETONES

Nitriles can also be used to synthesize ketones when they react with Grignards as shown below.

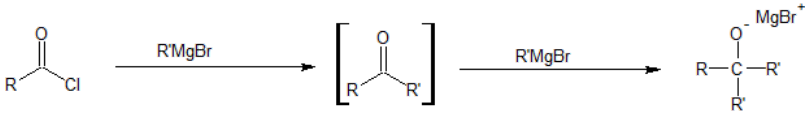


Nitrile

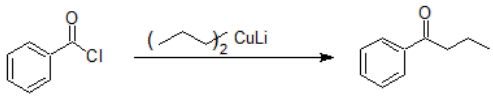
ORGANOCUPRATE REAGENTS REACT WITH ACID CHLORIDES TO FORM KETONES

Organocuprate reagents are the least reactive of the organometallic reagents studied so far. While we learned to synthesize alcohols by reacting Grignard reagents with aldehydes and ketones, organocuprates will not react with aldehydes and ketones.

Grignard reagents will keep reacting with the product of the acid chloride reaction.

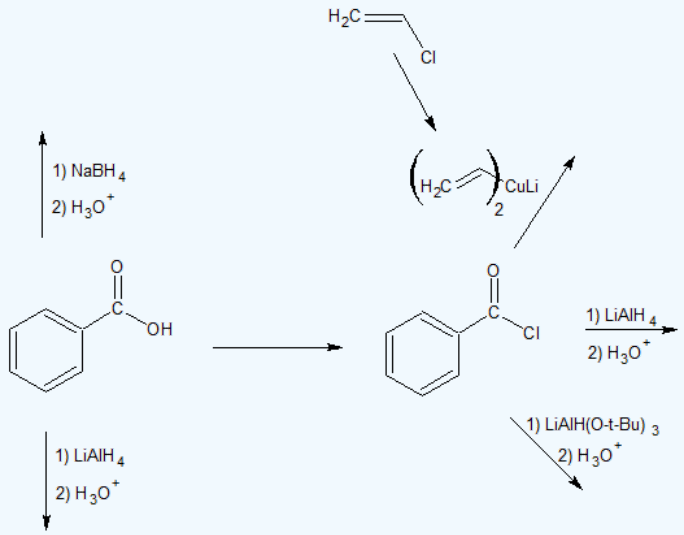


Organocuprate reactions with acid chlorides stop at the ketone as shown below.



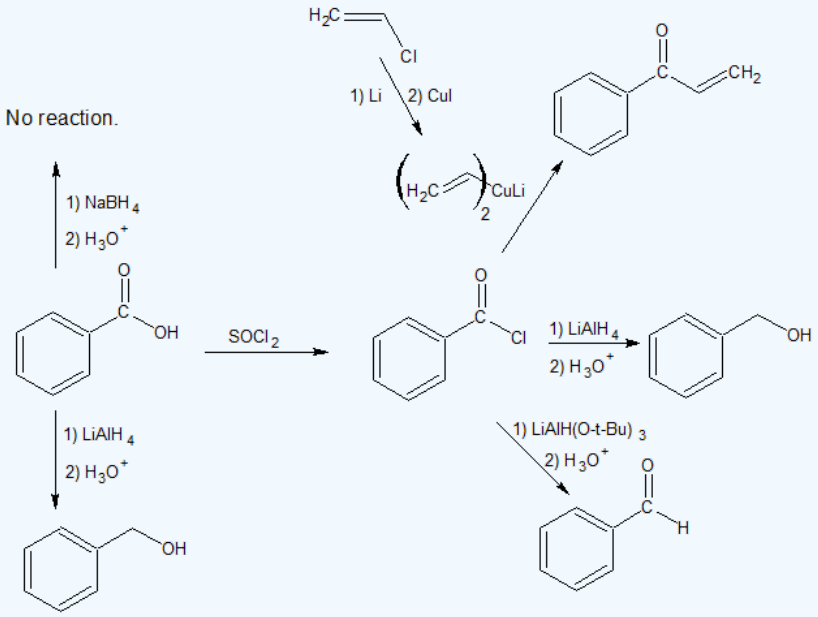
Exercise

3. Complete the reaction map below.



Answer

3.



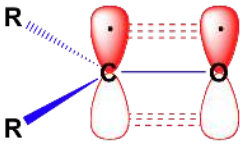
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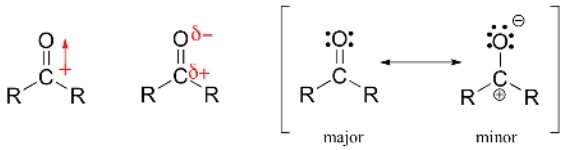
19.5: NUCLEOPHILIC ADDITION REACTIONS OF KETONES AND ALDEHYDES

CARBONYLS ARE ELECTROPHILES

Before we consider in detail the reactivity of aldehydes and ketones, we need to look back and remind ourselves of what the bonding picture looks like in a carbonyl. Carbonyl carbons are sp^2 hybridized, with the three sp^2 orbitals forming soverlaps with orbitals on the oxygen and on the two carbon or hydrogen atoms. These three bonds adopt trigonal planar geometry. The remaining unhybridized 2p orbital on the central carbonyl carbon is perpendicular to this plane, and forms a 'side-by-side' pbond with a 2p orbital on the oxygen.

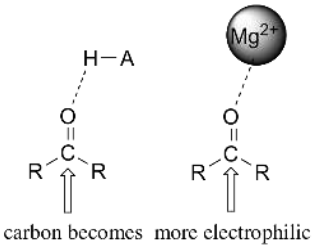


The carbon-oxygen double bond is polar: oxygen is more electronegative than carbon, so electron density is higher on the oxygen side of the bond and lower on the carbon side. Recall that bond polarity can be depicted with a dipole arrow, or by showing the oxygen as holding a partial negative charge and the carbonyl carbon a partial positive charge.



A third way to illustrate the carbon-oxygen dipole is to consider the two main resonance contributors of a carbonyl group: the major form, which is what you typically see drawn in Lewis structures, and a minor but very important contributor in which both electrons in the pbond are localized on the oxygen, giving it a full negative charge. The latter depiction shows the carbon with an empty 2p orbital and a full positive charge.

The result of carbonyl bond polarization, however it is depicted, is straightforward to predict. The carbon, because it is electron-poor, is an electrophile: it is a great target for attack by an electron-rich nucleophilic group. Because the oxygen end of the carbonyl double bond bears a partial negative charge, anything that can help to stabilize this charge by accepting some of the electron density will increase the bond's polarity and make the carbon more electrophilic. Very often a general acid group serves this purpose, donating a proton to the carbonyl oxygen.

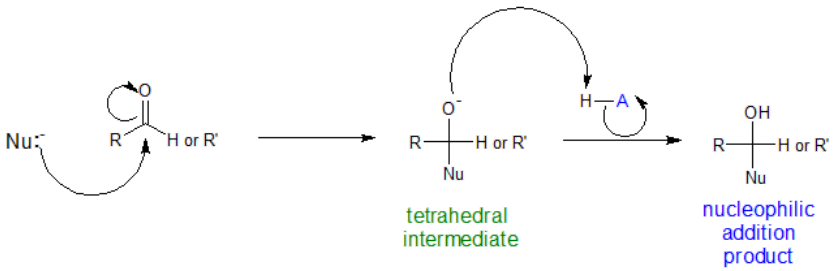


The same effect can also be achieved if a Lewis acid, such as a magnesium ion, is located near the carbonyl oxygen.

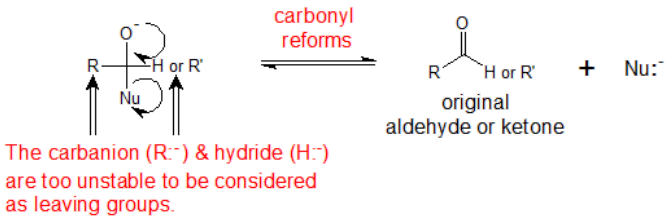
NUCELOPHILIC ADDITION TO A CARBONYL

When a nucleophile reacts with the carbonyl carbon of an aldehyde or ketone, there is no leaving group – the incoming nucleophile simply 'pushes' the electrons in the pi bond up to the oxygen. After the carbonyl has reacted with the nucleophile, the negatively charged oxygen has the capacity to act as a nucleophile. The nucleophile can be charged or neutral. However, most commonly the oxygen acts as a base, abstracting a proton from a nearby acid group in the solvent or enzyme active site. The nucelophiiles studied in this chapter are water (H_2O), cyanide (CN^-), Grignard reagent (RMgX), amines (and ammonia), hydrazine (N_2H_4), alcohols (ROH), and phosphorus ylides (R_3P=CRH).

The generic mechanism for a strong nucleophile generally occurs under basic conditions as shown below.

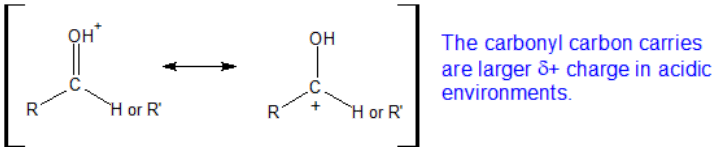


A closer look at the tetrahedral intermediate shows us that if the carbonyl reforms, then the original aldehyde or ketone is reformed.

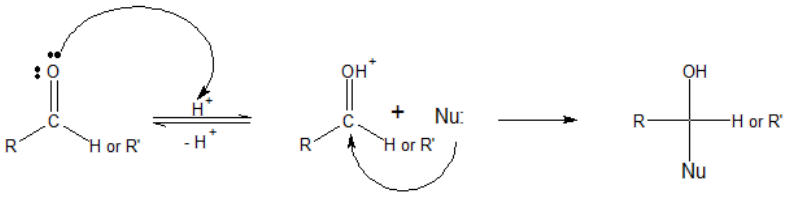


It is possible for the nucleophile to repeatedly add and leave the carbonyl group. Protonation of the tetrahedral intermediate to form the nucleophilic additon product is favored by the low activation energy of proton transfer reactions.

For reaction with weak nucleophiles generally occurs under acidic conditions to increase the electrophilicity of the carbonyl group as resonance form below illustrates.

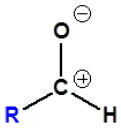


While the net result of the reaction is similar, the mechanism is slightly different due to the order of the proton transfer reactions.

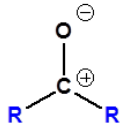


RELATIVE REACTIVITY OF CARBONYL COMPOUNDS TO NUCLEOPHILIC ADDITION

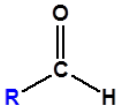
In general aldehydes are more reactive than ketones because of the lack of stabilizing alkly groups. The primary carbocation formed in the in the polarizing resonance structure of an aldehyde (discussed above) is less stable and therefore more reactive than the secondary carbocation formed by a ketone.



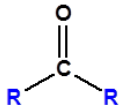
1° Carbocation
(Less Stable, More Reactive)



2° Carbocation
(MoreStable, Less Reactive)



Aldehyde
Less Stabilization
More Reactive



Ketone
Less Stabilization
More Reactive

Exercise

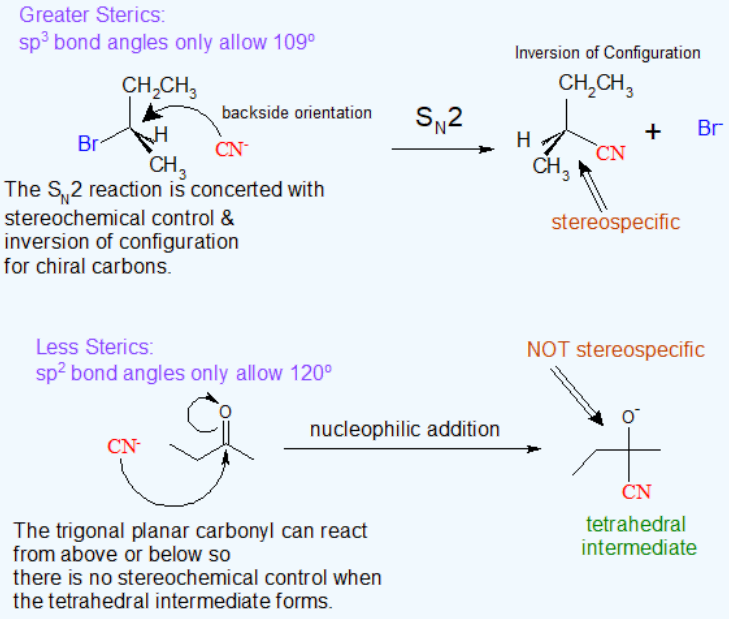
4. Compare the mechanisms of

an S_N2 reaction between 2-bromobutane and cyanide

tetrahedral complex formation between 2-butanone and cyanide.

Answer

4.



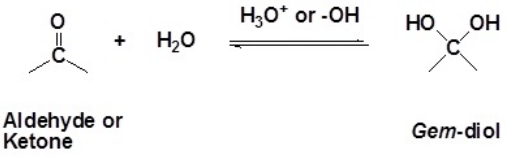
CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

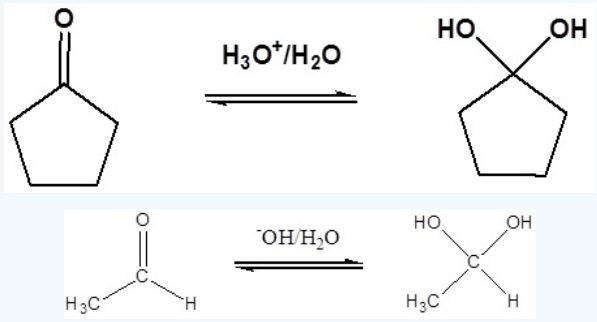
19.5: Nucleophilic Addition Reactions of Ketones and Aldehydes is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

19.6: NUCLEOPHILIC ADDITION OF WATER (HYDRATION)

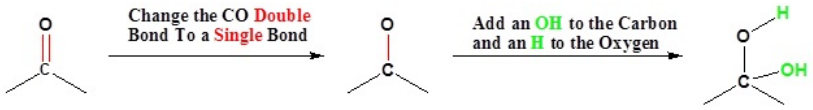
It has been demonstrated that water, in the presence of an acid or a base, adds rapidly to the carbonyl function of aldehydes and ketones establishing a reversible equilibrium with a **hydrate** (geminal-diol or *gem*-diol). The word germinal or gem comes from the Latin word for twin, *geminus*.



Example

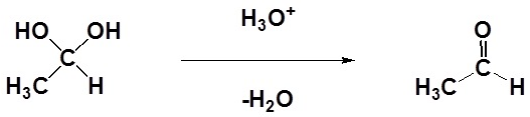


GOING FROM REACTANTS TO PRODUCTS SIMPLIFIED



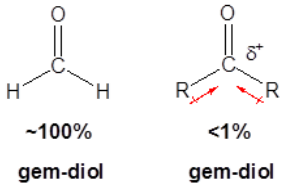
REVERSIBILITY OF THE REACTION

Isolation of *gem*-diols is difficult because the reaction is reversibly. Removal of the water during a reaction can cause the conversion of a gem-diol back to the corresponding carbonyl.

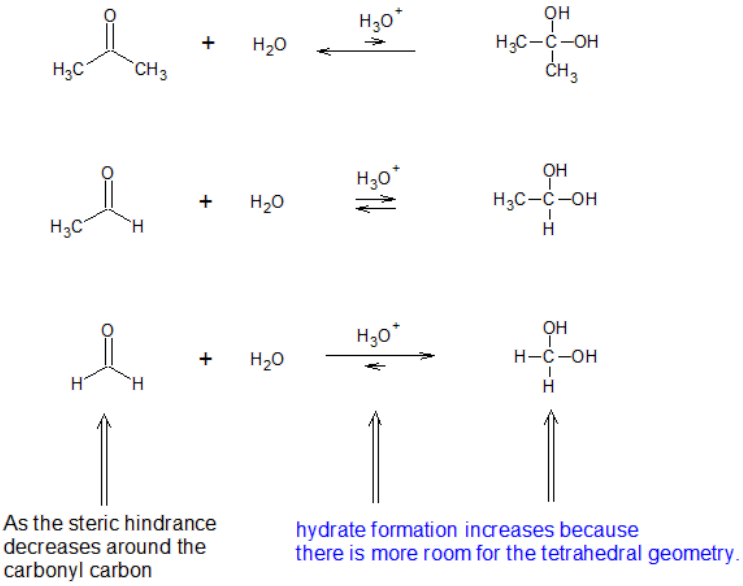


FACTORS AFFECTING THE *GEM*-DIOL EQUILIBRIUM

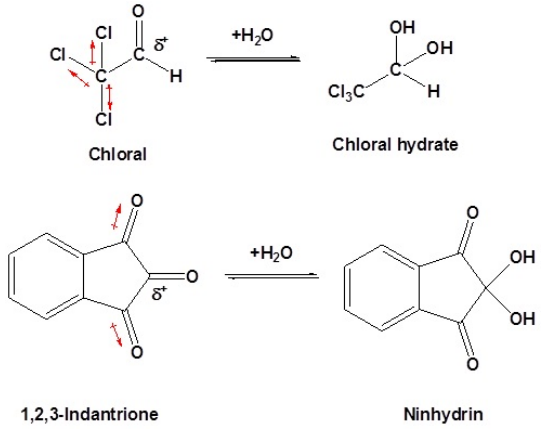
In most cases the resulting *gem*-diol is unstable relative to the reactants and cannot be isolated. Exceptions to this rule exist, one being formaldehyde where the weaker pi-component of the carbonyl double bond, relative to other aldehydes or ketones, and the small size of the hydrogen substituents favor addition. Thus, a solution of formaldehyde in water (formalin) is almost exclusively the hydrate, or polymers of the hydrate. The addition of electron donating alkyl groups stabilized the partial positive charge on the carbonyl carbon and decreases the amount of *gem*-diol product at equilibrium. Because of this ketones tend to form less than 1% of the hydrate at equilibrium. Likewise, the addition of strong electron-withdrawing groups destabilizes the carbonyl and tends to form stable *gem*-diols.



The relative equilbrium between the carbonyl and gem-diol builds understanding about steric effects in reaction mechanisms. This relationship is summarized below.



Two examples of this are chloral, and 1,2,3-indantrione. It should be noted that chloral hydrate is a sedative and has been added to alcoholic beverages to make a “Knock-out” drink also called a Mickey Finn. Also, ninhydrin is commonly used by forensic investigators to resolve finger prints.

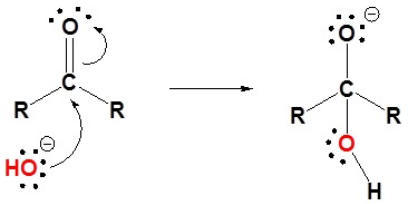


MECHANISM OF *GEM*-DIOL FORMATION

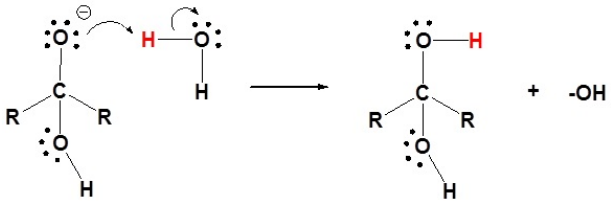
The mechanism is catalyzed by the addition of an acid or base. Note! This may speed up the reaction but is has not effect on the equilibriums discussed above. Basic conditions speed up the reaction because hydroxide is a better nucleophilic than water. Acidic conditions speed up the reaction because the protonated carbonyl is more electrophilic.

BASIC CONDITIONS

1) Nucleophilic hydroxide reacts with carbonyl carbon

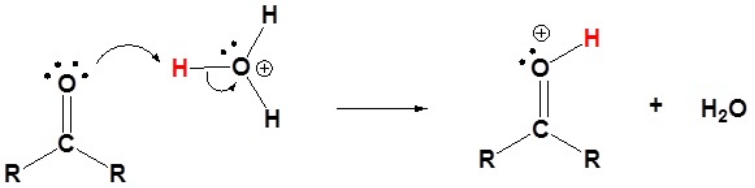


2) Protonation of the alkoxide

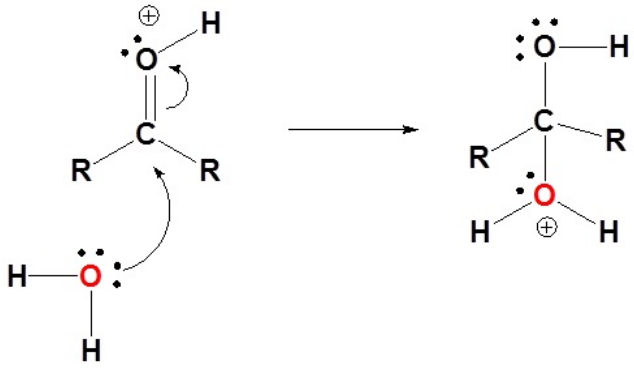


ACIDIC CONDITIONS

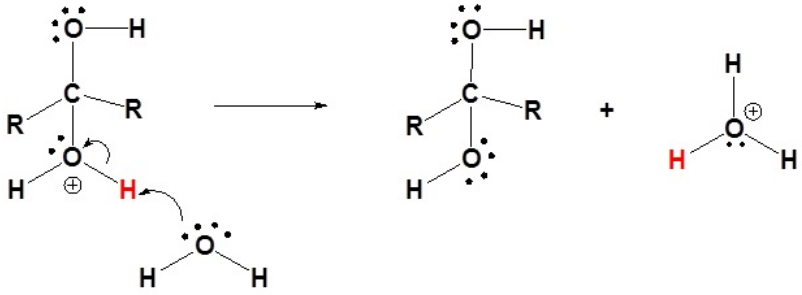
1) Protonation of the carbonyl



2) Nucleophilic water reacts with carbonyl carbon

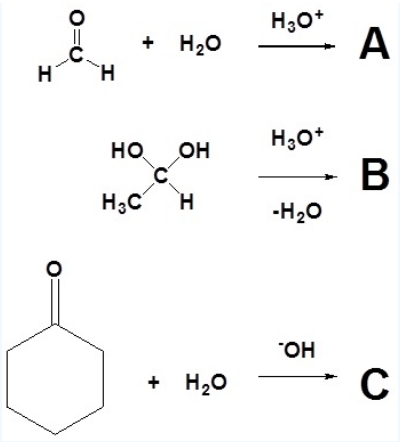


3) Deprotonation

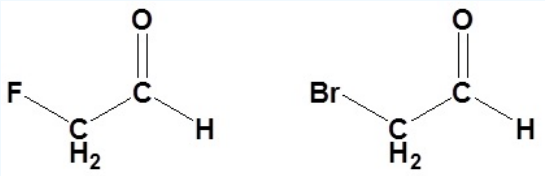


Exercise

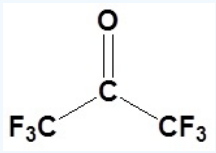
5. Draw the expected products of the following reactions.



6. Of the following pairs of molecules which would you expect to form a larger percentage of *gem*-diol at equilibrium? Please explain your answer.

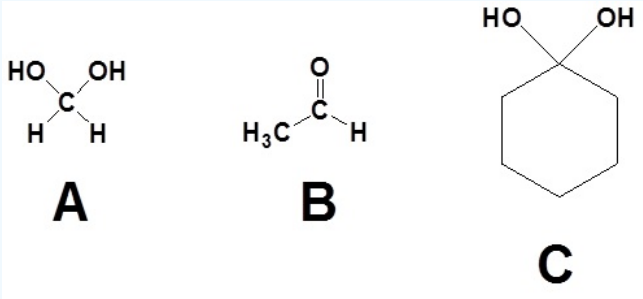


7. Would you expect the following molecule to form appreciable amount of *gem*-diol in water? Please explain your answer.



Answer

5.



6. The compound on the left would. Fluorine is more electronegative than bromine and would remove more electron density from the carbonyl carbon. This would destabilize the carbonyl allowing for more *gem*-diol to form.

7. Although ketones tend to not form *gem*-diols this compound exists almost entirely in the *gem*-diol form when placed in water. Ketones tend to not form *gem*-diols because of the stabilizing effect of the electron donating alkyl group. However, in this case the electron donating effects of alkyl group is dominated by the presence of six highly electronegative fluorines.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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19.7: NUCLEOPHILIC ADDITION OF CYANIDE AND ACETYLIDE

Cyanohydrins have the structural formula of $R_2C(OH)CN$. The “R” on the formula represents an alkyl, aryl, or hydrogen. To form a cyanohydrin, a hydrogen cyanide adds reversibly to the carbonyl group of an organic compound thus forming a hydroxyalkanenitrile adducts (commonly known and called as cyanohydrins).

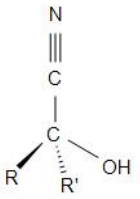
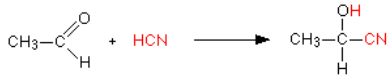


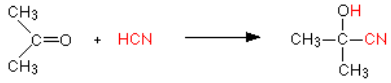
Figure **1:** General structure of a cyanohydrin

THE REACTION OF ALDEHYDES AND KETONES WITH HYDROGEN CYANIDE

Hydrogen cyanide adds across the carbon-oxygen double bond in aldehydes and ketones to produce compounds known as hydroxynitriles. For example, with ethanal (an aldehyde) you get 2-hydroxypropanenitrile:



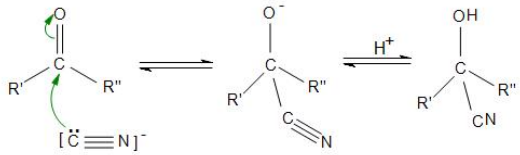
With propanone (a ketone) you get 2-hydroxy-2-methylpropanenitrile:



The reaction isn't normally done using hydrogen cyanide itself, because this is an extremely poisonous gas. Instead, the aldehyde or ketone is mixed with a solution of sodium or potassium cyanide in water to which a little sulphuric acid has been added. The pH of the solution is adjusted to about 4 - 5, because this gives the fastest reaction. The solution will contain hydrogen cyanide (from the reaction between the sodium or potassium cyanide and the sulphuric acid), but still contains some free cyanide ions. This is important for the mechanism.

MECHANISM OF CYANOHYDRIN FORMATION

Acid-catalyzed hydrolysis of silylated cyanohydrins has recently been shown to give cyanohydrins instead of ketones; thus an efficient synthesis of cyanohydrins has been found which works with even highly hindered ketones.



ACETONE CYANOHYDRINS

Acetone cyanohydrins (ACH) have the structural formula of $(CH_3)_2C(OH)CN$. It is an organic compound serves in the production of methyl methacrylate (also known as acrylic).

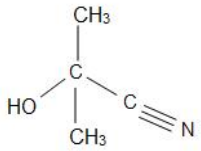


Figure 2: Acetone cyanohydrins

It is classified as an extremely hazardous substance, since it rapidly decomposes when it's in contact with water. In ACH, sulfuric acid is treated to give the sulfate ester of the methacrylamid. Preparations of other cyanohydrins are also used from ACH: for HACN to Michael acceptors and for the formylation of arenas. The treatment with lithium hydride affords anhydrous lithium cyanide.

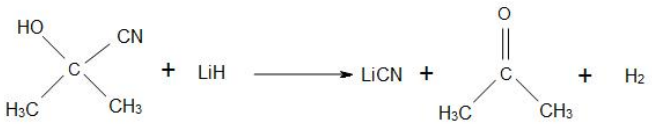
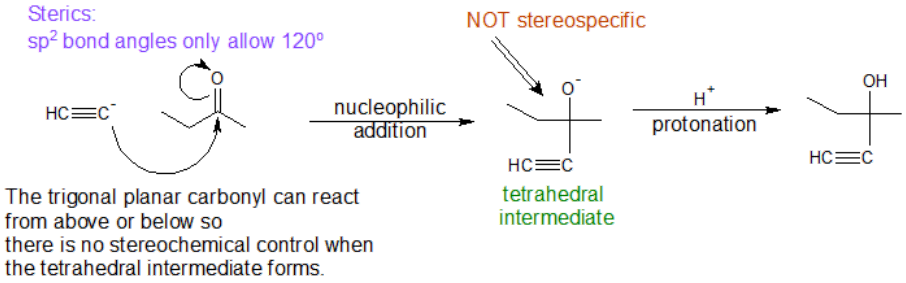


Figure 3: Reduction of Acetone cyanohydrins

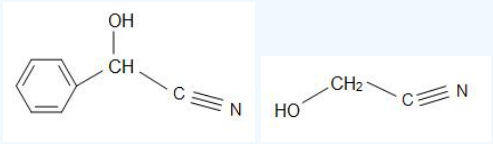
ACETYLIDE IONS (RCC^-)

The reactivity of acetylide ions with aldehydes and ketones follows the mechanism for cyanide. For example, 2-butanone reacts with acetylide as shown in the reaction below.



Exercise

8. Mandelonitrile occurs in pits of some fruits. Glycolonitrile is the simplest cyanohydrin. Their structures are shown below.

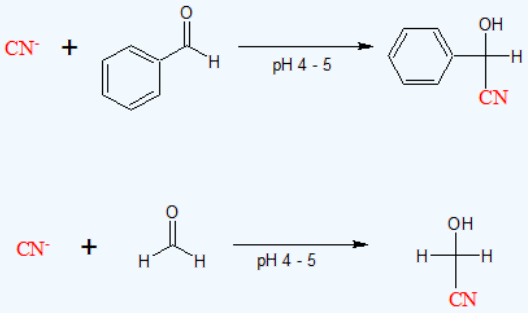


Madelonitrile glycolonitrile

Propose the reactants for mandelonitrile and glycolonitrile.

Answer

8.



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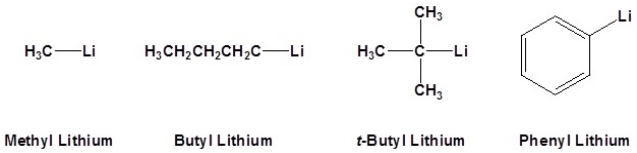
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

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19.8: NUCLEOPHILIC ADDITION OF GRIGNARDS

COMMON ORGANOMETALLIC REAGENTS

The alkali metals (Li, Na, K etc.) and the alkaline earth metals (Mg and Ca, together with Zn) are good reducing agents, the former being stronger than the latter. These same metals reduce the carbon-halogen bonds of alkyl halides. The halogen is converted to a halide anion, and the carbon bonds to the metal which has characteristics similar to a carbanion (R:-). Some common organometallic reagents are shown below



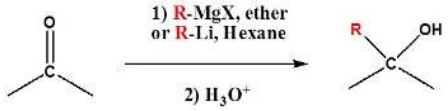
Methyl Lithium | Butyl Lithium | *t*-Butyl Lithium | Phenyl Lithium



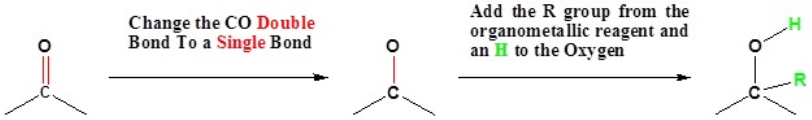
Methyl Magnesium Bromide | Phenylmagnesium Bromide

REACTION OF ORGANOMETALLIC REAGENTS WITH VARIOUS CARBONYLS

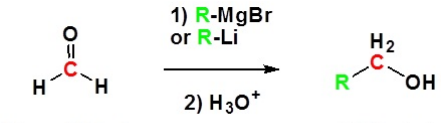
Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. The basic reaction involves the nucleophilic attack of the carbanionic carbon in the organometallic reagent with the electrophilic carbon in the carbonyl to form alcohols.



Both Grignard and Organolithium Reagents will perform these reactions going from Reactants to Products by this simplified pattern:

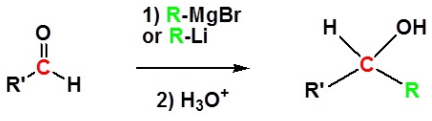


Addition to formaldehyde gives 1° alcohols



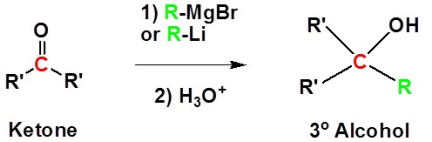
Formaldehyde | 1° Alcohol

Addition to aldehydes gives 2° alcohols



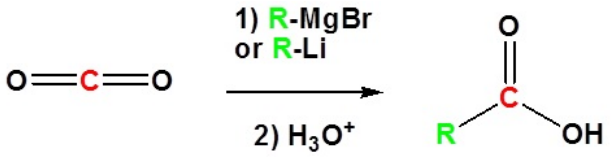
Aldehyde | 2° Alcohol

Addition to ketones gives 3° alcohols



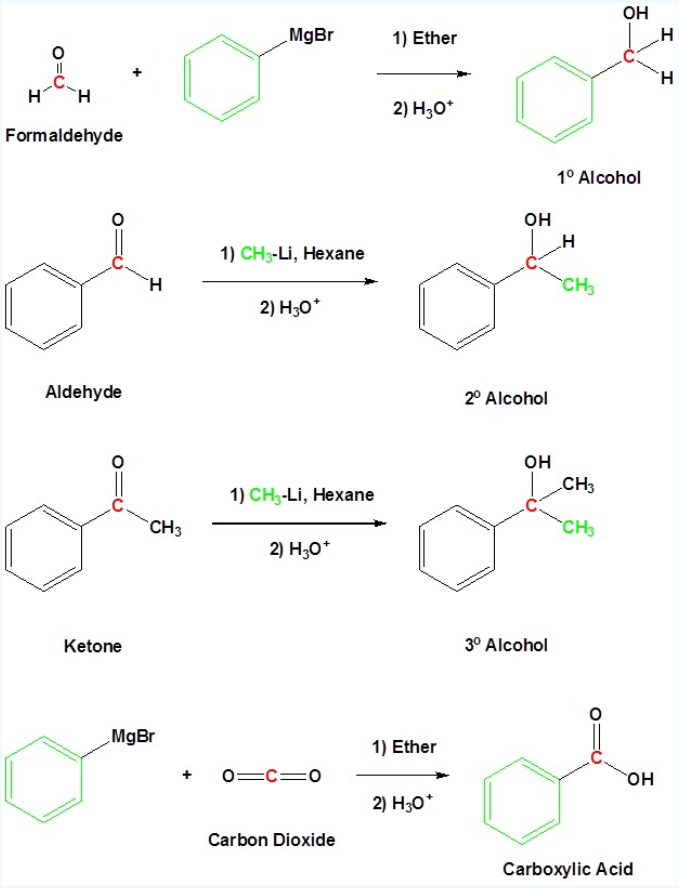
Ketone | 3° Alcohol

Addition to carbon dioxide (CO_2) forms a carboxylic acid



Carbon Dioxide Carboxylic Acid

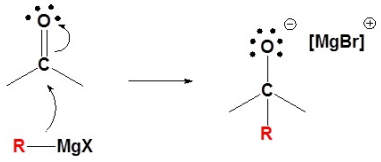
Example



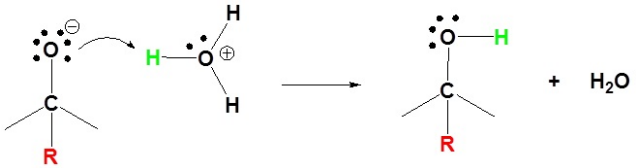
MECHANISM FOR THE ADDITION TO CARBONYLS

The mechanism for a Grignard agent is shown. The mechanism for an organometallic reagent is the same.

1) Nucleophilic reaction with carbonyl carbon



2) Protonation of tetrahedral intermediate

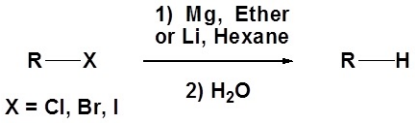


ORGANOMETALLIC REAGENTS AS BASES

These reagents are very strong bases (pKa's of saturated hydrocarbons range from 42 to 50). Although not usually done with Grignard reagents, organolithium reagents can be used as strong bases. Both Grignard reagents and organolithium reagents react with water to form the corresponding hydrocarbon. This is why so much care is needed to insure dry glassware and solvents when working with organometallic reagents.



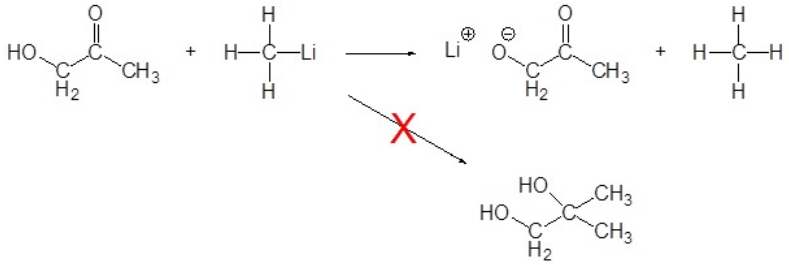
In fact, the reactivity of Grignard reagents and organolithium reagents can be exploited to create a new method for the conversion of halogens to the corresponding hydrocarbon (illustrated below). The halogen is converted to an organometallic reagent and then subsequently reacted with water to from an alkane.



Conjugate base anions of terminal alkynes (acetylide anions) are nucleophiles, and can do both nucleophilic substitution and nucleophilic addition reactions.

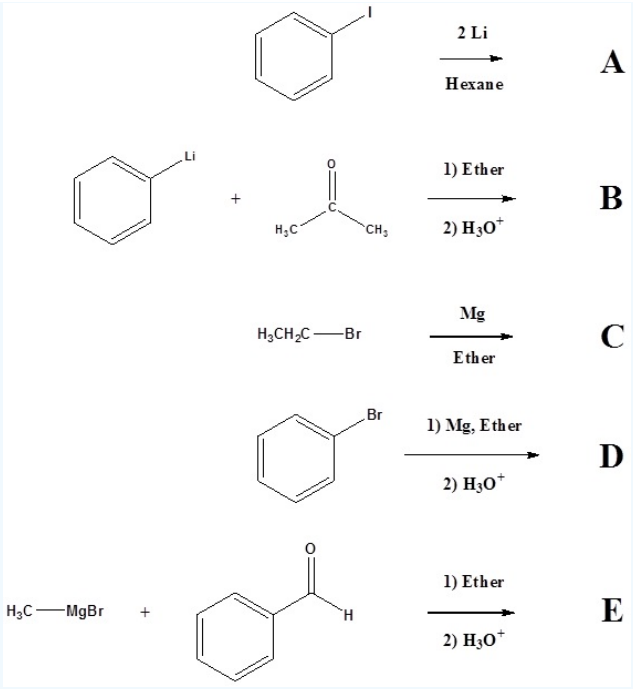
LIMITATION OF ORGANOMETALLIC REAGENTS

As discussed above, Grignard and organolithium reagents are powerful bases. Because of this they cannot be used as nucleophiles on compounds which contain acidic hydrogens. If they are used they will act as a base and deprotonate the acidic hydrogen rather than act as a nucleophile and react with the carbonyl. A partial list of functional groups which cannot be used are: alcohols, amides, 1° amines, 2° amines, carboxylic acids, and terminal alkynes.

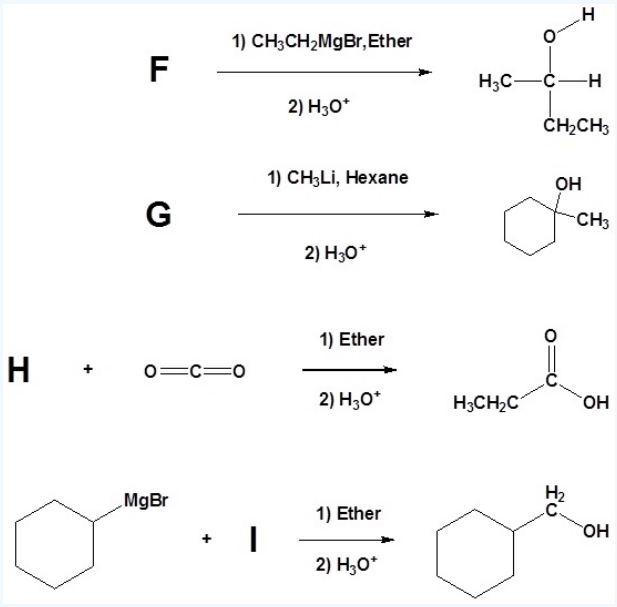


Exercises

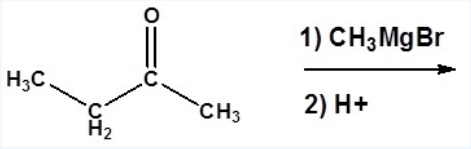
9. Please write the product of the following reactions.



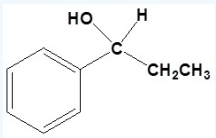
10. Please indicate the starting material required to produce the product.



11. Please give a detailed mechanism and the final product of this reaction

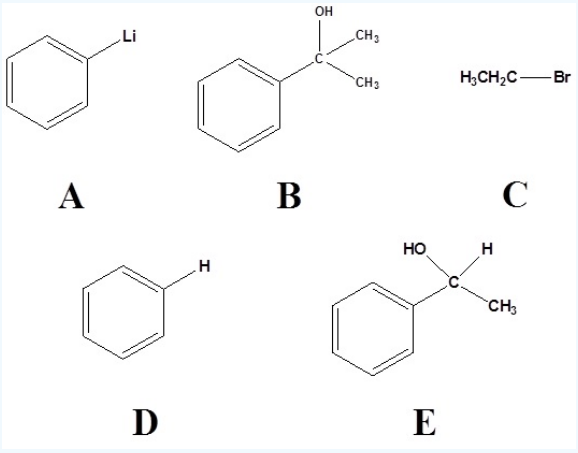


12. Please show two sets of reactants which could be used to synthesize the following molecule using a Grignard reaction.

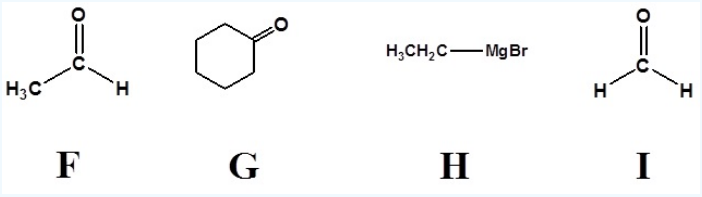


Answers

9.

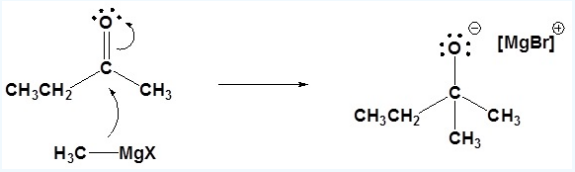


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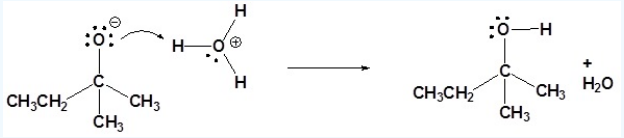


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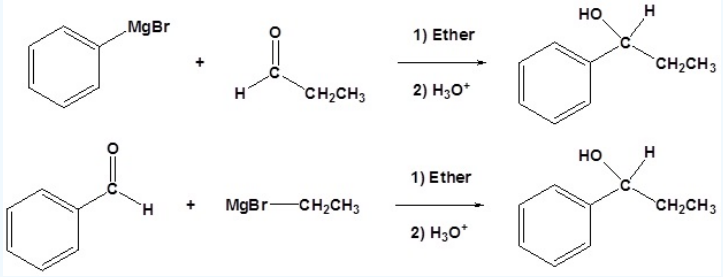
Nucleophilic addition reaction



Protonation



12.



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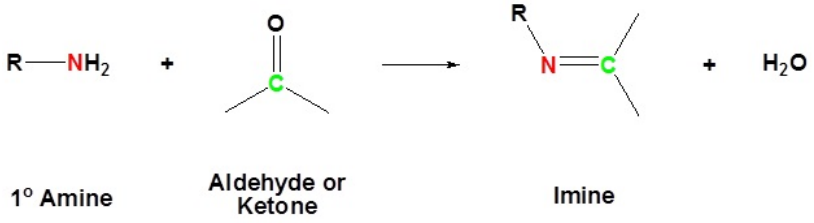
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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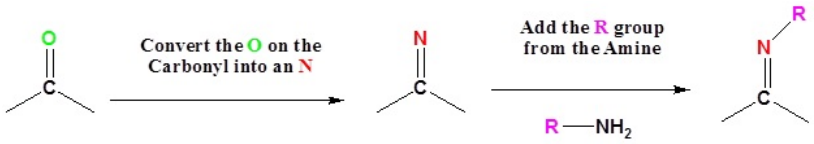
19.9: NUCELOPHILIC ADDITION OF AMINES (IMINE AND ENAMINE FORMATION)

REACTION WITH PRIMARY AMINES TO FORM IMINES

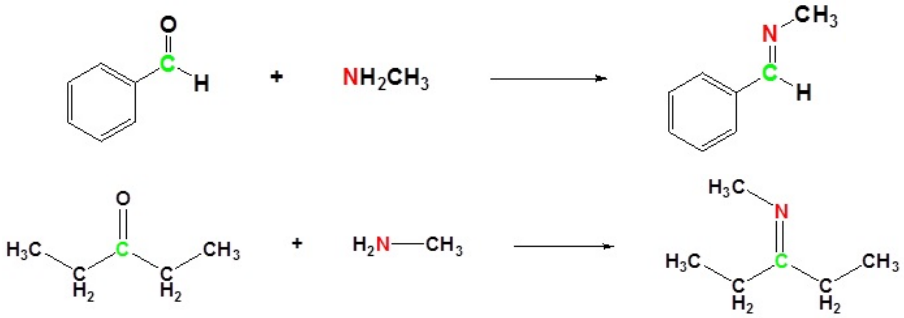
The reaction of aldehydes and ketones with ammonia or 1º-amines forms imine derivatives, also known as Schiff bases (compounds having a C=N function). Water is eliminated in the reaction, which is acid-catalyzed and reversible in the same sense as acetal formation. The pH for reactions which form imine compounds must be carefully controlled. The rate at which these imine compounds are formed is generally greatest near a pH of 5, and drops at higher and lower pH's. At high pH there will not be enough acid to protonate the OH in the intermediate to allow for removal as H_2O. At low pH most of the amine reactant will be tied up as its ammonium conjugate acid and will become non-nucleophilic.



Converting reactants to products simply

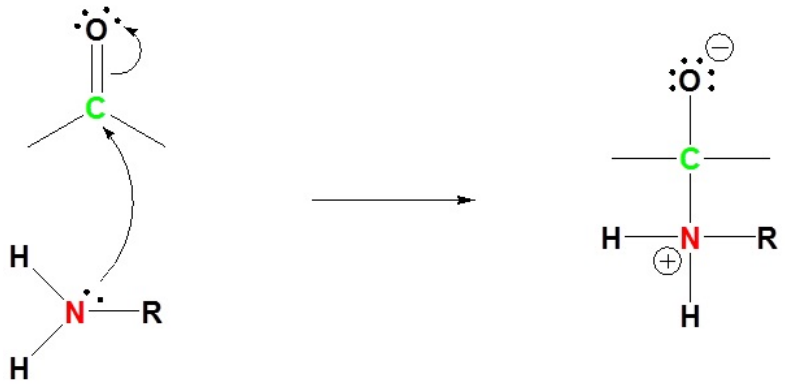


EXAMPLES OF IMINE FORMING REACTIONS

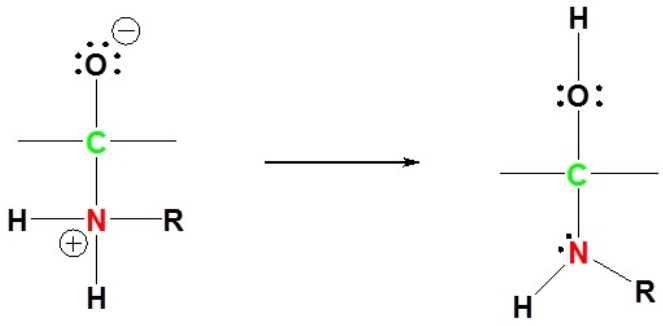


MECHANISM OF IMINE FORMATION

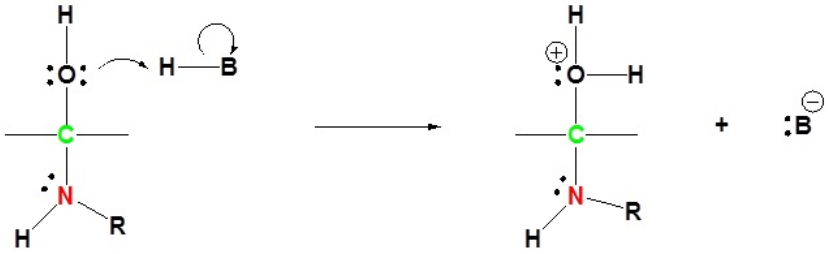
1) Nucleophilic addition reaction



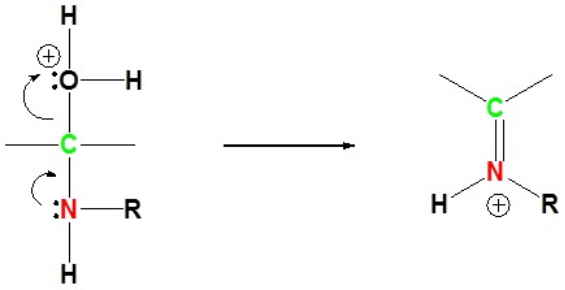
2) Proton transfer



3) Protonation of OH



4) Removal of water

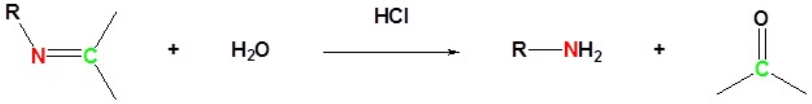


5) Deprotonation to form neutral final product



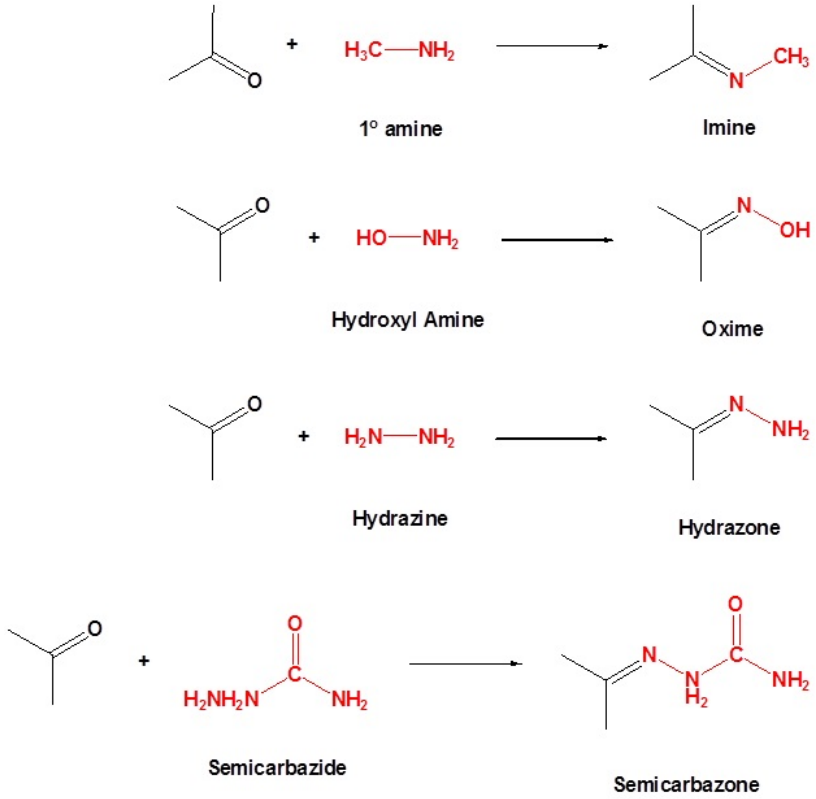
REVERSIBILITY OF IMINE FORMING REACTIONS

Imines can be hydrolyzed back to the corresponding primary amine under acidic aqueous conditons.



REACTIONS INVOLVING OTHER REAGENTS OF THE TYPE Y-NH_2

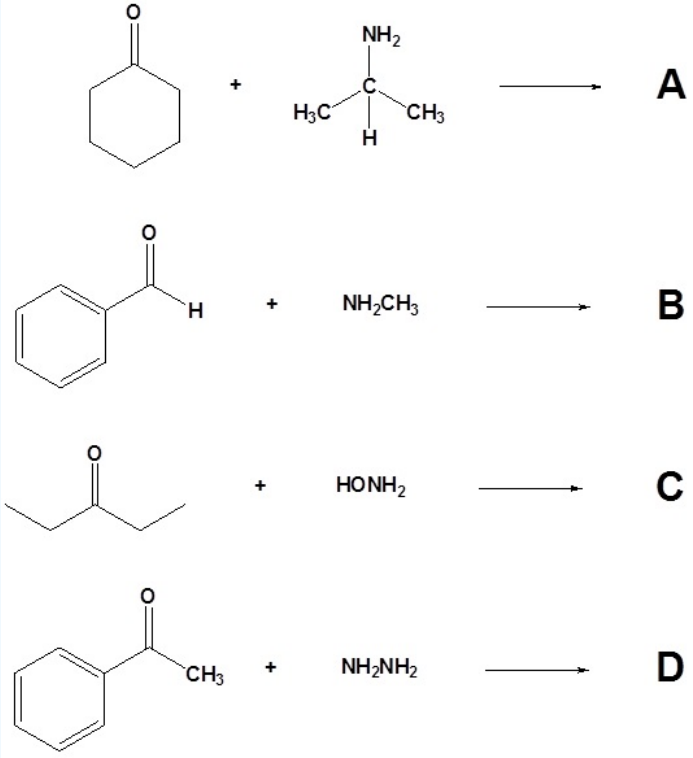
Imines are sometimes difficult to isolate and purify due to their sensitivity to hydrolysis. Consequently, other reagents of the type Y–NH_2 have been studied, and found to give stable products (R_2C=N–Y) useful in characterizing the aldehydes and ketones from which they are prepared. Some of these reagents are listed in the following table, together with the structures and names of their carbonyl reaction products. Hydrazones are used as part of the Wolff-Kishner reduction and will be discussed in more detail in another module.



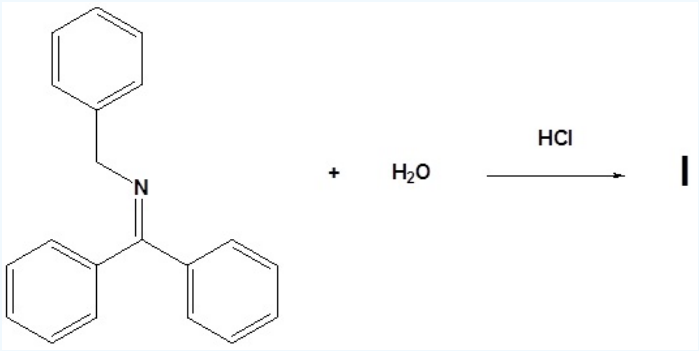
With the exception of unsubstituted hydrazones, these derivatives are easily prepared and are often crystalline solids - even when the parent aldehyde or ketone is a liquid. Since melting points can be determined more quickly and precisely than boiling points, derivatives such as these are useful for comparison and identification of carbonyl compounds. It should be noted that although semicarbazide has two amino groups ($-NH_2$) only one of them is a reactive amine. The other is amide-like and is deactivated by the adjacent carbonyl group.

Exercise

13. Draw the products of the following reactions.

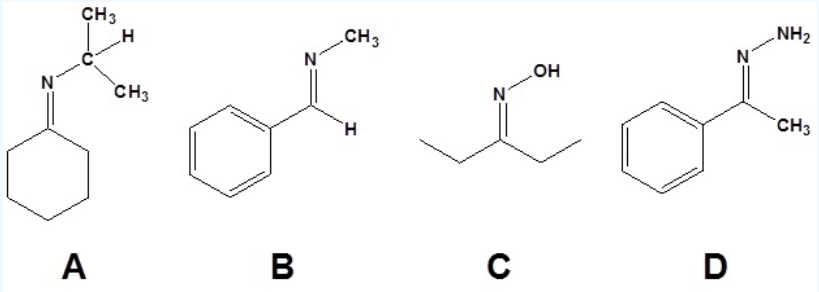


14. Draw the structure of the reactant needed to produce the indicated product.

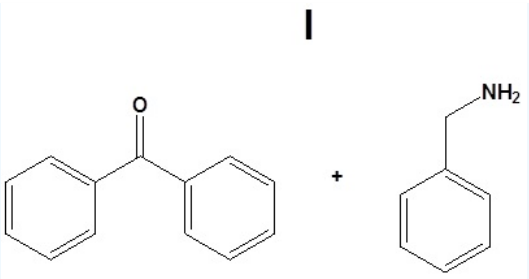


Answer

13.



14.



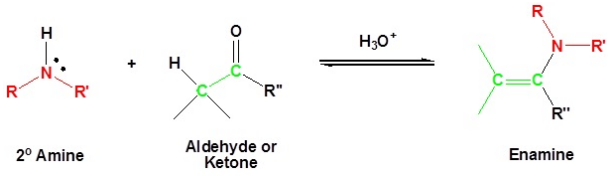
CONTRIBUTORS AND ATTRIBUTIONS

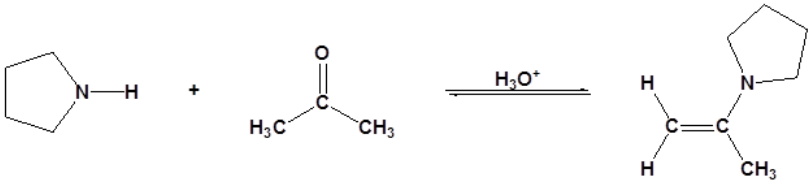
Prof. Steven Farmer (Sonoma State University)

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

REACTION WITH SECONDARY AMINES TO FORM ENAMINES

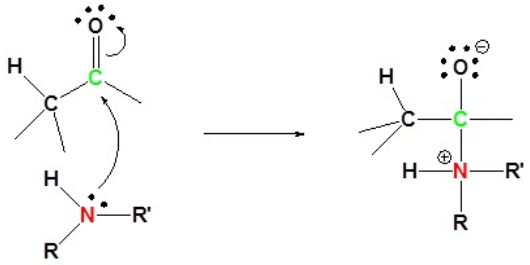
Most aldehydes and ketones react with 2º-amines to give products known as **enamines**. It should be noted that, like acetal formation, these are acid-catalyzed reversible reactions in which water is lost. Consequently, enamines are easily converted back to their carbonyl precursors by acid-catalyzed hydrolysis.



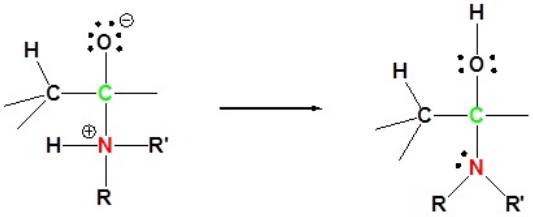


MECHANISM

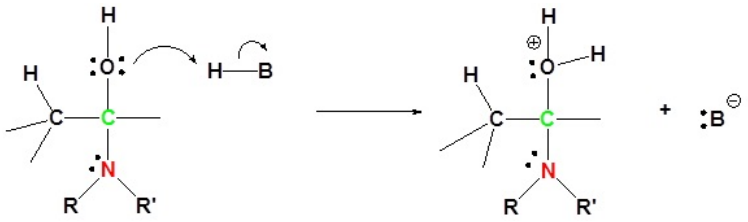
1) Nuleophilic addition reaction



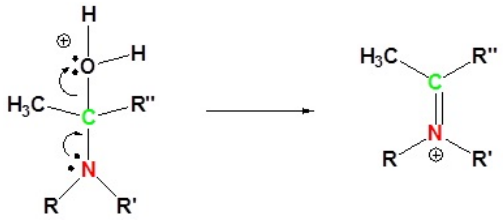
2) Proton transfer



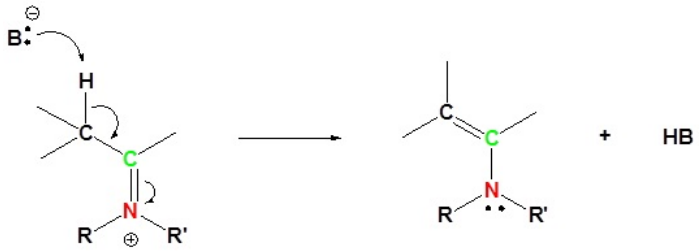
3) Protonation of OH



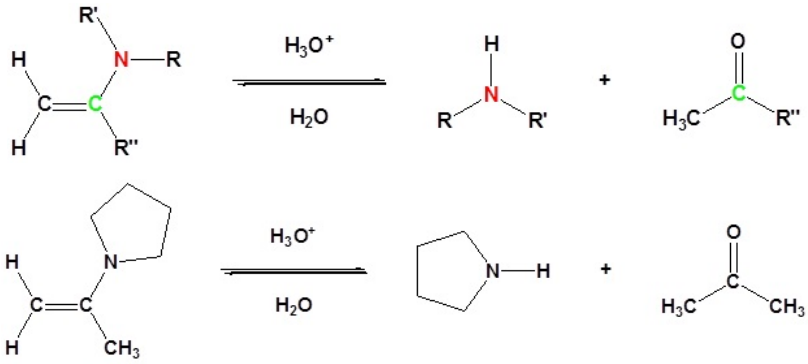
4) Removal of water



5) Deprotonation to neutralize final product

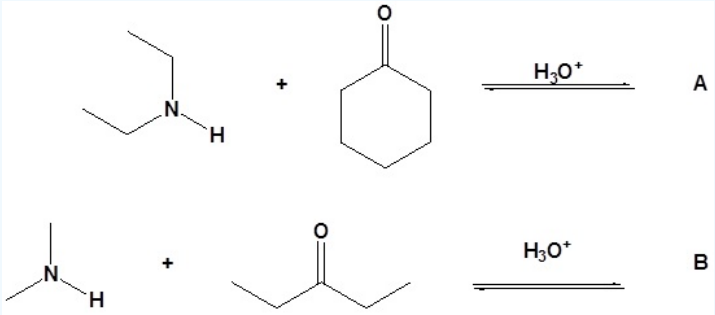


REVERSIBILITY OF ENAMINES

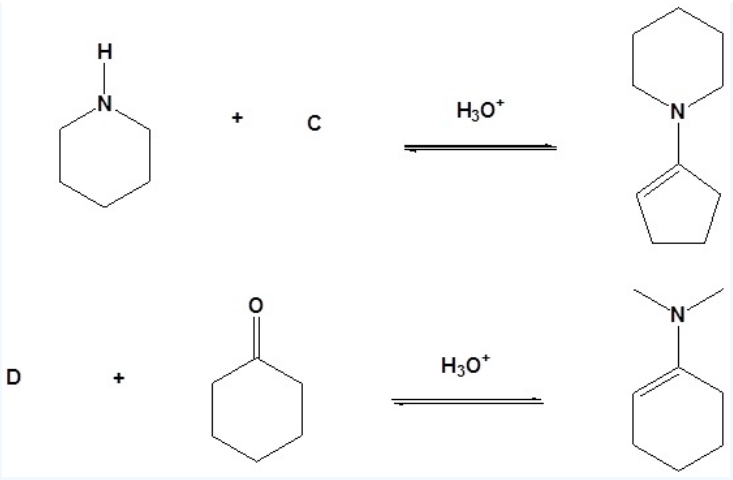


Exercise

15. Draw the products for the following reactions.

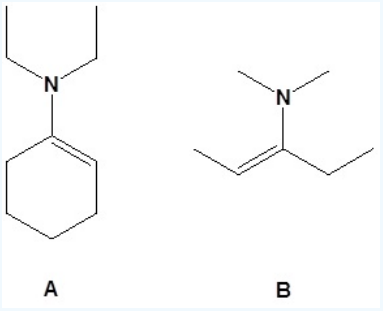


16. Draw the missing reactant to complete each reaction below.

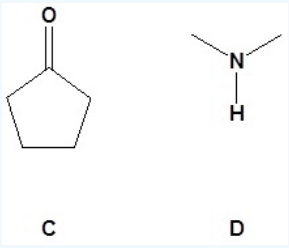


Answer

15.



16.



CONTRIBUTORS AND ATTRIBUTIONS

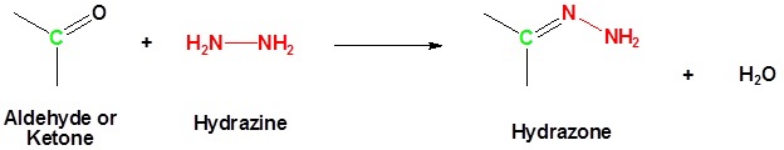
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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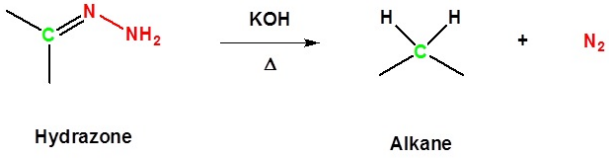
19.10: NUCLEOPHILIC ADDITION OF HYDRAZINE (WOLFF-KISHNER REACTION)

Aldehydes and ketones can be converted to a hydrazine derivative by reaction with hydrazine. These "hydrazones" can be further converted to the corresponding alkane by reaction with base and heat. These two steps can be combined into one reaction called the Wolff-Kishner Reduction which represents a general method for converting aldehydes and ketones into alkanes. Typically a high boiling point solvent, such as ethylene glycol, is used to provide the high temperatures needed for this reaction to occur. Note! Nitrogen gas is produced as part of this reaction.

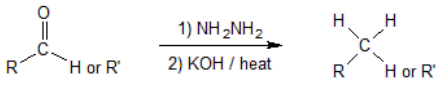
Reaction of Aldehydes or Ketones with Hydrazine Produces a Hydrazone



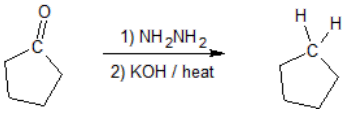
Reaction with a Base and Heat Converts a Hydrazone to an Alkane



Both Reactions Together Produces the Wolff-Kishner Reduction

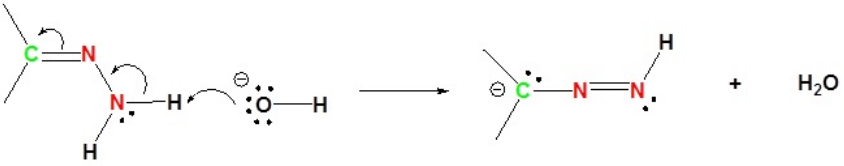


The Wolff-Kishner reaction for cyclopentanone is shown below.

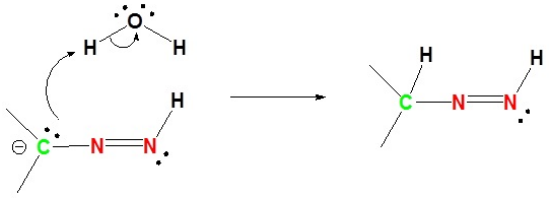


MECHANISM OF THE WOLFF-KISHNER REDUCTION

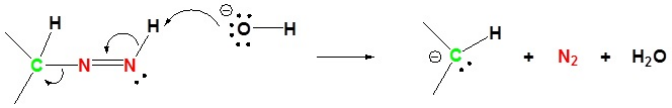
1) Deprotonation of Nitrogen



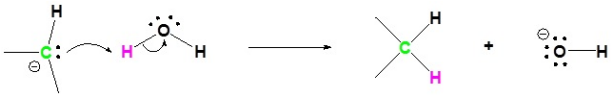
2) Protonation of the Carbon



3) Deprotonation of Nitrogen

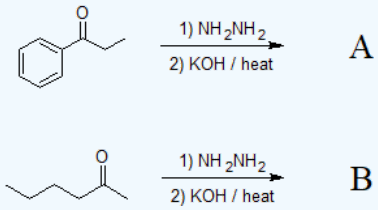


4) Protonation of Carbon



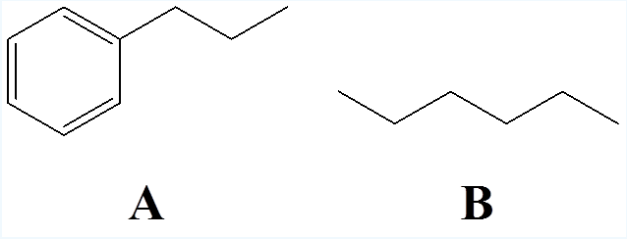
Exercise

17. Draw the products for the following reactions.



Answer

17.



CONTRIBUTORS AND ATTRIBUTIONS

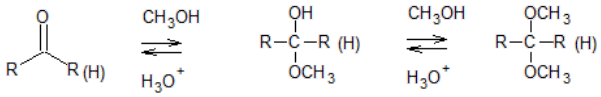
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

19.10: Nucleophilic Addition of Hydrazine (Wolff-Kishner Reaction) is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

19.11: NUCELOPHILIC ADDITION OF ALCOHOLS (ACETAL FORMATION)

INTRODUCTION

It has been demonstrated that water adds rapidly to the carbonyl function of aldehydes and ketones to form geminal-diol. In a similar reaction alcohols add reversibly to aldehydes and ketones to form hemiacetals (h*emi*, Greek, half). This reaction can continue by adding another alcohol to form an acetal. Hemiacetals and acetals are important functional groups because they appear in sugars.



hemiacetal acetal

To achieve effective hemiacetal or acetal formation, two additional features must be implemented. First, an acid catalyst must be used because alcohol is a weak nucleophile; and second, the water produced with the acetal must be removed from the reaction by a process such as a molecular sieves or a **Dean-Stark trap**. The latter is important, since acetal formation is reversible. Indeed, once pure hemiacetal or acetals are obtained they may be hydrolyzed back to their starting components by treatment with aqueous acid and an excess of water.

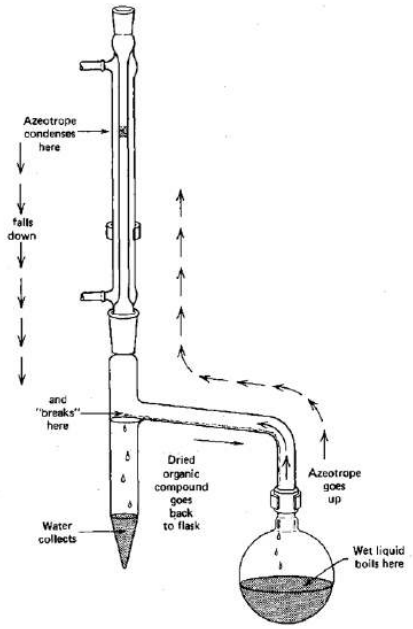
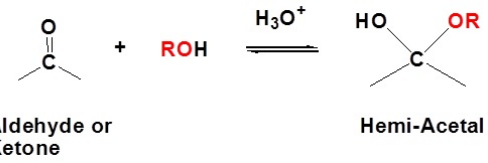
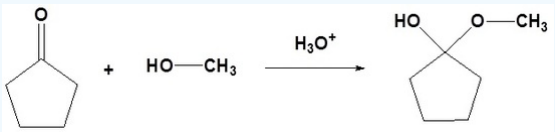


Figure: Dean-Stark Trap for Isolating Hemiacetals and Ketals

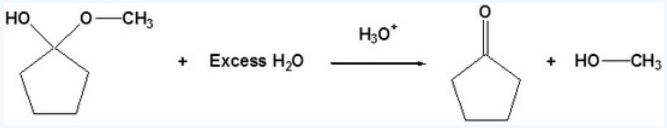
FORMATION OF HEMIACETALS



Example: Formation of Hemiacetals

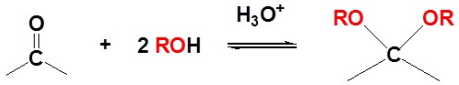


Example: Hemiacetal Reversibility



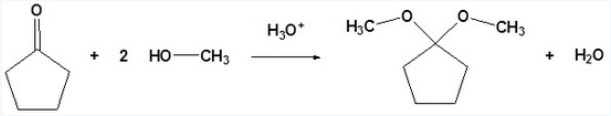
FORMATION OF ACETALS

Acetals are geminal-diether derivatives of aldehydes or ketones, formed by reaction with two equivalents (or an excess amount) of an alcohol and elimination of water. Ketone derivatives of this kind were once called ketals, but modern usage has dropped that term. It is important to note that a hemiacetal is formed as an intermediate during the formation of an acetal.

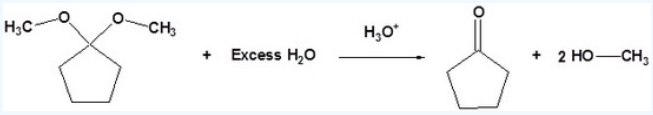


Aldehyde or Ketone **Acetal**

Example: Formation of Acetals



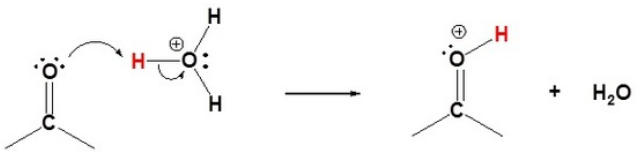
Example: Acetal Reversibility



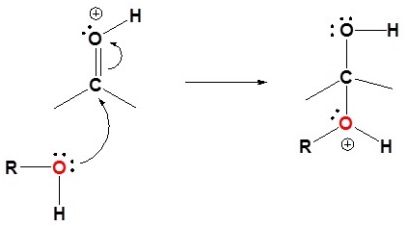
MECHANISM FOR HEMIACETAL AND ACETAL FORMATION

The mechanism shown here applies to both acetal and hemiacetal formation

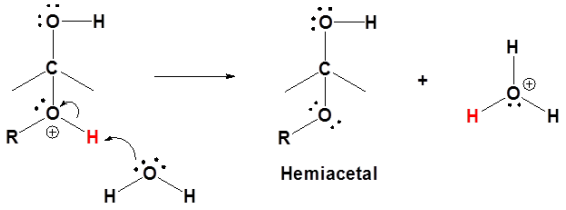
1) Protonation of the carbonyl



2) Nucleophilic additional reaction by the alcohol

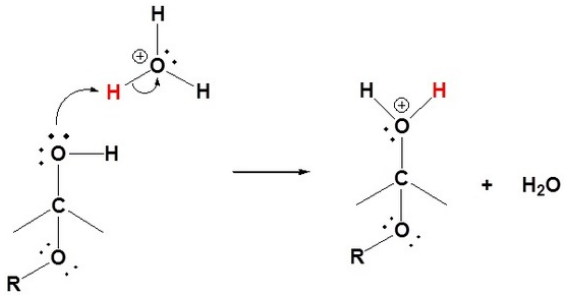


3) Deprotonation to form a hemiacetal

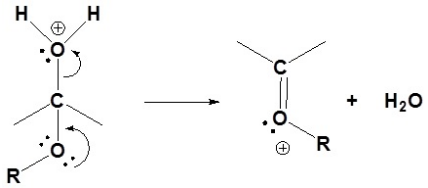


Hemiacetal

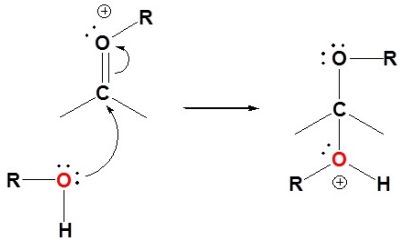
4) Protonation of the alcohol



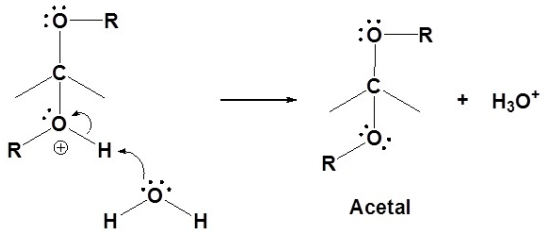
5) Removal of water



6) Nucleophilic addition reaction by the alcohol

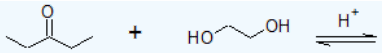


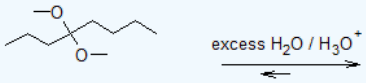
7) Deprotonation by water

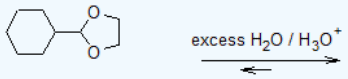


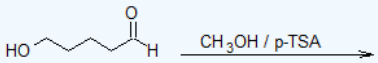
Exercise

18. Draw the products for the following reactions.

a) 

b) 

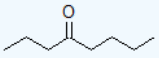
c) 

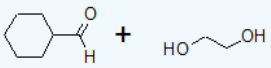
d) 

Answer

18.

a) 

b) 

c) 

d) 

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

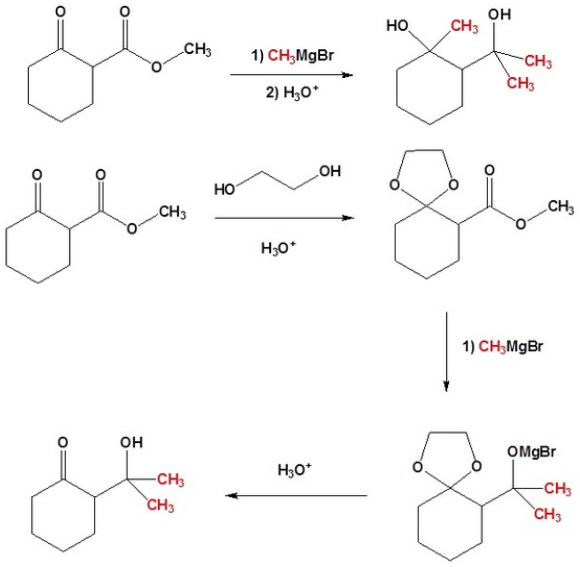
19.11: Nucelophilic Addition of Alcohols (Acetal Formation) is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

19.12: ACETALS AS PROTECTING GROUPS

ACETALS AS PROTECTING GROUPS

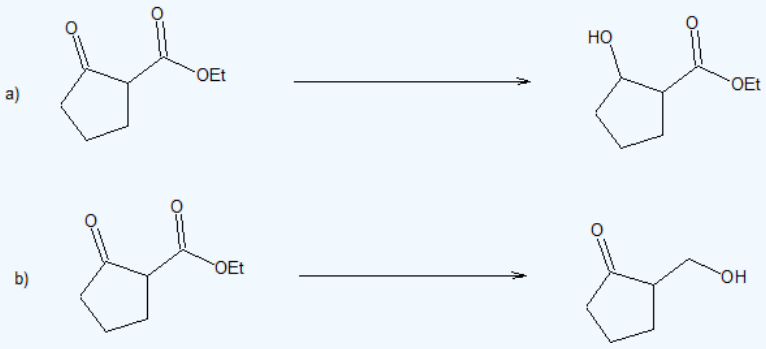
The importance of acetals as carbonyl derivatives lies chiefly in their stability and lack of reactivity in neutral to strongly basic environments. As long as they are not treated by acids, especially aqueous acid, acetals exhibit all the lack of reactivity associated with ethers in general. Among the most useful and characteristic reactions of aldehydes and ketones is their reactivity toward strongly nucleophilic (and basic) metallo-hydride, alkyl and aryl reagents. If the carbonyl functional group is converted to an acetal these powerful reagents have no effect; thus, acetals are excellent protective groups, when these irreversible addition reactions must be prevented.

In the following example we would like a Grignard reagent to react with the ester and not the ketone. This cannot be done without a protecting group because Grignard reagents react with esters and ketones.



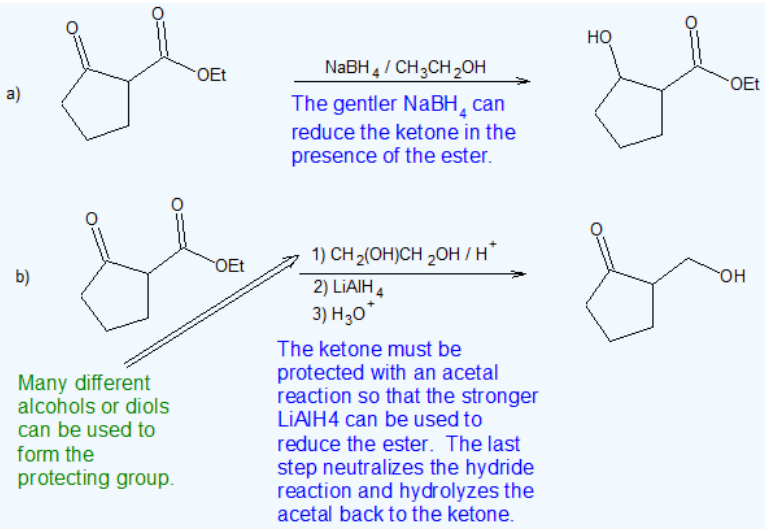
Exercise

19. Specify the reagents to perform the following chemical transformations.



Answer

19.



CONTRIBUTORS AND ATTRIBUTIONS

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19.13: NUCELOPHILIC ADDITION OF PHOSPHORUS YLIDES (THE WITTIG REACTION)

Organophosphorus ylides react with aldehydes or ketones to give substituted alkenes in a transformation called the Wittig reaction. This reaction is named for George Wittig who was awarded the Nobel prize for this work in 1979. A principal advantage of alkene synthesis by the Wittig reaction is that the location of the double bond is absolutely fixed, in contrast to the mixtures often produced by alcohol dehydration.

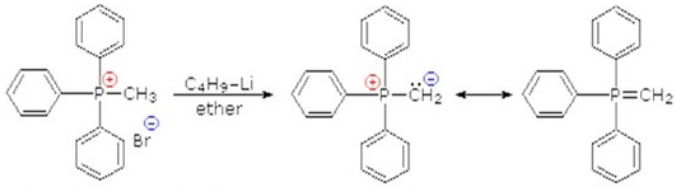
PREPARATION OF PHOSPHORUS YLIDES

It has been noted that dipolar phosphorus compounds are stabilized by p-d bonding. This bonding stabilization extends to carbanions adjacent to phosphonium centers, and the zwitterionic conjugate bases derived from such cations are known as ylides. An **ylide** is defined as a compound with opposite charges on adjacent atoms both of which have complete octets. For the Wittig reaction discussed below an organophosphorus ylide, also called Wittig reagents, will be used. The ability of phosphorus to hold more than eight valence electrons allows for a resonance structure to be drawn forming a double bonded structure.



An Ylide

The stabilization of the carbanion provided by the phosphorus causes an increase in acidity (pKa ~35). Very strong bases, such as butyl lithium, are required for complete formation of ylides.

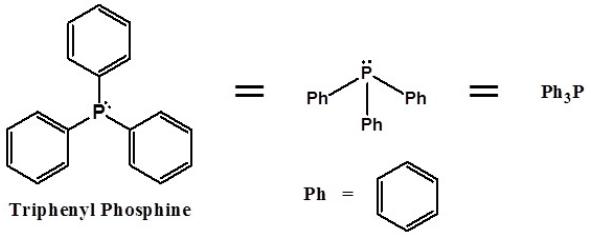


methyltriphenylphosphonium bromide — methylenetriphenylphosphorane, a phosphorous ylide

The ylides shown here are all strong bases. Like other strongly basic organic reagents, they are protonated by water and alcohols, and are sensitive to oxygen. Water decomposes phosphorous ylides to hydrocarbons and phosphine oxides, as shown.

$$R_3P{=}CR'_2 \;+\; H_2O \longrightarrow R_3P{=}O \;+\; R'_2CH_2$$

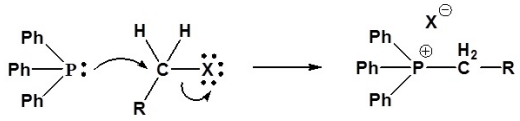
Although many ylides are commercially available it is often necessary to create them synthetically. Ylides can be synthesized from an alkyl halide and a trialkyl phosphine. Typically triphenyl phosphine is used to synthesize ylides. Because a S_N2 reaction is used in the ylide synthesis methyl and primary halides perform the best. Secondary halides can also be used but the yields are generally lower. This should be considered when planning out a synthesis which involves a synthesized Wittig reagent.



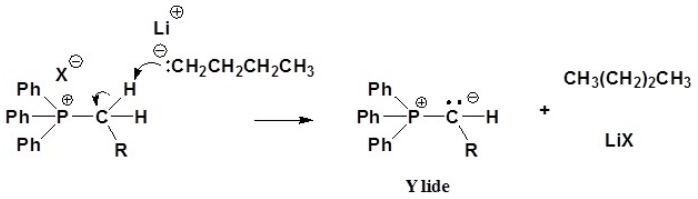
Triphenyl Phosphine

MECHANISM OF YLIDE FORMATION

1) S_N2 reaction

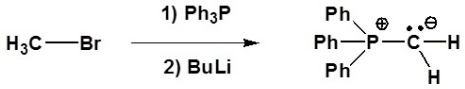


2) Deprotonation



Ylide

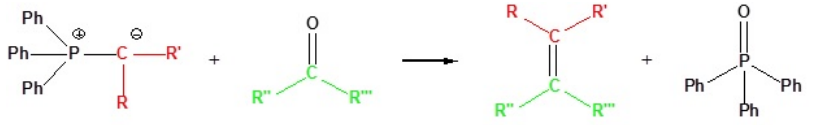
EXAMPLES OF YLIDE FORMATION



Methyltriphenylphosphonium bromide

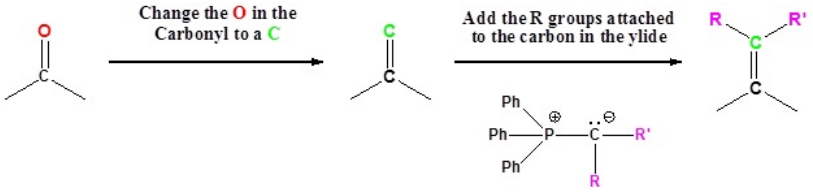
THE WITTIG REACTION

The most important use of ylides in synthesis comes from their reactions with aldehydes and ketones, which are initiated in every case by a covalent bonding of the nucleophilic alpha-carbon to the electrophilic carbonyl carbon. Ylides react to give substituted alkenes in a transformation called the Wittig reaction. This reaction is named for George Wittig who was awarded the Nobel prize for this work in 1979. A principal advantage of alkene synthesis by the Wittig reaction is that the location of the double bond is absolutely fixed, in contrast to the mixtures often produced by alcohol dehydration.

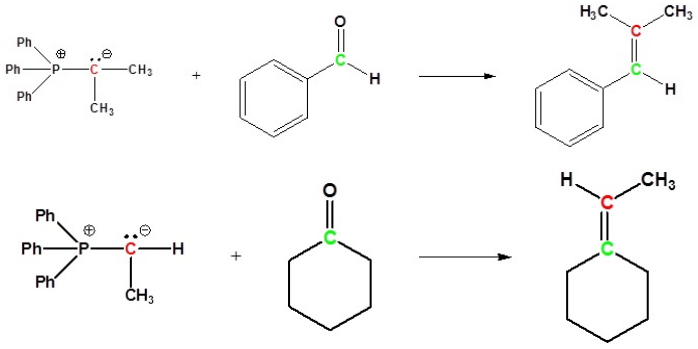


Ylide | Aldehyde or Ketone | Alkene | Triphenyl-phosphine oxide

Going from reactants to products simplified



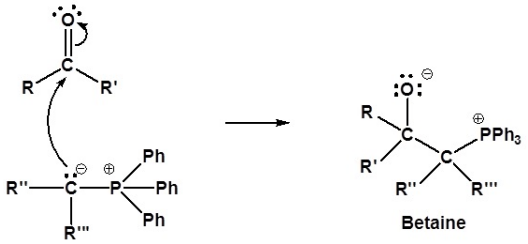
EXAMPLES OF THE WITTIG REACTION



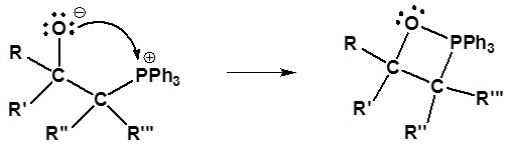
MECHANISM OF THE WITTIG REACTION

Following the initial carbon-carbon bond formation, two intermediates have been identified for the Wittig reaction, a dipolar charge-separated species called a betaine and a four-membered heterocyclic structure referred to as an oxaphosphatane. Cleavage of the oxaphosphatane to alkene and phosphine oxide products is exothermic and irreversible.

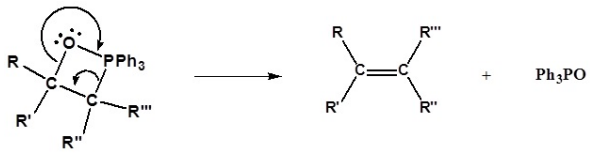
1) Nucleophillic reaction with the carbonyl



2) Formation of a 4 membered ring

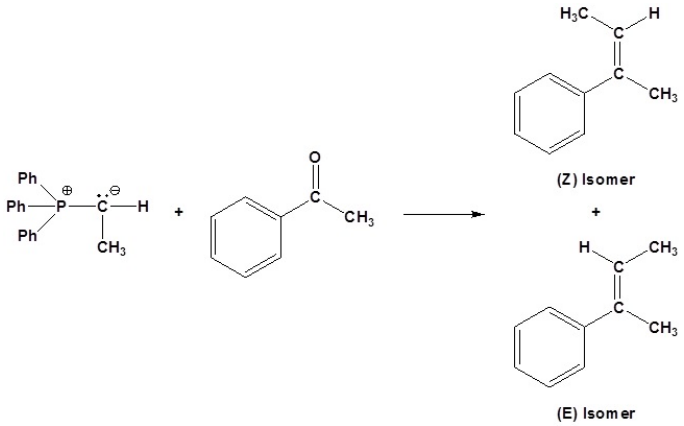


3) Formation of the alkene



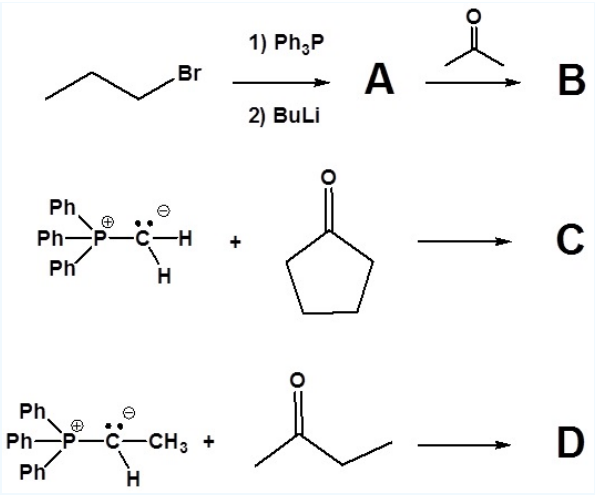
LIMITATION OF THE WITTIG REACTION

If possible both E and Z isomer of the double bond will be formed. This should be considered when planning a synthesis involving a Wittig Reaction.

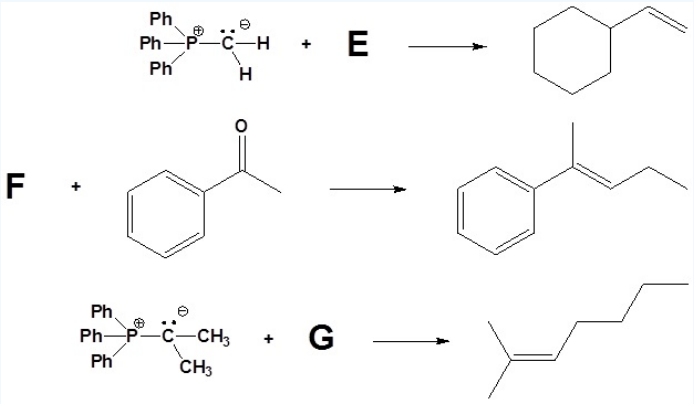


Exercise

20. Draw the products of the following reactions.



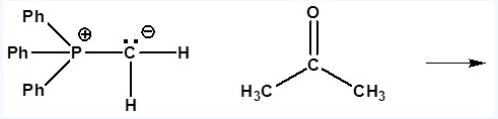
21. Please indicate the starting material required to produce the product.



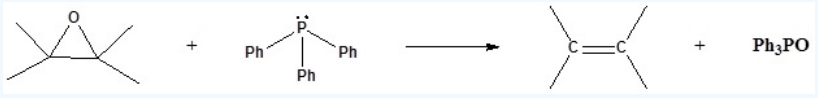
22. Draw the structure of the oxaphosphetane which is made during the mechanism of the reaction given that produces product **C**.

23. Draw the structure of the betaine which is made during the mechanism of the reaction given that produces product **D**.

24. Propose a detailed mechanism and the final product of this reaction

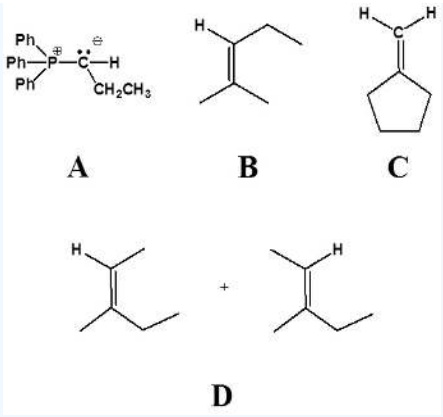


25. It has been shown that reacting and epoxide with triphenylphosphine forms an alkene. Propose a mechanism for this reaction. Review the section on epoxide reactions if you need help.

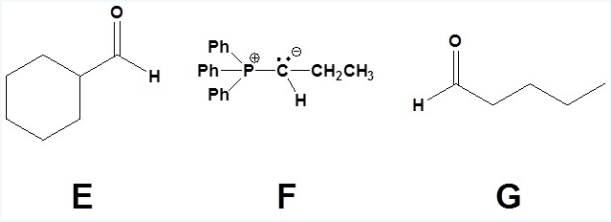


Answer

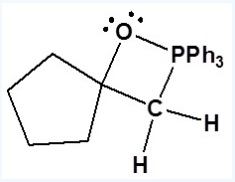
20.



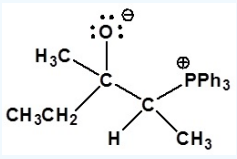
21.



22.

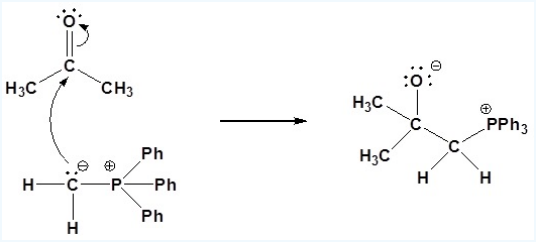


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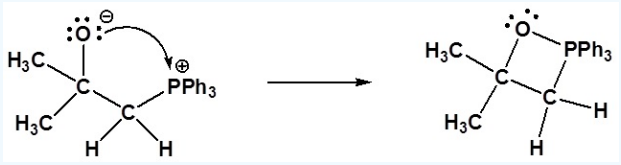


24.

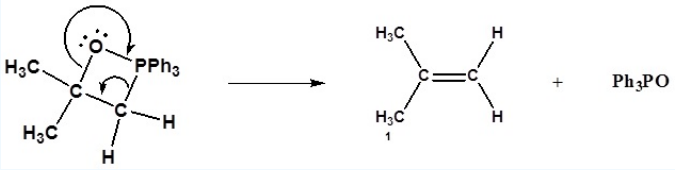
Nucleophillic reaction with the carbonyl



Formation of a 4 membered ring

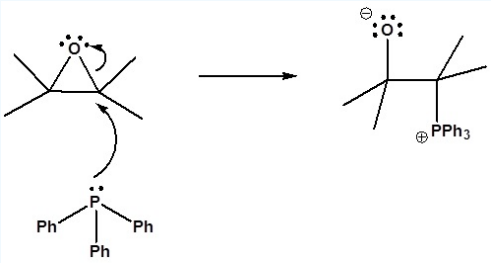


Formation of the alkene

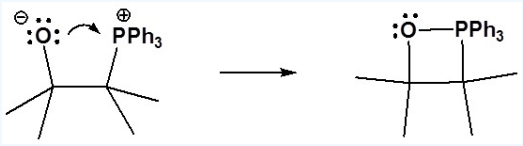


25.

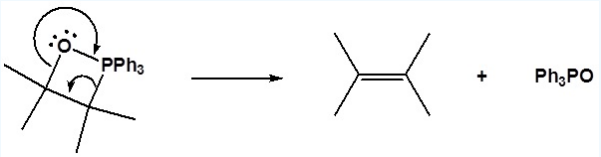
Nucleophillic reaction with the epoxide



Formation of a 4 membered ring



Formation of the alkene



CONTRIBUTORS AND ATTRIBUTIONS

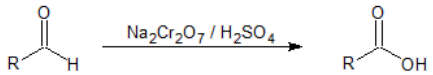
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

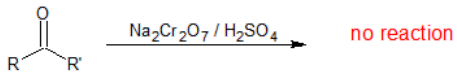
19.13: Nucelophilic Addition of Phosphorus Ylides (The Wittig Reaction) is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

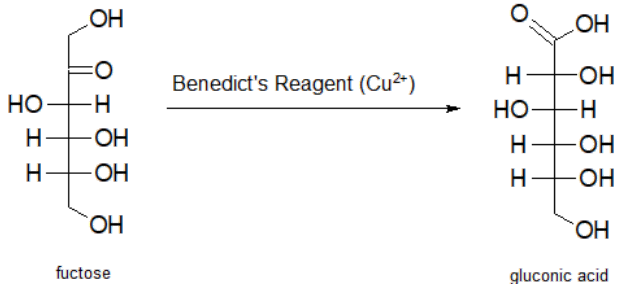
19.14: OXIDATION OF ALDEHYDES

OXIDATION AND CARBONYLS

Aldehydes are so easily oxidized that oxidation reactions can be an unwanted side reaction. Isolated ketones cannot be oxidized. The poly-hydroxy ketones of monosaccharides can be oxidized as seen in carbohydrate chemistry.

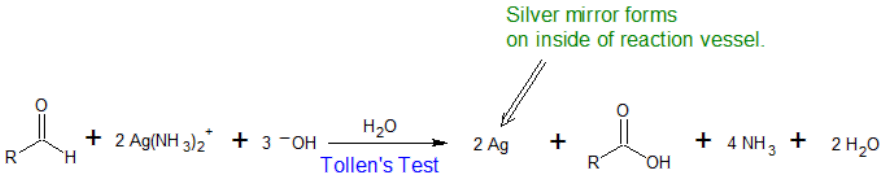


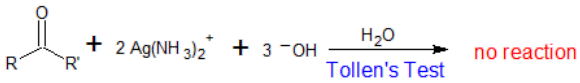




Tollen's Test

The Tollen's Test differentiates between aldehydes and ketones based on one of their few differences in chemical reactivity. Aldehydes can be oxidized and ketones cannot. In the Tollen's Test, silver ions (Ag^+) oxidize aldehydes to carboxylic acids and are reduces to silver metals which can form a beautiful coating on the inside of the reaction flask.





Exercise

26. Draw and name the oxidation products for the following compounds.

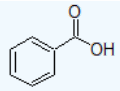
a) benzaldehyde

b) acetaldehyde

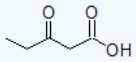
c) 3-hydroxypentanal

Answer

26.

a)  benzoic acid

b)  acetic acid

c)  3-oxopentanoic acid

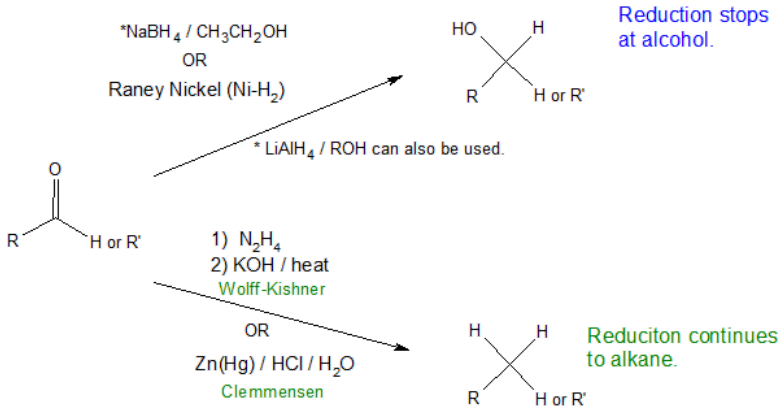
CONTRIBUTORS AND ATTRIBUTIONS

19.14: Oxidation of Aldehydes is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

19.15: REDUCTIONS OF KETONES AND ALDEHYDES

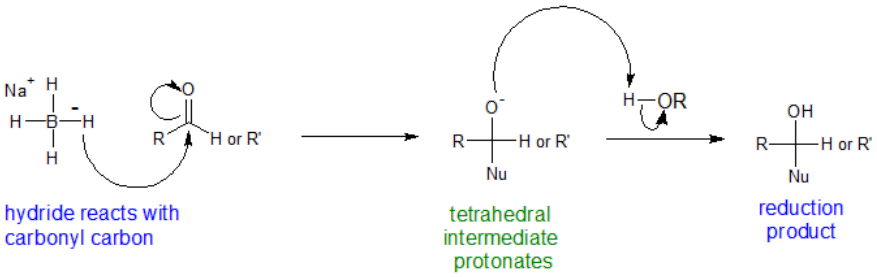
CARBONYL REDUCTION REACTIONS

Aldehydes and ketones can be partially reduced to alcohols with sodium borohydride or Raney nickel. Of course, $LiAlH_4$ could be used in stead of $NaBH_4$. However, $LiAlH_4$ is a stronger reducing agent so some benefits of selectivity are lost. Depending on the presence of more than one functional group within a single molecule, reaction selectivity can be useful. Aldehydes and ketones can be fully reduced to alkanes the Wolff-Kishner or Clemmensen Reduction.



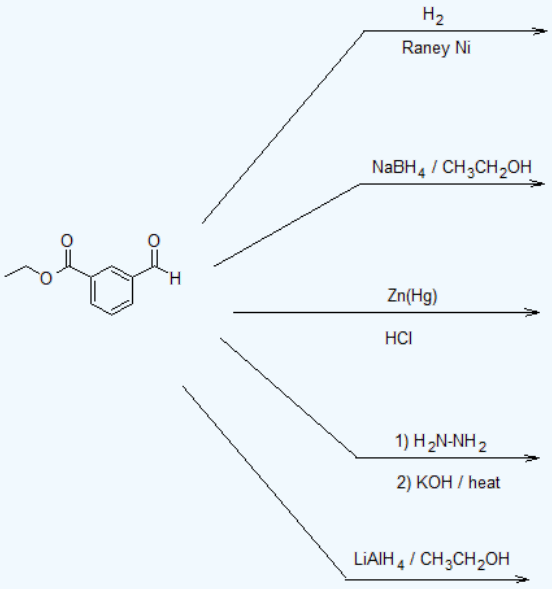
HYDRIDE REDUCTION MECHANISM

The hydride reduction mechanism follows the pattern we have learned for other nucleophilic addition reactions.



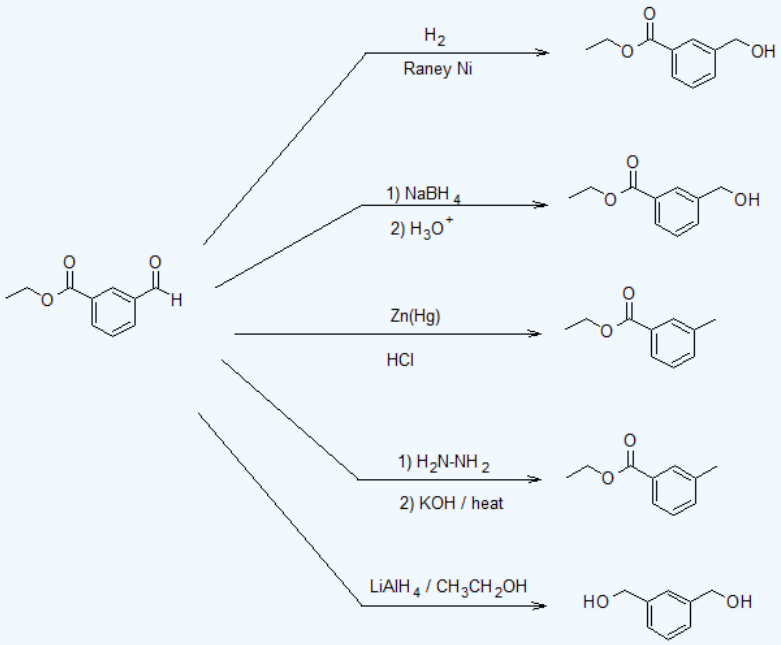
Exercise

27. Complete the reaction map below.



Answer

27.



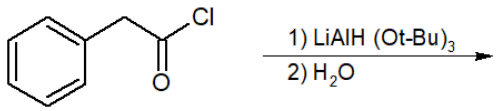
CONTRIBUTORS AND ATTRIBUTIONS

19.15: Reductions of Ketones and Aldehydes is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

19.16: ADDITIONAL EXERCISES

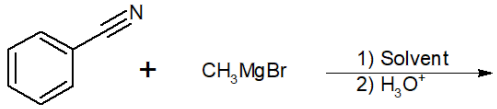
General Review

19-1 Give the product of the following reaction.

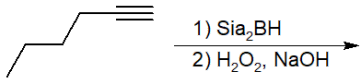


19-2 For each of the following reactions, give the final product.

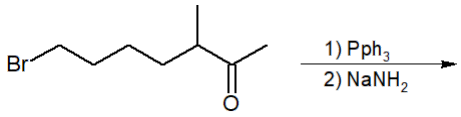
a)



b)

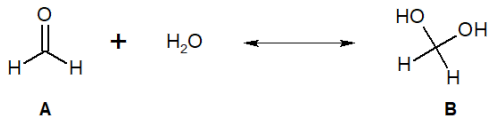


19-3 For the following reaction, give the final product.



19-4 For the following reactions, identify the side favored at equilibrium.

1)



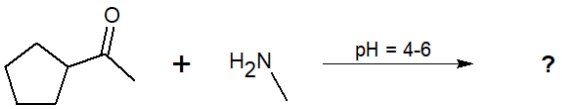
A **B**

2)

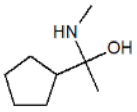


A **B**

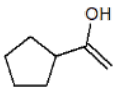
19-5 Identify the correct product of the following reaction.



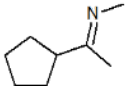
a)



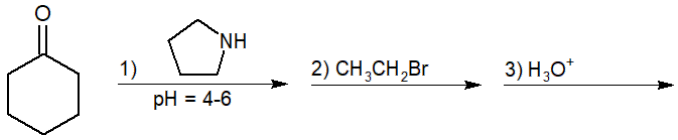
b)



c)

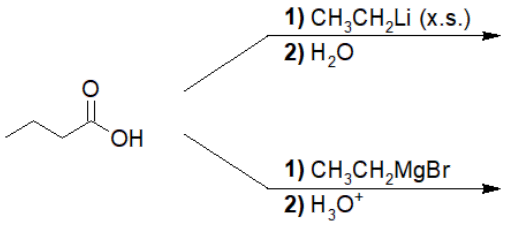


19-6 Give the final product of the following chain of reactions.

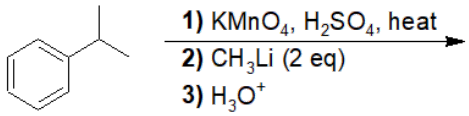


Synthesis of Ketones from Carboxylic Acids

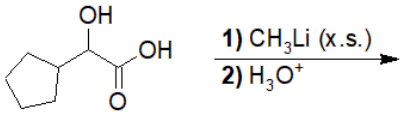
19-7 Provide the structures of the products of the following reactions.



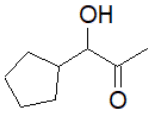
19-8 Provide the structure and IUPAC nomenclature of the product of the following reaction.



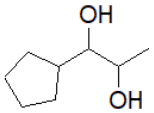
19-9 Choose the correct answer.



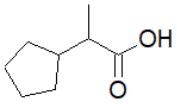
a)



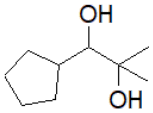
b)



c)



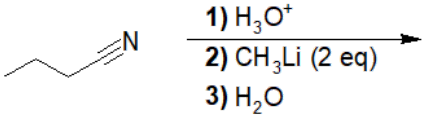
d)



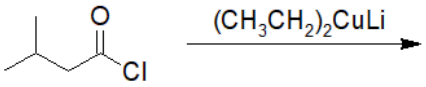
Synthesis of Ketones and Aldehydes from Acid Chlorides, Esters, and Nitriles

19-10 Provide the structures of the products of the following reactions.

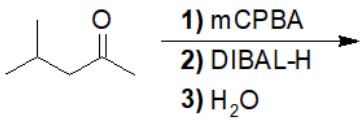
a)



b)



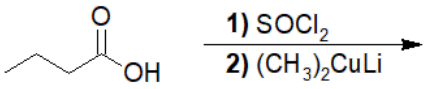
19-11 Choose the correct product of the following reaction.



a) b) c) d)



19-12 Choose the correct IUPAC nomenclature of the product of the following reaction.



a) butanal

b) 2-methylhexan-3-one

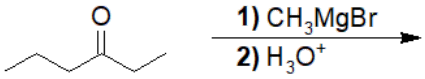
c) pentan-2-one

d) 2-methylpentan-2-ol

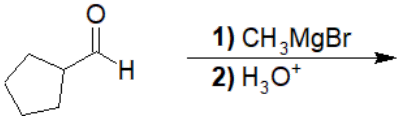
Reactions of Ketones and Aldehydes

19-13 Provide the products of the following reactions.

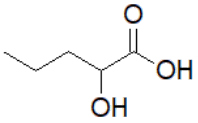
a)



b)

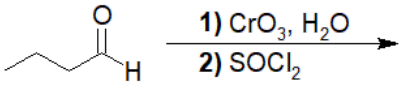


19-14 Suggest a way to make the following compound from butanol. Use any necessary reagents.



2-hydroxypentanoic acid

19-15 Choose the correct product of the following reaction.



a) 2-chloropentane

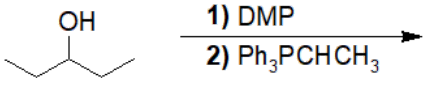
b) 1-chlorobutan-1-ol

c) 2-chlorobutanoic acid

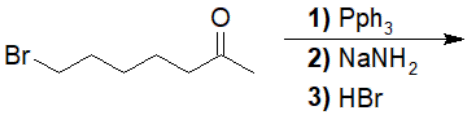
d) butanoyl chloride

The Wittig Reaction

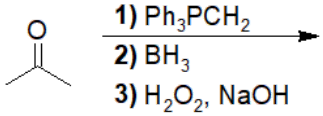
19-16 Predict the structure of the product of the following reaction.



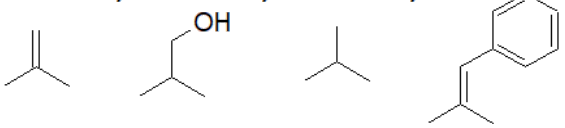
19-17 Provide the product of the following reaction.



19-18 Choose the correct product of the following reaction.

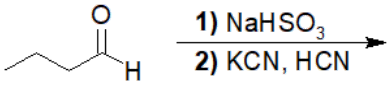


a) **b)** **c)** **d)**

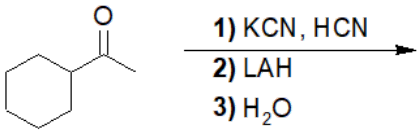


Formation of Cyanohydrins

19-19 Predict the structure of the product of the following reaction.



19-20 Provide the structure of the product of the following reaction.



19-21 Choose the correct IUPAC nomenclature of the product of the following reaction.



a) 3-ethylhex-1-yn-3-ol

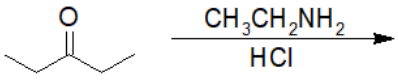
b) 2-ethyl-2-hydroxypentanenitrile

c) 3-(aminomethyl)hexan-3-ol

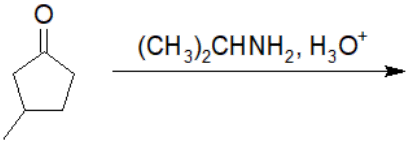
d) butanoyl cyanide

Formation of Imines

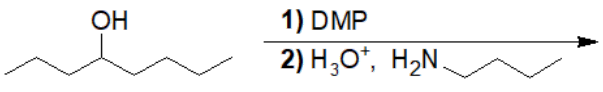
19-22 Predict the product of the following reaction.



19-23 Provide the structure of the product of the following reaction.



19-24 Choose the correct IUPAC nomenclature of the product of the following reaction.



a) (4Z)-N-butyloctan-4-imine

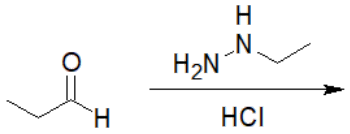
b) (4Z)-N-propyloctan-4-imine

c) (4Z)-5-propylnon-4-en-1-amine

d) 4-(butylamino)octan-4-ol

Condensations with Hydroxylamine and Hydrazines

19-25 Choose the correct IUPAC nomenclature of the product of the following reaction.



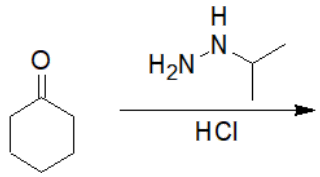
a) 1-ethyl-2-propylhydrazine

b) N-propoxyethanamine

c) (1E)-N-ethylbut-1-en-1-amine

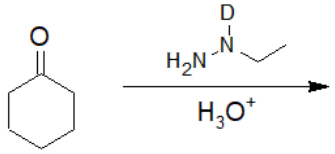
d) (2E)-1-ethyl-2-propylidenehydrazine

19-26 Provide the structure of the product of the following reaction.

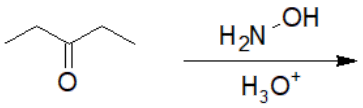


19-27 Provide the structure of the products of the following reactions.

a)

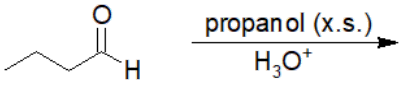


b)

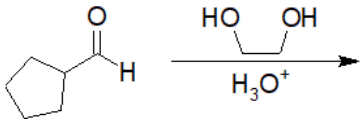


Formation and Use of Acetals

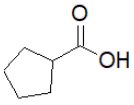
19-28 Provide the structure of the resulting acetal.



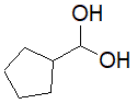
19-29 Choose the correct structure of the product of the following reaction.



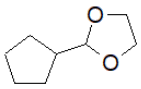
a)



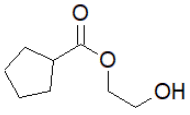
b)



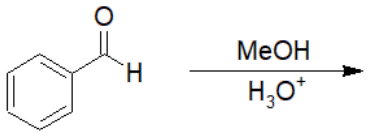
c)



d)



19-30 Choose the correct IUPAC nomenclature of the product of the following reaction.



a) (dimethoxymethyl)benzene

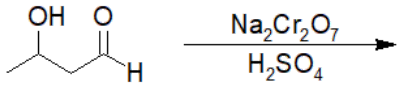
b) benzoic acid

c) phenylmethanediol

d) (methoxymethyl)benzene

Oxidation of Aldehydes and Reductions of Ketones and Aldehydes

19-31 Draw the structure of the product of the following oxidation reaction.

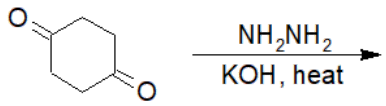


19-32 Draw the structures of the products of the following reduction reactions.

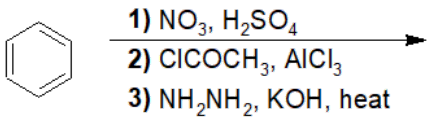
a)



b)



19-33 Predict the product of the following reaction and provide its IUPAC nomenclature.

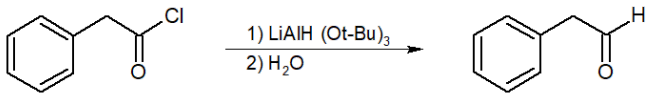


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19.17: SOLUTIONS TO ADDITIONAL EXERCISES

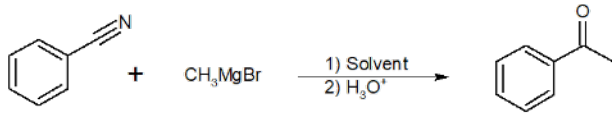
General Review

19-1

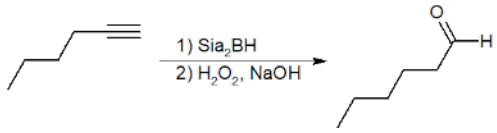


19-2

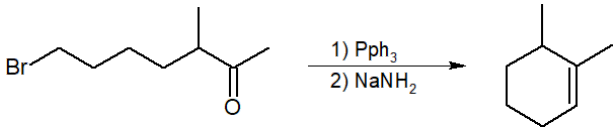
a)



b)



19-3

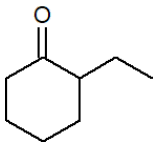


19-4

1. B
2. A

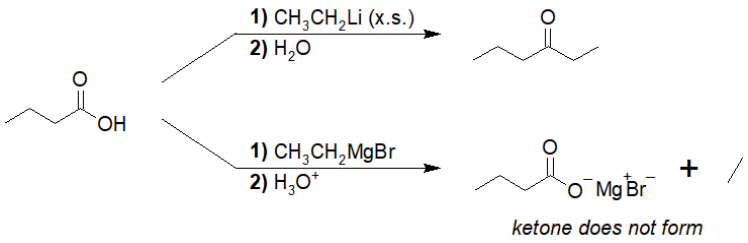
19-5 Answer: C

19-6

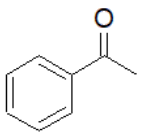


Synthesis of Ketones from Carboxylic Acids

19-7:



19-8:



1-phenylethan-1-one

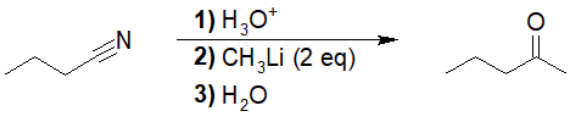
19-9:

Answer: A

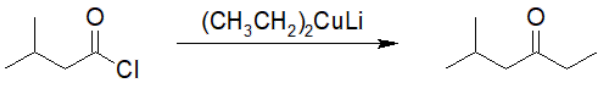
Synthesis of Ketones and Aldehydes from Acid Chlorides, Esters, and Nitriles

19-10:

a)



b)



19-11:

Answer: A

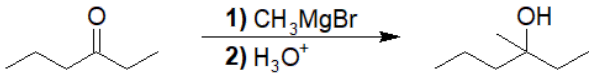
19-12:

Answer: C

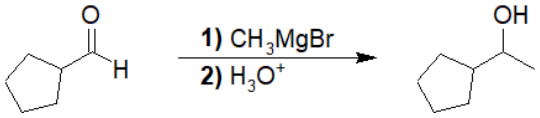
Reactions of Ketones and Aldehydes

19-13:

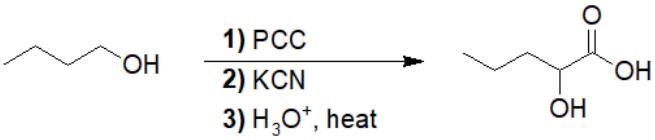
a)



b)



19-14:

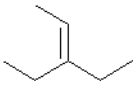


19-15:

Answer: D

The Wittig Reaction

19-16:



19-17:

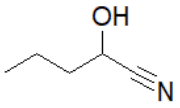


19-18:

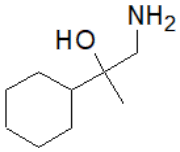
Answer: B

Formation of Cyanohydrins

19-19:



19-20:

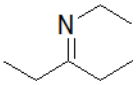


19-21:

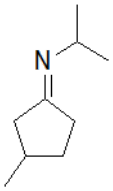
Answer: B

Formation of Imines

19-22:



19-23:



19-24:

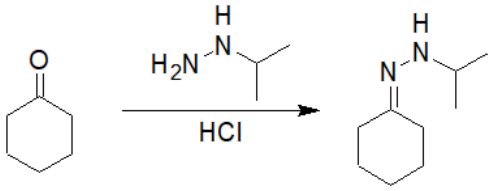
Answer: A

Condensations with Hydroxylamine and Hydrazines

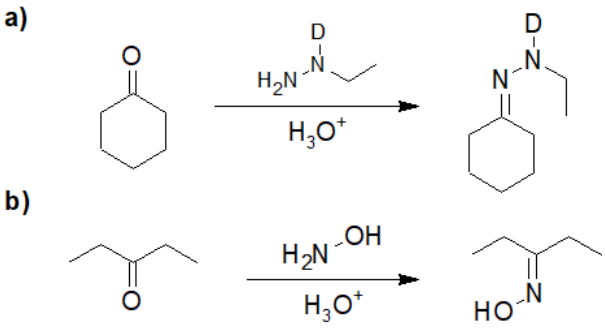
19-25:

Answer: D

18-26:

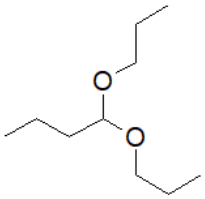


19-27:



Formation and Use of Acetals

19-28:



19-29:

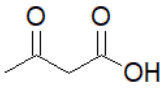
Answer: C

19-30:

Answer: A

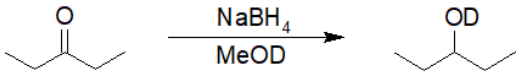
Oxidation of Aldehydes and Reductions of Ketones and Aldehydes

19-31:

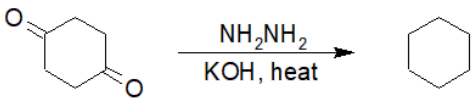


19-32:

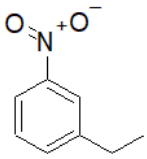
a)



b)



19-33:



1-ethyl-3-nitrobenzene

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CHAPTER OVERVIEW

20: AMINES

After reading this chapter and completing ALL the exercises, a student can be able to

- describe the structure and physical properties of amines and ammonium salts (section 20.1)
- explain and predict the relative basicity of amines using resonance, hybridization, substituent effects, and aromaticity (section 20.2)
- determine the structure of amines from their elemental analysis and spectral data (MS, IR ^{1}H NMR & ^{13}C NMR) (section 20.3)
- predict the products and specify the reagents to synthesize amines (section 20.4)
- predict the products and specify the reagents to synthesize primary amines (section 20.5)
- predict the products and specify the reagents for reactions of amines with
  - aldehydes & ketones (section 20.6)
  - alkyl halides and tosylates (section 20.6)
  - acyl chlorides (section 20.6)
  - sulfonyl chlorides (section 20.6)
  - nitrous acid (section 20.7)
  - oxidizing agents via Cope Elimination (section 20.9)
- explain the activating effects of aryl amines during electrophilic aromatic substitution reactions (section 20.7)
- use amides as protecting groups in multiple step synthesis (section 20.7)
- use diazonium salts to design multiple step syntheses using the Sandmeyer reactions (section 20.7)
- specify the reagents and predict the products for Hofmann Elimination reactions (section 20.8)
- Specify reagents for chemical transformations using all of the reactions studied to date
- combine the reactions studied to date to develop efficient and effective multiple-step synthesis including the use of amides as protecting groups

Please note: IUPAC nomenclature and important common names of amines were explained in Chapter 3.

20.1: Structure and Physical Properties of Amines

20.2: Basicity of Amines and Ammonium Salt Formation

20.3: Spectroscopy of Amines

20.4: Synthesis of Amines

20.5: Synthesis of Primary Amines

20.6: Reactions of Amines

20.7: Reactions of Arylamines

20.8: The Hofmann Elimination- Amines as Leaving Groups

20.9: Oxidation of Amines - The Cope Elimination

20.10: Sulfa Drugs - a closer look

20.11: Additional Exercises

20.12: Solutions to Additional Exercises

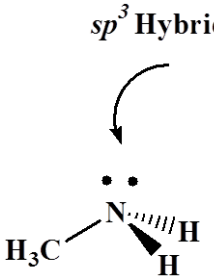
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20.1: STRUCTURE AND PHYSICAL PROPERTIES OF AMINES

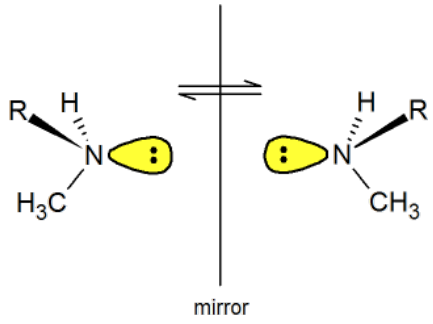
STRUCTURE

Amines typically have three bonds and one pair of lone pair electrons. This makes the nitrogen sp^3 hybridized, trigonal pyramidal, with a bond angle of roughly 109.5º.

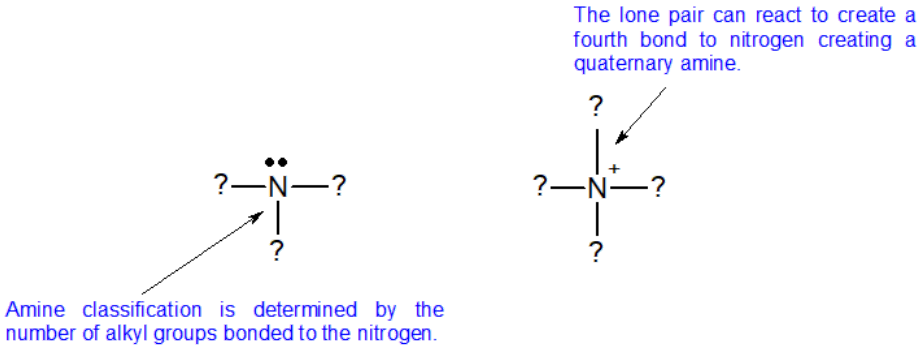


STEREOCHEMISTRY

Single-bonded nitrogen is pyramidal in shape, with the non-bonding electron pair pointing to the unoccupied corner of a tetrahedral region. Since the nitrogen in these compounds is bonded to three different groups, it is stereogenic and its configuration is chiral. The non-identical mirror-image configurations are illustrated in the following diagram (the remainder of the molecule is represented by *R*, and the electron pair is colored yellow). If these configurations were stable, there would be four additional stereoisomers of ephedrine and pseudoephedrine. However, pyramidal nitrogen is normally not configurationally stable. It rapidly inverts its configuration (equilibrium arrows) by passing through a planar, sp^2-hybridized transition state, leading to a mixture of interconverting *R* and *S* configurations. If the nitrogen atom were the only chiral center in the molecule, a 50:50 (racemic) mixture of *R* and *S* configurations would exist at equilibrium. If other chiral centers are present, as in the ephedrin isomers, a mixture of diastereomers will result. The take-home message is that nitrogen does not contribute to isolable stereoisomers.

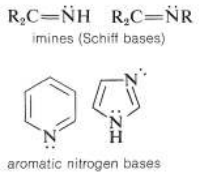


Amines are classified according to the number of alkyl or aryl groups attached to nitrogen. Amines are classified differently from alkyl halides and alcohols because nitrogen has a neutral bonding pattern of three bonds with a single lone pair. To classify amines, we look at the nitrogen atom of the amine and count the number of alkyl groups bonded to it. This number is the classification of the amine.



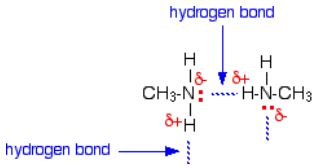


There are two additional classifications of amines. When the nitrogen is double bonded to carbon, then it is call am imine. When nitrogen is part of a ring that includes double bonds, then it is classified as heterocyclic, as seen in the aromatic nitrogen bases shown below.



BOILING POINT AND WATER SOLUBILITY

It is instructive to compare the boiling points and water solubility of amines with those of corresponding alcohols and ethers. The dominant factor here is hydrogen bonding, and the first table below documents the powerful intermolecular attraction that results from -O-H---O- hydrogen bonding in alcohols (light blue columns). Corresponding -N-H---N- hydrogen bonding is weaker, as the lower boiling points of similarly sized amines (light green columns) demonstrate. Alkanes provide reference compounds in which hydrogen bonding is not possible, and the increase in boiling point for equivalent 1º-amines is roughly half the increase observed for equivalent alcohols.



Compound	CH_3CH_3	CH_3OH	CH_3NH_2	$CH_3CH_2CH_3$	CH_3CH_2OH	$CH_3CH_2NH_2$
Mol.Wt.	30	32	31	44	46	45
Boiling Point ºC	-88.6º	65º	-6.0º	-42º	78.5º	16.6º

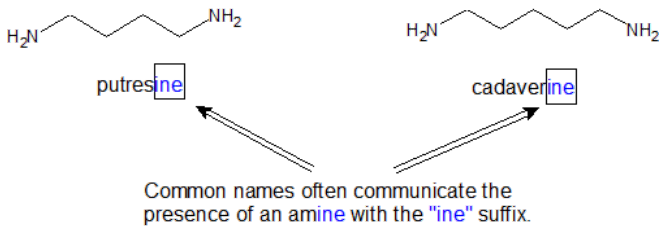
The second table illustrates differences associated with isomeric 1º, 2º & 3º-amines, as well as the influence of chain branching. Since 1º-amines have two hydrogens available for hydrogen bonding, we expect them to have higher boiling points than isomeric 2º-amines, which in turn should boil higher than isomeric 3º-amines (no hydrogen bonding). Indeed, 3º-amines have boiling points similar to equivalent sized ethers; and in all but the smallest compounds, corresponding ethers, 3º-amines and alkanes have similar boiling points. In the examples shown here, it is further demonstrated that chain branching reduces boiling points by 10 to 15 ºC.

Compound	$CH_3(CH_2)_2CH_3$	$CH_3(CH_2)_2OH$	$CH_3(CH_2)_2NH_2$	$CH_3CH_2NHCH_3$	$(CH_3)_3CH$	$(CH_3)_2CHOH$	$(CH_3)_2CHNH_2$	$(CH_3)_3N$
Mol.Wt.	58	60	59	59	58	60	59	59
Boiling Point ºC	-0.5º	97º	48º	37º	-12º	82º	34º	3º

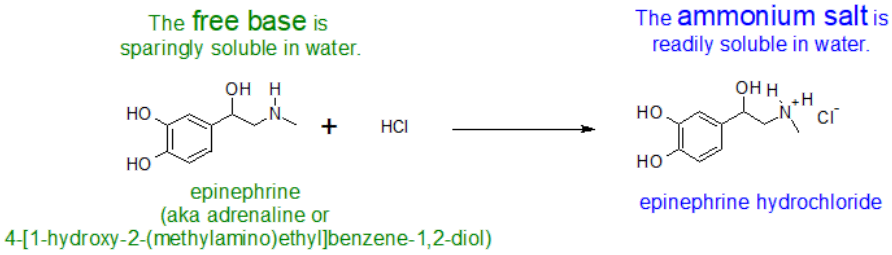
The water solubility of 1º and 2º-amines is similar to that of comparable alcohols. As expected, the water solubility of 3º-amines and ethers is also similar. These comparisons, however, are valid only for pure compounds in neutral water. The basicity of amines (next section) allows them to be dissolved in dilute mineral acid solutions, and this property facilitates their separation from neutral compounds such as alcohols and hydrocarbons by partitioning between the phases of non-miscible solvents.

ODOR

The free base form of amines can be quite odiferous. The foul smell of dying flesh is primarily from the amines released during decomposition of the proteins in an organism. The common names for the amines below emphasize this aspect of amines. It is also useful to note that common names frequently indicate the presence of an amine with the "ine" suffix.



The smell of amines can be reduced by reacting them with strong acids to form the ammonium salts. For example, the acid from lemons can be used to disguise the smell of fish that is past optimum freshness. While the free base forms of amines can be thermally unstable and smelly, the ammonium salt formed from the conjugate acid of the amine have increased thermal stability and reduced odor. If the amine is not soluble as a free base, its ammonium salt will be water soluble.

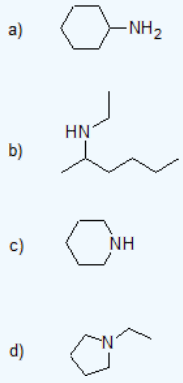


Exercise

1. Draw the structures for the following amines in order of decreasing water solubility: methanamine, 2-octanamine, 2-butanamine.

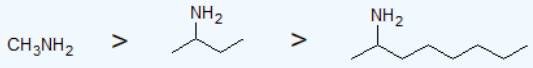
2. Draw the for the following amines in order of decreasing boiling point: cyclohexanamine, 2-octanamine, 2-butanamine.

3. Classify the following amines.

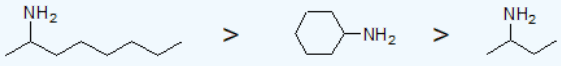


Answer

1.



2.



3. a) primary b) secondary c) secondary d) tertiary

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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20.2: BASICITY OF AMINES AND AMMONIUM SALT FORMATION

BASICITY OF NITROGEN GROUPS

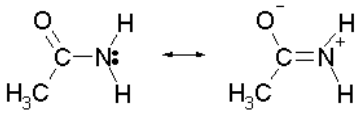
When evaluating the relative basicity of several nitrogen-containing functional groups: amines, amides, anilines, imines, and nitriles, the central question is: how reactive (and thus how basic) is the lone pair on the nitrogen? In other words, how much does that lone pair want to break away from the nitrogen nucleus and form a new bond with a hydrogen?

COMPARING THE BASICITY OF ALKYL AMINES TO AMMONIA

Alkyl groups donate electrons to the more electronegative nitrogen. This inductive effect makes the electron density on the alkylamine's nitrogen greater than the nitrogen of ammonium. Correspondingly, primary, secondary, and tertiary alkyl amines are more basic than ammonia. Inductive effects are also moderated by the increased steric hindrance of alkyl groups (R grps).

COMPARING THE BASICITY OF ALKYLAMINES TO AMIDES

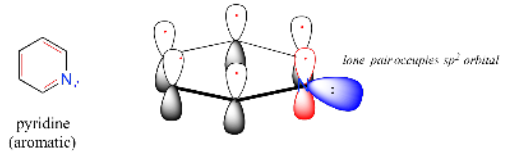
With an alkyl amine the lone pair electron is localized on the nitrogen. However, the lone pair electron on an amide are delocalized between the nitrogen and the oxygen through resonance. This makes amides much less basic compared to alkylamines.

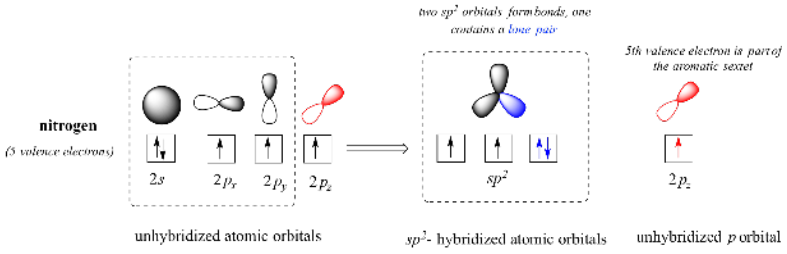


When an amide reacts with an acid, the protonation occurs at the carbonyl oxygen and not the nitrogen. The cation resulting from oxygen protonation is resonance stabilized., while the cation resulting for the protonation of nitrogen is not resonance stabilized.

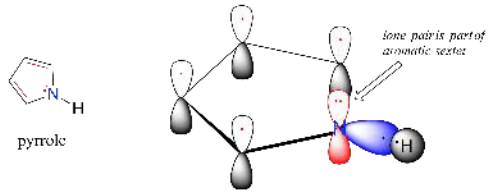
BASICITY OF HETEROCYCLIC AMINES

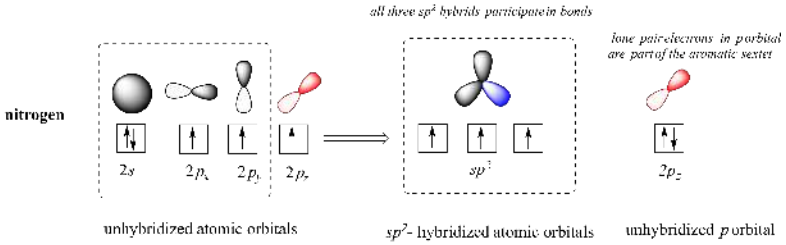
When a nitrogen atom is incorporated directly into an aromatic ring, its basicity depends on the bonding context. In a pyridine ring, for example, the nitrogen lone pair occupies an sp^2-hybrid orbital, and is *not* part of the aromatic sextet - it is essentially an imine nitrogen. Its electron pair is available for forming a bond to a proton, and thus the pyridine nitrogen atom is somewhat basic.



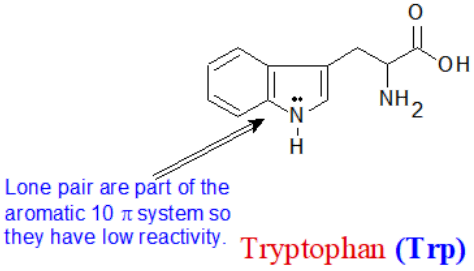


In a pyrrole ring, in contrast, the nitrogen lone pair *is* part of the aromatic sextet. This means that these electrons are very stable right where they are (in the aromatic system), and are much less available for bonding to a proton (and if they *do* pick up a proton, the aromic system is destroyed). For these reasons, pyrrole nitrogens are not strongly basic.





The aniline, pyridine, and pyrrole examples are good models for predicting the reactivity of nitrogen atoms in more complex ring systems (a huge diversity of which are found in nature). The tryptophan side chain, for example, contains a non-basic 'pyrrole-like' nitrogen, while adenine (a DNA/RNA base) contains all three types.



The lone pair electrons on the nitrogen of a **nitrile** are contained in a *sp* hybrid orbital. The 50% *s* character of an *sp* hybrid orbital means that the electrons are close to the nucleus and therefore not significantly basic.

BASE STRENGTH AND PKA VALUES

Like ammonia, most amines are Brønsted and Lewis bases, but their base strength can be changed enormously by substituents. It is common to compare basicity's quantitatively by using the pK_a's of their conjugate acids rather than their pK_b's. Since $pK_a + pK_b = 14$, **the higher the pK_a the stronger the base**, in contrast to the usual inverse relationship of pK_a with acidity. Most simple alkyl amines have pK_a's in the range 9.5 to 11.0, and their water solutions are basic (have a pH of 11 to 12, depending on concentration).

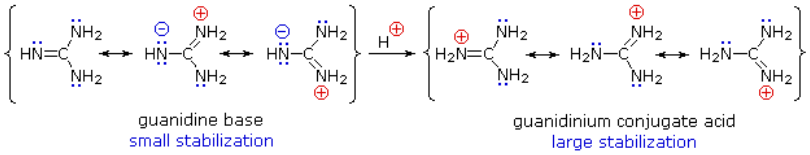
Compound		NH_3	pyridine	aniline	4-nitroaniline	pyrrole		$CH_3C{\equiv}N$ acetonitrile
pK_a	11.0 10.7 10.7	9.3	5.2	4.6	1.0	0.0	-1.0	-10.

The first four compounds in the table above are all weak bases. The last five compounds are significantly less basic to neutral and even acidic as a consequence of two possible factors:

- orbital hybridization
- electron delocalization through resonance.

In pyridine, the nitrogen is sp^2 hybridized, and in nitriles (last entry) an sp hybrid nitrogen is part of the triple bond. In each of these compounds, the non-bonding electron pair is localized on the nitrogen atom, but increasing s-character brings it closer to the nitrogen nucleus, reducing its tendency to bond to a proton. For aniline and 4-nitroaniline, the nitrogen lone pair is stabilized through hyperconjugation with the aromatic ring. Pyrrole exhibits exceptional delocalization of the nitrogen electron pair because of its incorporation into the aromatic ring.

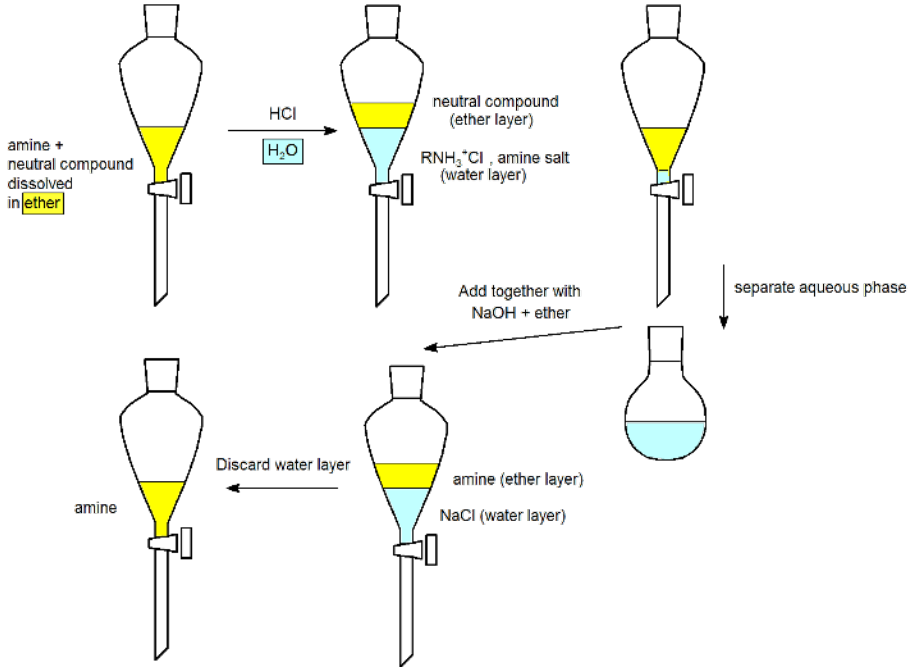
Although resonance delocalization generally reduces the basicity of amines, a dramatic example of the reverse effect is found in the compound guanidine (pK_a = 13.6). Here, as shown below, resonance stabilization of the base is small, due to charge separation, while the conjugate acid is stabilized strongly by charge delocalization. Consequently, aqueous solutions of guanidine are nearly as basic as are solutions of sodium hydroxide.



> *Strong bases have weak conjugate acids, and weak bases have strong conjugate acids.*

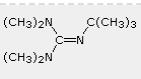
AMINE EXTRACTION IN THE LABORATORY

Extraction is often employed in organic chemistry to purify compounds. Liquid-liquid extractions take advantage of the difference in solubility of a substance in two immiscible liquids (e.g. ether and water). The two immiscible liquids used in an extraction process are (1) the solvent in which the solids are dissolved, and (2) the extracting solvent. The two immiscible liquids are then easily separated using a separatory funnel. For amines one can take advantage of their basicity by forming the protonated salt ($RNH_2^+Cl^-$), which is soluble in water. The salt will extract into the aqueous phase leaving behind neutral compounds in the non-aqueous phase. The aqueous layer is then treated with a base (NaOH) to regenerate the amine and NaCl. A second extraction-separation is then done to isolate the amine in the non-aqueous layer and leave behind NaCl in the aqueous layer.



IMPORTANT REAGENT BASES

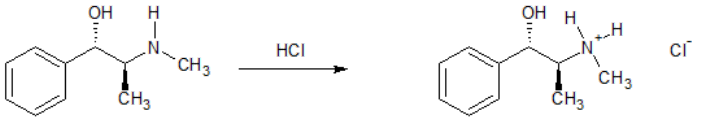
The significance of all these acid-base relationships to practical organic chemistry lies in the need for organic bases of varying strength, as reagents tailored to the requirements of specific reactions. The common base sodium hydroxide is not soluble in many organic solvents, and is therefore not widely used as a reagent in organic reactions. Most base reagents are alkoxide salts, amines or amide salts. Since alcohols are much stronger acids than amines, their conjugate bases are weaker than amide bases, and fill the gap in base strength between amines and amide salts. In the following table, pK_a again refers to the conjugate acid of the base drawn above it.

Base Name	Pyridine	Triethyl Amine	Hünig's Base	Barton's Base	Potassium t-Butoxide	Sodium HMDS	LDA
Formula		$(C_2H_5)_3N$			$(CH_3)_3CO^{(-)}\ K^{(+)}$	$[(CH_3)_3Si]_2N^{(-)}\ Na^{(+)}$	$[(CH_3)_2CH]_2N^{(-)}\ Li^{(+)}$
pK_a	5.3	10.7	11.4	14	19	26	35.7

Pyridine is commonly used as an acid scavenger in reactions that produce mineral acid co-products. Its basicity and nucleophilicity may be modified by steric hindrance, as in the case of 2,6-dimethylpyridine (pK_a=6.7), or resonance stabilization, as in the case of 4-dimethylaminopyridine (pK_a=9.7). Hünig's base is relatively non-nucleophilic (due to steric hindrance), and like DBU is often used as the base in E2 elimination reactions conducted in non-polar solvents. Barton's base is a strong, poorly-nucleophilic, neutral base that serves in cases where electrophilic substitution of DBU or other amine bases is a problem. The alkoxides are stronger bases that are often used in the corresponding alcohol as solvent, or for greater reactivity in DMSO. Finally, the two amide bases see widespread use in generating enolate bases from carbonyl compounds and other weak carbon acids.

AMMONIUM SALT FORMATION AND WATER SOLUBILITY

Many pharmaceuticals include amine functional groups. Sometimes the basicity of these amine groups is used to increase the water solubility of a drug so that it can be administered orally or intravenously. Ammonium salts are also thermally more stable and have less odor than their "free base" conjugates. The antihistamine, pseudoephedrine, reacts with hydrochloric acid to form the water soluble ammonium salt as shown below.



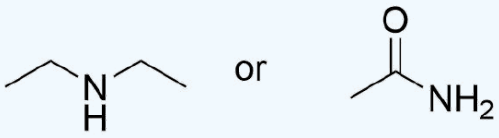
pseudoephedrine
H_2O solubility: 7 mg/L

pseudoephedrine hydrochloride
H_2O solubility: 1.06 x 10^5 mg/L
over 15,000 x more water soluble

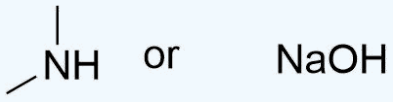
Exercise

4. Select the more basic compound from each of the following pairs of compounds.

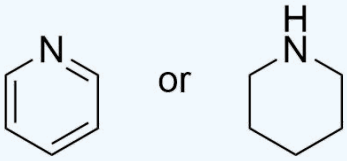
(a)



(b)

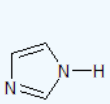


(c)

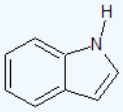


5. The 4-methylbenzylammonium ion has a pKa of 9.51, and the butylammonium ion has a pKa of 10.59. Which is more basic? What's the pKb for each compound?

6. The structures for indole and imidazole are shown below. One compound has a pKa of -2 while the other compound has a pKa of 7. Assign the pKa values to the corresponding compound and explain your reasoning.



imidazole

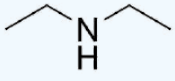


indole

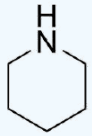
Answer

4.

(a)



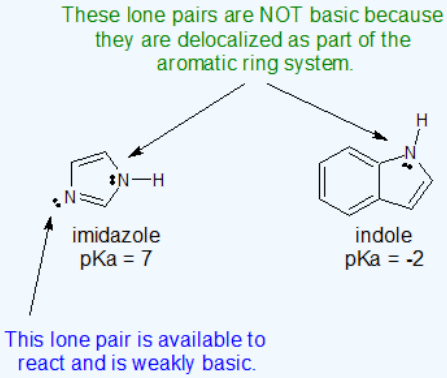
(b) NaOH



(c)

5. The butylammonium is more basic. The pKb for butylammonium is 3.41, the pKb for 4-methylbenzylammonium is 4.49.

6.



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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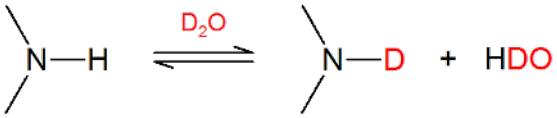
20.3: SPECTROSCOPY OF AMINES

NMR

The hydrogens attached to an amine show up ~ 0.5-5.0 ppm. The location is dependent on the amount of hydrogen bonding and the sample's concentration.

The hydrogens on carbons directly bonded to an amine typically appear ~2.3-3.0 ppm.

Addition of D_2O will normally cause all hydrogens on non-carbon atoms to exchange with deuteriums, thus making these resonances "disappear." Addition of a few drops of D_2O causing a signal to vanish can help confirm the presence of -NH.



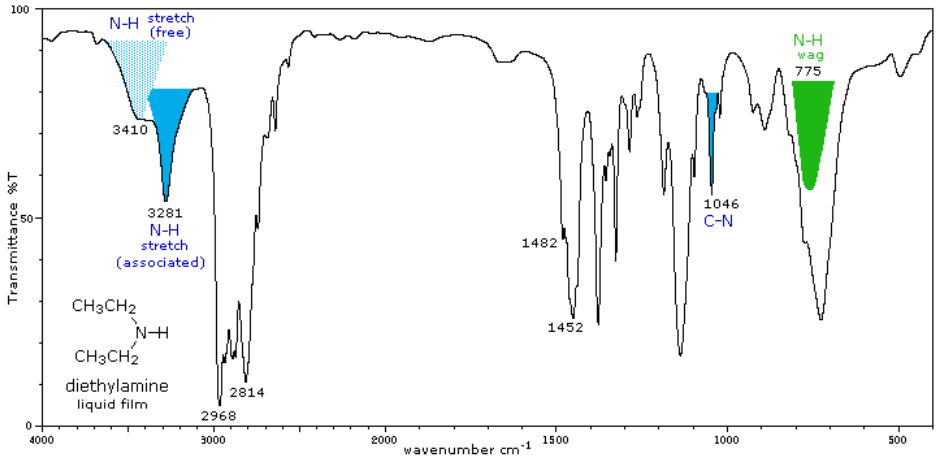
IR

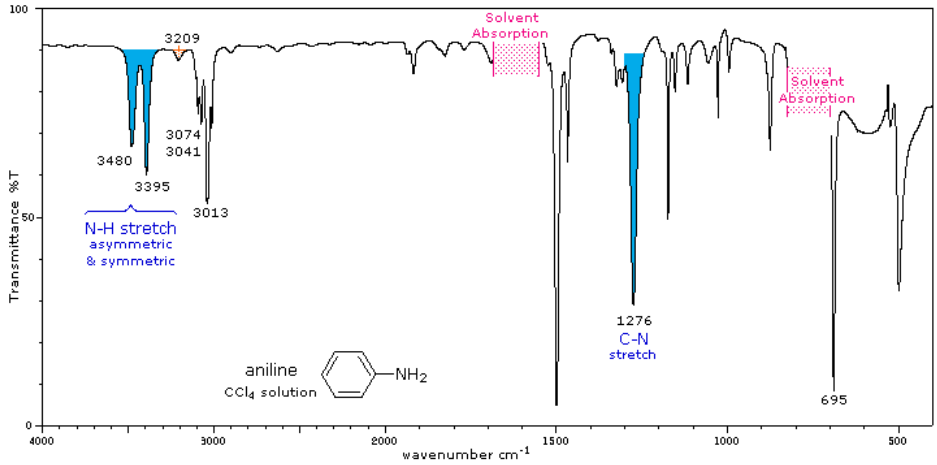
The infrared spectrum of aniline is shown beneath the following table. Some of the characteristic absorptions for C-H stretching and aromatic ring substitution are also marked, but not colored.

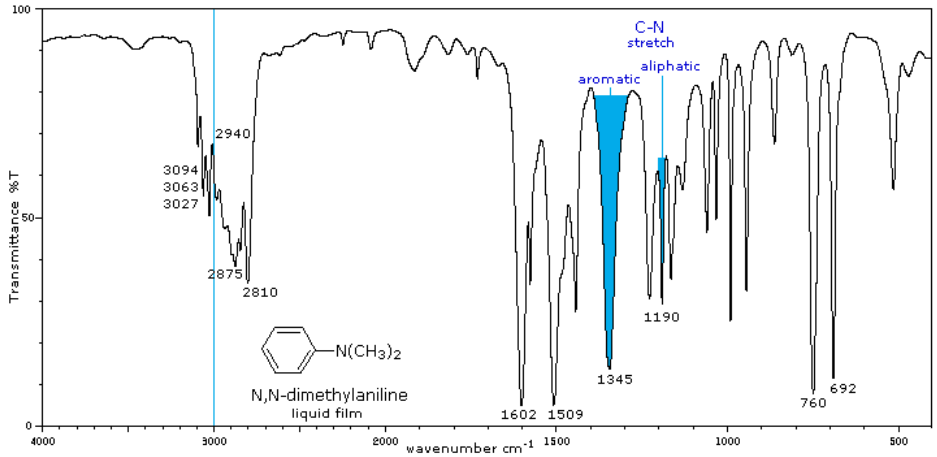
Amine Class	Stretching Vibrations	Bending Vibrations
Primary (1°)	The N-H stretching absorption is less sensitive to hydrogen bonding than are O-H absorptions. In the gas phase and in dilute CCl_4 solution free N-H absorption is observed in the 3400 to 3500 cm^{-1} region. Primary aliphatic amines display two well-defined peaks due to asymmetric (higher frequency) and symmetric N-H stretching, separated by 80 to 100 cm^{-1}. In aromatic amines these absorptions are usually 40 to 70 cm^{-1} higher in frequency. A smaller absorption near 3200 cm^{-1} (shaded orange in the spectra) is considered to be the result of interaction between an overtone of the 1600 cm^{-1} band with the symmetric N-H	Strong in-plane NH_2 scissoring absorptions at 1550 to 1650 cm^{-1}, and out-of-plane wagging at 650 to 900 cm^{-1} (usually broad) are characteristic of 1°-amines.

	stretching band. C-N stretching absorptions are found at 1200 to 1350 cm^{-1} for aromatic amines, and at 1000 to 1250 cm^{-1} for aliphatic amines.	
Secondary (2°)	Secondary amines exhibit only one absorption near 3420 cm^{-1}. Hydrogen bonding in concentrated liquids shifts these absorptions to lower frequencies by about 100 cm^{-1}. Again, this absorption appears at slightly higher frequency when the nitrogen atom is bonded to an aromatic ring. The C-N absorptions are found in the same range, 1200 to 1350 cm^{-1}(aromatic) and 1000 to 1250 cm^{-1} (aliphatic) as for 1°-amines.	A weak N-H bending absorption is sometimes visible at 1500 to 1600 cm^{-1}. A broad wagging absorption at 650 to 900 cm^{-1} may be discerned in liquid film samples.
Tertiary (3°)	No N-H absorptions. The C-N absorptions are found in the same range, 1200 to 1350 cm^{-1} (aromatic) and 1000 to	Aside from the C-N stretch noted on the left, these compounds have spectra characteristic of their alkyl and aryl substituents.

	1250 cm^{-1} (aliphatic) as for 1°-amines.



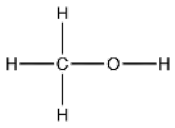




MASS SPECTROMETRY AND THE NITROGEN RULE

The nitrogen rule states that a molecule that has no or even number of nitrogen atoms has an even nominal mass, whereas a molecule that has an odd number of nitrogen atoms has an odd nominal mass.

eg. 1:



molecular formula = CH_4O

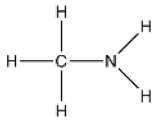
nominal mass = (1x12) + (4x1) + (1x16)

= 32

N atoms = 0

nominal mass = 32 (even #)

eg. 2:



molecular formula = CH_5N

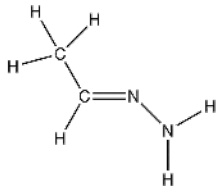
nominal mass = (1x12) + (5x1) + (1x14)

= 31

N atoms = 1 (odd #)

nominal mass = 31 (odd #)

eg. 3:



molecular formula = $C_2H_6N_2$

nominal mass = (2x12) + (6x1) + (2x14)

= 58

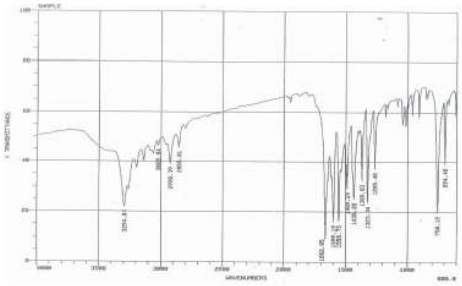
N atoms = 2 (even #)

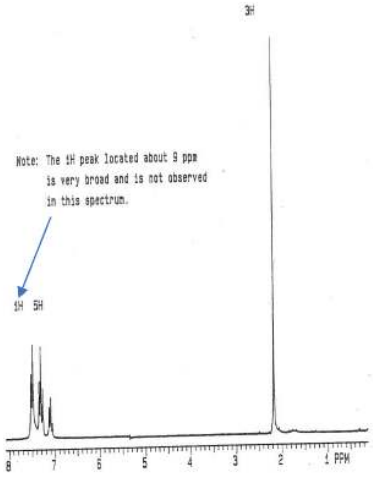
nominal mass = 58 (even #)

Exercise

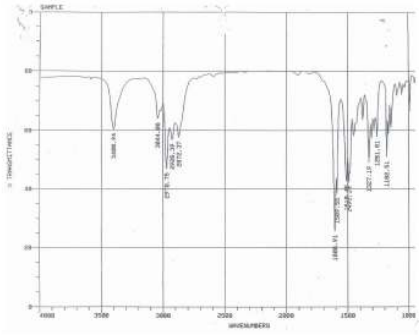
7. Oh no! The labels have fallen off two samples: Q and R. The elemental analysis for the samples indicated the following composition: compound Q is 81.15% C, 8.34% H, and 10.52% O and compound R is 71.08% C, 6.72% H, 10.36% N, and 11.84% O. Fortunately, we can analyze the samples using IR and ^{1}H NMR spectroscopy. Name and draw the bond-line structures for compounds Q and R using the information provided. Support your answer by correlating the spectral data to the compound structures.

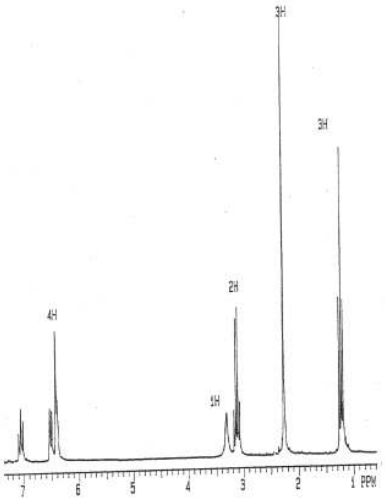
Vial 1





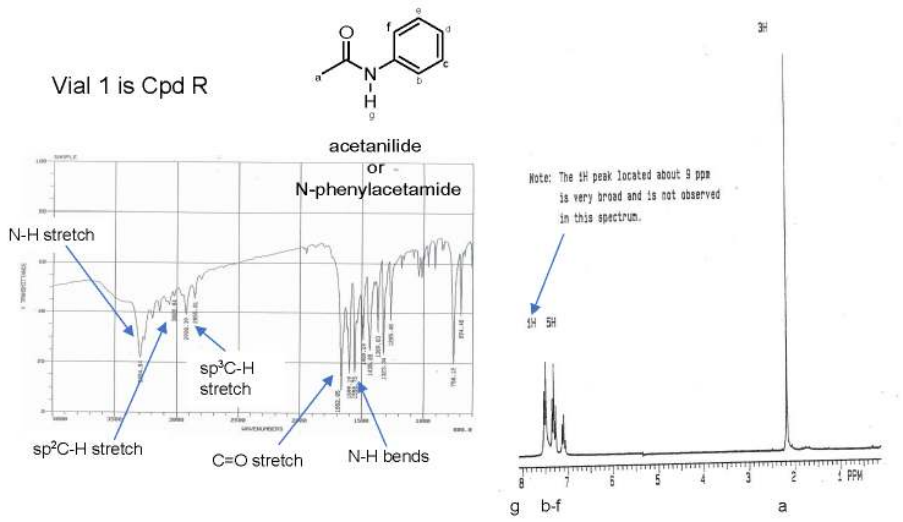
Vial 2

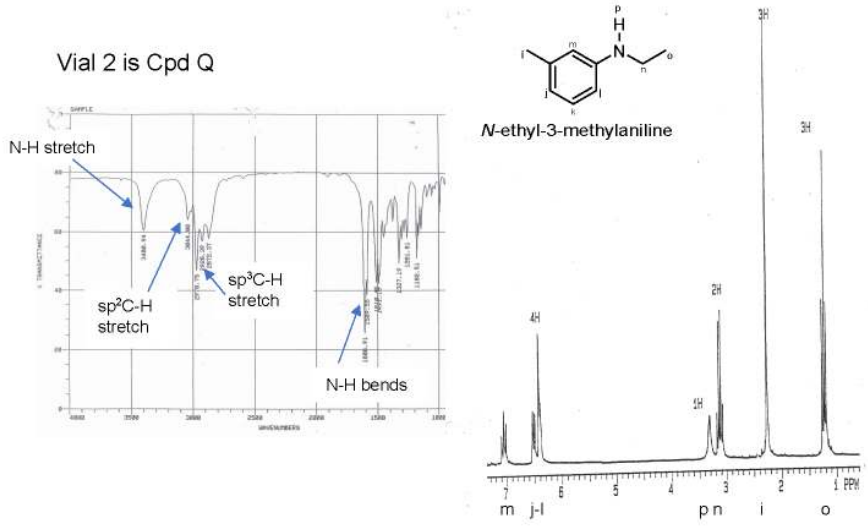




Answer

7. Vial 1 contains compound R which is acetanilide. Vial 2 contains compound Q which is N-ethyl-3-methylaniline.





CONTRIBUTORS AND ATTRIBUTIONS

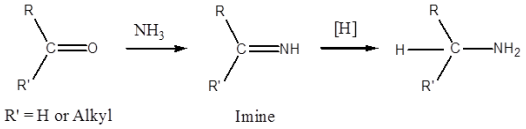
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

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20.4: SYNTHESIS OF AMINES

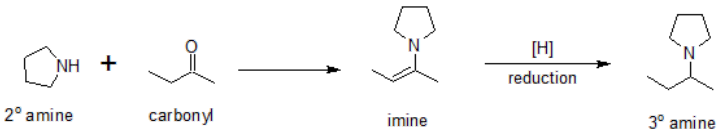
REDUCTIVE AMINATION OF ALDEHYDES AND KETONES (CARBONYLS)

Aldehydes and ketones can be converted into 1º, 2º and 3º amines using reductive amination. The reaction takes place in two parts. The first step is the nucleophiic addition of the carbonyl group to form an imine. The second step is the reduction of the imine to an amine using an reducing agent. A reducing agent commonly used for this reaction is sodium cyanoborohydride ($NaBH_3CN$).



R' = H or Alkyl Imine

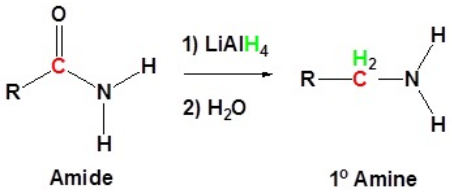
The nitrogen gains a bond to carbon during this reaction sequence. When carbonyls react with ammonia, a primary amine is produced. The reaction pattern continues for each amine classification. For example, pyrrolidine reacts with 2-butanone to produce the imine, which can be reduced by $LiAlH_4$, sodium cyanoborohydride ($NaBH_3CN$), or H_2 with an active metal catalyst to produce a tertiary amine.



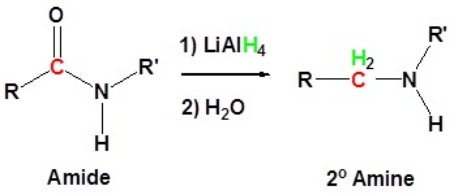
2° amine carbonyl imine 3° amine

AMIDE REDUCTION TO 1°, 2° OR 3° AMINES USING LIALH$_4$

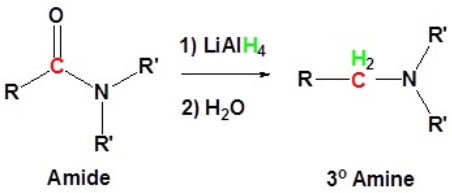
There is a direct correlation between the structure of the amide and the structure of the amine produced. Primary amides are reduced to primary amines. Secondary amides are reduced to secondary amines. Tertiary amides are reduced to tertiary amines. Lithium aluminum hydride is a stronger reducing agent than sodium borohydride, which is not strong enough for this reaction.



Amide 1º Amine



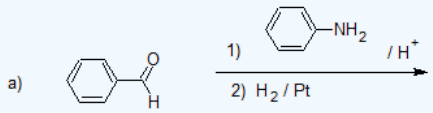
Amide 2º Amine

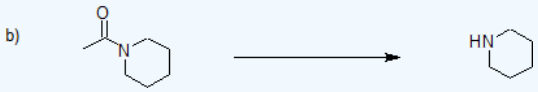


Amide 3º Amine

Exercise

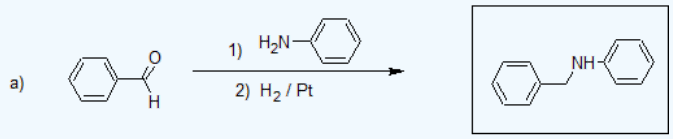
8. Add the missing reactants/products to the following reactions.

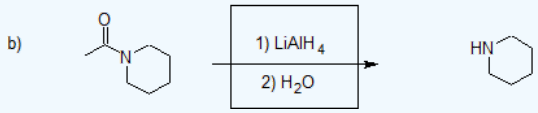




Answer

8.





CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

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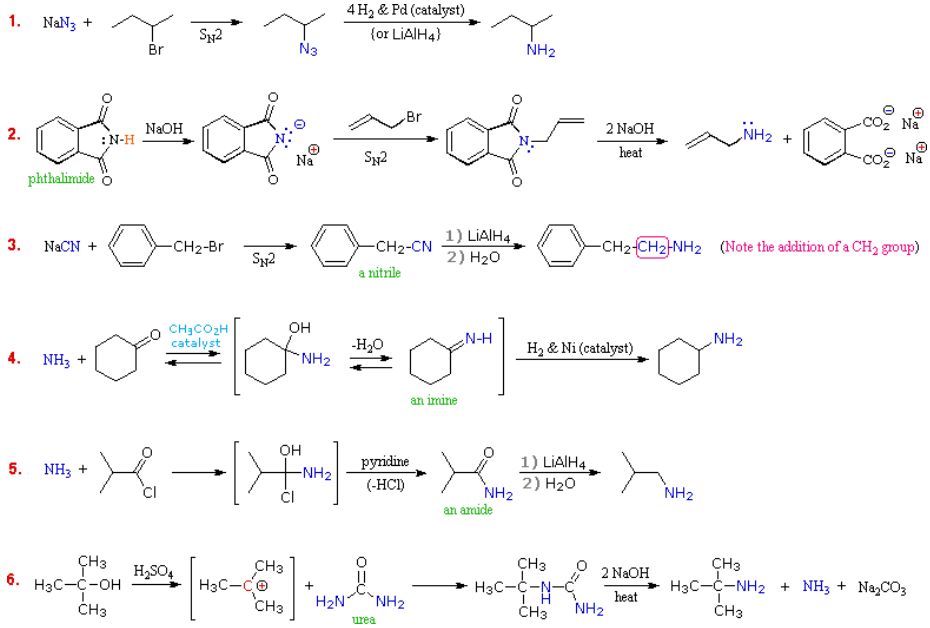
20.5: SYNTHESIS OF PRIMARY AMINES

PREPARATION OF PRIMARY AMINES

Although direct alkylation of ammonia by alkyl halides leads to 1°-amines, alternative procedures are preferred in many cases. These methods require two steps, but they provide pure product, usually in good yield. The general strategy is to first form a carbon-nitrogen bond by reacting a nitrogen nucleophile with a carbon electrophile. The following table lists several general examples of this strategy in the rough order of decreasing nucleophilicity of the nitrogen reagent. In the second step, extraneous nitrogen substituents that may have facilitated this bonding are removed to give the amine product.

Nitrogen Reactant	Carbon Reactant	1st Reaction Type	Initial Product	2nd Reaction Conditions	2nd Reaction Type	Final Product
$N_3^{(-)}$	RCH_2-X or R_2CH-X	S_N2	RCH_2-N_3 or R_2CH-N_3	$LiAlH_4$ or 4 H_2 & Pd	Hydrogenolysis	RCH_2-NH_2 or R_2CH-NH_2
$C_6H_5C_2O_2NH$ / OH^-	RCH_2-X or R_2CH-X	S_N2	RCH_2-$NC_2O_2C_6H_5$ or R_2CH-$NC_2O_2C_6H_5$	NaOH / heat	Hydrogenolysis	RCH_2-NH_2 or R_2CH-NH_2
$CN^{(-)}$	RCH_2-X or R_2CH-X	S_N2	RCH_2-CN or R_2CH-CN	$LiAlH_4$	Reduction	RCH_2-CH_2NH_2 or R_2CH-CH_2NH_2
NH_3	RCH=O or R_2C=O	Addition / Elimination	RCH=NH or R_2C=NH	H_2 & Ni or $NaBH_3CN$	Reduction	RCH_2-NH_2 or R_2CH-NH_2
NH_3	RCOX	Addition / Elimination	RCO-NH_2	$LiAlH_4$	Reduction	RCH_2-NH_2
NH_2CONH_2 (urea)	$R_3C^{(+)}$	S_N1	R_3C-$NHCONH_2$	NaOH soln.	Hydrolysis	R_3C-NH_2

A specific example of each general class is provided in the diagram below. In the first two, an anionic nitrogen species undergoes an S_N2 reaction with a modestly electrophilic alkyl halide reactant. For example #2, the Gabriel synthesis is shown. The alkaline conditions deprotonate phthalmide to create a strong nucleophile for S_N2 reactions with alkyl halides. Example #3 also starts with an S_N2 reaction of cyanide with an alkyl halide following by reduction of the cyano group to form a primary amine that extends the carbon system of the alkyl halide by a methylene group (CH_2). In all three of these methods 3°-alkyl halides cannot be used because the major reaction path is an E2 elimination.



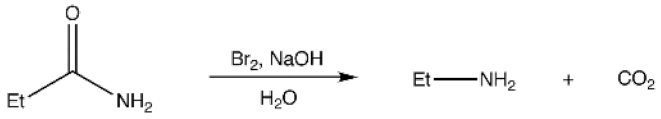
The methods illustrated by examples #4 and #5 proceed by the reaction of ammonia, or equivalent nitrogen nucleophiles, with the electrophilic carbon of a carbonyl group. A full discussion of carbonyl chemistry is presented in an independent chapter, but for present purposes it is sufficient to recognize that the C=O double bond is polarized so that the carbon atom is electrophilic. Nucleophilic addition to aldehydes and ketones is often catalyzed by acids. Acid halides and anhydrides are even more electrophilic, and do not normally require catalysts to react with nucleophiles. The reaction of ammonia with aldehydes or ketones occurs by a reversible addition-elimination pathway

to give **imines** (compounds having a C=N function). These intermediates are not usually isolated, but are reduced as they are formed (i.e. *in situ*). Acid chlorides react with ammonia to give amides, also by an addition-elimination path, and these are reduced to amines by $LiAlH_4$.

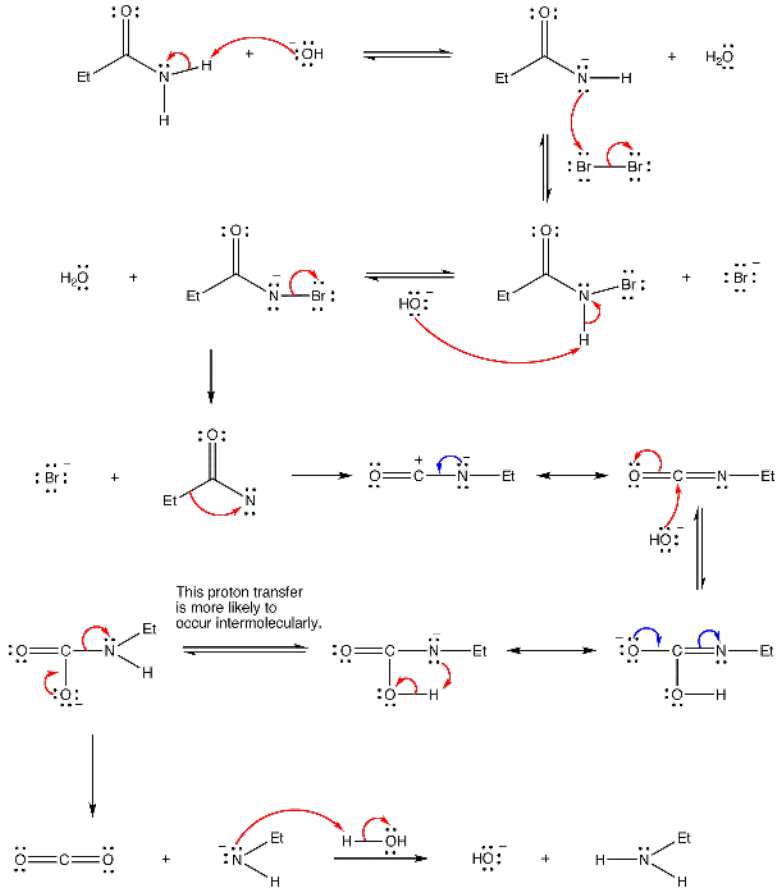
The 6th example is a specialized procedure for bonding an amino group to a 3º-alkyl group (none of the previous methods accomplishes this). Since a carbocation is the electrophilic species, rather poorly nucleophilic nitrogen reactants can be used. Urea, the diamide of carbonic acid, fits this requirement nicely. The resulting 3º-alkyl-substituted urea is then hydrolyzed to give the amine. One important method of preparing 1º-amines, especially aryl amines, uses a reverse strategy. Here a strongly electrophilic nitrogen species ($NO_2^{(+)}$) bonds to a nucleophilic carbon compound. This nitration reaction gives a nitro group that can be reduced to a 1º-amine by any of several reduction procedures.

HOFMANN REARRANGEMENT

Hofmann rearrangement, also known as Hofmann degradation and not to be confused with Hofmann elimination, is the reaction of a primary amide with a halogen (chlorine or bromine) in strongly basic (sodium or potassium hydroxide) aqueous medium, which converts the amide to a primary amine. For example:

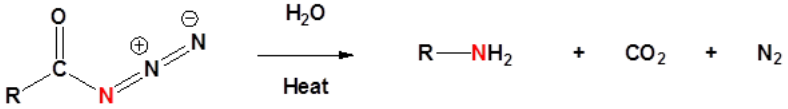


Mechanism:

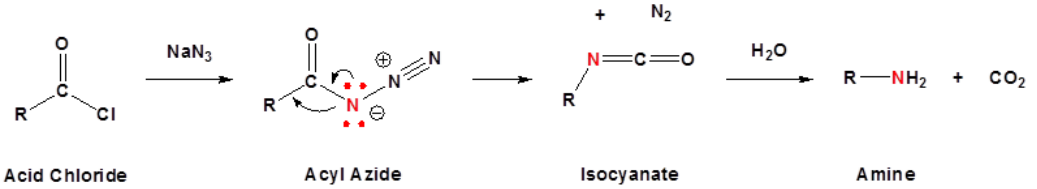


CURTIUS REARRANGEMENT

The Curtius rearrangement involves an acyl azide.



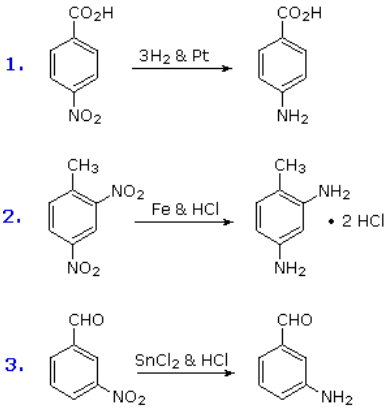
The mechanism of the Curtius rearrangement involves the migration of an -R group form the carbonyl carbon to the the neighboring nitrogen.



REDUCTION OF NITRO GROUPS

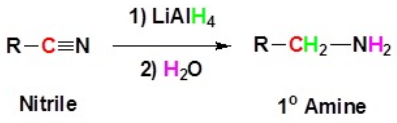
Several methods for reducing nitro groups to amines are known. These include catalytic hydrogenation (H_2 + catalyst), zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution. The procedures described above are sufficient for most case

Nitro Group Reduction



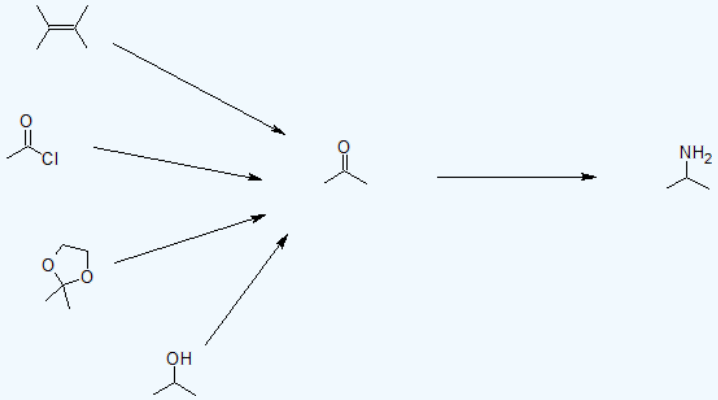
REDUCTION OF NITRILES

Nitriles can be converted to primary amines by reaction with lithium aluminum hydride. During this reaction the hydride nucleophile reacts with the electrophilic carbon in the nitrile to form an imine anion. Once stabilized by a Lewis acid-base complexation the imine salt can accept a second hydride to form a dianion. The dianion can then be converted to an amine by addition of water.



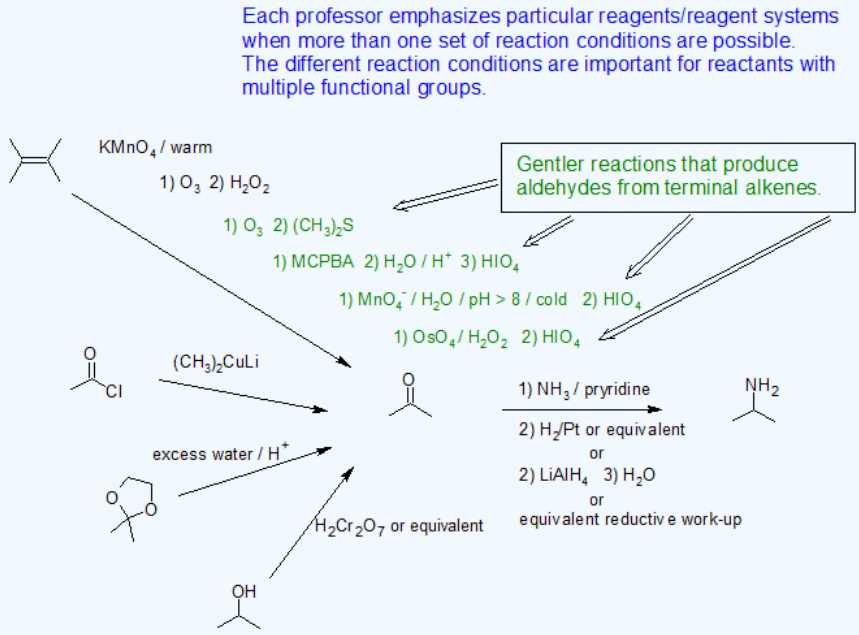
Exercise

9. Complete the reaction map below to build reaction patterns for multiple step synthesis.



Answer

9.



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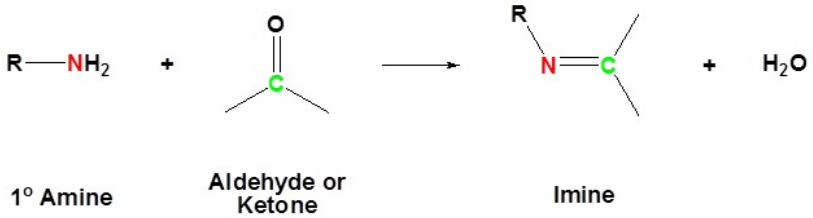
20.6: REACTIONS OF AMINES

AMINES AS NUCLEOPHILES

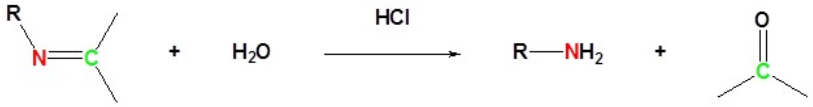
Amines seldom serve as leaving groups in nucleophilic substitution or base-catalyzed elimination reactions. Indeed, they are even less effective in this role than are hydroxyl and alkoxyl groups. While we will see another section that it is possible to coax the amine to serve as a leaving group. As weak bases, amines are good nucleophiles.

AMINES AND CARBONYLS

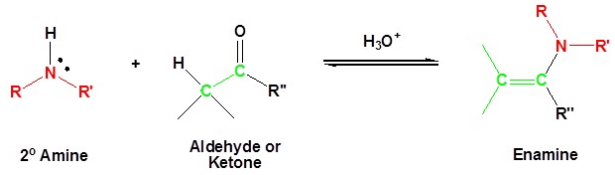
The reaction of aldehydes and ketones with ammonia or 1º-amines forms imine derivatives, also known as Schiff bases (compounds having a C=N function). Water is eliminated in the reaction, which is acid-catalyzed and reversible in the same sense as acetal formation. The pH for reactions which form imine compounds must be carefully controlled. The rate at which these imine compounds are formed is generally greatest near a pH of 5, and drops at higher and lower pH's. At high pH there will not be enough acid to protonate the OH in the intermediate to allow for removal as H_2O. At low pH most of the amine reactant will be tied up as its ammonium conjugate acid and will become non-nucleophilic.



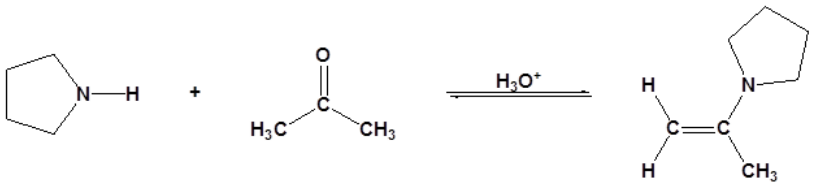
Imine formation is reversible. Imines can be hydrolyzed back to the corresponding primary amine under acidic aqueous conditions.



Most aldehydes and ketones react with 2º-amines to give products known as **enamines**.

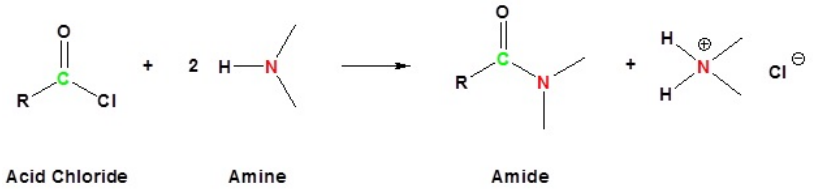


It should be noted that, like acetal and imine formation, these are acid-catalyzed reversible reactions in which water is lost. Consequently, enamines are easily converted back to their carbonyl precursors by acid-catalyzed hydrolysis.

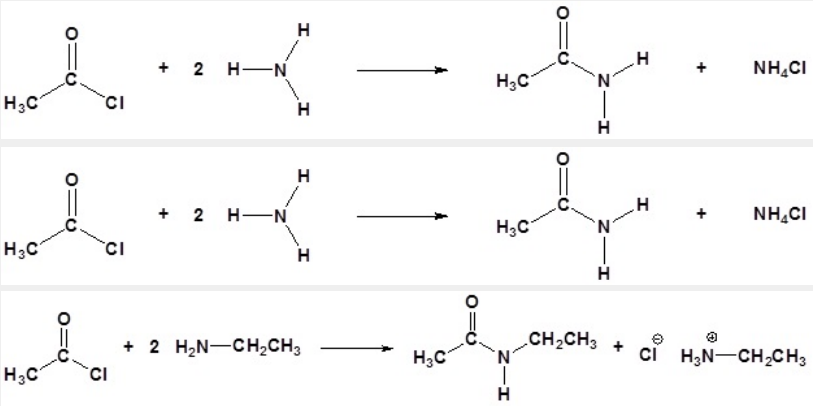


AMINES AND ACID CHLORIDES

Acid chlorides react with ammonia, 1º amines and 2º amines to form amides.

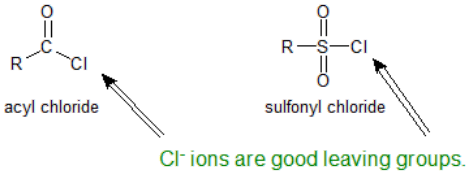


Examples:

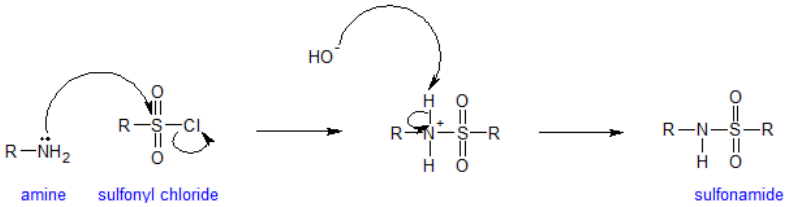


AMINES AND SULFONYL CHLORIDE

The sulfonyl group is the sulfur-analog to the carbonyl group. Both groups contain an electrophilic carbonyl carbon with chloride as an excellent leaving group. Because sulfur is a third shell element it can form "expanded octets".



Amines react with sulfonyl groups to form sulfonamides. Sulfonamides are used as antimicrobial agents therapeutically and called sulfa drugs. The reaction to form sulfonamides occurs under alkaline conditions to keep the amine nucleophilic. Any time amines are present in an aqueous solution, measurable hydroxide is present. The mechanism for the sulfonation reaction is analogous to the acylation mechanism as is shown below.



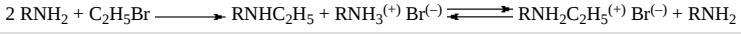
The end of this chapter includes some additional information on sulfonamides.

ALKYLATIONS

IT IS INSTRUCTIVE TO EXAMINE NITROGEN SUBSTITUTION REACTIONS USING COMMON ALKYL HALIDES AS THE ELECTROPHILES. THUS, REACTION OF A PRIMARY ALKYL BROMIDE WITH A LARGE EXCESS OF AMMONIA YIELDS THE CORRESPONDING 1º-AMINE, PRESUMABLY BY AN S_N2 MECHANISM. THE HYDROGEN BROMIDE PRODUCED IN THE REACTION COMBINES WITH SOME OF THE EXCESS AMMONIA, GIVING AMMONIUM BROMIDE AS A BY-PRODUCT. WATER DOES NOT NORMALLY REACT WITH 1º-ALKYL HALIDES TO GIVE ALCOHOLS, SO THE ENHANCED NUCLEOPHILICITY OF NITROGEN RELATIVE TO OXYGEN IS CLEARLY DEMONSTRATED.



It follows that simple amines should also be more nucleophilic than their alcohol or ether equivalents. If, for example, we wish to carry out an S_N2 reaction of an alcohol with an alkyl halide to produce an ether (the Williamson synthesis), it is necessary to convert the weakly nucleophilic alcohol to its more nucleophilic conjugate base for the reaction to occur. In contrast, amines react with alkyl halides directly to give N-alkylated products. Since this reaction produces HBr as a co-product, hydrobromide salts of the alkylated amine or unreacted starting amine (in equilibrium) will also be formed.



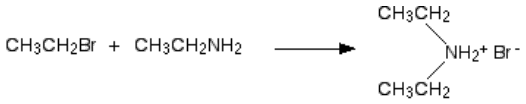
Unfortunately, the direct alkylation of 1º or 2º-amines to give a more substituted product does not proceed cleanly. If a 1:1 ratio of amine to alkyl halide is used, only 50% of the amine will react because the remaining amine will be tied up as an ammonium halide salt (remember that one equivalent of the strong acid HX is produced). If a 2:1 ratio of amine to alkylating agent is used, as in the above equation, the HX issue is solved, but another problem arises. Both the starting amine and the product amine are nucleophiles. Consequently, once the reaction has started, the product amine competes with the starting material in the later stages of alkylation, and some higher alkylated products are also formed. Even 3º-amines may be alkylated to form quaternary (4º) ammonium salts. When tetraalkyl ammonium salts are desired, as shown in the following example, Hünig's base may be used to scavenge the HI produced in the three S_N2 reactions. Steric hindrance prevents this 3º-amine (Hünig's base) from being methylated.

$$C_6H_5NH_2 + 3\ CH_3I + \text{Hünig's base} \longrightarrow C_6H_5N(CH_3)_3^{(+)}\ I^{(-)} + \text{HI salt of Hünig's base}$$

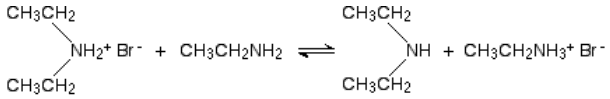
You get a complicated series of reactions on heating primary amines with halogenoalkanes to give a mixture of products - probably one of the most confusing sets of reactions you will meet at this level. The products of the reactions include secondary and tertiary amines and their salts, and quaternary ammonium salts.

MAKING SECONDARY AMINES AND THEIR SALTS

In the first stage of the reaction, you get the salt of a secondary amine formed. For example if you started with ethylamine and bromoethane, you would get diethylammonium bromide



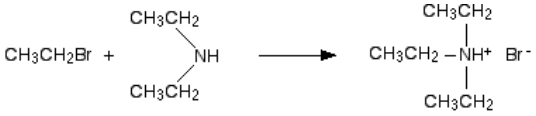
In the presence of excess ethylamine in the mixture, there is the possibility of a reversible reaction. The ethylamine removes a hydrogen from the diethylammonium ion to give free diethylamine - a secondary amine.



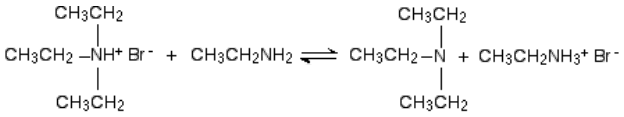
MAKING TERTIARY AMINES AND THEIR SALTS

But it doesn't stop here! The diethylamine also reacts with bromoethane - in the same two stages as before. This is where the reaction would start if you reacted a secondary amine with a halogenoalkane.

In the first stage, you get triethylammonium bromide.



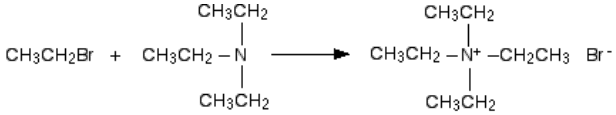
There is again the possibility of a reversible reaction between this salt and excess ethylamine in the mixture.



The ethylamine removes a hydrogen ion from the triethylammonium ion to leave a tertiary amine - triethylamine.

MAKING A QUATERNARY AMMONIUM SALT

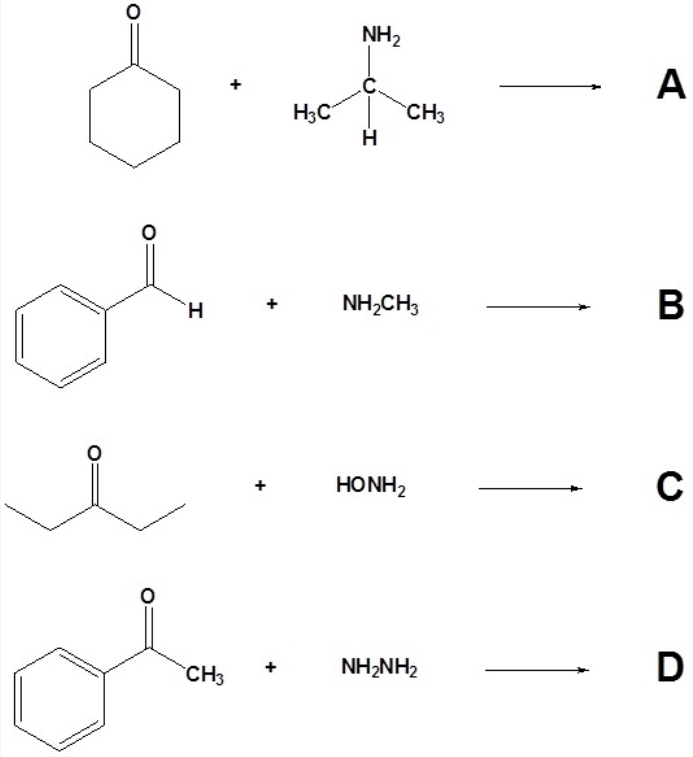
The final stage! The triethylamine reacts with bromoethane to give tetraethylammonium bromide - a quaternary ammonium salt (one in which all four hydrogens have been replaced by alkyl groups).



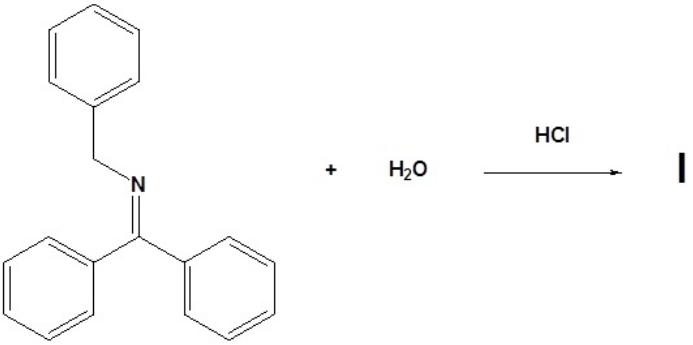
This time there isn't any hydrogen left on the nitrogen to be removed. The reaction stops here.

EXERCISE

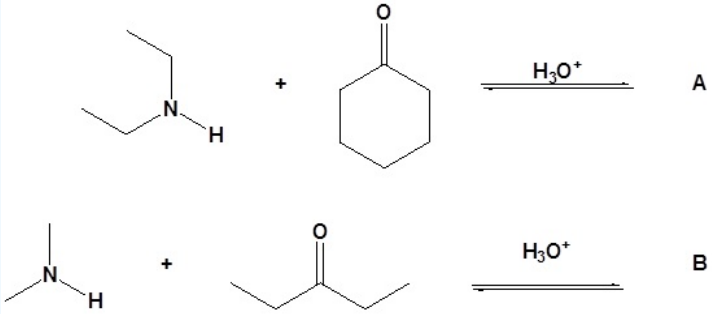
10. Draw the products of the following reactions.



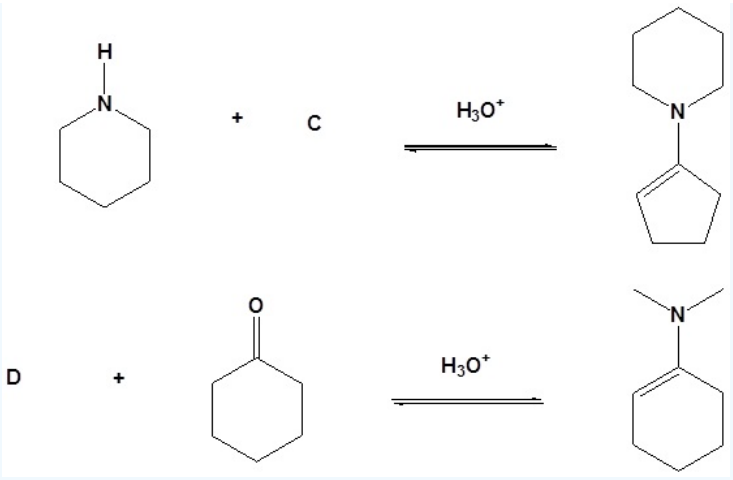
11. Draw the structure of the reactant needed to produce the indicated product.



12. Draw the products for the following reactions.

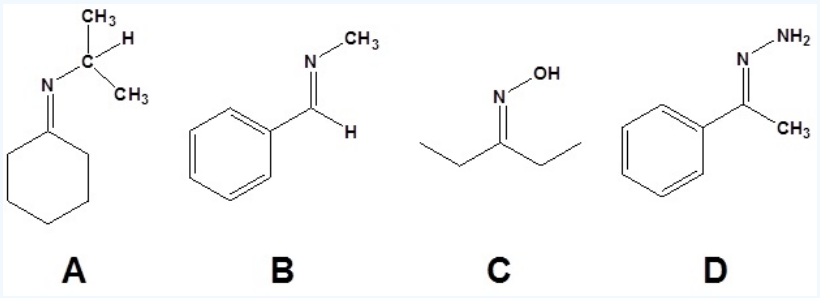


13. Draw the missing reactant to complete each reaction below.

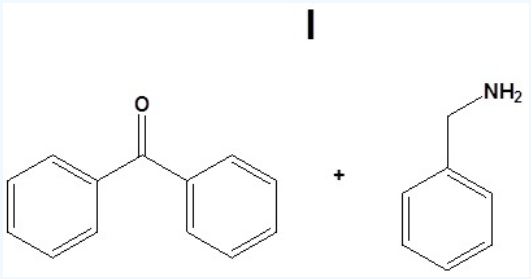


Answer

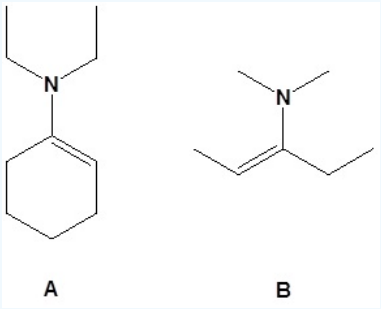
10.



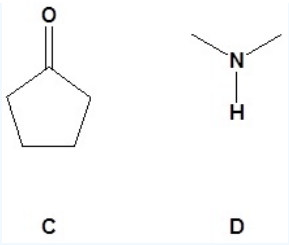
11.



12.



13.



CONTRIBUTORS AND ATTRIBUTIONS

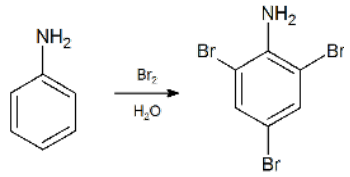
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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20.7: REACTIONS OF ARYLAMINES

OVERREACTION OF ANILINE

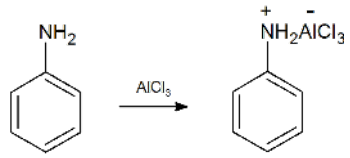
Arylamines are very reactive towards electrophilic aromomatic substitution. The strongest activating and ortho/para-directing substituents are the amino (-NH_2) and hydroxyl (-OH) groups. Direct nitration of phenol (hydroxybenzene) by dilute nitric acid gives modest yields of nitrated phenols and considerable oxidative decomposition to tarry materials; aniline (aminobenzene) is largely destroyed. Monobromination of both phenol and aniline is difficult to control, with di- and tri-bromo products forming readily.



Because of their high nucleophilic reactivity, aniline and phenol undergo substitution reactions with iodine, a halogen that is normally unreactive with benzene derivatives. The mixed halogen iodine chloride (ICl) provides a more electrophilic iodine moiety, and is effective in iodinating aromatic rings having less powerful activating substituents.



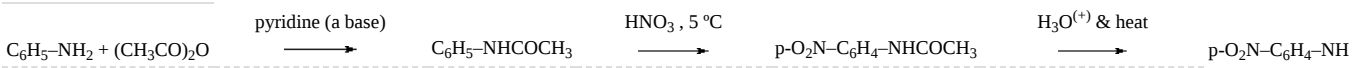
In addition to overreactivity, we have previously seen that Friedel-Crafts reactions employing $AlCl_3$ catalyst do not work with aniline. A salt complex forms and prevents electrophilic aromatic substitution.



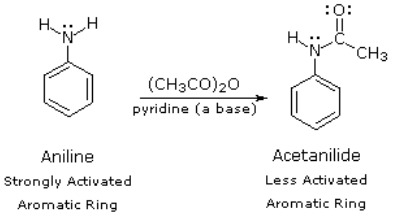
Both this problem and the aniline overreactivity can be circumvented by first going through the corresponding amide.

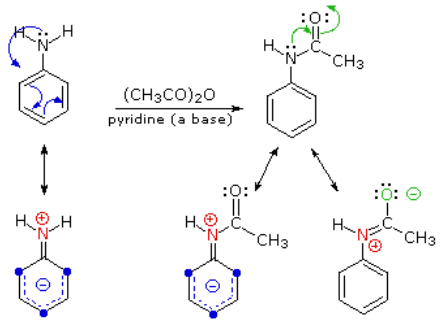
MODIFYING THE INFLUENCE OF STRONG ACTIVATING GROUPS

By acetylating the heteroatom substituent on aniline, its activating influence can be substantially attenuated. For example, acetylation of aniline gives acetanilide (first step in the following equation), which undergoes nitration at low temperature, yielding the para-nitro product in high yield. The modifying acetyl group can then be removed by acid-catalyzed hydrolysis (last step), to yield para-nitroaniline. Although the activating influence of the amino group has been reduced by this procedure, the acetyl derivative remains an ortho/para-directing and activating substituent.



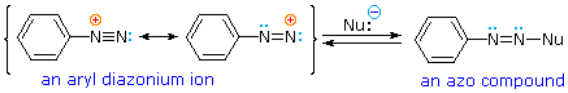
The following diagram illustrates how the acetyl group acts to attenuate the overall electron donating character of oxygen and nitrogen. The non-bonding valence electron pairs that are responsible for the high reactivity of these compounds (blue arrows) are diverted to the adjacent carbonyl group (green arrows). However, the overall influence of the modified substituent is still activating and ortho/para-directing.





DIAZONIUM IONS AND THEIR SALTS

A resonance description of diazonium ions shows that the positive charge is delocalized over the two nitrogen atoms. It is not possible for nucleophiles to bond to the inner nitrogen, but bonding (or coupling) of negative nucleophiles to the terminal nitrogen gives neutral azo compounds. As shown in the following equation, this coupling to the terminal nitrogen should be relatively fast and reversible. The azo products may exist as E / Z stereoisomers. In practice it is found that the E-isomer predominates at equilibrium.



Unless these azo products are trapped or stabilized in some manner, reversal to the diazonium ion and slow nucleophilic substitution at carbon (with irreversible nitrogen loss) will be the ultimate course of reaction, as described in the previous section. For example, if phenyldiazonium bisufate is added rapidly to a cold solution of sodium hydroxide a relatively stable solution of sodium phenyldiazoate (the conjugate base of the initially formed diazoic acid) is obtained. Lowering the pH of this solution regenerates phenyldiazoic acid (pK_a ca. 7), which disassociates back to the diazonium ion and eventually undergoes substitution, generating phenol.

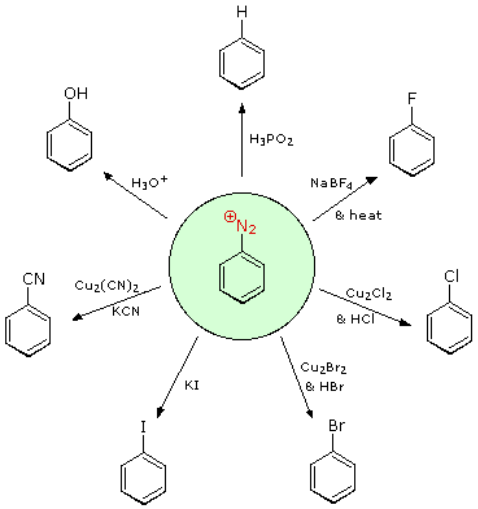
$C_6H_5N_2^{(+)}\ HSO_4^{(-)}$ + NaOH (cold solution)	$C_6H_5N_2$–OH + NaOH (cold)	$C_6H_5N_2$–$O^{(-)}\ Na^{(+)}$
phenyldiazonium bisulfate	phenyldiazoic acid	sodium phenyldiazoate

Aryl diazonium salts may be reduced to the corresponding hydrazines by mild reducing agents such as sodium bisulfite, stannous chloride or zinc dust. The bisulfite reduction may proceed by an initial sulfur-nitrogen coupling, as shown in the following equation.

$$Ar\text{-}N_2^{(+)}\ X^{(-)} \xrightarrow{NaHSO_3} Ar\text{-}N{=}N\text{-}SO_3H \xrightarrow{NaHSO_3} Ar\text{-}NH\text{-}NH\text{-}SO_3H \xrightarrow{H_2O} Ar\text{-}NH\text{-}NH_2 + H_2SO_4$$

DIAZONIUM SALTS: THE SANDMEYER REACTIONS

Aryl diazonium salts are important intermediates. They are prepared in cold (0 º to 10 ºC) aqueous solution, and generally react with nucleophiles with loss of nitrogen. Some of the more commonly used substitution reactions are shown in the following diagram. Since the leaving group (N_2) is thermodynamically very stable, these reactions are energetically favored. Those substitution reactions that are catalyzed by cuprous salts are known as **Sandmeyer reactions**. Fluoride substitution occurs on treatment with $BF_4^{(-)}$, a reaction known as the **Schiemann reaction**. Stable diazonium tetrafluoroborate salts may be isolated, and on heating these lose nitrogen to give an arylfluoride product. The top reaction with hypophosphorus acid, H_3PO_2, is noteworthy because it achieves the reductive removal of an amino (or nitro) group. Unlike the nucleophilic substitution reactions, this reduction probably proceeds by a radical mechanism.



These aryl diazonium substitution reactions significantly expand the tactics available for the synthesis of polysubstituted benzene derivatives. Consider the following options:

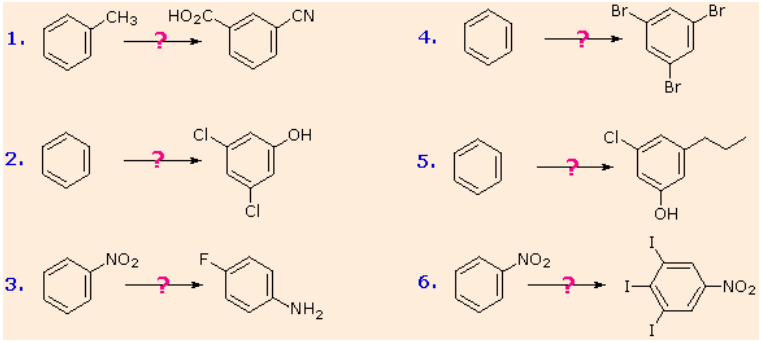
I. The usual precursor to an aryl amine is the corresponding nitro compound. A nitro substituent deactivates an aromatic ring and directs electrophilic substitution to meta locations.

II. Reduction of a nitro group to an amine may be achieved in several ways. The resulting amine substituent strongly activates an aromatic ring and directs electrophilic substitution to ortho & para locations.

III. The activating character of an amine substituent may be attenuated by formation of an amide derivative (reversible), or even changed to deactivating and meta-directing by formation of a quaternary-ammonium salt (irreversible).

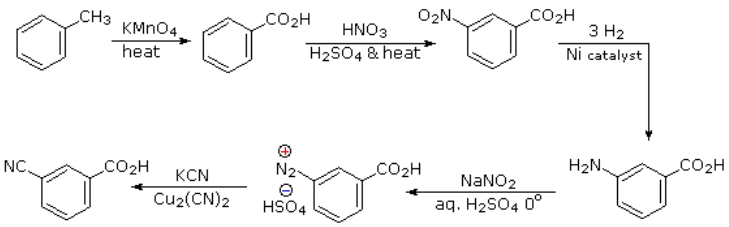
IV. Conversion of an aryl amine to a diazonium ion intermediate allows it to be replaced by a variety of different groups (including hydrogen), which may in turn be used in subsequent reactions.

The following examples illustrate some combined applications of these options to specific cases. You should try to conceive a plausible reaction sequence for each. Once you have done so, you may check suggested answers below.



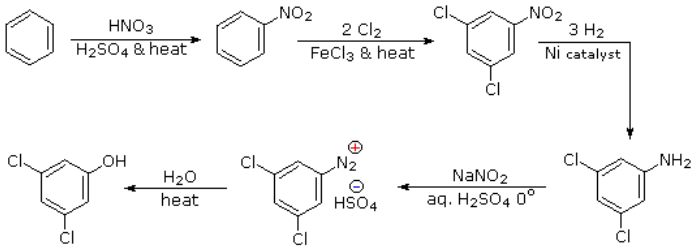
Answer 1:

It should be clear that the methyl substituent will eventually be oxidized to a carboxylic acid function. The timing is important, since a methyl substituent is ortho/para-directing and the carboxyl substituent is meta-directing. The cyano group will be introduced by a diazonium intermediate, so a nitration followed by reduction to an amine must precede this step.



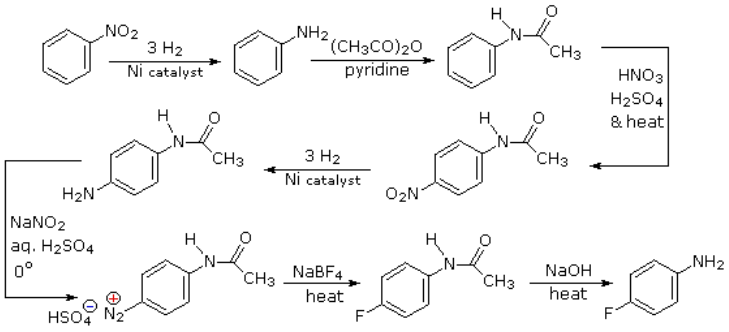
Answer 2:

The hydroxyl group is a strong activating substituent and would direct aromatic ring chlorination to locations ortho & para to itself, leading to the wrong product. As an alternative, the nitro group is not only meta-directing, it can be converted to a hydroxyl group by way of a diazonium intermediate. The resulting strategy is self evident.



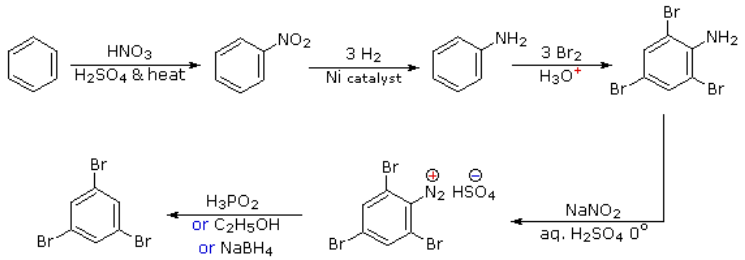
Answer 3:

Selective introduction of a fluorine is best achieved by treating a diazonium intermediate with boron tetrafluoride anion. To get the necessary intermediate we need to make p-nitroaniline. Since the nitro substituent on the starting material would direct a new substituent to a meta-location, we must first reduce it to an ortho/para-directing amino group. Amino groups are powerful activating substituents, so we deactivate it by acetylation before nitration. The acetyl substituent also protects the initial amine function from reaction with nitrous acid later on. It is removed in the last step.



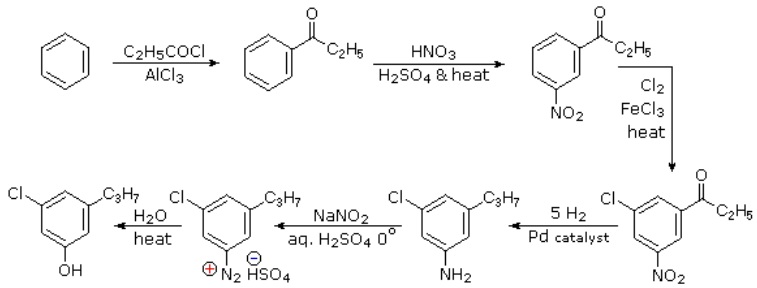
Answer 4:

Polybromination of benzene would lead to ortho/para substitution. In order to achieve the mutual meta-relationship of three bromines, it is necessary to introduce a powerful ortho/para-directing prior to bromination, and then remove it following the tribromination. An amino group is ideal for this purpose. Reductive removal of the diazonium group may be accomplished in several ways (three are shown).



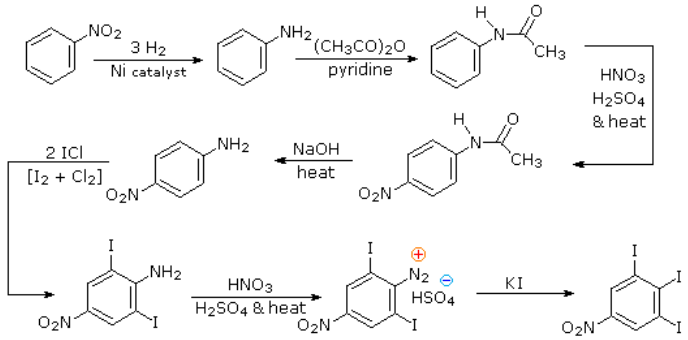
Answer 5:

The propyl substituent is best introduced by Friedel-Crafts acylation followed by reduction, and this cannot be carried out in the presence of a nitro substituent. Since an acyl substituent is a meta-director, it is logical to use this property to locate the nitro and chloro groups before reducing the carbonyl moiety. The same reduction method can be used to reduce both the nitro group (to an amine) and the carbonyl group to propyl. We have already seen the use of diazonium intermediates as precursors to phenols.



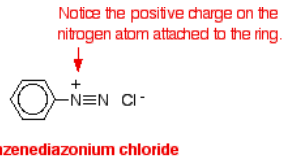
Answer 6:

Aromatic iodination can only be accomplished directly on highly activated benzene compounds, such as aniline, or indirectly by way of a diazonium intermediate. Once again, a deactivated amino group is the precursor of p-nitroaniline (prb.#3). This aniline derivative requires the more electrophilic iodine chloride (ICl) for ortho-iodination because of the presence of a deactivating nitro substituent. Finally, the third iodine is introduced by the diazonium ion procedure.



SUBSTITUTION REACTIONS OF DIAZONIUM IONS

Diazonium ions are present in solutions such as benzenediazonium chloride solution. They contain an $-N_2^+$ group. In the case of benzenediazonium chloride, this is attached to a benzene ring. Benzenediazonium chloride looks like this:

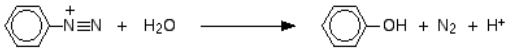


benzenediazonium chloride

In this set of reactions of the diazonium ion, the $-N_2^+$ group is replaced by something else. The nitrogen is released as nitrogen gas.

SUBSTITUTION BY AN -OH GROUP

To get this reaction, all you need to do is warm the benzenediazonium chloride solution. The diazonium ion reacts with the water in the solution and phenol is formed - either in solution or as a black oily liquid (depending on how much is formed). Nitrogen gas is evolved.

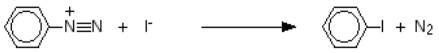


This is the same reaction that you get if you react phenylamine with nitrous acid in the warm. The diazonium ion is formed first and then immediately reacts with the water in the solution to give phenol.

SUBSTITUTION BY AN IODINE ATOM

This is a good example of the use of diazonium salts to substitute things into a benzene ring which are otherwise quite difficult to attach. (That's equally true of the previous reaction, by the way.) If you add potassium iodide solution to the benzenediazonium chloride solution in the cold, nitrogen gas is given off, and you get oily droplets of iodobenzene formed.

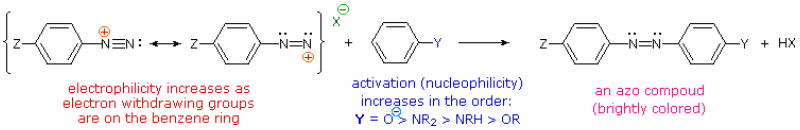
There is a simple reaction between the diazonium ions and the iodide ions from the potassium iodide solution.



COUPLING REACTIONS OF DIAZONIUM IONS

In the substitution reactions above, the nitrogen in the diazonium ion is lost. In the rest of the reactions on this page, the nitrogen is retained and used to make a bridge between two benzene rings.

The most important application of diazo coupling reactions is electrophilic aromatic substitution of activated benzene derivatives by diazonium electrophiles. The products of such reactions are highly colored aromatic azo compounds that find use as synthetic dyestuffs, commonly referred to as azo dyes. Azobenzene (Y=Z=H) is light orange; however, the color of other azo compounds may range from red to deep blue depending on the nature of the aromatic rings and the substituents they carry. Azo compounds may exist as cis/trans isomer pairs, but most of the well-characterized and stable compounds are trans.



THE REACTION WITH PHENOL

Phenol is dissolved in sodium hydroxide solution to give a solution of sodium phenoxide.



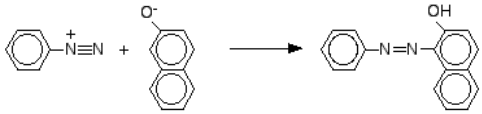
The solution is cooled in ice, and cold benzenediazonium chloride solution is added. There is a reaction between the diazonium ion and the phenoxide ion and a yellow-orange solution or precipitate is formed. The product is one of the simplest of what are known as azo compounds, in which two benzene rings are linked by a nitrogen bridge.



THE REACTION WITH NAPHTHALEN-2-OL

Naphthalen-2-ol is also known as 2-naphthol or beta-naphthol. It contains an -OH group attached to a naphthalene molecule rather than to a simple benzene ring. Naphthalene has two benzene rings fused together. The reaction is done under exactly the same conditions as with phenol. The naphthalen-2-ol is dissolved in sodium hydroxide solution to produce an ion just like the phenol one. This solution is cooled and mixed with the benzenediazonium chloride solution.

An intense orange-red precipitate is formed - another azo compound.



THE REACTION WITH PHENYLAMINE (ANILINE)

Some liquid phenylamine is added to a cold solution of benzenediazonium chloride, and the mixture is shaken vigorously. A yellow solid is produced.

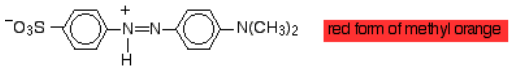


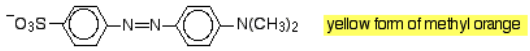
These strongly coloured azo compounds are frequently used as dyes known as azo dyes. The one made from phenylamine (aniline) is known as "aniline yellow" (amongst many other things - see note above). Azo compounds account for more than half of modern dyes.

THE USE OF AN AZO DYE AS AN INDICATOR - METHYL ORANGE

Azo compounds contain a highly delocalized system of electrons which takes in both benzene rings and the two nitrogen atoms bridging the rings. The delocalization can also extend to things attached to the benzene rings as well. If white light falls on one of these molecules, some wavelengths are absorbed by these delocalized electrons. The colour you see is the result of the non-absorbed wavelengths. The groups which contribute to the delocalization (and so to the absorption of light) are known as a chromophore.

Modifying the groups present in the molecule can have an effect on the light absorbed, and so on the color you see. You can take advantage of this in indicators. Methyl orange is an azo dye which exists in two forms depending on the pH:





As the hydrogen ion is lost or gained there is a shift in the exact nature of the delocalisation in the molecule, and that causes a shift in the wavelength of light absorbed. Obviously that means that you see a different colour. When methyl orange is added, a hydrogen ion attaches to give the red form. Methyl orange is red in acidic solutions (in fact solutions of pH less than 3.1). If an alkali is added or hydrogen ions are removed, then the yellow form if generated. Methyl orange is yellow at pH's greater than 4.4.

In between, at some point there will be equal amounts of the red and yellow forms and so methyl orange looks orange.

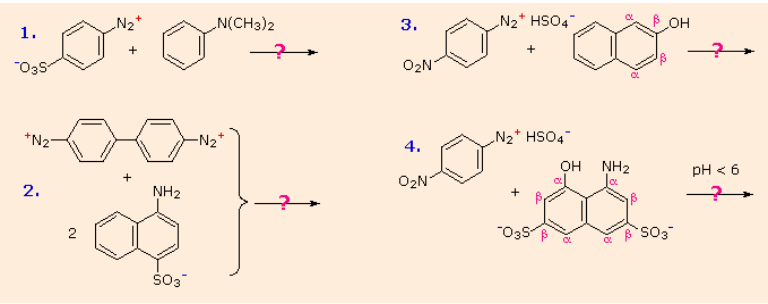
Some examples of azo coupling reactions are shown below. A few simple rules are helpful in predicting the course of such reactions:

I. At acid pH (< 6) an amino group is a stronger activating substituent than a hydroxyl group (i.e. a phenol). At alkaline pH (> 7.5) phenolic functions are stronger activators, due to increased phenoxide base concentration.

II. Coupling to an activated benzene ring occurs preferentially para to the activating group if that location is free. Otherwise ortho-coupling will occur.

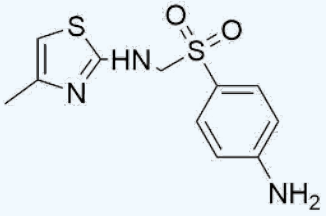
III. Naphthalene normally undergoes electrophilic substitution at an alpha-location more rapidly than at beta-sites; however, ortho-coupling is preferred. See the diagram for examples of α / β notation in naphthalenes.

You should try to conceive a plausible product structure for each of the following couplings.



Exercise

14. Propose a synthesis for the following compound via benzene and any amine you may require.



15. Proposes synthesis for each of the following compounds via benzene.

(a) *N*,*N*-Diethylaniline

(b) *p*-Bromoaniline

(c) *m*-Bromoaniline

(d) 2,4-Diethylaniline

16. Propose a synthesis for each of the following molecules from benzene via the diazonium ion.

(a) *p*-Chlorobenzoic acid

(b) *m*-Chlorobenzoic acid

(c) *m*-Dichlorobenzene

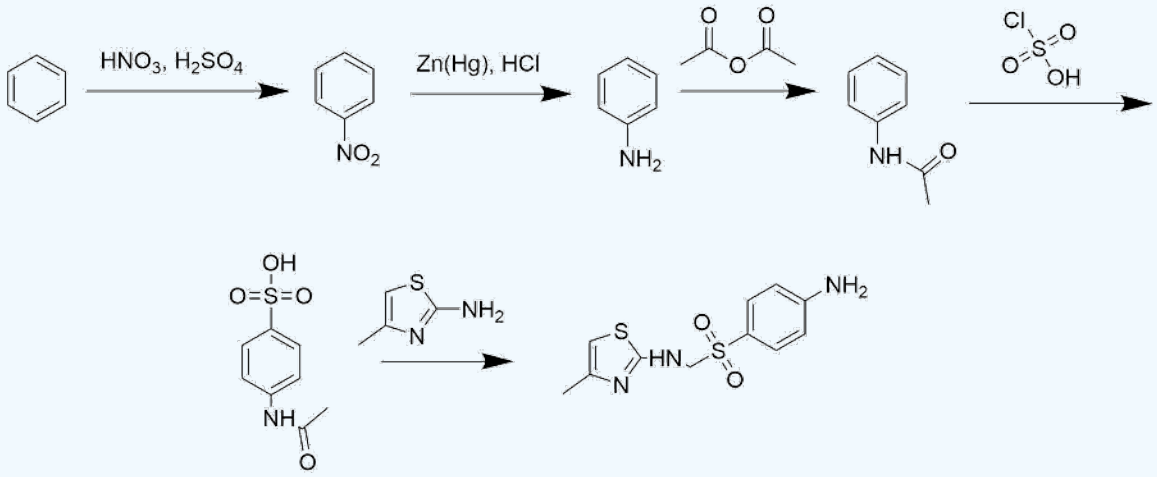
(d) *p*-Ethylbenzoic acid

(e) 1,2,4-Trichlorobenzene

Classify the following alcohols as primary, secondary, or tertiary.

Answer

14.



15.

(a) 1. HNO_3, H_2SO_4; 2. Zn(Hg), HCl; 3. EtBr

(b) 1. HNO_3, H_2SO_4; 2. Zn(Hg), HCl; 3. $(CH_3CO)O_2$; 4. Br_2, $FeBr_3$; 5. H_2O, NaOH

(c) 1. HNO_3, H_2SO_4; 2. Br_2, $FeBr_3$; 3. Zn(Hg), HCl

(d) 1. HNO_3, H_2SO_4; 2. Zn(Hg), HCl; 3. $(CH_3CO)O_2$; 4. EtCl, $AlCl_3$; 5. H_2O, NaOH

16.

(a) 1. CH_3CH_2Cl, $AlCl_3$; 2. HNO_3, H_2SO_4; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuBr; 6. $KMnO_4$, H_2O

(b) 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$; 3. $SnCl_2$, H_3O^+; 4. $NaNO_2$, H_2SO_4; 5. CuCN; 6. H_3O^+

(c) 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuCl

(d) 1. CH_3CH_2Cl, $AlCl_3$; 2. HNO_3, H_2SO_4; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuCN; 6. H_3O^+

(e) 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. $(CH_3CO)_2O$; 4. 2 Cl_2; 5. H_2O, NaOH; 6. $NaNO_2$, H_2SO_4; 7. CuCl

CONTRIBUTORS AND ATTRIBUTIONS

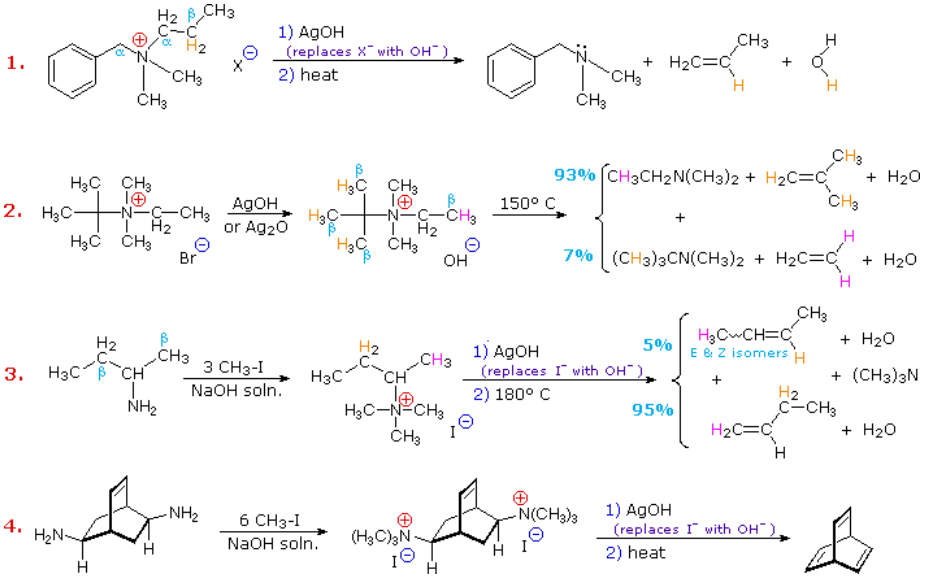
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

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20.8: THE HOFMANN ELIMINATION- AMINES AS LEAVING GROUPS

HOFMANN ELIMINATION

Elimination reactions of 4º-ammonium salts are termed **Hofmann eliminations**. Since the counter anion in most 4º-ammonium salts is halide, this is often replaced by the more basic hydroxide ion through reaction with silver hydroxide (or silver oxide). The resulting hydroxide salt must then be heated (100 - 200 ºC) to effect the E2-like elimination of a 3º-amine. Example #1 below shows a typical Hofmann elimination. Obviously, for an elimination to occur one of the alkyl substituents on nitrogen must have one or more beta-hydrogens, as noted earlier in examining elimination reactions of alkyl halides.



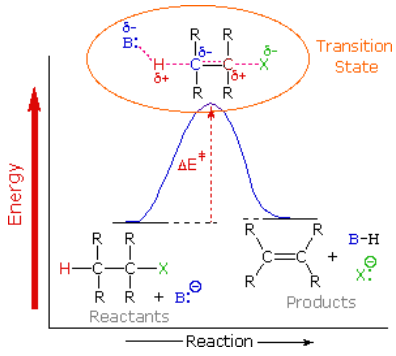
In example #2 above, two of the alkyl substituents on nitrogen have beta-hydrogens, all of which are on methyl groups (colored orange & magenta). The chief product from the elimination is the alkene having the more highly substituted double bond, reflecting not only the 3:1 numerical advantage of those beta-hydrogens, but also the greater stability of the double bond.

Example #3 illustrates two important features of the Hofmann elimination:

1. Simple amines are easily converted to the necessary 4º-ammonium salts by exhaustive alkylation, usually with methyl iodide (methyl has no beta-hydrogens and cannot compete in the elimination reaction). Exhaustive methylation is shown again in example #4.
2. When a given alkyl group has two different sets of beta-hydrogens available to the elimination process (colored orange & magenta here), the major product is often the alkene isomer having the less substituted double bond.

The tendency of Hofmann eliminations to give the less-substituted double bond isomer is commonly referred to as the **Hofmann Rule**, and contrasts strikingly with the Zaitsev Rule formulated for dehydrohalogenations and dehydrations. In cases where other activating groups, such as phenyl or carbonyl, are present, the Hofmann Rule may not apply. Thus, if 2-amino-1-phenylpropane is treated in the manner of example #3, the product consists largely of 1-phenylpropene (E & Z-isomers).

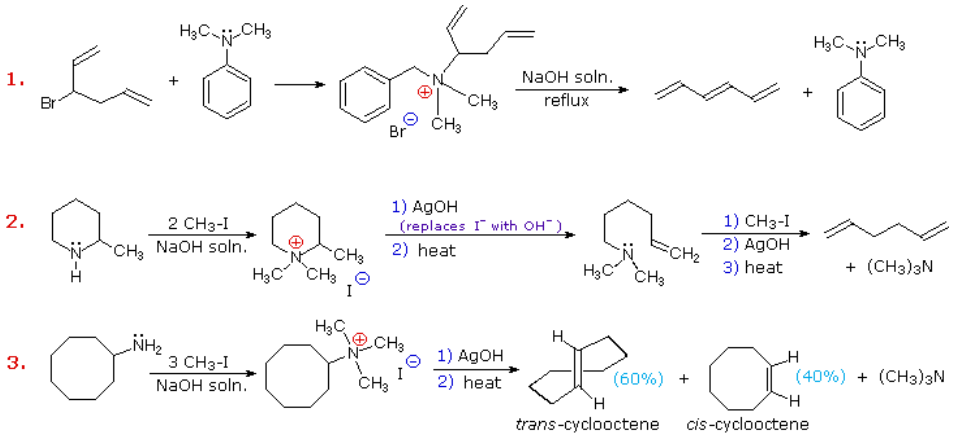
To understand why the base-induced elimination of 4º-ammonium salts behaves differently from that of alkyl halides it is necessary to reexamine the nature of the E2 transition state, first described for dehydrohalogenation. The energy diagram shown earlier for a single-step bimolecular E2 mechanism is repeated below.



The E2 transition state is less well defined than is that of S_N2 reactions. More bonds are being broken and formed, with the possibility of a continuum of states in which the extent of C–H and C–X bond-breaking and C=C bond-making varies. For example, if the bond to the leaving group (X) is substantially broken relative to the other bond changes, the transition state approaches that for an E1 reaction (initial ionization followed by a fast second step). At the other extreme, if the acidity of the beta-hydrogens is enhanced, then substantial breaking of C–H may occur before the other bonds begin to be affected. For most simple alkyl halides it was proper to envision a balanced transition state, in which there was a synchronous change in all the bonds. Such a model was consistent with the **Zaitsev Rule**.

When the leaving group X carries a positive charge, as do the 4º-ammonium compounds discussed here, the inductive influence of this charge will increase the acidity of both the alpha and the beta-hydrogens. Furthermore, the 4º-ammonium substituent is much larger than a halide or hydroxyl group and may perturb the conformations available to substituted beta-carbons. It seems that a combination of these factors acts to favor base attack at the least substituted (least hindered and most acidic) set of beta-hydrogens. The favored anti orientation of the leaving group and beta-hydrogen, noted for dehydrohalogenation, is found for many Hofmann eliminations; but syn-elimination is also common, possibly because the attraction of opposite charges orients the hydroxide base near the 4º-ammonium leaving group.

Three additional examples of the Hofmann elimination are shown in the following diagram. Example #1 is interesting in two respects. First, it generates a 4º-ammonium halide salt in a manner different from exhaustive methylation. Second, this salt is not converted to its hydroxide analog prior to elimination. A concentrated aqueous solution of the halide salt is simply dropped into a refluxing sodium hydroxide solution, and the volatile hydrocarbon product is isolated by distillation.

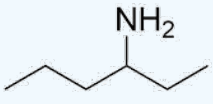


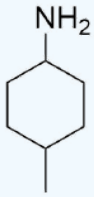
Example #2 illustrates an important aspect of the Hofmann elimination. If the nitrogen atom is part of a ring, then a single application of this elimination procedure does not remove the nitrogen as a separate 3º-amine product. In order to sever the nitrogen function from the molecule, a second Hofmann elimination must be carried out. Indeed, if the nitrogen atom was a member of two rings (fused or spiro), then three repetitions of the Hofmann elimination would be required to sever the nitrogen from the remaining molecular framework.

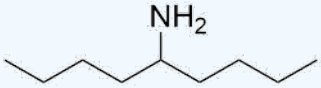
Example #3 is noteworthy because the less stable trans-cyclooctene is the chief product, accompanied by the cis-isomer. An anti-E2-transition state would necessarily give the cis-cycloalkene, so the trans-isomer must be generated by a syn-elimination. The cis-cyclooctene produced in this reaction could also be formed by a syn-elimination. Cyclooctane is a conformationally complex structure. Several puckered conformations that avoid angle strain are possible, and one of the most stable of these is shown on the right. Some eclipsed bonds occur in all these conformers, and transannular hydrogen crowding is unavoidable. Since the trimethylammonium substituent is large (about the size of tert-butyl) it will probably assume an equatorial-like orientation to avoid steric crowding. An anti-E2 transition state is likely to require an axial-like orientation of this bulky group, making this an unfavorable path.

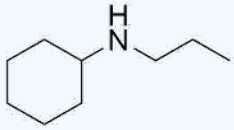
Exercise

17. Draw the product for a Hoffman elimination for each of the following molecules.

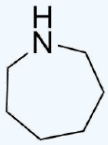
(a) 

(b) 

(c) 

(d) 

18. Draw the product of a Hoffman elimination for the following molecule.

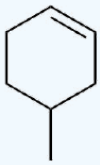


SOLUTIONS

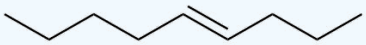
Answer

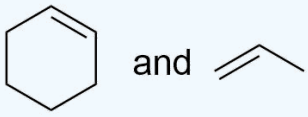
17.

(a) 



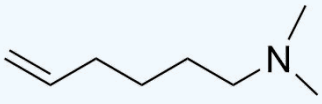
(b)

(c) 



(d)

18.



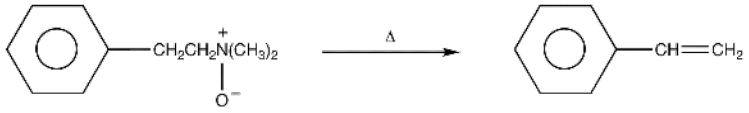
CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

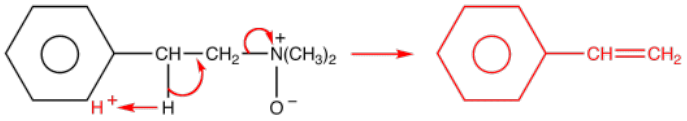
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20.9: OXIDATION OF AMINES - THE COPE ELIMINATION

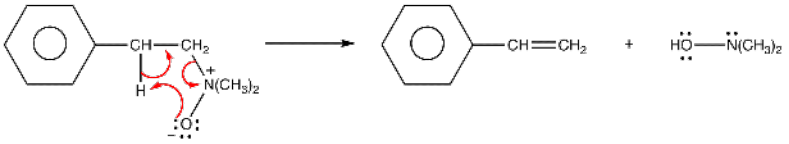
When a tertiary amine oxide bearing one or more beta hydrogens is heated, it is converted to an alkene. The reaction is known as *Cope elimination* or *Cope reaction*, not to be confused with Cope Rearrangement. For example:



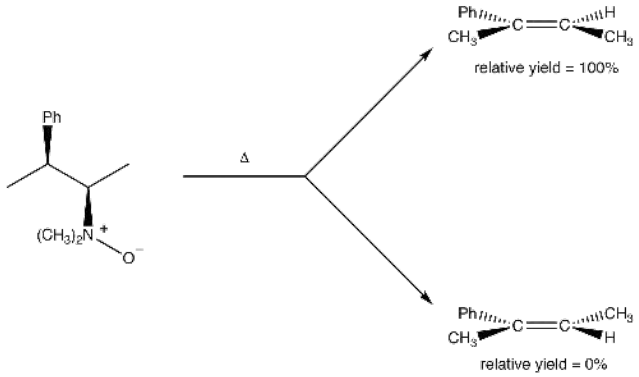
The net reaction is 1,2-elimination, hence the name Cope elimination.



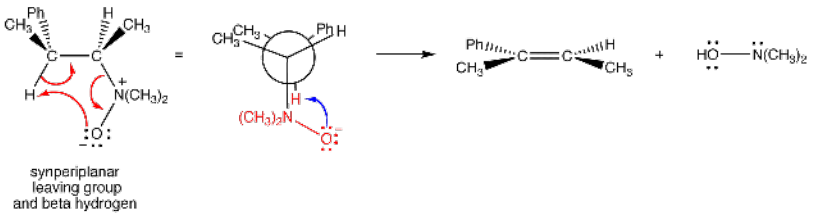
mechanism: Cope elimination is an intramolecular E2 reaction. It is also a pericyclic reaction.

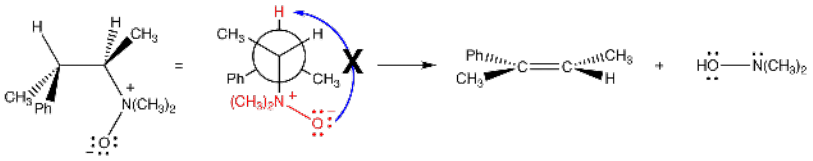


Intermolecular E2 reactions occur preferentially from the conformation of the substrate in which the leaving group and the beta hydrogen abstracted by the base are antiperiplanar, which is not possible in intramolecular E2 reactions in which the base is built into the leaving group because the basic atom is too far away from the beta hydrogen anti to the leaving group. Intramolecular E2 reactions occur preferentially from the conformation of the substrate in which the leaving group and the beta hydrogen abstracted by the base are synperiplanar. The basic atom and the beta hydrogen abstracted by it are closest to each other in this conformation. For example:

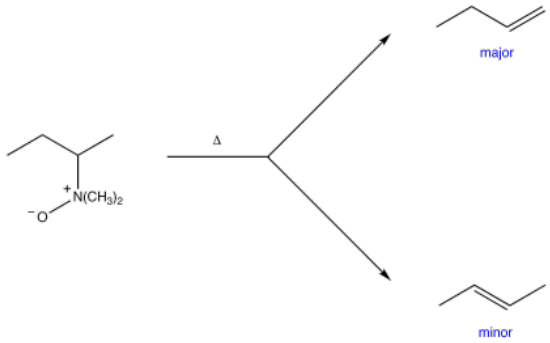


mechanism:





Cope elimination is regioselective. Unlike intermolecular E2 reactions, it does not follow Zaitsev's rule; the major product is always the least stable alkene, i.e., the alkene with the least highly substituted double bond. For example:



This trend is most likely due to the fact that the less highly substituted β-carbon bears more hydrogen atoms than the more highly substituted one; at a given moment, in a sample of the substrate, there are more molecules in which a hydrogen atom on the less highly substituted beta carbon is *synperiplanar* to the leaving group than there are in which a hydrogen atom on the more highly substituted beta carbon is.

CONTRIBUTORS AND ATTRIBUTIONS

- Gamini Gunawardena from the OChemPal site (Utah Valley University)

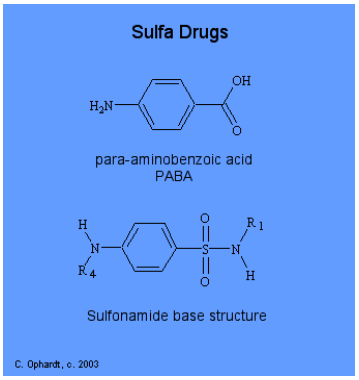
20.9: Oxidation of Amines - The Cope Elimination is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

20.10: SULFA DRUGS - A CLOSER LOOK

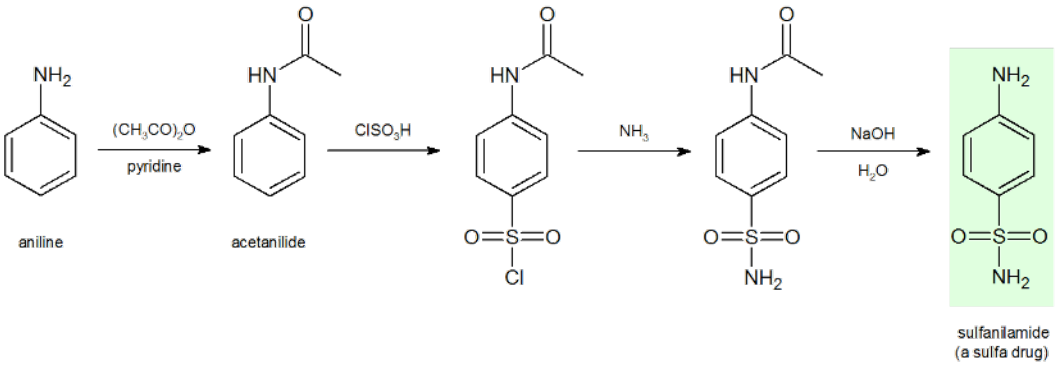
SULFA DRUG SYNTHESIS

Sulfa drugs are an important group of synthetic antimicrobial agents (pharmaceuticals) that contain the sulfonamide group. The synthesis of sulfanilamide (a sulfa drug) illustrates how the reactivity of aniline can be modified to make possible an electrophilic aromatic substitution. The corresponding acetanilide undergoes chlorosulfonation. The resulting 4-acetamidobenzenesulfanyl chloride is treated with ammonia to replace the chlorine with an amino group and affords 4-acetamidobenzenesulfonamide. The subsequent hydrolysis of the sulfonamide produces the sulfanilamide.

Their use introduced and substantiated the concept of metabolic antagonism. Sulfonamides, as antimetabolites, compete with para-aminobenzoic acid (PABA) for incorporation into folic acid. The action of sulfonamides illustrates the principle of selective toxicity where some difference between mammal cells and bacterial cells is exploited. All cells require folic acid for growth. Folic acid (as a vitamin is in food) diffuses or is transported into human cells. However, folic acid cannot cross bacterial cell walls by diffusion or active transport. For this reason bacteria must synthesize folic acid from p-aminobenzoic acid. Sulfonamides or sulfa drugs have the following general structures as shown below.



Sulfanilamide which was the first compound used of this type has H's at R1 and R4. To date about 15,000 sulfonamide derivatives, analogues, and related compounds have been synthesized. This has lead to the discovery of many useful drugs which are effective for diuretics, antimalerial and leprosy agents, and antithyroid agents. The basic structure of sulfonamide cannot be modified if it is to be an effective competitive "mimic" for p-aminobenzoic acid. Essential structural features are the benzene ring with two substituents para to each other; an amino group in the fourth position; and the singly substituted 1-sulfonamido group.



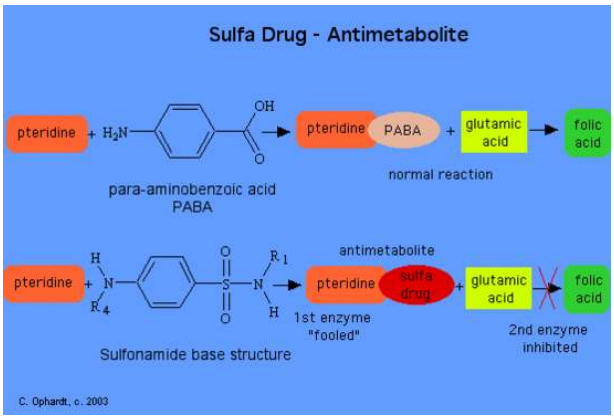
MECHANISM FOR ACTION

Normally folic acid is synthesized in two steps in bacteria by the top reaction on the left. If A sulfa drug is used, the first enzyme is not to specific and can use the sulfonamide in the first reaction. This reaction produces the product containing pteridine and the sulfa drug. The next and final step is the reaction PABA + with glutamic acid to make folic acid. If the sulfa drug has been substituted for the PABA, then the final enzyme is inhibited and no folic acid is produced.

Recent studies indicate that substituents on the N(1) nitrogen may play the role of competing for a site on the enzyme surface reserved for the glutamate residue in p-aminobenzoic acid-glutamate through one of the following two ways:

1. Direct competition in the linking of PABA-glutamate with the pteridine derivative.

2. Indirect interference with the coupling of glutamate to dihydropteroic acid.



QUESTIONS

1. In your own words explain how the sulfa drug works including enzyme inhibition, folic acid, and antimetabolite.

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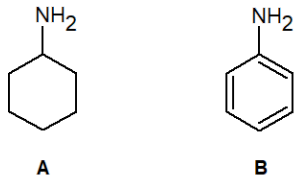
Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

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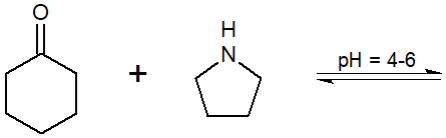
20.11: ADDITIONAL EXERCISES

General Review

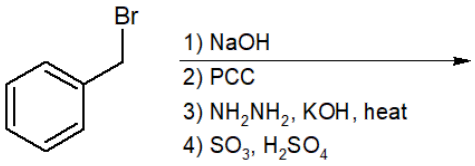
20-1 Predict which amine is more basic and provide a reason for your answer.



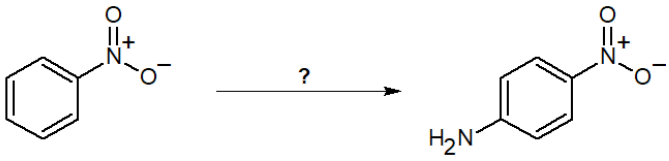
20-2 Give the product of the following reaction.



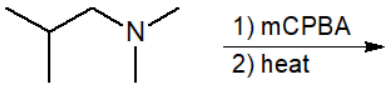
20-3 Predict the final product of the following reaction chain and give its IUPAC name.



20-4 Propose a route of synthesis from nitrobenzene to the given product. Assume the given molecule is the major product, and for the purposes of this problem, ignore its isomers.



20-5 Choose the correct answer that describes the product of the following Cope elimination reaction.



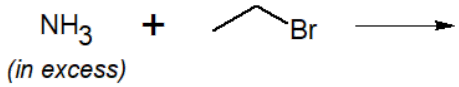
a) N,N,2-trimethylpropan-1-iminium

b) N,N,2-trimethylpropan-1-amine

c) 2-methylprop-1-ene and N-hydroxy-N-methylmethanamine

d) N-hydroxy-N,2-dimethylpropan-1-amine

20-6 Explain why the following reaction might not be the best way to synthesize ethanamine.

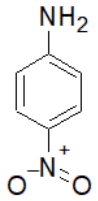


Basicity and Effects of Amines

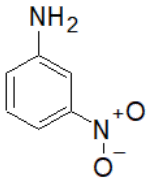
20-7 Draw all possible resonance structures for aniline and cyclohexanamine.



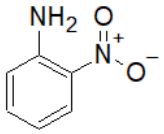
20-8 Identify which of the following nitroaniline isomers is the most basic and give a reason for your answer.



p-nitroaniline



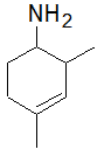
m-nitroaniline



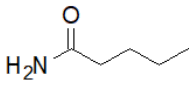
o-nitroaniline

20-9 For the following compounds, identify which substituents are pi-acceptors of the electrons from the amine group (if applicable) and if they are, draw their resonance structure to show the movement of electrons.

a)



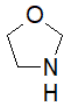
b)



c)

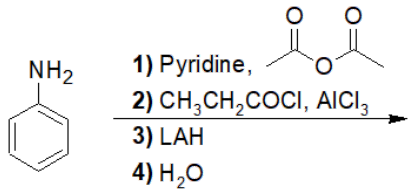


d)



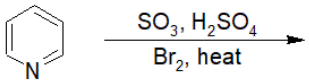
Aromatic Substitution of Arylamines and Pyridin

20-10 Explain why the following arylamine needs to be turned into an amide before a Friedel-Crafts acylation and then predict the final product of the reaction.

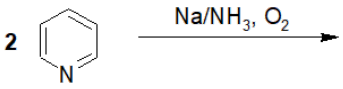


20-11 Predict the products of the following reactions.

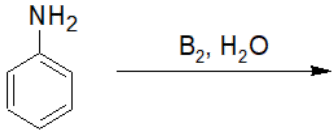
a)



b)

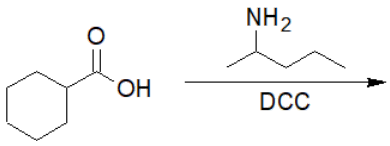


20-12 Predict the product of the following reaction and provide the correct IUPAC nomenclature.

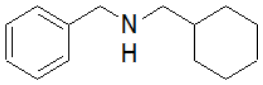


Alkylation and Acylation of Amines

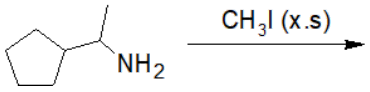
20-13 Predict the product of the following acylation reaction.



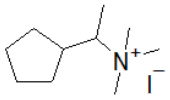
20-14 Suggest a route of synthesis for the following compound, starting with benzoyl chloride.



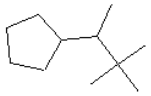
20-15 Choose the correct product of the following reaction.



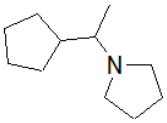
a)



b)

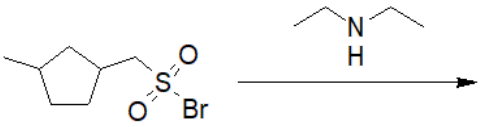


c)

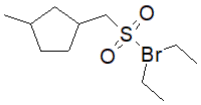


Formation of Sulfonamides

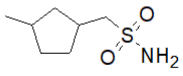
20-16 Choose the correct structure of the product of the following reaction.



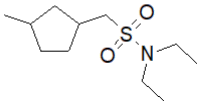
a)



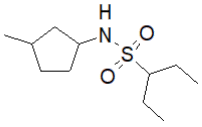
b)



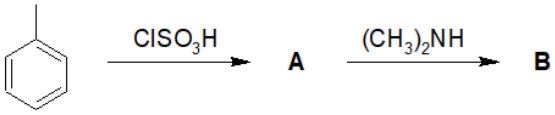
c)



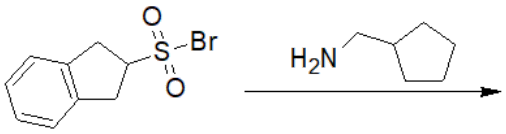
d)



20-17 Provide the structure of the intermediate compound and final product of the following reaction.

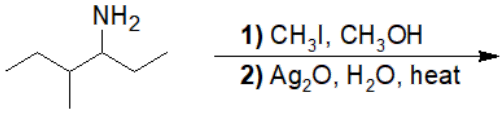


20-18 Predict the product of the following reaction.

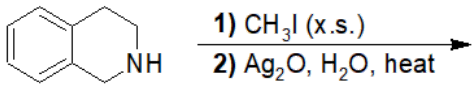


Amines as Leaving Groups: The Hofmann Elimination

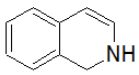
20-19 Predict the major alkene product of the following Hofmann elimination reaction and give the proper IUPAC nomenclature.



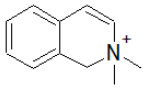
20-20 Choose the correct product of the following reaction.



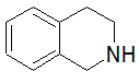
a)



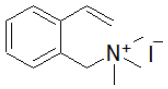
b)



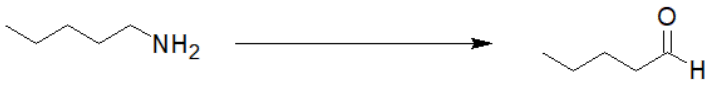
c)



d)

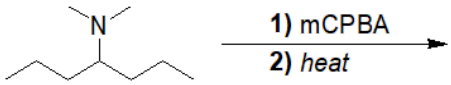


20-21 Propose a route of synthesis from pentan-1-amine to pentanal (include a Hofmann elimination reaction).

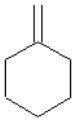


Oxidation of Amines: The Cope Elimination

20-22 Predict the structure and give the proper IUPAC nomenclature of the product of the following reaction.

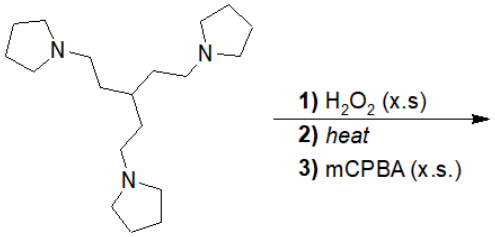


20-23 Propose a route of synthesis for the following compound, starting with cyclohexanecarboxylic acid and include a Cope elimination reaction.



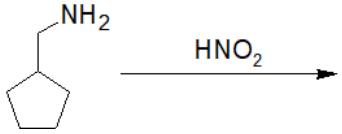
methylidenecyclohexane

20-24 Predict the structure of the product of the following reaction.



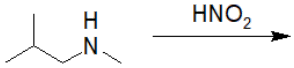
Reactions of Amines with Nitrous Acid

20-25 Predict the product of the following reaction and provide the correct IUPAC nomenclature.

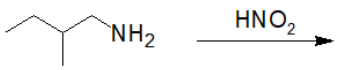


20-26 Predict the products of the following reactions.

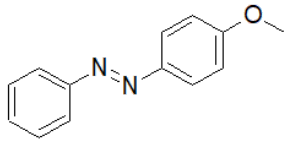
a)



b)



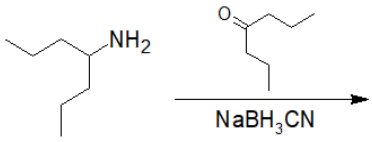
20-27 Suggest a route of synthesis for the following product, starting with aniline.



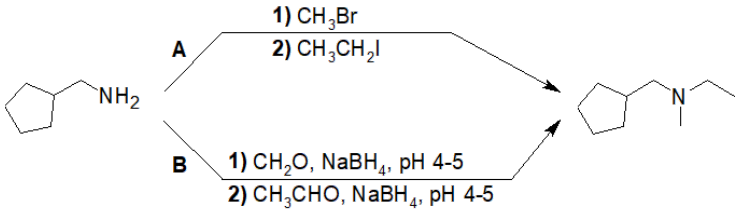
(*E*)-1-(4-methoxyphenyl)-2-phenyldiazene

Synthesis of Amines by Reductive Amination and Acylation-Reduction

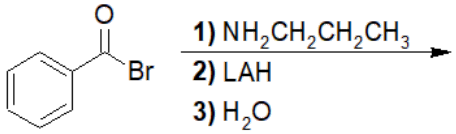
20-28 Predict the product of the following reaction and provide its IUPAC nomenclature.



20-29 Identify which route of synthesis is the better way to make N-(cyclopentylmethyl)- -N-methylethanamine and then show the intermediate molecules for the correct path.



20-30 Choose the correct IUPAC nomenclature of the product of the following reaction.



a) N-propylbenzamide

b) phenyl(propylamino)methanol

c) N-benzylpropan-1-amine

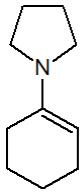
d) benzamide

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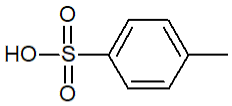
20.12: SOLUTIONS TO ADDITIONAL EXERCISES

20-1 Amine A is the more basic of the two amines. Since its lone pair of electrons cannot resonance into the ring like that of amine B, it is more basic. Amine B can delocalize its electrons, making it a weaker base but a stronger acid.

20-2

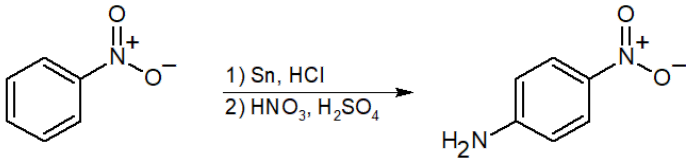


20-3



4-methylbenzene-1-sulfonic acid

20-4



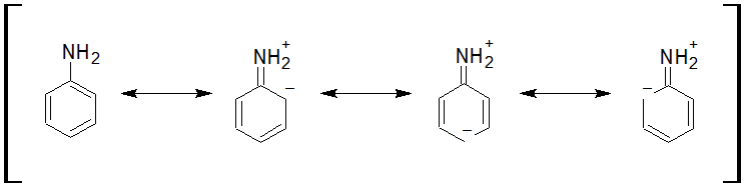
20-5 Answer: C

20-6 This reaction is not the best way to synthesize ethanamine because of the high ratio of mixed products obtained. Because the reaction occurs so fast, we are unable to stop the reaction at only the primary alkylation; the amine will continue on to make many secondary and tertiary amines in addition to our desired product.

Basicity and Effects of Amines

20-7:

Cyclohexanamine has no resonance structure that can contribute to delocalizing its lone pair of electrons.



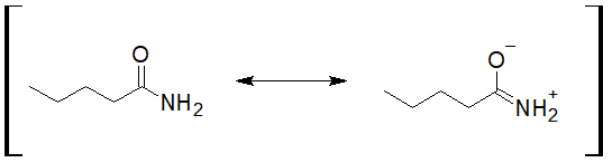
20-8:

Unlike on the para- and ortho-nitroaniline isomers, m-nitroaniline's nitro and amine groups cannot form any resonance structures to delocalize their pi-electrons with each other, making m-nitroaniline the most basic.

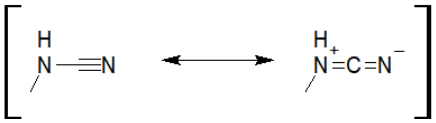
20-9:

a) and d) have no pi-acceptors directly attached to the amine.

b)



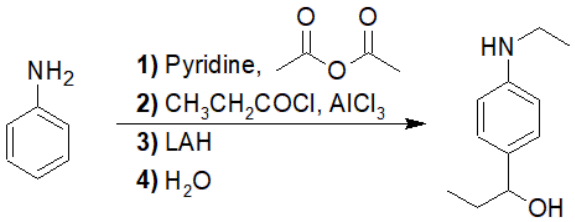
c)



Aromatic Substitution of Arylamines and Pyridine

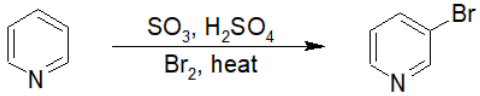
20-10:

If a protecting group is not placed on the amino group of aniline, it will form a complex with AlCl3 during the acylation step of the reaction and prevent the reaction from occurring. By placing a protecting group on the amine, we still maintain an activated ring that can give us ortho- or para- substituted products, but won't interfere with the reaction itself.

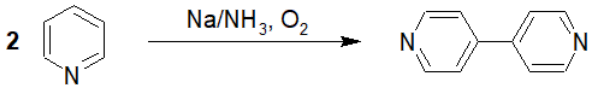


20-11:

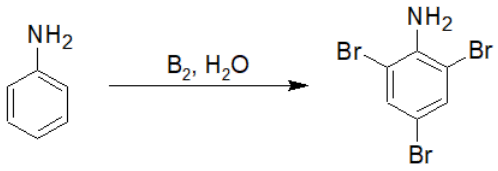
a)



b)



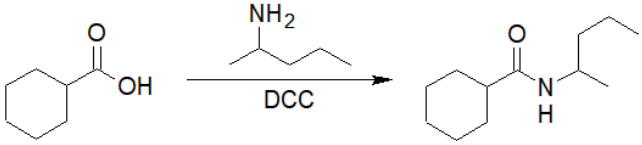
20-12:



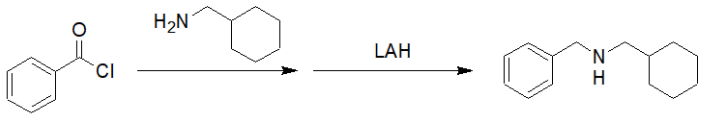
2,4,6-tribromoaniline

Alkylation and Acylation of Amines

20-13:

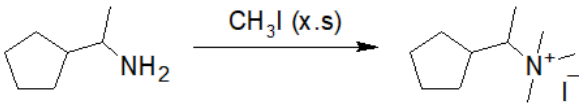


20-14:



20-15:

Answer: A

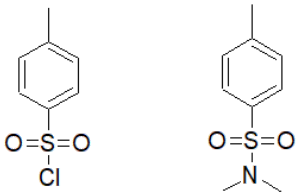


Formation of Sulfonamides

20-16:

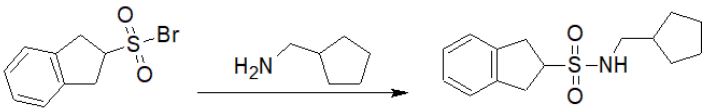
Answer: C

20-17:



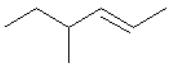
A **B**

20-18:



Amines as Leaving Groups: The Hofmann Elimination

20-19:



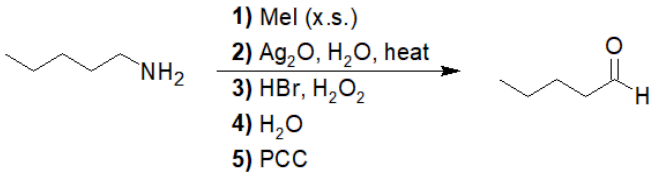
(2*E*)-4-methylhex-2-ene

20-20:

Answer: D

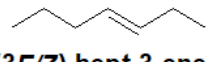
20-21:

Possible route of synthesis:



Oxidation of Amines: The Cope Elimination

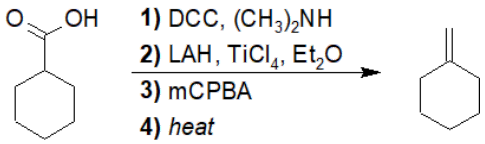
20-22:



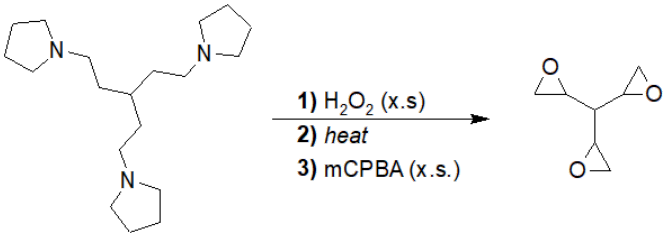
(3*E*/*Z*)-hept-3-ene

20-23:

Possible route of synthesis:

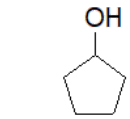


20-24:



Reactions of Amines with Nitrous Acid

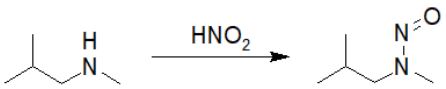
20-25:



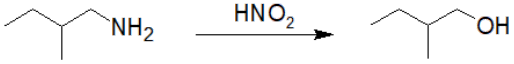
cyclopentanol

20-26:

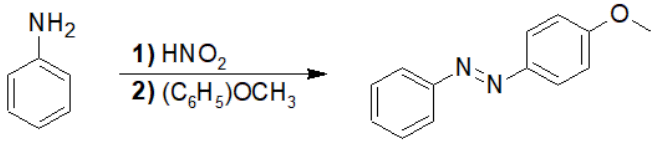
a)



b)

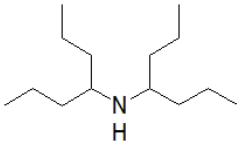


20-27:



Synthesis of Amines by Reductive Amination and Acylation-Reduction

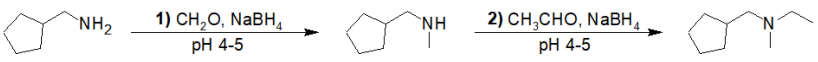
20-28:



***N*-(heptan-4-yl)heptan-4-amine**

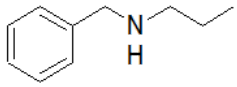
20-29:

Answer: B



20-30:

Answer: C



***N*-benzylpropan-1-amine**

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CHAPTER OVERVIEW

21: CARBOXYLIC ACIDS

After reading this chapter and completing ALL the exercises, a student can be able to

- describe the structure and physical properties of carboxylic acids and carboxylate salts (section 21.1)
- explain and predict the relative acidity of carboxylic acids using resonance, hybridization, and substituent effects (section 21.2)
- determine the structure of carboxylic acids from their elemental analysis and spectral data (MS, IR ^{1}H NMR & ^{13}C NMR) (section 21.3)
- predict the products and specify the reagents to synthesize carboxylic acids (section 21.4)
- recognize and classify the major reactions of carboxylic acids (section 21.5)
- show the general mechanism for Nucleophilic Acyl Substitution Reactions (section 21.5)
- predict the products and specify the reagents for reactions of carboxylic acids with
  - sulfonyl chlorides (section 21.5)
  - alcohols (section 21.6)
  - diazomethane (section 21.7)
  - amines (section 21.8)
  - reducing agents (section 21.9)
- combine the reactions studied to date to develop efficient and effective multiple-step synthesis

Please note: IUPAC nomenclature and important common names of carboxylic acids were explained in Chapter 3.

It can useful is often required to memorize the structures for the following common names: formic acid, acetic acid, acetyl chloride, acetic anhydride, acetic formic anhydride, ethyl acetate, sodium and potassium salts of formate, acetate, and benzoate, acetamide, benzamide, acetonitrile, benzonitrile, carbonic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, and phthalic acid

21.1: Structure and Properties of Carboxylic Acids and their Salts
21.2: Acidity of Carboxylic Acids
21.3: Spectroscopy of Carboxylic Acids
21.4: Synthesis of Carboxylic Acids
21.5: Reactions of Carboxylic Acids Overview
21.6: Condensation of Acids with Alcohols- The Fischer Esterification
21.7: Methyl Ester Synthesis Using Diazomethane
21.8: Condensation of Acids with Amines
21.9: Reduction of Carboxylic Acids
21.10: Biochemically Interesting Carboxylic Acids
21.11: Additional Exercises
21.12: Solutions to Additional Exercises

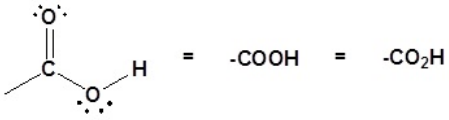
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21.1: STRUCTURE AND PROPERTIES OF CARBOXYLIC ACIDS AND THEIR SALTS

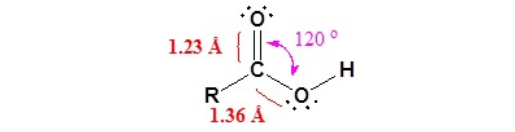
STRUCTURE OF THE CARBOXYL ACID GROUP

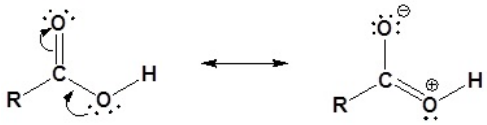
Carboxylic acids are organic compounds which incorporate a carboxyl functional group, CO_2H. The name carboxyl comes from the fact that a carbonyl and a hydroxyl group are attached to the same carbon.



Carboxyl Group

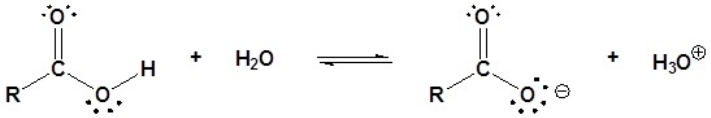
The carbon and oxygen in the carbonyl are both sp^2 hybridized which give a carbonyl group a basic trigonal shape. The hydroxyl oxygen is also sp^2 hybridized which allows one of its lone pair electrons to conjugate with the pi system of the carbonyl group. This make the carboxyl group planar an can represented with the following resonance structure.





Major Contributor Minor Contributor

Carboxylic acids are named such because they can donate a hydrogen to produce a carboxylate ion. The factors which affect the acidity of carboxylic acids are discussed in the next section of this chapter.



Carboxylic acid Carboxylate ion

PHYSICAL PROPERTIES OF SOME CARBOXYLIC ACIDS

Formula	Common Name	Source	IUPAC Name	Melting Point	Boiling Point
HCO_2H	formic acid	ants (L. formica)	methanoic acid	8.4 ºC	101 ºC
CH_3CO_2H	acetic acid	vinegar (L. acetum)	ethanoic acid	16.6 ºC	118 ºC
$CH_3CH_2CO_2H$	propionic acid	milk (Gk. protus prion)	propanoic acid	-20.8 ºC	141 ºC
$CH_3(CH_2)_2CO_2H$	butyric acid	butter (L. butyrum)	butanoic acid	-5.5 ºC	164 ºC
$CH_3(CH_2)_3CO_2H$	valeric acid	valerian root	pentanoic acid	-34.5 ºC	186 ºC
$CH_3(CH_2)_4CO_2H$	caproic acid	goats (L. caper)	hexanoic acid	-4.0 ºC	205 ºC
$CH_3(CH_2)_5CO_2H$	enanthic acid	vines (Gk. oenanthe)	heptanoic acid	-7.5 ºC	223 ºC
$CH_3(CH_2)_6CO_2H$	caprylic acid	goats (L. caper)	octanoic acid	16.3 ºC	239 ºC
$CH_3(CH_2)_7CO_2H$	pelargonic acid	pelargonium (an herb)	nonanoic acid	12.0 ºC	253 ºC
$CH_3(CH_2)_8CO_2H$	capric acid	goats (L. caper)	decanoic acid	31.0 ºC	219 ºC

Saturated			Unsaturated		
Formula	Common Name	Melting Point	Formula	Common Name	Melting Point
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 ºC	$CH_3(CH_2)_5CH{=}CH(CH_2)_7CO_2H$	palmitoleic acid	0 ºC
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 ºC	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	oleic acid	13 ºC
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 ºC	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linoleic acid	-5 ºC
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 ºC	$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linolenic acid	-11 ºC
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 ºC	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 ºC

The table at the beginning of this page gave the melting and boiling points for a homologous group of carboxylic acids having from one to ten carbon atoms. The boiling points increased with size in a regular manner, but the melting points did not. Unbranched acids made up of an even number of carbon atoms have melting points higher than the odd numbered homologs having one more or one less carbon. This reflects differences in intermolecular attractive forces in the crystalline state. In the table of fatty acids we see that the presence of a cis-double bond significantly lowers the melting point of a compound. Thus, palmitoleic acid melts over 60º lower than palmitic acid, and similar decreases occur for the C_{18} and C_{20} compounds. Again, changes in crystal packing and intermolecular forces are responsible.

The factors that influence the relative boiling points and water solubilities of various types of compounds were discussed earlier. In general, dipolar attractive forces between molecules act to increase the boiling point of a given compound, with hydrogen bonds being an extreme example. Hydrogen bonding is also a major factor in the water solubility of covalent compounds To refresh your understanding of these principles Click Here. The following table lists a few examples of these properties for some similar sized polar compounds (the non-polar hydrocarbon hexane is provided for comparison).

The first five entries all have oxygen functional groups, and the relatively high boiling points of the first two is clearly due to hydrogen bonding. Carboxylic acids have exceptionally high boiling points, due in large part to dimeric associations involving two hydrogen bonds. A structural formula for the dimer of acetic acid is shown here. When the mouse pointer passes over the drawing, an electron cloud diagram will appear. The high boiling points of the amides and nitriles are due in large part to strong dipole attractions, supplemented in some cases by hydrogen bonding.

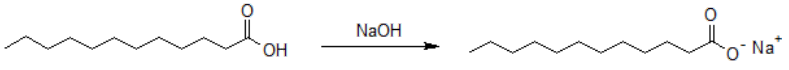


Physical Properties of Some Organic Compounds

Formula	IUPAC Name	Molecular Weight	Boiling Point	Water Solubility
$CH_3(CH_2)_2CO_2H$	butanoic acid	88	164 ºC	very soluble
$CH_3(CH_2)_4OH$	1-pentanol	88	138 ºC	slightly soluble
$CH_3(CH_2)_3CHO$	pentanal	86	103 ºC	slightly soluble
$CH_3CO_2C_2H_5$	ethyl ethanoate	88	77 ºC	moderately soluble
$CH_3CH_2CO_2CH_3$	methyl propanoate	88	80 ºC	slightly soluble
$CH_3(CH_2)_2CONH_2$	butanamide	87	216 ºC	soluble
$CH_3CON(CH_3)_2$	N,N-dimethylethanamide	87	165 ºC	very soluble
$CH_3(CH_2)_4NH_2$	1-aminobutane	87	103 ºC	very soluble
$CH_3(CH_2)_3CN$	pentanenitrile	83	140 ºC	slightly soluble
$CH_3(CH_2)_4CH_3$	hexane	86	69 ºC	insoluble

CARBOXYLATE SALTS

The water solubility of carboxylic acids is determined by the ratio of carboxyl groups to the the number of carbon atoms in the molecule following the "4 to 6 Rule". As seen with amines, water solubility of carboxylic acids can be increased when they are ionized. Typically a strong base is used to deprotonate the carboxylic acid and drive the reaction to completion as shown below.



NOT H_2O Soluble $\qquad$ H_2O Soluble

Exercise

1. Use acid-base chemistry and differences in water solubility to separate 1-octanol from octanoic acid using the following solutions: 1 M NaOH, ether, and 6 M HCl and any lab equipment.

Answer

1.

CONTRIBUTORS AND ATTRIBUTIONS

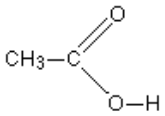
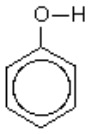
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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21.2: ACIDITY OF CARBOXYLIC ACIDS

COMPARING THE STRENGTHS OF WEAK ACIDS

The strengths of weak acids are measured on the pK_a scale. The smaller the number on this scale, the stronger the acid is. Three of the compounds we shall be looking at, together with their pK_a values are:

		pK_a
ethanoic acid		4.76
phenol		10.00
ethanol	$CH_3—CH_2—O—H$	about 16

Remember - the smaller the pKa, the stronger the acid. Comparing the other two to ethanoic acid, we see that phenol is very much weaker with a pK_a of 10.00, and ethanol is so weak with a pK_a of about 16 that it hardly counts as acidic at all! The pKa of ethanol is about 17, while the pKa of acetic acid is about 5: this is a 10^{12}-fold difference in the two acidity constants. In both compounds, the acidic proton is bonded to an oxygen atom. How can they be so different in terms of acidity? We begin by considering the conjugate bases.

In both species, the negative charge on the conjugate base is held by an oxygen, so periodic trends cannot be invoked. For acetic acid, however, there is a key difference: a resonance contributor can be drawn in which the negative charge is localized on the second oxygen of the group. The two resonance forms for the conjugate base are equal in energy. What this means is that the negative charge on the acetate ion is not located on one oxygen or the other: rather it is shared between the two. Chemists use the term ‘delocalization of charge’ to describe this situation. In the ethoxide ion, by contrast, the negative charge is ‘locked’ on the single oxygen – it has nowhere else to go.

Recall the fundamental idea that electrostatic charges, whether positive or negative, are more stable when they are ‘spread out’ than when they are confined to one atom. Here, a charge is being ‘spread out’ (in other words, delocalized) *by resonance*, rather than simply by the size of the atom involved.

The delocalization of charge by resonance has a very powerful effect on the reactivity of organic molecules, enough to account for the difference of over 12 pK_a units between ethanol and acetic acid. The acetate ion is that much more stable than the ethoxide ion, all due to the effects of resonance delocalization.

RESONANCE EFFECTS ON THE ACIDITY OF CARBOXYLIC ACIDS

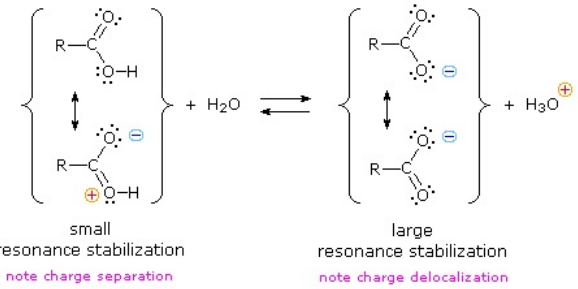
Why should the presence of a carbonyl group adjacent to a hydroxyl group have such a profound effect on the acidity of the hydroxyl proton? To answer this question we must return to the nature of acid-base equilibria and the definition of pK_a , illustrated by the general equations given below.

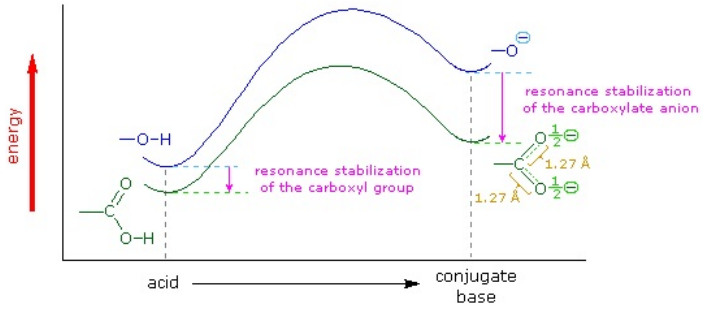
$$H–A + H_2O \rightleftharpoons H_3O^{\oplus} + A:^{\ominus} \qquad K_{eq} = \frac{[H_3O^{\oplus}]\,[A:^{\ominus}]}{[HA]\,[H_2O]}$$

$$K_a = \frac{[H_3O^{\oplus}]\,[A:^{\ominus}]}{[HA]} \qquad pK_a = -\log K_a = \log\left(\frac{1}{K_a}\right)$$

We know that an equilibrium favors the thermodynamically more stable side, and that the magnitude of the equilibrium constant reflects the energy difference between the components of each side. In an acid base equilibrium the equilibrium always favors the weaker acid and base (these are the more stable components). Water is the standard base used for pK_a measurements; consequently, anything that stabilizes the conjugate base ($A:^{(-)}$) of an acid will necessarily make that acid (H–A) stronger and shift the equilibrium to the right. Both the carboxyl group and the carboxylate anion are stabilized by resonance, but the stabilization of the anion is much greater than that of the neutral function, as shown in the following diagram. In the carboxylate anion the two contributing structures have equal weight in the hybrid, and

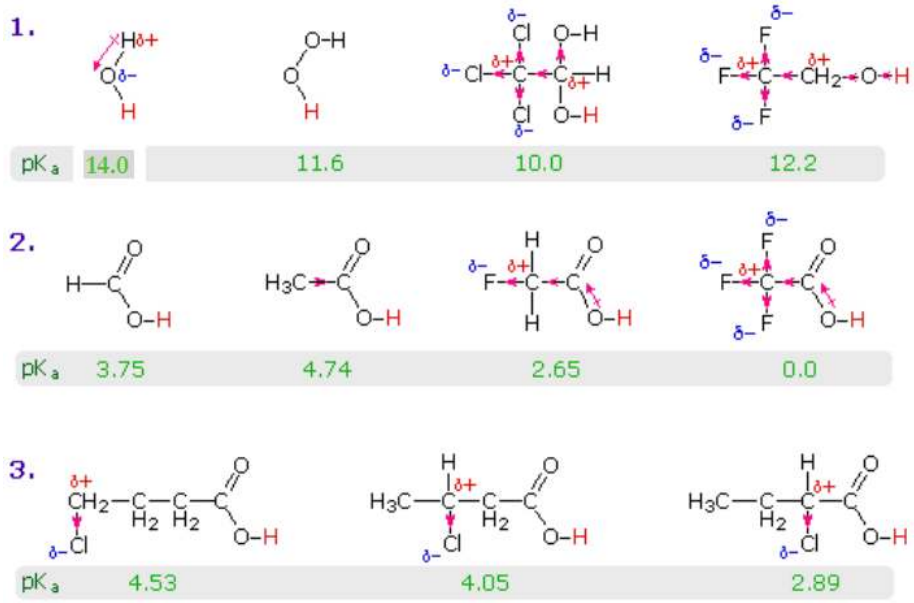
the C–O bonds are of equal length (between a double and a single bond). This stabilization leads to a markedly increased acidity, as illustrated by the energy diagram displayed by clicking the "Toggle Display" button.



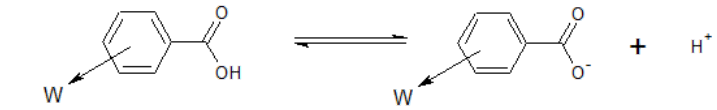


INDUCTIVE EFFECTS ON RELATIVE ACIDITY

The resonance effect described here is undoubtedly the major contributor to the exceptional acidity of carboxylic acids. However, inductive effects also play a role. For example, alcohols have pK_a's of 16 or greater but their acidity is increased by electron withdrawing substituents on the alkyl group. The following diagram illustrates this factor for several simple inorganic and organic compounds (row #1), and shows how inductive electron withdrawal may also increase the acidity of carboxylic acids (rows #2 & 3). The acidic hydrogen is colored red in all examples. Water is less acidic than hydrogen peroxide because hydrogen is less electronegative than oxygen, and the covalent bond joining these atoms is polarized in the manner shown. Alcohols are slightly less acidic than water, due to the poor electronegativity of carbon, but chloral hydrate, $Cl_3CCH(OH)_2$, and 2,2,2,-trifluoroethanol are significantly more acidic than water, due to inductive electron withdrawal by the electronegative halogens (and the second oxygen in chloral hydrate). In the case of carboxylic acids, if the electrophilic character of the carbonyl carbon is decreased the acidity of the carboxylic acid will also decrease. Similarly, an increase in its electrophilicity will increase the acidity of the acid. Acetic acid is ten times weaker an acid than formic acid (first two entries in the second row), confirming the electron donating character of an alkyl group relative to hydrogen, as noted earlier in a discussion of carbocation stability. Electronegative substituents increase acidity by inductive electron withdrawal. As expected, the higher the electronegativity of the substituent the greater the increase in acidity (F > Cl > Br > I), and the closer the substituent is to the carboxyl group the greater is its effect (isomers in the 3rd row). Substituents also influence the acidity of benzoic acid derivatives, but resonance effects compete with inductive effects. The methoxy group is electron donating and the nitro group is electron withdrawing (last three entries in the table of pK_a values).



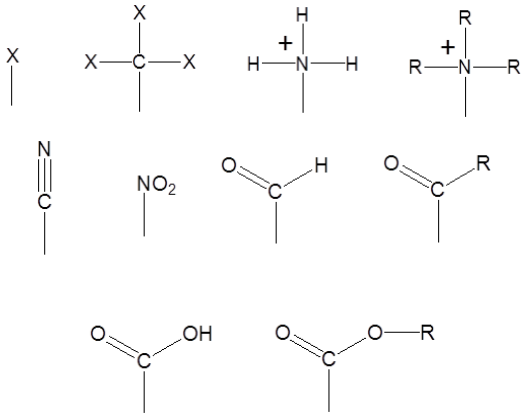
A closer look at the effects of electron-withdrawing and electron-donating groups on the stability of the conjugate bases can be seen in the pKa values of benzoic acid as shown in the table below. The conjugate base of benzoic acid is stabilized by electron-withdrawing groups. This makes the acid more acidic



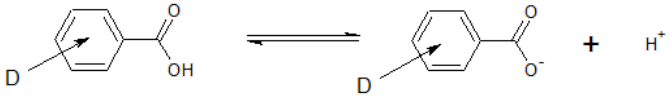
W = electron Withdrawing group

The carboxylate anion is stabilized by the electron withdrawing group increasing the acidity of the conjugate acid.

Electron-withdrawing groups deactivate the benzene ring to electrophilic reactions and make benzoic acids more acidic.



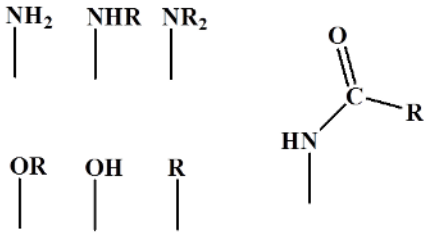
The conjugate base of benzoic acid is destabilized by electron-donating groups. This makes the acid less acidic



D = electron Donating group

The carboxylate anion is destabilized by the electron withdrawing group decreasing the acidity of the conjugate acid.

Electron-donating groups activate the benzene ring to electrophilic reactions and make benzoic acids less acidic.

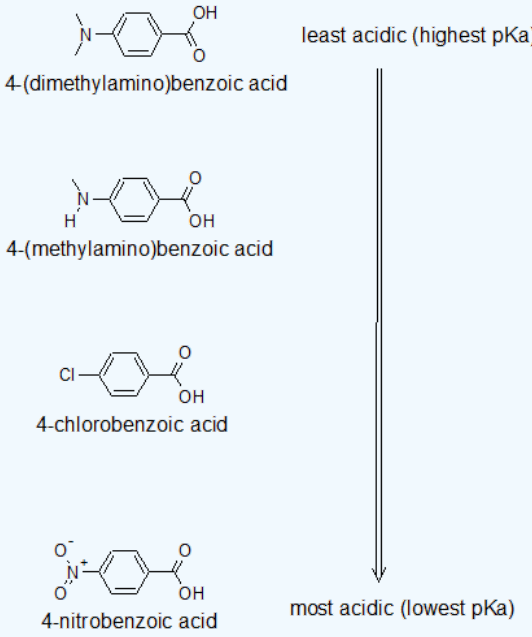


Exercise

2. Draw the bond-line structures and arrange the following compounds in order of increasing acidity: 4-nitrobenzoic acid; 4-(methylamino)benzoic acid; p-chlorobenzoic acid; 4-(dimethylamino)benzoic acid.

Answer

2.



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Tom Neils (Grand Rapids Community College)

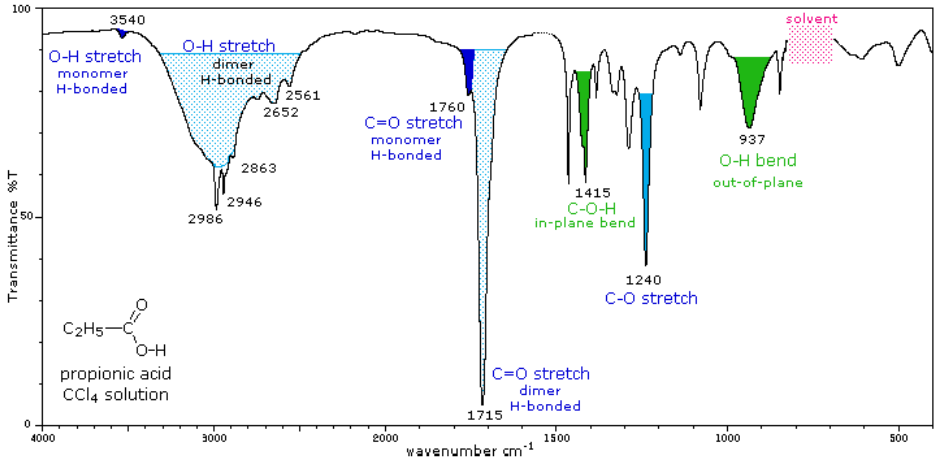
21.2: Acidity of Carboxylic Acids is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

21.3: SPECTROSCOPY OF CARBOXYLIC ACIDS

IR

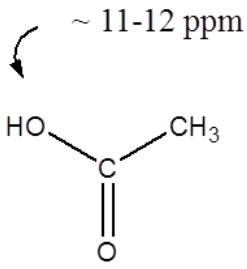
The carboxyl group is associated with two characteristic infrared stretching absorptions which change markedly with hydrogen bonding. The spectrum of a CCl_4 solution of propionic acid (propanoic acid), shown below, is illustrative. Carboxylic acids exist predominantly as hydrogen bonded dimers in condensed phases. The O-H stretching absorption for such dimers is very strong and broad, extending from 2500 to 3300 cm^{-1}.

This absorption overlaps the sharper C-H stretching peaks, which may be seen extending beyond the O-H envelope at 2990, 2950 and 2870 cm^{-1}. The smaller peaks protruding near 2655 and 2560 are characteristic of the dimer. In ether solvents a sharper hydrogen bonded monomer absorption near 3500 cm^{-1} is observed, due to competition of the ether oxygen as a hydrogen bond acceptor. The carbonyl stretching frequency of the dimer is found near 1710 cm^{-1}, but is increased by 25 cm^{-1} or more in the monomeric state. Other characteristic stretching and bending absorptions are marked in the spectrum.

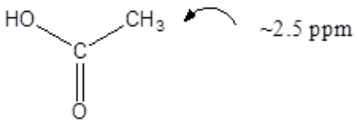


NMR

The combination of anisotropy and electronegativity causes the O-H hydrogen in a carboxylic acid to be very deshielded.



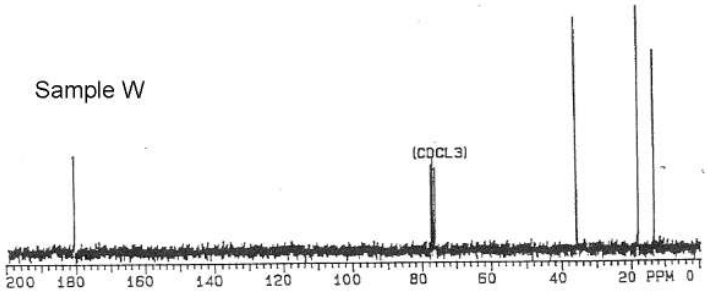
Hydrogen environments adjacent to a carboxylic acid are shifted to the region of 2.5-3.0 ppm.Deshielding occurs due to the fact that the sp2 hybridized carbon the the carboxylic acid is more electronegative than a sp3 hybridized carbon.

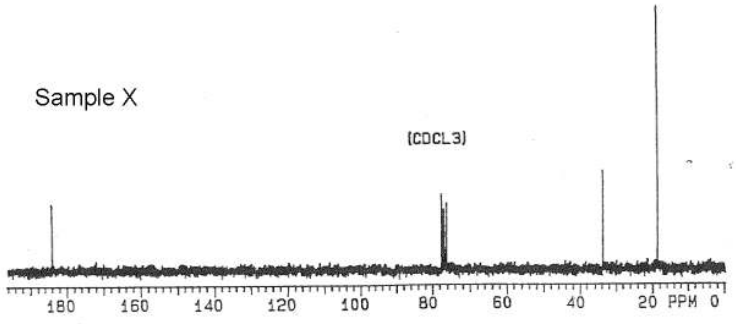


Exercise

2. Sample W is a reactant for a wide range of biochemical processes. Sample X was isolated from vanilla beans. Elemental analysis indicated the compounds are structural isomers with the composition: 54.52% C, 9.16% H and 36.32% O. The IR spectrum for each compound showed a broad absorption from 3500 - 2500 cm-1 and a strong band near 1710 cm-1. The ^{1}H NMR is being serviced, so only the ^{13}C NMR spectra shown below were available.

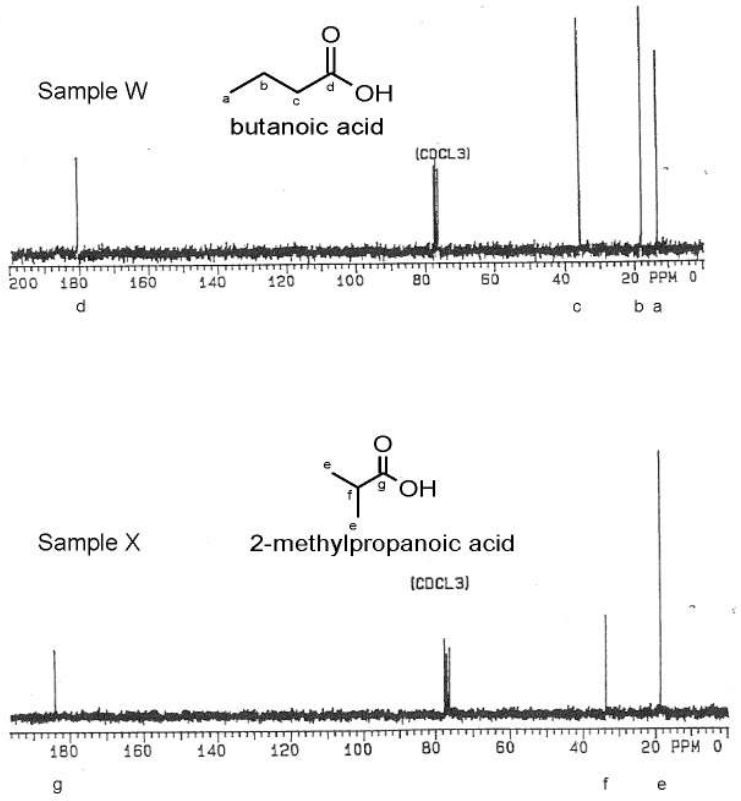
Name and draw the bond-line structures for Samples W and X and correlate the 13C NMR spectral signals to their respective compounds.





Answer

2.



CONTRIBUTORS AND ATTRIBUTIONS

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

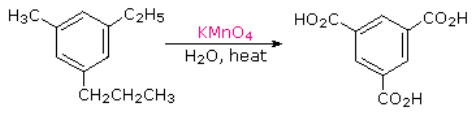
21.3: Spectroscopy of Carboxylic Acids is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

21.4: SYNTHESIS OF CARBOXYLIC ACIDS

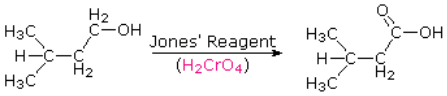
CARBOXYLIC ACID SYNTHESIS - REVIEW

The carbon atom of a carboxyl group has a high oxidation state. It is not surprising, therefore, that many of the chemical reactions used for their preparation are oxidations. Such reactions have been discussed in previous sections of this text, and the following diagram summarizes most of these. To review the previous discussion of any of these reaction classes simply click on the number (**1** to **4**) or descriptive heading for the group.

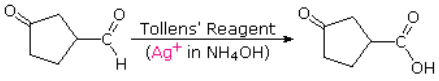
1. Oxidation of Arene Side-Chains



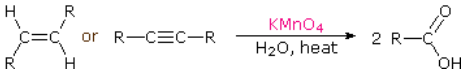
2. Oxidation of 1°-Alcohols



3. Oxidation of Aldehydes



4. Oxidative Cleavage of Alkenes and Alkynes

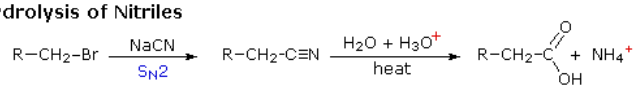


CARBOXYLIC ACID SYNTHESIS - NEW

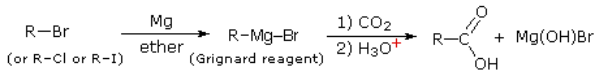
Two other useful procedures for preparing carboxylic acids involve hydrolysis of nitriles and carboxylation of organometallic intermediates. As shown in the following diagram, both methods begin with an organic halogen compound and the carboxyl group eventually replaces the halogen. Both methods require two steps, but are complementary in that the nitrile intermediate in the first procedure is generated by a S_N2 reaction, in which cyanide anion is a nucleophilic precursor of the carboxyl group. The hydrolysis may be either acid or base-catalyzed, but the latter give a carboxylate salt as the initial product.

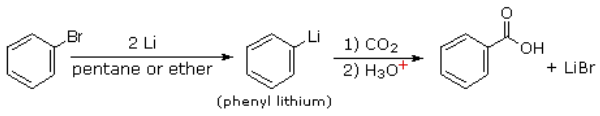
In the second procedure the electrophilic halide is first transformed into a strongly nucleophilic metal derivative, and this adds to carbon dioxide (an electrophile). The initial product is a salt of the carboxylic acid, which must then be released by treatment with strong aqueous acid.

Hydrolysis of Nitriles



Carboxylation of Organometallic Reagents



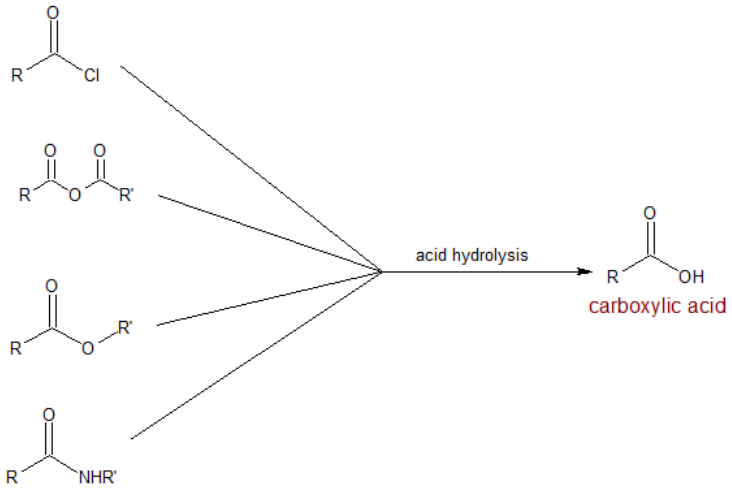


An existing carboxylic acid may be elongated by one methylene group, using a homologation procedure called the **Arndt-Eistert reaction**. To learn about this useful method Click Here.

HYDROLYSIS OF CARBOXYLIC ACID DERIVATIVES AND NITRILES

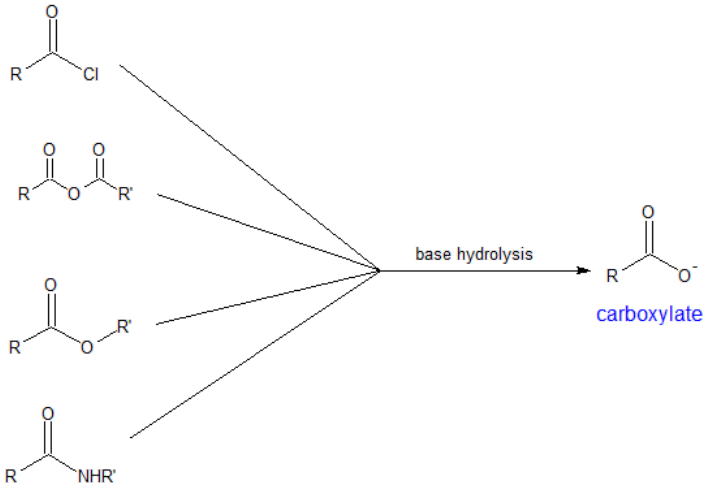
In this chapter we learn that all of the carboxylic acid derivatives can be synthesized from carboxylic acids. These reactions tend to be more useful for multiple-step syntheses to build large and complex molecules. The carboxylic acid derivatives along can be hydrolyzed to produce carboxylic acids. These hydrolysis reactions have limited use in multiple-step synthesis because the acidic proton can be problematic for many organic reactions. Biochemically, hydrolysis reactions are very important in the metabolism of food, drugs, and other nutrients. Hydrolysis can occur under acidic or basic conditions that determine the ionization of the carboxylic acid. Reactions under basic conditions will require a final neutralization step with dilute H^+ to recover the carboxylic acid. To reinforce our awareness of the pH sensitivity of carboxylic acids, both reaction maps are shown below.

- Acid Hydrolysis of the Carboxylic Acid Derivatives



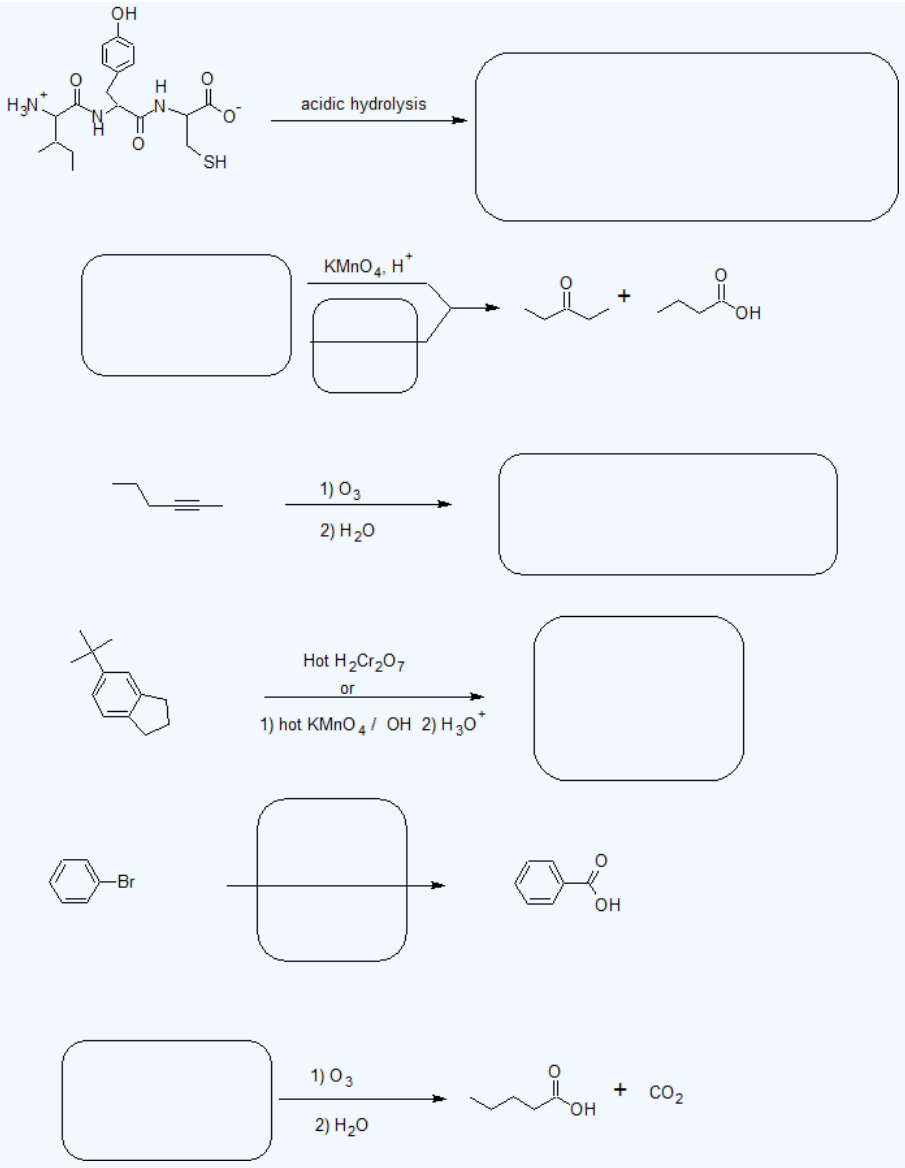
Helpful Hint: Different professors tend to use different proton sources. It is helpful to recognize reagents for their role in a reaction. For example, H_2SO_4, HCl, H_3PO_4, CH_3CO_2H, and p-TSA are all sources of H^+. It does not matter which one is used for catalysis or neutralization. Nitric acid is oxidizing, so it is typically only used in oxidation reactions. As we continue learning more reactions/reagents, it can help to group them by their reactivity: acids, bases, neutral, oxidizing, reducing, protic, aprotic, etc. For example, peroxides are oxidizing - whether is it H_2O_2 or MCPBA (m-chloroperoxybenzoic acid).

- Basic Hydrolysis of the Carboxylic Acid Derivatives



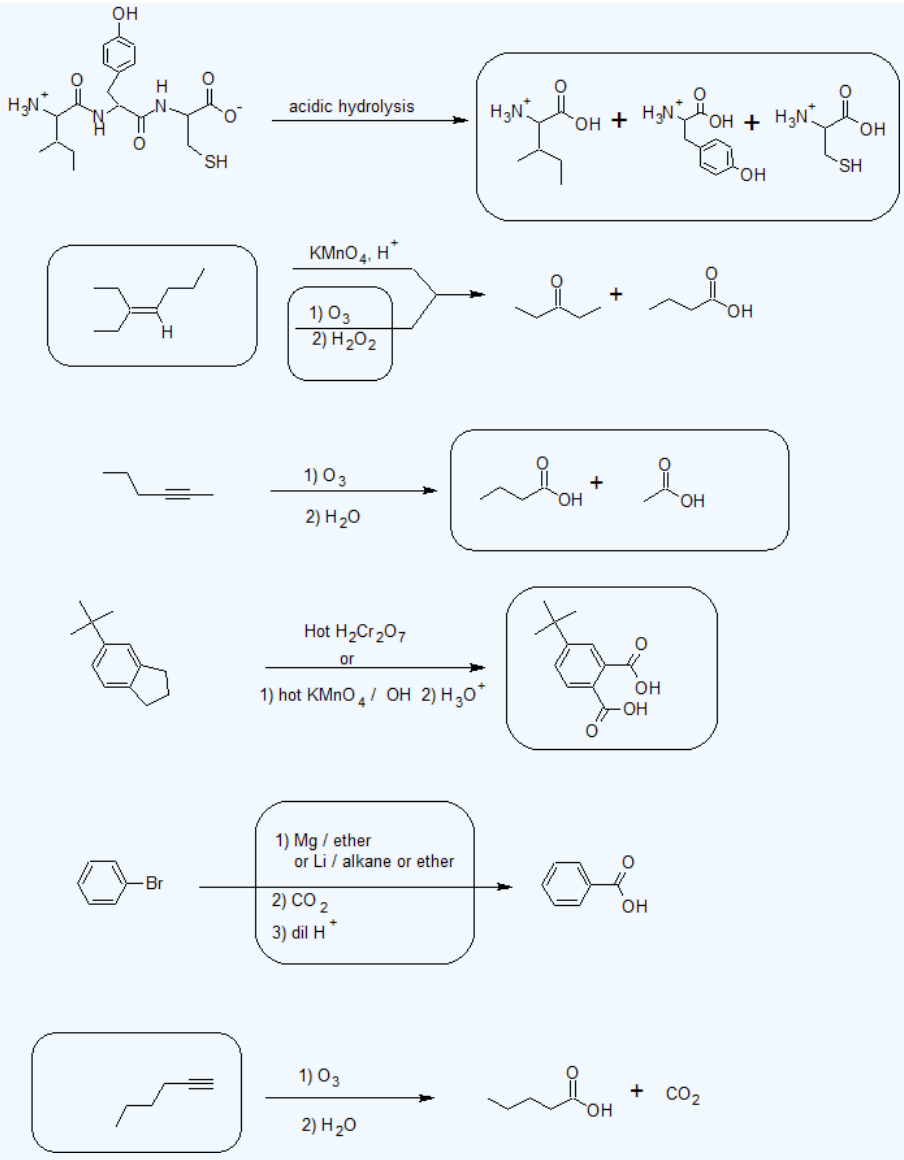
Exercise

4. Complete the reactions below.


OH
acidic hydrolysis
SH
KMnO4, H+
OH
1) O3
2) H2O
Hot H2Cr2O7
or
1) hot KMnO4 / OH 2) H3O+
Br
OH
1) O3
2) H2O
OH
+ CO2

Answer

4.



CONTRIBUTORS AND ATTRIBUTIONS

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

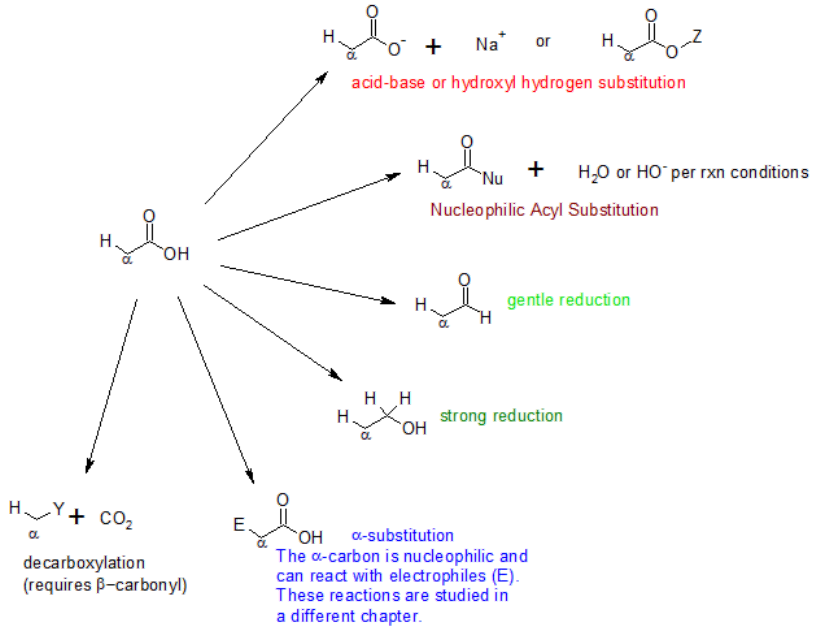
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21.5: REACTIONS OF CARBOXYLIC ACIDS OVERVIEW

CARBOXYLIC ACID REACTIONS OVERVIEW

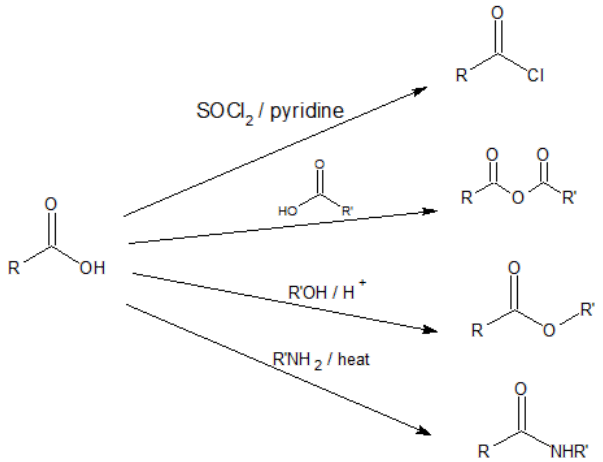
Four general reaction categories are represented here: (1) As carboxylic acid deprotonates quite readily, it is quite easy to form a carboxylate salt or to substitute the hydroxyl hydrogen. (2) The category of nucleophilic acyl substitution represents the substitution of the whole hydroxyl group, which we will see later in more detail leads to several carboxylic acid derivatives (e.g. acid halides, esters, amides, thioesters, acid anhydrides etc.). (3) Like other carbonyl compounds, carboxylic acids can be reduced by reagents like $LiAlH_4$. (4) While the proton on the carbon alpha to the carbonyl group is not as acidic as the hydroxyl hydrogen, it can be removed leading to substitution at the alpha site.

The scheme summarizes some of the general reactions that carboxylic acids undergo. The reaction details can be found in other sections of this text.

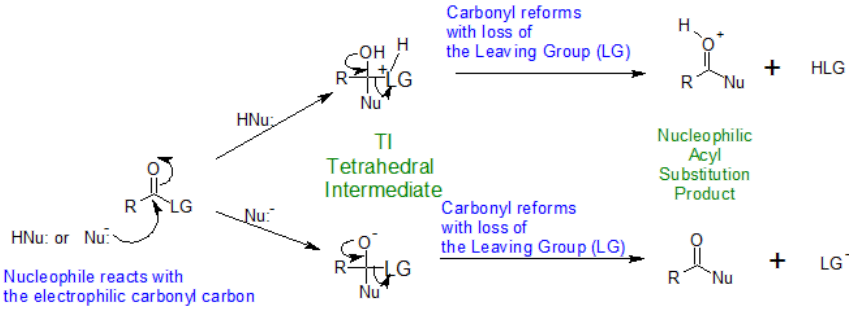


NUCLEOPHILIC ACYL SUBSTITUTION REACTIONS AND THE CARBOXYLIC ACID DERIVATIVES

In subsequent sections, the reaction details to synthesize acyl chlorides, anhydrides, esters, and amides from carboxylic acids will be discussed. Because acyl chlorides, anhydrides, esters, and amides can all be synthesized from carboxylic acids, these functional groups are called "carboxylic acid derivatives".

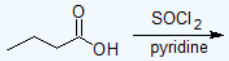


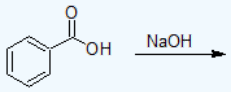
These reactions all share the same general mechanism. The nucleophile reacts with the electrophilic carbonyl carbon to produce the "Tetrahedral Intermediate or TI". The carbonyl reforms forcing the loss of the leaving group (LG) to produce the "Nucleophilic Acyl Substitution Product". The reaction mechanism depends on the pH of the reaction conditions. The reaction mechanisms for both acidic and basic conditions are shown below.

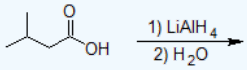


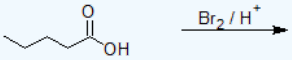
Exercise

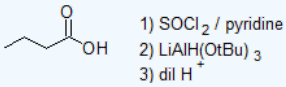
5. Draw the bond-line structures for the products and classify each reaction using the terms from the top diagram: acid-base, NAS (Nucleophilic Acyl Substitutioin), gentle reduction, strong reduction, or alpha-substitution.





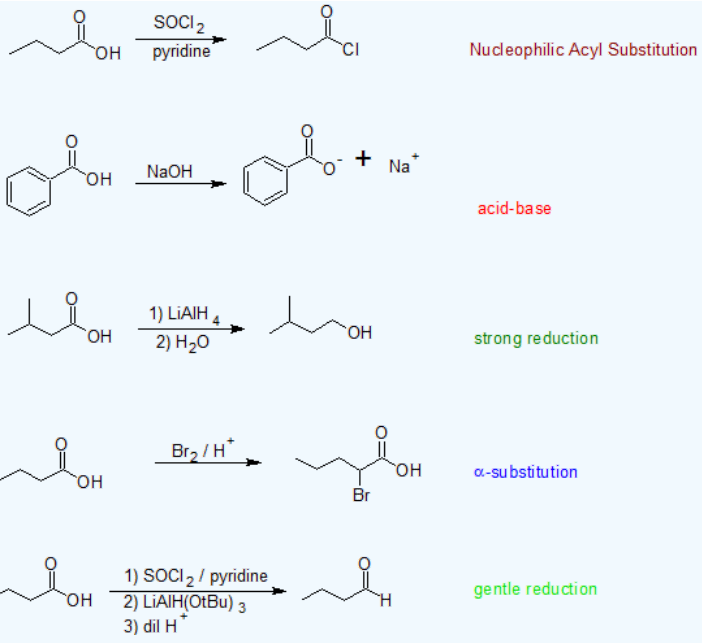






Answer

5.



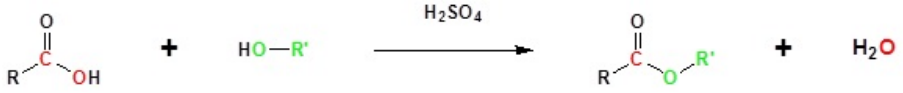
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- Prof. Steven Farmer (Sonoma State University)

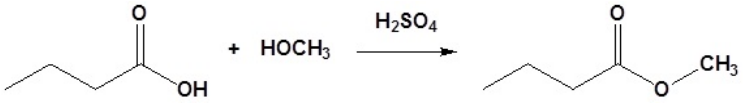
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21.6: CONDENSATION OF ACIDS WITH ALCOHOLS- THE FISCHER ESTERIFICATION

Carboxylic acids can react with alcohols to form esters in a process called Fischer esterification. An acid catalyst is required and the alcohol is also used as the reaction solvent. The oxygen atoms are color-coded in the reaction below to help understand the reaction mechanism.

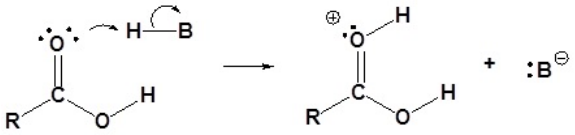


For example, butanoic acid reacts with methanol to synthsize methylbutanoate. It is important to note that any proton source can be used as the catalyst. Sulfuric acid is shown in the example below.

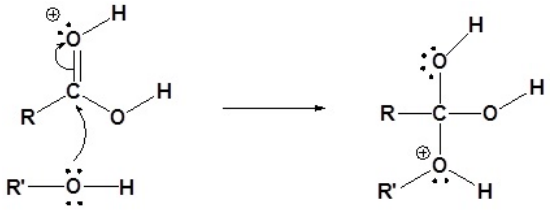


MECHANISM

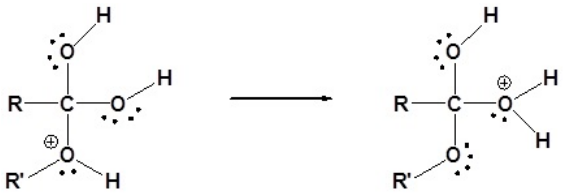
1) Protonation of the carbonyl by the acid. The carbonyl is now activated toward nucleophilic reactions.



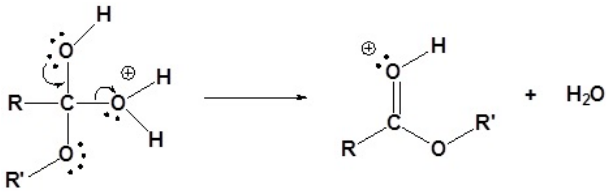
2) Nucleophilic reaction at the carbonyl



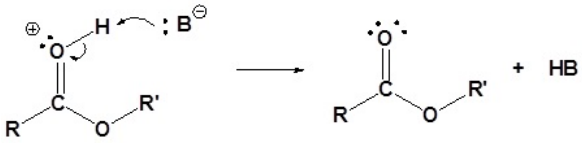
3) Proton transfer



4) Water leaves

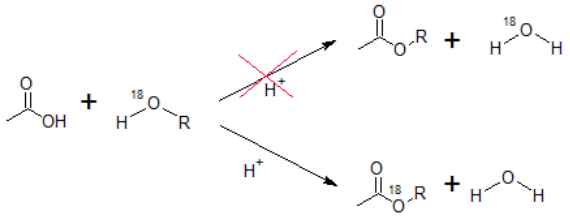


5) Deprotonation



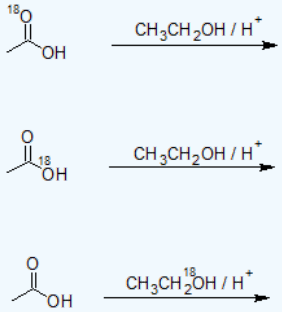
ISOTOPIC LABELING

Evidence to support the Fischer esterfication mechanism comes from isotopic labeling experiments with oxygen-18. If the reaction is carried out with oxygen-18 labeled alcohol, the isotope is found exclusively in the ester and not the water generated.



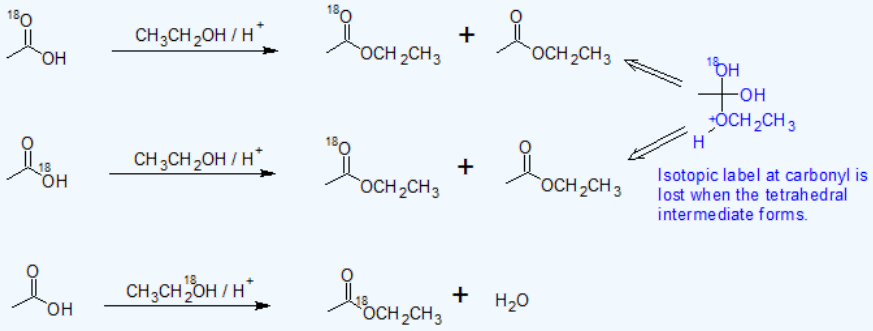
Exercise

6. Draw the bond-line structures for the products of the following reactions.



Answer

6.



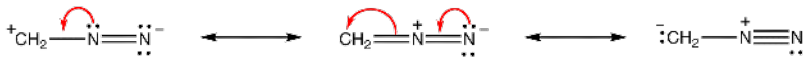
CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

21.6: Condensation of Acids with Alcohols- The Fischer Esterification is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

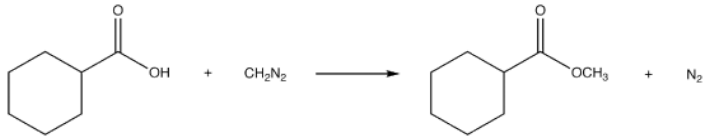
21.7: METHYL ESTER SYNTHESIS USING DIAZOMETHANE

Diazomethane, CH_2N_2, is a yellow, poisonous, potentially explosive compound, which is a gas at room temperature. The structure of diazomethane is explained using three resonance forms.

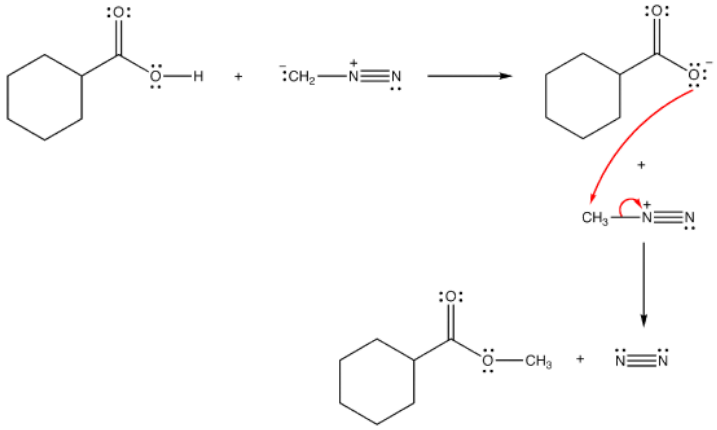


CONVERSION OF CARBOXYLIC ACIDS TO METHYL ESTERS

Carboxylic acids react with diazomethane to produce methyl esters. Because of the high reactivity of diazomethane, it is produced in-situ and then immediately reacted with the carboxylic acid to produce the methyl ester.



The first step of the mechanism is a simple acid-base reaction to deprotonate the carboxylic acid. The carboxylate is then the nucleophile of an S_N2 reaction with protonated diazomethane to produce the methyl ester with nitrogen gas as a leaving group. It is important to keep reaction vessels vented when gases are produced to avoid explosions.



CONTRIBUTORS AND ATTRIBUTIONS

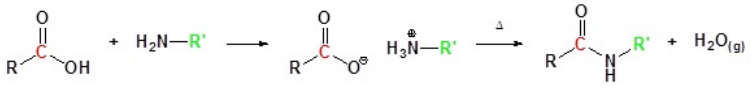
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

21.7: Methyl Ester Synthesis Using Diazomethane is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

21.8: CONDENSATION OF ACIDS WITH AMINES

CONVERSION OF CARBOXYLIC ACIDS TO AMIDES

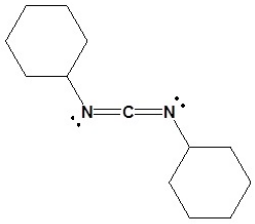
The direct reaction of a carboxylic acid with an amine would be expected to be difficult because the basic amine would deprotonate the carboxylic acid to form a highly unreactive carboxylate. However when the ammonium carboxylate salt is heated to a temperature above 100 ^{o}C water is driven off and an amide is formed.



Ammonium Carboxylate Salt

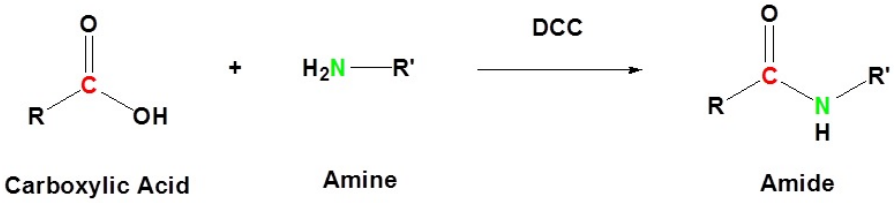
CONVERSION OF CARBOXYLIC ACIDS TO AMIDE USING DCC AS AN ACTIVATING AGENT

The direct conversion of a carboxylic acid to an amide is difficult because amines are basic and tend to convert carboxylic acids to their highly unreactive carboxylates. In this reaction the carboxylic acid adds to the DCC molecule to form a good leaving group which can then be displaced by an amine during nucleophilic substitution.



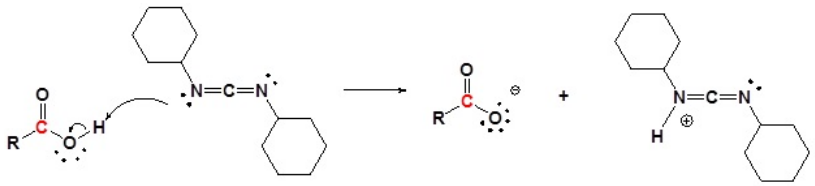
Dicyclohexylcarbodiimide (DCC)

DCC induced coupling to form an amide linkage is an important reaction in the synthesis of peptides.

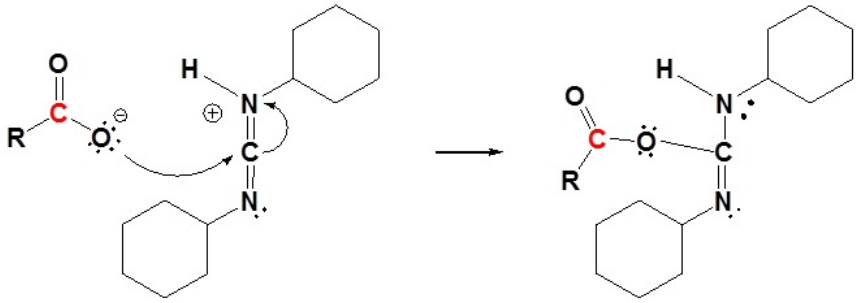


MECHANISM

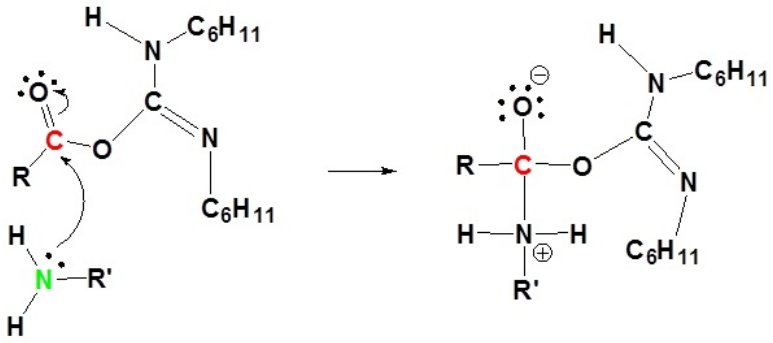
1) Deprotonation



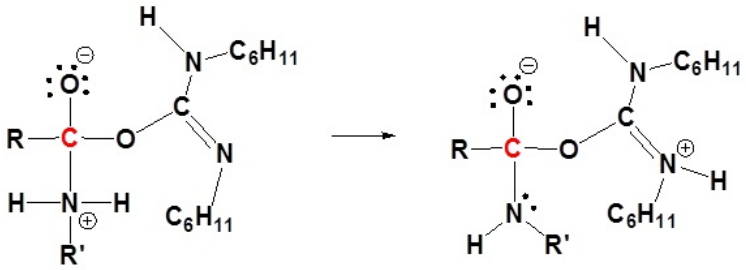
2) Nucleophilic reaction with carboxylate acting as the nucleophile



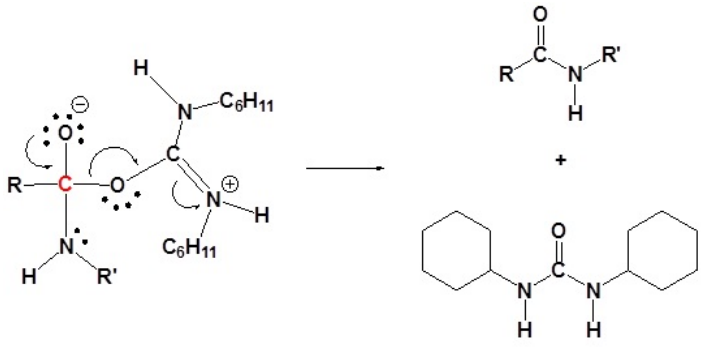
3) Nucleophilic reaction with the amine acting as the nucleophile



4) Proton transfer

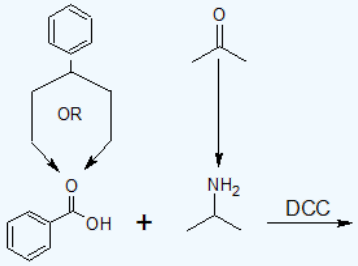


5) Leaving group removal



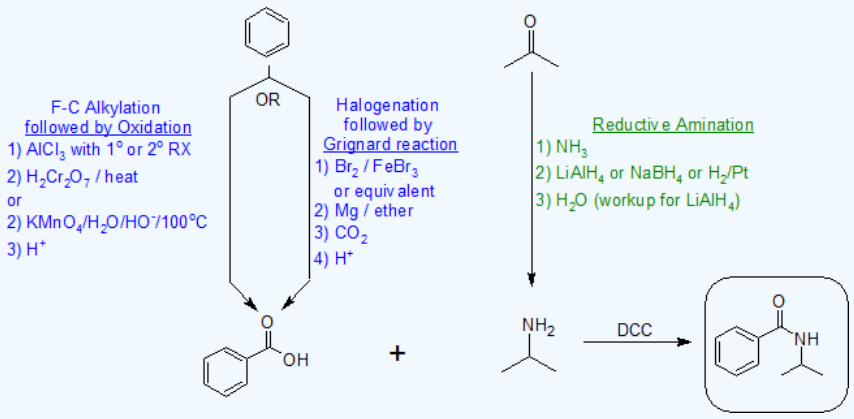
Exercise

7. Complete the reaction map below proposing two different ways to synthesize benzoic acid from benzene.



Answer

7.



CONTRIBUTORS AND ATTRIBUTIONS

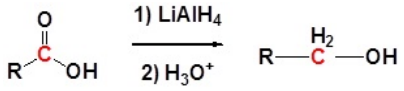
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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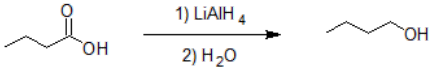
21.9: REDUCTION OF CARBOXYLIC ACIDS

CARBOXYLIC ACIDS CAN BE CONVERTED TO 1^{O} ALCOHOLS USING LITHIUM ALUMINUM HYDRIDE ($LiAlH_4$)

Note that $NaBH_4$ is not strong enough to convert carboxylic acids or esters to alcohols. An aldehyde is produced as an intermediate during this reaction, but it cannot be isolated because it is more reactive than the original carboxylic acid.



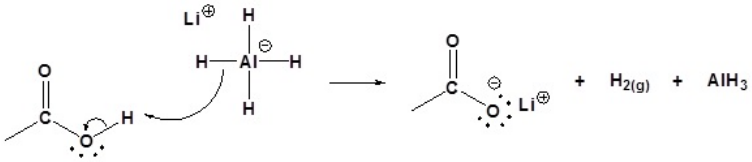
For example, butanoic acid can be reduced to butanol when reacted with lithium aluminum hydride as shown below.



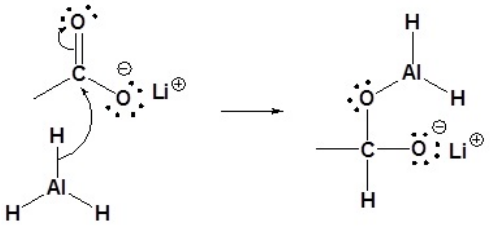
POSSIBLE MECHANISM

There is not complete agreement on the mechanism for this reaction. However, the mechanism below is considered probable by many chemists.

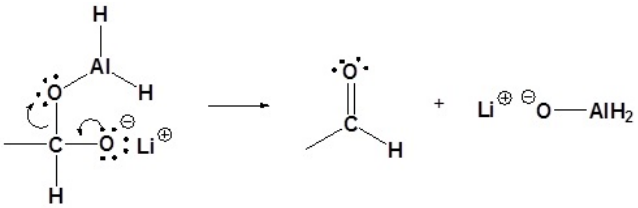
1) Deprotonation



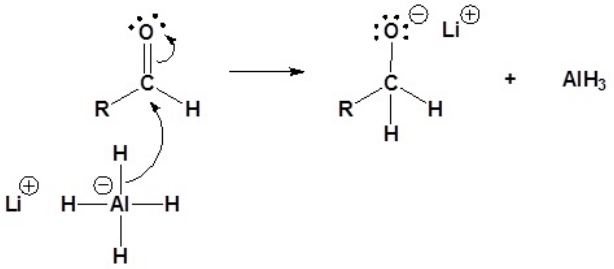
2) Nucleopilic reaction by the hydride anion



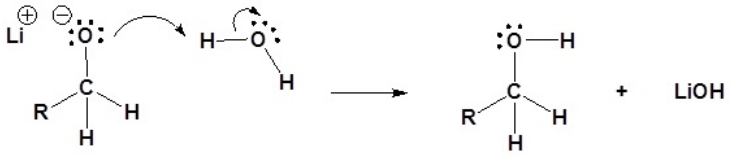
3) Leaving group removal



4) Nucleopilic reaction by the hydride anion



5) The alkoxide is protonated

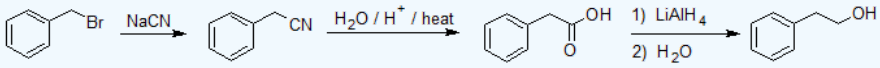


Exercise

8. Using benzyl bromide and sodium cyanide as the only source of carbons, propose a synthetic strategy to produce 2-phenyl-ethan-1-ol.

Answer

8.



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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21.10: BIOCHEMICALLY INTERESTING CARBOXYLIC ACIDS

Carboxylic acids are widespread in nature, often combined with other functional groups. Simple alkyl carboxylic acids, composed of four to ten carbon atoms, are liquids or low melting solids having very unpleasant odors. The **fatty acids** are important components of the biomolecules known as **lipids**, especially fats and oils. As shown in the following table, these long-chain carboxylic acids are usually referred to by their common names, which in most cases reflect their sources. A mnemonic phrase for the C_{10} to C_{20} natural fatty acids capric, lauric, myristic, palmitic, stearic and arachidic is: "**C**urly, **L**arry & **M**oe **P**erform **S**illy **A**ntics" (note that the names of the three stooges are in alphabetical order).

Interestingly, the molecules of most natural fatty acids have an even number of carbon atoms. Analogous compounds composed of odd numbers of carbon atoms are perfectly stable and have been made synthetically. Since nature makes these long-chain acids by linking together acetate units, it is not surprising that the carbon atoms composing the natural products are multiples of two. The double bonds in the unsaturated compounds listed on the right are all cis (or Z).

FATTY ACIDS

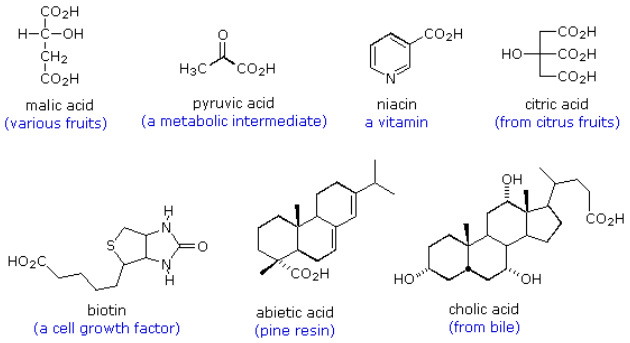
Saturated

Formula	Common Name	Melting Point
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 °C
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 °C
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 °C
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 °C
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 °C

UNSATURATED

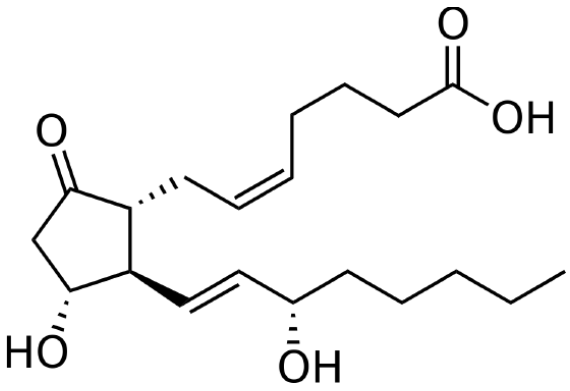
Formula	Common Name	Melting Point
$CH_3(CH_2)_5CH=CH(CH_2)_7CO_2H$	palmitoleic acid	0 °C
$CH_3(CH_2)_7CH=CH(CH_2)_7CO_2H$	oleic acid	13 °C
$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linoleic acid	-5 °C
$CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linolenic acid	-11 °C
$CH_3(CH_2)_4(CH=CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 °C

The following formulas are examples of other naturally occurring carboxylic acids. The molecular structures range from simple to complex, often incorporate a variety of other functional groups, and many are chiral.



ASPIRIN, ARACHIDONIC ACID, AND PROSTAGLANDINS

Prostaglandins were first discovered and isolated from human semen in the 1930s by Ulf von Euler of Sweden. Thinking they had come from the prostate gland, he named them prostaglandins. It has since been determined that they exist and are synthesized in virtually every cell of the body. Prostaglandins, are like hormones in that they act as chemical messengers, but do not move to other sites, but work right within the cells where they are synthesized. Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring. They are biochemically synthesized from the fatty acid, arachidonic acid. See the graphic on the left. The unique shape of the arachidonic acid caused by a series of cis double bonds helps to put it into position to make the five member ring.

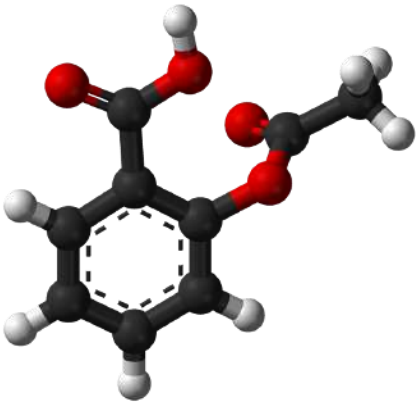


Structure of prostaglandin E2 (PGE_2)

Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring and are based upon the fatty acid, arachidonic acid. There are a variety of structures one, two, or three double bonds. On the five member ring there may also be double bonds, a ketone, or alcohol groups.

There are a variety of physiological effects associated with prostaglandins including:

1. Activation of the inflammatory response, production of pain, and fever. When tissues are damaged, white blood cells flood to the site to try to minimize tissue destruction. Prostaglandins are produced as a result.
2. Blood clots form when a blood vessel is damaged. A type of prostaglandin called thromboxane stimulates constriction and clotting of platelets. Conversely, PGI2, is produced to have the opposite effect on the walls of blood vessels where clots should not be forming.
3. Certain prostaglandins are involved with the induction of labor and other reproductive processes. PGE2 causes uterine contractions and has been used to induce labor.
4. Prostaglandins are involved in several other organs such as the gastrointestinal tract (inhibit acid synthesis and increase secretion of protective mucus), increase blood flow in kidneys, and leukotriens promote constriction of bronchi associated with asthma.



Ball-and-stick model of the aspirin molecule, as found in the solid state. Single-crystal X-ray diffraction data from Kim, Y.; Machida, K.; Taga, T.; Osaki, K. (1985). "Structure Redetermination and Packing Analysis of Aspirin Crystal". Chem. Pharm. Bull. ***33*** *(7): 2641-2647. ISSN 1347-5223.*

EFFECTS OF ASPIRIN AND OTHER PAIN KILLERS ON PROSTAGLANDIN PRODUCTION

When you see that prostaglandins induce inflammation, pain, and fever, what comes to mind but aspirin. Aspirin blocks an enzyme called cyclooxygenase, COX-1 and COX-2, which is involved with the ring closure and addition of oxygen to arachidonic acid converting to prostaglandins. The acetyl group on aspirin is hydrolzed and then bonded to the alcohol group of serine as an ester. This has the effect of blocking the channel in the enzyme and arachidonic can not enter the active site of the enzyme. By inhibiting or blocking this enzyme, the synthesis of prostaglandins is blocked, which in turn relives some of the effects of pain and fever. Aspirin is also thought to inhibit the prostaglandin synthesis involved with unwanted blood clotting in coronary heart disease. At the same time an injury while taking aspirin may cause more extensive bleeding.

CONTRIBUTORS

Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

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

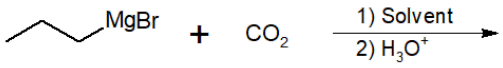
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21.11: ADDITIONAL EXERCISES

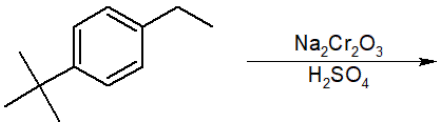
General Review

21-1 Provide the products for the following reactions.

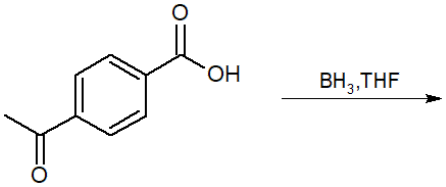
a)



b)



21-2 Provide the proper IUPAC name for the product of the following reaction.



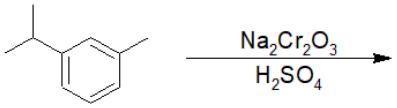
Synthesis of Carboxylic Acids

21-3 For the following reactions, predict the final product and provide their proper IUPAC nomenclature.

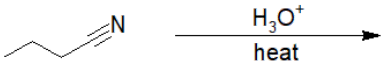
a)



b)



c)



21-4 Propose another method of synthesis (starting with cyclopentane) to make the product in the previous question, **21-3.a**.

21-5 Choose the correct alkene that was oxidatively cleaved by hot, concentrated potassium permanganate to form 3-methylbutanoic acid.

a) (4E/Z)-oct-4-ene

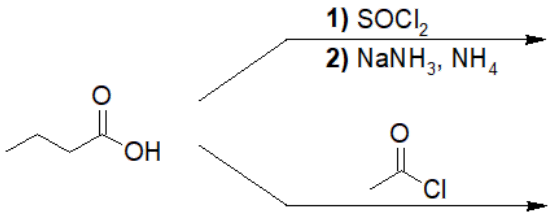
b) (4E/Z)-2-methyloct-4-ene

c) (4E/Z)-2,7-dimethyloct-4-ene

d) (3E/Z)-2,5-dimethylhex-3-ene

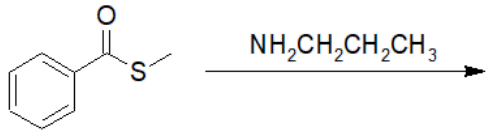
Reactions of Carboxylic Acids and Derivatives: Nucleophilic Acyl Substitution

21-6 Provide the structures of the products of the following reactions.

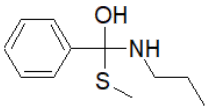


21-7 Provide the structure of the product that forms when propanoic acid reacts with thionyl chloride, then an excess of CH3CH2MgBr and finally followed by an acid workup.

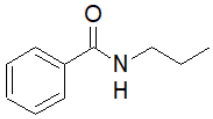
21-8 Choose the correct product of the following reaction.



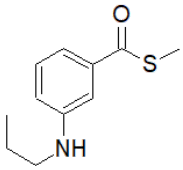
a)



b)

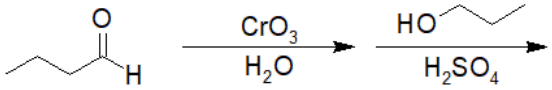


c)

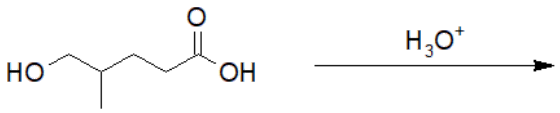


Condensation of Acids with Alcohols: the Fischer Esterification

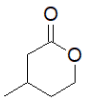
21-9 Predict the product of the following Fischer Esterification reaction.



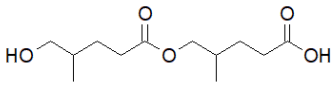
21-10 Choose the correct product of the following Fischer Esterification reaction.



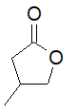
a)



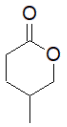
b)



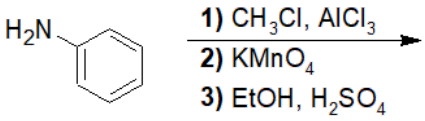
c)



d)

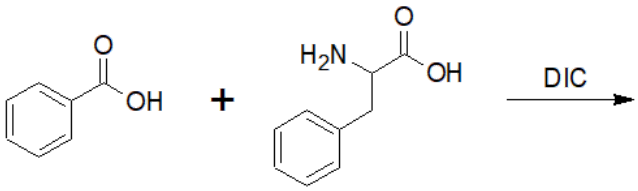


21-11 Predict the product of the following reaction (use a benzene ring with a total of two para-oriented substituents).

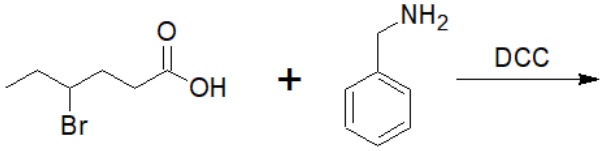


Condensation of Acids with Amines: Direct Synthesis of Amides

21-12 Give the structure of the product of the following reaction.



21-13 Choose the correct IUPAC nomenclature of the product and provide its structure.



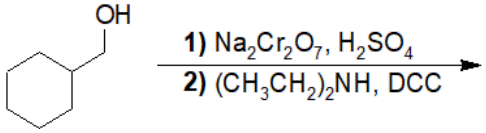
a) benzyl 4-bromohexanoate

b) (4E)-N-benzylhex-4-enamide

c) N-benzyl-4-bromohexanamide

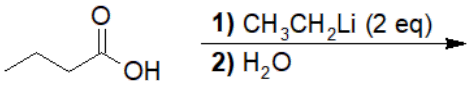
d) 4-bromo-N-phenylhexanamide

21-14 Provide the structure of the final product.



Alkylation of Carboxylic Acids to Form Ketones

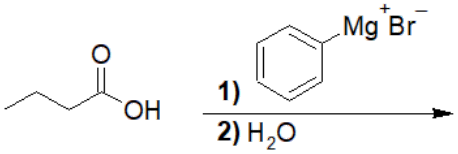
21-15 Predict the product of the following reaction.



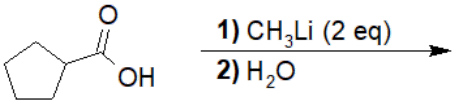
21-16 Explain why two equivalents of organolithium reagent is necessary to alkylate carboxylic acids (see problem **20-1**).

21-17 Give the products of the following reactions.

a)



b)

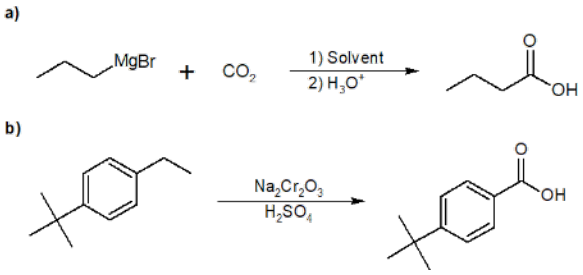


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21.12: SOLUTIONS TO ADDITIONAL EXERCISES

General Review

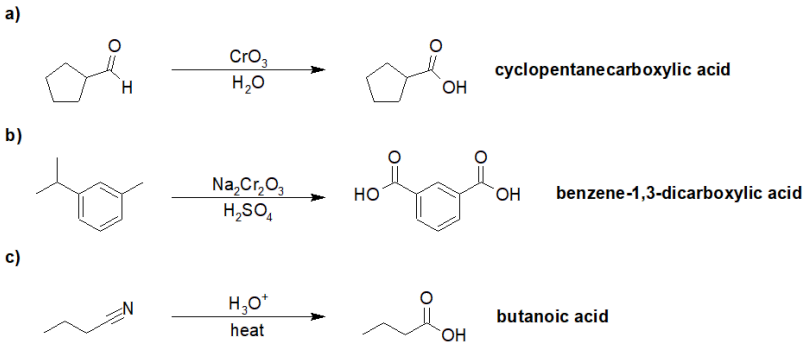
21-1



21-2 1-[4-(hydroxymethyl)phenyl]ethan-1-one

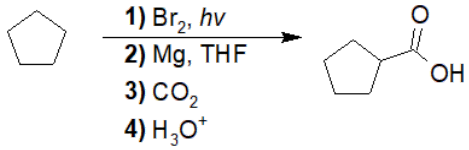
Synthesis of Carboxylic Acids

21-3:



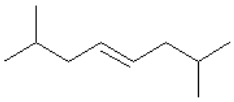
21-4:

Possible route of synthesis:



21-5:

Answer: C

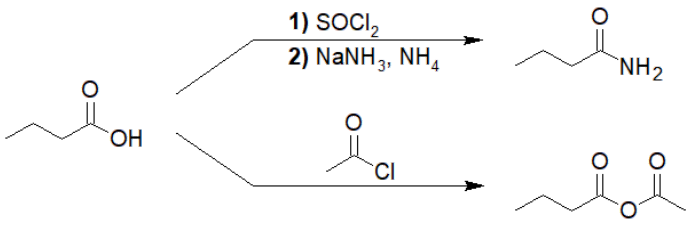


(4*E*)-2,7-dimethyloct-4-ene

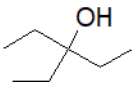
(E or Z orientation allowed)

Reactions of Carboxylic Acids and Derivatives: Nucleophilic Acyl Substitution

21-6:



21-7:

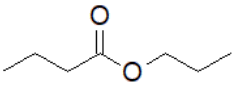


21-8:

Answer: B

Condensation of Acids with Alcohols: the Fischer Esterification

21-9:

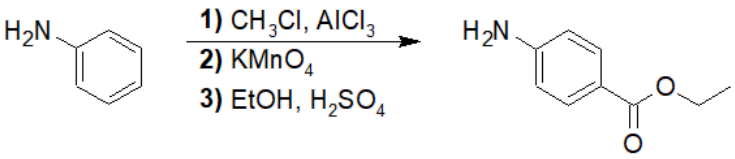


propyl butanoate

21-10:

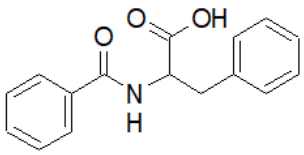
Answer: D

21-11:



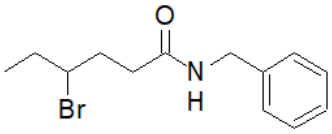
Condensation of Acids with Amines: Direct Synthesis of Amides

21-12:



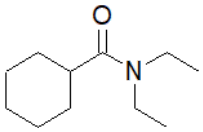
21-13:

Answer: C



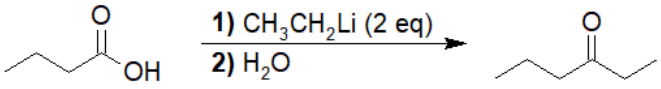
***N*-benzyl-4-bromohexanamide**

21-14:



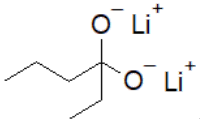
Alkylation of Carboxylic Acids to Form Ketones

21-15:



21-16:

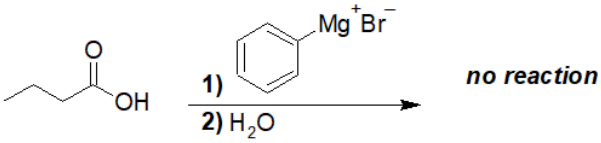
Two equivalents of the organolithium reagent is necessary for the alkylation of carboxylic acids because one equivalent is used to form a salt with the carboxylic acid and the other equivalent is the nucleophile that adds to the carbonyl carbon.



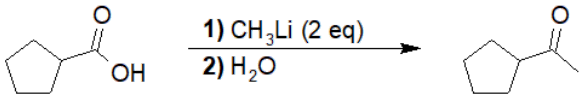
An example of the intermediate from problem **20-1**.

21-17:

a)



b)



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CHAPTER OVERVIEW

22: CARBOXYLIC ACID DERIVATIVES AND NITRILES

After reading this chapter and completing ALL the exercises, a student can be able to

- describe the structure and physical properties of carboxylic acid derivatives and nitriles (section 22.1)
- determine the structure of carboxylic acid derivatives and nitriles from their elemental analysis and spectral data (MS, IR ^{1}H NMR & ^{13}C NMR) (section 22.2)
- predict the products and specify the reagents to interconvert between a carboxylic acid and its derivatives (section 22.3)
- predict the products and specify the reagents to hydrolyze carboxylic acid derivatives (22.4)
- predict the products and specify the reagents for transesterification reactions (section 22.5)
- predict the products and specify the reagents for reduction reactions of carboxylic acid derivatives (section 22.6)
- predict the products and specify the reagents for organometallic reactions with carboxylic acid derivatives (section 22.7)
- predict the products and specify the reagents for the synthesis and reactions of
  - acyl chlorides (section 22.4)
  - anhydrides (section 22.5)
  - esters (section 22.6)
  - amides (section 22.7)
  - nitriles (section 22.8)
  - thioesters (section 22.9)
  - step-growth (condensation) polymers via ester and amide bonds (section 22.10)
- discuss the chemistry of beta-lactams and biological acylation (section 22.11 and 22.12 respectively)
- combine the reactions studied to date to develop efficient and effective multiple-step synthesis

Please note: IUPAC nomenclature and important common names of carboxylic acid derivatives and nitriles were explained in Chapter 3.

22.1: Structure and Physical Properties of Acid Derivatives
22.2: Spectroscopy of Carboxylic Acid Derivatives
22.3: Interconversion of Acid Derivatives by Nucleophilic Acyl Substitution
22.4: Acid Halide Chemistry
22.5: Acid Anhydride Chemistry
22.6: Ester Chemistry
22.7: Amide Chemistry
22.8: Nitrile Chemistry
22.9: Thioesters- Biological Carboxylic Acid Derivatives
22.10: Polyamides and Polyesters- Step-Growth Polymers
22.11: Beta-Lactams- An Application
22.12: Biological Acylation Reactions
22.13: Additional Exercises
22.14: Solutions to Additional Exercises

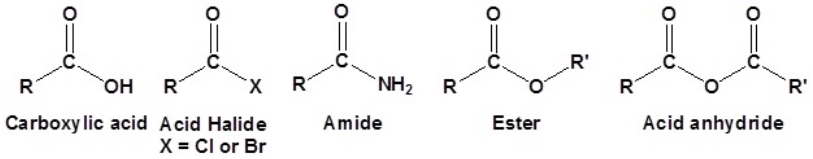
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22: Carboxylic Acid Derivatives and Nitriles is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

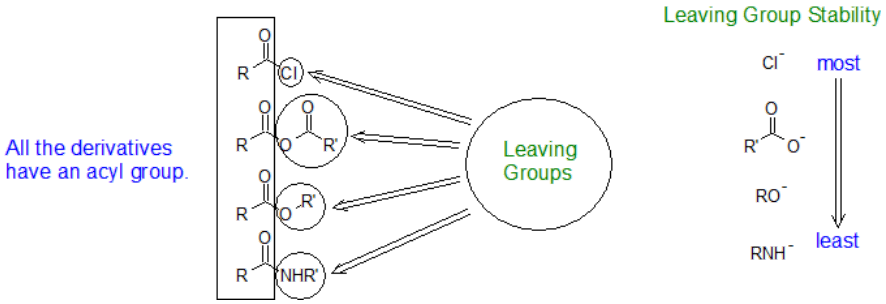
22.1: STRUCTURE AND PHYSICAL PROPERTIES OF ACID DERIVATIVES

THE STRUCTURE OF CARBOXYLIC ACID DERIVATIVES

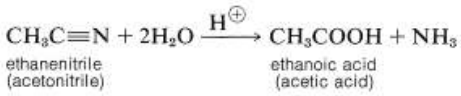
Carboxylic acid and its derivatives are functional groups with closely related chemistry.



The carboxylic acid derivatives all include an acyl group, an R-group bonded to a carbonyl carbon. The "other group" bonded to the carbonyl carbon distinguishes the derivatives from each other and has a strong influence on the relative reactivity between the derivatives. This "other group" takes the role of the "Leaving Group or LG" in Nucleophilic Acyl Substitution (NAS) reactions.



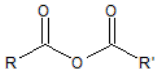
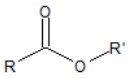
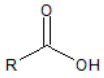
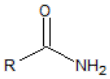
Although there are many types of carboxylic acid derivatives known, this chapter focuses on four: acid halides (acyl halides), acid anhydrides, esters, and amides. Another common feature of carboxylic acid derivatives is that they can be hydrolyzed back to the original carboxylic acid. For this reason, nitriles are sometimes grouped with the carboxylic acid derivatives and will also be discussed in this chapter. The hydrolysis reaction for acetonitrile is shown below as an example.



PHYSICAL PROPERTIES OF CARBOXYLIC ACID DERIVATIVES

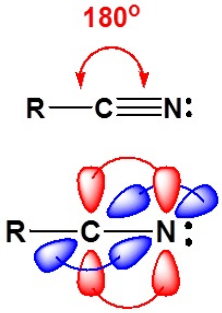
The intermolecular forces of the respective acyl group combine with the size and structure of the R-group to determine the physical properties of the the carboxylic acid derivatives as shown in the summary below.

Carboxylic Acid Derivatives and their Physical Properties

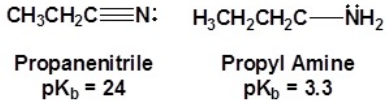
Name	Carboxylic Acid Derivative	Polarity & IMF's	Relative BP	Soluble in H_2O	General Comments
acyl chloride		polar no H's to donate	51	no	acrid piercing odors
acid anhydride		polar no H's to donate	140	no	acrid piercing odors
ester		polar no H's to donate	57	no	volatile fragrant liquids
carboxylic acid		H-bond dimers	118	yes if ≤ C4	acrid piercing odors
amide		complex H-bonds	221	yes if ≤ C3	biologically important (proteins)
nitrile	R—C≡N	among most polar cpds w/o H-bonds	82	yes if ≤ C3	CH_3CN is useful, polar aprotic solvent

STRUCTURE AND PROPERTIES OF NITRILES

The electronic structure of nitriles is very similar to that of an alkyne with the main difference being the presence of a set of lone pair electrons on the nitrogen. Both the carbon and the nitrogen are *sp* hydridized which leaves them both with two p orbitals which overlap to form the two π bond in the triple bond. The R-C-N bond angle in and nitrile is 180° which give a nitrile functional group a linear shape.

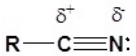


The lone pair electrons on the nitrogen are contained in a *sp* hybrid orbital which makes them much less basic and an amine. The 50% character of an *sp* hybrid orbital close to the nucleus and therefore less basic compared to other nitrogen containing compounds such as amines.



Propanenitrile $pK_b = 24$ **Propyl Amine** $pK_b = 3.3$

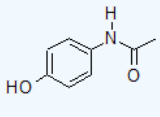
The presence of an electronegative nitrogen causes nitriles to be very polar molecules. Consequently, nitriles tend to have higher boiling points than molecules with a similar size.



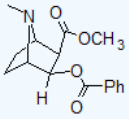
	Boiling Point
$CH_3CH_2C{\equiv}N$	96-98 °C
Propanenitrile	
$CH_3CH_2C{\equiv}C{-}H$	8.1 °C
Butyne	
$CH_3CH_2CH_2CH_3$	-1-1 °C
Butane	

Exercise

1. Design an extraction separation strategy to separate acetaminophen from cocaine using ether, 1 M HCl, and 3 M $NaHCO_3$. The structures for acetaminophen and cocaine are shown below.



acetaminophen

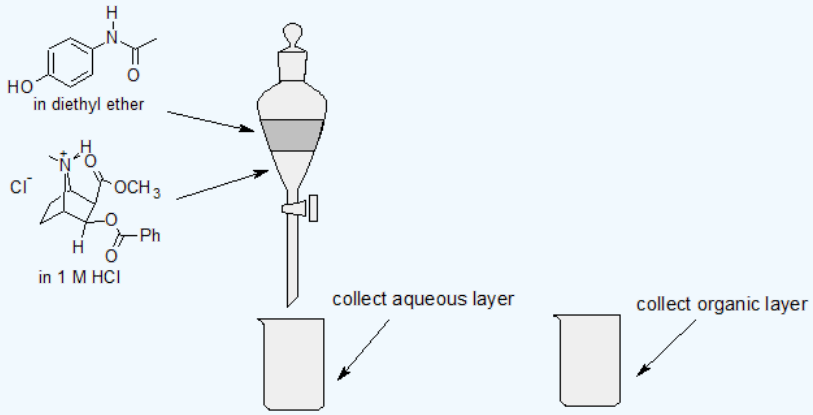


cocaine (free base form)

Answer

1.

Step 1: Dissolve both compounds in ether and add to a separatory funnel.
Step 2: Add 1 M HCl to the separatory funnel.
Step 3: Mix well to protonate the cocaine to a water soluble ammonium ion.
Step 4: Collect the aqueous and organic layers.



Step 5: Neutralize the aqueous layer using 3 M $NaHCO_3$ to deprotonate cocaine hydrochloride to the free base.
Step 6 Isolate the free base cocaine by vacuum filtration and allow the sample to dry.
Step 7: Isolate the acetaminophen by removing the ether from the organic layer with evaporation using a warm water bath & a gentle flow of nitrogen gas.

CONTRIBUTORS AND ATTRIBUTIONS

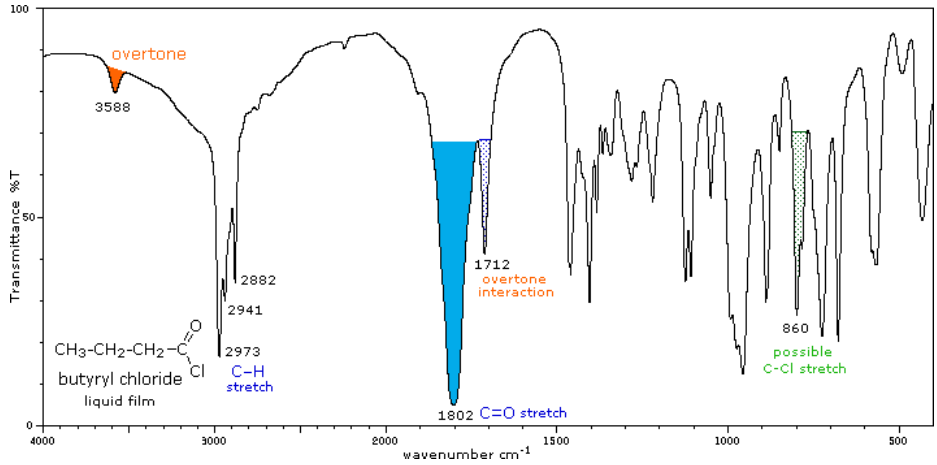
22.1: Structure and Physical Properties of Acid Derivatives is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

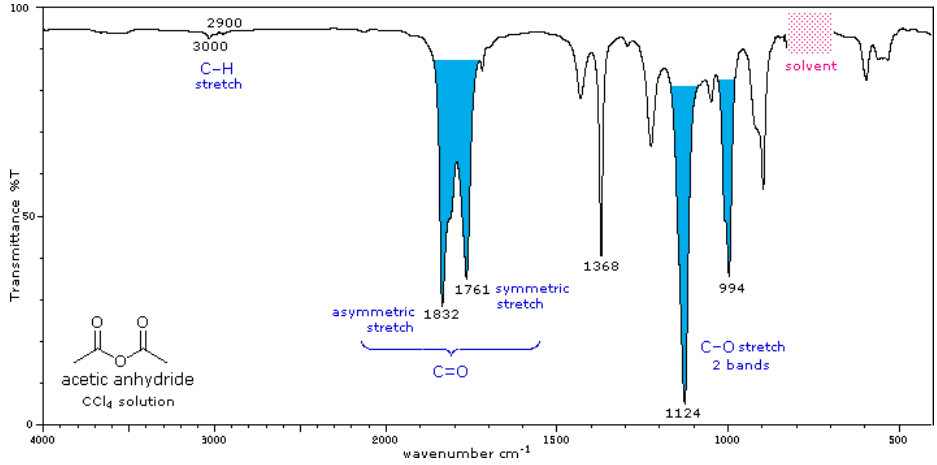
22.2: SPECTROSCOPY OF CARBOXYLIC ACID DERIVATIVES

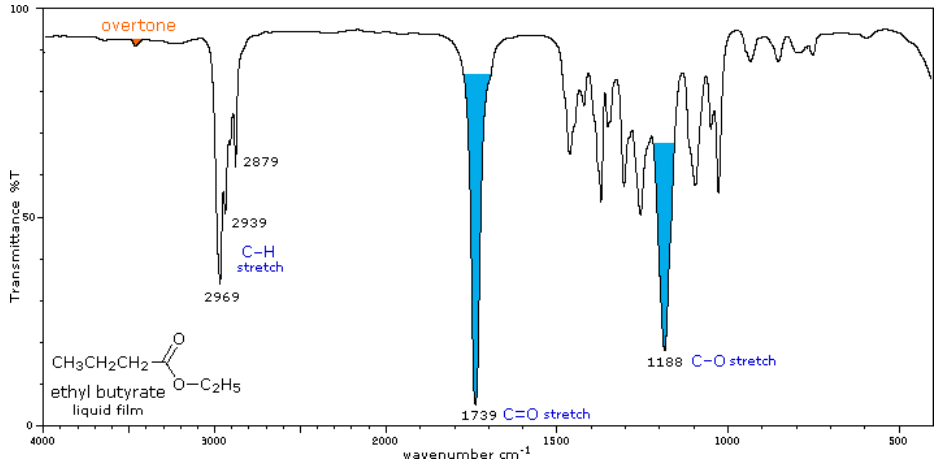
INFRARED SPECTROSCOPY (IR)

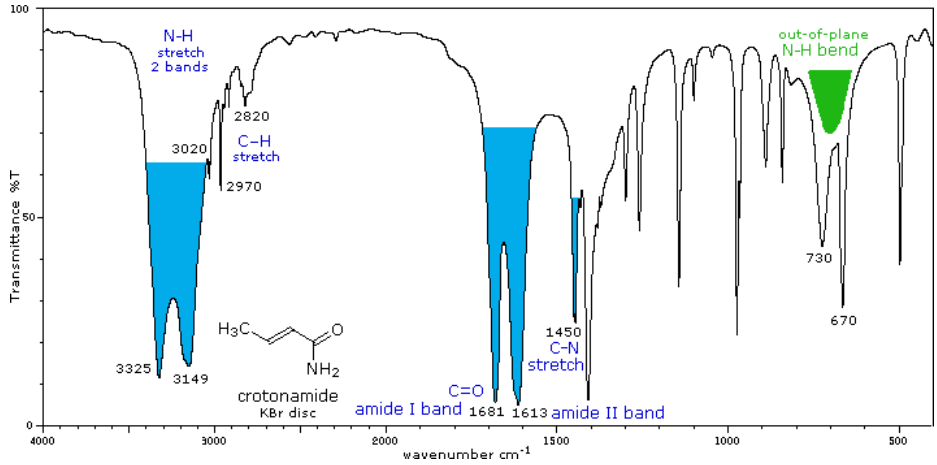
While all of the carboxylic acid derivatives include a carbonyl group, the heteroatoms that characterize the derivative can be used to distinguish between the derivatives. Additionally, there is a useful correlation between the reactivity of the carboxylic acid derivatives and their carbonyl stretching frequencies. Thus, the very reactive acyl halides and anhydrides absorb at frequencies significantly higher, while the relatively unreactive amides absorb at lower frequencies. The IR spectral characteristics that can be used to determine the identity of carboxylic acid derivatives are listed below. Infrared spectra of many carboxylic acid derivatives will be displayed in the figure below the table by clicking the appropriate buttons presented there.

Carbonyl Derivative	Carbonyl Absorption	Comments
Acyl Halides (RCOX)	**C=O stretch**	Conjugation lowers the C=O frequencies reported here, as with aldehydes & ketones.
X = F	1860 ± 20 cm^{-1}	In acyl chlorides a lower intensity shoulder or peak near 1740 cm^{-1} is due to an overtone interaction.
X = Cl	1800 ± 15	
X = Br	1800 ± 15	
Acid Anhydride, $(RCO)_2O$	**C=O stretch** (2 bands)	Conjugation lowers the C=O frequencies reported here, as with aldehydes & ketones.
acyclic	1750 & 1820 cm^{-1}	The two stretching bands are separated by 60 ± 30 cm^{-1}, and for acyclic anhydrides the higher frequency (asymmetric stretching) band is stronger than the lower frequency (symmetric) absorption.
6-membered ring	1750 &1820	Cyclic anhydrides also display two carbonyl stretching absorptions, but the lower frequency band is the strongest.
5-membered ring	1785 & 1865	One or two -CO-O-CO- stretching bands are observed in the 1000 to 1300 cm^{-1} region.
Esters & Lactones (RCOOR')	**C=O stretch**	
esters	1740 cm ± 10 cm^{-1}	Conjugation lowers the C=O frequencies reported here, as with aldehydes & ketones
6-membered lactone	1740 cm ± 10	Strong CO-O stretching absorptions (one ot two) are found from 1150 to 1250 cm^{-1}
5-membered lactone	1765 cm± 5	
4-membered lactone	1840 cm ± 5	
Amides & Lactams $(RCONR_2)$	**C=O bands**	
1° & 2°-amides	1510 to 1700 cm^{-1}	The effect of conjugation is much less than for aldehydes & ketones.
3°-amides	(2 bands)	The higher frequency absorption (1665± 30) is called the **Amide I band**. The lower frequency **Amide II band** (1620± 30 in 1° amides & 1530± 30 in 2° amides) is largely due to N-H bending trans to the carbonyl oxygen. In concentrated samples this absorption is often obscured by the stronger amide I absorption. Hydrogen bonded association shifts some of these absorptions, as well as the prominent N-H stretching absorptions.
6-membered lactams	1650± 15 (one band)	**N-H stretch**: 3170 to 3500 cm^{-1}. Two bands for 1°-amides, one for 2°-amides.
5-membered lactams	1670 ± 10 (one band)	
4-membered lactams	1700 ± 15	
	1745 ± 15	


overtone
3588
2882
2941
2973
C–H
stretch
1712
overtone
interaction
1802 C=O stretch
860
possible
C-Cl stretch
CH3-CH2-CH2-C(=O)-Cl
butyryl chloride
liquid film
Transmittance %T
wavenumber cm-1


2900
3000
C–H
stretch
solvent
1761 symmetric
stretch
asymmetric
stretch
1832
C=O
1368
994
C–O stretch
2 bands
1124
acetic anhydride
CCl4 solution
Transmittance %T
wavenumber cm-1


overtone
2879
2939
C–H
stretch
2969
1188 C–O stretch
1739 C=O stretch
CH3CH2CH2-C(=O)-O-C2H5
ethyl butyrate
liquid film
Transmittance %T
wavenumber cm-1



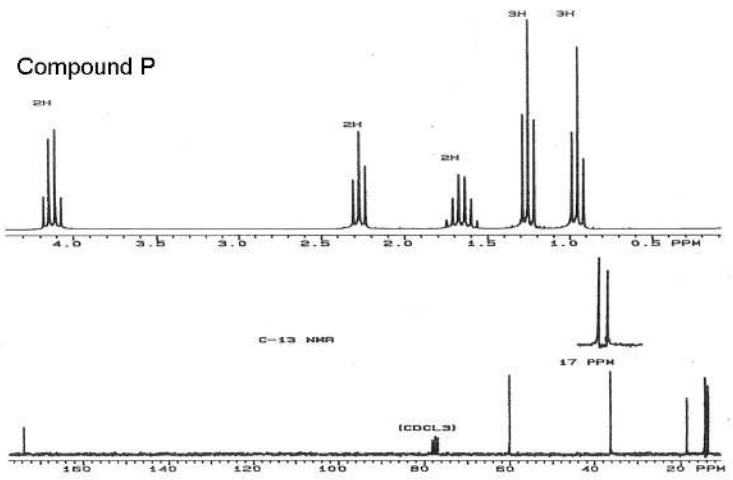
NMR SPECTRA

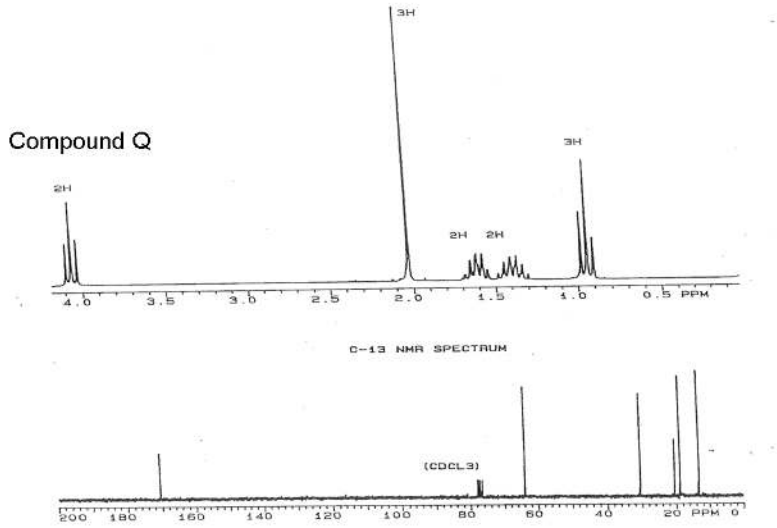
For NMR, there are a few spectral characteristics that can help identify the carboxylic acid derivative. The protons on carbons adjacent to carbonyls absorb at ~2.0-2.5 ppm. For amides, the N-H protons attached to primary and secondary amines absorb at ~7.5-8.5. For ^{13}C NMR, the carbonyl carbon in carboxylic acid derivatives shows up betweem ~ 160-180 ppm with the carbon in a nitrile appearing ~ 115-120 ppm in their ^{13}C NMR because of its *sp* hybridization.

Exercise

2. Esters are known for their sweet, fruity aromas. Compound P smells like pineapple and is used as a flavor enhancer for orange juices. Compound Q is responsible for the sweet smell of Red Delicious apples. Compounds P and Q are structural isomers with the following composition: 62.04% C, 0.41% H, and 27.55% O. The IR spectrum for each compound includes several moderate bands around 2940 cm-1, a strong band near 1740 cm-1, and a moderate band near 1200 cm-1. The 1H and 13C NMR spectrum for each compound is shown below.

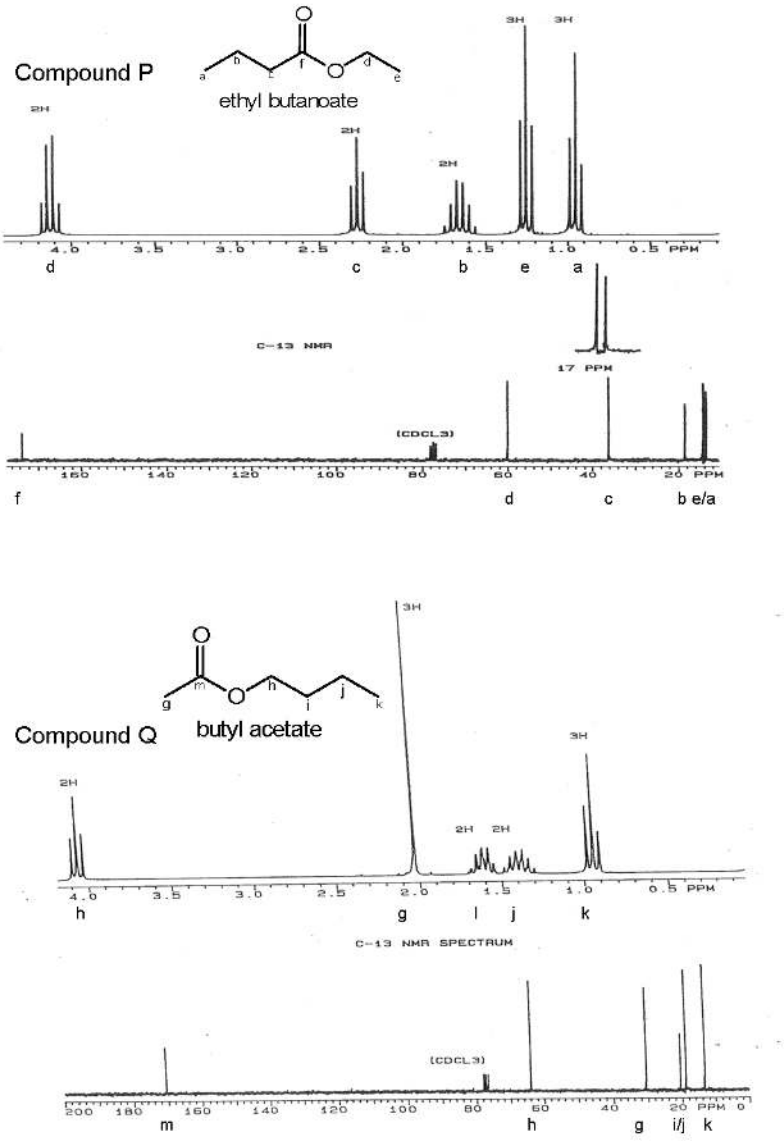
Name, draw the bond-line structure, and correlate the NMR signals to their respective compound.


Compound P
3H
3H
2H
2H
2H
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5 PPM
C-13 NMR
17 PPM
(CDCL3)
160
140
120
100
80
60
40
20 PPM


Compound Q
3H
3H
2H
2H 2H
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5 PPM
C-13 NMR SPECTRUM
(CDCL3)
200
180
160
140
120
100
80
60
40
20 PPM 0

Answer

2.



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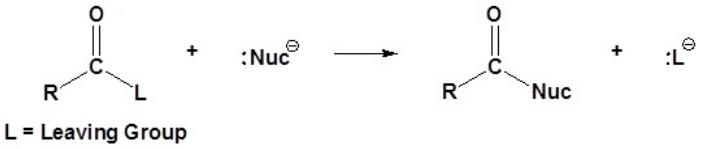
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

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22.3: INTERCONVERSION OF ACID DERIVATIVES BY NUCLEOPHILIC ACYL SUBSTITUTION

GENERAL REACTION

Carboxylic acid derivatives are electrophilic and can react with nucleophiles to form nucleophilic acyl substitution products. The driving force of these reactions is the stability of the leaving group shown as $:L^-$ below.

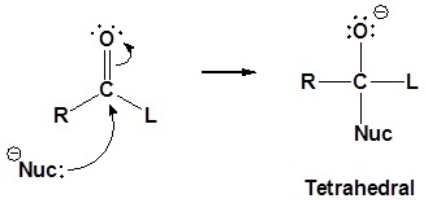


L = Leaving Group

GENERAL MECHANISM

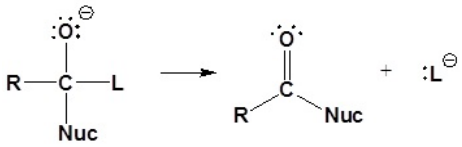
The nucleophile reacts with the electrophilic carbonyl carbon to form the tetrahedral intermediate. When the carbonyl reforms, the leaving group is lost to form the substitution product as shown in the mechanism below.

1) Nucleophilic reaction at the carbonyl



Tetrahedral Intermediate

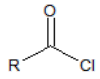
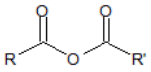
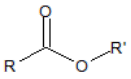
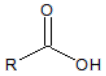
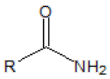
2) Carbonyl reforms and leaving group is removed



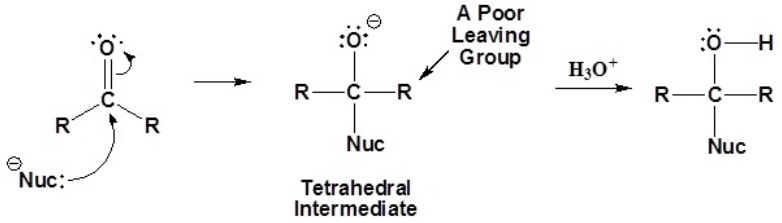
RELATIVE REACTIVITY TO NUCLEOPHILIC ACYL SUBSTITUTION

The relative reactivity of carbonyl compounds toward nucleophile substitutions is related to the stability of the leaving group - the more stable the leaving group, the more favorable the substitution reaction. Evaluating leaving group stability is analogous to evaluating conjugate base stability as shown in the table below.

Carbonyl Compounds and their Leaving Groups

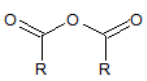
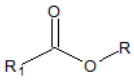
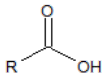
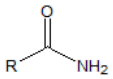
Name	Carbonyl Compound	Leaving Group	Conjugate acid of the Leaving Group	pKa
acyl chloride		Cl^-	HCl	-7
acid anhydride				3-5
ester		$^-OR_2$	ROH	15-16
carboxylic acid		HO^-	H_2O	15.7
amide		$^-NH_2$	NH_3	36
ketone		$R^{'-}$	RH	50
aldehyde		H^-	H_2	very large

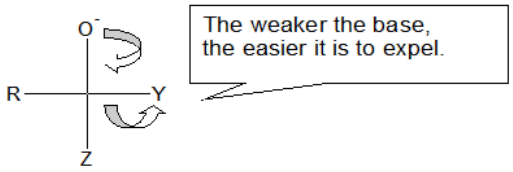
Although aldehydes and ketones also contain carbonyls, their chemistry is distinctly different because they do not contain suitable leaving groups. Once a tetrahedral intermediate is formed, aldehydes and ketones cannot reform their carbonyls because the carbide (RC^-) and hydride (H^-) leaving groups are too unstable. Therefore, aldehydes and ketones typically undergo nucleophilic additions and not substitutions.



Integrating all of this information into the single table below summarizes the relative reactivity of carboxylic acids and their derivatives.

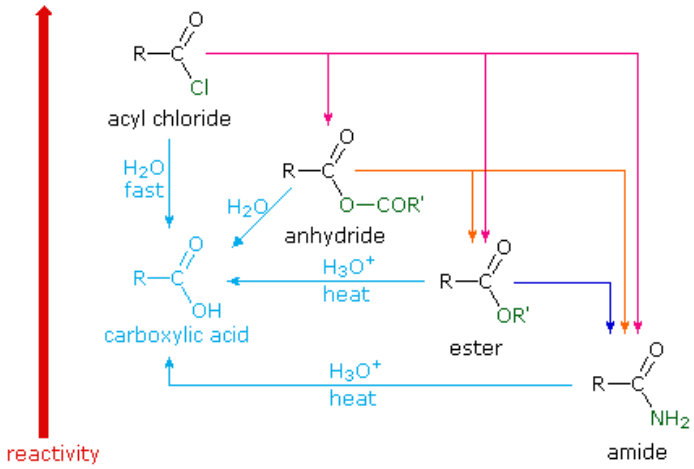
Carboxylic Acid Derivatives and their Relative Reactivity

Name	Carboxylic Acid Derivative	LG	Relative Basicity	Relative Reactivity
acyl chloride		Cl^-	weakest base	most reactive
anhydride				
ester		$^-OR_2$		
carboxylic acid		^-OH		
amide		$^-NH_2$	strongest base	least reactive



ACID DERIVATIVE INTERCONVERSION

From this understanding, multiple step synthesis strategies can be developed. The derivatives with the most stable leaving groups can be used to synthesize the derivatives with the least stable leaving groups as illustrated in the diagram below.



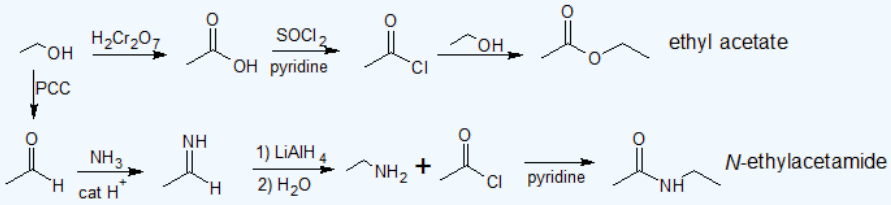
While it may appear from diagram above that the acyl chlorides are the "source" of the acid derivatives, acyl chlorides are so highly reactive that it is common to convert the carboxylic acid to the acid chloride and then immediately form the derivative. From a laboratory synthesis perspective, the reaction sequence begins with the carboxylic acid.

Exercise

3. Using ethanol as the only source of carbons in the final products, show how to synthesize ethyl acetate and N-ethylacetamide.

Answer

3.



CONTRIBUTORS AND ATTRIBUTIONS

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

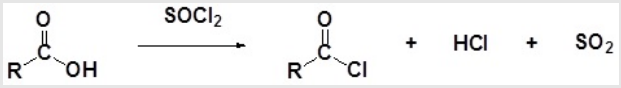
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22.4: ACID HALIDE CHEMISTRY

Please Note: The terms "acid halide" and "acyl halide" are synonymous and are both used in this text. In biochemistry, the term "acyl" is used more frequently.

ACID HALIDE SYNTHESIS

Carboxylic acids react with thionyl chloride ($SOCl_2$) or oxalyl chloride ($C_2O_2Cl_2$) to form acid chlorides. Typically the reactions occur in the presence of a proton scavanger like pyridine to minimize unwanted side reactions. During the reaction the hydroxyl group of the carboxylic acid is converted to a chlorosulfite intermediate making it a better leaving group. The chloride anion produced during the reaction acts a nucleophile.

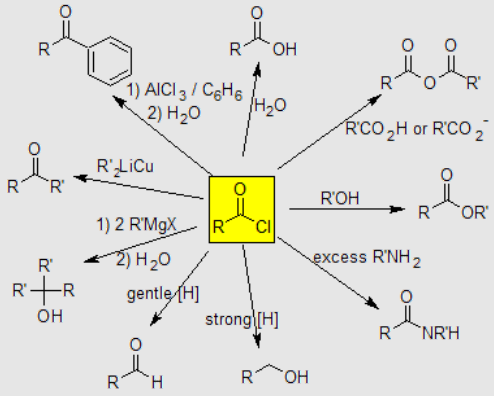


Analogous to the reactions of primary and secondary alcohols with PBr_3 to produce the corresponding alkyl bromide, acid bromides can be formed from the reaction of phosphorous tribromide with carboxylic acids.



ACYL HALIDE REACTIVITY

Acyl halides can be hydrolyzed to carboxylic acids and converted to carboxylic acid derivatives. Acid halides can also undergo reduction reactions and reactions with Grignard reagents and organolithium cuprates along with Fridel-Crafts acylation of benzene. The reaction map below summarizes the reactivity of acyl halides.



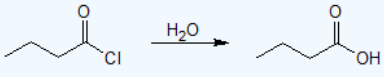
ACID HALIDE HYDROLYSIS

The hydrolysis reaction of acid chlorides is shown below.



The hydrolysis of butonyl chloride is shown below as an example.

Example: Acyl Chloride Hydrolysis

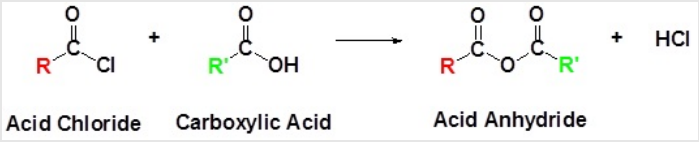


CARBOXYLIC ACID DERIVATIVE SYNTHESIS FROM ACYL CHLORIDES

Carboxylic acid derivatives can be synthesized from acyl chlorides via the nucleophilic acyl substitution mechanism previously discussed.

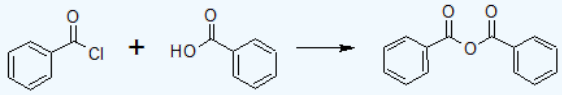
ANHYDRIDE SYNTHESIS

Acid chlorides react with carboxylic acids to form acid anhydrides as shown in the reaction below.



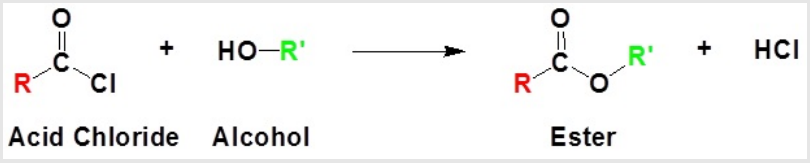
The synthesis of benzoic anhydride from benzoyl chloride and benzoic acid is shown as an example.

Example: Anhydride Synthesis from Acyl Chlorides



ESTER SYNTHESIS

Acid chlorides react with alcohols for form esters are shown in the reaction below.



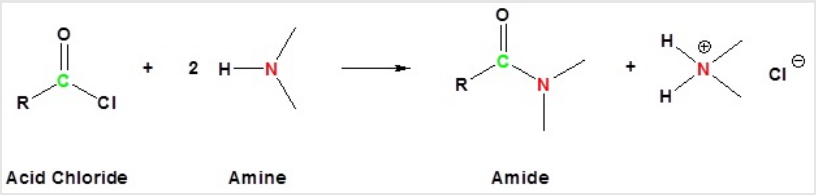
The synthesis of ethyl benzoate from benzoyl chloride and ethanol is shown as an example.

Example: Ester Synthesis from Acid Chlorides



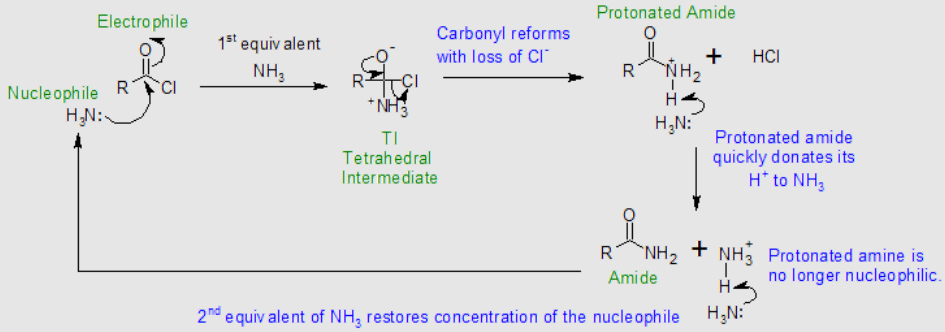
AMIDE SYNTHESIS

Acid chlorides react with "ammonia, 1º amines and 2º amines" to form amides as shown in the reaction below.



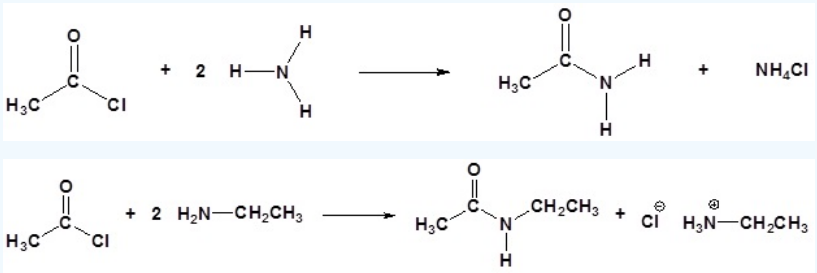
The reaction requires 1 equivalent of the "ammonia/1º or 2º amine" with a proton scavenger (aka base) like pyridine OR two equivalents of "ammonia/1º or 2º amine". The additional equivalent the nucleophile or base is needed to maintain the nucleophilic character of "ammonia/1º or 2º amine". As shown in the mechanism below, the amide is briefly protonated after the carbonyl reforms from the tetrahedral complex. Since amides are considered neutral with no significant basicity, the "ammonia/1º or 2º amine" quickly accepts their proton and is no longer a nucleophile. The second equivalent of "ammonia/1º or 2º amine" restores the concentration of the nucleophile. For clarity, the mechanism below is shown with ammonia as the nucleophile.

MECHANISM



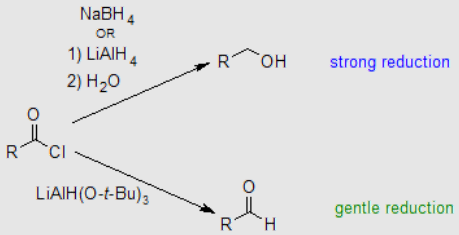
The syntheses of acetamide and N-ethylacetamide from acetyl chloride are shown as examples.

Example: Amide Synthesis from Acyl Chlorides



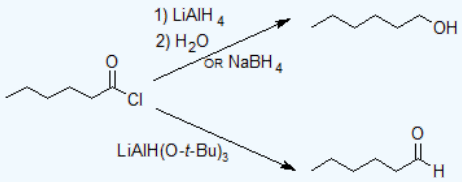
ACID CHLORIDE REDUCTION

Acid chlorides can be fully reduced to primary alcohols using either sodium borohydride or lithium aluminum hydride. Acid chlorides can be partially reduced to aldehydes using the lithium tri-tert-butoxyaluminum hydride ($LiAlH(O\text{-}t\text{-}Bu)_3$. These reactions are summarized in the reaction map below.



The syntheses of 1-hexanol and hexanal from hexanoyl chloride are shown as examples.

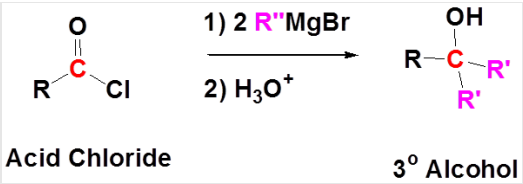
Example: Reduction Acyl Chlorides



ACID CHLORIDE REACTIONS WITH ORGANOMETALLIC COMPOUNDS

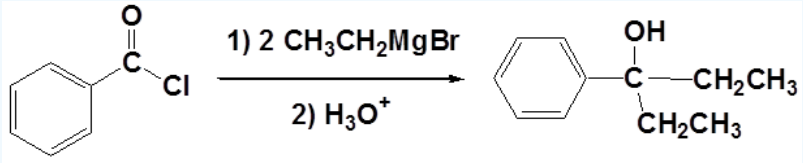
GRIGNARD REAGENTS

Acid chlorides react with Grignard reagents to produce tertiary alcohols. Two equivalents of the Grignard reagent are needed because the first equivalent reacts to form a ketone which then reacts with the second equivalent. Because of the high reactivity of the Grigard reagent, the reaction can NOT be stopped at the ketone.



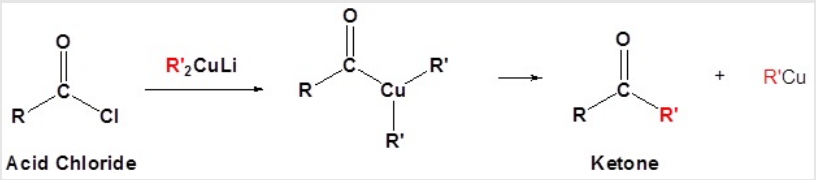
The syntheses of 3-phenylpentan-3-ol from benzoyl chloride is shown as an example.

Example: Acyl Chloride Reactions with Grignard Reagents



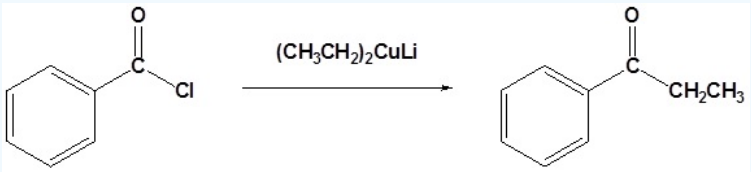
ORGANOLITHIUM CUPRATES

Organolithium cuprate reagents are less reactive than Grignard reagents and can convert acid chlorides to ketones as shown below.



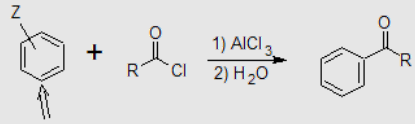
The synthesis of 1-phenylpropan-1-one from benzoyl chloride is shown as an example.

Example: Acyl Chloride Reactions with Organolithium Cuprates



FRIEDEL-CRAFTS ACYLATION OF BENZENE

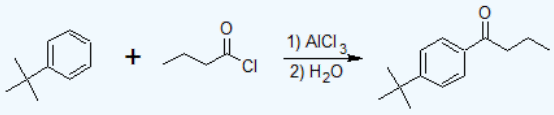
Benzene rings can be acylated via the Friedel-Crafts acylation reaction with acid chlorides in the presence of aluminum chloride followed by an aqueous work-up as shown below.



For F-C Acylation, the benzene ring can have electron donating groups or a halogen, but cannot contain electron withdrawing groups, such as the nitro (-NO_2) or sulfono (-SO_3H) groups.

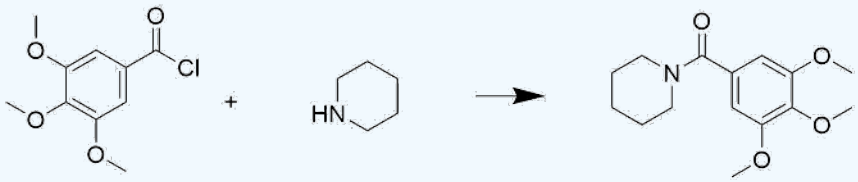
The synthesis of 1-(4-tert-butylphenyl)butan-1-one from t-butylbenzene and butonyl chloride is shown as an example.

Example: Friedel-Crafts Acylation



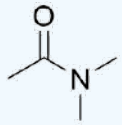
Exercise

4. Draw the mechanism for the following reaction

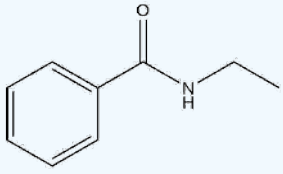


5. Propose a synthesis of the following molecules from an acid chloride and an amide.

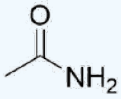
(a)



(b)

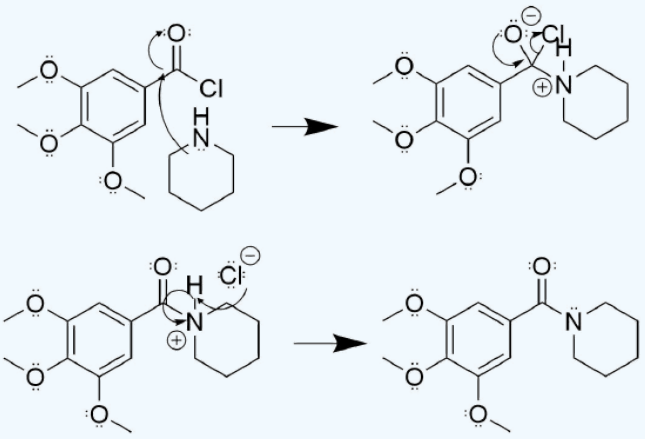


(c)



Answer

4.



5.

a) Acetyl chloride and dimethylamine

b) Benzoyl chloride and ethylamine

c) Acetyl chloride and ammonia

CONTRIBUTORS AND ATTRIBUTIONS

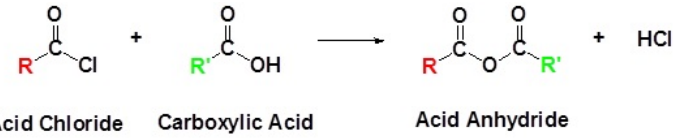
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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22.5: ACID ANHYDRIDE CHEMISTRY

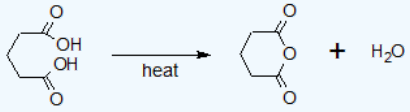
SYNTHESIS OF ACID ANHYDRIDES

Acid chlorides react with carboxylic acids to form anhydrides as shown in the reaction below.



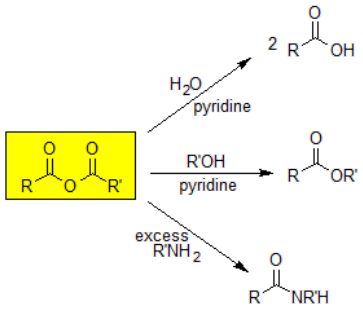
Some cyclic anhydrides can be synthesized from the corresponding dicarboxylic acid with gentle heating. The example below shows the reaction of glutaric acid to form a cyclic anhydride.

Example: Acid Anhydride Synthesis



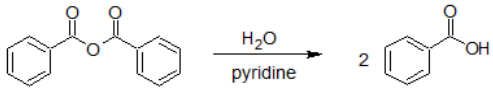
ACID ANHYDRIDE REACTIVITY

Acid anhydrides undergo hydrolysis and nucleophilic acyl substitution reactions.



ACID ANHYDRIDE HYDROLYSIS

Acid anhydrides readily hydrolyze to carboxylic acids. In many cases, this reaction is an unwanted side reaction and steps will be taken in the lab to keep the system "dry" (aka water free). The presence of pyridine facilitates proton transfers during the reaction. The hydrolysis reaction for benzoic anhydride is shown below.



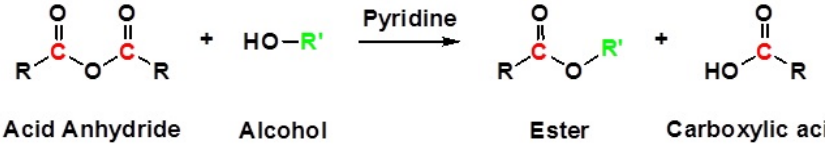
The mechanism is analogous to the mechanism for ester synthesis from acid anhydrides and is shown below is detail.

NUCLEPHILIC ACYL SUBSTITUTION REACTIONS FROM ACID ANHYDRIDES

Carboxylic acid derivatives can be synthesized from acid anhydrides via the nucleophilic acyl substitution mechanism previously discussed.

ESTER SYNTHESIS

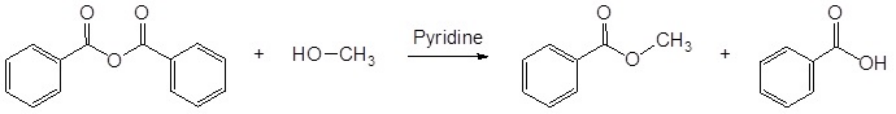
Acid anhydrides react with alcohols to produce esters as shown in the reaction below. The reactions of anhydrides frequently use pyridine as a solvent.



A carboxylic acid is also produced, but is not considered a synthetic product. The ester is considered the "product of interest".

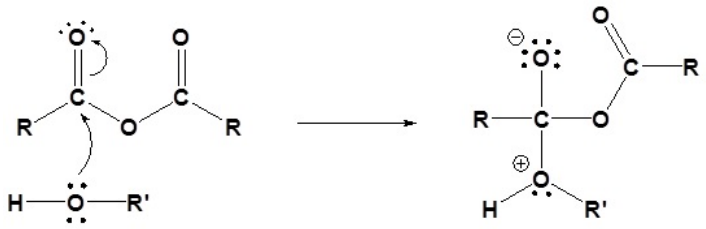
The synthesis of methyl benzoate from benzoic anhydride and methanol is shown in the example.

Example: Ester Sythesis

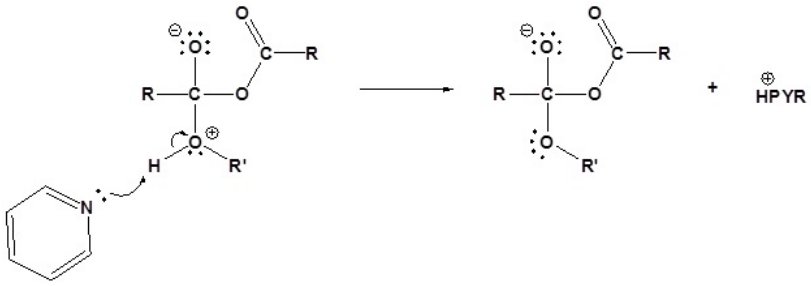


The mechanism follows the nucleophililc acyl substitution mechanism as previously discussed and reviewed below.

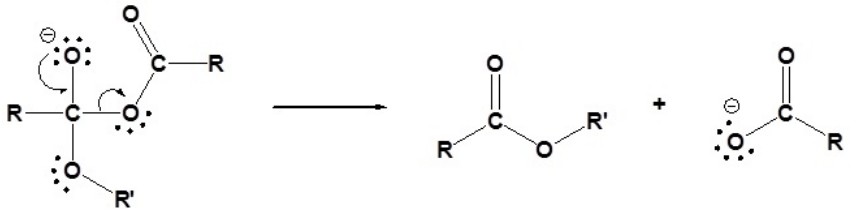
1) Nucleophilic Alcohol reacts with Electrophilic Carbonyl



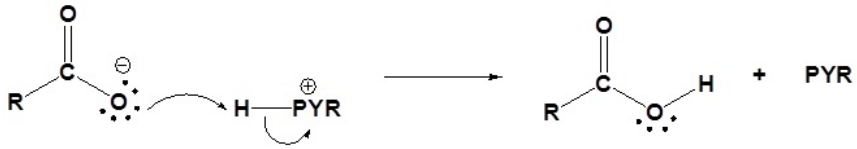
2) Deprotonation by pyridine



3) Leaving group removal

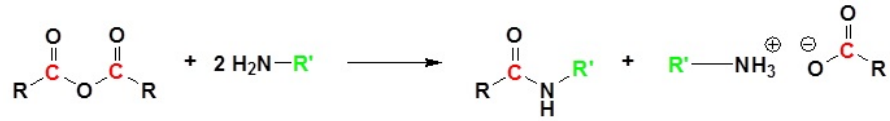


4) Protonation of the carboxylate

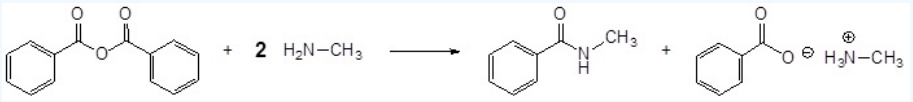


AMIDE SYNTHESIS

Acid Anhydrides react with amines to form amides. As seen with acid halide reactions, a second equivalent of the amine must be present for the reaction to proceed.

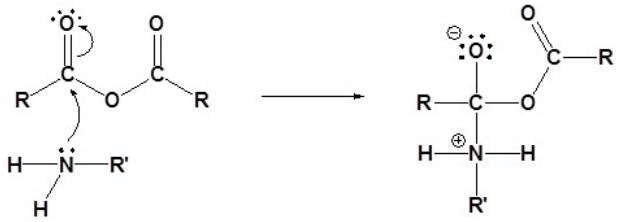


Example: Amide Synthesis

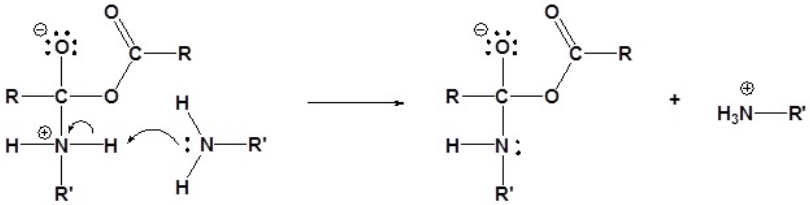


The mechanism for amide synthesis is analogous to the mechanism for ester formation. The only minor difference is that a second equivalent of the amine or ammonia is used instead of the pyridine.

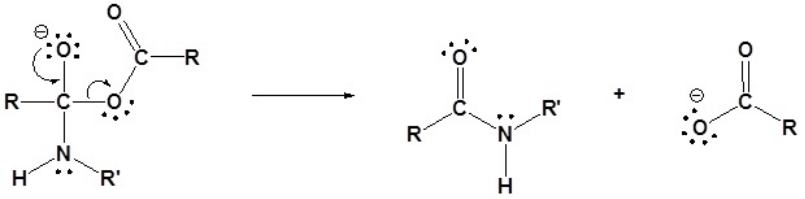
1) Nucleophilic Amine reacts with Electrophilic Carbonyl



2) Deprotonation by the amine

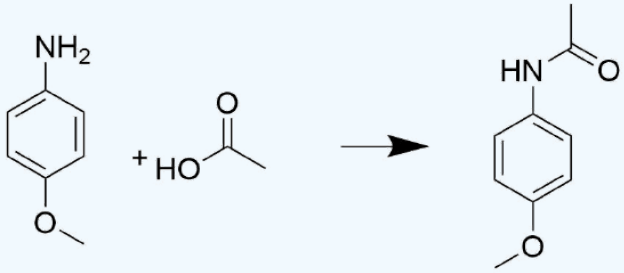


3) Leaving group removal

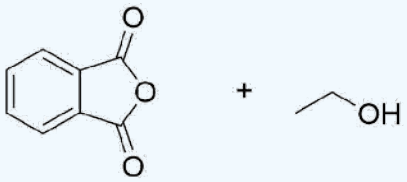


Exercise

6. Draw out the mechanism for the following reaction.

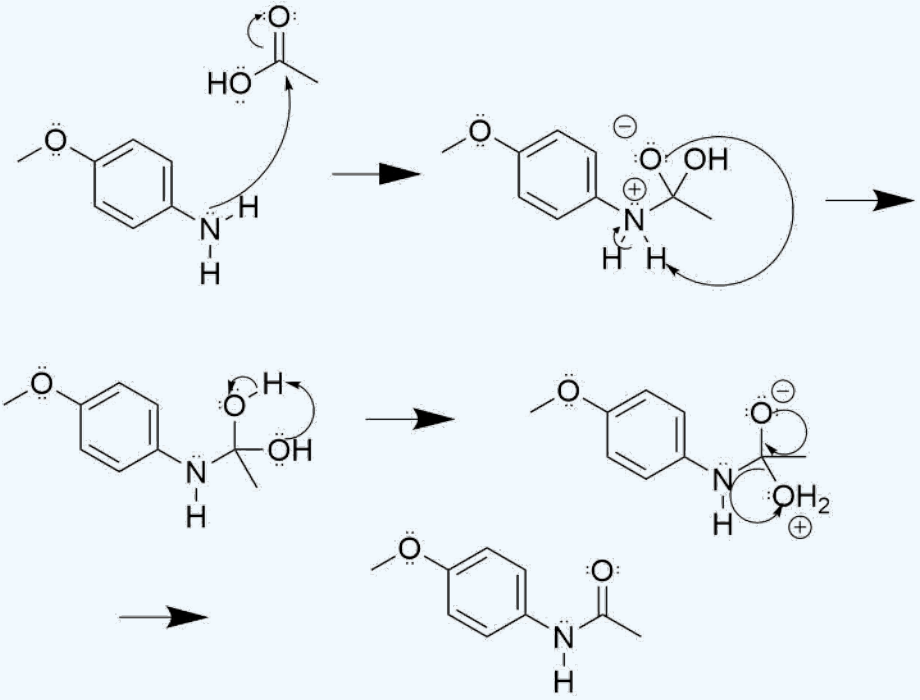


7. Draw the product of the reaction between these two molecules.

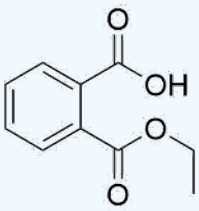


Answer

6.



7.



CONTRIBUTORS AND ATTRIBUTIONS

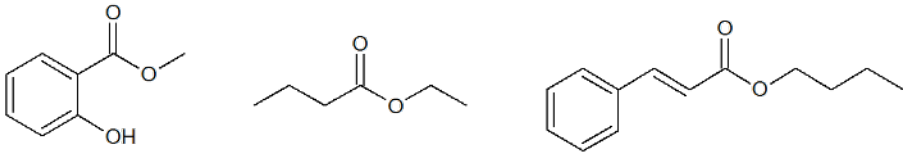
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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22.6: ESTER CHEMISTRY

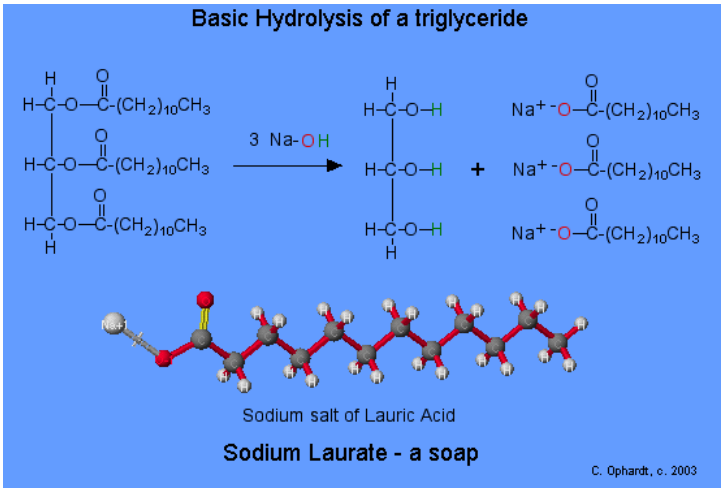
INTRODUCTION

Esters are readily synthesized and naturally abundant. Esters are frequently the source of flavors and aromas in many fruits and flowers.



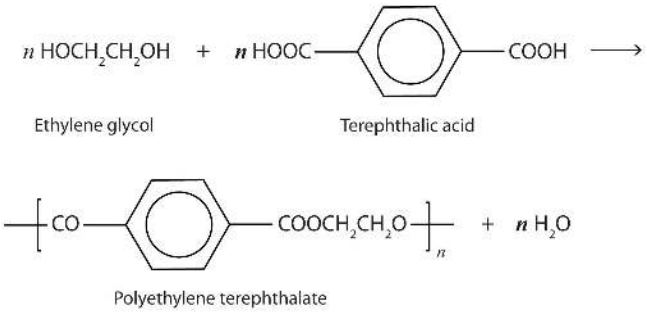
oil of wintergreen | pineapple | chocolate

Esters also make up the bulk of animal fats and vegetable oils—glycerides (fatty acid esters of glycerol). Soap is produced by a saponification (basic hydrolysis) reaction of a fat or oil.



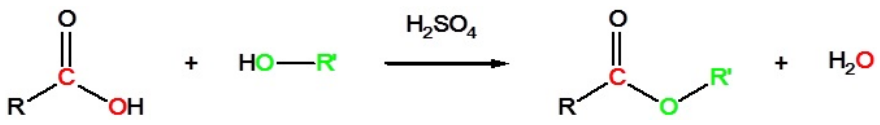
Esters are also present in a number of important biological molecules and have several commercial and synthetic application. For example, polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or replace diseased sections of blood vessels. PET is used to make bottles for soda pop and other beverages. It is also formed into films called Mylar. When magnetically coated, Mylar tape is used in audio- and videocassettes. Synthetic arteries can be made from PET, polytetrafluoroethylene, and other polymers.

The most important polyester, polyethylene terephthalate (PET), is made from terephthalic acid and ethylene glycol monomers:

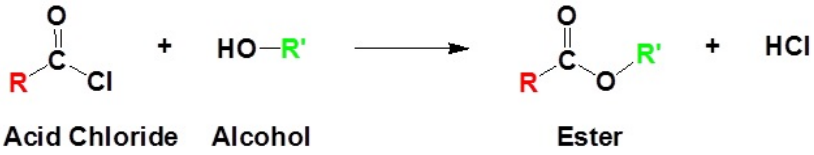


SYNTHESIS OF ESTERS

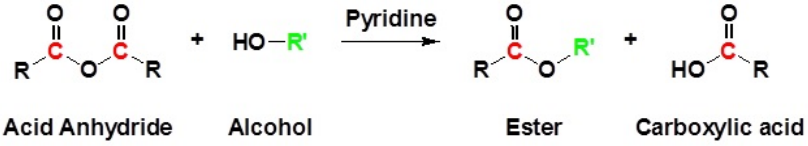
Carboxylic acids can react with alcohols to form esters in the presence of an acid catalyst as shown in the reaction below.



Acid chlorides react with alcohols to form esters as shown in the reaction below.

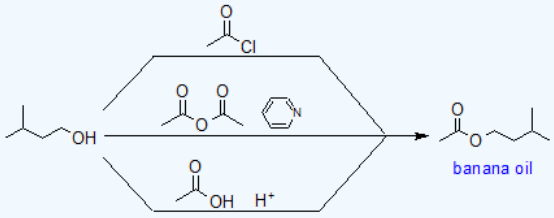


Acid anhydrides also react with alcohols to form esters as shown in the reaction below.



As an example, the synthesis of banana oil (isoamyl acetate) is an example of these two reactions.

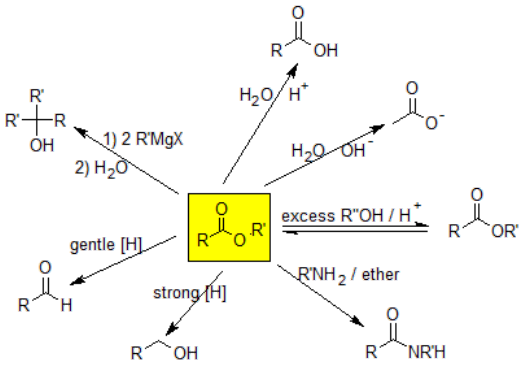
Example: Ester Synthesis



Esters can be also be synthesized from trans-esterification reactions. Trans-esterification is discussed in the next section on Reactivity of Esters

REACTIVITY OF ESTERS

Esters can be hydrolyzed to carboxylic acids under acidic or basic conditions. Basic hydrolysis can be used to convert fats and oils into soap and is called a saponification reaction. Esters can be converted to amides via an aminolysis reaction. Esters can undergo trans-esterification reactions to form different esters by applying LeChatlier's principle to this equilibrium reaction. Esters can be reduced to form alcohols or aldehydes depending on the reducing agent. Esters also react with organometallic compounds to form tertiary alcohols. The reaction map for esters is shown below.

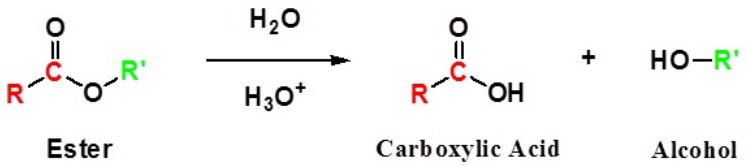


ESTER HYDROLYSIS

Ester hydrolysis requires an acid catalyst or base promotion to occur. Esters are less reactive than acyl halides and acid anhydrides because the alkoxide group is a poor leaving group with its negative charge fully localized on a single oxygen atom.

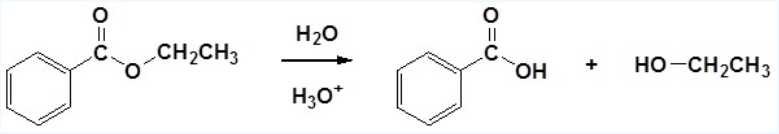
Ester Hydrolysis - Acid Catalyzed

Esters can be cleaved back into a carboxylic acid and an alcohol by reaction with water and a catalytic amount of acid as shown in the reaction below.



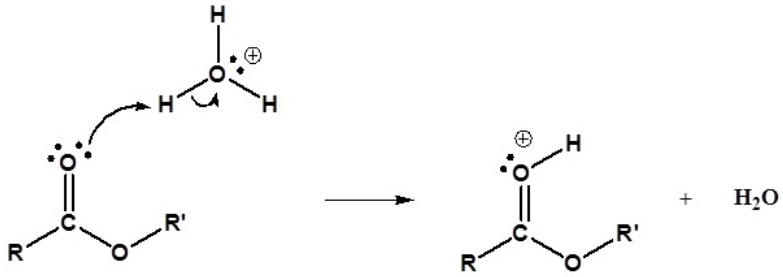
The acid catalyzed hydrolysis of ethyl benzoate is shown below as an example.

Example: Acid Catalyzed Ester Hydrolysis

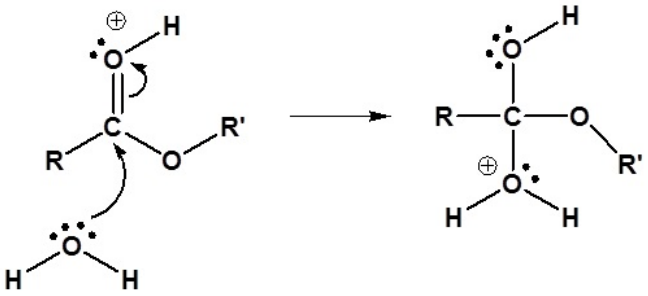


The mechanism for the acid catalyzed hydrolysis reaction begins with protonation of the carbonyl oxygen to increase the reactivity of the ester. The nucleophilic water reacts with the electrophilic carbonyl carbon atom to form the tetrahedral intermediate. Proton transfer reactions occur to create a good leaving group when the carbonyl reforms. The complete mechanism is shown below.

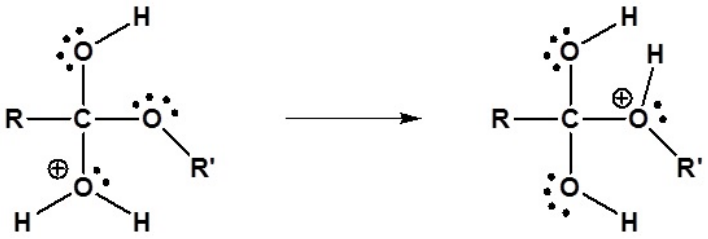
1) Protonation of the Carbonyl



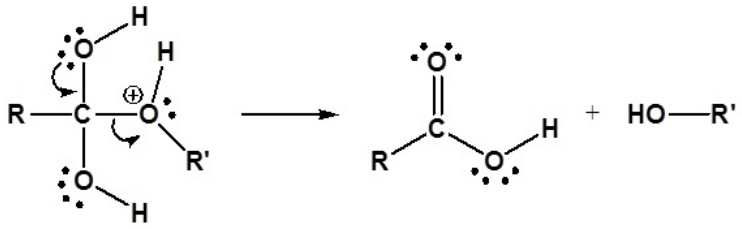
2) Nucleophilic reaction by water



3) Proton transfer

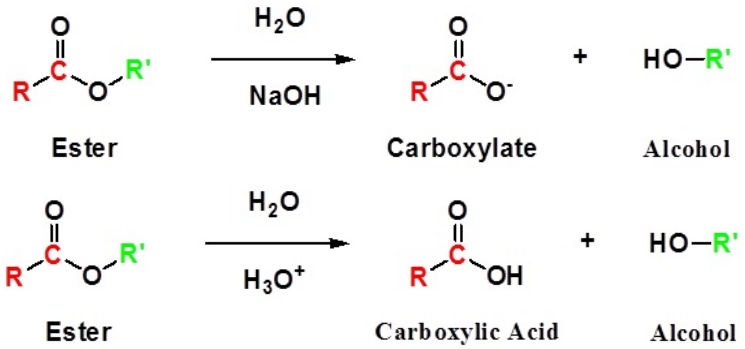


4) Leaving group removal



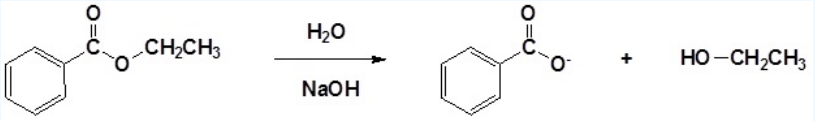
ESTER HYDROLYSIS - BASE PROMOTED

Esters can be cleaved back into a carboxylic acid and an alcohol by reaction with water and a base. The reaction is called a saponification from the Latin *sapo* which means soap. The name comes from the fact that soap used to me made by the ester hydrolysis of fats. Due to the basic conditions, a carboxylate ion is made rather than a carboxylic acid. The hydroxide ions are consumed in the reaction so it is described as "base promoted".



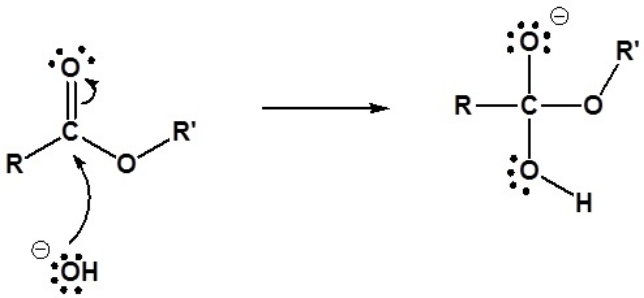
The base promoted hydrolysis of ethyl benzoate is shown below as an example.

Example: Base Promoted Hydrolysis of Esters

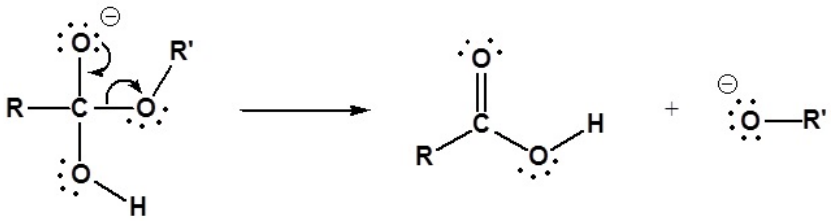


The mechanism for the base promoted hydrolysis reaction begins with the nucleophilic hydroxide reacting with the electrophilic carbonyl carbon atom to form the tetrahedral intermediate. The carbonyl reforms with the loss of the alkoxide leaving group. The alkoxide then deprotonates the resulting carboxylic acid. The complete mechanism is shown below.

1) Nucleophilic reaction by hydroxide



2) Leaving group removal



3) Deprotonation

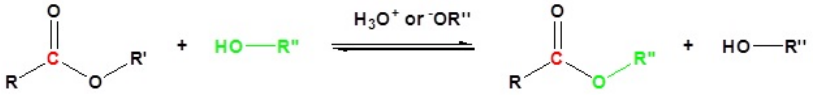


NUCLEPHILIC ACYL SUBSTITUTION REACTIONS FROM ESTERS

Carboxylic acid derivatives can be synthesized from esters via the nucleophilic acyl substitution mechanism previously discussed.

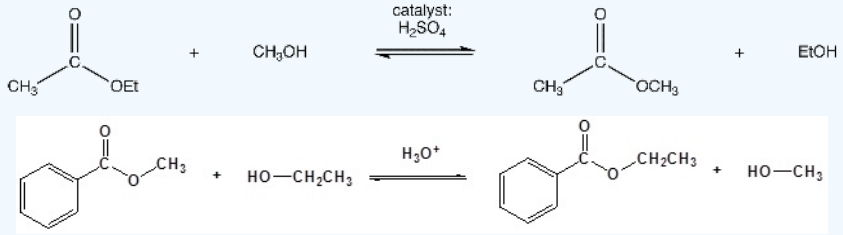
ESTER SYNTHESIS: TRANS-ESTERIFICATION

Trans-esterification is the conversion of a carboxylic acid ester into a different carboxylic acid ester. When an ester is placed in a large excess of an alcohol along with presence of either an acid or a base there can be an exchange of alkoxy groups. The large excess of alcohol is used to drive the reaction forward. The most common method of trans-esterification is the reaction of the ester with an alcohol in the presence of an acid catalyst as shown below.

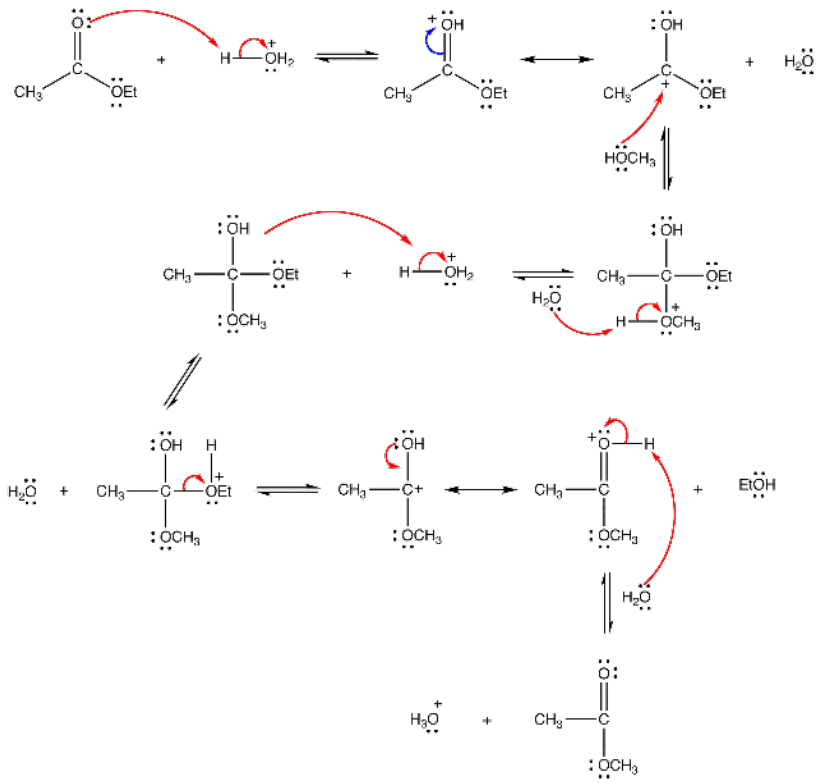


The trans-esterification of ethyl acetate to methyl acetate and methyl benzoate to ethyl benzoate are shown below as examples.

Example: Trans-esterification Reactions



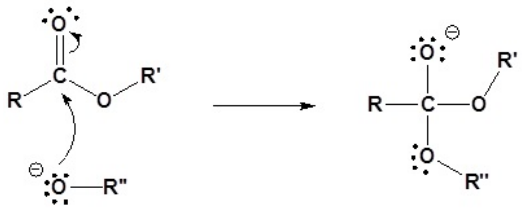
Under acidic conditions, the reaction mechanism begins with protonation of the carbonyl oxygen which increases the reactivity of the ester. An alcohol then reactions with protonated ester to form the tetrahedral intermediate. After several proton transfers, the carbonyl reforms to produce a new ester. The complete mechanism is shown below for the trans-esterification of ethyl actetae to methyl acetate.



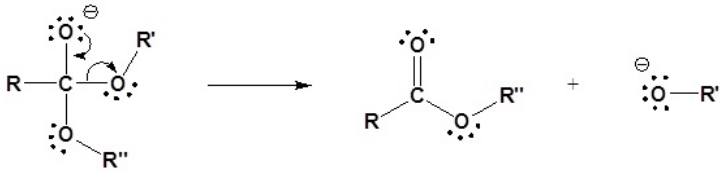
Since both the reactants and the products are an ester and an alcohol, the reaction is reversible and the equilibrium constant is close to one. Consequently, the Le Chatelier's principle has to be exploited to drive the reaction to completion. The simplest way to do so is to use the alcohol as the solvent as well.

Under basic conditions, the mechanism begins with the nucleophilic reaction of the alkoxide with the carbonyl carbon to produce the tetrahedral intermediate. The carbonyl reforms with the loss of the leaving group to produce a new ester.

1) Nucleophilic reaction by an alkoxide

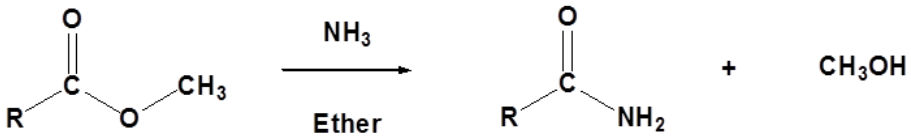


2) Leaving group removal



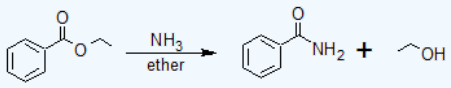
AMINOLYSIS: CONVERSION OF ESTERS INTO AMIDES

Esters react with ammonia and 1° or 2° alkyl amines to yield amides in a reaction called aminolysis.



The aminolysis of ethyl benzoate is shown below as an example. The mechanism for this reaction is analogous to the base promoted hydrolysis reaction of esters shown above.

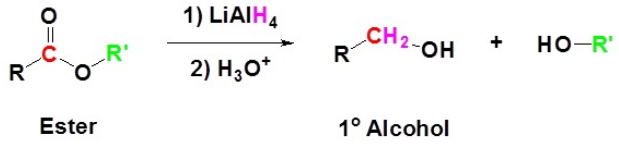
Example: Aminolysis of Esters



ESTER REDUCTION REACTIONS

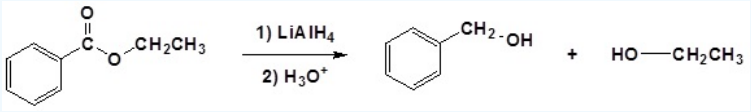
ESTER REDUCTION TO A 1^{O} ALCOHOL

Esters can be converted to 1° alcohols using $LiAlH_4$, while sodium borohydride ($NaBH_4$) is not a strong enough reducing agent to perform this reaction.



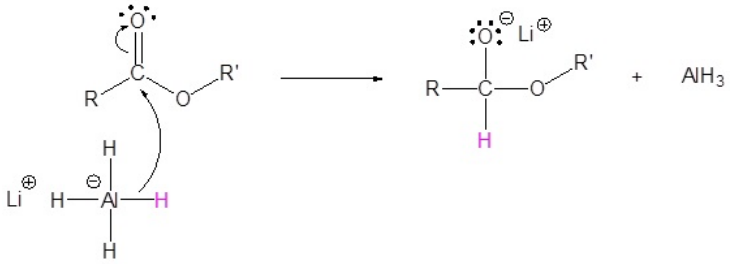
The reduction of ethyl benzoate to benzyl alcohol and ethanol is shown as an example.

Example: Ester Reduction to a 1^{O} Alcohol

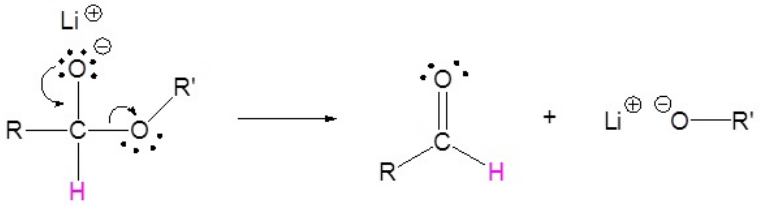


The mechanism begins with a hydride nucleophile reacting with the ester carbonyl carbon to form the tetrahedral intermediate. The carbonyl reforms to produce an aldehyde with the loss of the alkoxide ion. The resulting aldehyde undergoes a subsequent reaction with a hydride nucleophile to form another tetrahedral intermediate. The carbonyl is not able to reform, because there are no stable leaving groups. Therefore, the alkoxide (tetrahedral intermediate) is protonated to produce a primary alcohol. The complete mechanism is shown below.

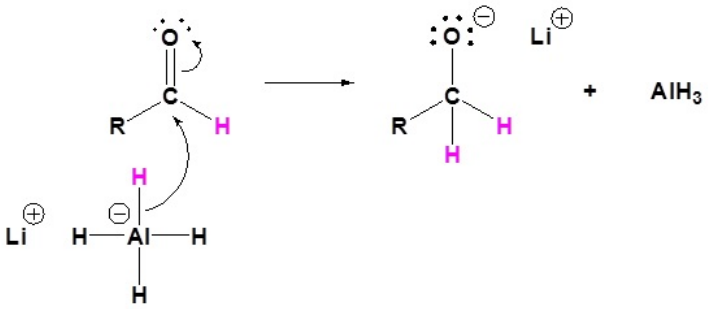
1) Nucleophilic reaction by the hydride



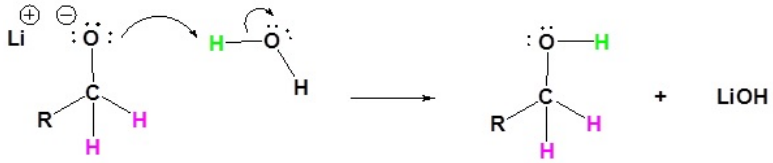
2) Leaving group removal



3) Nucleopilic reaction by the hydride anion

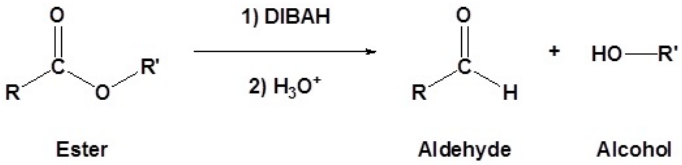


4) The alkoxide is protonated



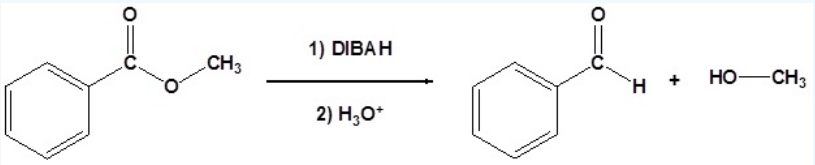
ESTER REDUCTION TO AN ALDEHYDE

Esters can be converted to aldehydes using diisobutylaluminum hydride (DIBAH). The reaction is usually carried out at -78 ºC to prevent reaction with the aldehyde product.



The reduction of methyl benzoate to form benzaldehyde is shown as an example. The mechanism is analogous to the $LiAlH_4$ mechanism shown above with the important difference that the reaction stops after the aldehyde is produced because the DIBAH reducing agent is not strong enough to reduce the aldehyde at low temperatures.

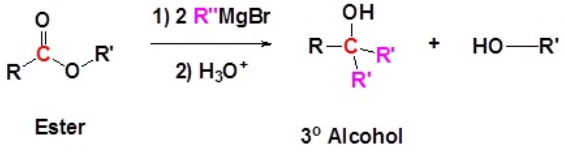
Example: Ester Reduction to an Aldehyde



ESTER REACTIONS WITH ORGANOMETALLIC COMPOUNDS

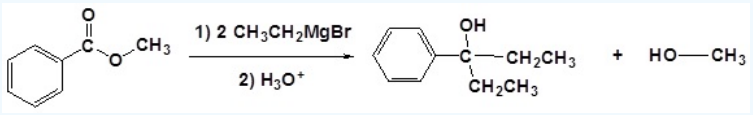
GRIGNARD REAGENTS

Esters react with Grignard reagents to form tertiary alcohols. This reaction is analogous to the reaction discussed for acid chlorides with Grignard reagents. The first equivalent of the Grignard reagent produces a ketone which reacts with the second equivalent of the Grignard reagent to produce a tertiary alcohol. In effect, the Grignard reagent adds twice as shown in the reaction below.



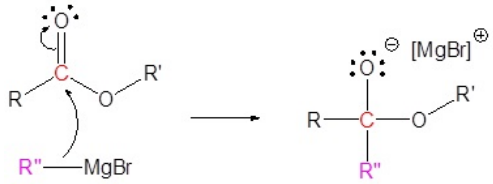
The reaction of methyl benzoate with a Grignard reagent to produce 3-phenyl-3-pentanol.

Example: Ester Reaction with a Grignard Reagent

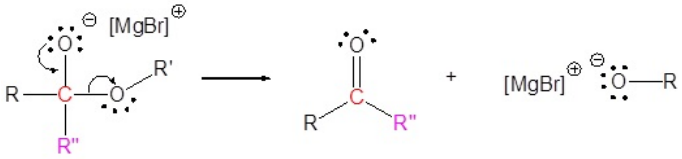


The mechanism begins with a carbide nucleophile from the Grignard reagent reacting with the ester carbonyl carbon to form the tetrahedral intermediate. The carbonyl reforms to produce a ketone with the loss of the alkoxide ion. The resulting ketone undergoes a subsequent reaction with a carbide nucleophile from the Grignard reagent to form another tetrahedral intermediate. The carbonyl is not able to reform, because there are no stable leaving groups. Therefore, the alkoxide (tetrahedral intermediate) is protonated to produce a tertiary alcohol. The complete mechanism is shown below.

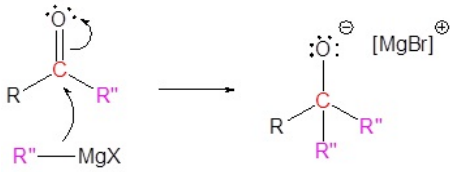
1) Nucleophilic reaction



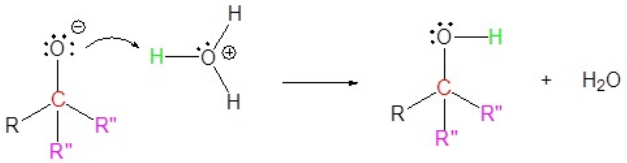
2) Leaving group removal



3) Nucleophilic reaction



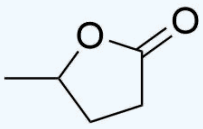
4) Protonation



Exercise

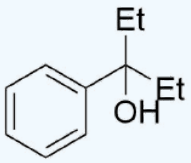
8. Why is the alkaline hydrolysis of an ester not a reversible process? Why doesn't the reaction with a hydroxide ion and a carboxylic acid produce an ester?

9. Draw the product of the reaction between the following molecule and $LiAlH_4$, and the product of the reaction between the following molecule and DIBAL.

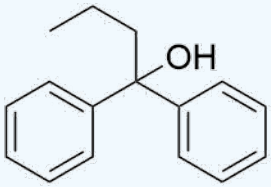


10. Prepare the following molecules from esters and Grignards?

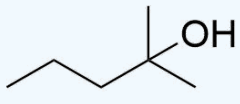
(a)



(b)



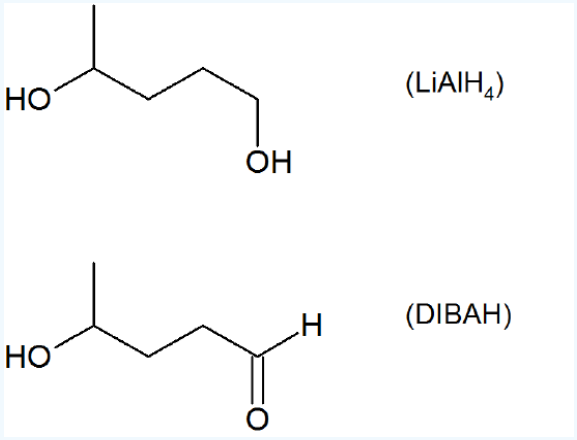
(c)



Answer

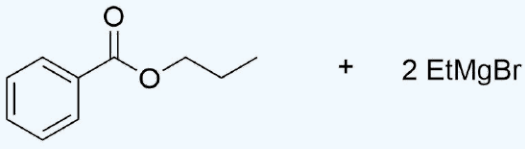
8. The reaction between a carboxylic acid and a hydroxide ion is an acid base reaction, which produces water and a carboxylate anion.

9.

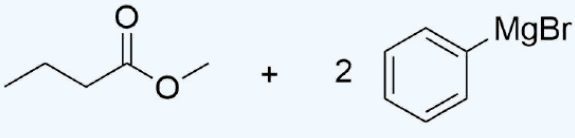


10.

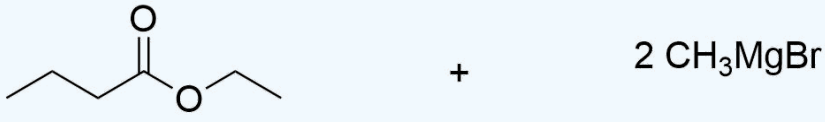
(a)



(b)



(c)



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

- Gamini Gunawardena from the OChemPal site (Utah Valley University)

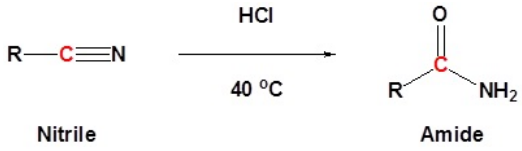
22.6: Ester Chemistry is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

22.7: AMIDE CHEMISTRY

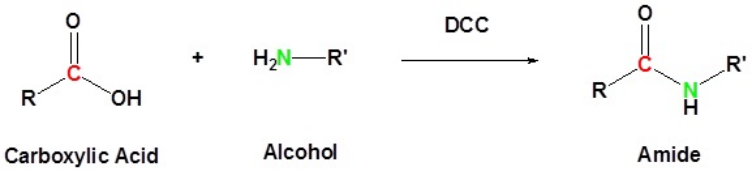
SYNTHESIS OF AMIDES

There are five synthetic routes to produce amides: nitrile conversion and the acyl nucleophilic substitution reactions of acid halides, acid anhydrides, and carboxylic acids.

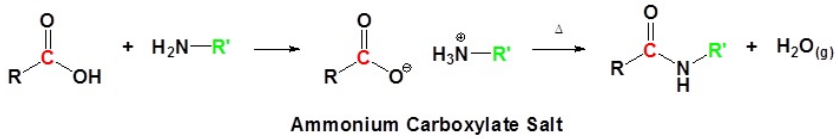
Nitriles can be converted to amides. This reaction can be acid or base catalyzed



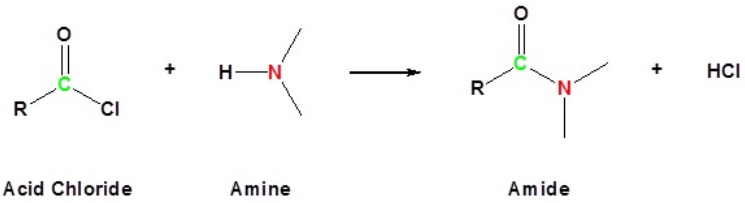
Carboxylic acid can be converted to amides by using DCC as an activating agent



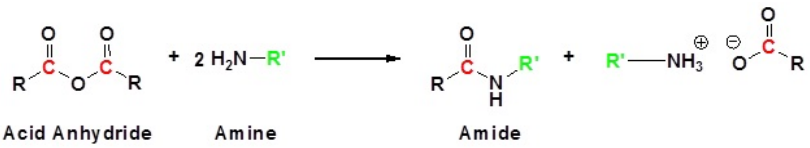
Direct conversion of a carboxylic acid to an amide by reaction with an amine.



Acid chlorides react with ammonia, 1° amines and 2° amines to form amides



Acid Anhydrides react with ammonia, 1° amines and 2° amines to form amides



HYDROLYSIS OF AMIDES

HYDROLYSIS UNDER ACIDIC CONDITIONS

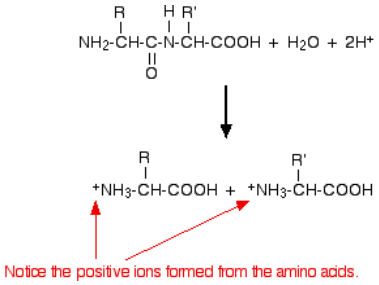
Taking acetamide (ethanamide) as a typical amide. If acetamide is heated with a dilute acid (such as dilute hydrochloric acid), acetic acid is formed together with ammonium ions. So, if you were using hydrochloric acid, the final solution would contain ammonium chloride and acetic acid.

HYDROLYSIS UNDER ALKALINE CONDITIONS

Also, if acetamide is heated with sodium hydroxide solution, ammonia gas is given off and you are left with a solution containing sodium acetate.

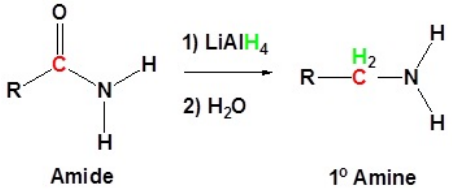
PEPTIDE HYDROLYSIS

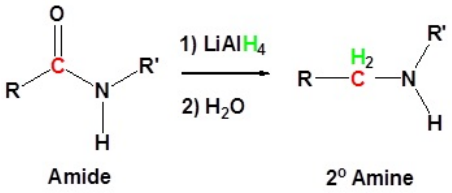
Peptide hydrolysis of proteins is amide hydrolysis. What biologists and biochemists call a peptide link (in proteins, for example) is what chemists call an amide link. Apply either hydrolysis reaction above to the dipeptide below to produce two amino acids. The amines in the products are shown in their protonated form because this hydrolysis reaction was performed under acidic conditions.

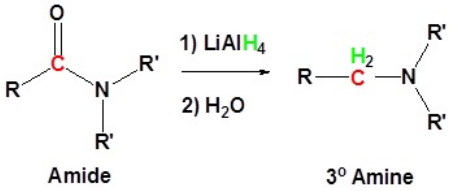


REDUCTION OF AMIDES INTO AMINES

Amides can be converted to 1°, 2° or 3° amines using $LiAlH_4$ followed by an aqueous work-up. Alkyl groups attached to the amide nitrogen do not affect the reaction. The amine classification correlates with the amide as shown in the reaction summary below.

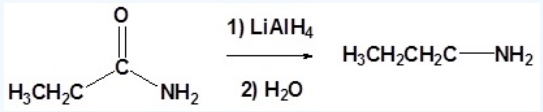


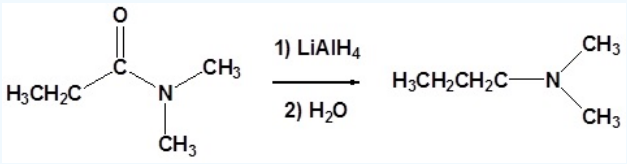




The reductions of propanamide and N,N-dimethylpropanamide are shown as examples.

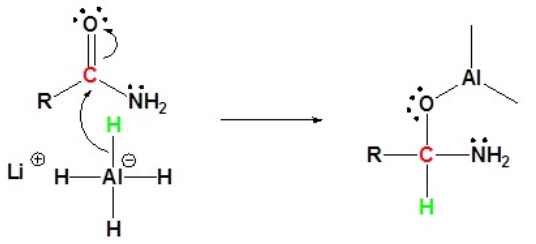
Example: Amide Reductions



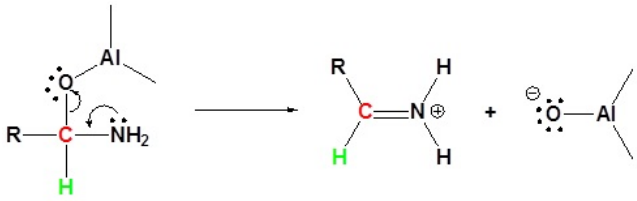


The mechanism begins with nucleophilic hydride reacting with the carbonyl carbon to produce the tetrahedral intermediate. An imine forms in concert with the loss on the leaving group. A second hydride nucleophile reacts with the imine carbon to produce the final product.

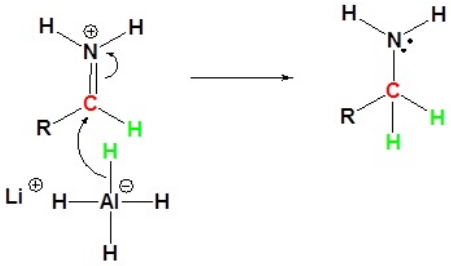
1) Nucleophilic reaction by the hydride



2) Imine formation with loss of leaving group



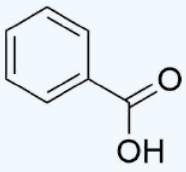
3) Nucleophilic reaction by the hydride



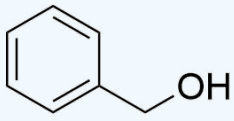
Exercise

11. How would you prepare the following compounds from N-Propypl benzamide?

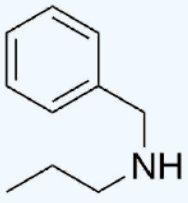
(a)



(b)

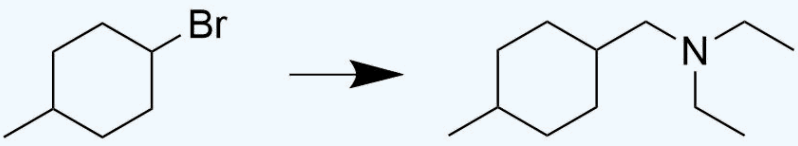


(c)



12.

Propose a synthesis for the following.



Answer

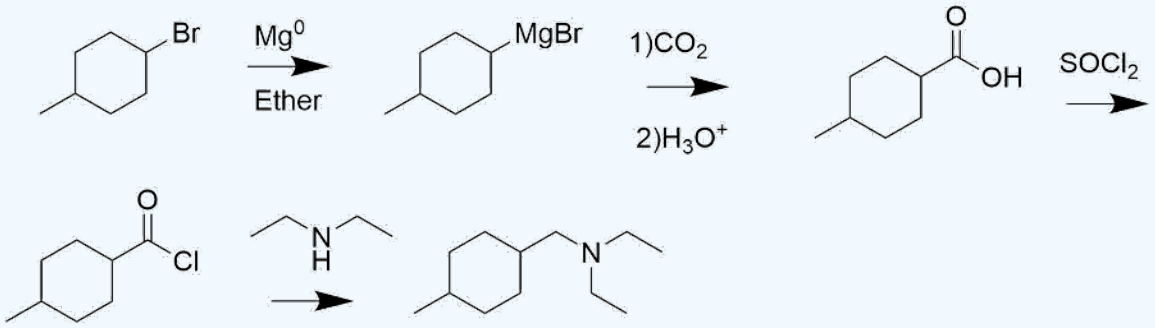
11.

a) NaOH, H_2O

b) NaOH, H_2O, then $LiAlH_4$

c) $LiAlH_4$

12.



CONTRIBUTORS AND ATTRIBUTIONS

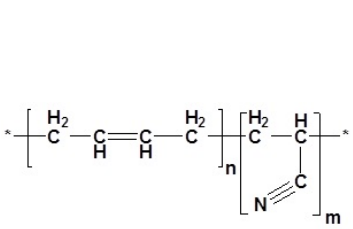
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)

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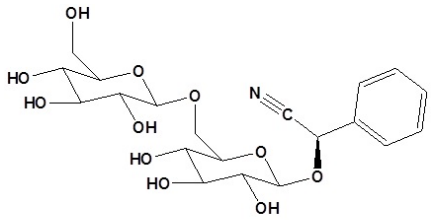
22.8: NITRILE CHEMISTRY

INTERESTING NITRILES

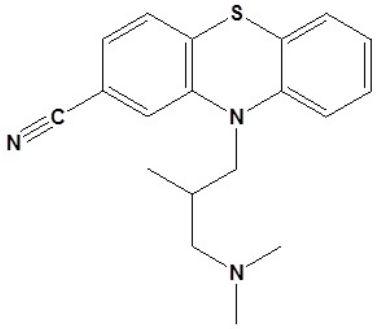
One of the most common occurrences of nitriles is nitrile rubber. Nitrile rubber is a synthetic copolymer of acrylonitrile and butadiene. This form of rubber is highly resistant to chemicals and is used to make protective gloves, hoses and seals.



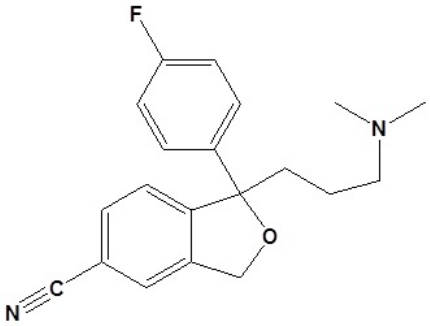
Nitrile Rubber



Amygdalin: Found in Bitter Almonds



Cyamemazine: an antipsychotic

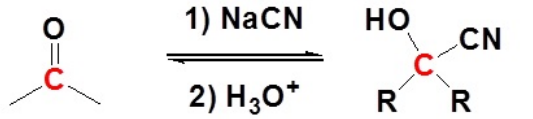


Citalopram: an antidepressant

SYNTHESIS OF NITRILES

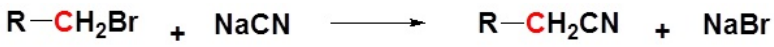
Nitriles can be synthesized from the reaction of nucleophilic cyanide with electrophilic groups, such as the carbonyls (aldehydes and ketones) and alkyl halides that are suitable for S_N2 reactions. Amides can react with thionyl chloride to produce nitriles.

Addition of cyanide ($^-$:C≡N) to an aldehyde or ketone forms a cyanohydrin.

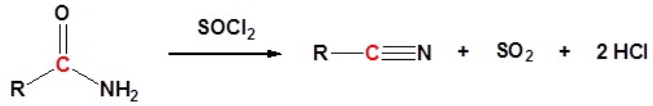


Aldehyde or Ketone — Cyanohydrin

Nitriles are formed by an S_N2 reaction between an alkyl bromide and sodium cyanide



Primary (1°) amides can be converted to nitriles by dehydration with thionyl chloride (or other dehydrating agents like P_2O_5, or $POCl_3$).



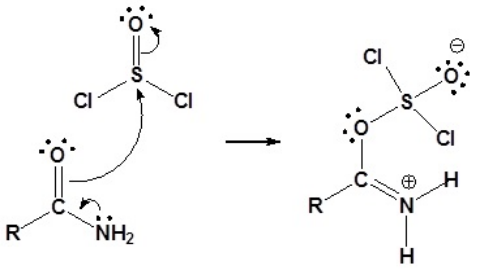
1° Amide — Nitrile

For the reaction of primary amides with thionyl chloride, the mechanism begins with the lone pair of the nitrogen atom formimg a protonated imine and pushing the pi electrons of the carbonyl to form a sigma bond with the sulfur of thionyl chloride. The sulfonyl bond

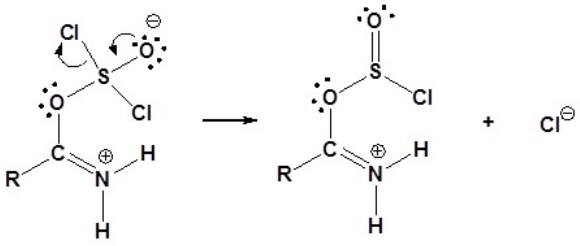
reforms in concert with the loss of the leaving group (Cl^-). The protonated imine is neutralized by any base. The nitrile is produced by one last deprotonation reaction with a loss of sulfur dioxide and chloride as the leaving groups.

The complete mechanism is shown below.

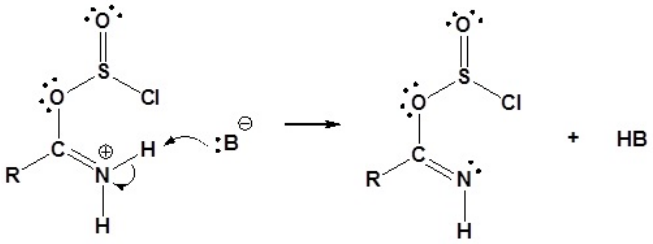
1) Protonated imine formation with Nucleophilic reaction of carbonyl pi bond



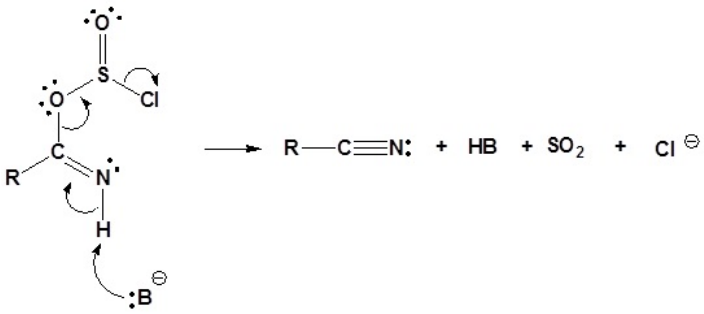
2) Leaving group removal



3) Deprotonation

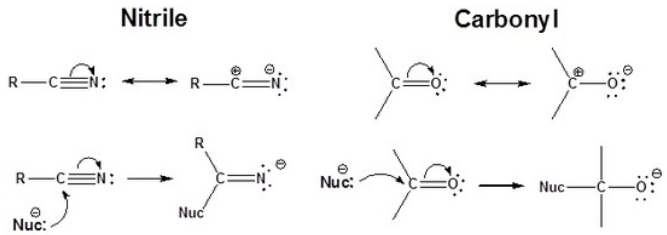


4) Deprotonation & Leaving group removal

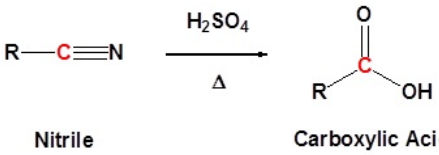


REACTIVITY OF NITRILES

The carbon in a nitrile is electrophilic because a resonance structure can be drawn which places a positive charge on it. Because of this the triple bond of a nitrile accepts a nucleophile in a manner similar to a carbonyl.

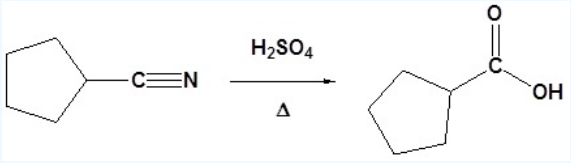


Nitriles can be converted to carboxylic acid with heating in sulfuric acid. During the reaction an amide intermediate is formed.



The hydrolysis of cyclopentanecarbonitrile is shown below as an example.

Example: Nitrile Hydrolysis



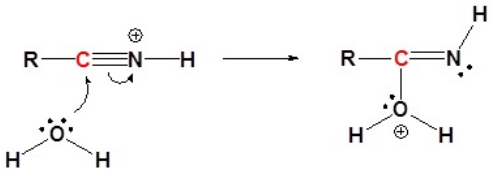
Note that the presence of water is understood.

The mechanism begins with the protonation of the nitrile to make it more electrophilic to nucleophilic water. Once the water has reacted with the nitrile carbon, proton transfers occur to produce a resonance stabilized intermediate. Water acts as a weak base to deprotonate the carbonyl to form the amide which is hydrolyzed to the carboxylic acid.

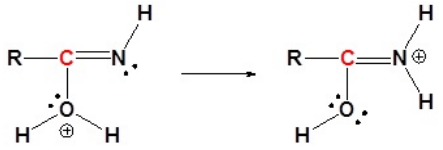
1) Protonation



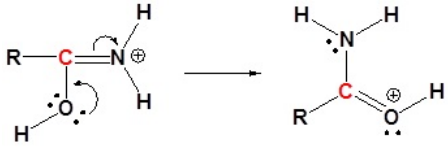
2) Nucleophilic reaction by water



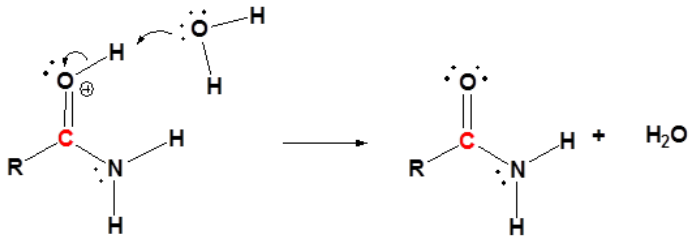
3) Proton Transfer



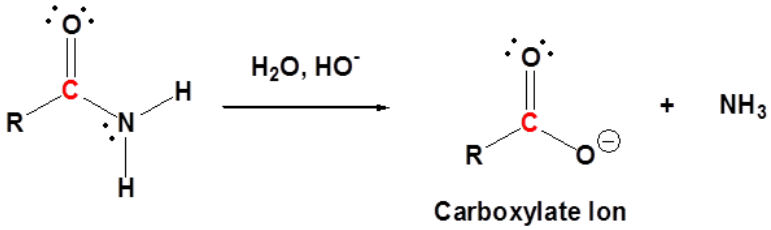
4) Resonance



5) Deprotonation

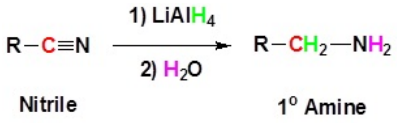


6) Further hydrolysis of the amide shown in amide section of this chapter.



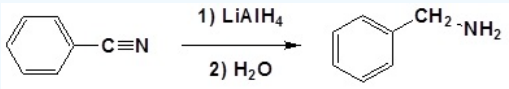
NITRILE REDUCTION

Nitriles can be reduced to primary amines with lithium aluminum hydride followed by an aqueous work-up. During this reaction the hydride nucleophile reacts with the electrophilic carbon in the nitrile to form an imine anion. Once stabilized by a Lewis acid-base complexation, the imine salt can accept a second hydride to form a dianion. The dianion can then be converted to an amine by addition of water to neutralize the reaction environment. The general reaction is shown below.



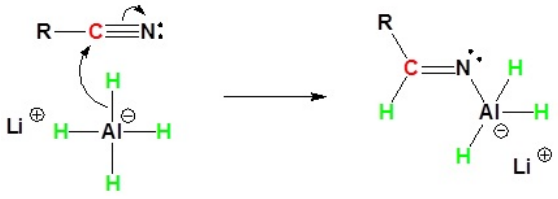
The reduction of cyclopentanecarbonitrile is shown below as an example.

Example: Nitrile Reduction

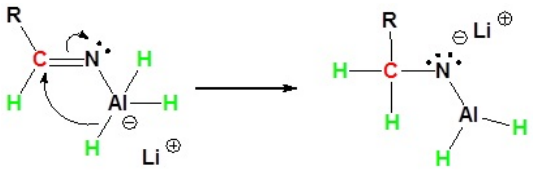


The mechanism begins with the nucleophilic hydride reacting with the electrophilc carbon of the nitrile to form an anionic aluminum complex. A second hydride nucleophile reacts with the same electrophilic carbon to form a tetrahedral complex. Protonation by addition of water produces the primary amine in its neutral form.

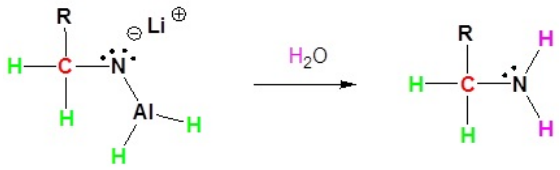
1) Nucleophilic reaction by the Hydride



2) Second nucleophilic reaction by the hydride.

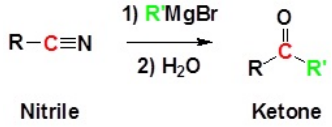


3) Protonation by addition of water to give an amine



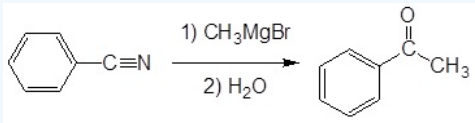
ORGANOMETALLIC REACTION WITH NITRILES

Grignard reagents can react with nitriles to form an imine salt that can be hydrolyzed to form a ketone as shown in the reaction below.



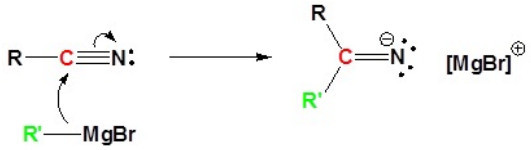
The reaction of benzonitrile with the methyl-Grignard reagent to form acetophenone is shown below as an example.

Example: Nitrile reaction with a Grignard Reagent

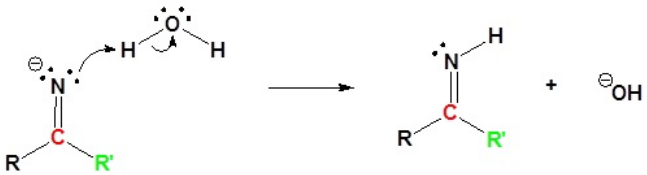


The mechanism begins with the nucleophilic Grignard Reagent reacting with the electrophilic carbon of the nitrile to form an imine salt. The imine salt is hydrolyzed to produce a ketone through a series of nucleophilic and proton transfer reactions. The complete mechanism is shown below for those who are curious.

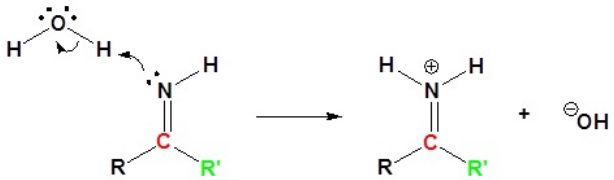
1) Nucleophilic reaction by the Grignard Reagent



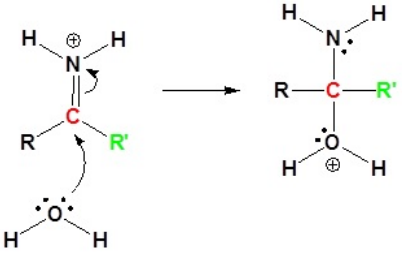
2) Protonation



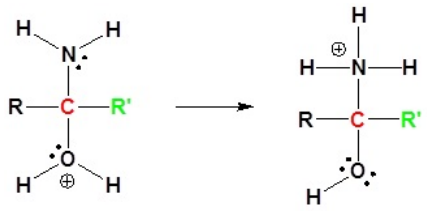
3) Protonation



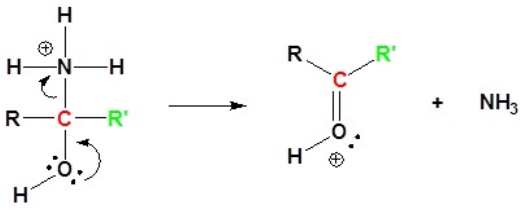
4) Nucleophilic reaction by water



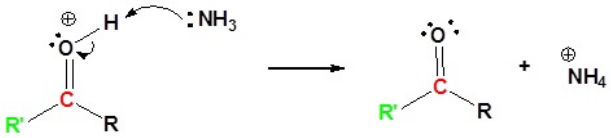
5) Proton Transfer



6) Leaving group removal



7) Deprotonation

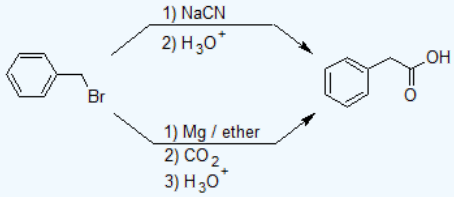


Exercise

13. Propose two different synthetic routes to convert benzyl bromide into 2-phenyl acetic acid.

Answer

13.



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

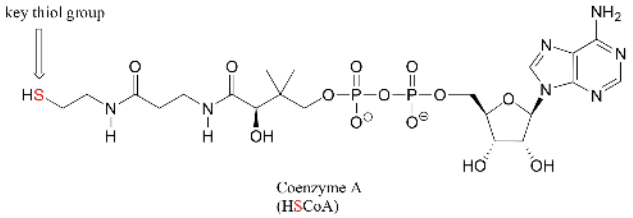
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22.9: THIOESTERS- BIOLOGICAL CARBOXYLIC ACID DERIVATIVES

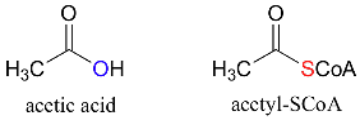
INTRODUCTION TO THIOESTERS AND COENZYME A

In the metabolism of lipids (fats and oils), thioesters are the principal form of activated carboxylate groups. They are employed as acyl carriers, assisting with the transfer of acyl groups such as fatty acids from one acyl X substrate to another.

The 'acyl X group' in a thioester is a thiol. The most important thiol compound used to make thioesters is called coenzyme A, which has the following structure:

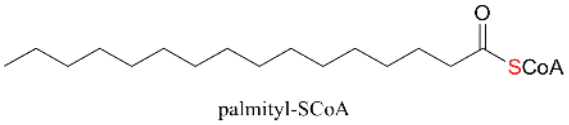


Coenzyme A is often abbreviated HSCoA, in order to emphasize that it is the thiol sulfur that provides the critical thioester linkage to acyl groups. When fuel (carbohydrate and fat) is broken down in your body, it is eventually converted to a simple two-carbon unit called acetyl CoA, which is essentially a thioester derivative of acetic acid:

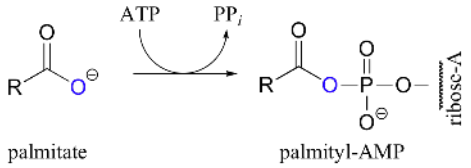


ACTIVATION OF FATTY ACIDS BY COENZYME A: A THIOESTERIFICATION REACTION

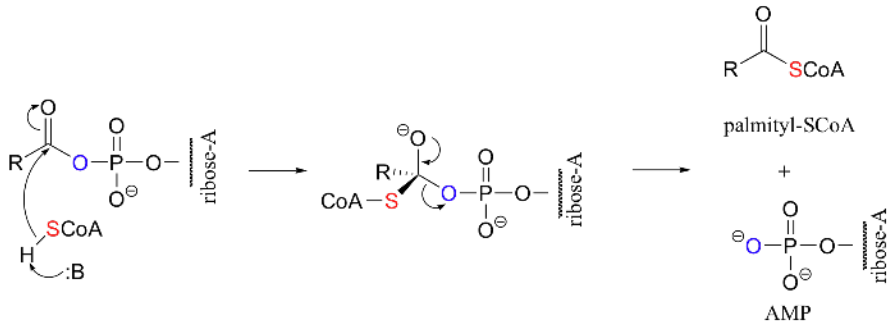
In the biologically active form of fatty acids, the carboxylate groups have been converted to thioesters using coenzyme A. For example, the activated form of the C_{16} fatty acid palmitate is:



Let's take a look at how this activation takes place, in a reaction catalyzed by an enzyme called acyl CoA synthetase. You already know that carboxylates are not themselves good substrates for acyl substitution reactions, and must be activated. Thus, you might predict that the first step of this reaction requires ATP to make a high-energy acyl phosphate intermediate. In fact, the activated carboxylate in this case is an acyl-AMP, formed in the same way as the acyl-AMP intermediate in the asparagine synthetase reaction.

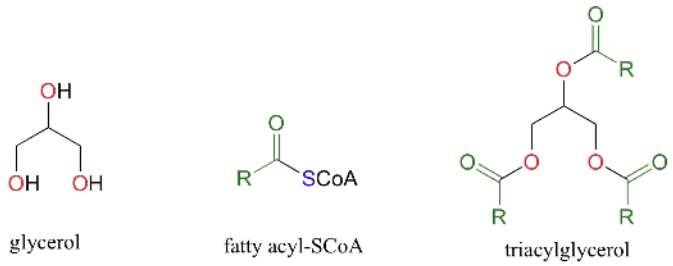


The activated acyl-AMP intermediate is then attacked by the thiol sulfur of coenzyme A, and the AMP group is expelled to form the fatty acyl CoA.

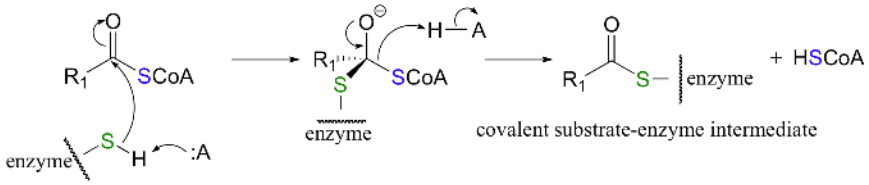


TRANSFER OF FATTY ACYL GROUPS TO GLYCEROL: A THIOESTER TO ESTER SUBSTITUTION

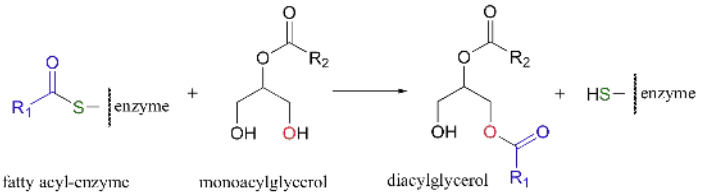
The -SCoA thioester form of the fatty acid is a good substrate for a number of metabolic transformations. This is the form of fatty acid, for example, that is oxidized and broken down for energy in the mitochondria of your cells. Fatty acyl CoA also serves as substrate for the construction of triacylglycerol, which is the fat molecule that your body uses to store energy in fat cells. Recall that triacylglycerol is composed of a glycerol 'backbone' connected to three fatty acid groups through ester linkages.



The reaction in which a fatty acid acyl group is linked to glycerol represents the conversion of a thioester (fatty acyl CoA) to an ester. First, however, a **transthioesterification** reaction occurs. A transthioesterification is merely the conversion of one thioester to another. In the case of monoacylglycerolacyltransferase, the fatty acyl group first trades its thioester link to coenzyme A for another thioester link to a cysteine residue in the active site of the enzyme. It is a common strategy for enzymes to first form a covalent link to one substrate before catalyzing the principle chemical reaction.



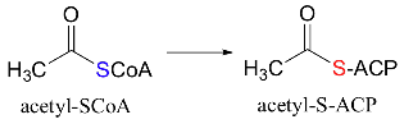
The fatty acyl group is now ready to be transferred to glycerol, trading its thioester linkage to the cysteine for a new ester linkage to one of the alcohol groups on glycerol. The attacking nucelophile in this reaction is of course the alcohol oxygen of monoacylglycerol.

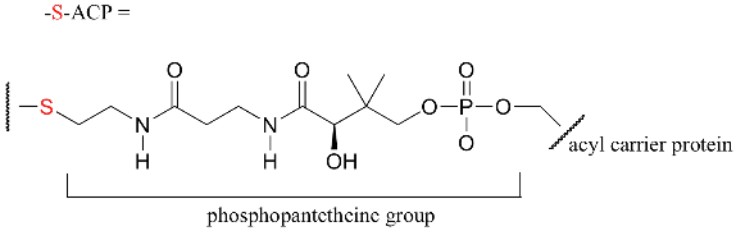


Because esters are more stable than thioesters, this is an energetically downhill reaction.

TRANSTHIOESTERIFICATION REACTIONS

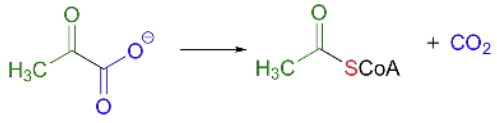
In the previous section we saw one example of a transthioesterification. Another important transthioesterification reaction involves acetyl CoA, the activated form of acetic acid and the basic two-carbon building block for fats and oils. Before it can be incorporated into a growing fatty acid molecule, acetyl CoA must first be linked to a so-called 'acyl carrier protein' (ACP). The acetyl group is linked to the acyl carrier protein *via* a thiol group on a carrier molecule that is covalently attached to the protein.



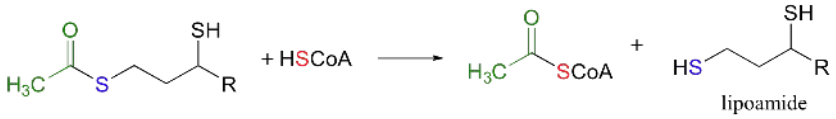


Notice that the structure of this carrier group (called phosphopantetheine) is identical to the region of coenzyme A (structure shown earlier in this section) near the thiol group. Once attached to the ACP, the two-carbon acetyl group condenses with another acyl group (which is also attached to its own ACP), and the fatty acid chain begins to grow.

Finally, a transthioesterification is the final step in one of the most important and well-studied reactions in animal metabolism: the conversion of pyruvate to acetyl CoA by a cluster of enzymes called the pyruvate dehydrogenase complex.



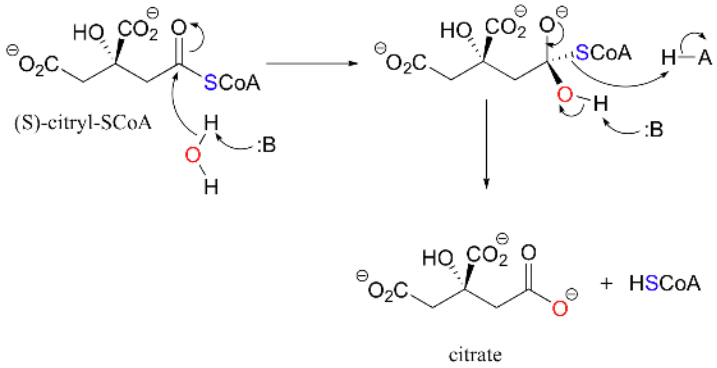
The overall reaction looks simple, but is actually quite complex and involves several intermediate species. The final step in the process is a transthioesterification, involving a dithiol molecule called lipoamide:



We will look more closely at the complete biochemical transformation catalyzed by the pyruvate dehydrogenase complex in section 16.12B.

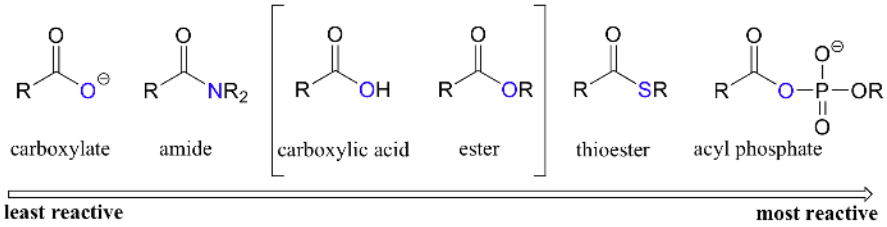
HYDROLYSIS OF THIOESTERS

The acyl group of a thioester can be transferred to a water molecule in a hydrolysis reaction, resulting in a carboxylate. An example of thioester hydrolysis is the conversion of (S)-citryl CoA to citrate in the citric acid cycle (also known as the Krebs cycle).



REACTIVITY OF THIOESTERS AND ACYL PHOSPHATES

Thioesters are reactive among the biologically relevant acyl groups. However, thioesters are not as reactive as an acid chlorides or acid anhydrides.



Relative reactivity of biologically relevant acyl groups

CONTRIBUTORS AND ATTRIBUTIONS

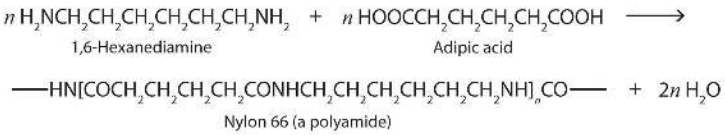
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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22.10: POLYAMIDES AND POLYESTERS- STEP-GROWTH POLYMERS

POLYAMIDES

Just as the reaction of a diol and a diacid forms a polyester, the reaction of a diacid and a diamine yields a polyamide. The two difunctional monomers often employed are adipic acid and 1,6-hexanediamine. The monomers condense by splitting out water to form a new product, which is still difunctional and thus can react further to yield a polyamide polymer.

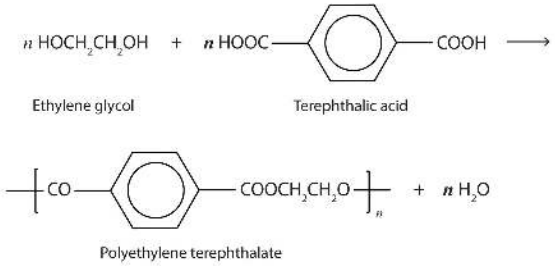


Some polyamides are known as *nylons*. Nylons are among the most widely used synthetic fibers—for example, they are used in ropes, sails, carpets, clothing, tires, brushes, and parachutes. They also can be molded into blocks for use in electrical equipment, gears, bearings, and valves.

POLYESTERS

A commercially important esterification reaction is condensation polymerization, in which a reaction occurs between a dicarboxylic acid and a dihydric alcohol (diol), with the elimination of water. Such a reaction yields an ester that contains a free (unreacted) carboxyl group at one end and a free alcohol group at the other end. Further condensation reactions then occur, producing polyester polymers.

The most important polyester, polyethylene terephthalate (PET), is made from terephthalic acid and ethylene glycol monomers:

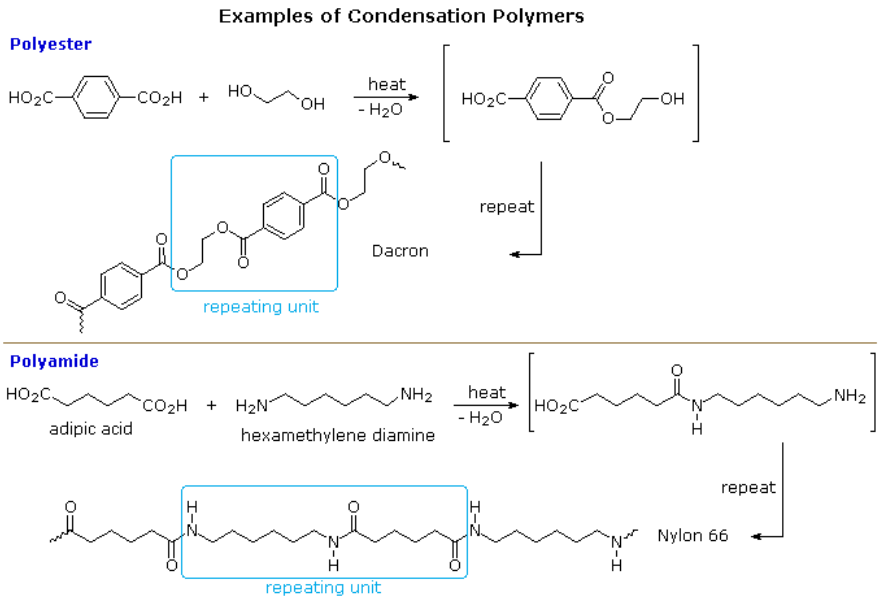


Polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or replace diseased sections of blood vessels. PET is used to make bottles for soda pop and other beverages. It is also formed into films called Mylar. When magnetically coated, Mylar tape is used in audio- and videocassettes. Synthetic arteries can be made from PET, polytetrafluoroethylene, and other polymers.

CONDENSATION POLYMERS

A large number of important and useful polymeric materials are not formed by chain-growth processes involving reactive species such as radicals, but proceed instead by conventional functional group transformations of polyfunctional reactants. These polymerizations often (but not always) occur with loss of a small byproduct, such as water, and generally (but not always) combine two different components in an alternating structure. The polyester Dacron and the polyamide Nylon 66, shown here, are two examples of synthetic condensation polymers, also known as step-growth polymers. In contrast to chain-growth polymers, most of which grow by carbon-carbon bond formation, step-growth polymers generally grow by carbon-heteroatom bond formation (C-O & C-N in Dacron & Nylon respectively). Although polymers of this kind might be considered to be alternating copolymers, the repeating monomeric unit is usually defined as a combined moiety.

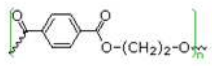
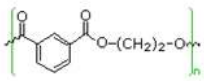
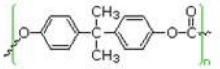
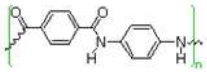
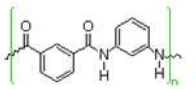
Examples of naturally occurring condensation polymers are cellulose, the polypeptide chains of proteins, and poly(β-hydroxybutyric acid), a polyester synthesized in large quantity by certain soil and water bacteria. Formulas for these will be displayed below by clicking on the diagram.



CHARACTERISTICS OF CONDENSATION POLYMERS

Condensation polymers form more slowly than addition polymers, often requiring heat, and they are generally lower in molecular weight. The terminal functional groups on a chain remain active, so that groups of shorter chains combine into longer chains in the late stages of polymerization. The presence of polar functional groups on the chains often enhances chain-chain attractions, particularly if these involve hydrogen bonding, and thereby crystallinity and tensile strength. The following examples of condensation polymers are illustrative.

Note that for commercial synthesis the carboxylic acid components may actually be employed in the form of derivatives such as simple esters. Also, the polymerization reactions for Nylon 6 and Spandex do not proceed by elimination of water or other small molecules. Nevertheless, the polymer clearly forms by a step-growth process. Some Condensation Polymers

Formula	Type	Components	T_g ºC	T_m ºC
~[CO(CH$_2$)$_4$CO-OCH$_2$CH$_2$O]$_n$~	**polyester**	HO$_2$C-(CH$_2$)$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH	< 0	50
	**polyester** Dacron, Mylar	para HO$_2$C-C$_6$H$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH	70	265
	**polyester**	meta HO$_2$C-C$_6$H$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH	50	240
	**polycarbonate** Lexan	(HO-C$_6$H$_4$-)$_2$C(CH$_3$)$_2$ (Bisphenol A) X$_2$C=O (X = OCH$_3$ or Cl)	150	267
~[CO(CH$_2$)$_4$CO-NH(CH$_2$)$_6$NH]$_n$~	**polyamide** Nylon 66	HO$_2$C-(CH$_2$)$_4$-CO$_2$H H$_2$N-(CH$_2$)$_6$-NH$_2$	45	265
~[CO(CH$_2$)$_5$NH]$_n$~	**polyamide** Nylon 6 Perlon		53	223
	**polyamide** Kevlar	para HO$_2$C-C$_6$H$_4$-CO$_2$H para H$_2$N-C$_6$H$_4$-NH$_2$	---	500
	**polyamide** Nomex	meta HO$_2$C-C$_6$H$_4$-CO$_2$H meta H$_2$N-C$_6$H$_4$-NH$_2$	273	390

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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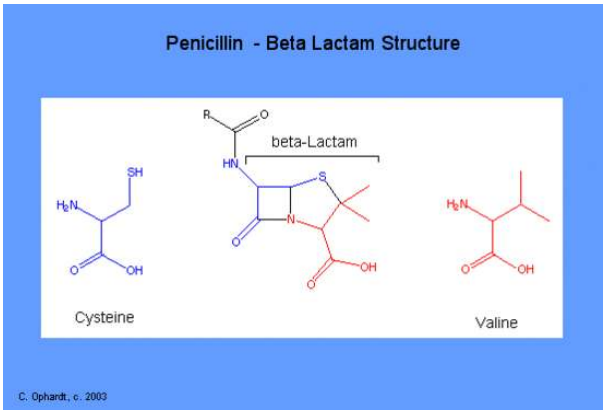
22.11: BETA-LACTAMS- AN APPLICATION

THE MECHANISM OF ACTION OF B-LACTAM ANTIBIOTICS

Antibiotics are specific chemical substances derived from or produced by living organisms that are capable of inhibiting the life processes of other organisms. The first antibiotics were isolated from microorganisms but some are now obtained from higher plants and animals. Over 3,000 antibiotics have been identified but only a few dozen are used in medicine. Antibiotics are the most widely prescribed class of drugs comprising 12% of the prescriptions in the United States. The penicillins were the first antibiotics discovered as natural products from the mold Penicillium.

INTRODUCTION

In 1928, Sir Alexander Fleming, professor of bacteriology at St. Mary's Hospital in London, was culturing Staphylococcus aureus. He noticed zones of inhibition where mold spores were growing. He named the mold Penicillium rubrum. It was determined that a secretion of the mold was effective against Gram-positive bacteria.



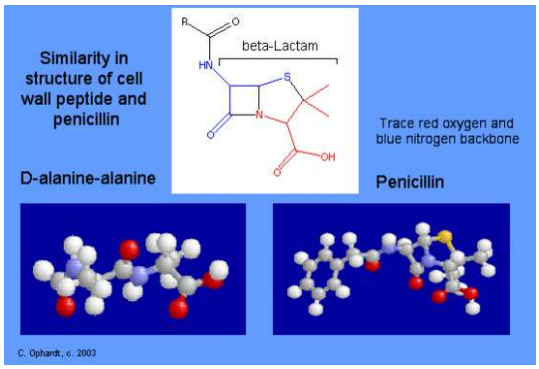
Penicillins as well as cephalosporins are called beta-lactam antibiotics and are characterized by three fundamental structural requirements: the fused beta-lactam structure (shown in the blue and red rings, a free carboxyl acid group (shown in red bottom right), and one or more substituted amino acid side chains (shown in black). The lactam structure can also be viewed as the covalent bonding of pieces of two amino acids - cysteine (blue) and valine (red).

Penicillin-G where R = an ethyl pheny group, is the most potent of all penicillin derivatives. It has several shortcomings and is effective only against gram-positive bacteria. It may be broken down in the stomach by gastric acids and is poorly and irregularly absorbed into the blood stream. In addition many disease producing staphylococci are able to produce an enzyme capable of inactivating penicillin-G. Various semisynthetic derivatives have been produced which overcome these shortcomings.

Powerful electron-attracting groups attached to the amino acid side chain such as in phenethicillin prevent acid attack. A bulky group attached to the amino acid side chain provides steric hindrance which interferes with the enzyme attachment which would deactivate the pencillins i.e. methicillin. Refer to Table 2 for the structures. Finally if the polar character is increased as in ampicillin or carbenicillin, there is a greater activity against Gram-negative bacteria.

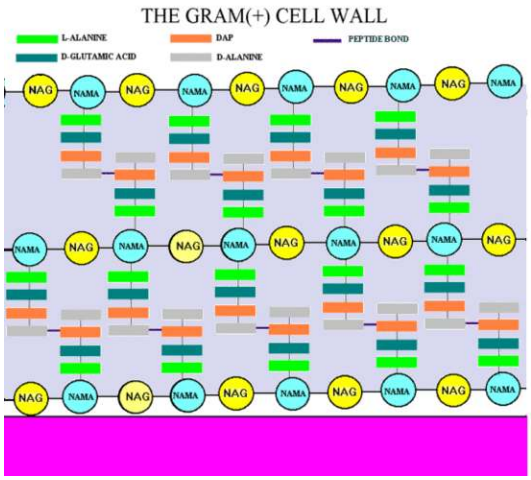
PENICILLIN MODE OF ACTION

All penicillin derivatives produce their bacteriocidal effects by inhibition of bacterial cell wall synthesis. Specifically, the cross linking of peptides on the mucosaccharide chains is prevented. If cell walls are improperly made cell walls allow water to flow into the cell causing it to burst. Resemblances between a segment of penicillin structure and the backbone of a peptide chain have been used to explain the mechanism of action of beta-lactam antibiotics. The structures of a beta-lactam antibiotic and a peptide are shown on the left for comparison. Follow the trace of the red oxygens and blue nitrogen atoms.



Gram-positive bacteria possess a thick cell wall composed of a cellulose-like structural sugar polymer covalently bound to short peptide units in layers.The polysaccharide portion of the peptidoglycan structure is made of repeating units of N-acetylglucosamine linked b-1,4 to N-acetylmuramic acid (NAG-NAM). The peptide varies, but begins with L-Ala and ends with D-Ala. In the middle is a dibasic amino acid, diaminopimelate (DAP). DAP (orange) provides a linkage to the D-Ala (gray) residue on an adjacent peptide.

The bacterial cell wall synthesis is completed when a cross link between two peptide chains attached to polysaccharide backbones is formed. The cross linking is catalyzed by the enzyme transpeptidase. First the terminal alanine from each peptide is hydrolyzed and secondly one alanine is joined to lysine through an amide bond.



Penicillin binds at the active site of the transpeptidase enzyme that cross-links the peptidoglycan strands. It does this by mimicking the D-alanyl-D-alanine residues that would normally bind to this site. Penicillin irreversibly inhibits the enzyme transpeptidase by reacting with a serine residue in the transpeptidase. This reaction is irreversible and so the growth of the bacterial cell wall is inhibited. Since mammal cells do not have the same type of cell walls, penicillin specifically inhibits only bacterial cell wall synthesis.

BACTERIAL RESISTANCE

As early as the 1940s, bacteria began to combat the effectiveness of penicillin. Penicillinases (or beta-lactamases) are enzymes produced by structurally susceptable bacteria which renders penicillin useless by hydrolysing the peptide bond in the beta-lactam ring of the nucleus. Penicillinase is a response of bacterial adaptation to its adverse environment, namely the presence of a substance which inhibits its growth. Many other antibiotics are also rendered ineffective because of this same type of resistance.

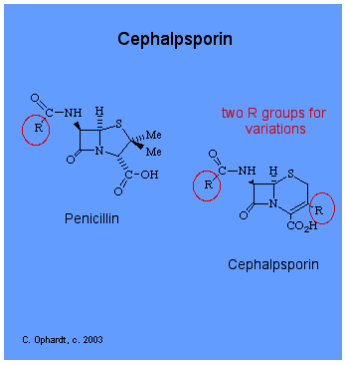
SEVERE ALLERGIC SHOCK

It is estimated that between 300-500 people die each year from penicillin-induced anaphylaxis, a severe allergic shock reaction to penicillin. In afflicted individuals, the beta-lactam ring binds to serum proteins, initiating an IgE-mediated inflammatory response. Penicillin and ala-ala peptide - Chime in new window

CEPHALOSPORINS

Cephalosporins are the second major group of beta-lactam antibiotics. They differ from penicillins by having the beta-lactam ring as a 6 member ring. The other difference, which is more significant from a medicinal chemistry stand point, is the existence of a functional group

(R) at position 3 of the fused ring system. This now allows for molecular variations to effect changes in properties by diversifying the groups at position 3.



The first member of the newer series of beta-lactams was isolated in 1956 from extracts of Cephalosporium acremonium, a sewer fungus. Like penicillin, cephalosporins are valuable because of their low toxicity and their broad spectrum of action against various diseases. In this way, cephalosporin is very similar to penicillin. Cephalosporins are one of the most widely used antibiotics, and economically speaking, has about 29% of the antibiotic market. The cephalosporins are possibly the single most important group of antibiotics today and are equal in importance to penicillin.

The structure and mode of action of the cephalosporins are similar to that of penicillin. They affect bacterial growth by inhibiting cell wall synthesis, in Gram-positive and negative bacteria. Some brand names include: cefachlor, cefadroxil, cefoxitin, ceftriaxone. Cephalexin - Chime in new window

CONTRIBUTORS AND ATTRIBUTIONS

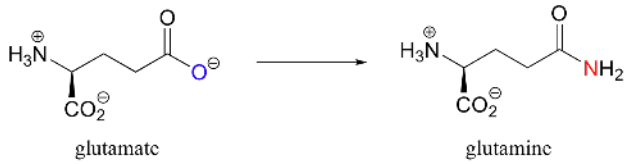
Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

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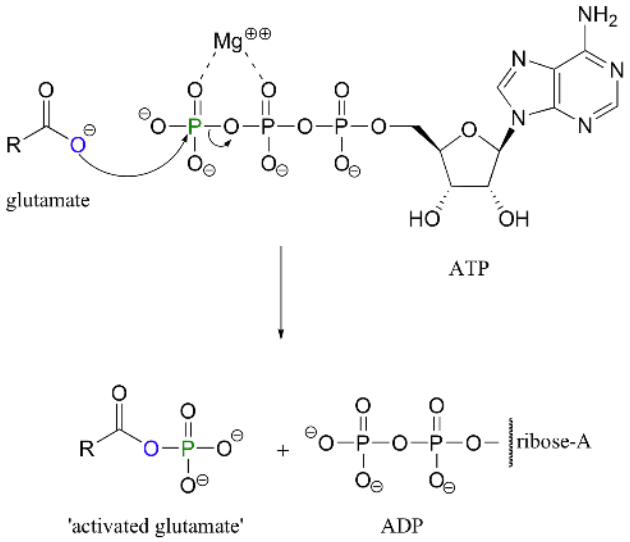
22.12: BIOLOGICAL ACYLATION REACTIONS

GLUTAMINE SYNTHETASE

The carboxylate functional group is a very unreactive substrate for an enzyme-catalyzed acyl substitution reactions. How, then, does a living system accomplish an 'uphill' reaction such as the one shown below, where glutamate (a carboxylate) is converted to glutamine (an amide)?

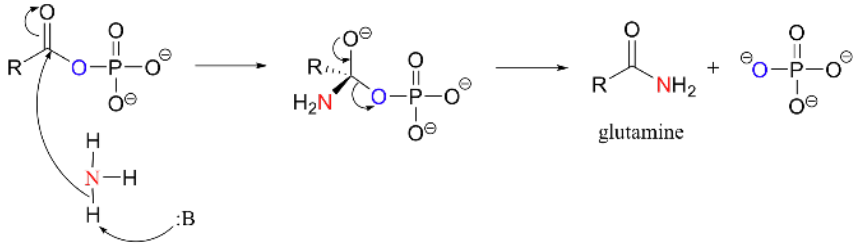


It turns out that this conversion is not carried out directly. Rather, the first conversion is from a carboxylate (the *least* reactive acyl transfer substrate) to an acyl phosphate (the *most* reactive acyl transfer substrate). This transformation requires a reaction that we are familiar with from chapter 10: phosphorylation of a carboxylate oxygen with ATP as the phosphate donor.

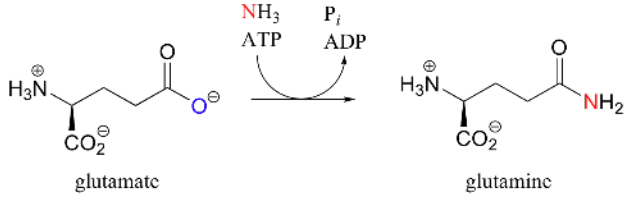


Note that this is just one of the many ways that ATP is used as a energy storage unit: in order to make a high energy acyl phosphate molecule from a low energy carboxylate, the cell must 'spend' the energy of one ATP molecule.

The acyl phosphate version of glutamate is now ready to be converted directly to an amide (glutamine) *via* a nucleophilic acyl substitution reaction, as an ammonia molecule attacks the carbonyl and the phosphate is expelled.

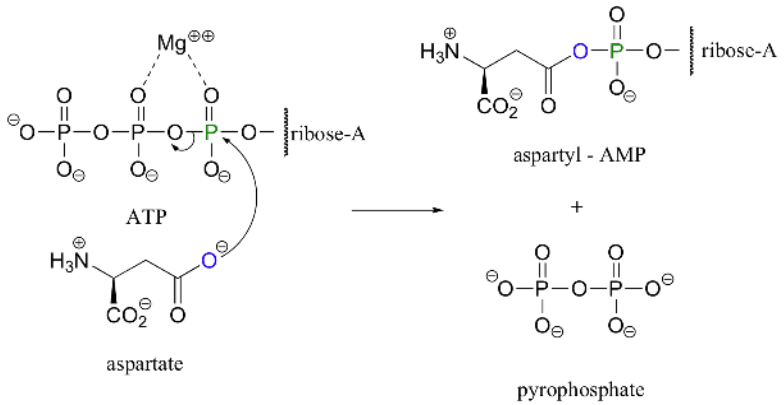


Overall, this reaction can be written as:



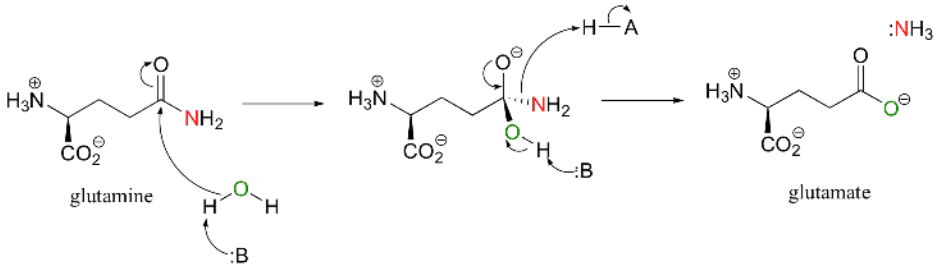
ASPARAGINE SYNTHETASE

Another common form of activated carboxylate group is an acyl adenosine phosphate. Consider another amino acid reaction, the conversion of aspartate to asparagine. In the first step, the carboxylate group of aspartate must be activated:

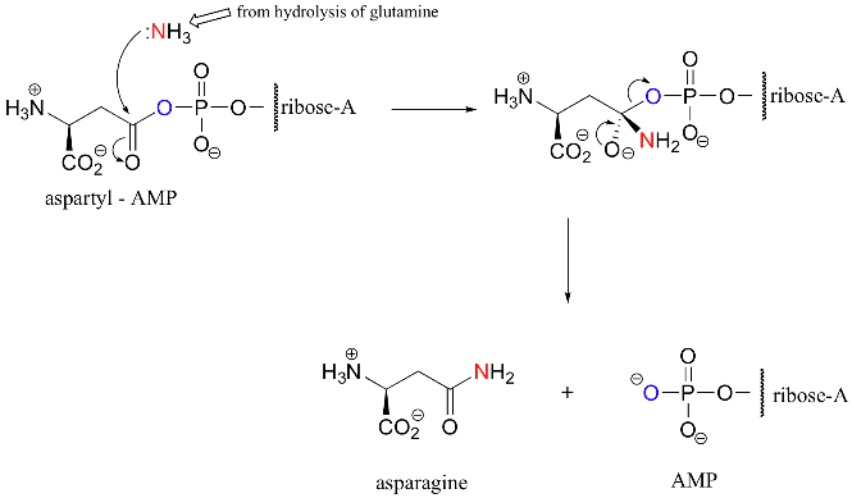


Once again, ATP provides the energy for driving the uphill reaction. This time, however, the activated carboxylate takes the form of an acyl adenosine (mono)phosphate. All that has happened is that the carboxylate oxygen has attacked the a-phosphate of ATP rather than the g-phosphate.

The reactive acyl-AMP version of aspartate is now ready to be converted to an amide (asparagine) via nucleophilic attack by ammonia. In the case of glutamine synthase, the source of ammonia was free ammonium ion in solution. In the case of asparagine synthase, the NH_3 is derived from the hydrolysis of glutamine (this is simply another acyl substitution reaction):

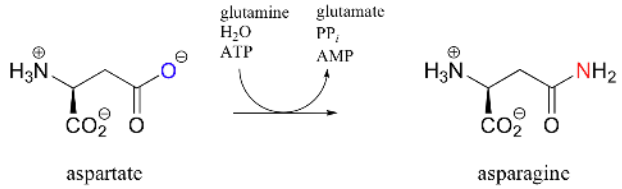


The hydrolysis reaction is happening in the same enzyme active site – as the NH_3 is expelled in the hydrolysis of glutamine, it immediately turns around and acts as the nucleophile in the conversion of aspartyl-AMP to asparagine:



Keep in mind that the same enzyme is also binding ATP and using it to activate aspartate – this is a busy construction zone!

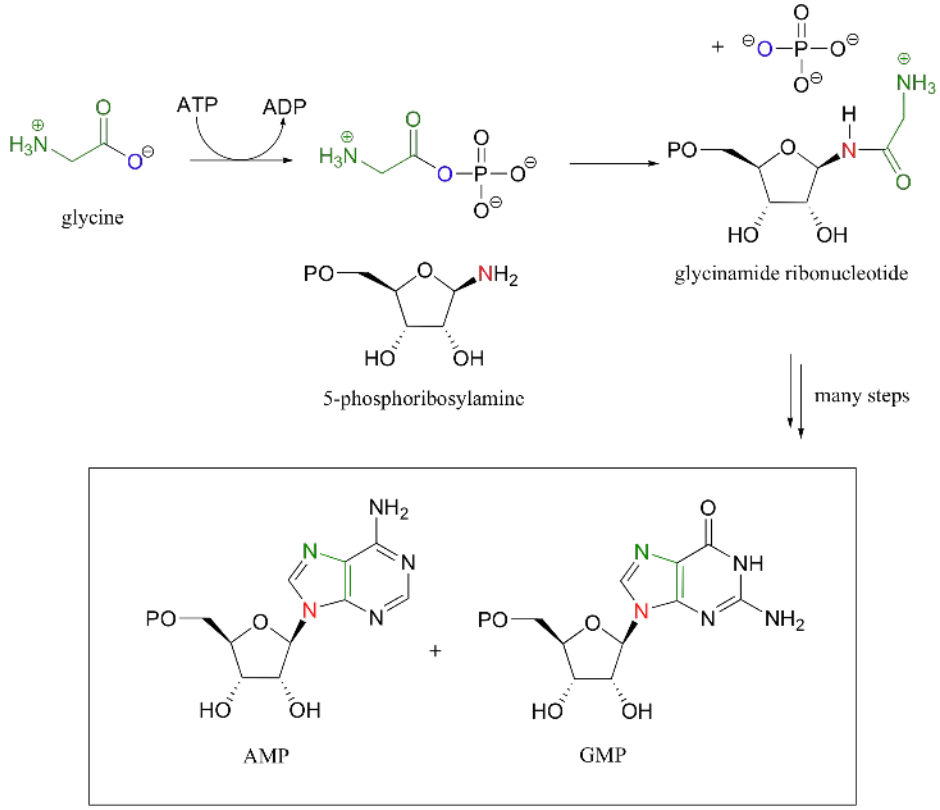
Overall, this reaction can be written in condensed form as:



The use of glutamine as a 'carrier' for ammonia is a fairly common strategy in metabolic pathways. This strategy makes sense, as it allows cells to maintain a constant source of NH_3 for reactions that require it, without the need for high solution concentrations of free ammonia.

GLYCINAMIDE RIBONUCLEOTIDE SYNTHETASE

One of the early steps in the construction of purine bases (the adenine and guanine bases in DNA and RNA) involves an acyl substitution reaction with an acyl phosphate intermediate. In this case, the attacking nucleophile is not ammonia but a primary amine. The strategy, however, is similar to that of glutamine synthase. The carboxylate group on glycine is converted to an acyl phosphate, at the cost of one ATP molecule. The acyl group is then transferred to 5-phosphoribosylamine, resulting in an amide product.



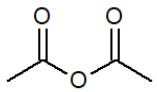
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

22.12: Biological Acylation Reactions is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

22.13: ADDITIONAL EXERCISES

General Review

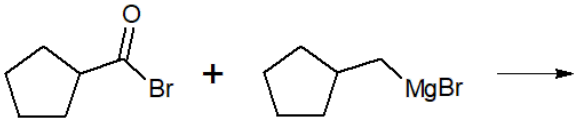
22-1 Suggest a carboxylic acid and an acid derivative that could be reacted together to form the following molecule.



acetic anhydride

22-2 For the following reaction, predict the product if:

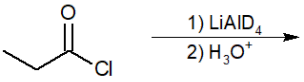
- only one equivalent of the Grignard reagent was used (and the product could be isolated)
- if two equivalents were used (followed by an acid workup)



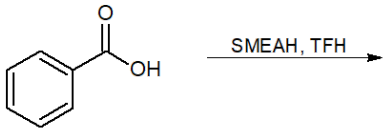
(Grignard Reagent)

22-3 Provide the final products of the following reactions.

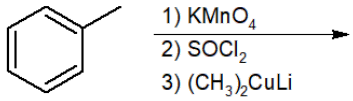
a)



b)



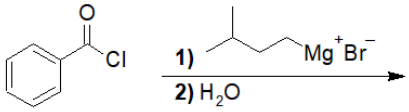
22-4 Predict the final product of the following reaction.



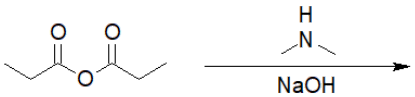
Interconversion of Acid Derivatives by Nucleophilic Acyl Substitution

22-5 Predict the interconverted acid derivatives of the following reactions.

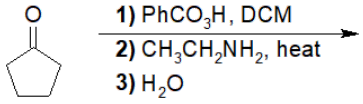
a)



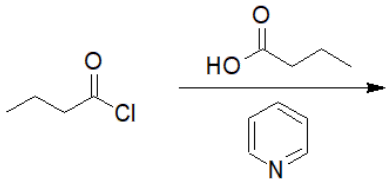
b)

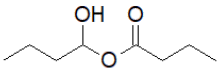


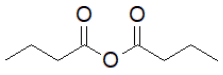
22-6 Predict the structure of the product and give its IUPAC nomenclature.

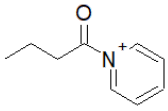


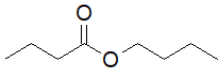
22-7 Choose the correct answer for the product of the following reaction.



a) 

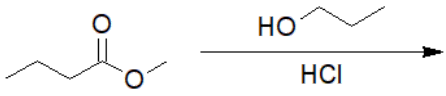
b) 

c) 

d) 

Transesterification

22-8 Choose the correct IUPAC nomenclature of the product of the following reaction.



a) ethyl butanoate

b) propan-2-yl butanoate

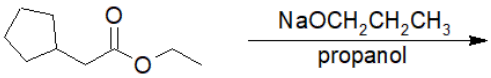
c) dipropyl carbonate

d) propyl butanoate

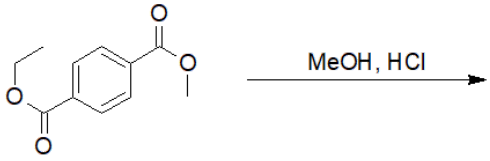
22-9 Explain why transesterification can be done under acidic or basic conditions.

22-10 Give the products of the following transesterification reactions.

a)

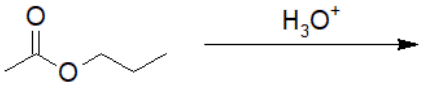


b)

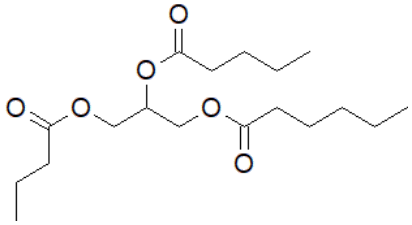


Hydrolysis of Carboxylic Acid Derivatives

22-11 Provide the correct structure of the product of the following hydrolysis reaction.

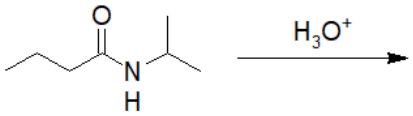


22-12 Provide the structure of all the products resulting from the hydrolysis of the following triglyceride.

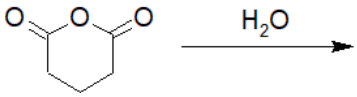


22-13 Provide the structures and IUPAC nomenclature of the products.

a)

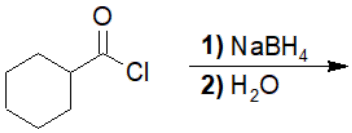


b)

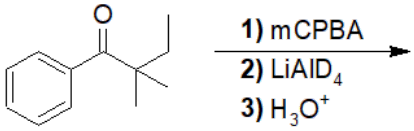


Reduction of Acid Derivatives

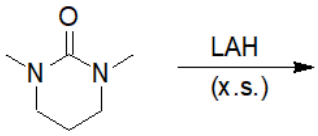
22-14 Give the structure of the product of the following reaction.



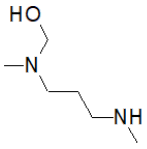
22-15 Provide the structure of all the products (including leaving groups) formed in the following reaction.



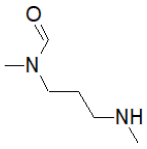
22-16 Choose the correct answer that gives the products of a fully reduced 1,3-dimethyl-1,3-diazinan-2-one.



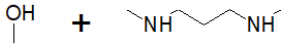
a)



b)

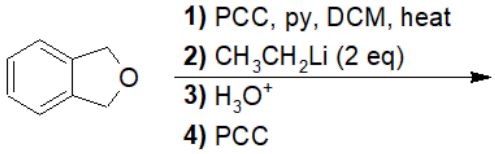


c)

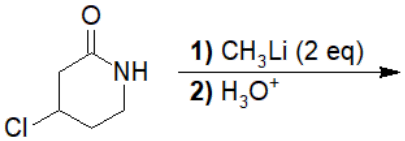


Reactions of Acid Derivatives with Organometallic Reagents

22-17 Predict the product of the following reaction.



22-18 Choose the correct IUPAC nomenclature of the product of the following reaction.



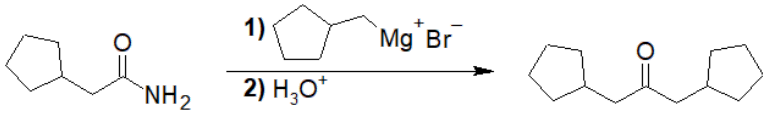
a) 6-amino-5-chlorohexan-2-one

b) 6-amino-5-chloro-2-methylhexan-2-ol

c) 6-amino-4-chloro-2-methylhexan-2-ol

d) 4-chloro-2-methylpiperidin-2-ol

22-19 Decide whether or not the following reaction is the best way to obtain the final product. If not, suggest a better route of synthesis.



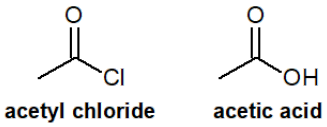
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22.14: SOLUTIONS TO ADDITIONAL EXERCISES

General Review

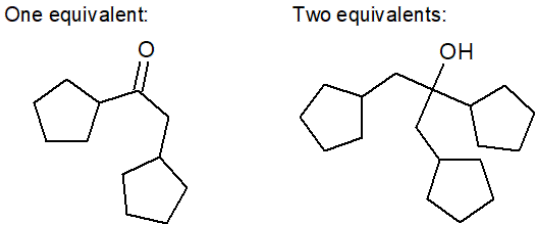
22-1

Possible set of reactants:



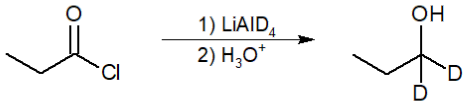
acetyl chloride **acetic acid**

22-2

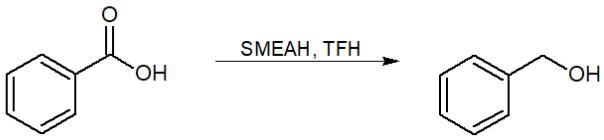


22-3

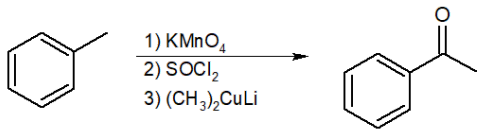
a)



b)



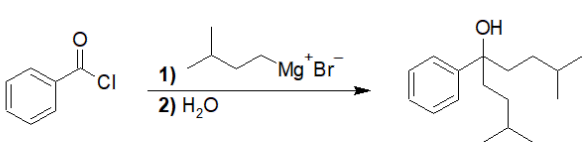
22-4



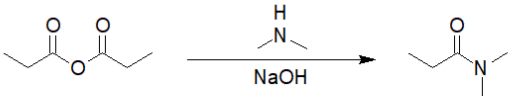
Interconversion of Acid Derivatives by Nucleophilic Acyl Substitution

22-5:

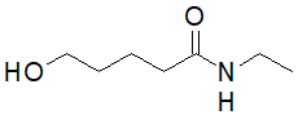
a)



b)



22-6:



***N*-ethyl-5-hydroxypentanamide**

22-7:

Answer: B

Transesterification

22-8:

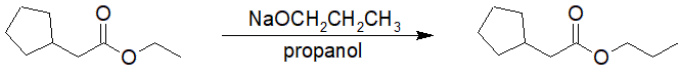
Answer: D

22-9:

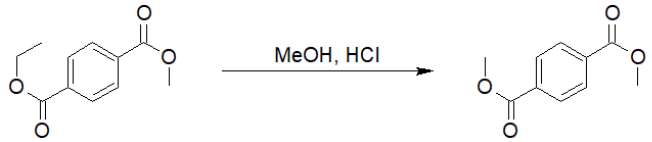
Under acidic conditions, the carbonyl oxygen atom is protonated, making it a better electrophile for the reaction to occur. Under basic conditions, the alcohol we are trying to add is deprotonated, making it a better nucleophile.

22-10:

a)

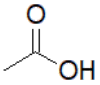


b)

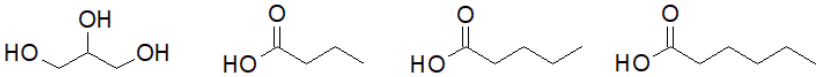


Hydrolysis of Carboxylic Acid Derivatives

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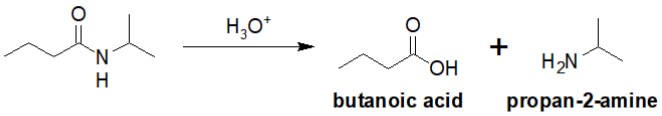


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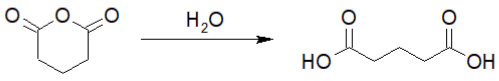


22-13:

a)

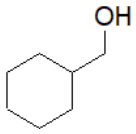


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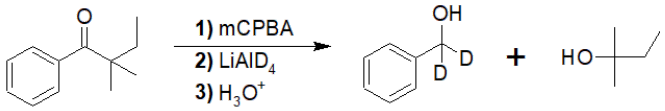


Reduction of Acid Derivatives

22-14:



22-15:

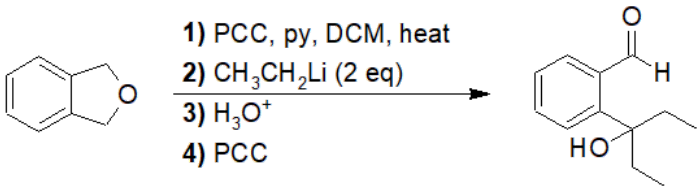


22-16:

Answer: C

Reactions of Acid Derivatives with Organometallic Reagents

22-17:

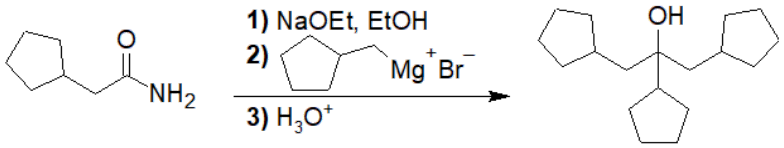


22-18:

Answer: C

22-19:

A possibly better route of synthesis:



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CHAPTER OVERVIEW

23: ALPHA SUBSTITUTIONS AND CONDENSATIONS OF CARBONYL COMPOUNDS

After reading this chapter and completing ALL the exercises, a student can be able to

- predict the relative acidity of the a-hydrogens on various carbonyl compounds (section 23.1)
- explain or predict the equilibrium of enol-keto tautomers (section 23.2)
- predict the products and specify the reagents for the following reactions
  - Halogenation of the a-carbon of aldehydes and ketones (section 23.3 and 23.4)
  - Halogenation of the a-carbon of carboxylic acids (Hell-Vollhard-Zelinski) (section 23.3 and 23.5)
  - Alkylation of the a-carbon of carbonyl compounds via the LDA pathway (section 23.3 and 23.6)
  - Alkylation of the a-carbon of aldehydes and ketones via the enamine intermediate (section 23.3 and 3.7)
  - Aldol addition and condensation reactions – 2 aldehydes, 2 ketones, 1 aldehyde with 1 ketone (section 23.3 and 23.8)
  - Claisen condensation reactions – 2 esters or 1 ester with 1 ketone (section 23.3 and 23.9)
  - Diekmann condensation reactions (intramolecular Claisen) - (section 23.9)
  - Conjugate Addition a.k.a. Michael reaction (section 23.3 and 23.10)
  - Robinson annulation (section 23.10)
  - Decarboxylation of 3-oxocarboxylic acids (section 23.3 and 23.12)
    - Malonic ester synthesis of carboxylic acids
    - Acetoacetic ester synthesis of methyl ketones

Designing synthesis using all of the reactions through this chapter with an emphasis on increasing the size of the carbon backbone by forming new carbon-carbon bonds

23.1: Relative Acidity of alpha-Hydrogens
23.2: Enols, Enolate Ions and Tautomerization
23.3: Reaction Overview
23.4: Alpha Halogenation of Carbonyls
23.5: Bromination of Acids- The HVZ Reaction
23.6: Alkylation of the alpha-Carbon via the LDA pathway
23.7: Alkylation of the Alpha-Carbon via the Enamine Pathway
23.8: The Aldol Reaction and Condensation of Ketones and Aldehydes
23.9: The Claisen Condensation Reactions of Esters
23.10: Conjugate Additions- The Michael Reaction
23.11: Decarboxylation Reactions
23.12: Additional Exercises
23.13: Solutions to Additional Exercises

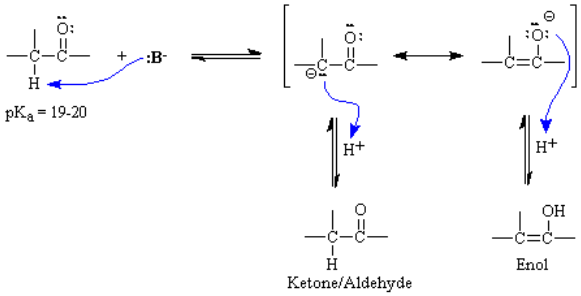
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23: Alpha Substitutions and Condensations of Carbonyl Compounds is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

23.1: RELATIVE ACIDITY OF ALPHA-HYDROGENS

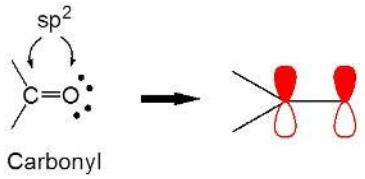
ACIDITY OF ALPHA HYDROGENS

Alkyl hydrogen atoms bonded to a carbon atom in a a (alpha) position relative to a carbonyl group display unusual acidity. While the pK_a values for alkyl C-H bonds is typically on the order of 40-50, pK_a values for these alpha hydrogens is more on the order of 19-20. This can most easily be explained by resonance stabilization of the product carbanion, as illustrated in the diagram below.

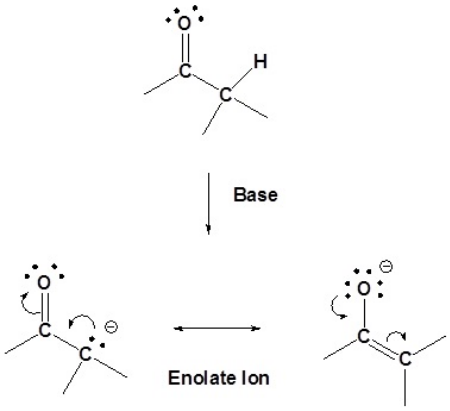


In the presence of a proton source, the product can either revert back into the starting ketone or aldehyde or can form a new product, the enol. The equilibrium reaction between the ketone or aldehyde and the enol form is commonly referred to as "keto-enol tautomerism". The ketone or aldehyde is generally strongly favored in this reaction.

Because carbonyl groups are sp^2 hybridized the carbon and oxygen both have unhybridized p orbitals which can overlap to form the C=O π bond.



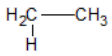
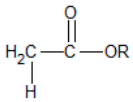
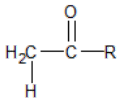
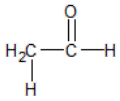
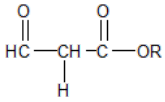
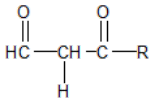
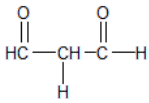
The presence of these overlapping p orbitals gives α hydrogens (Hydrogens on carbons adjacent to carbonyls) special properties. In particular, α hydrogens are weakly acidic because the conjugate base, called an enolate, is stabilized though conjugation with the π orbitals of the carbonyl. The effect of the carbonyl is seen when comparing the pK_a for the α hydrogens of aldehydes (~16-18), ketones (~19-21), and esters (~23-25) to the pK_a of an alkane (~50).



Of the two resonance structures of the enolate ion the one which places the negative charge on the oxygen is the most stable. This is because the negative change will be better stabilized by the greater electronegativity of the oxygen.

RELATIVE ACIDITY OF ALPHA HYDROGENS

The acidity of alpha hydrogens varies by carbonyl functional group as shown in the table below. Evaluating the stability of the conjugate bases can explain the differences in the relative acidity of the alpha hydrogens.

Compound	pKa
	50
	25
	20
	17
	11
	9
	6

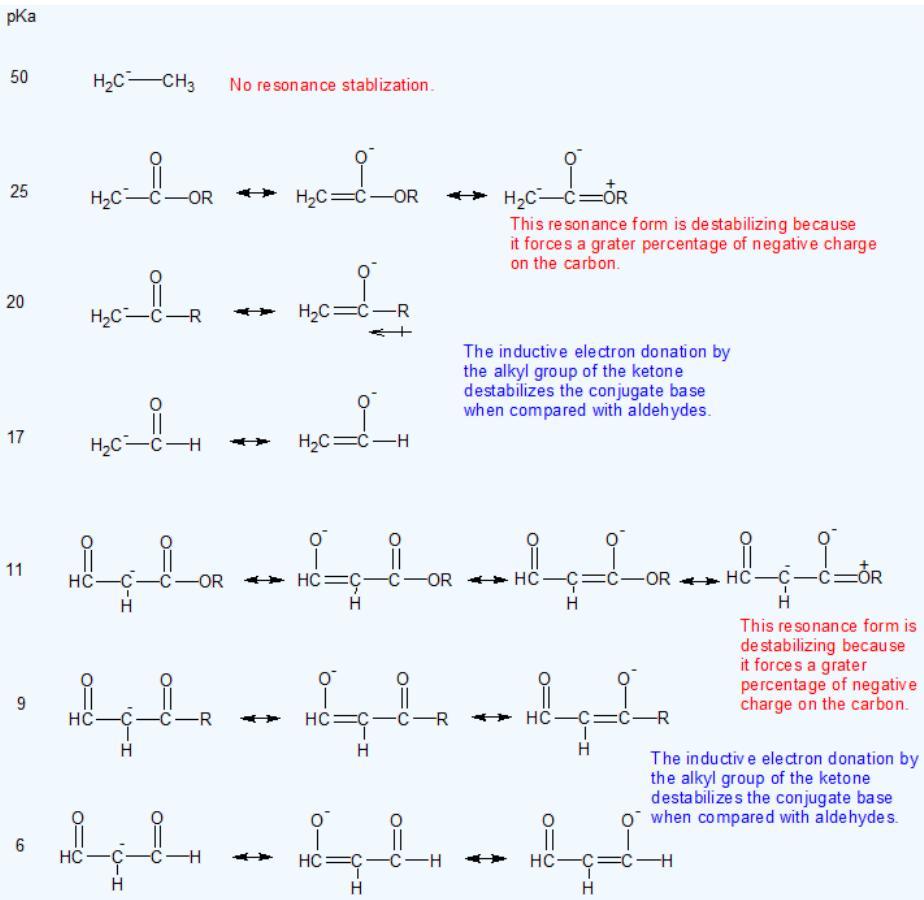
The ionizable proton for each compound is bonded to an sp^3 hydbridized carbon.

Exercise

1. Draw the bond line structure for each compound in the table above including all relevant resonance forms to explain the relative acidity.

Answer

1.



CONTRIBUTORS AND ATTRIBUTIONS

CONTRIBUTORS AND ATTRIBUTIONS

Prof. Steven Farmer (Sonoma State University)

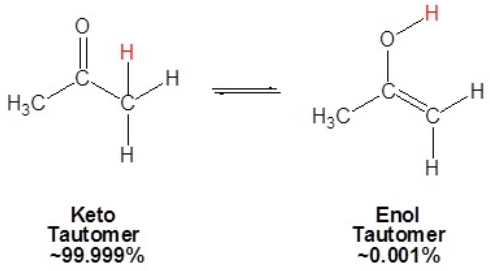
- Clarke Earley (Department of Chemistry, Kent State University Stark Campus)

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23.2: ENOLS, ENOLATE IONS AND TAUTOMERIZATION

INTRODUCTION

Because of the acidity of the alpha-hydrogens, carbonyls undergo keto-enol tautomerism. Tautomers are rapidly interconverted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom and a differently located double bond. The equilibrium between tautomers is not only rapid under normal conditions, but it often strongly favors one of the isomers (acetone, for example, is 99.999% keto tautomer). Even in such one-sided equilibria, evidence for the presence of the minor tautomer comes from the chemical behavior of the compound. Tautomeric equilibria are catalyzed by traces of acids or bases that are generally present in most chemical samples.

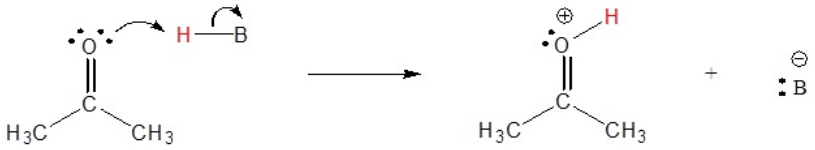


MECHANISM FOR ENOL AND ENOLATE FORMATION

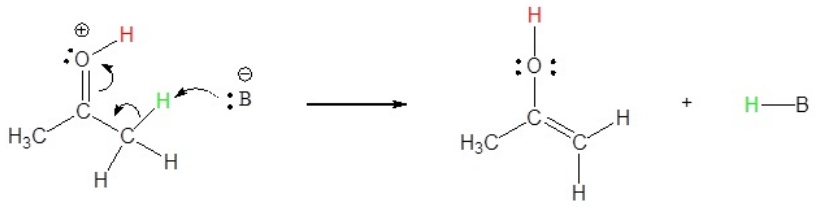
Under acidic conditions, the enol tautomer forms. Under basic conditions, the enolate tautomer forms. Both the enol and enolate are nucleophiles that can undergo subsequent reactions. The mechanism for both acidic and basic reaction conditions are shown below.

Acid conditions

1) Protonation of the Carbonyl

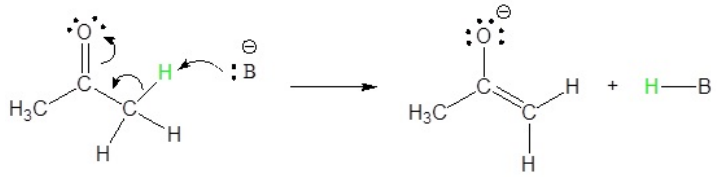


2) Enol formation

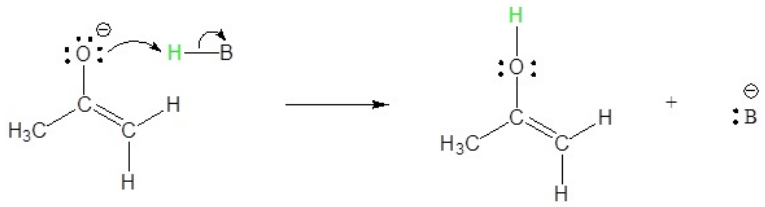


Basic conditions

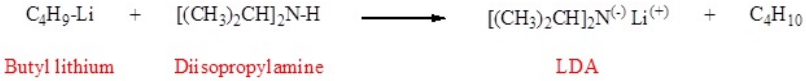
1) Enolate formation

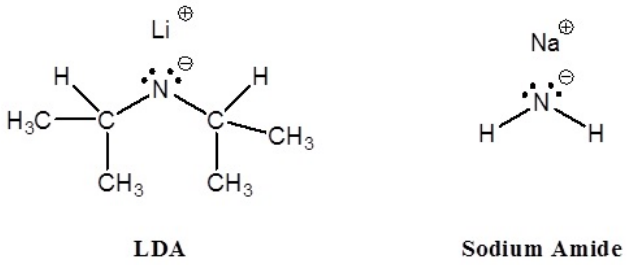


2) Protonation



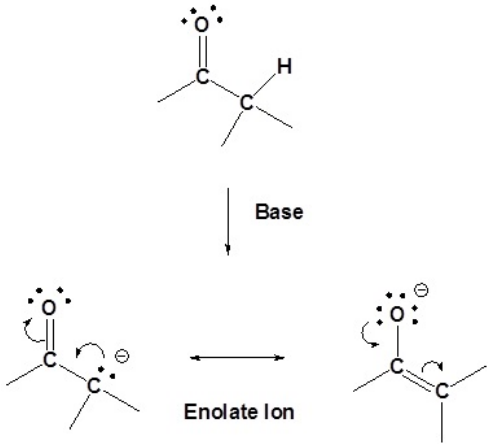
For reactions of enolate anions to be useful, these intermediates must be generated in high concentration in the absence of other strong nucleophiles and bases. The aqueous base conditions used for the aldol condensation are not suitable because the enolate anions of simple carbonyl compounds are formed in very low concentration, and hydroxide or alkoxide bases induce competing S_N2 and E2 reactions of alkyl halides. It is necessary, therefore, to achieve complete conversion of aldehyde or ketone reactants to their enolate conjugate bases by treatment with a very strong base (pK_a > 25) in a non-hydroxylic solvent before any alkyl halides are added to the reaction system. Some bases that have been used for enolate anion formation are: NaH (sodium hydride, pK_a > 45), $NaNH_2$ (sodium amide, pK_a = 34), and $LiN[CH(CH_3)_2]_2$ (lithium diisopropylamide, LDA, pK_a 36). Ether solvents like tetrahydrofuran (THF) are commonly used for enolate anion formation. With the exception of sodium hydride and sodium amide, most of these bases are soluble in THF. Certain other strong bases, such as alkyl lithium and Grignard reagents, cannot be used to make enolate anions because they rapidly and irreversibly add to carbonyl groups. Nevertheless, these very strong bases are useful in making soluble amide bases. In the preparation of lithium diisopropylamide (LDA), for example, the only other product is the gaseous alkane butane.





Because of its solubility in THF, LDA is a widely used base for enolate anion formation. In this application, one equivalent of diisopropylamine is produced along with the lithium enolate, but this normally does not interfere with the enolate reactions and is easily removed from the products by washing with aqueous acid. Although the reaction of carbonyl compounds with sodium hydride is heterogeneous and slow, sodium enolates are formed with the loss of hydrogen, and no other organic compounds are produced.

The presence of these overlapping p orbitals gives α hydrogens (Hydrogens on carbons adjacent to carbonyls) special properties. In particular, α hydrogens are weakly acidic because the conjugate base, called an enolate, is stabilized though conjugation with the π orbitals of the carbonyl. The effect of the carbonyl is seen when comparing the pK_a for the α hydrogens of aldehydes (~16-18), ketones (~19-21), and esters (~23-25) to the pK_a of an alkane (~50).

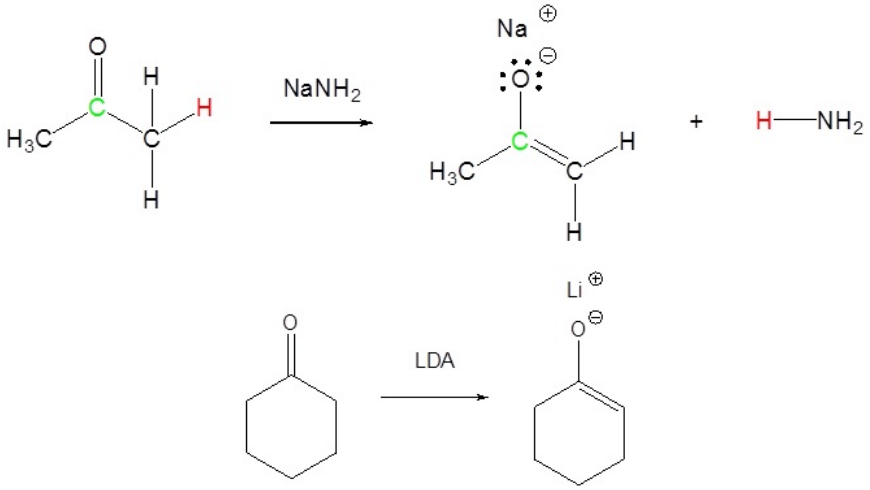


Of the two resonance structures of the enolate ion the one which places the negative charge on the oxygen is the most stable. This is because the negative change will be better stabilized by the greater electronegativity of the oxygen.

Functional Group	Structure	pK_a
carboxylic acid	HO–(C=O)R	5
nitro	RCH_2–NO_2	9
β-diketone *	R(O=C)–CH_2–(C=O)R	9
β-ketoester *	R(O=C)–CH_2–(C=O)OR	11
β-diester *	RO(O=C)–CH_2–(C=O)OR	13
amide	RNH–(C=O)R	15
alcohol	RCH_2–OH	16
aldehyde	RCH_2–(C=O)H	17
ketone	RCH_2–(C=O)R	20
thioester	RCH_2–(C=O)SR	21
ester	RCH_2–(C=O)OR	25
nitrile	RCH_2–C≡N	25
sulfone	RCH_2–SO_2R	25
amide	RCH_2–(C=O)$N(CH_3)_2$	30
alkane	CH_3–R	50

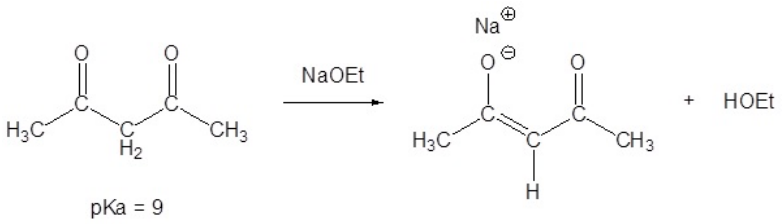
* Note methylene groups bridging between two electron withdrawing groups are more acidic than alpha protons next to only one carbonyl group.

EXAMPLES



If the formed enolate is stabilized by more than one carbonyl it is possible to use a weaker base such as sodium ethoxide.

$NaOCH_2CH_3$ = Na^+ $^-OCH_2CH_3$ = NaOEt



Because of the acidity of α hydrogens, carbonyls undergo keto-enol tautomerism. Tautomers are rapidly interconverted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom and a differently located double bond. The

equilibrium between tautomers is not only rapid under normal conditions, but it often strongly favors one of the isomers (acetone, for example, is 99.999% keto tautomer). Even in such one-sided equilibria, evidence for the presence of the minor tautomer comes from the chemical behavior of the compound. Tautomeric equilibria are catalyzed by traces of acids or bases that are generally present in most chemical samples.

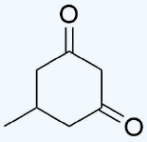
Exercises

2. Draw the enol forms of the following molecules

a. 4-methylcyclohexanone
b. Ethyl thioactetate
c. Methyl acetate
d. Butanal
e. Propionic Acid
f. 1-phenyl-2-butanone

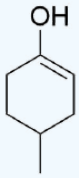
3. How many acid protons do each of the molecules from the previous question have? Label them.

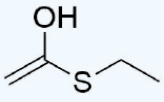
4. Draw all of the monoenol forms for the following molecule. Which ones are most stable? Why?

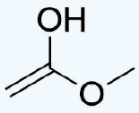


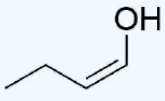
Answers

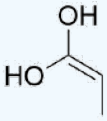
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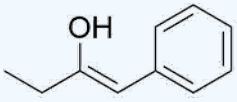
(a)


(b)


(c)


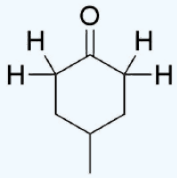
(d)


(e)


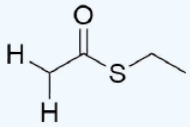
(f)


3.

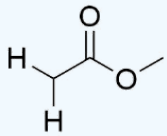
(a)



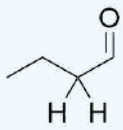
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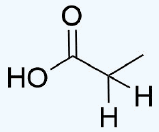
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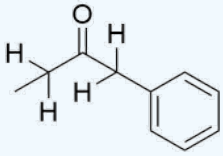
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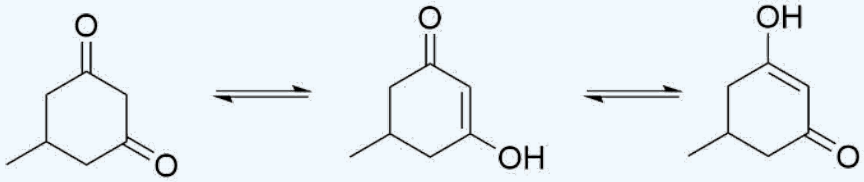
(e)



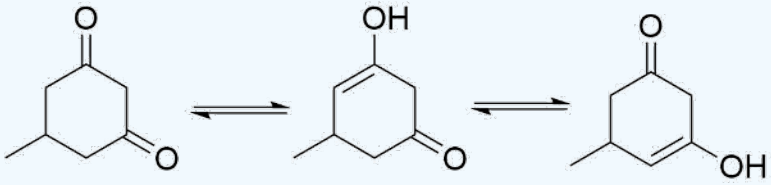
(f)



4.



The ability to resonate stabilizes this enol form.



This enol has no resonance forms and is therefore less stable.

CONTRIBUTORS AND ATTRIBUTIONS

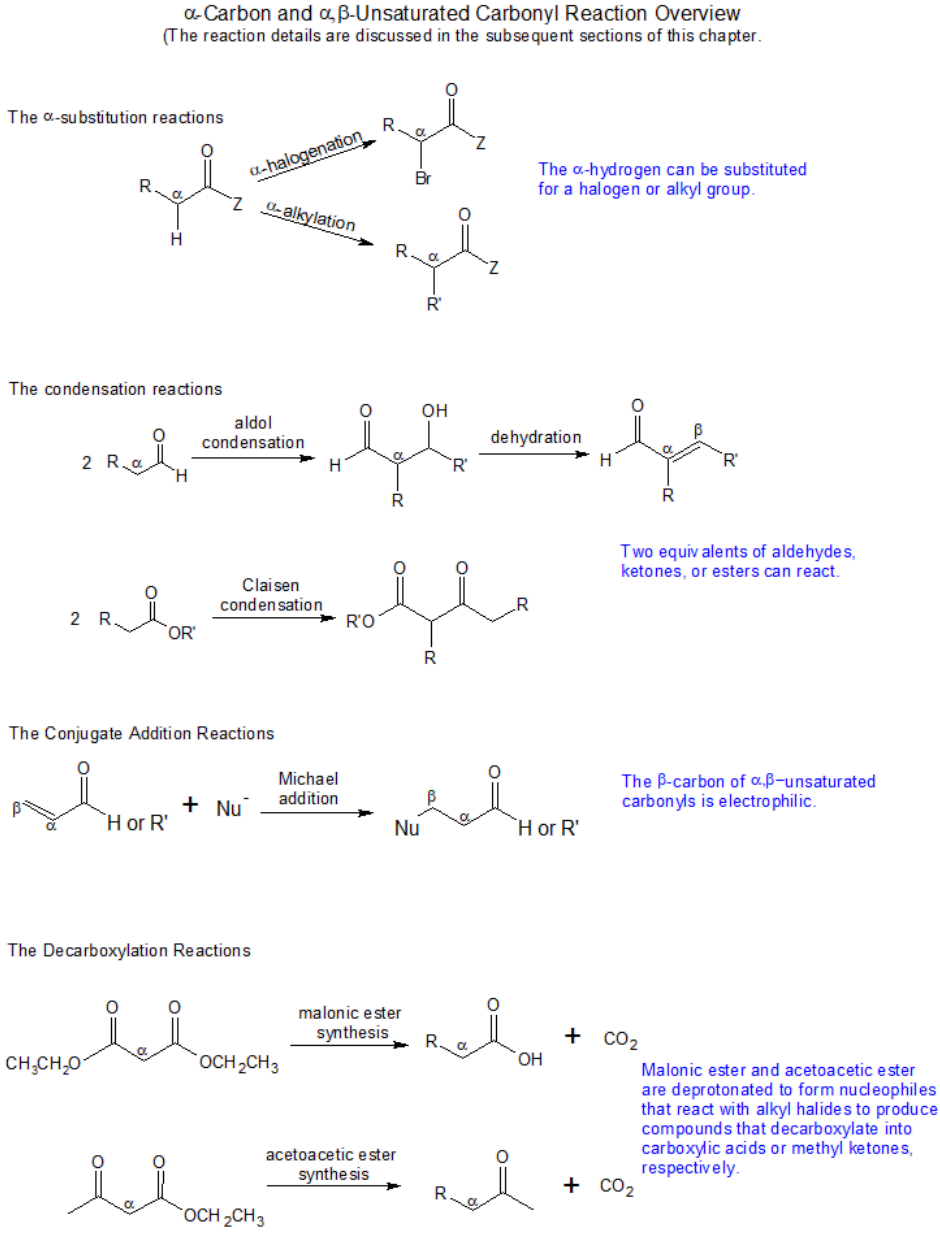
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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23.3: REACTION OVERVIEW

OVERVIEW

The reactivity of the alpha-carbon can be grouped into three main categories: alpha-substitution, condensation, and decarboxylation. Alpha,beta-unsaturated carbonyls can undergo conjugate addition reactions that are called Michael Additions when the nucleophile is an alpha-carbon. Because the reactants, reagents and products can contain multiple functional groups, it is helpful to initially focus on the overall conversions between functional groups BEFORE digging into the details of each reaction pathway. It is also useful to label the alpha and beta carbons to help follow the reactivity. An overview of the reactions that will be studied in this chapter are shown below.

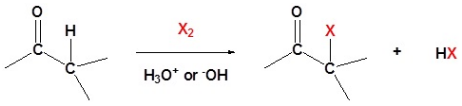


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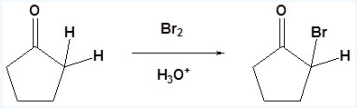
23.4: ALPHA HALOGENATION OF CARBONYLS

Ketones with alpha hydrogens can undergo a substitution reaction with halogens. This reaction occurs because of the tendency of carbonyl compounds to form enolates in basic condition and enols in acidic condition. In these cases even weak bases, such as the hydroxide anion, is sufficient enough to cause the reaction to occur because it is not necessary for a complete conversion to the enolate. For this reaction Cl_2, Br_2 or I_2 can be used as the halogens.

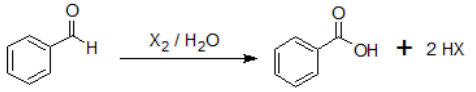
General reaction



Example 1



Aldehydes are oxidized by the halogens so this reaction pathway is not synthetically useful. For example, when benzaldehyde is added to either set of reagents described above for ketones, the majore product is benzoic acid.

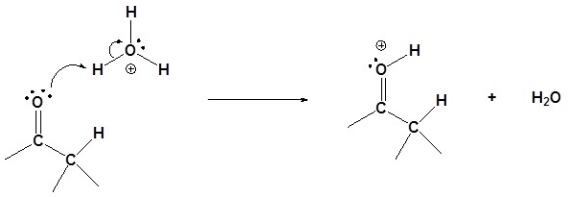


The redox reaction occurs without acidic or basic conditions.

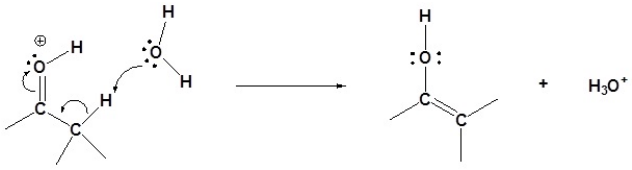
ACID CATALYZED MECHANISM

Under acidic conditions the reaction occurs thought the formation of an enol which then reacts with the halogen.

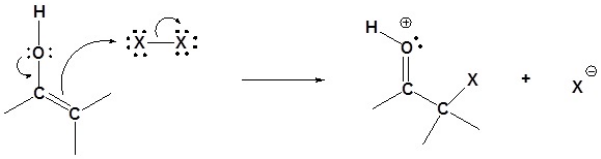
1) Protonation of the carbonyl



2) Enol formation



3) S_N2 reaction



4) Deprotonation



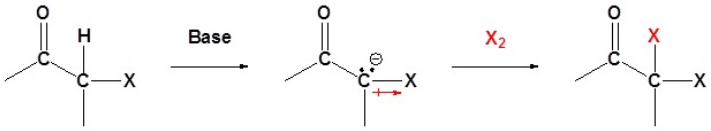
Kinetic studies provide some evidence for the mechanism shown above. The rate law for the alpha-halogenation of a ketone can be given by:

$$\text{rate} = [\text{ketone}][H^+]$$

The implication is that the rate determining step is dependent on the concentrations of the ketone and acid catalyst and therefore associated with the enol formation part of the mechanism. The halogen does not even appear in the rate law. Indeed, the overall rate is completely independent of the concentration of the halogen and suggests the halogenation step occurs rapidly.

BASE PROMOTED MECHANISM

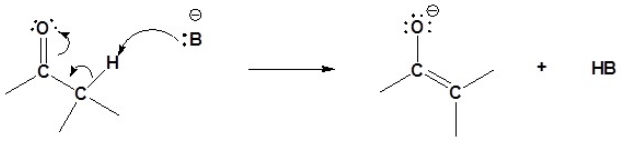
Under basic conditions the enolate forms and then reacts with the halogen.



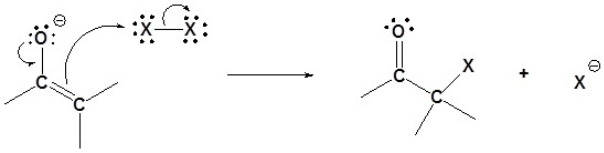
Note! This is base *promoted* and not base *catalyzed* because an entire equivalent of base is required.

It is difficult to stop the base promoted reaction after a single substitution, so acidic conditons are used when a monohalo product is required.

1) Enolate formation

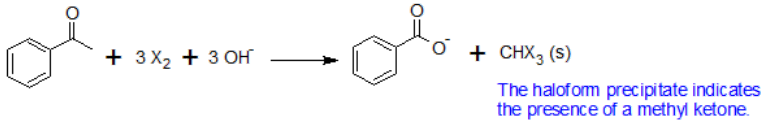


2) S_N2 reaction



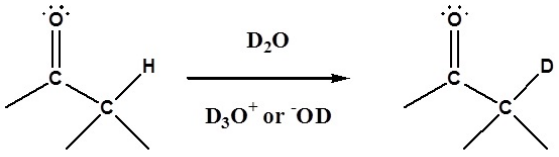
THE HALOFORM QUALITATIVE REACTION TO IDENTIFY METHYL KETONES

The overreaction during base promotion of alpha halogenation is used as a qualitative test called the haloform reaction to identify methyl ketones. Under basic conditions, subsequent halogenation reactions occur because the halogenated product is more reactive than the starting material due to the electron withdrawing effect of the halogen. The halogen inductively stabilizes the conjugate base and increases the relative acidity of the remaining alpha-carbons. Halogenations occur at the alpha-carbon until the haloform becomes a leaving group and is observed as a precipitate as shown in the example below.

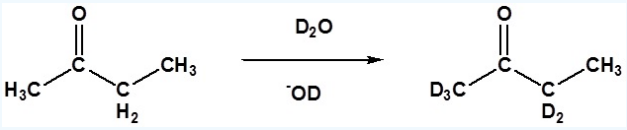


DEUTERIUM EXCHANGE

Due to the acidic nature of α hydrogens they can be exchanged with deuterium by reaction with D_2O (heavy water). The process is accelerated by the addition of an acid or base; an excess of D_2O is required. The end result is the complete exchange of all α hydrogens with deuteriums.

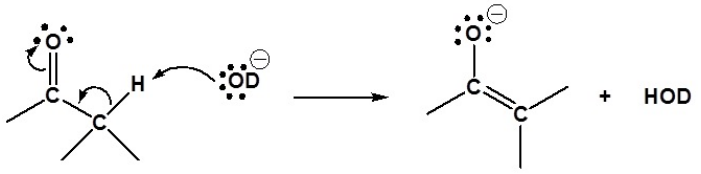


Example 2

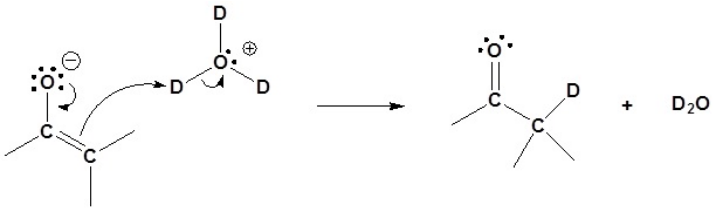


MECHANISM IN BASIC CONDITIONS

1) Enolate Formation

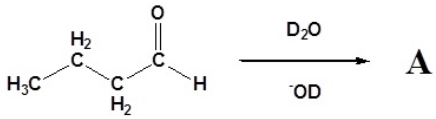


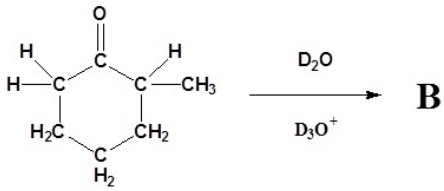
2) Deuteration



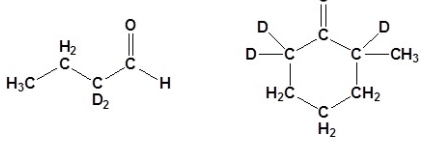
EXAMPLE QUESTION

Draw the product for the following reactions.





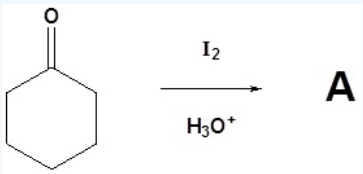
SOLUTIONS TO EXAMPLE QUESTION



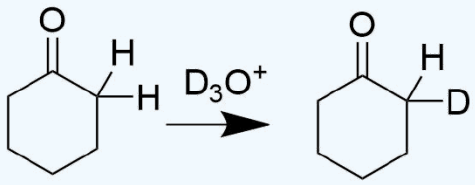
A **B**

Exercises

5. Draw the products of the following reactions



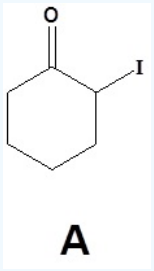
6. Draw out the mechanism for the following reaction.



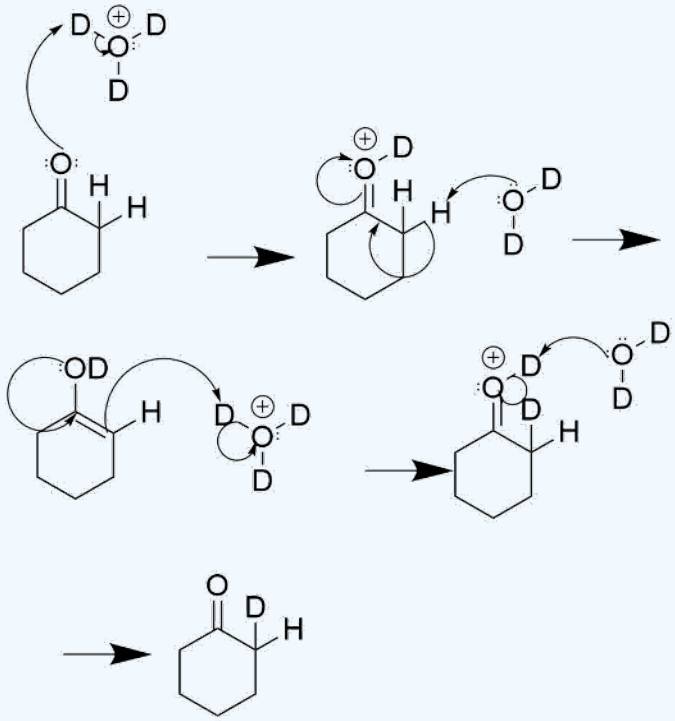
7. How might you form 2-hepten-4-one from 4-heptanone?

Answer

5.



6.



7. 1) Br_2, H_3O^+; 2) Pyridine, Heat

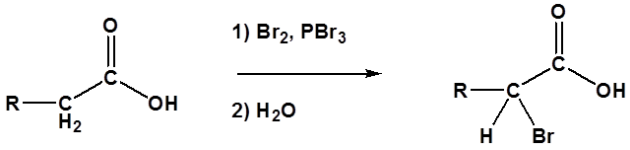
CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

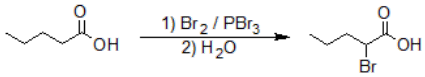
23.4: Alpha Halogenation of Carbonyls is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

23.5: BROMINATION OF ACIDS- THE HVZ REACTION

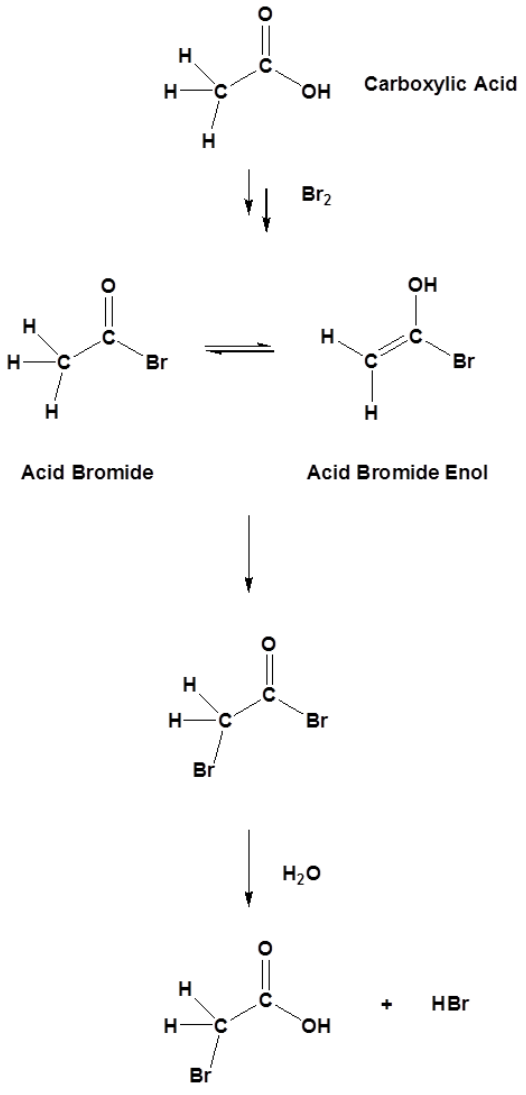
Although the alpha bromination of some carbonyl compounds, such as aldehydes and ketones, can be accomplished with Br_2 under acidic conditions, the reaction will generally not occur with acids, esters, and amides. This is because only aldehydes and ketones enolize to a sufficient extent to allow the reaction to occur. However, carboxylic acids, can be brominated in the alpha position with a mixture of Br_2 and PBr_3 in a reaction called the Hell-Volhard-Zelinskii (HVZ) reaction.



For example, pentanoic acid can be converted to 2-bromopentanoic acid as shown in the example below.

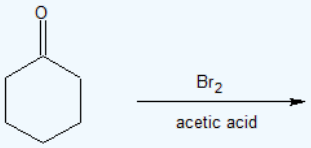


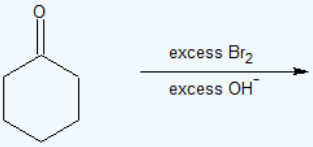
The mechanism of this reaction involves an acid bromide enol instead of the expected carboxylic acid enol. The reaction starts with the reaction of the carboxylic acid with PBr_3 to form the acid bromide and HBr. The HBr then catalyzes the formation of the acid bromide enol which subsequently reacts with Br_2 to give alpha bromination. Lastly, the acid bromide reacts with water to reform the carboxylic acid.

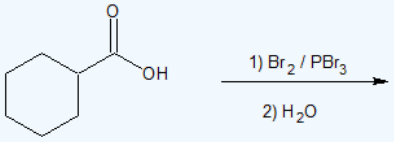


Exercise

8. Draw the bond-line structure for the product of each reaction below.

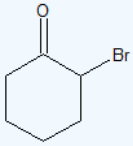
a) 

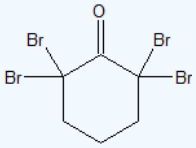
b) 

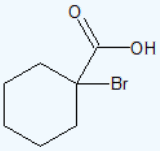
c) 

Answer

8.

a) 

b) 

c) 

CONTRIBUTORS AND ATTRIBUTIONS

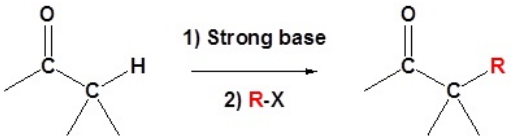
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

23.5: Bromination of Acids- The HVZ Reaction is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

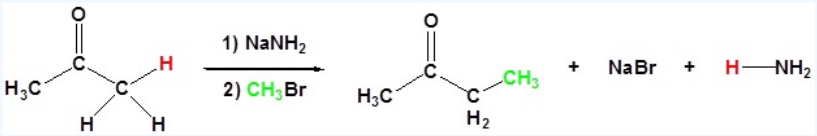
23.6: ALKYLATION OF THE ALPHA-CARBON VIA THE LDA PATHWAY

ALPHA ALKYLATION

A strong base, such as lithium diisopropyl amide (LDA), sodium hydride, or sodium amide, creates the nucleophilic enolate ion which reacts with an alkyl halide suitable for the S_N2 reactivity to form an alpha-alkylated product.



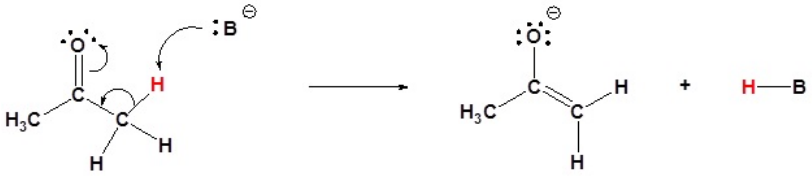
Example 1: Alpha Alkylation



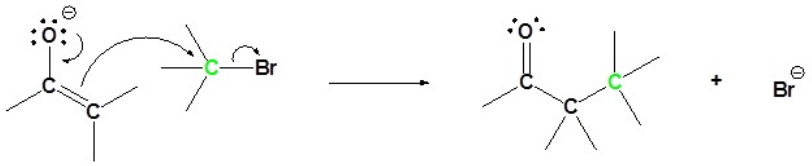
MECHANISM

The mechanism begins with enolate formation. The resulting enolate is the nucleophile in an S_N2 reaction with a suitable alkyl halide.

1) Enolate formation

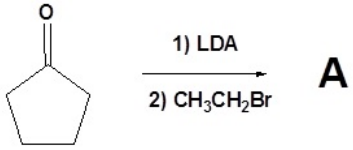


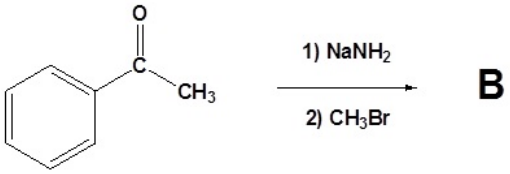
2) S_N2 reaction



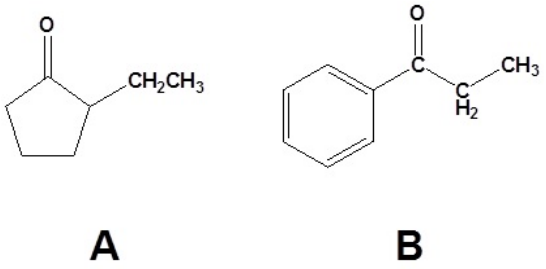
EXAMPLE QUESTION

Write the structure of the product for the following reactions.





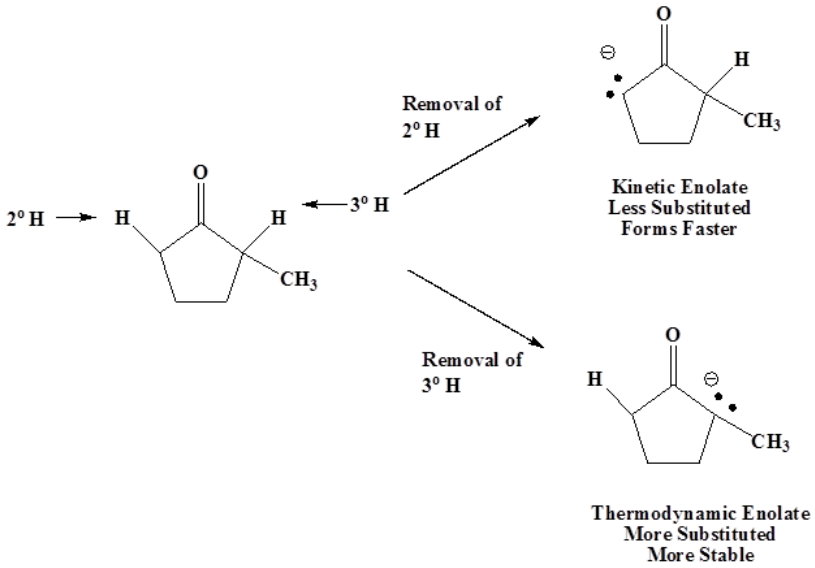
SOLUTION TO EXAMPLE QUESTION



A **B**

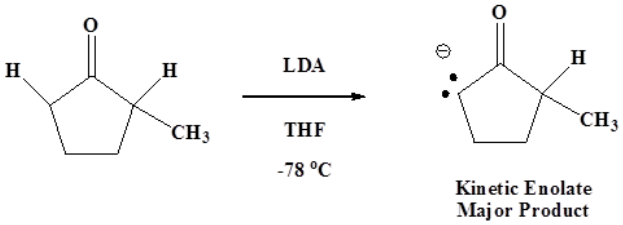
ENOLATE OF UNSYMMETRICAL CARBONYL COMPOUNDS

Now let's consider what happens when an unsymmetrical carbonyl is treated with a base. In the case displayed below there are two possible enolates which can form. The removal of the 2o hydrogen forms the kinetic enolate and is formed faster because it is less substituted and thereby less sterically hindered. The removal of the 3o hydrogen forms the thermodynamic enolate which is more stable because it is more substituted.



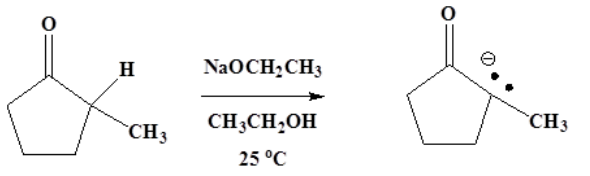
KINETIC ENOLATES

Kinetic enolates are formed when a strong bulky base like LDA is used. The bulky base finds the 2o hydrogen less sterically hindered and preferable removes it. Low temperature are typically used when forming the kinetic enolate to prevent equilibration to the more stable thermodynamic enolate. Typically a temperature of -78 oC is used.



THERMODYNAMIC ENOLATES

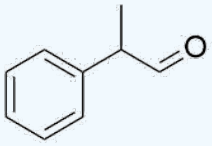
The thermodynamic enolate is favored by conditions which allow for equilibration. The thermodynamic enolate is usually formed by using a strong base at room temperature. At equilibrium the lower energy of the thermodynamic enolate is preferred, so that the more stable, more stubstituted enolate is formed.

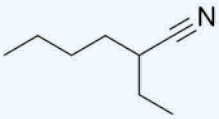


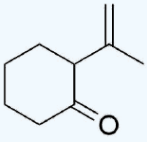
Thermodynamic Enolate
Major Product

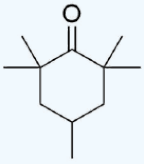
Exercises

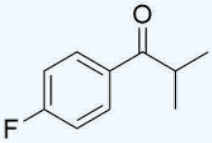
9. How might you prepare the following compounds from an alkylation reaction?

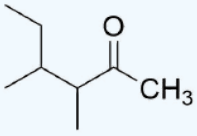
(a) 

(b) 

(c) 

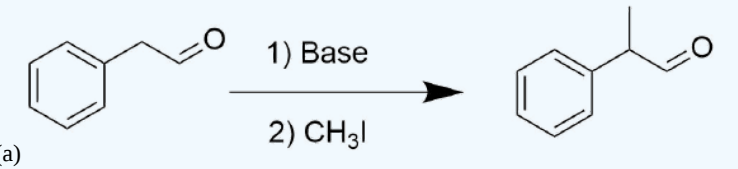
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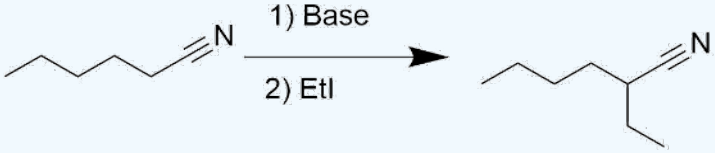
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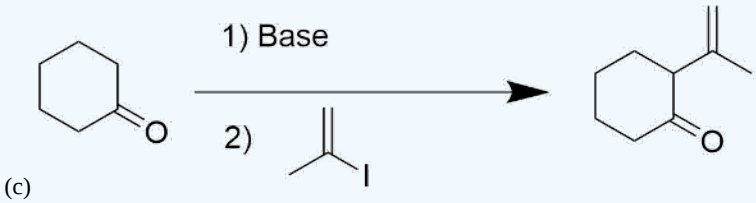
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Answer

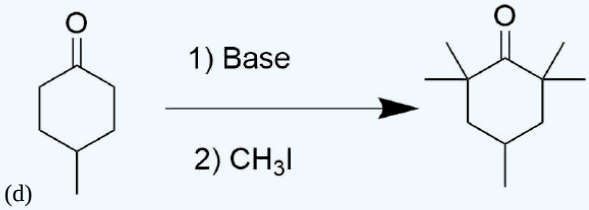
9.

(a) 

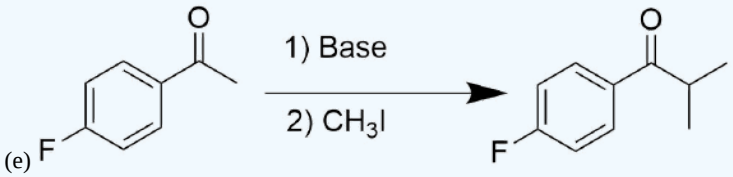
(b) 



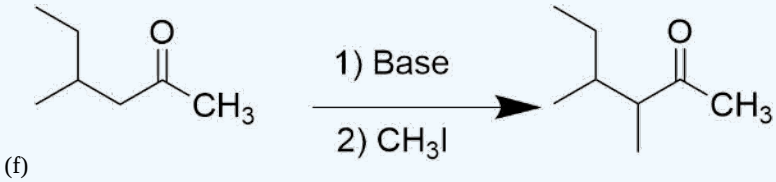
(c)



(d)



(e)



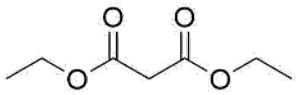
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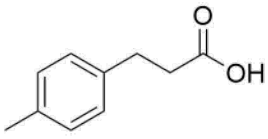
EXERCISES

QUESTIONS

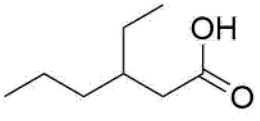
Q22.7.1

Propose a synthesis for each of the following molecules from this malonic ester.

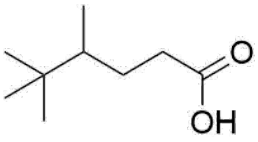




(a)



(b)



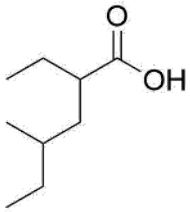
(c)

Q22.7.2

Why can't you prepare tri substituted acetic acids from a malonic ester?

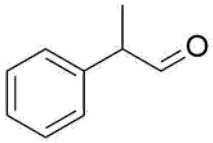
Q22.7.3

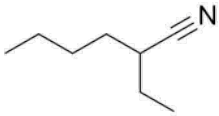
Propose a synthesis for the following molecule via a malonic ester.

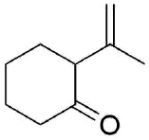


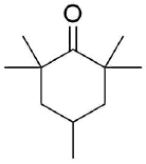
Q22.7.4

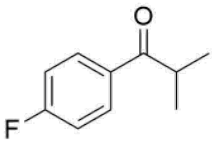
How might you prepare the following compounds from an alkylation reaction?

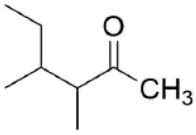
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

SOLUTIONS

S22.7.1

(a) 1) Malonic Ester, NaOEt, 2) 4-Methylbenzyl Bromide, 3) Base, 4) Acid, Heat

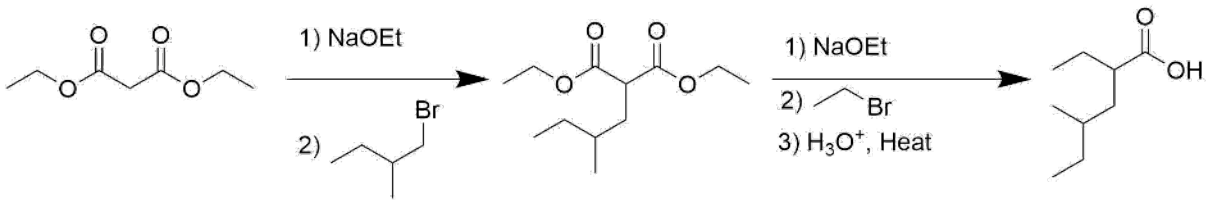
(b) 1) Malonic Ester, NaOEt, 2) 3-bromohexane, 3) Base, 4) Acid, Eat

(c) 1) Malonic Ester, NaOEt, 2) 1-Bromo-2,3,3-trimethylbutane, 3) Base, 4) Acid, Heat

S22.7.2

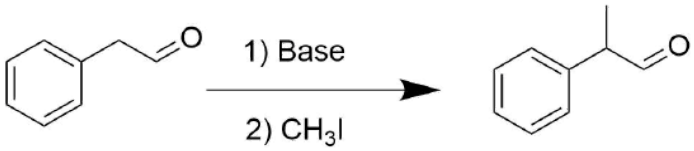
Malonic esters only contain two acid protons.

S22.7.3

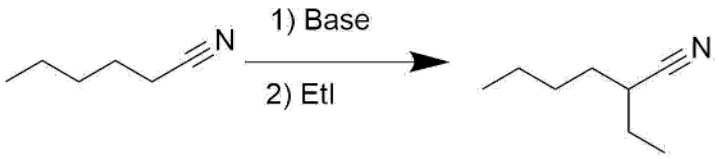


S22.7.4

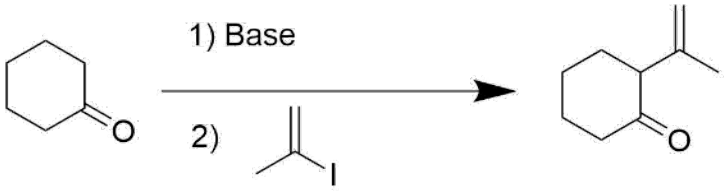
(a)



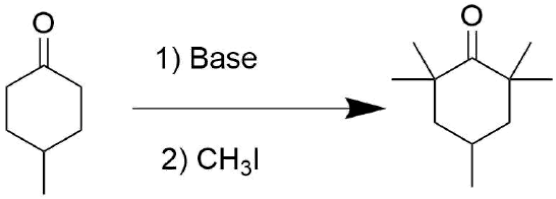
(b)



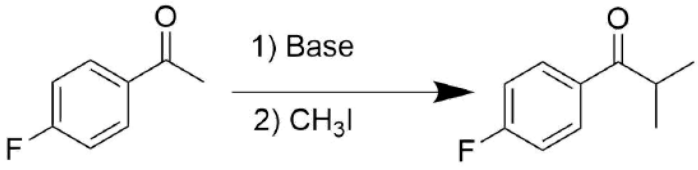
(c)



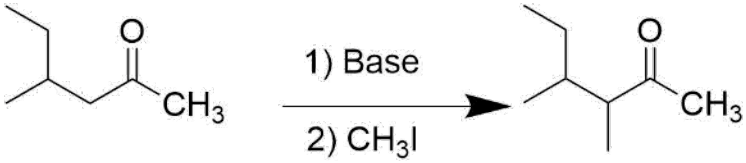
(d)



(e)



(f)



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

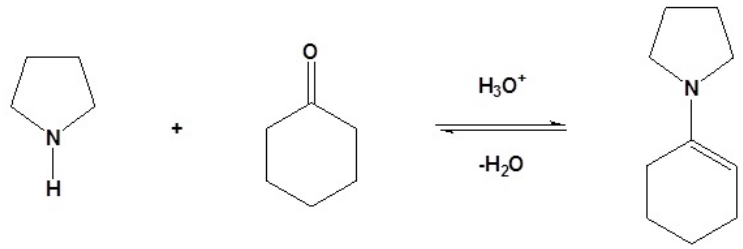
23.6: Alkylation of the alpha-Carbon via the LDA pathway is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

23.7: ALKYLATION OF THE ALPHA-CARBON VIA THE ENAMINE PATHWAY

OVERVIEW OF THE STORK ENAMINE REACTION

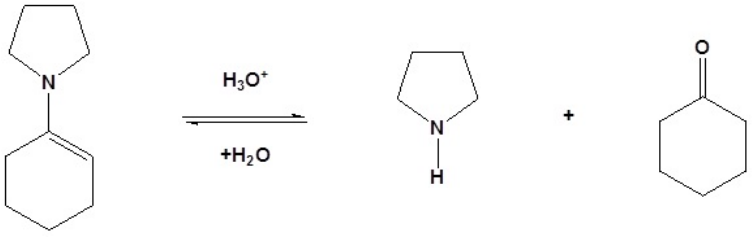
The reaction conditions for the direct alkylation of the alpha carbon with LDA or other very strong base are quite harsh. Many organic compounds cannot withstand the reaction environment at synthetically useful amounts. Therefore, an alternate synthetic pathway was developed by Gilbert Stork of Columbia University. Some of the advantages of using an enamine over an enolate are that enamines are neutral, easier to prepare, and usually prevent the overreaction problems plagued by enolates. As shown in the example below, the aldehyde or ketone can be recovered from the enamine via a hydrolysis reaction.

Example

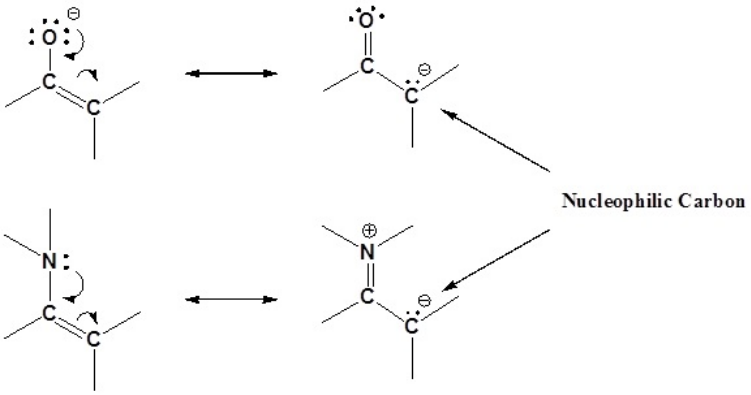


2° Amine Enamine

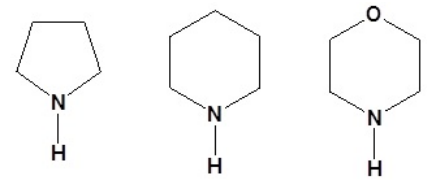
Reversible



Enamines act as nucleophiles in a fashion similar to enolates. Because of this, enamines can be used as synthetic equivalents as enolates in many reactions. This process requires a three steps: 1) Formation of the enamine, 2) Reaction with an eletrophile to form an iminium salt, 3) Hydrolysis of the iminium salt to reform the aldehyde or ketone.



Typically we use the following 2° amines for enamine reactions



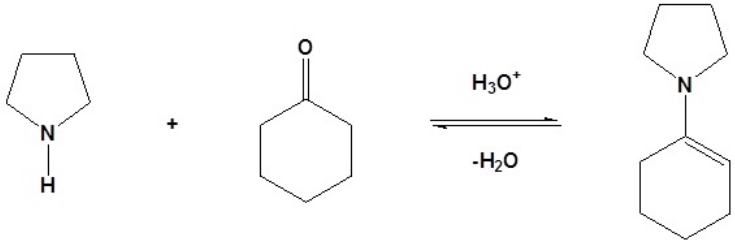
Pyrrolidine Piperidine Morpholine

ALKYLATION OF AN ENAMINE

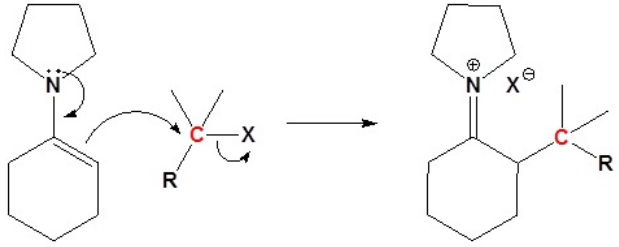
Enamined undergo an S_N2 reaction with reactive alkyl halides to give the iminium salt. The iminium salt can be hydrolyzed back into the carbonyl.

Individual steps

1) Formation of an enamine

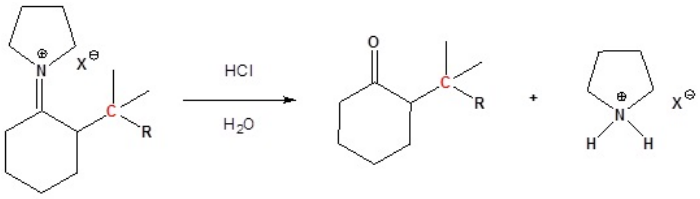


2) S_N2 Alkylation

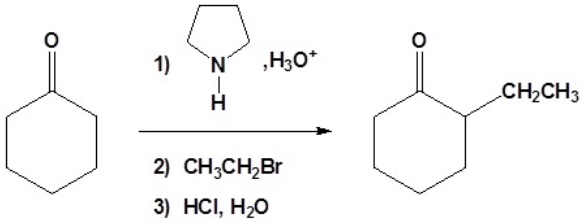


Iminium Salt

3) Reform the carbonyl by hydrolysis



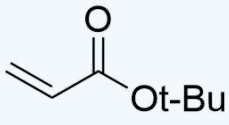
All three steps together:



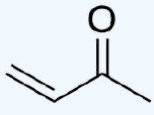
Exercises

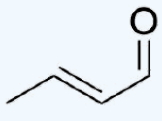
10. Draw the product of the reaction with the enamine prepared from cyclopentanone and pyrrolidine, and the following molecules.

(a)

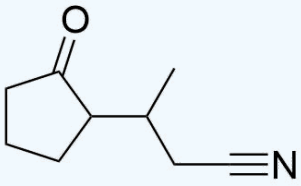


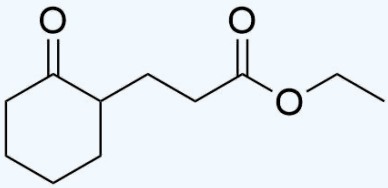
(b)



(c) 

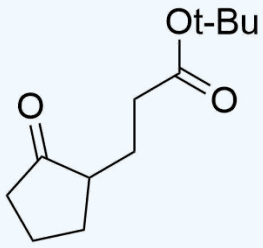
11. Propose a synthesis for the following compounds via an enamine.

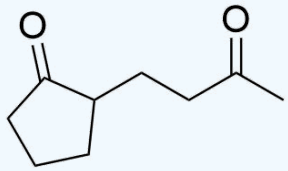
(a) 

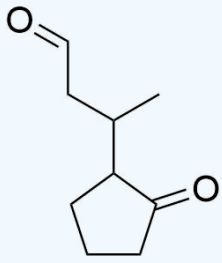
(b) 

Answers

10.

(a) 

(b) 

(c) 

11.

(a) cyclopentanone enamine + 2-cyanopropene

(b) cyclohexanone enamine + ethyl acrylate

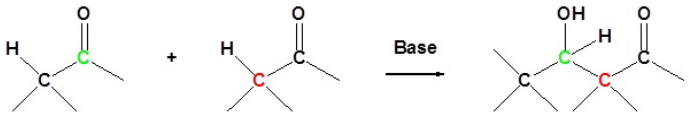
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- Prof. Steven Farmer (Sonoma State University)

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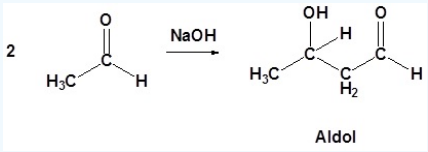
23.8: THE ALDOL REACTION AND CONDENSATION OF KETONES AND ALDEHYDES

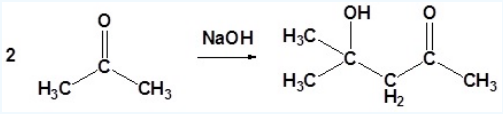
A useful carbon-carbon bond-forming reaction known as the **Aldol Reaction** is yet another example of electrophilic substitution at the alpha carbon in enolate anions. The fundamental transformation in this reaction is a dimerization of an aldehyde (or ketone) to a beta-hydroxy aldehyde (or ketone) by alpha C–H addition of one reactant molecule to the carbonyl group of a second reactant molecule. Due to the carbanion like nature of enolates they can add to carbonyls in a similar manner as Grignard reagents. For this reaction to occur at least one of the reactants must have alpha hydrogens.



The aldol reactions for acetaldehyde and acetone are shown as examples.

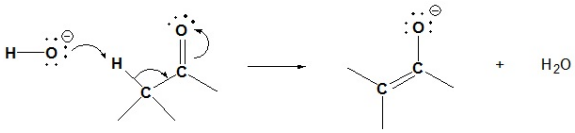
Example: Aldol Reactions



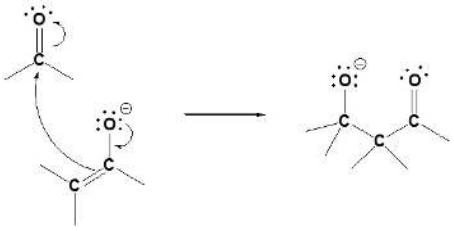


ALDOL REACTION MECHANISM

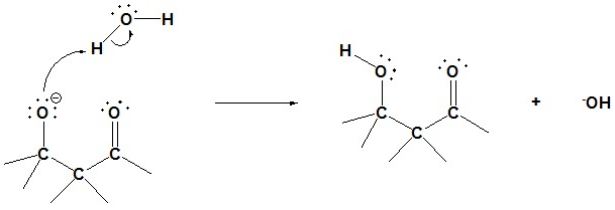
Step 1: Enolate formation



Step 2: Nucleophilic reaction by the enolate



Step 3: Protonation



ALDOL CONDENSATION: THE DEHYDRATION OF ALDOL PRODUCTS TO SYNTHESIZE A, B UNSATURATED CARBONYLS (ENONES)

The products of aldol reactions often undergo a subsequent elimination of water, made up of an alpha-hydrogen and the beta-hydroxyl group. The product of this ***β*-elimination** reaction is an α,β-unsaturated aldehyde or ketone. Base-catalyzed elimination occurs with heating.

The additional stability provided by the conjugated carbonyl system of the product makes some aldol reactions thermodynamically driven and mixtures of stereoisomers (*E* & *Z*) are obtained from some reactions. Reactions in which a larger molecule is formed from smaller components, with the elimination of a very small by-product such as water, are termed **Condensations**. Hence, the following examples are properly referred to as **aldol condensations**. Overall the general reaction involves a dehydration of an aldol product to form an alkene:

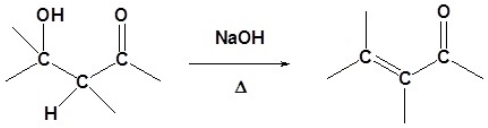


Figure: General reaction for an aldol condensation

Going from reactants to products simply

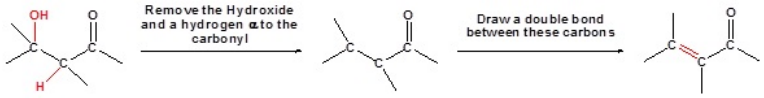
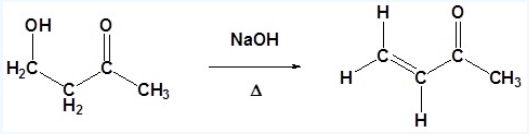


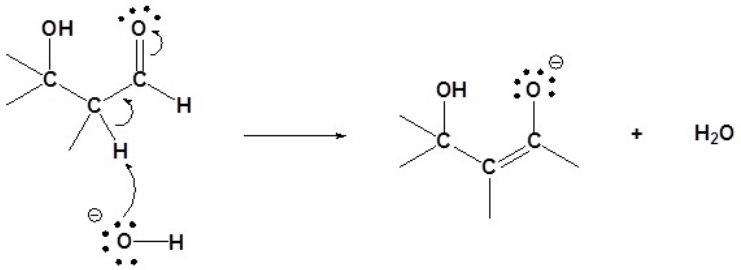
Figure: The aldol condensatio example

Example: Aldol Condensation from an Aldol Reaction Product

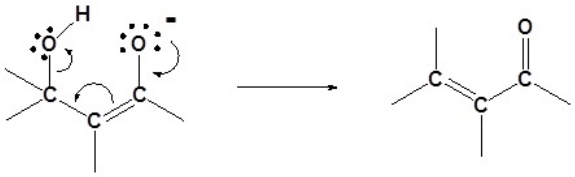


ALDOL CONDENSATION BASE CATALYZED MECHANISM

1) Form enolate

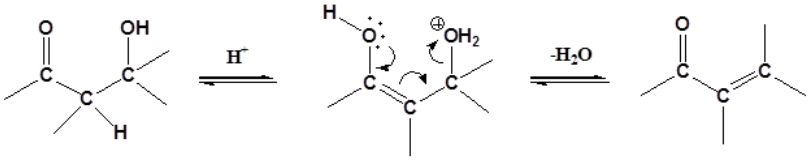


2) Form enone



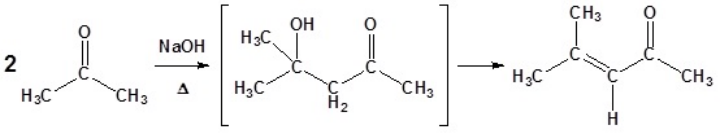
ALDOL CONDENSATION ACID CATALYZED MECHANISM

Under acidic conditions an enol is formed and the hydroxy group is protonated. Water is expelled by either and E1 or E2 reaction.



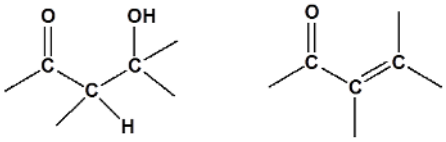
When performing both reactions together always consider the aldol product first then convert to the enone. Note! The double bond always forms in conjugation with the carbonyl.

Example: Aldol Condensation Directly from the Ketones or Aldehydes



ALDOL REACTIONS IN MULTIPLE STEP SYNTHESIS

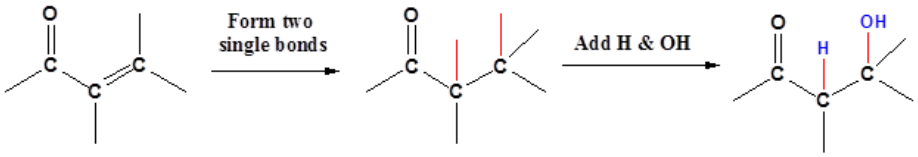
Aldol reactions are excellent methods for the synthesis of many enones or beta hydroxy carbonyls. Because of this, being able to predict when an aldol reaction might be used in a synthesis in an important skill. This accomplished by mentally breaking apart the target molecule and then considering what the starting materials might be.



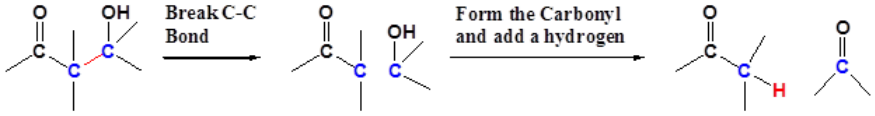
Fragments which are easily made by an aldol reaction

Steps to 'reverse' the aldol reaction (from the final aldol product towards identifying the starting compounds).

1) From an enone break the double bond and form two single bonds. Place and OH on the bond furthest from the carbonyl and an H on the bond closest to the carbonyl.

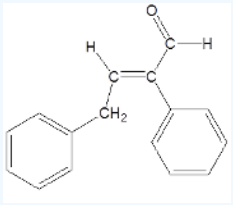


2) From the aldol product break the C-C bond between the alpha carbon and the carbon attached to the OH. Then turn the OH into a carbonyl and add an hydrogen to the other carbon.

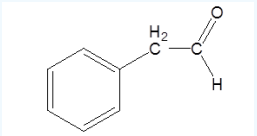


Example: Determining the Reactant when given the Aldol Condensation Product

What reactant must be used to make the following molecule using an aldol condensation?



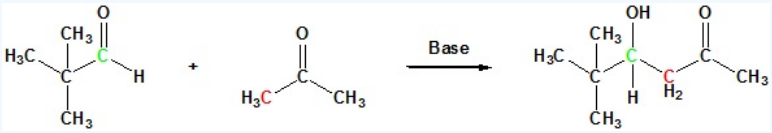
Solution



MIXED ALDOL REACTIONS AND CONDENSATIONS

The previous examples of aldol reactions and condensations used a common reactant as both the enolic donor and the electrophilic acceptor. The product in such cases is always a dimer of the reactant carbonyl compound. Aldol condensations between different carbonyl reactants are called **crossed** or **mixed** reactions, and under certain conditions such crossed aldol condensations can be effective.

Example: Mixed Aldol Reaction (One Product)

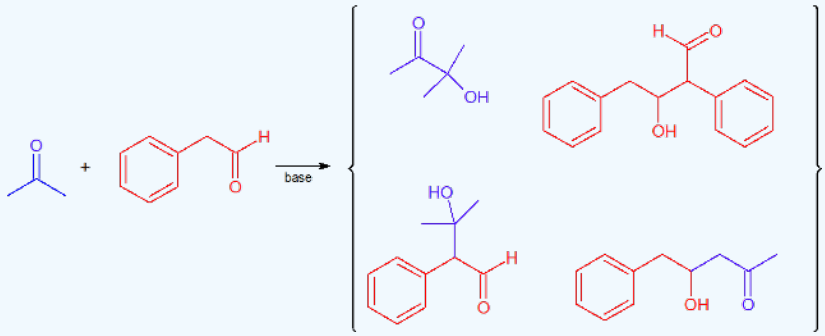


The success of these mixed aldol reactions is due to two factors. First, aldehydes are more reactive acceptor electrophiles than ketones, and formaldehyde is more reactive than other aldehydes. Second, aldehydes lacking alpha-hydrogens can only function as acceptor reactants, and this reduces the number of possible products by half. Mixed aldols in which both reactants can serve as donors and acceptors generally give complex mixtures of both dimeric (homo) aldols and crossed aldols. Because of this most mixed aldol reactions are usually not performed unless one reactant has no alpha hydrogens.

The following abbreviated formulas illustrate the possible products in such a case, red letters representing the acceptor component and blue the donor. If all the reactions occurred at the same rate, equal quantities of the four products would be obtained. Separation and purification of the components of such a mixture would be difficult.

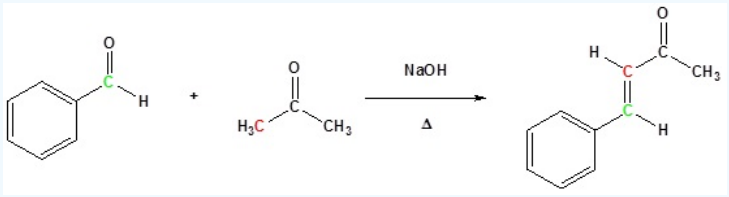
ACH_2CHO + **B**CH_2CHO + NaOH ⟶ A–A + B–B + A–B + B–A

Example: Products of a Mixed Aldol Reaction



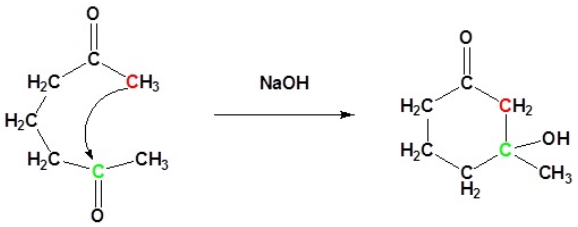
The aldol condensation of ketones with aryl aldehydes to form α,β-unsaturated derivatives is called the **Claisen-Schmidt** reaction.

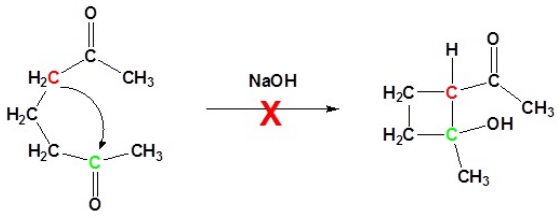
Example: Claisen-Schmidt Reaction



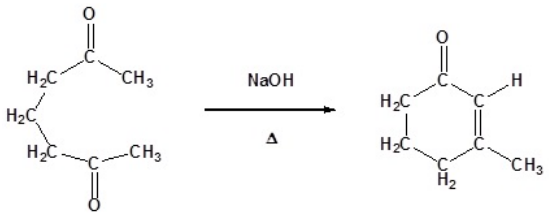
INTRAMOLECULAR ALDOL REACTION

Molecules which contain two carbonyl functionalities have the possibility of forming a ring through an intramolecular aldol reaction. In most cases two sets of ***α*** hydrogens need to be considered. As with most ring forming reaction five and six membered rings are preferred (less ring strain).



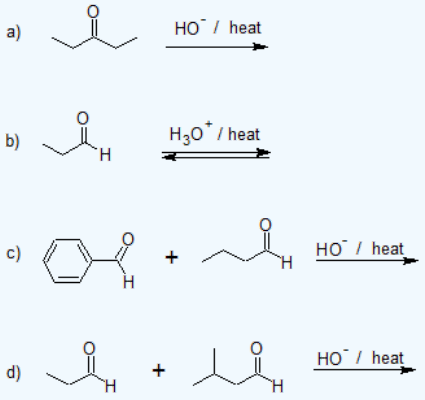


As with other aldol reaction the addition of heat causes an aldol condensation to occur.



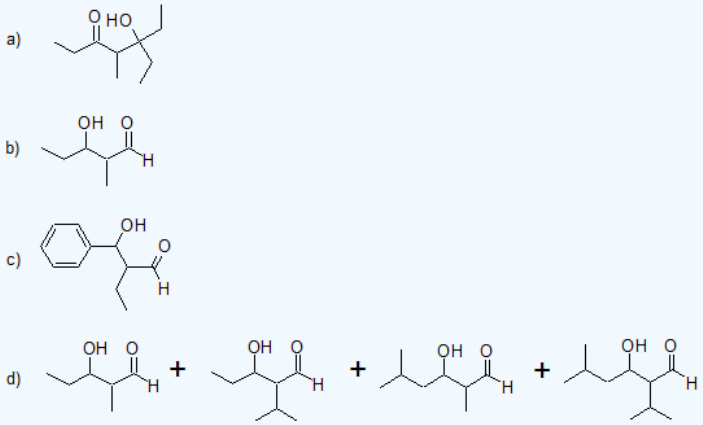
Exercise

12. Draw the bond-line structures for the products of the reactions below. Note: One of the reactions is a poorly designed aldol condensation producing four different products.



Answer

12.



CONTRIBUTORS AND ATTRIBUTIONS

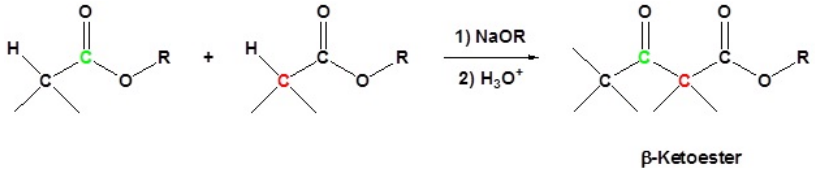
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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23.9: THE CLAISEN CONDENSATION REACTIONS OF ESTERS

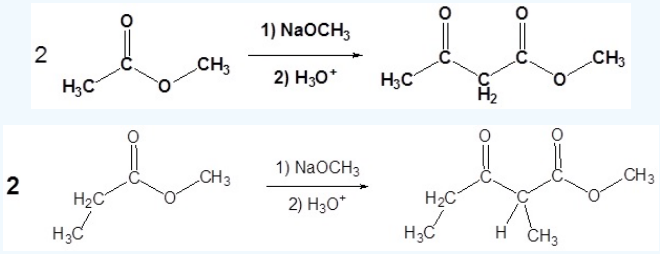
Because esters can contain alpha hydrogens, they can undergo a condensation reaction similar to the aldol reaction called a **Claisen Condensation**. In a fashion similar to the aldol, one ester acts as a nucleophile while a second ester acts as the electrophile. During the reaction a new carbon-carbon bond is formed. The product is a β-keto ester. A major difference with the aldol reaction is the fact that hydroxide cannot be used as a base because it could possibly react with the ester. Instead, an alkoxide version of the alcohol used to synthesize the ester is used to prevent transesterification side products.

CLAISEN CONDENSATION



The Claisen condensation reactions of methyl acetate and methyl propanoate are shown as examples.

Example: Claisen Condensation

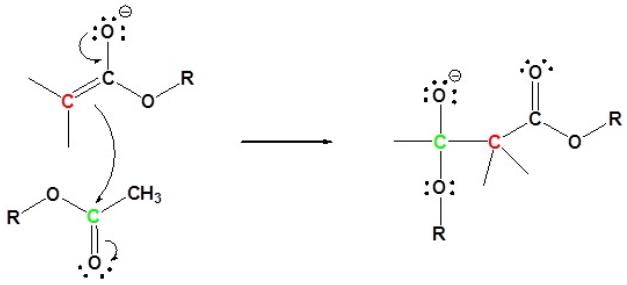


CLAISEN CONDENSATION MECHANISM

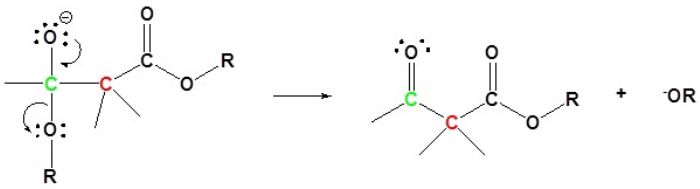
1) Enolate formation



2) Nucleophilic reaction

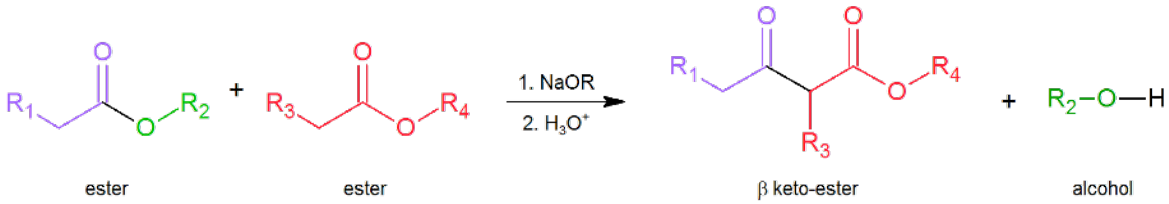


3) Removal of leaving group

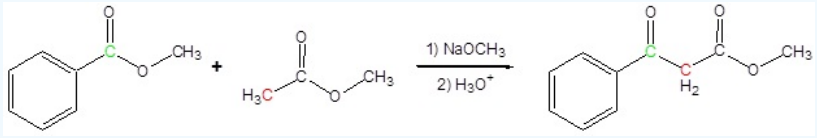


CROSSED CLAISEN CONDENSATION

Claisen condensations between different ester reactants are called **Crossed Claisen** reactions. Crossed Claisen reactions in which both reactants can serve as donors and acceptors generally give complex mixtures. Because of this most Crossed Claisen reactions are usually not performed unless one reactant has no alpha hydrogens.



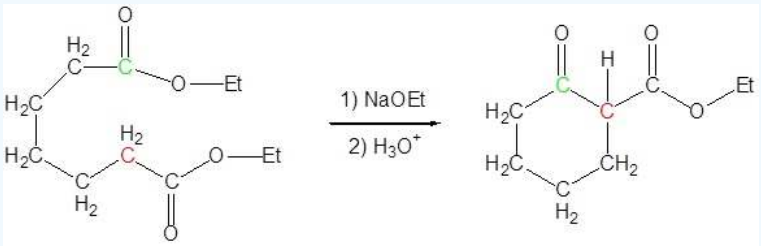
Example: Crossed Claisen Condensation



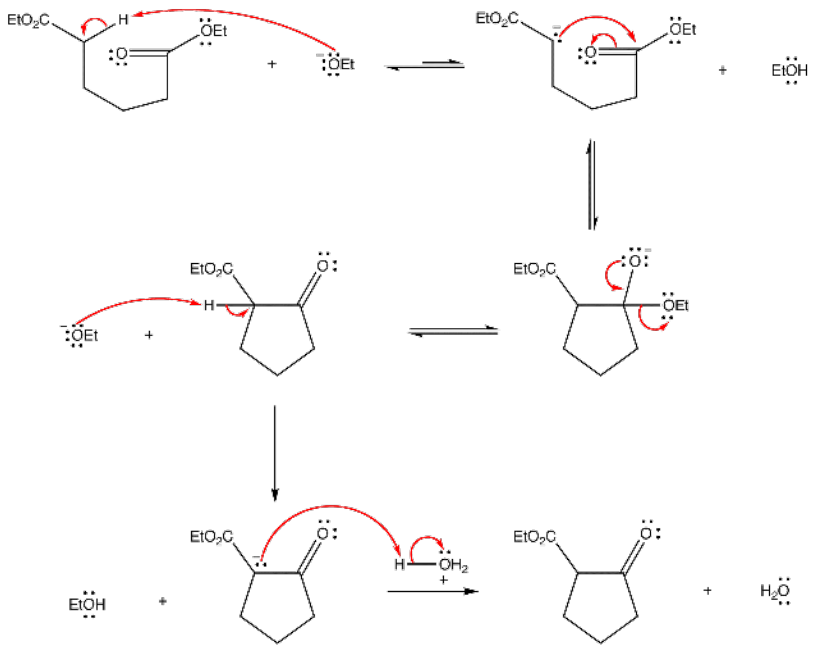
DIECKMANN CONDENSATION

A diester can undergo an intramolecular reaction called a Dieckmann condensation.

Example: Dieckman Condensation



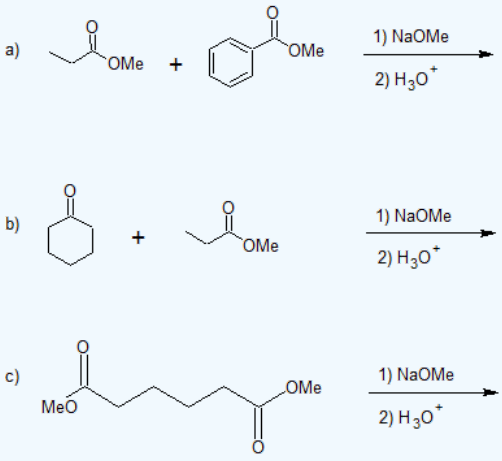
MECHANISM



1. Dieckmann, W. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 102–103.

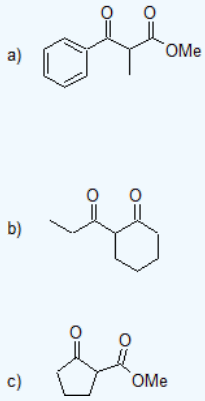
Exercise

13. Draw the bond-line structures for the products of the following reactions.



Answer

13.



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

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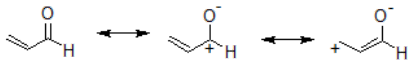
- **Dieckmann condensation** is licensed CC BY-NC-SA 4.0.

23.10: CONJUGATE ADDITIONS- THE MICHAEL REACTION

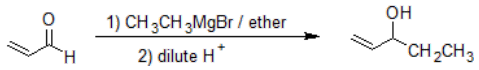
1,2 (DIRECT) VERSUS 1,4 (CONJUGATE) ADDITION

There are two electrophilic sites in alpha,beta-unsaturated carbonyls: the carbonyl carbon and the beta carbon. The second electrophilic site is created through resonance as shown below.

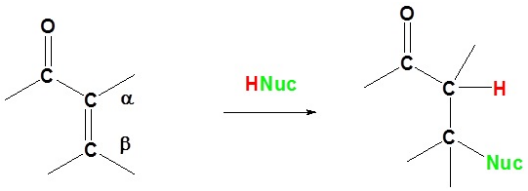




It is the strength of the nucleophile that determines the dominant reaction pathway. Strong nucleophiles like Grignard reagents and hydrides will react directly at the carbonyl carbon following the reactivity previously studied. The strong nucleophile reacts with the carbonyl carbon to produce a tetrahedral intermediate that is protonated to form an alcohol. The 1,2 direct addition reaction of prop-2-enal with a Grignard reagent is shown as an example below.

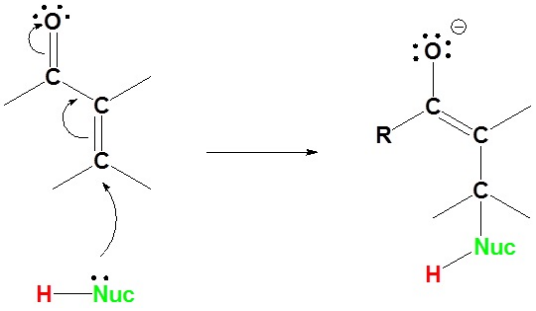


In 1,4 conjugate addition, the nucleophile reacts with the carbon β to the carbonyl driving the formation of an enolate ion that tautermerizes back to the carbonyl upon protonation.while the hydrogen is added to the carbon alpha to the carbonyl.

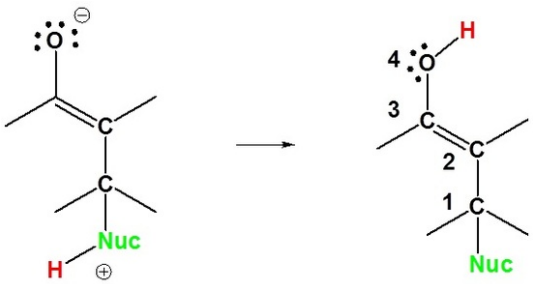


MECHANISM FOR 1,4 CONJUGATE ADDITION

1) Nucleophilic reaction at the carbon β to the carbonyl

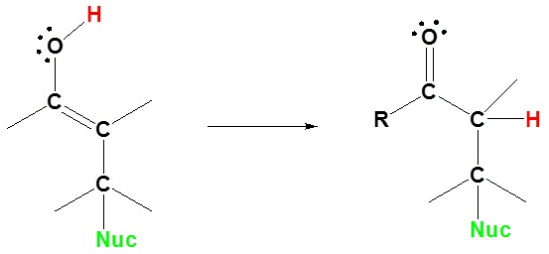


2) Proton Transfer



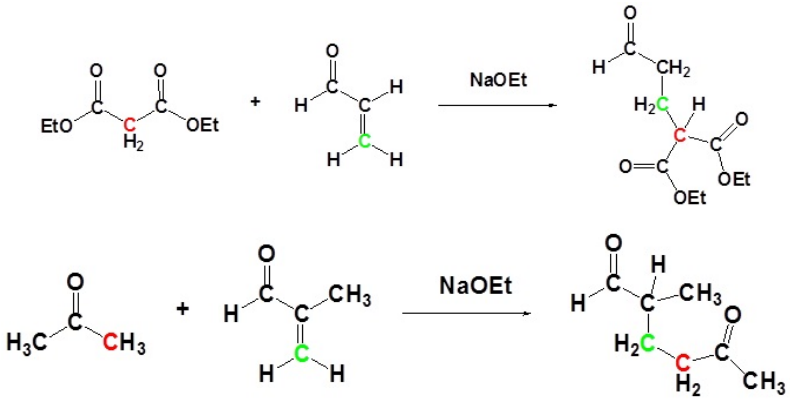
Here we can see why this addition is called 1,4. The nucleophile bonds to the carbon in the one position and the hydrogen adds to the oxygen in the four position.

3) Tautomerization

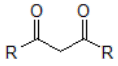
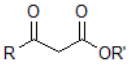
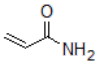
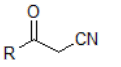
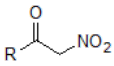


MICHAEL ADDITIONS

Enolates are weak nucleophiles and undergo 1,4 addition to α, β-unsaturated carbonyl compounds in a process called a Michael addition. The reaction is named after American chemist Arthur Michael (1853-1942). Two examples are shown below.

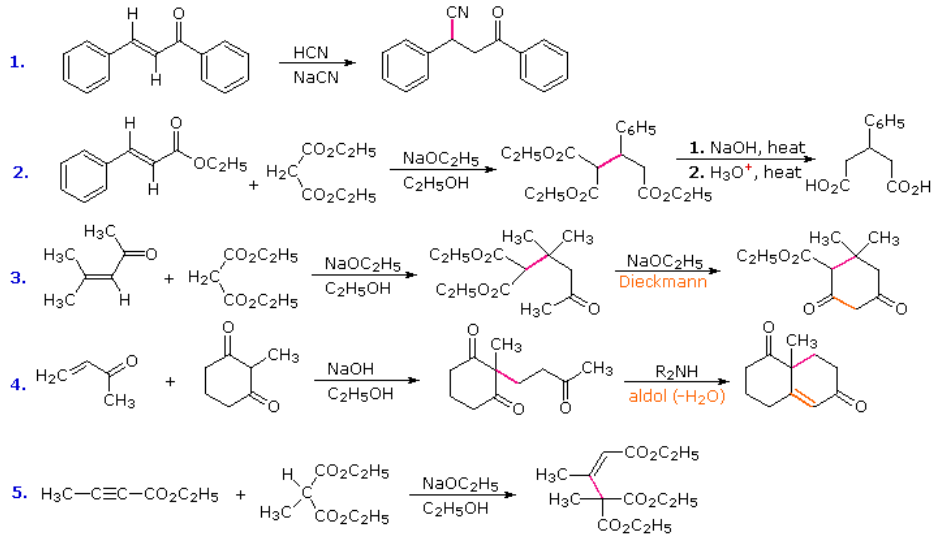


In combination with alkylations and condensations, the Michael reaction may be used to construct a wide variety of complex molecules from relatively simple starting materials. The nucleophile is called the Michael Donor and the electrophile (the alpha,beta-unsaturated carbonyl) is called the Michael Acceptor. The table below shows common reagents used for Michael addition reactions.

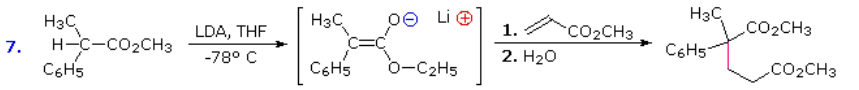
Michael Donors (aka nucleophile)		Michael Acceptors (aka electrophile)	
R_2CuLi	Gilman reagent		α,β-unsaturated aldehyde
	enamine		α,β-unsaturated ketone
	β-diketone		α,β-unsaturated ester
	β-ketoester		α,β-unsaturated amide
	β-keto nitrile		α,β-unsaturated nitrile
	α-nitro ketone		nitroethylene

There are several examples shown below including cyanide as another potential Michael donor. These anions are sufficiently stable that their addition reactions may be presumed reversible. If this is so, the thermodynamic argument used for hetero-nucleophile additions would apply here as well, and would indicate preferential formation of 1,4-addition products. Cyanide addition does not always follow this rule,

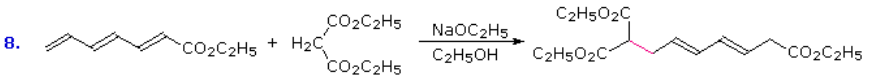
and aldehydes often give 1,2-products (cyanohydrins). In each case the initial reaction is a Michael addition, and the new carbon-carbon bond is colored magenta. Any subsequent bonds that are formed by other reactions are colored orange.



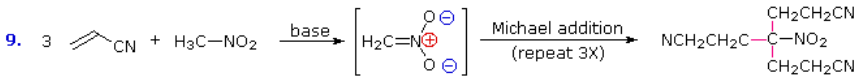
Enamine nucleophiles are good Michael donors. Hydrolysis is necessary to obtain the ketone product.



Weak carbon acids may be converted to their enolate anions prior to addition of the Michael acceptor.



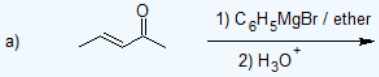
Extended vinylagous Michael acceptors have been used. This is a 1,6-addition (1,8 if the enol is counted).



Nitroalkanes have acidic α-hydrogens and make excellent Michael donors.

Exercise2

14. Draw the bond-line structures for the products of the reactions below.



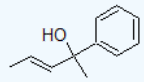


15. Specify the reagents needed to perform the following chemical transformation.



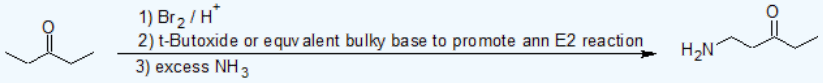
Answers

14.

a) 

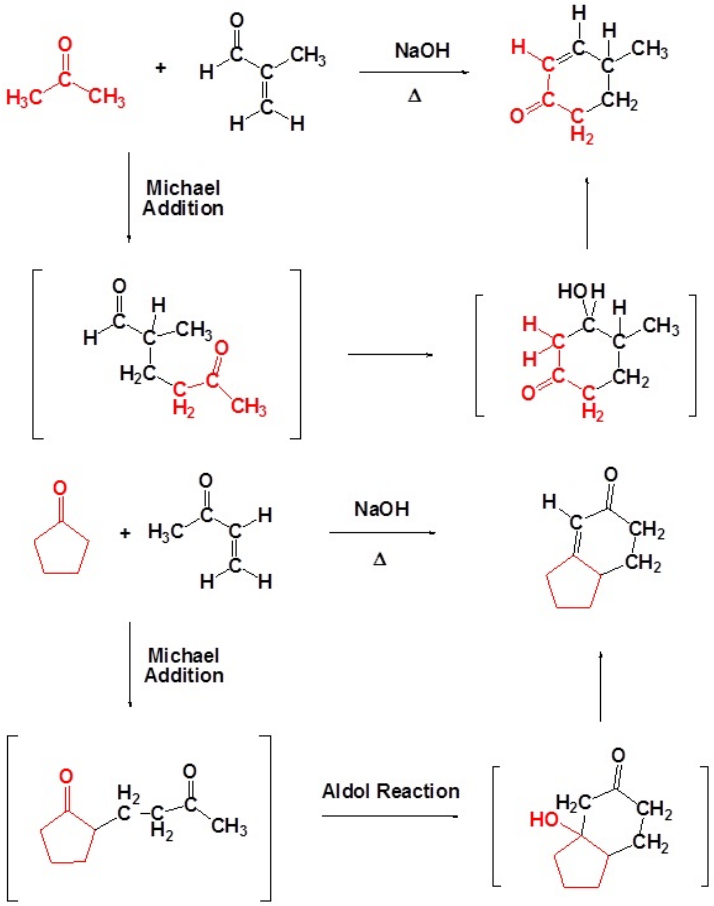
b) 

15.



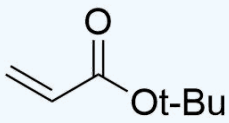
ROBINSON ANNULATIONS

Many times the product of a Michael addition produces a dicarbonyl which can then undergo an intramolecular aldol reaction. These two processes together in one reaction creates two new carbon-carbon bonds and also creates a ring. Ring-forming reactions are called annulations after the Latin work for ring annulus. The reaction is named after English chemist Sir Robert Robinson (1886-1975) who developed it. He received the Nobel prize in chemistry in 1947. Remember that during annulations five and six membered rings are preferred.

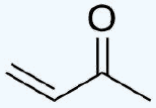


Exercise

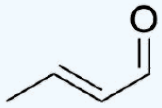
16. Draw the product of the reaction with the enamine prepared from cyclopentanone and pyrrolidine, and the following molecules.

(a) 

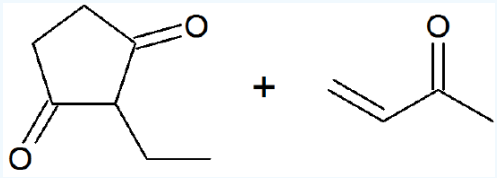
(b)



(c)



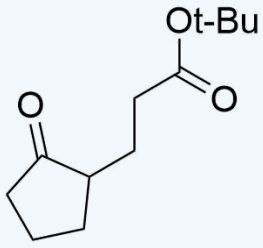
17. Draw the product of the following reaction.



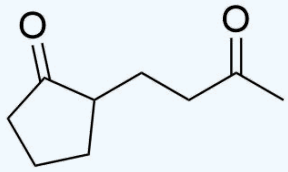
Answer

16.

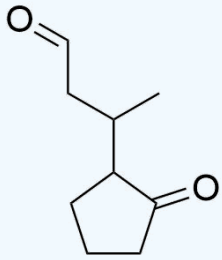
(a)



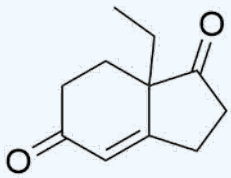
(b)



(c)



17.



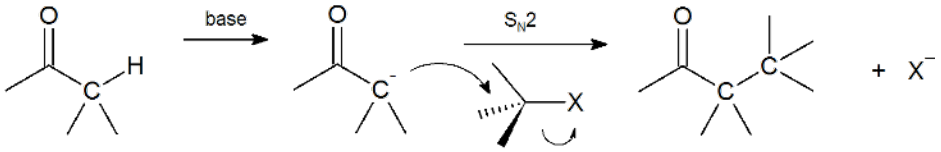
CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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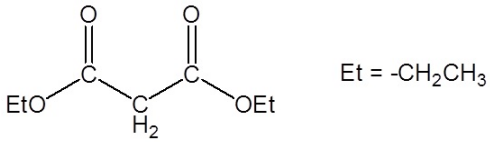
23.11: DECARBOXYLATION REACTIONS

Enolates can act as a nucleophile in S_N2 type reactions. Overall an α hydrogen is replaced with an alkyl group. This reaction is one of the more important for enolates because a carbon-carbon bond is formed. These alkylations are affected by the same limitations as S_N2 reactions previously discussed. A good leaving group, X= chloride, bromide, iodide, tosylate, should be used. Also, secondary and tertiary leaving groups should not be used because of poor reactivity and possible competition with elimination reactions. Lastly, it is important to use a strong base, such as LDA or sodium amide, for this reaction. Using a weaker base such as hydroxide or an alkoxide leaves the possibility of multiple alkylation's occurring.



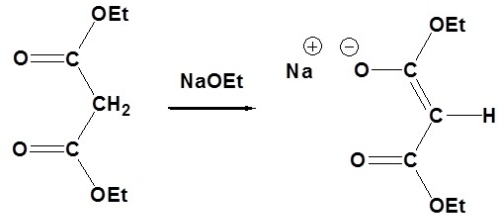
MALONIC ESTER SYNTHESIS

Malonic ester is a reagent specifically used in a reaction which converts alkyl halides to carboxylic acids called the Malonic Ester Synthesis. Malonic ester synthesis is a synthetic procedure used to convert a compound that has the general structural formula 1 into a carboxylic acid that has the general structural formula 2.



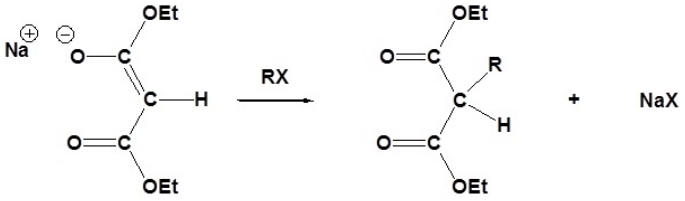
Malonic Ester

Due to the fact that Malonic ester's α hydrogens are adjacent to two carbonyls, they can be deprotonated by sodium ethoxide (NaOEt) to form Sodio Malonic Ester.

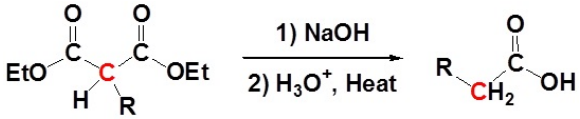


Malonic Ester **Sodio Malonic Ester**

Because Sodio Malonic Ester is an enolate, it can then be alkylated with alkyl halides.

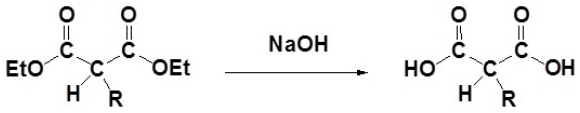


After alkylation the product can be converted to a dicarboxylic acid through saponification and subsequently one of the carboxylic acids can be removed through a decarboxylation step.

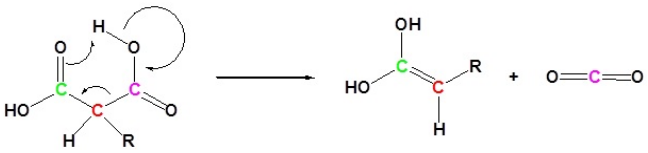


MECHANISM

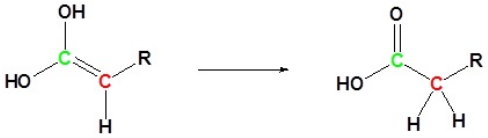
1) Saponification



2) Decarboxylation



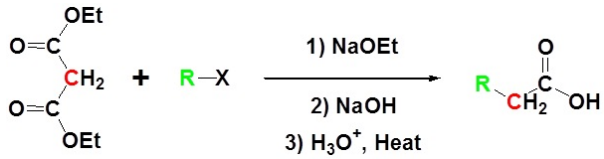
3) Tautomerization



All of the steps together form the Malonic ester synthesis.

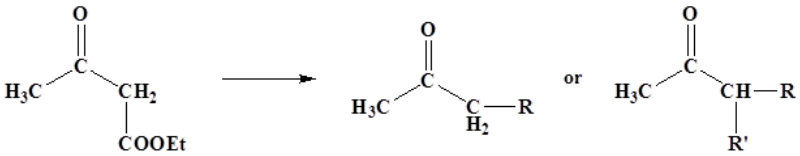
$$RX \rightarrow RCH\text{-}_2CO_2H \tag{23.11.1}$$

Example



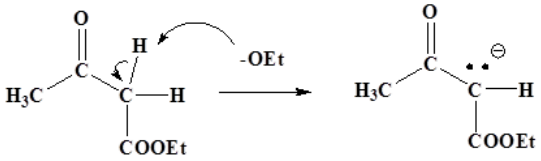
THE ACETOACETIC ESTER SYNTHESIS

The acetoacetic ester synthesis allows for the conversion of ethyl acetoacetate into a methyl ketone with one or two alkyl groups on the alpha carbon.

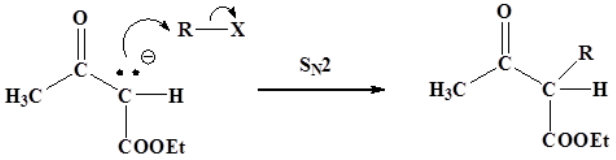


STEPS

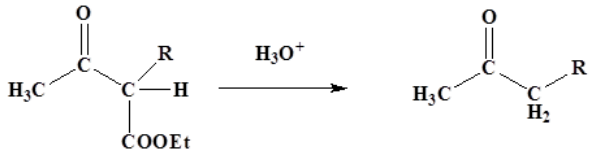
1) Deprotonation with ethoxide



2) Alkylation via and SN2 Reaction

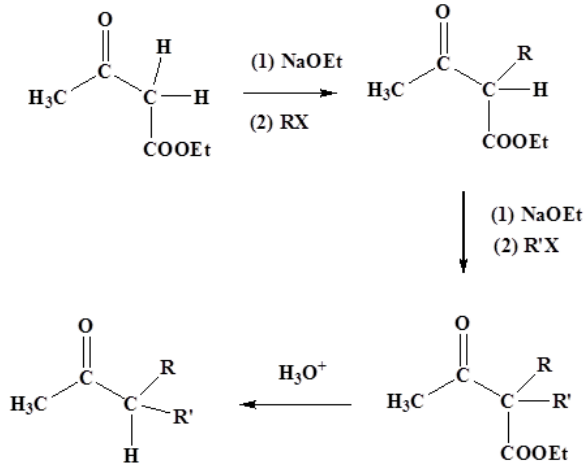


3) Hydrolysis and decarboxylation



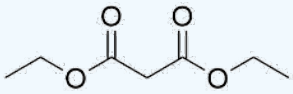
ADDITION OF A SECOND ALKY GROUP

After the first step and additional alkyl group can be added prior to the decarboxylation step. Overall this allows for the addition of two different alkyl groups.

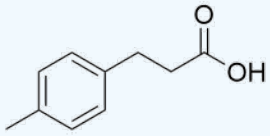


Exercise

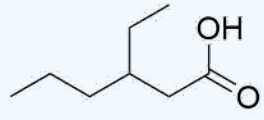
18. Propose a synthesis for each of the following molecules from this malonic ester.



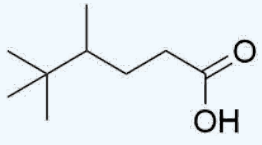
(a)



(b)

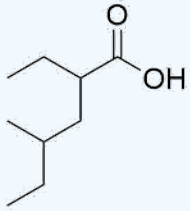


(c)



19. Why can't we prepare tri substituted acetic acids from a malonic ester?

20. Propose a synthesis for the following molecule via a malonic ester.



Answer

18.

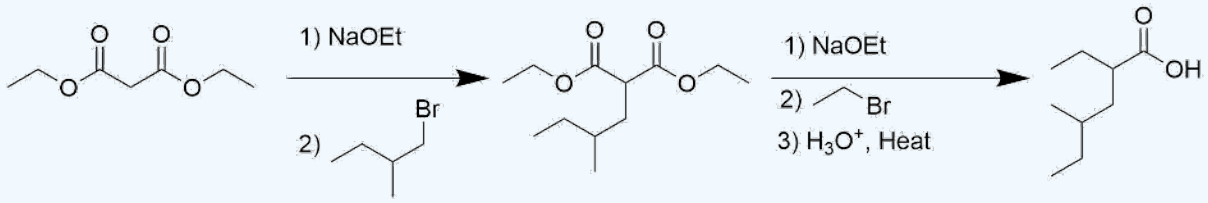
(a) 1) Malonic Ester, NaOEt, 2) 4-Methylbenzyl Bromide, 3) Base, 4) Acid, Heat

(b) 1) Malonic Ester, NaOEt, 2) 3-bromohexane, 3) Base, 4) Acid, Eat

(c) 1) Malonic Ester, NaOEt, 2) 1-Bromo-2,3,3-trimethylbutane, 3) Base, 4) Acid, Heat

19. Malonic esters only contain two acid protons.

20.



CONTRIBUTORS AND ATTRIBUTIONS

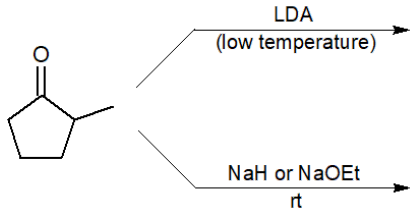
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

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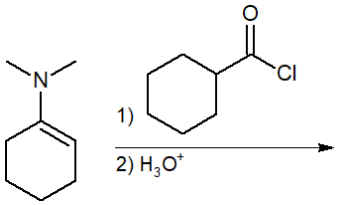
23.12: ADDITIONAL EXERCISES

General Review

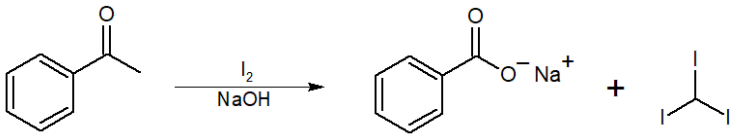
23-1 For each of the following reactions, predict the product. Then identify which one gives the kinetic product and which one gives the thermodynamic product. Explain your reasoning.



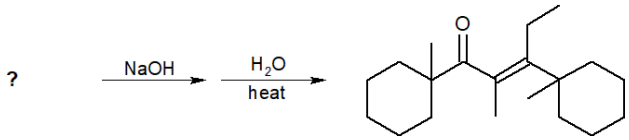
23-2 Predict the final product of the following reaction.



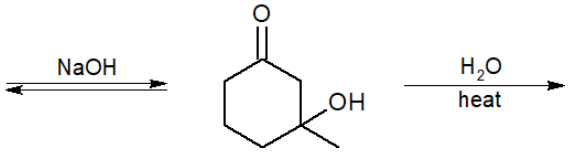
23-3 Explain why we obtain the products shown below as a result of the base catalyzed α-halogenation reaction, instead of a single or double halogenated product.



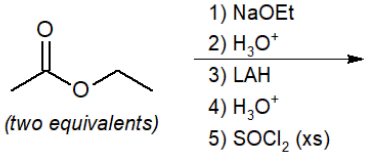
23-4 Identify the starting molecule of the aldol addition-condensation reaction that resulted in the final product below.



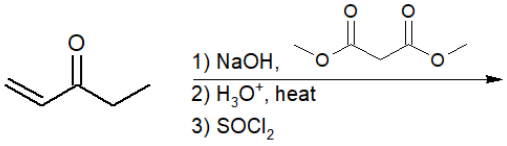
23-5 The following reaction is an example of an intramolecular aldol addition-condensation reaction. Given the aldol product, identify the starting molecule and the condensation product.



23-6 Provide the final product of the following reaction (for now, ignore any stereochemistry).

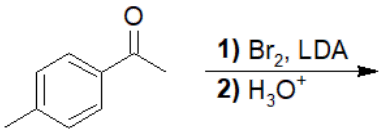


23-7 Predict the final product of the following reaction.



Enols and Enolate Ions

23-8 Choose the correct IUPAC nomenclature of the product of the following reaction and provide its structure.



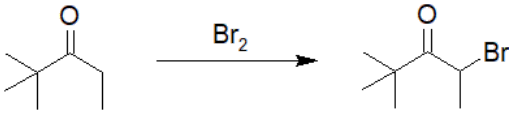
a) dibromo(4-methylphenyl)methanol

b) 4-methylbenzoic acid

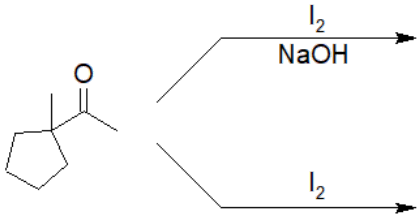
c) 4-methylbenzoyl bromide

d) bromo(4-methylphenyl)methanol

23-9 Draw the mechanism for the following self-catalyzed halogenation reaction.

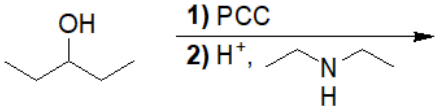


23-10 Predict the product of the following reaction.



Formation and Alkylation of Enamines

23-11 Choose the correct IUPAC nomenclature for the product of the following reaction.



a) (2Z)-N,N-diethylpent-2-en-3-amine

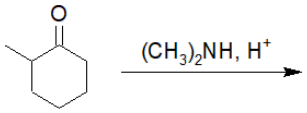
b) N,N-diethylpentan-3-amine

c) 3-(diethylamino)pentan-3-ol

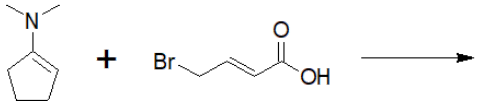
d) Tetraethylhydrazine

23-12 Predict the major products of the following reactions.

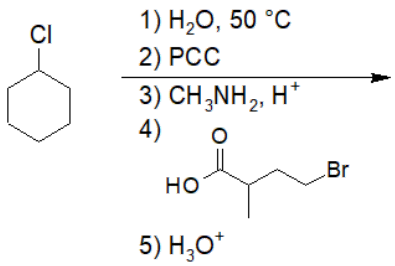
a)



b)

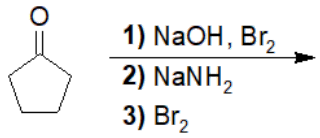


23-13 Predict the product of the following reaction.



Alpha Halogenation of Ketones

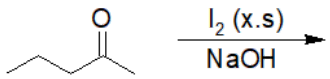
23-14 Predict the product of the following reaction.



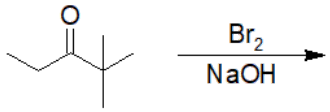
23-15 Draw the mechanism for the α-halogenation step of the ketone in problem **23-14**.

23-16 Provide the structures of the products of the following reactions.

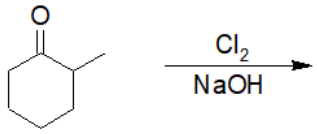
a)



b)

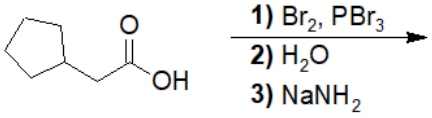


c)

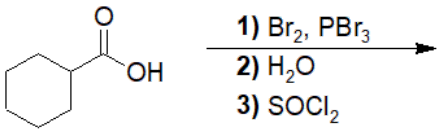


Alpha Bromination of Acids: The HVZ Reaction

23-17 Give the product of the following reaction.



23-18 Choose the correct IUPAC nomenclature of the product of the following reaction.



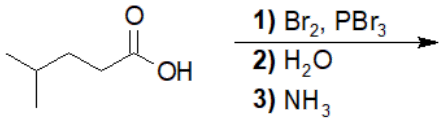
a) 1-chlorocyclohexane-1-carboxylic acid

b) 1-bromocyclohexane-1-carbonyl chloride

c) 1-chlorocyclohexane-1-carbonyl chloride

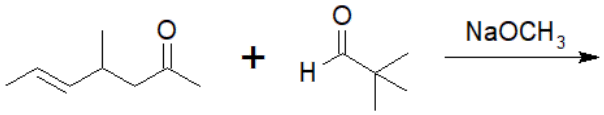
d) 1-hydroxycyclohexane-1-carbonyl bromide

23-19 Provide the structure and IUPAC nomenclature of the product of the following reaction.

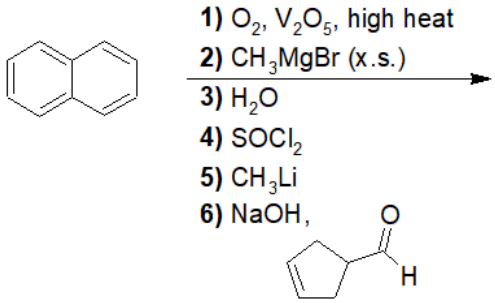


The Aldol Condensation of Ketones and Aldehydes

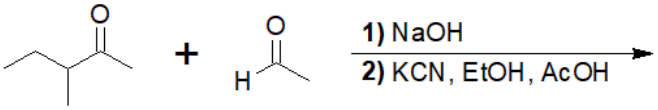
23-20 Give the structure of the product of the following aldol condensation reaction.



23-21 Predict the structure of the product of the following reaction.

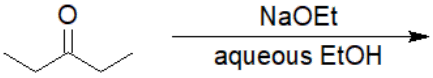


23-22 Provide the structure of the product of the following reaction.



Dehydration of Aldol Products

23-23 Choose the correct IUPAC nomenclature for the product of the following aldol condensation reaction.



a) 5-ethyl-4-methylheptan-3-one

b) 5-ethyl-4-methylhept-4-en-3-one

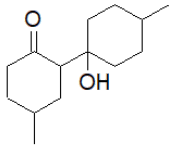
c) 5-ethyl-5-hydroxy-4-methylheptan-3-one

d) (5Z)-5-ethyl-4-methylhept-5-en-3-one

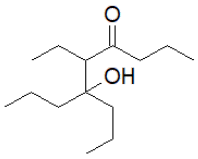
23-24 Provide the mechanism for the reaction to the answer for the previous question.

23-25 For the following compounds, draw a possible product of the condensation step.

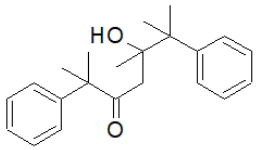
a)



b)

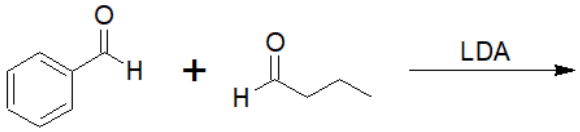


c)

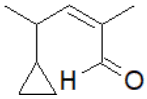


Crossed Aldol Condensations

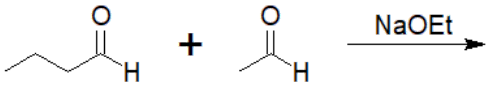
23-26 Provide the structure of the product of the following reaction.



23-27 Suggest the structures of the starting compounds that were reacted to create this final crossed aldol condensation product.

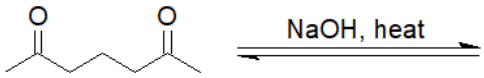


23-28 Provide the structures of all possible products of the following crossed aldol condensation reaction.



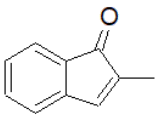
Aldol Cyclizations

23-29 Provide the IUPAC name for the product of the following intramolecular aldol condensation reaction.

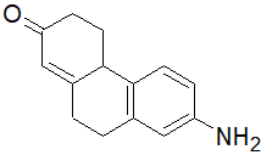


23-30 Identify the starting material used to create the following products of aldol cyclization.

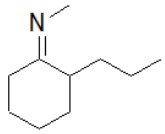
a)



b)



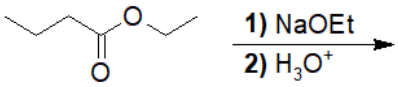
23-31 Starting with a single diketone molecule, propose a method of synthesis for the following compound that includes an aldol cyclization step.



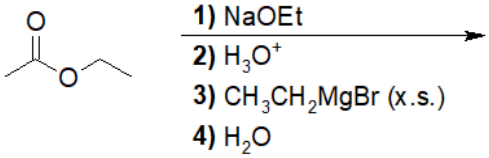
(1*Z*)-*N*-methyl-2-propylcyclohexan-1-imine

Claisen Condensations

23-32 Predict the product of the following Claisen condensation reaction.

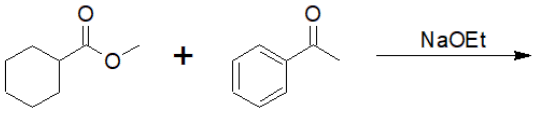


23-33 Predict the final product of the following reaction.

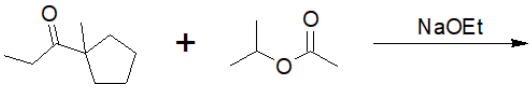


23-34 Provide the structure of the products of the following crossed Claisen condensation reactions.

a)

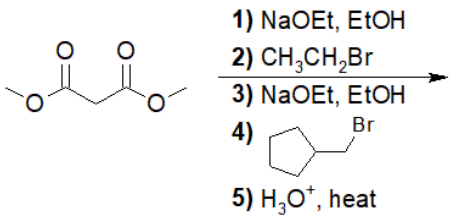


b)

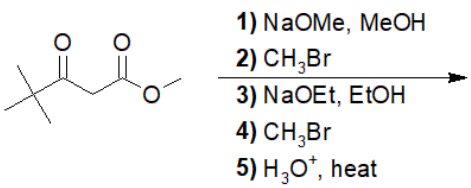


Syntheses Using *β*-Dicarbonyl Compounds

23-35 Give the structure and IUPAC nomenclature of the product of the following reaction.



23-36 Choose the correct IUPAC nomenclature of the product of the following reaction.



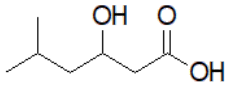
a_ 2,2,2,4,4-tetramethylpentan-3-one

b) 2,2,4-trimethylpentan-3-one

c) 2,4,4-trimethylpent-1-en-3-one

d) 2,4,4-trimethyl-3-oxopentanoic acid

23-37 Suggest a way to make (5-methylhexyl)benzene from 3-hydroxy-5-methylhexanoic acid.



3-hydroxy-5-methylhexanoic acid

Conjugate Additions: The Michael Reaction

23-38 For the following pairs of compounds, identify the Michael acceptor and the Michael donor.

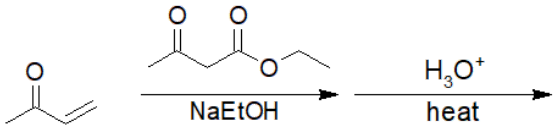
a)



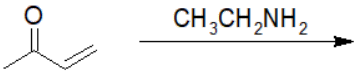
b)



23-39 Predict the product of the following reaction chain.



23-40 Pick the answer that correctly names the product of the following Michael addition reaction.



a) 3-(ethylamino)butan-2-one

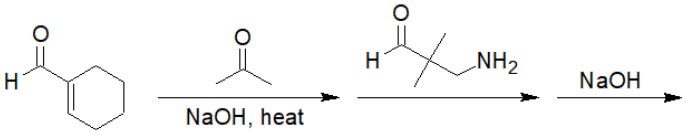
b) 2-(ethylamino)butan-2-ol

c) 4-(ethylamino)butan-2-one

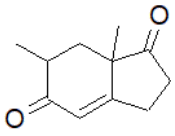
d) 4-(methylamino)butan-2-one

The Robinson Annulation

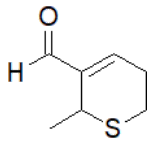
23-41 Predict a possible product of the following reactions.



23-42 Given the following compound, predict the Michael acceptor and donor that initially reacted to allow for the aldol condensation to occur.



23-43 Given the following Robinson annulation product, identify the intermediate compound that results from the Michael addition and exists before the aldol condensation.

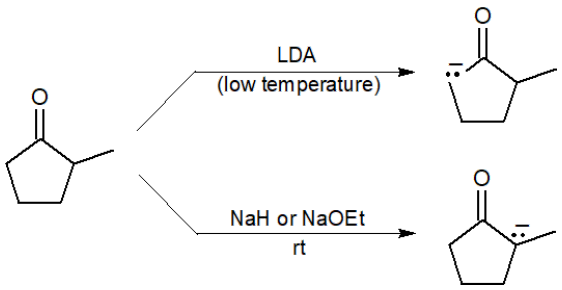


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23.13: SOLUTIONS TO ADDITIONAL EXERCISES

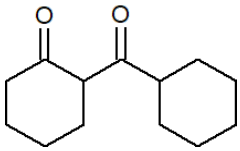
General Review

23-1



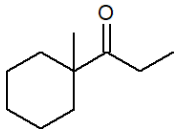
When a bulky base, such as LDA, is used, it will almost always deprotonate the least hindered position. In this case, the reaction is performed under low temperatures (to prevent the thermodynamic product from forming) and we get the kinetic product. When we use a strong base that is not bulky, it will favor deprotonating the position that will provide the most stable product at equilibrium. As a result, the enolate that forms when using NaH or NaOEt is more substituted and more stable.

23-2

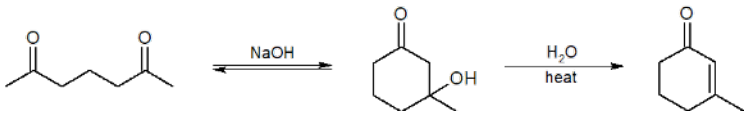


23-3 When acetophenone is halogenated at the α-position, the α-carbon becomes more acidic as a result of the electron-withdrawing halogen. This makes it more likely to go through α-halogenation again, until it no longer has any α-protons. When the base performs a nucleophilic attack on the ketone, the triiodomethyl group becomes a good leaving group. The resulting products are sodium benzoate and triiodomethane.

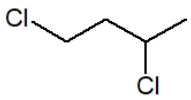
23-4



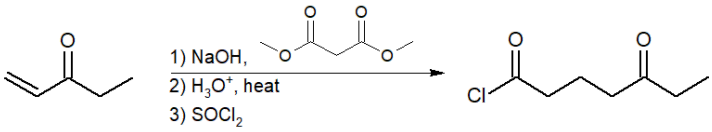
23-5



23-6



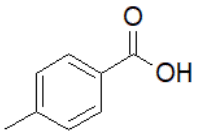
23-7



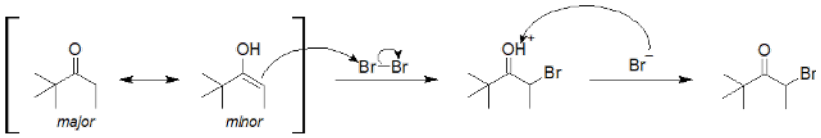
Enols and Enolate Ions

23-8:

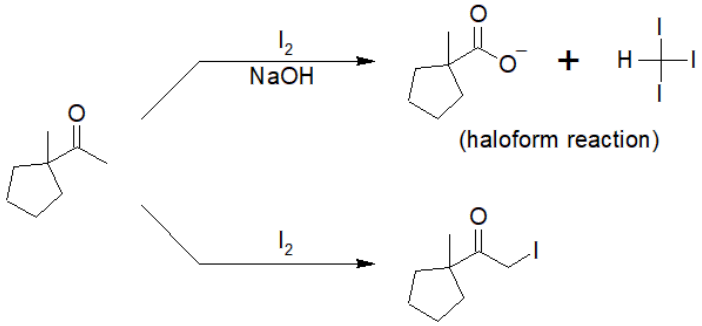
Answer: B



23-9:



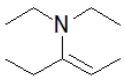
23-10:



Formation and Alkylation of Enamines

23-11:

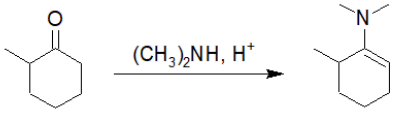
Answer: A



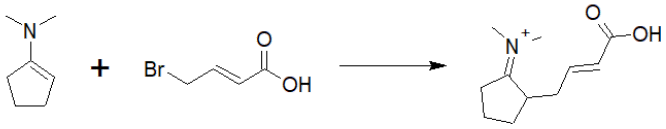
(2*Z*)-*N*,*N*-diethylpent-2-en-3-amine

23-12:

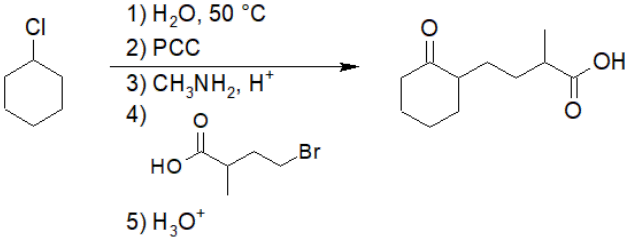
a)



b)

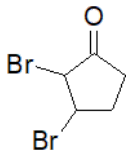


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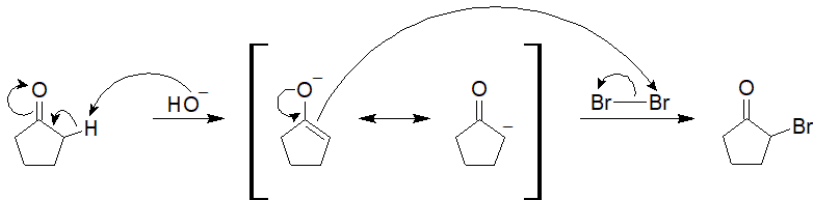


Alpha Halogenation of Ketones

23-14:

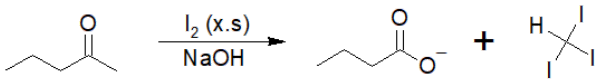


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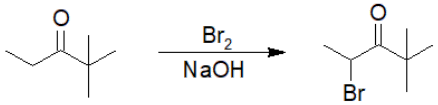


23-16:

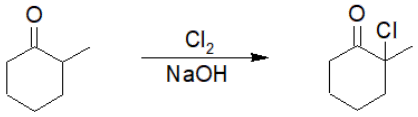
a)



b)

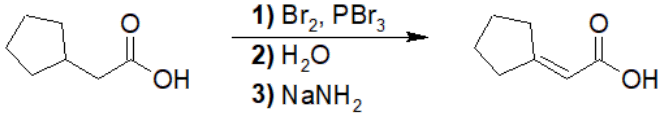


c)



Alpha Bromination of Acids: The HVZ Reaction

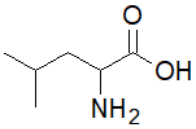
23-17:



23-18:

Answer: B

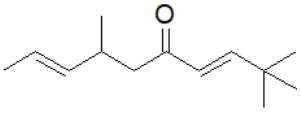
23-19:



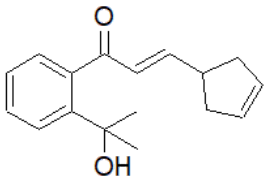
2-amino-4-methylpentanoic acid
(also known as the amino acid Leucine)

The Aldol Condensation of Ketones and Aldehydes

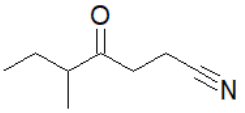
23-20:



23-21:



23-22:

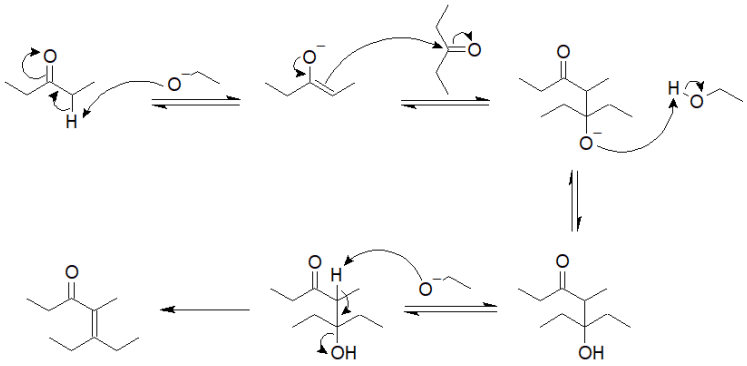


Dehydration of Aldol Products

23-23:

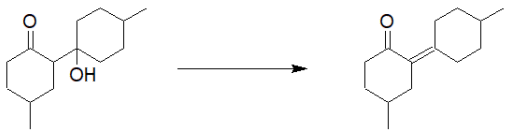
Answer: B

23-24:

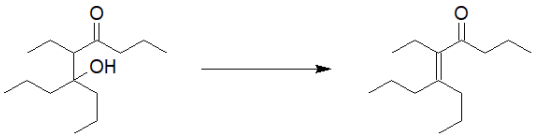


23-25:

a)



b)

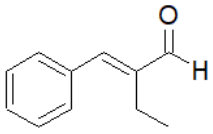


c)

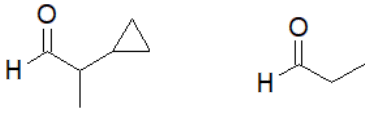


Crossed Aldol Condensations

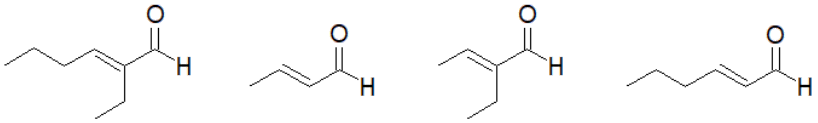
23-26:



23-27:

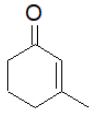


23-28:



Aldol Cyclizations

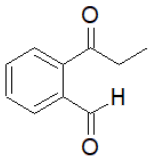
23-29:



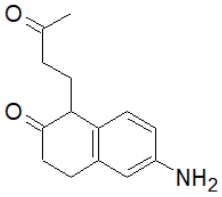
3-methylcyclohex-2-en-1-one

23-30:

a)

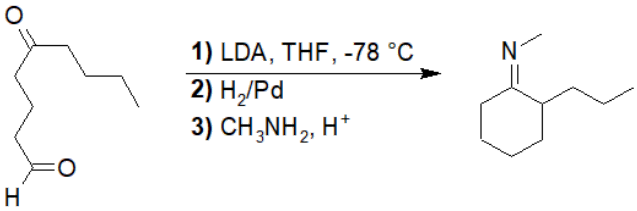


b)



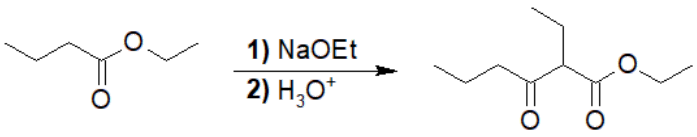
23-31:

Several answers possible. One plausible method of synthesis:

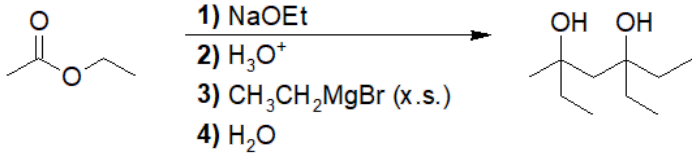


Claisen Condensations

23-32:

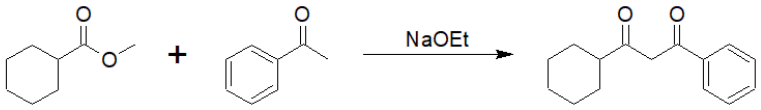


23-33:

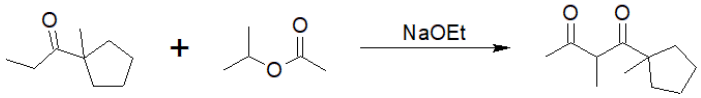


23-34:

a)

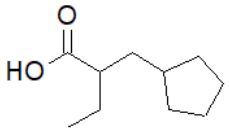


b)



Syntheses Using *β*-Dicarbonyl Compounds

23-35:



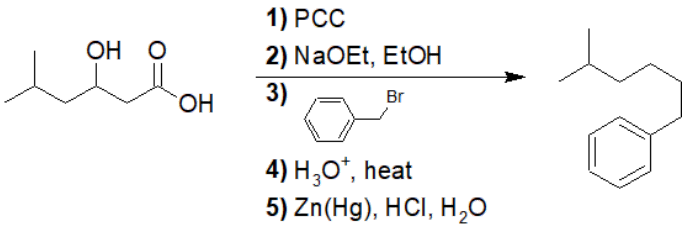
2-(cyclopentylmethyl)butanoic acid

23-36:

Answer: B

23-37:

Possible route of synthesis:



Conjugate Additions: The Michael Reaction

23-38:

Michael acceptors are generally α,β-unsaturated ketones; however, aldehydes or acid derivatives can also function as acceptors. Michael donors are weak bases/strong nucleophiles.

a)



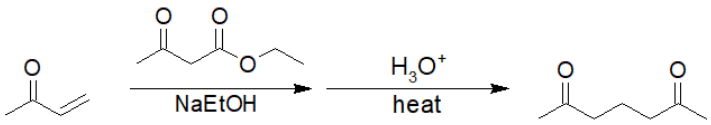
acceptor **donor**

b)



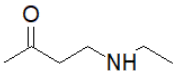
donor **acceptor**

23-39:



23-40

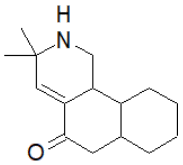
Answer: C



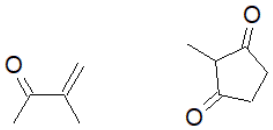
4-(ethylamino)butan-2-one

The Robinson Annulation

23-41:

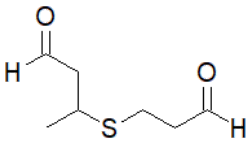


23-42:



acceptor donor

23-43:



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CHAPTER OVERVIEW

24: CARBOHYDRATES

24.1: Introduction
24.2: Classification of Carbohydrates
24.3: Fischer Projections
24.4: D and L Sugars
24.5: Configuration of Aldoses
24.6: Cyclic Structures of Monosaccharides
24.7: Reactions of Monosaccharides
24.8: Disaccharides and Glycosidic Bonds
24.9: Polysaccharides
24.10: Other Important Carbohydrates
24.11: Cell Surface Carbohydrates and Influenza Viruses

Template:HideTOC

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24.1: INTRODUCTION

Objectives

After completing this section, you should be able to

1. identify carbohydrates (sugars) as being polyhydroxylated aldehydes and ketones.
2. describe, briefly, the process of photosynthesis, and identify the role played by carbohydrates as an energy source for living organisms.

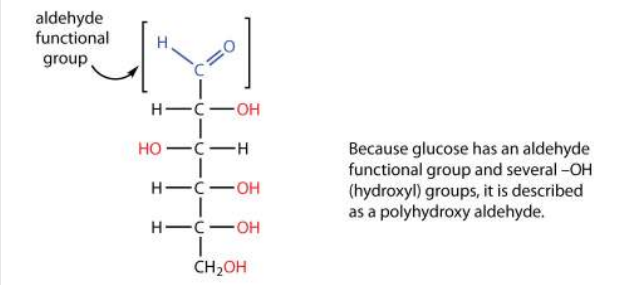
Key Terms

Make certain that you can define, and use in context, the key term below.

- carbohydrate

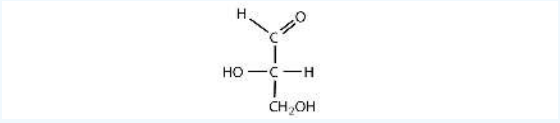
INTRODUCTION

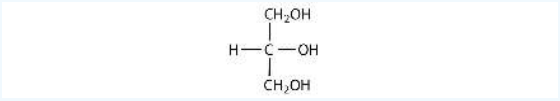
All carbohydrates consist of carbon, hydrogen, and oxygen atoms and are polyhydroxy aldehydes or ketones or are compounds that can be broken down to form such compounds. Examples of carbohydrates include starch, fiber, the sweet-tasting compounds called sugars, and structural materials such as cellulose. The term *carbohydrate* had its origin in a misinterpretation of the molecular formulas of many of these substances. For example, because its formula is $C_6H_{12}O_6$, glucose was once thought to be a "carbon hydrate" with the structure $C_6 \cdot 6H_2O$.

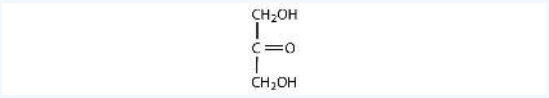


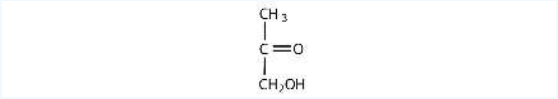
Example 1

Which compounds would be classified as carbohydrates?

a. 

b. 

c. 

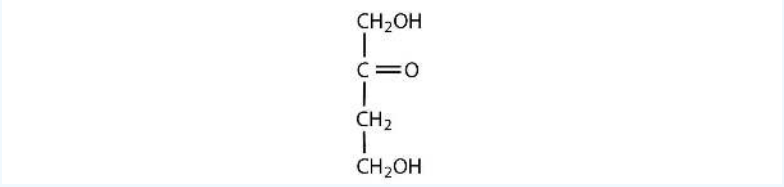
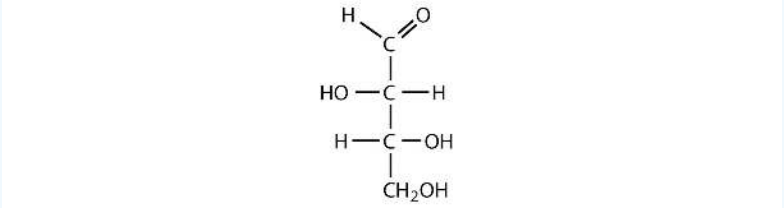
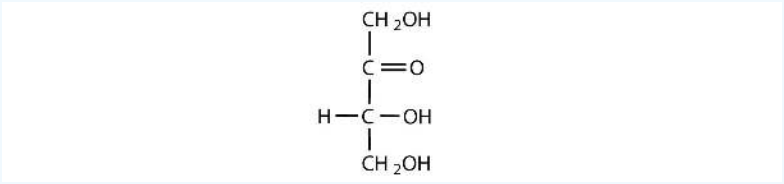
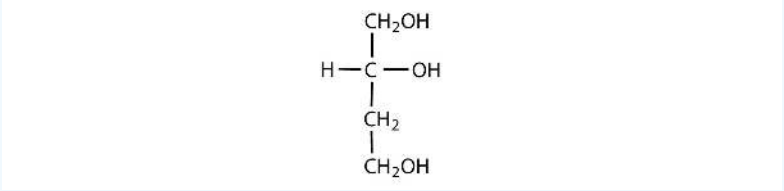
d. 

Solution

a. This is a carbohydrate because the molecule contains an aldehyde functional group with OH groups on the other two carbon atoms.
b. This is not a carbohydrate because the molecule does not contain an aldehyde or a ketone functional group.
c. This is a carbohydrate because the molecule contains a ketone functional group with OH groups on the other two carbon atoms.
d. This is not a carbohydrate; although it has a ketone functional group, one of the other carbons atoms does not have an OH group attached.

Exercise 1

Which compounds would be classified as carbohydrates?

1. 
2. 
3. 
4. 

Green plants are capable of synthesizing glucose ($C_6H_{12}O_6$) from carbon dioxide (CO_2) and water (H_2O) by using solar energy in the process known as photosynthesis:

$$6CO_2 + 6H_2O + 2870\ \text{kJ} \rightarrow C_6H_{12}O_6 + 6O_2 \quad (1)$$

(The 2870 kJ comes from solar energy.) Plants can use the glucose for energy or convert it to larger carbohydrates, such as starch or cellulose. Starch provides energy for later use, perhaps as nourishment for a plant's seeds, while cellulose is the structural material of plants. We can gather and eat the parts of a plant that store energy—seeds, roots, tubers, and fruits—and use some of that energy ourselves. Carbohydrates are also needed for the synthesis of nucleic acids and many proteins and lipids.

Animals, including humans, cannot synthesize carbohydrates from carbon dioxide and water and are therefore dependent on the plant kingdom to provide these vital compounds. We use carbohydrates not only for food (about 60%–65% by mass of the average diet) but also for clothing (cotton, linen, rayon), shelter (wood), fuel (wood), and paper (wood).

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- *The Basics of General, Organic, and Biological Chemistry* by David W. Ball, John W. Hill, and Rhonda J. Scott.

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24.2: CLASSIFICATION OF CARBOHYDRATES

Objectives

After completing this section, you should be able to

1. classify a specific carbohydrate as being a monosaccharide, disaccharide, trisaccharide, etc., given the structure of the carbohydrate or sufficient information about its structure.
2. classify a monosaccharide according to the number of carbon atoms present and whether it contains an aldehyde or ketone group.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- aldose
- disaccharide
- ketose
- monosaccharide (simple sugar)
- polysaccharide

Carbohydrates are the most abundant class of organic compounds found in living organisms. They originate as products of **photosynthesis**, an endothermic reductive condensation of carbon dioxide requiring light energy and the pigment chlorophyll.

$$nCO_2 + nH_2O + Energy \rightarrow C_nH_{2n}O_n + nO_2 \quad (24.2.1)$$

As noted here, the formulas of many carbohydrates can be written as carbon hydrates, $C_n(H_2O)_n$, hence their name. The carbohydrates are a major source of metabolic energy, both for plants and for animals that depend on plants for food. Aside from the sugars and starches that meet this vital nutritional role, carbohydrates also serve as a structural material (cellulose), a component of the energy transport compound ATP/ADP, recognition sites on cell surfaces, and one of three essential components of DNA and RNA.

Carbohydrates are called **saccharides** or, if they are relatively small, sugars. Several classifications of carbohydrates have proven useful, and are outlined in the following table.

Complexity	**Simple Carbohydrates** monosaccharides		**Complex Carbohydrates** disaccharides, oligosaccharides & polysaccharides		
Size	**Tetrose** C_4 sugars	**Pentose** C_5 sugars	**Hexose** C_6 sugars	**Heptose** C_7 sugars	etc.
C=O Function	**Aldose** sugars having an aldehyde function or an acetal equivalent. **Ketose** sugars having a ketone function or an acetal equivalent.				
Reactivity	**Reducing** sugars oxidized by Tollens' reagent (or Benedict's or Fehling's reagents). **Non-reducing** sugars not oxidized by Tollens' or other reagents.				

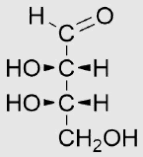
EXERCISES

QUESTIONS

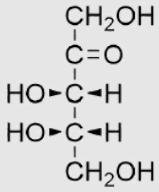
Q25.1.1

Classify each of the following sugars.

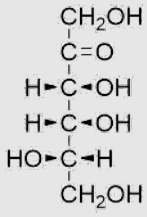
(a)



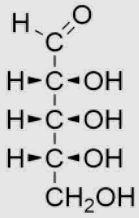
(b)



(c)



(d)



SOLUTIONS

S25.1.1

(a) Aldoterose

(b) Ketopentose

(c) Ketohexose

(d) Aldopentose

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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24.3: FISCHER PROJECTIONS

Objectives

After completing this section, you should be able to

1. draw the Fischer projection of a monosaccharide, given its wedge-and-broken-line structure or a molecular model.
2. draw the wedge-and-broken-line structure of a monosaccharide, given its Fischer projection or a molecular model.
3. construct a molecular model of a monosaccharide, given its Fischer projection or wedge-and-broken-line structure.

Key Terms

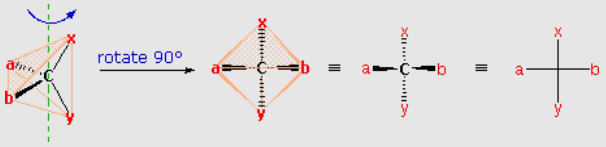
Make certain that you can define, and use in context, the key term below.

- Fischer projection

Study Notes

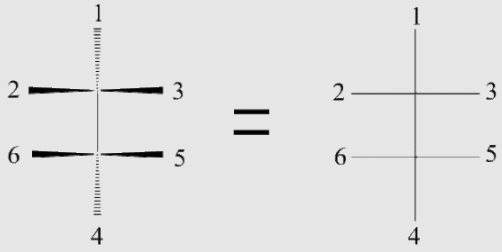
When studying this section, use your molecular model set to assist you in visualizing the structures of the compounds that are discussed. It is important that you be able to determine whether two apparently different Fischer projections represent two different structures or one single structure. Often the simplest way to check is to construct a molecular model corresponding to each projection formula, and then compare the two models.

The problem of drawing three-dimensional configurations on a two-dimensional surface, such as a piece of paper, has been a long-standing concern of chemists. The wedge and hatched line notations we have been using are effective, but can be troublesome when applied to compounds having many chiral centers. As part of his Nobel Prize-winning research on carbohydrates, the great German chemist Emil Fischer, devised a simple notation that is still widely used. In a Fischer projection drawing, the four bonds to a chiral carbon make a cross with the carbon atom at the intersection of the horizontal and vertical lines. The two horizontal bonds are directed toward the viewer (forward of the stereogenic carbon). The two vertical bonds are directed behind the central carbon (away from the viewer). Since this is not the usual way in which we have viewed such structures, the following diagram shows how a stereogenic carbon positioned in the common two-bonds-in-a-plane orientation (x–C–y define the reference plane) is rotated into the Fischer projection orientation (the far right formula). When writing Fischer projection formulas it is important to remember these conventions. Since the vertical bonds extend away from the viewer and the horizontal bonds toward the viewer, a Fischer structure may only be turned by 180º within the plane, thus maintaining this relationship. **The structure must not be flipped over or rotated by 90º**.

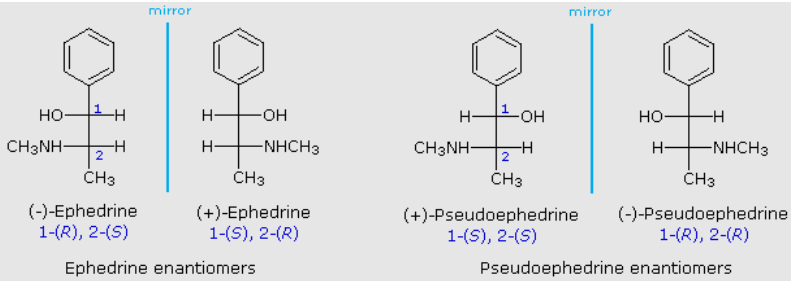


In the above diagram, if x = CO_2H, y = CH_3, a = H & b = OH, the resulting formula describes (*R*)-(–)-lactic acid. The mirror-image formula, where x = CO_2H, y = CH_3, a = OH & b = H, would, of course, represent (*S*)-(+)-lactic acid.

The Fischer Projection consists of both horizontal and vertical lines, where the horizontal lines represent the atoms that are pointed toward the viewer while the vertical line represents atoms that are pointed away from the viewer. The point of intersection between the horizontal and vertical lines represents the central carbon.

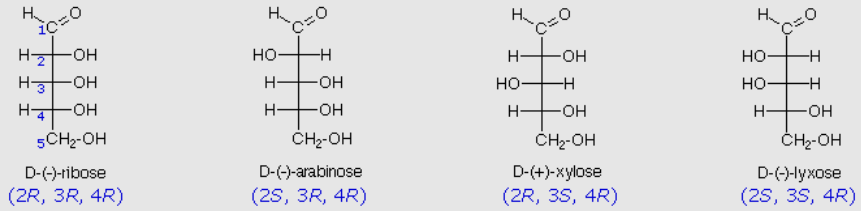


Using the Fischer projection notation, the stereoisomers of 2-methylamino-1-phenylpropanol are drawn in the following manner. Note that it is customary to set the longest carbon chain as the vertical bond assembly.



The usefulness of this notation to Fischer, in his carbohydrate studies, is evident in the following diagram. There are eight stereoisomers of 2,3,4,5-tetrahydroxypentanal, a group of compounds referred to as the aldopentoses. Since there are three chiral centers in this constitution, we should expect a maximum of 2^3 stereoisomers. These eight stereoisomers consist of four sets of enantiomers. If the configuration at C-4 is kept constant (*R* in the examples shown here), the four stereoisomers that result will be **diastereomers**. Fischer formulas for these isomers, which Fischer designated as the "D"-family, are shown in the diagram. Each of these compounds has an enantiomer, which is a member of the "L"-family so, as expected, there are eight stereoisomers in all. Determining whether a chiral carbon is R or S may seem difficult when using Fischer projections, but it is actually quite simple. If the lowest priority group (often a hydrogen) is on a vertical bond, the configuration is given directly from the relative positions of the three higher-ranked substituents. If the lowest priority group is on a horizontal bond, the positions of the remaining groups give the wrong answer (you are in looking at the configuration from the wrong side), so you simply reverse it.

Four Diastereomeric $C_5H_{10}O_5$ Aldopentoses



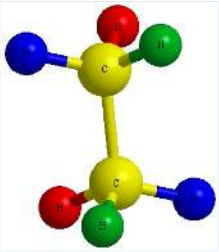
The aldopentose structures drawn above are all diastereomers. A more selective term, **epimer**, is used to designate diastereomers that differ in configuration at only one chiral center. Thus, ribose and arabinose are epimers at C-2, and arabinose and lyxose are epimers at C-3. However, arabinose and xylose are not epimers, since their configurations differ at both C-2 and C-3.

HOW TO MAKE FISCHER PROJECTIONS

To make a Fischer Projection, it is easier to show through examples than through words. Lets start with the first example, turning a 3D structure of ethane into a 2D Fischer Projection.

Example 25.2.1

Start by mentally converting a 3D structure into a Dashed-Wedged Line Structure. Remember, the atoms that are pointed toward the viewer would be designated with a wedged lines and the ones pointed away from the viewer are designated with dashed lines.



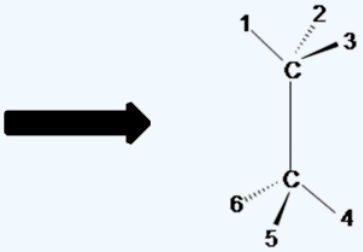


Figure B

Notice the red balls (atoms) in Figure A above are pointed away from the screen. These atoms will be designated with dashed lines like those in Figure B by number 2 and 6. The green balls (atoms) are pointed toward the screen. These atoms will be designated with wedged lines like those in Figure B by number 3 and 5. The blue atoms are in the plane of the screen so they are designated with straight lines.

Now that we have our Dashed- Wedged Line Structure, we can convert it to a Fischer Projection. However, before we can convert this Dashed-Wedged Line Structure into a Fischer Projection, we must first convert it to a "flat" Dashed-Wedged Line Structure. Then from there we can draw our Fischer Projection. Lets start with a more simpler example. Instead of using the ethane shown in Figure A and B, we will start with a methane. The reason being is that it allows us to only focus on one central carbon, which make things a little bit easier.

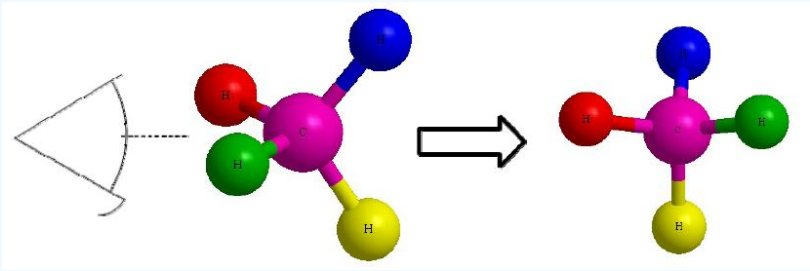
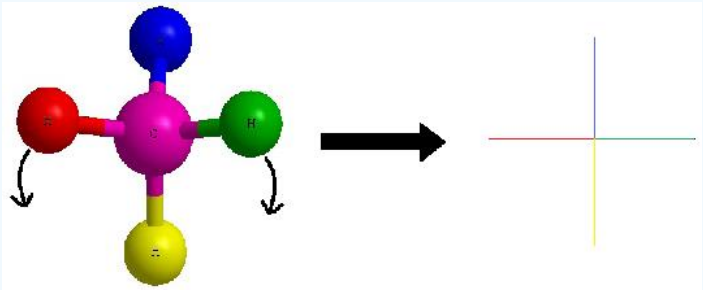


Figure D

Lets start with this 3D image and work our way to a dashed-wedged image. Start by imagining yourself looking directly at the central carbon from the left side as shown in Figure C. It should look something like Figure D. Now take this Figure D and flatten it out on the surface of the paper and you should get an image of a cross.



As a reminder, the horizontal line represents atoms that are coming out of the paper and the vertical line represents atoms that are going into the paper. The cross image to the right of the arrow is a Fischer projection.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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24.4: D AND L SUGARS

Objectives

After completing this section, you should be able to

1. identify a specific enantioner of a monosaccharide as being D or L, given its Fischer projection.
2. identify the limitations of the D, L system of nomenclature for carbohydrates.
3. assign an *R* or *S* configuration to each of the chiral carbon atoms present in a monosaccharide, given its Fischer projection.
4. draw the Fischer projection formula for a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.
5. construct a molecular model of a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.

Key Terms

Make certain that you can define, and use in context, the key terms below.

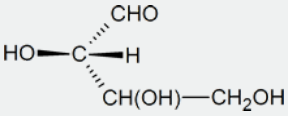
- D sugar
- L sugar

Study Notes

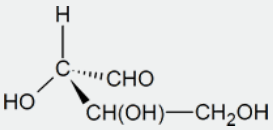
If you find that you have forgotten the meanings of terms such as dextrorotatory and polarimeter, refer back to Section 5.3 in which the fundamentals of optical activity were introduced.

How would you set about the task of deciding whether each chiral carbon has an *R* or an *S* configuration? True, you could use molecular models, but suppose that a model set had not been available—what would you have done then?

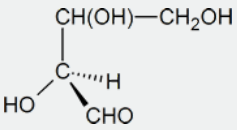
One approach is to focus on the carbon atom of interest and sketch a three-dimensional representation of the configuration around that atom, remembering the convention used in Fischer projections: vertical lines represent bonds going into the page, and horizontal lines represent bonds coming out of the page. Thus, the configuration around carbon atom 2 in structure a can be represented as follows:



In your mind, you should be able to imagine how this molecule would look if it was rotated so that the bonds that are shown as coming out of the page are now in the plane of the page. [One possible way of doing this is to try and imagine how the molecule would look if it was viewed from a point at the bottom of the page.] What you should see in your mind is a representation similar to the one drawn below.



To determine whether the configuration about the central carbon atom is *R* or *S*, we must rotate the molecule so that the group with the lowest priority (H), is directed away from the viewer. This effect can be achieved by keeping the hydroxyl group in its present position and moving each of the other three groups one position clockwise.



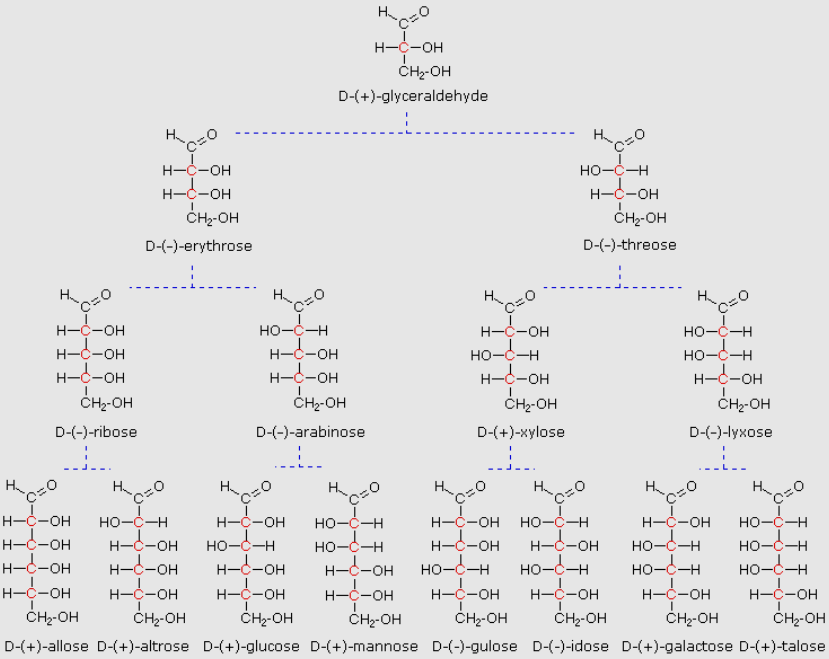
The Cahn-Ingold-Prelog order of priority for the three remaining groups is OH > CHO > $CH(OH)CH_2OH$; thus, we see that we could trace out a counterclockwise path going from the highest-priority group to the second- and third-highest, and we conclude that the central carbon atom has an *S* configuration.

THE CONFIGURATION OF GLUCOSE

The four chiral centers in glucose indicate there may be as many as sixteen (2^4) stereoisomers having this constitution. These would exist as eight diastereomeric pairs of enantiomers, and the initial challenge was to determine which of the eight corresponded to glucose. This challenge was accepted and met in 1891 by the German chemist Emil Fischer. His successful negotiation of the stereochemical maze presented by the aldohexoses was a logical tour de force, and it is fitting that he received the 1902 Nobel Prize for chemistry for this accomplishment. One of the first tasks faced by Fischer was to devise a method of representing the configuration of each chiral center in an unambiguous manner. To this end, he invented a simple technique for drawing chains of chiral centers, that we now call the Fischer projection formula. Click on this link for a review.

At the time Fischer undertook the glucose project it was not possible to establish the **absolute configuration** of an enantiomer. Consequently, Fischer made an arbitrary choice for (+)-glucose and established a network of related aldose configurations that he called the **D**-family. The mirror images of these configurations were then designated the **L**-family of aldoses. To illustrate using present day knowledge, Fischer projection formulas and names for the D-aldose family (three to six-carbon atoms) are shown below, with the asymmetric carbon atoms (chiral centers) colored red. The last chiral center in an aldose chain (farthest from the aldehyde group) was chosen by Fischer as the D / L designator site. If the hydroxyl group in the projection formula pointed to the right, it was defined as a member of the D-family. A left directed hydroxyl group (the mirror image) then represented the L-family. Fischer's initial assignment of the D-configuration had a 50:50 chance of being right, but all his subsequent conclusions concerning the relative configurations of various aldoses were soundly based. In 1951 x-ray fluorescence studies of (+)-tartaric acid, carried out in the Netherlands by Johannes Martin Bijvoet, proved that Fischer's choice was correct.

It is important to recognize that the sign of a compound's specific rotation (an experimental number) does not correlate with its configuration (D or L). It is a simple matter to measure an optical rotation with a polarimeter. Determining an absolute configuration usually requires chemical interconversion with known compounds by stereospecific reaction paths.



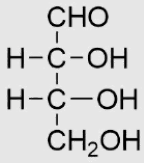
EXERCISES

QUESTIONS

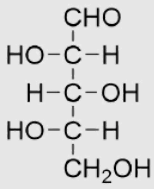
Q25.3.1

Assign R and S for each chiral center and determine whether each sugar is a D or L sugar.

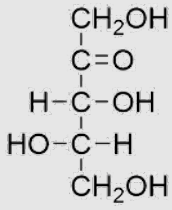
(a)



(b)



(c)



SOLUTIONS

S25.3.1

(a) From top to bottom, 2R, 3R, and it is a D sugar.

(b) From top to bottom, 2S, 3R, 4S, and it is an L sugar.

(c) From to to bottom, 3R, 4S, and it is an L sugar.

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- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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24.5: CONFIGURATION OF ALDOSES

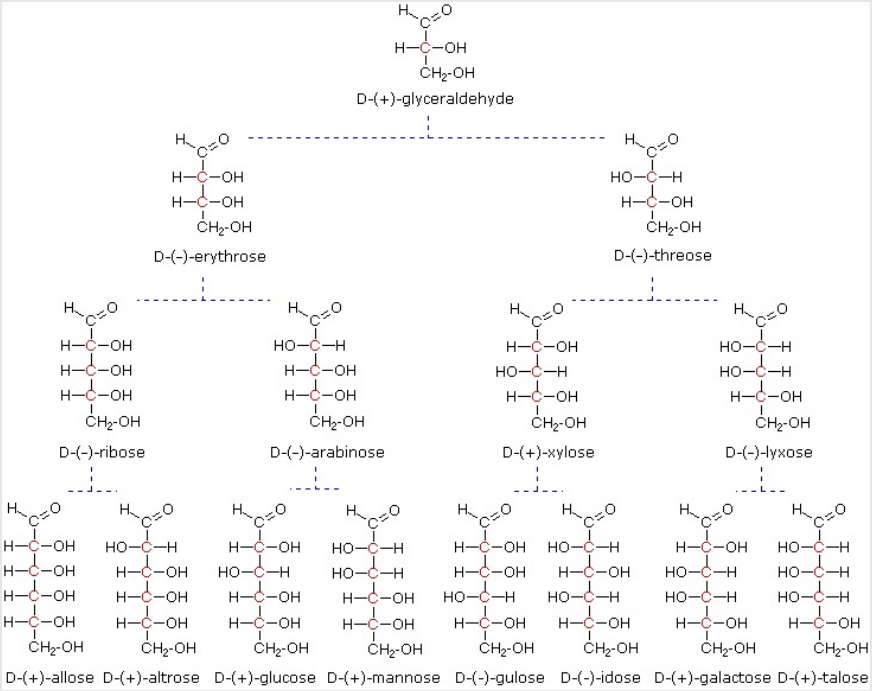
Objectives

After completing this section, you should be able to

1. draw the structures of all possible aldotetroses, aldopentoses, and aldohexoses, without necessarily being able to assign names to the individual compounds.
2. draw the Fischer projection of D-glyceraldehyde, D-ribose and D-glucose from memory.

The four chiral centers in glucose indicate there may be as many as sixteen (2^4) stereoisomers having this constitution. These would exist as eight diastereomeric pairs of enantiomers, and the initial challenge was to determine which of the eight corresponded to glucose. This challenge was accepted and met in 1891 by the German chemist Emil Fischer. His successful negotiation of the stereochemical maze presented by the aldohexoses was a logical tour de force, and it is fitting that he received the 1902 Nobel Prize for chemistry for this accomplishment. One of the first tasks faced by Fischer was to devise a method of representing the configuration of each chiral center in an unambiguous manner. To this end, he invented a simple technique for drawing chains of chiral centers, that we now call the Fischer projection formula.

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It is important to recognize that the sign of a compound's specific rotation (an experimental number) does not correlate with its configuration (D or L). It is a simple matter to measure an optical rotation with a polarimeter. Determining an absolute configuration usually requires chemical interconversion with known compounds by stereospecific reaction paths.

EXERCISES

QUESTIONS

Q25.4.1

Draw the following sugars.

(a) D-Xylose

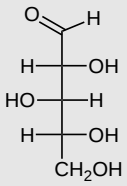
(b) D-Galactose

(c) D-Allose

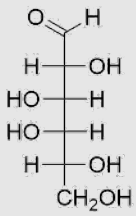
SOLUTIONS

S25.4.1

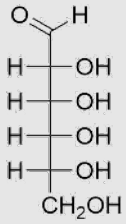
(a)



(b)



(c)



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

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24.6: CYCLIC STRUCTURES OF MONOSACCHARIDES

Objectives

After completing this section, you should be able to

1. determine whether a given monosaccharide will exist as a pyranose or furanose.
2. draw the cyclic pyranose form of a monosaccharide, given its Fischer projection.
3. draw the Fischer projection of a monosaccharide, given its cyclic pyranose form.
4. draw, from memory, the cyclic pyranose form of D-glucose.
5. determine whether a given cyclic pyranose form represents the D or L form of the monosaccharide concerned.
6. describe the phenomenon known as mutarotation.
7. explain, through the use of chemical equations, exactly what happens at the molecular level during the mutarotation process.

Key Terms

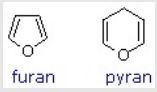
Make certain that you can define, and use in context, the key terms below.

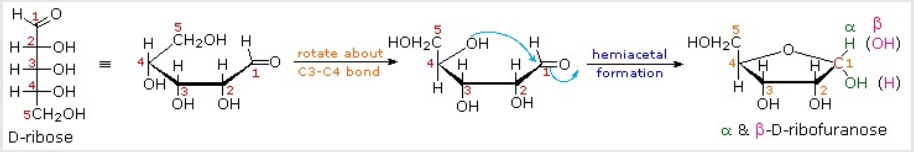
- alpha anomer
- anomer
- anomeric centre
- beta anomer
- furanose
- mutarotation
- pyranose

Study Notes

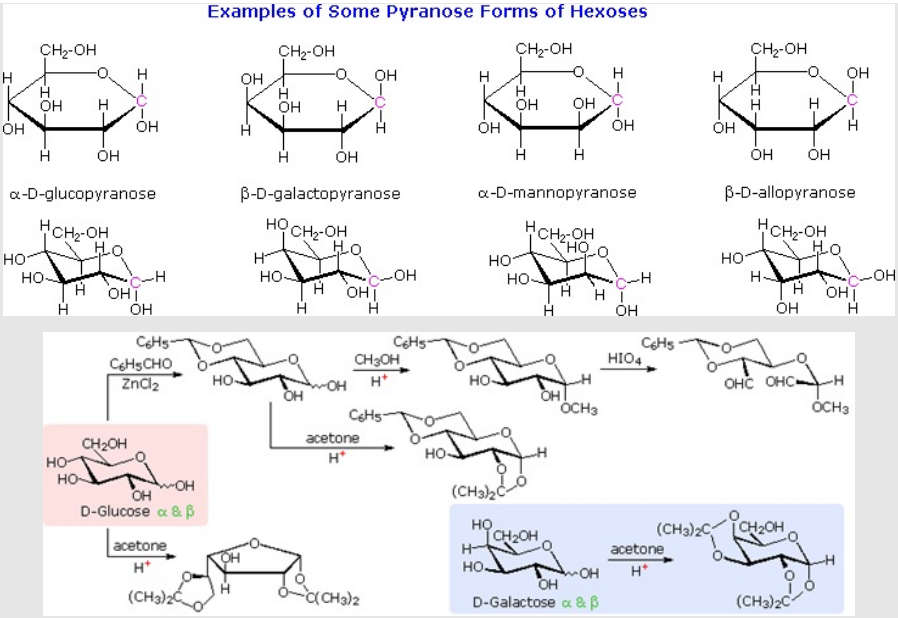
If necessary, before you attempt to study this section, review the formation of hemiacetals discussed in Section 19.10.

As noted above, the preferred structural form of many monosaccharides may be that of a cyclic hemiacetal. Five and six-membered rings are favored over other ring sizes because of their low angle and eclipsing strain. Cyclic structures of this kind are termed furanose (five-membered) or pyranose (six-membered), reflecting the ring size relationship to the common heterocyclic compounds furan and pyran shown on the right. Ribose, an important aldopentose, commonly adopts a furanose structure, as shown in the following illustration. By convention for the D-family, the five-membered furanose ring is drawn in an edgewise projection with the ring oxygen positioned away from the viewer. The anomeric carbon atom (colored red here) is placed on the right. The upper bond to this carbon is defined as beta, the lower bond then is alpha.





The cyclic pyranose forms of various monosaccharides are often drawn in a flat projection known as a Haworth formula, after the British chemist, Norman Haworth. As with the furanose ring, the anomeric carbon is placed on the right with the ring oxygen to the back of the edgewise view. In the D-family, the alpha and beta bonds have the same orientation defined for the furanose ring (beta is up & alpha is down). These Haworth formulas are convenient for displaying stereochemical relationships, but do not represent the true shape of the molecules. We know that these molecules are actually puckered in a fashion we call a chair conformation. Examples of four typical pyranose structures are shown below, both as Haworth projections and as the more representative chair conformers. The anomeric carbons are colored red.



The size of the cyclic hemiacetal ring adopted by a given sugar is not constant, but may vary with substituents and other structural features. Aldolhexoses usually form pyranose rings and their pentose homologs tend to prefer the furanose form, but there are many counter examples. The formation of acetal derivatives illustrates how subtle changes may alter this selectivity. A pyranose structure for D-glucose is drawn in the rose-shaded box on the left. Acetal derivatives have been prepared by acid-catalyzed reactions with benzaldehyde and acetone. As a rule, benzaldehyde forms six-membered cyclic acetals, whereas acetone prefers to form five-membered acetals. The top equation shows the formation and some reactions of the 4,6-O-benzylidene acetal, a commonly employed protective group. A methyl glycoside derivative of this compound (see below) leaves the C-2 and C-3 hydroxyl groups exposed to reactions such as the periodic acid cleavage, shown as the last step. The formation of an isopropylidene acetal at C-1 and C-2, center structure, leaves the C-3 hydroxyl as the only unprotected function. Selective oxidation to a ketone is then possible. Finally, direct di-O-isopropylidene derivatization of glucose by reaction with excess acetone results in a change to a furanose structure in which the C-3 hydroxyl is again unprotected. However, the same reaction with D-galactose, shown in the blue-shaded box, produces a pyranose product in which the C-6 hydroxyl is unprotected. Both derivatives do not react with Tollens' reagent. This difference in behavior is attributed to the cis-orientation of the C-3 and C-4 hydroxyl groups in galactose, which permits formation of a less strained five-membered cyclic acetal, compared with the trans-C-3 and C-4 hydroxyl groups in glucose. Derivatizations of this kind permit selective reactions to be conducted at different locations in these highly functionalized molecules.

ANOMERS OF SIMPLE SUGARS: MUTAROTATION OF GLUCOSE

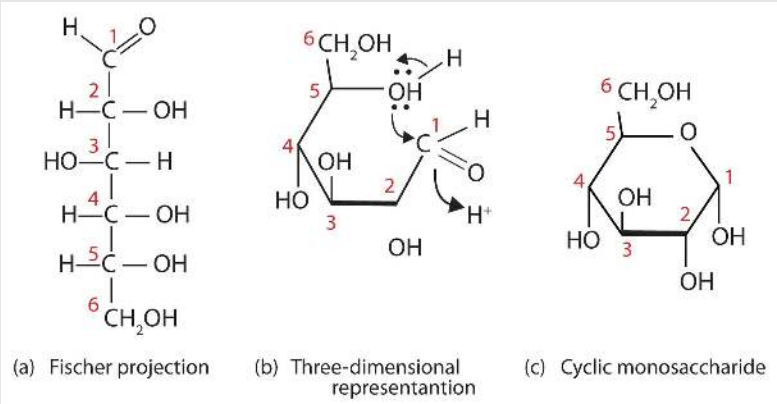


Figure 1: Cyclization of D-Glucose. D-Glucose can be represented with a Fischer projection (a) or three dimensionally (b). By reacting the OH group on the fifth carbon atom with the aldehyde group, the cyclic monosaccharide (c) is produced.

When a straight-chain monosaccharide, such as any of the structures shown in Figure 1, forms a cyclic structure, the carbonyl oxygen atom may be pushed either up or down, giving rise to two stereoisomers, as shown in Figure 2. The structure shown on the left side of Figure 2, with the OH group on the first carbon atom projected downward, represent what is called the *alpha (α) form*. The structures on the right side, with the OH group on the first carbon atom pointed upward, is the *beta (β) form*. These two stereoisomers of a cyclic

monosaccharide are known as anomers; they differ in structure around the anomeric carbon—that is, the carbon atom that was the carbonyl carbon atom in the straight-chain form.

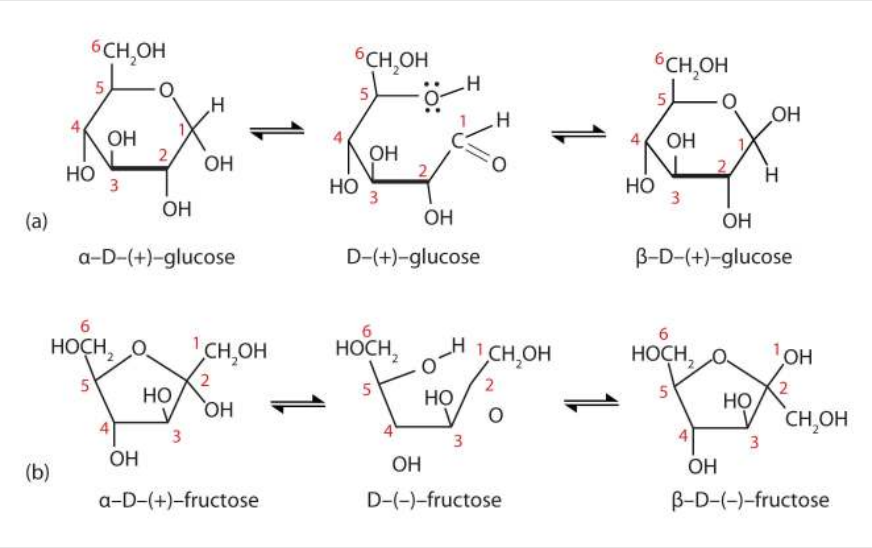


Figure 2: Monosaccharides. In an aqueous solution, monosaccharides exist as an equilibrium mixture of three forms. The interconversion between the forms is known as *mutarotation*, which is shown for D-glucose (a) and D-fructose (b).

It is possible to obtain a sample of crystalline glucose in which all the molecules have the α structure or all have the β structure. The α form melts at 146°C and has a specific rotation of +112°, while the β form melts at 150°C and has a specific rotation of +18.7°. When the sample is dissolved in water, however, a mixture is soon produced containing both anomers as well as the straight-chain form, in dynamic equilibrium (part (a) of Figure 2). You can start with a pure crystalline sample of glucose consisting entirely of either anomer, but as soon as the molecules dissolve in water, they open to form the carbonyl group and then reclose to form either the α or the β anomer. The opening and closing repeats continuously in an ongoing interconversion between anomeric forms and is referred to as mutarotation (Latin *mutare*, meaning "to change"). At equilibrium, the mixture consists of about 36% α-D-glucose, 64% β-D-glucose, and less than 0.02% of the open-chain aldehyde form. The observed rotation of this solution is +52.7°.

Even though only a small percentage of the molecules are in the open-chain aldehyde form at any time, the solution will nevertheless exhibit the characteristic reactions of an aldehyde. As the small amount of free aldehyde is used up in a reaction, there is a shift in the equilibrium to yield more aldehyde. Thus, *all* the molecules may eventually react, even though very little free aldehyde is present at a time.

Commonly, (e.g., in Figures 1 and 2) the cyclic forms of sugars are depicted using a convention first suggested by Walter N. Haworth, an English chemist. The molecules are drawn as planar hexagons with a darkened edge representing the side facing toward the viewer. The structure is simplified to show only the functional groups attached to the carbon atoms. Any group written to the right in a Fischer projection appears below the plane of the ring in a Haworth projection, and any group written to the left in a Fischer projection appears above the plane in a Haworth projection.

The difference between the α and the β forms of sugars may seem trivial, but such structural differences are often crucial in biochemical reactions. This explains why we can get energy from the starch in potatoes and other plants but not from cellulose, even though both starch and cellulose are polysaccharides composed of glucose molecules linked together.

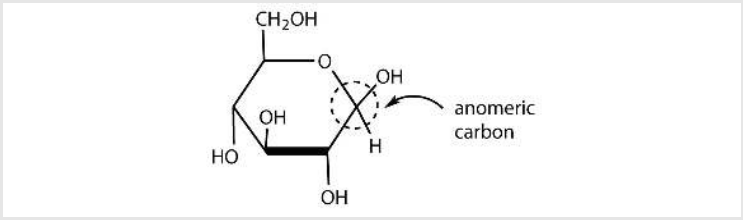
SUMMARY

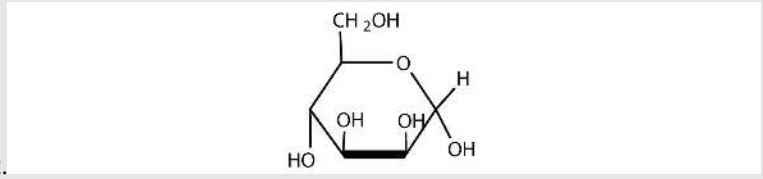
Monosaccharides that contain five or more carbons atoms form cyclic structures in aqueous solution. Two cyclic stereoisomers can form from each straight-chain monosaccharide; these are known as anomers. In an aqueous solution, an equilibrium mixture forms between the two anomers and the straight-chain structure of a monosaccharide in a process known as mutarotation.

EXERCISES

1. Draw the cyclic structure for β-D-glucose. Identify the anomeric carbon.
2. Given that the aldohexose D-mannose differs from D-glucose only in the configuration at the second carbon atom, draw the cyclic structure for α-D-mannose.

ANSWERS

1. 

2. 

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- *The Basics of General, Organic, and Biological Chemistry* by David W. Ball, John W. Hill, and Rhonda J. Scott.

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24.7: REACTIONS OF MONOSACCHARIDES

Objectives

After completing this section, you should be able to

1. a. write equations to illustrate that the hydroxyl groups of carbohydrates can react to form esters and ethers.
   b. identify the product formed when a given monosaccharide is reacted with acetic anhydride or with silver oxide and an alkyl halide.
   c. identify the reagents required to convert a given monosaccharide to its ester or ether.
2. a. write an equation to show how a monosaccharide can be converted to a glycoside using an alcohol and an acid catalyst.
   b. identify the product formed when a given monosaccharide is treated with an alcohol and an acid catalyst.
   c. write a detailed mechanism for the formation of a glycoside by the reaction of the cyclic form of a monosaccharide with an alcohol and an acid catalyst.
3. identify the ester formed by phosphorylation in biologically important compounds.
4. a. identify the product formed when a given monosaccharide is reduced with sodium borohydride.
   b. identify the monosaccharide which should be reduced in order to form a given polyalcohol (alditol).
5. a. explain that a sugar with an aldehyde or hemiacetal can be oxidized to the corresponding carboxylic acid (also known as aldonic acid). **Note:** The sugar is able to reduce an oxidizing agent, and is thus called a reducing sugar. Tests for reducing sugars include the use of Tollens' reagent, Fehling's reagent and Benedict's reagent.
   b. explain why certain ketoses, such as fructose, behave as reducing sugars even though they do not contain an aldehyde group.
   c. identify warm HNO_3 as the reagent needed to form dicarboxylic acid (an aldaric acid).
6. a. describe the chain-lengthening effect of the Kiliani-Fischer synthesis.
   b. predict the product that would be produced by the Kiliani-Fischer synthesis of a given aldose.
   c. identify the aldose that would yield a given product following Kiliani-Fischer synthesis.
7. a. describe the chain-shortening effect of the Wohl degradation.
   b. predict the product that would be produced by the Wohl degradation of a given aldose.
   c. identify the aldose or aldoses that would yield a given product following Wohl degradation.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- aldaric acid
- aldonic acid
- alditol
- aldonic acid
- glycoside
- Kiliani-Fischer synthesis
- neighbouring group effect
- reducing sugar
- Wohl degradation

Study Notes

While several reactions are covered in this section, keep in mind that you have encountered them in previous sections. The active functional groups on monosaccharides are essentially carbonyls and hydroxyls. Although they now are a part of much larger molecules, their chemistry should be familiar.

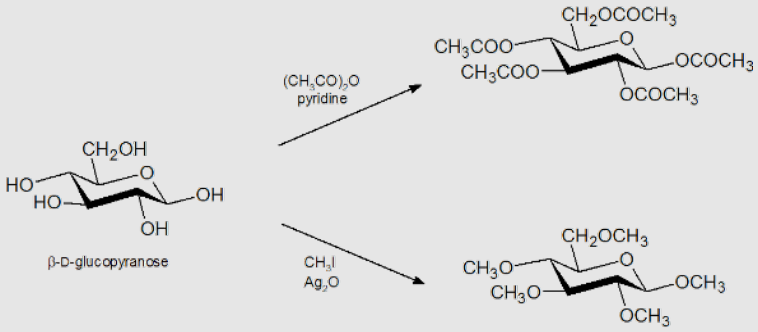
The formation of esters and ethers is quite straightforward and should not require further clarification.

Note that glycosides are in fact acetals, and that glycoside formation is therefore analogous to acetal formation. To refresh your memory about the chemistry of acetals, quickly review Section 19.10

ESTER AND ETHER FORMATION

The -OH groups on a monosaccharide can be readily converted to esters and ethers. Esterfication can be done with an acid chloride (Section 21.4) or acid anhydride (Section 21.5), while treatment with an alkyl halide by a Williamson ether synthesis (Section 18.2)

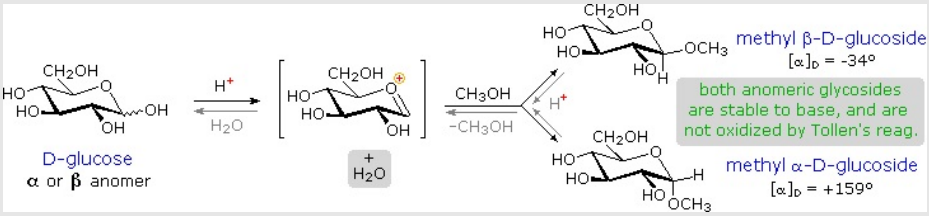
leads to the ether.

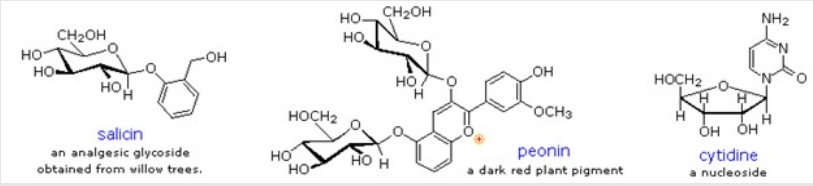


GLYCOSIDE FORMATION

Acetal derivatives formed when a monosaccharide reacts with an alcohol in the presence of an acid catalyst are called glycosides. This reaction is illustrated for glucose and methanol in the diagram below. In naming of glycosides, the "ose" suffix of the sugar name is replaced by "oside", and the alcohol group name is placed first. As is generally true for most acetals, glycoside formation involves the loss of an equivalent of water. The diether product is stable to base and alkaline oxidants such as Tollen's reagent. Since acid-catalyzed aldolization is reversible, glycosides may be hydrolyzed back to their alcohol and sugar components by aqueous acid.

The anomeric methyl glucosides are formed in an equilibrium ratio of 66% alpha to 34% beta. From the structures in the previous diagram, we see that pyranose rings prefer chair conformations in which the largest number of substituents are equatorial. In the case of glucose, the substituents on the beta-anomer are all equatorial, whereas the C-1 substituent in the alpha-anomer changes to axial. Since substituents on cyclohexane rings prefer an equatorial location over axial (methoxycyclohexane is 75% equatorial), the preference for alpha-glycopyranoside formation is unexpected, and is referred to as the anomeric effect.





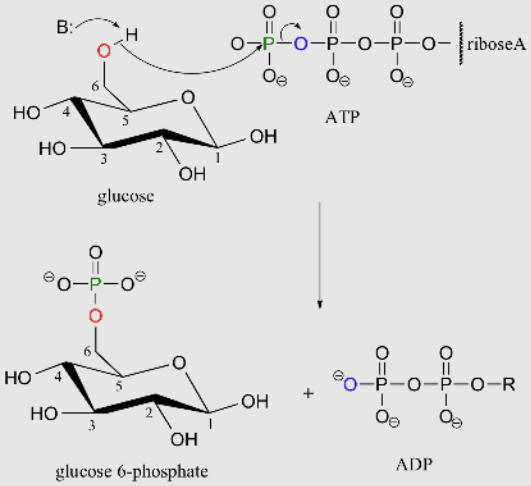
Glycosides abound in biological systems. By attaching a sugar moiety to a lipid or benzenoid structure, the solubility and other properties of the compound may be changed substantially. Because of the important modifying influence of such derivatization, numerous enzyme systems, known as glycosidases, have evolved for the attachment and removal of sugars from alcohols, phenols and amines. Chemists refer to the sugar component of natural glycosides as the glycon and the alcohol component as the aglycon.

Two examples of naturally occurring glycosides and one example of an amino derivative are displayed above. Salicin, one of the oldest herbal remedies known, was the model for the synthetic analgesic aspirin. A large class of hydroxylated, aromatic oxonium cations called anthocyanins provide the red, purple and blue colors of many flowers, fruits and some vegetables. Peonin is one example of this class of natural pigments, which exhibit a pronounced pH color dependence. The oxonium moiety is only stable in acidic environments, and the color changes or disappears when base is added. The complex changes that occur when wine is fermented and stored are in part associated with glycosides of anthocyanins. Finally, amino derivatives of ribose, such as cytidine play important roles in biological phosphorylating agents, coenzymes and information transport and storage materials.

BIOLOGICAL ESTER FORMATION: PHOSPHORYLATION

Recall that almost all biomolecules are charged species, which 1) keeps them water soluble, and 2) prevents them from diffusing across lipid bilayer membranes. Although many biomolecules are ionized by virtue of negatively charged carboxylate and positively charged amino groups, the most common ionic group in biologically important organic compounds is phosphate - thus the phosphorylation of alcohol groups is a critical metabolic step. In alcohol phosphorylations, ATP is almost always the phosphate donor, and the mechanism

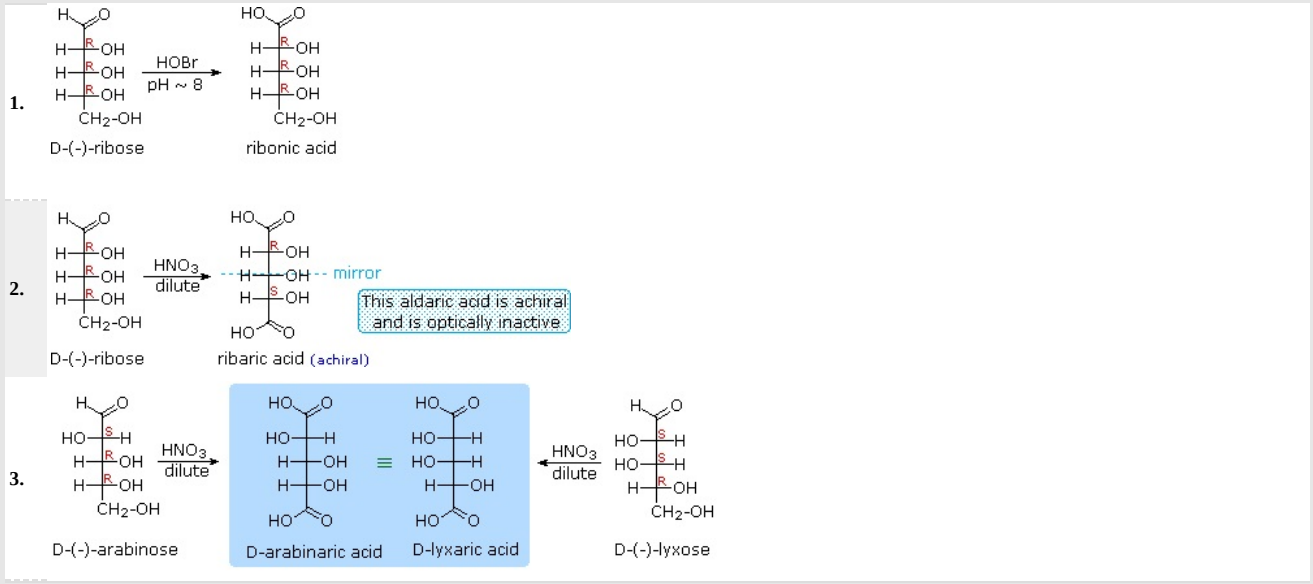
is very consistent: the alcohol oxygen acts as a nucleophile, attacking the gamma-phosphorus of ATP and expelling ADP (look again, for example, at the glucose kinase reaction that we first saw in section 10.1D).



OXIDATION

As noted above, sugars may be classified as **reducing** or **non-reducing** based on their reactivity with **Tollens'**, **Benedict's** or **Fehling's** reagents. If a sugar is oxidized by these reagents it is called reducing, since the oxidant ($Ag^{(+)}$ or $Cu^{(+2)}$) is reduced in the reaction, as evidenced by formation of a silver mirror or precipitation of cuprous oxide. The Tollens' test is commonly used to detect aldehyde functions; and because of the facile interconversion of ketoses and aldoses under the basic conditions of this test, ketoses such as fructose also react and are classified as reducing sugars.

When the aldehyde function of an aldose is oxidized to a carboxylic acid the product is called an **aldonic acid**. Because of the 2º hydroxyl functions that are also present in these compounds, a mild oxidizing agent such as hypobromite must be used for this conversion (equation 1). If both ends of an aldose chain are oxidized to carboxylic acids the product is called an aldaric acid. By converting an aldose to its corresponding aldaric acid derivative, the ends of the chain become identical (this could also be accomplished by reducing the aldehyde to CH_2OH, as noted below). Such an operation will disclose any latent symmetry in the remaining molecule. Thus, ribose, xylose, allose and galactose yield achiral aldaric acids which are, of course, not optically active. The ribose oxidation is shown in equation 2 below.



Other aldose sugars may give identical chiral aldaric acid products, implying a unique configurational relationship. The examples of arabinose and lyxose shown in equation 3 above illustrate this result. Remember, a Fischer projection formula may be rotated by 180º in the plane of projection without changing its configuration.

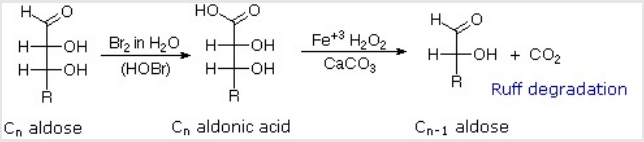
REDUCTION

Sodium borohydride reduction of an aldose makes the ends of the resulting **alditol** chain identical, $HOCH_2(CHOH)_nCH_2OH$, thereby accomplishing the same configurational change produced by oxidation to an aldaric acid. Thus, allitol and galactitol from reduction of allose and galactose are achiral, and altrose and talose are reduced to the same chiral alditol. A summary of these redox reactions, and derivative nomenclature is given in the following table.

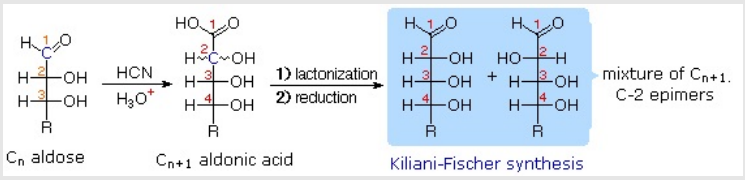
Table: Derivatives of $HOCH_2(CHOH)_nCHO$

$HOBr$ Oxidation	→	$HOCH_2(CHOH)_nCO_2H$ an Aldonic Acid
HNO_3 Oxidation	→	$H_2OC(CHOH)_nCO_2H$ an Aldaric Acid
$NaBH_4$ Reduction	→	$HOCH_2(CHOH)_nCH_2OH$ an Alditol

CHAIN SHORTENING AND LENGTHENING



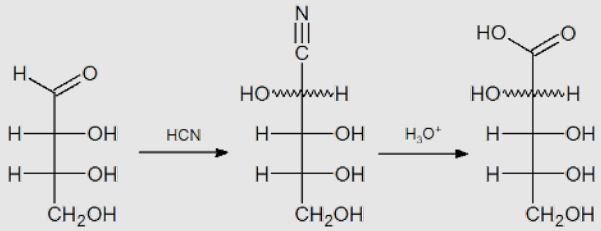
1. Ruff Degradation



2. Kiliani-Fischer Synthesis

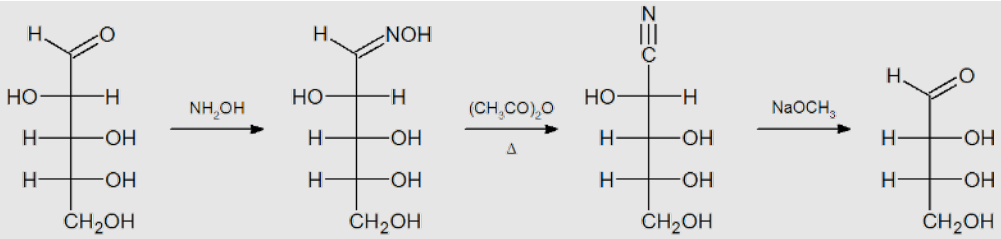
These two procedures permit an aldose of a given size to be related to homologous smaller and larger aldoses. The importance of these relationships may be seen in the array of aldose structures presented earlier, where the structural connections are given by the dashed blue lines. Thus Ruff degradation of the pentose arabinose gives the tetrose erythrose. Working in the opposite direction, a Kiliani-Fischer synthesis applied to arabinose gives a mixture of glucose and mannose. An alternative chain shortening procedure known as the Wohl degradation is essentially the reverse of the Kiliani-Fischer synthesis.

Note that in the Kiliani-Fischer synthesis the first step is to generate a cyanohydrin intermediate, which is then has its nitrile group hydrolyzed to the carboxylic acid. From there the cyclic ester (lactone) is formed and reduced to the final products (epimers).



WOHL DEGRADATION

The ability to shorten (degrade) an aldose chain by one carbon was an important tool in the structure elucidation of carbohydrates. This was commonly accomplished by the Ruff procedure. An interesting alternative technique, known as the **Wohl degradation** has also been used. The following equation illustrates the application of this procedure to the aldopentose, arabinose. Based on your knowledge of carbonyl chemistry, and considering that the Wohl degradation is in essence the reverse of the Kiliani-Fischer synthesis.



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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24.8: DISACCHARIDES AND GLYCOSIDIC BONDS

Objectives

After completing this section, you should be able to

1. identify disaccharides as compounds consisting of two monosaccharide units joined by a glycoside link between the C1 of one sugar and one of the hydroxyl groups of a second sugar.
2. identify the two monosaccharide units in a given disaccharide.
3. identify the type of glycoside link (e.g., 1,4′-β) present in a given disaccharide structure.
4. draw the structure of a specific disaccharide, given the structure of the monosaccharide units and the type of glycoside link involved.

   Note: If α- or β-D-glucose were one of the monosaccharide units, its structure would not be provided.
5. identify the structural feature that determines whether or not a given disaccharide behaves as a reducing sugar and undergoes mutarotation, and write equations to illustrate these phenomena.
6. identify the products formed from the hydrolysis of a given disaccharide.

Key Terms

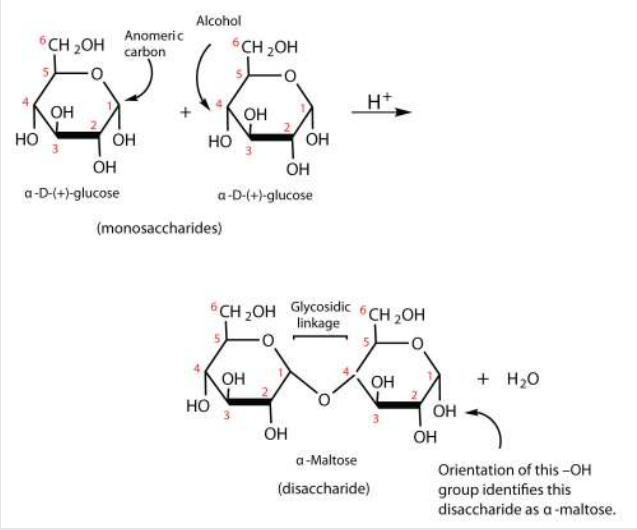
Make certain that you can define, and use in context, the key terms below.

- 1,4′ link
- disaccharide (see Section 25.1)
- invert sugar

Study Notes

Notice that most of the disaccharides discussed in this section contain one unit of D-glucose. You are not expected to remember the detailed structures of maltose, lactose and sucrose. Similarly, we do not expect you to remember the systematic names of these substances.

Previously, you learned that monosaccharides can form cyclic structures by the reaction of the carbonyl group with an OH group. These cyclic molecules can in turn react with another alcohol. Disaccharides ($C_{12}H_{22}O_{11}$) are sugars composed of two monosaccharide units that are joined by a carbon–oxygen-carbon linkage known as a glycosidic linkage. This linkage is formed from the reaction of the anomeric carbon of one cyclic monosaccharide with the OH group of a second monosaccharide.



The disaccharides differ from one another in their monosaccharide constituents and in the specific type of glycosidic linkage connecting them. There are three common disaccharides: maltose, lactose, and sucrose. All three are white crystalline solids at room temperature and are soluble in water. We'll consider each sugar in more detail.

MALTOSE

Maltose occurs to a limited extent in sprouting grain. It is formed most often by the partial hydrolysis of starch and glycogen. In the manufacture of beer, maltose is liberated by the action of malt (germinating barley) on starch; for this reason, it is often referred to as *malt sugar*. Maltose is about 30% as sweet as sucrose. The human body is unable to metabolize maltose or any other disaccharide directly from the diet because the molecules are too large to pass through the cell membranes of the intestinal wall. Therefore, an ingested disaccharide must first be broken down by hydrolysis into its two constituent monosaccharide units. In the body, such hydrolysis reactions are catalyzed by enzymes such as *maltase*. The same reactions can be carried out in the laboratory with dilute acid as a catalyst, although in that case the rate is much slower, and high temperatures are required. Whether it occurs in the body or a glass beaker, the hydrolysis of maltose produces two molecules of D-glucose.

$$\text{maltose} \xrightarrow{\text{H}^+ \text{ or maltase}} 2\ \text{D-glucose} \tag{24.8.1}$$

Maltose is a reducing sugar. Thus, its two glucose molecules must be linked in such a way as to leave one anomeric carbon that can open to form an aldehyde group. The glucose units in maltose are joined in a *head-to-tail* fashion through an α-linkage from the first carbon atom of one glucose molecule to the fourth carbon atom of the second glucose molecule (that is, an α-1,4-glycosidic linkage; see Figure 1). The bond from the anomeric carbon of the first monosaccharide unit is directed downward, which is why this is known as an α-glycosidic linkage. The OH group on the anomeric carbon of the second glucose can be in either the α or the β position, as shown in Figure 1.

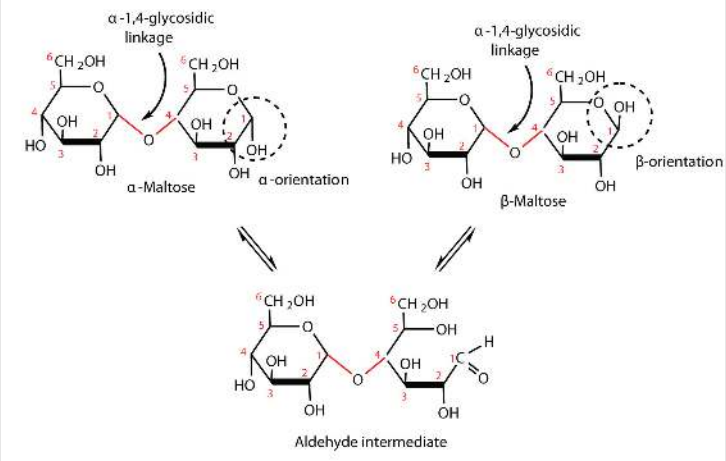
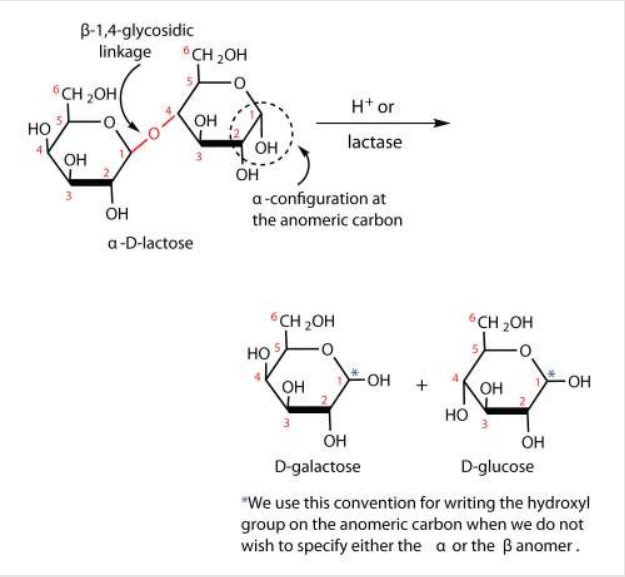


Figure 1 An Equilibrium Mixture of Maltose Isomers

LACTOSE

Lactose is known as *milk sugar* because it occurs in the milk of humans, cows, and other mammals. In fact, the natural synthesis of lactose occurs only in mammary tissue, whereas most other carbohydrates are plant products. Human milk contains about 7.5% lactose, and cow's milk contains about 4.5%. This sugar is one of the lowest ranking in terms of sweetness, being about one-sixth as sweet as sucrose. Lactose is produced commercially from whey, a by-product in the manufacture of cheese. It is important as an infant food and in the production of penicillin.

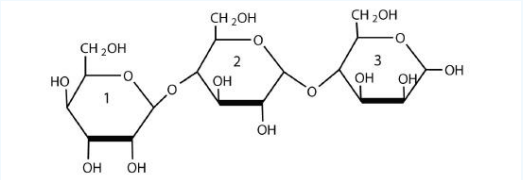
Lactose is a reducing sugar composed of one molecule of D-galactose and one molecule of D-glucose joined by a β-1,4-glycosidic bond (the bond from the anomeric carbon of the first monosaccharide unit being directed upward). The two monosaccharides are obtained from lactose by acid hydrolysis or the catalytic action of the enzyme *lactase*:



Many adults and some children suffer from a deficiency of lactase. These individuals are said to be lactose intolerant because they cannot digest the lactose found in milk. A more serious problem is the genetic disease galactosemia, which results from the absence of an enzyme needed to convert galactose to glucose. Certain bacteria can metabolize lactose, forming lactic acid as one of the products. This reaction is responsible for the "souring" of milk.

Example 1

For this trisaccharide, indicate whether each glycosidic linkage is α or β.



Solution

The glycosidic linkage between sugars 1 and 2 is β because the bond is directed up from the anomeric carbon. The glycosidic linkage between sugars 2 and 3 is α because the bond is directed down from the anomeric carbon.

To Your Health: Lactose Intolerance and Galactosemia

Lactose makes up about 40% of an infant's diet during the first year of life. Infants and small children have one form of the enzyme lactase in their small intestines and can digest the sugar easily; however, adults usually have a less active form of the enzyme, and about 70% of the world's adult population has some deficiency in its production. As a result, many adults experience a reduction in the ability to hydrolyze lactose to galactose and glucose in their small intestine. For some people the inability to synthesize sufficient enzyme increases with age. Up to 20% of the US population suffers some degree of lactose intolerance.

In people with lactose intolerance, some of the unhydrolyzed lactose passes into the colon, where it tends to draw water from the interstitial fluid into the intestinal lumen by osmosis. At the same time, intestinal bacteria may act on the lactose to produce organic acids and gases. The buildup of water and bacterial decay products leads to abdominal distention, cramps, and diarrhea, which are symptoms of the condition.

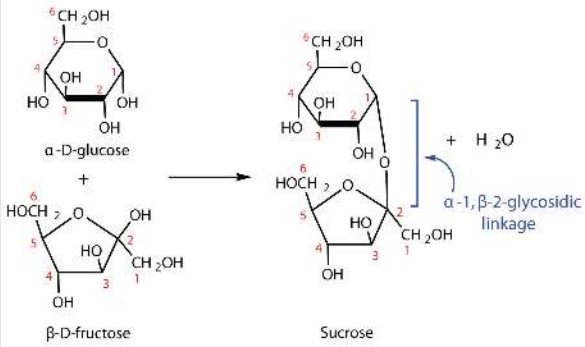
The symptoms disappear if milk or other sources of lactose are excluded from the diet or consumed only sparingly. Alternatively, many food stores now carry special brands of milk that have been pretreated with lactase to hydrolyze the lactose. Cooking or fermenting milk causes at least partial hydrolysis of the lactose, so some people with lactose intolerance are still able to enjoy cheese, yogurt, or cooked foods containing milk. The most common treatment for lactose intolerance, however, is the use of lactase preparations (e.g., Lactaid), which are available in liquid and tablet form at drugstores and grocery stores. These are taken orally with dairy foods—or may be added to them directly—to assist in their digestion.

> Galactosemia is a condition in which one of the enzymes needed to convert galactose to glucose is missing. Consequently, the blood galactose level is markedly elevated, and galactose is found in the urine. An infant with galactosemia experiences a lack of appetite, weight loss, diarrhea, and jaundice. The disease may result in impaired liver function, cataracts, mental retardation, and even death. If galactosemia is recognized in early infancy, its effects can be prevented by the exclusion of milk and all other sources of galactose from the diet. As a child with galactosemia grows older, he or she usually develops an alternate pathway for metabolizing galactose, so the need to restrict milk is not permanent. The incidence of galactosemia in the United States is 1 in every 65,000 newborn babies.

SUCROSE

Sucrose, probably the largest-selling pure organic compound in the world, is known as *beet sugar*, *cane sugar*, *table sugar*, or simply *sugar*. Most of the sucrose sold commercially is obtained from sugar cane and sugar beets (whose juices are 14%–20% sucrose) by evaporation of the water and recrystallization. The dark brown liquid that remains after the recrystallization of sugar is sold as molasses.

The sucrose molecule is unique among the common disaccharides in having an α-1,β-2-glycosidic (head-to-head) linkage. Because this glycosidic linkage is formed by the OH group on the anomeric carbon of α-D-glucose and the OH group on the anomeric carbon of β-D-fructose, it ties up the anomeric carbons of both glucose and fructose.



This linkage gives sucrose certain properties that are quite different from those of maltose and lactose. As long as the sucrose molecule remains intact, neither monosaccharide “uncyclizes” to form an open-chain structure. Thus, sucrose is incapable of mutarotation and exists in only one form both in the solid state and in solution. In addition, sucrose does not undergo reactions that are typical of aldehydes and ketones. Therefore, sucrose is a nonreducing sugar.

The hydrolysis of sucrose in dilute acid or through the action of the enzyme *sucrase* (also known as invertase) gives an equimolar mixture of glucose and fructose. This 1:1 mixture is referred to as *invert sugar* because it rotates plane-polarized light in the opposite direction than sucrose. The hydrolysis reaction has several practical applications. Sucrose readily recrystallizes from a solution, but invert sugar has a much greater tendency to remain in solution. In the manufacture of jelly and candy and in the canning of fruit, the recrystallization of sugar is undesirable. Therefore, conditions leading to the hydrolysis of sucrose are employed in these processes. Moreover, because fructose is sweeter than sucrose, the hydrolysis adds to the sweetening effect. Bees carry out this reaction when they make honey.

The average American consumes more than 100 lb of sucrose every year. About two-thirds of this amount is ingested in soft drinks, presweetened cereals, and other highly processed foods. The widespread use of sucrose is a contributing factor to obesity and tooth decay. Carbohydrates such as sucrose, are converted to fat when the caloric intake exceeds the body’s requirements, and sucrose causes tooth decay by promoting the formation of plaque that sticks to teeth.

SUMMARY

Maltose is composed of two molecules of glucose joined by an α-1,4-glycosidic linkage. It is a reducing sugar that is found in sprouting grain. Lactose is composed of a molecule of galactose joined to a molecule of glucose by a β-1,4-glycosidic linkage. It is a reducing sugar that is found in milk. Sucrose is composed of a molecule of glucose joined to a molecule of fructose by an α-1,β-2-glycosidic linkage. It is a nonreducing sugar that is found in sugar cane and sugar beets.

CONCEPT REVIEW EXERCISE

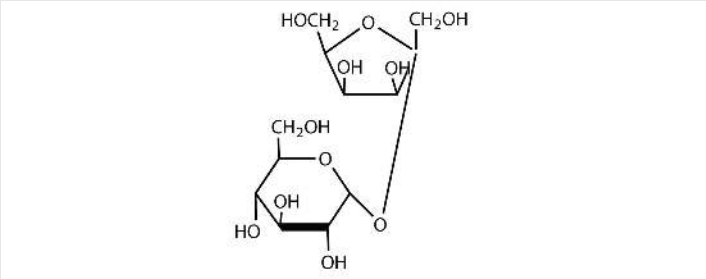
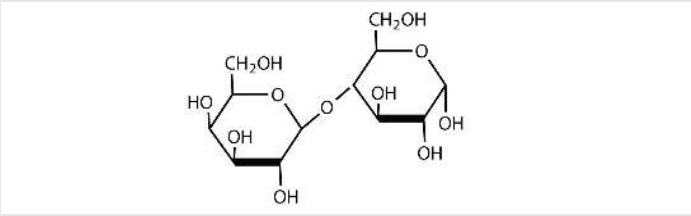
1. What monosaccharides are obtained by the hydrolysis of each disaccharide?
    a. sucrose

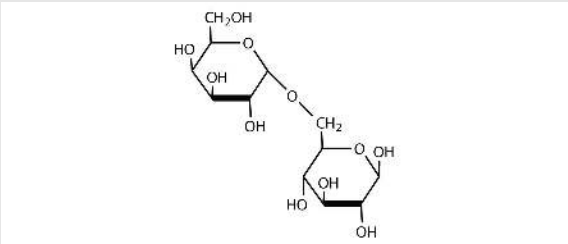
b. maltose
c. lactose

ANSWER

1. a. D-glucose and D-fructose
   b. two molecules of D-glucose
   c. D-glucose and D-galactose

EXERCISES

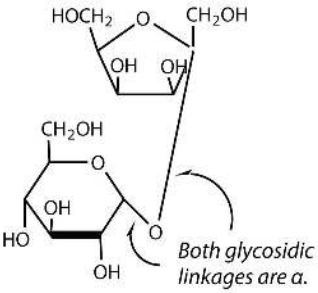
1. Identify each sugar by its common chemical name.
   a. milk sugar
   b. table sugar
2. For each disaccharide, indicate whether the glycosidic linkage is α or β.
   a. 
   b. 
3. Identify each disaccharide in Exercise 2 as a reducing or nonreducing sugar. If it is a reducing sugar, draw its structure and circle the anomeric carbon. State if the OH group at the anomeric carbon is in the α or the β position
4. Melibiose is a disaccharide that occurs in some plant juices. Its structure is as follows:

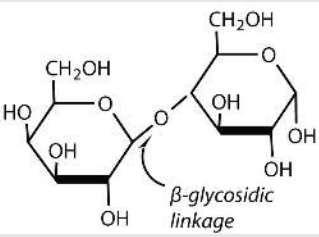


   a. What monosaccharide units are incorporated into melibiose?
   b. What type of linkage (α or β) joins the two monosaccharide units of melibiose?
   c. Melibiose has a free anomeric carbon and is thus a reducing sugar. Circle the anomeric carbon and indicate whether the OH group is α or β

ANSWERS

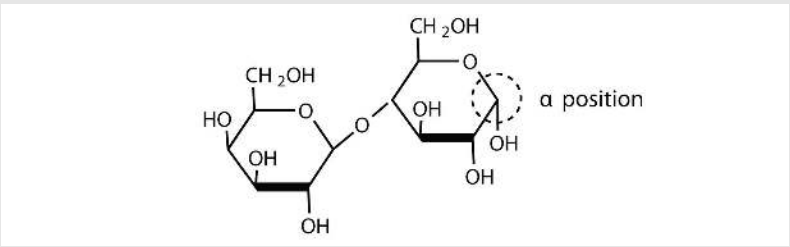
1. a. lactose
   b. sucrose

2. a. 

2. b. 

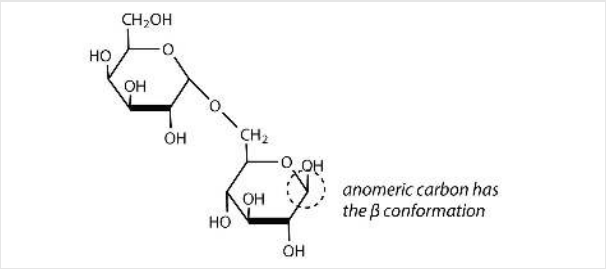
3. a. nonreducing

3. b. reducing



4. a. galactose and glucose

4. b.α-glycosidic linkage

4. c. 

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- *The Basics of General, Organic, and Biological Chemistry* by David W. Ball, John W. Hill, and Rhonda J. Scott.

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24.9: POLYSACCHARIDES

LEARNING OBJECTIVES

After completing this section, you should be able to

1. identify the structural difference between cellulose and the cold-water-insoluble fraction of starch (amylose), and identify both of these substances as containing many glucose molecules joined by 1,4′-glycoside links.
2. identify the cold-water-soluble fraction of starch (amylopectin) as having a more complex structure than amylose because of the existence of 1,6′-glycoside links in addition to the 1,4′-links.
3. compare and contrast the structures and uses of starch, glycogen and cellulose.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- amylopectin
- amylose
- polysaccharide

LEARNING OBJECTIVES

- To compare and contrast the structures and uses of starch, glycogen, and cellulose.

The polysaccharides are the most abundant carbohydrates in nature and serve a variety of functions, such as energy storage or as components of plant cell walls. Polysaccharides are very large polymers composed of tens to thousands of monosaccharides joined together by glycosidic linkages. The three most abundant polysaccharides are starch, glycogen, and cellulose. These three are referred to as *homopolymers* because each yields only one type of monosaccharide (glucose) after complete hydrolysis. *Heteropolymers* may contain sugar acids, amino sugars, or noncarbohydrate substances in addition to monosaccharides. Heteropolymers are common in nature (gums, pectins, and other substances) but will not be discussed further in this textbook. The polysaccharides are nonreducing carbohydrates, are not sweet tasting, and do not undergo mutarotation.

STARCH

Starch is the most important source of carbohydrates in the human diet and accounts for more than 50% of our carbohydrate intake. It occurs in plants in the form of granules, and these are particularly abundant in seeds (especially the cereal grains) and tubers, where they serve as a storage form of carbohydrates. The breakdown of starch to glucose nourishes the plant during periods of reduced photosynthetic activity. We often think of potatoes as a “starchy” food, yet other plants contain a much greater percentage of starch (potatoes 15%, wheat 55%, corn 65%, and rice 75%). Commercial starch is a white powder.

Starch is a mixture of two polymers: amylose and amylopectin. Natural starches consist of about 10%–30% amylose and 70%–90% amylopectin. Amylose is a linear polysaccharide composed entirely of D-glucose units joined by the α-1,4-glycosidic linkages we saw in maltose (part (a) of Figure **24.9.1**). Experimental evidence indicates that amylose is not a straight chain of glucose units but instead is coiled like a spring, with six glucose monomers per turn (part (b) of Figure **24.9.1**). When coiled in this fashion, amylose has just enough room in its core to accommodate an iodine molecule. The characteristic blue-violet color that appears when starch is treated with iodine is due to the formation of the amylose-iodine complex. This color test is sensitive enough to detect even minute amounts of starch in solution.

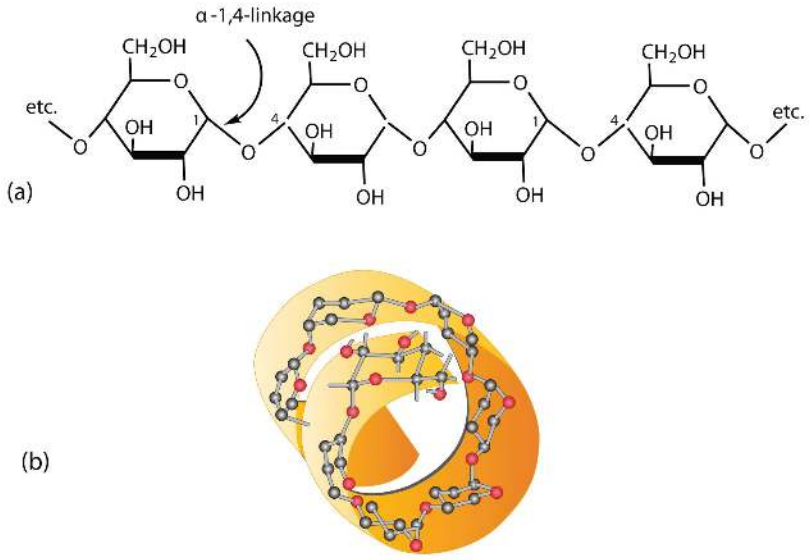


Figure **24.9.1**: Amylose. (a) Amylose is a linear chain of α-D-glucose units joined together by α-1,4-glycosidic bonds. (b) Because of hydrogen bonding, amylose acquires a spiral structure that contains six glucose units per turn.

Amylopectin is a branched-chain polysaccharide composed of glucose units linked primarily by α-1,4-glycosidic bonds but with occasional α-1,6-glycosidic bonds, which are responsible for the branching. A molecule of amylopectin may contain many thousands of glucose units with branch points occurring about every 25–30 units (Figure **24.9.2**). The helical structure of amylopectin is disrupted by the branching of the chain, so instead of the deep blue-violet color amylose gives with iodine, amylopectin produces a less intense reddish brown.

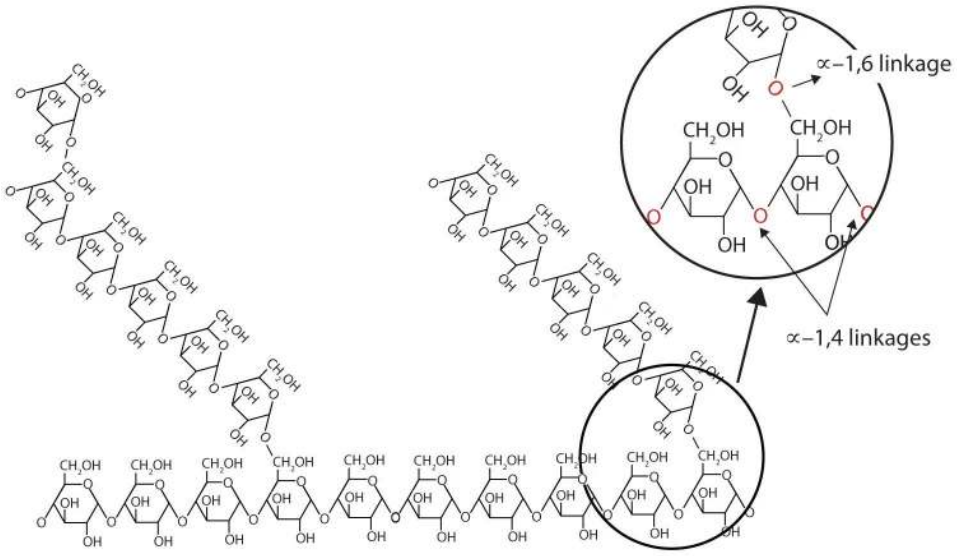


Figure **24.9.2**: Representation of the Branching in Amylopectin and Glycogen. Both amylopectin and glycogen contain branch points that are linked through α-1,6-linkages. These branch points occur more often in glycogen.

Dextrins are glucose polysaccharides of intermediate size. The shine and stiffness imparted to clothing by starch are due to the presence of dextrins formed when clothing is ironed. Because of their characteristic stickiness with wetting, dextrins are used as adhesives on stamps, envelopes, and labels; as binders to hold pills and tablets together; and as pastes. Dextrins are more easily digested than starch and are therefore used extensively in the commercial preparation of infant foods.

The complete hydrolysis of starch yields, in successive stages, glucose:

$$\text{starch} \rightarrow \text{dextrins} \rightarrow \text{maltose} \rightarrow \text{glucose}$$

In the human body, several enzymes known collectively as amylases degrade starch sequentially into usable glucose units.

GLYCOGEN

Glycogen is the energy reserve carbohydrate of animals. Practically all mammalian cells contain some stored carbohydrates in the form of glycogen, but it is especially abundant in the liver (4%–8% by weight of tissue) and in skeletal muscle cells (0.5%–1.0%). Like starch in plants, glycogen is found as granules in liver and muscle cells. When fasting, animals draw on these glycogen reserves during the first day without food to obtain the glucose needed to maintain metabolic balance.

Glycogen is structurally quite similar to amylopectin, although glycogen is more highly branched (8–12 glucose units between branches) and the branches are shorter. When treated with iodine, glycogen gives a reddish brown color. Glycogen can be broken down into its D-glucose subunits by acid hydrolysis or by the same enzymes that catalyze the breakdown of starch. In animals, the enzyme phosphorylase catalyzes the breakdown of glycogen to phosphate esters of glucose.

> *About 70% of the total glycogen in the body is stored in muscle cells. Although the percentage of glycogen (by weight) is higher in the liver, the much greater mass of skeletal muscle stores a greater total amount of glycogen.*

CELLULOSE

Cellulose, a fibrous carbohydrate found in all plants, is the structural component of plant cell walls. Because the earth is covered with vegetation, cellulose is the most abundant of all carbohydrates, accounting for over 50% of all the carbon found in the vegetable kingdom. Cotton fibrils and filter paper are almost entirely cellulose (about 95%), wood is about 50% cellulose, and the dry weight of leaves is about 10%–20% cellulose. The largest use of cellulose is in the manufacture of paper and paper products. Although the use of noncellulose synthetic fibers is increasing, rayon (made from cellulose) and cotton still account for over 70% of textile production.

Like amylose, cellulose is a linear polymer of glucose. It differs, however, in that the glucose units are joined by β-1,4-glycosidic linkages, producing a more extended structure than amylose (part (a) of Figure **24.9.3**). This extreme linearity allows a great deal of hydrogen bonding between OH groups on adjacent chains, causing them to pack closely into fibers (part (b) of Figure **24.9.3**). As a result, cellulose exhibits little interaction with water or any other solvent. Cotton and wood, for example, are completely insoluble in water and have considerable mechanical strength. Because cellulose does not have a helical structure, it does not bind to iodine to form a colored product.

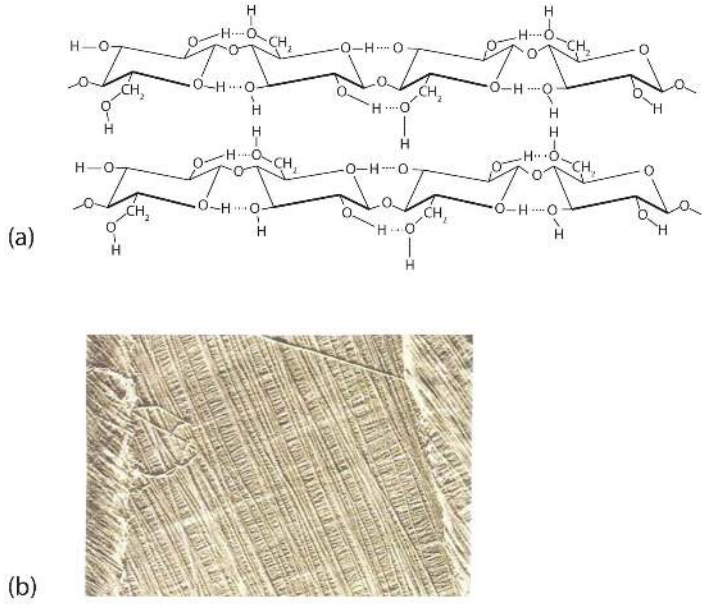


Figure **24.9.3**: Cellulose. (a) There is extensive hydrogen bonding in the structure of cellulose. (b) In this electron micrograph of the cell wall of an alga, the wall consists of successive layers of cellulose fibers in parallel arrangement.

Cellulose yields D-glucose after complete acid hydrolysis, yet humans are unable to metabolize cellulose as a source of glucose. Our digestive juices lack enzymes that can hydrolyze the β-glycosidic linkages found in cellulose, so although we can eat potatoes, we cannot eat grass. However, certain microorganisms can digest cellulose because they make the enzyme cellulase, which catalyzes the hydrolysis of cellulose. The presence of these microorganisms in the digestive tracts of herbivorous animals (such as cows, horses, and sheep) allows these animals to degrade the cellulose from plant material into glucose for energy. Termites also contain cellulase-secreting microorganisms and thus can subsist on a wood diet. This example once again demonstrates the extreme stereospecificity of biochemical processes.

CAREER FOCUS: CERTIFIED DIABETES EDUCATOR

Certified diabetes educators come from a variety of health professions, such as nursing and dietetics, and specialize in the education and treatment of patients with diabetes. A diabetes educator will work with patients to manage their diabetes. This involves teaching the patient to monitor blood sugar levels, make good food choices, develop and maintain an exercise program, and take medication, if required.



A certified diabetes educator at Naval Medical Center Portsmouth (left) and a registered dietician at the medical center (center), provide nutritional information to a diabetes patient and her mother at the Diabetes Boot Camp.

Diabetes educators also work with hospital or nursing home staff to improve the care of diabetic patients. Educators must be willing to spend time attending meetings and reading the current literature to maintain their knowledge of diabetes medications, nutrition, and blood monitoring devices so that they can pass this information to their patients.

SUMMARY

Starch is a storage form of energy in plants. It contains two polymers composed of glucose units: amylose (linear) and amylopectin (branched). Glycogen is a storage form of energy in animals. It is a branched polymer composed of glucose units. It is more highly branched than amylopectin. Cellulose is a structural polymer of glucose units found in plants. It is a linear polymer with the glucose units linked through β-1,4-glycosidic bonds.

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24.10: OTHER IMPORTANT CARBOHYDRATES

Objectives

After completing this section, you should be able to identify deoxy and amino sugars, given their structures.

Key Terms

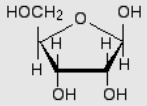
Make certain that you can define, and use in context, the key terms below.

- amino sugar
- deoxy sugar

THE SUGARS IN THE BACKBONE OF DNA

The backbone of DNA is based on a repeated pattern of a sugar group and a phosphate group. The full name of DNA, deoxyribonucleic acid, gives you the name of the sugar present - deoxyribose. Deoxyribose is a modified form of another sugar called ribose. I'm going to give you the structure of that first, because you will need it later anyway. Ribose is the sugar in the backbone of RNA, ribonucleic acid.

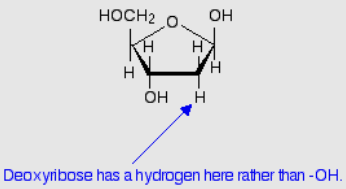
RIBOSE



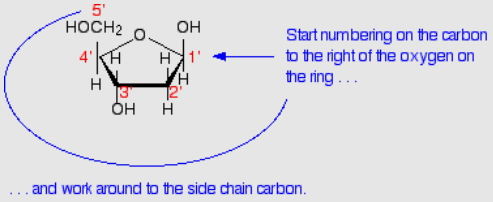
This diagram misses out the carbon atoms in the ring for clarity. Each of the four corners where there isn't an atom shown has a carbon atom. The heavier lines are coming out of the screen or paper towards you. In other words, you are looking at the molecule from a bit above the plane of the ring.

So that's ribose. Deoxyribose, as the name might suggest, is ribose which has lost an oxygen atom - "**de-oxy**".

DEOXYRIBOSE



The only other thing you need to know about deoxyribose (or ribose, for that matter) is how the carbon atoms in the ring are numbered. The carbon atom to the right of the oxygen as we have drawn the ring is given the number 1, and then you work around to the carbon on the CH_2OH side group which is number 5.



You will notice that each of the numbers has a small dash by it - 3' or 5', for example. If you just had ribose or deoxyribose on its own, that wouldn't be necessary, but in DNA and RNA these sugars are attached to other ring compounds. The carbons in the sugars are given the little dashes so that they can be distinguished from any numbers given to atoms in the other rings. You read 3' or 5' as "3-prime" or "5-prime".

AMINO SUGAR

An amino sugar (or more technically a 2-amino-2-deoxysugar) is a sugar molecule in which a hydroxyl group has been replaced with an amine group. More than 60 amino sugars are known, with one of the most abundant being *N*-acetylglucosamine, which is the main component of chitin.



Structure of the chitin molecule, showing two of the *N*-acetylglucosamine units that repeat to form long chains in β-(1→4)-linkage.

Chitin is is a polymer of *N*-acetylglucosamine and is found in many places throughout the natural world. It is a characteristic component of the cell walls of fungi, the exoskeletons of arthropods such as crustaceans (e.g., crabs, lobsters and shrimps) and insects, the radulae of molluscs, and the beaks and internal shells of cephalopods, including squid and octopuses and on the scales and other soft tissues of fish and lissamphibians.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)
- Wikipedia

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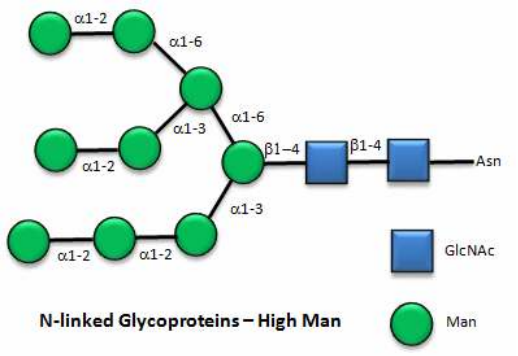
24.11: CELL SURFACE CARBOHYDRATES AND INFLUENZA VIRUSES

Objectives

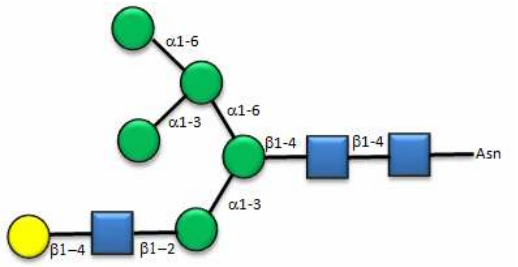
You may omit Section 25.11.

Carbohydrates are covalently attached to many different biomolecules, including lipids, to form glycolipids, and proteins, to form glycoproteins. Glycoproteins and glycolipids are often found in biological membranes, to which they are anchored by through nonpolar interactions. A special kind of glycoprotein, a proteoglycan, actually has more carbohydrate mass than protein. What is the function of these carbohydrates? Two are apparent. First, glycosylation of proteins helps protect the protein from degradation by enzyme catalysts within the body. However, there main functions arises from the fact that covalently attached carbohydrates that "decorate" the surface of glycoproteins or glycolipids provide new binding site interactions that allow interactions with other biomolecules. Hence glycosylation allows for cell:cell, cell:protein, or protein:protein interactions. Unfortunately, bacteria and viruses often recognize glycosylated molecules on cell membranes, allowing for their import into the cell.

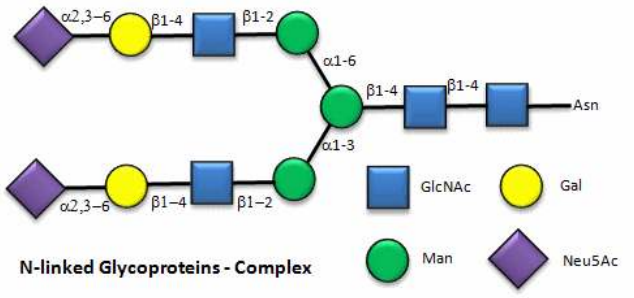
Here are some "cartoon" examples of carbohydrates covalently linked to the amino acid asparagine (Asn) on a glycoprotein.



N-linked Glycoproteins – High Man



N-linked Glycoproteins – Mixed (Hybrid)

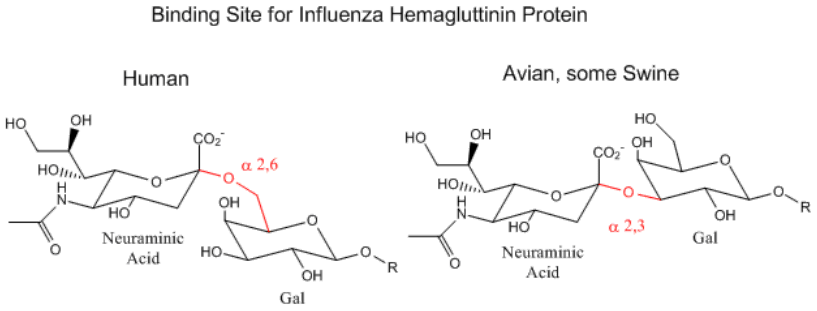


N-linked Glycoproteins - Complex

Here are some examples of biomolecular interactions promoted by IMFs involving carbohydrates.

Influenza Virus binding to Cell Surface Glycoproteins with Neu5Ac - A protein on the surface of influenza virus, hemagluttinin, bind to sialic acid (Sia), which is covalently attached to many cell membrane glycoproteins on host cells. The sialic acid is usually connected through an alpha (2,3) or alpha (2,6) link to galactose on N-linked glycoproteins. The subtypes found in avian (and equine) influenza isolates bind preferentially to Sia (alpha 2,3) Gal which predominates in avian GI tract where viruses replicate. Human virus of H1, H2, and

H3 subtype (cause of the 1918, 1957, and 1968 pandemics) recognize Sia (alpha 2,6) Gal, the major form in human respiratory tract. The swine influenza HA bind to Sia (alpha 2,6) Gal and some Sia (alpha 2,3)both of which found in swine.



- Jmol model of viral hemagluttinin bound to antiviral drugs and sialic (neuraminic acid) from Proteopedia

Leukocyte: Cell Wall binding - During inflammation, circulating leukocytes (a type of white blood cell) tether and roll on the walls of blood vessels where they become active. E-, L- and P-selectin proteins are the primary proteins responsible for the tethering and rolling of these leukocytes. P-selectin binds, in part, to a tetrasaccharide, sialyl-Lewisx (SLEX) on the cell surface.. The interaction between P-selectin and the cell mediates the initial binding/rolling of the leukocyte on the vessel wall.

- Jmol model of P-selectin binding to tetrasaccharide

CONTRIBUTORS AND ATTRIBUTIONS

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CHAPTER OVERVIEW

25: AMINO ACIDS, PEPTIDES, AND PROTEINS

25.1: Introduction
25.2: Structure and Stereochemistry of the Amino Acids
25.3: Isoelectric Points and Electrophoresis
25.4: Synthesis of Amino Acids
25.5: Peptides and Proteins
25.6: Amino Acid Analysis of Peptides
25.7: Peptide Sequencing- The Edman Degradation
25.8: Peptide Synthesis
25.9: Automated Peptide Synthesis- The Merrifield Solid-Phase Technique
25.10: Levels of Protein Structure
25.11: Enzymes and Coenzymes
25.12: How do enzymes work?

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25.1: INTRODUCTION

Objectives

After completing this section, you should be able to

1. give examples of the various biological roles played by proteins.
2. identify amino acids as being the building blocks from which all proteins are made.
3. show, in a general way, how the joining together of a number of amino acids through the formation of peptide bonds results in the formation of proteins.

Key Terms

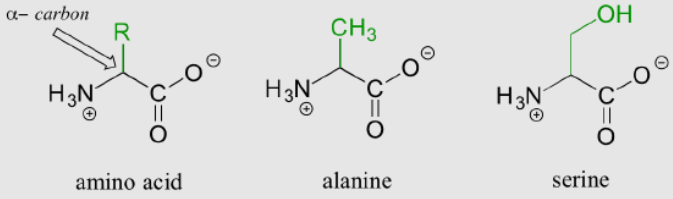
Make certain that you can define, and use in context, the key terms below.

- amino acid
- enzyme
- peptide bond
- protein

Study Notes

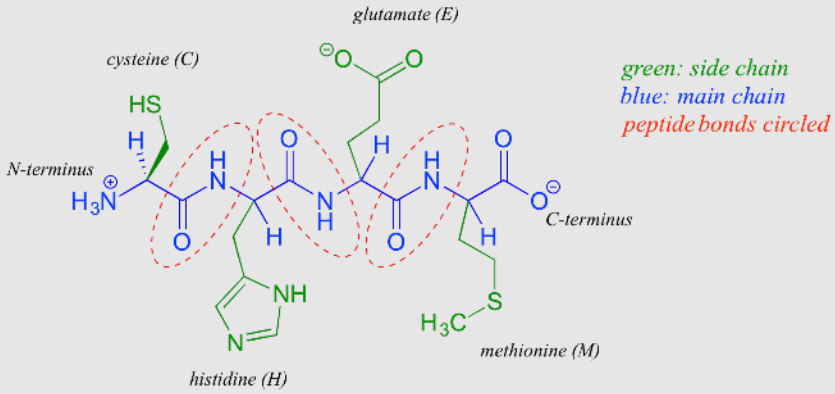
The “peptide bond” or “peptide linkage” that is formed between the amino group of one amino acid and the carboxyl group of a second amino acid is identical to the C—N bond present in amides (see Section 21.7). We shall review the nature of such bonds in Section 26.4.

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



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

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



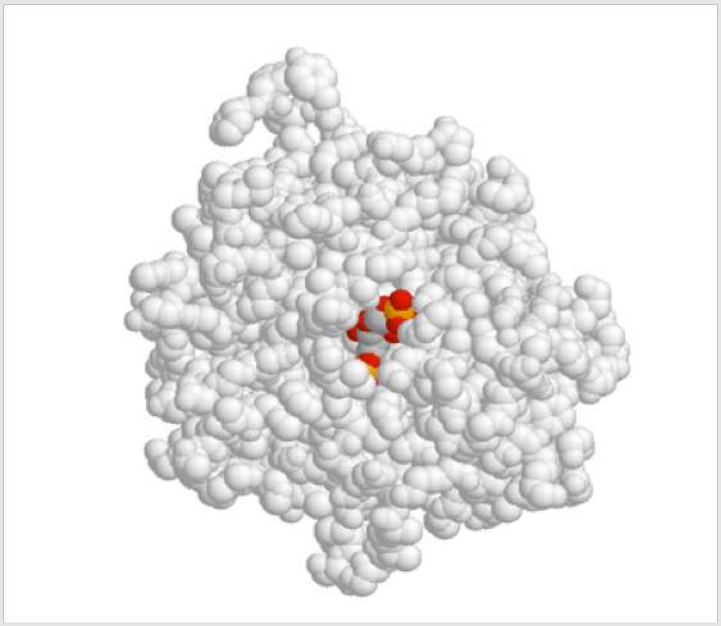
CHEM peptide

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

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

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

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



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

Intro to nucleic acids ⇒

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

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

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25.2: STRUCTURE AND STEREOCHEMISTRY OF THE AMINO ACIDS

Objectives

After completing this section, you should be able to

1. identify the structural features present in the 20 amino acids commonly found in proteins.

   Note: You are not expected to remember the detailed structures of all these amino acids, but you should be prepared to draw the structures of the two simplest members, glycine and alanine.

2. draw the Fischer projection formula of a specified enantiomer of a given amino acid.

   Note: To do so, you must remember that in the *S* enantiomer, the carboxyl group appears at the top of the projection formula and the amino group is on the left.

3. classify an amino acid as being acidic, basic or neutral, given its Kekulé, condensed or shorthand structure.
4. draw the zwitterion form of a given amino acid.
5. account for some of the typical properties of amino acids (e.g., high melting points, solubility in water) in terms of zwitterion formation.
6. write appropriate equations to illustrate the amphoteric nature of amino acids.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- α-amino acids
- amphoteric
- essential amino acids
- zwitterion

Study Notes

This is a good point at which to review some of the principles of stereochemistry presented in Chapter 5. Be sure to make full use of molecular models when any stereochemical issues arise.

You should recognize that a three-letter shorthand code is often used to represent individual amino acids. You need not memorize this code.

The distinction between essential and nonessential amino acids is not as clear-cut as one might suppose. For example, arginine is often regarded as being nonessential.

INTRODUCTION TO AMINO ACIDS

Amino acids form polymers through a condensation reaction by the amino group of an amino acid with the carboxyl group of another amino acid. The carboxyl group of the amino acid must first be activated to provide a better leaving group than OH^-. (We will discuss this activation by ATP later in the course.) The resulting link between the amino acids is an amide link which biochemists call a peptide bond. In this reaction, water is released. In a reverse reaction, the peptide bond can be cleaved by water (hydrolysis).

- Structure and Property of the Naturally-Occurring Amino Acids (Too large to include in text: print separately)

When two amino acids link together to form an amide link, the resulting structure is called a dipeptide. Likewise, we can have tripeptides, tetrapeptides, and other polypeptides. At some point, when the structure is long enough, it is called a protein. There are many different ways to represent the structure of a polypeptide or protein, each showing differing amounts of information.

Figure: Different Representations of a Polypeptide (Heptapeptide)

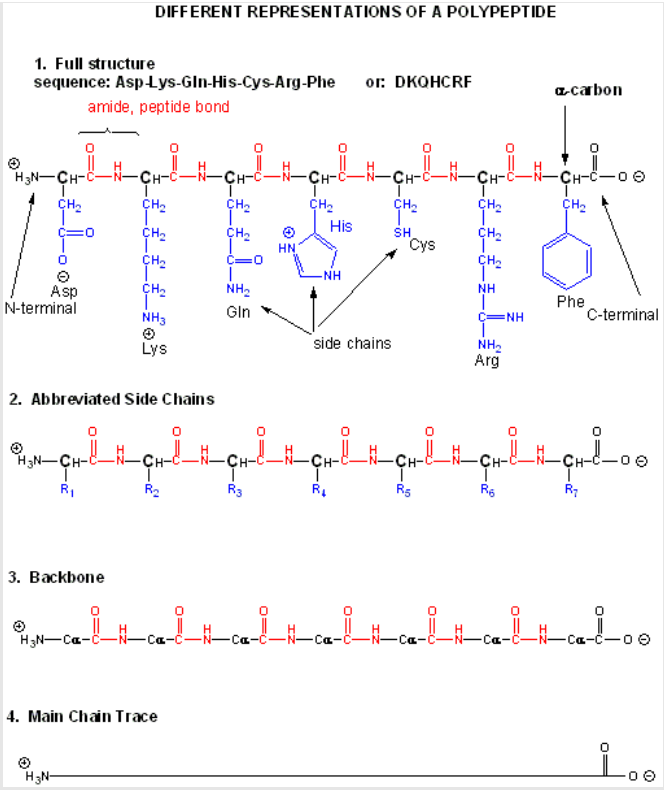
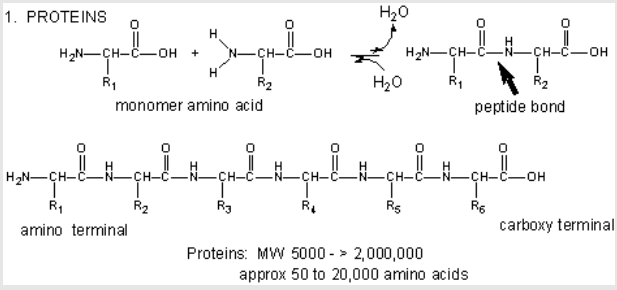


Figure: Amino Acids React to Form Proteins

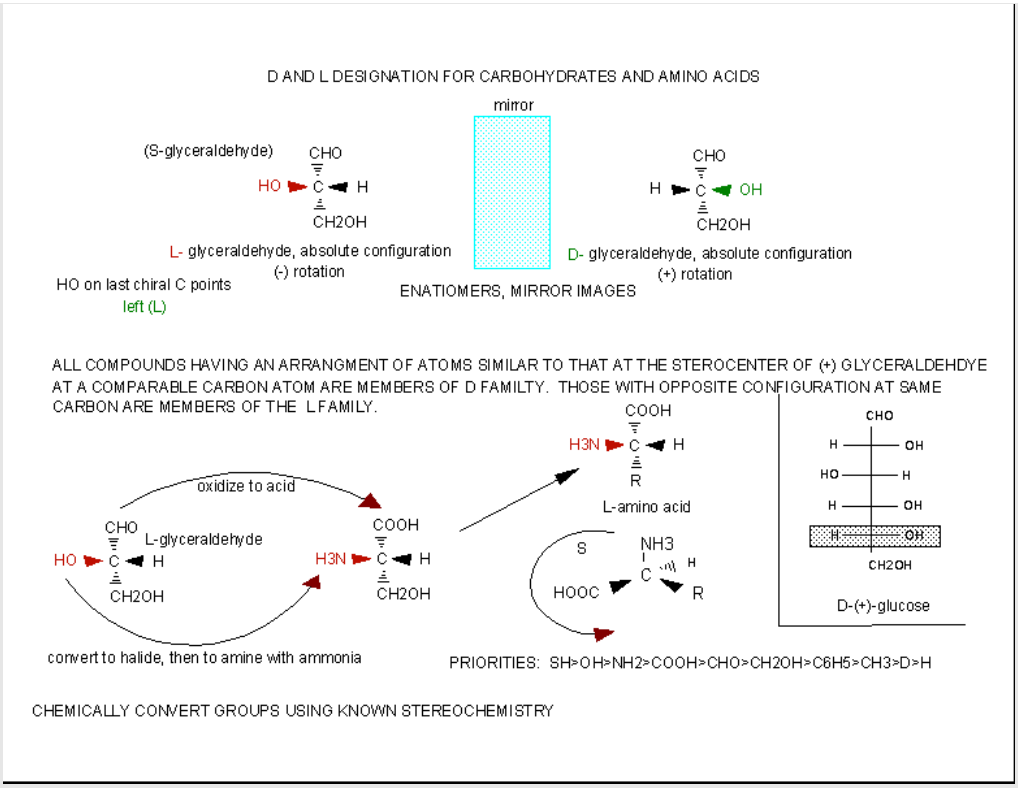


(Note: above picture represents the amino acid in an unlikely protonation state with the weak acid protonated and the weak base deprotonated for simplicity in showing removal of water on peptide bond formation and the hydrolysis reaction.) Proteins are polymers of twenty naturally occurring amino acids. In contrast, nucleic acids are polymers of just 4 different monomeric nucleotides. Both the sequence of a protein and its total length differentiate one protein from another. Just for an octapeptide, there are over 25 billion different possible arrangements of amino acids. Compare this to just 65536 different oligonucleotides of 8 monomeric units (8mer). Hence the diversity of possible proteins is enormous.

STEREOCHEMISTRY

The amino acids are all chiral, with the exception of glycine, whose side chain is H. As with lipids, biochemists use the L and D nomenclature. All naturally occuring proteins from all living organisms consist of L amino acids. The absolute stereochemistry is related to L-glyceraldehyde, as was the case for triacylglycerides and phospholipids. Most naturally occurring chiral amino acids are S, with the exception of cysteine. As the diagram below shows, the absolute configuration of the amino acids can be shown with the H pointed to the rear, the COOH groups pointing out to the left, the R group to the right, and the NH_3 group upwards. You can remember this with the anagram CORN.

Figure: *Stereochemistry of Amino Acids.*



Why do biochemists still use D and L for sugars and amino acids? This explanation (taken from the link below) seems reasonable.

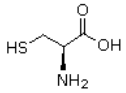
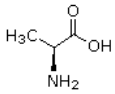
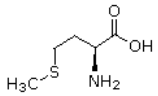
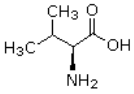
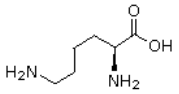
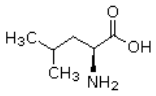
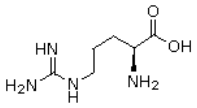
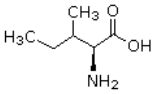
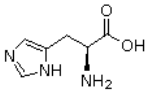
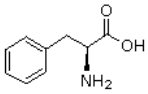
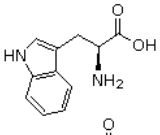
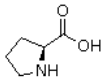
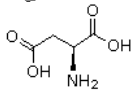
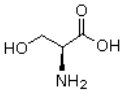
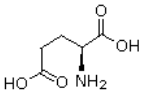
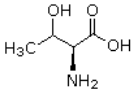
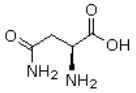
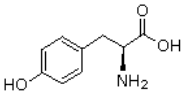
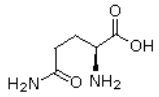
"In addition, however, chemists often need to define a configuration unambiguously in the absence of any reference compound, and for this purpose the alternative (R,S) system is ideal, as it uses priority rules to specify configurations. These rules sometimes lead to absurd results when they are applied to biochemical molecules. For example, as we have seen, all of the common amino acids are L, because they all have exactly the same structure, including the position of the R group if we just write the R group as R. However, they do not all have the same configuration in the (R,S) system: L-cysteine is also (R)-cysteine, but all the other L-amino acids are (S), but this just reflects the human decision to give a sulphur atom higher priority than a carbon atom, and does not reflect a real difference in configuration. Worse problems can sometimes arise in substitution reactions: sometimes inversion of configuration can result in no change in the (R) or (S) prefix; and sometimes retention of configuration can result in a change of prefix.

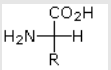
It follows that it is not just conservatism or failure to understand the (R,S) system that causes biochemists to continue with D and L: it is just that the DL system fulfils their needs much better. As mentioned, chemists also use D and L when they are appropriate to their needs. The explanation given above of why the (R,S) system is little used in biochemistry is thus almost the exact opposite of reality. This system is actually the only practical way of unambiguously representing the stereochemistry of complicated molecules with several asymmetric centres, but it is inconvenient with regular series of molecules like amino acids and simple sugars. "

NATURAL A-AMINO ACIDS

Hydrolysis of proteins by boiling aqueous acid or base yields an assortment of small molecules identified as α-aminocarboxylic acids. More than twenty such components have been isolated, and the most common of these are listed in the following table. Those amino acids having green colored names are **essential** diet components, since they are not synthesized by human metabolic processes. The best food source of these nutrients is protein, but it is important to recognize that not all proteins have equal nutritional value. For example, peanuts have a higher weight content of protein than fish or eggs, but the proportion of essential amino acids in peanut protein is only a third of that from the two other sources. For reasons that will become evident when discussing the structures of proteins and peptides, each amino acid is assigned a one or three letter abbreviation.

NATURAL A-AMINO ACIDS

Name	Formula	Abbreviations		Name	Formula	Abbreviations	
Glycine		Gly	G	Cysteine		Cys	C
Alanine		Ala	A	Methionine		Met	M
Valine		Val	V	Lysine		Lys	K
Leucine		Leu	L	Arginine		Arg	R
Isoleucine		Ile	I	Histidine		His	H
Phenylalanine		Phe	F	Tryptophan		Trp	W
Proline		Pro	P	Aspartic Acid		Asp	D
Serine		Ser	S	Glutamic Acid		Glu	E
Threonine		Thr	T	Asparagine		Asn	N
Tyrosine		Tyr	Y	Glutamine		Gln	Q


L-Amino Acid

Some common features of these amino acids should be noted. With the exception of proline, they are all 1°-amines; and with the exception of glycine, they are all chiral. The configurations of the chiral amino acids are the same when written as a Fischer projection formula, as in the drawing on the right, and this was defined as the **L-configuration** by Fischer. The R-substituent in this structure is the remaining structural component that varies from one amino acid to another, and in proline R is a three-carbon chain that joins the nitrogen to the alpha-carbon in a five-membered ring. Applying the Cahn-Ingold-Prelog notation, all these natural chiral amino acids, with the exception of cysteine, have an **S**-configuration. For the first seven compounds in the left column the R-substituent is a hydrocarbon. The last three entries in the left column have hydroxyl functional groups, and the first two amino acids in the right column incorporate thiol and sulfide groups respectively. Lysine and arginine have basic amine functions in their side-chains; histidine and tryptophan have less basic nitrogen heterocyclic rings as substituents. Finally, carboxylic acid side-chains are substituents on aspartic and glutamic acid, and the last two compounds in the right column are their corresponding amides.

The formulas for the amino acids written above are simple covalent bond representations based upon previous understanding of mono-functional analogs. **The formulas are in fact incorrect**. This is evident from a comparison of the physical properties listed in the following table. All four compounds in the table are roughly the same size, and all have moderate to excellent water solubility. The first two are simple carboxylic acids, and the third is an amino alcohol. All three compounds are soluble in organic solvents (e.g. ether) and have relatively low melting points. The carboxylic acids have pK_a's near 4.5, and the conjugate acid of the amine has a pK_a of 10. The simple amino acid alanine is the last entry. By contrast, it is very high melting (with decomposition), insoluble in organic solvents, and a million times weaker as an acid than ordinary carboxylic acids.

PHYSICAL PROPERTIES OF SELECTED ACIDS AND AMINES

Compound	Formula	Mol.Wt.	Solubility in Water	Solubility in Ether	Melting Point	pK_a
isobutyric acid	$(CH_3)_2CHCO_2H$	88	20g/100mL	complete	-47 ºC	5.0
lactic acid	$CH_3CH(OH)CO_2H$	90	complete	complete	53 ºC	3.9
3-amino-2-butanol	$CH_3CH(NH_2)CH(OH)CH_3$	89	complete	complete	9 ºC	10.0
alanine	$CH_3CH(NH_2)CO_2H$	89	18g/100mL	insoluble	ca. 300 ºC	9.8

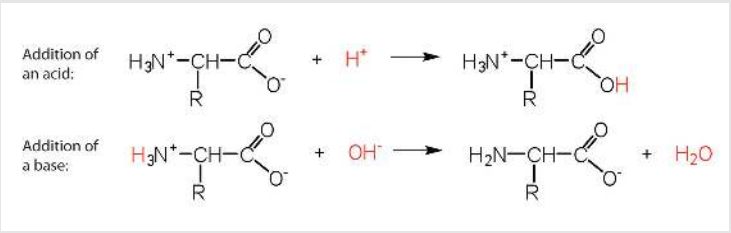
ZWITTERION

These differences above all point to internal salt formation by a proton transfer from the acidic carboxyl function to the basic amino group. The resulting ammonium carboxylate structure, commonly referred to as a **zwitterion**, is also supported by the spectroscopic characteristics of alanine.



As expected from its ionic character, the alanine zwitterion is high melting, insoluble in nonpolar solvents and has the acid strength of a 1º-ammonium ion. Examples of a few specific amino acids may also be viewed in their favored neutral zwitterionic form. Note that in lysine the amine function farthest from the carboxyl group is more basic than the alpha-amine. Consequently, the positively charged ammonium moiety formed at the chain terminus is attracted to the negative carboxylate, resulting in a coiled conformation.

The structure of an amino acid allows it to act as both an acid and a base. An amino acid has this ability because at a certain pH value (different for each amino acid) nearly all the amino acid molecules exist as zwitterions. If acid is added to a solution containing the zwitterion, the carboxylate group captures a hydrogen (H^+) ion, and the amino acid becomes positively charged. If base is added, ion removal of the H^+ ion from the amino group of the zwitterion produces a negatively charged amino acid. In both circumstances, the amino acid acts to maintain the pH of the system—that is, to remove the added acid (H^+) or base (OH^-) from solution.

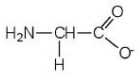


Example 26.1

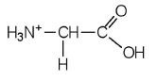
a. Draw the structure for the anion formed when glycine (at neutral pH) reacts with a base.
b. Draw the structure for the cation formed when glycine (at neutral pH) reacts with an acid.

Solution

a. The base removes H^+ from the protonated amine group.

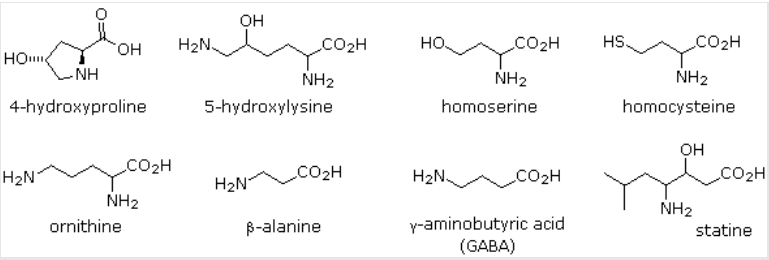


b. The acid adds H^+ to the carboxylate group.



OTHER NATURAL AMINO ACIDS

The twenty alpha-amino acids listed above are the primary components of proteins, their incorporation being governed by the genetic code. Many other naturally occurring amino acids exist, and the structures of a few of these are displayed below. Some, such as hydroxylysine and hydroxyproline, are simply functionalized derivatives of a previously described compound. These two amino acids are found only in collagen, a common structural protein. Homoserine and homocysteine are higher homologs of their namesakes. The amino group in beta-alanine has moved to the end of the three-carbon chain. It is a component of pantothenic acid, $HOCH_2C(CH_3)_2CH(OH)CONHCH_2CH_2CO_2H$, a member of the vitamin B complex and an essential nutrient. Acetyl coenzyme A is a pyrophosphorylated derivative of a pantothenic acid amide. The gamma-amino homolog GABA is a neurotransmitter inhibitor and antihypertensive agent.



Many unusual amino acids, including D-enantiomers of some common acids, are produced by microorganisms. These include ornithine, which is a component of the antibiotic bacitracin A, and statin, found as part of a pentapeptide that inhibits the action of the digestive enzyme **pepsin**.

EXERCISES

QUESTIONS

Q26.1.1

Why is cysteine the only L amino acid with an R configuration at the alpha carbon?

Q26.1.2

Isoleucine has two stereogenic centers.

(a) Draw a Fischer projection of isoleucine.

(b) Draw a Fischer projection of an isoleucine diastereomer, and label each stereocenter as R or S.

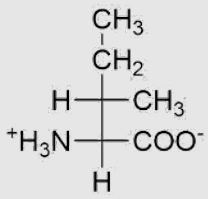
SOLUTIONS

S26.1.1

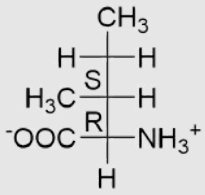
The sulfur atom in the side chain causes the side chain to have higher priority than the other substituents.

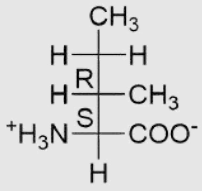
S26.1.2

(a)



(b)





CONTRIBUTORS AND ATTRIBUTIONS

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

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25.3: ISOELECTRIC POINTS AND ELECTROPHORESIS

Objectives

After completing this section, you should be able to

1. draw the predominant form of a given amino acid in a solution of known pH, given the isoelectric point of the amino acid.
2. describe, briefly, how a mixture of amino acids may be separated by paper electrophoresis.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- electrophoresis
- isoelectric point

Since amino acids, as well as peptides and proteins, incorporate both acidic and basic functional groups, the predominant molecular species present in an aqueous solution will depend on the pH of the solution. In order to determine the nature of the molecular and ionic species that are present in aqueous solutions at different pH's, we make use of the **Henderson-Hasselbalch Equation**, written below. Here, the pK_a represents the acidity of a specific conjugate acid function (HA). When the pH of the solution equals pK_a, the concentrations of HA and $A^{(-)}$ must be equal (log 1 = 0).

$$pK_a = pH + \log_{10} \frac{[HA]}{A^-] } \tag{25.3.1}$$

The titration curve for alanine in Figure **25.3.2** demonstrates this relationship. At a pH lower than 2, both the carboxylate and amine functions are protonated, so the alanine molecule has a net positive charge. At a pH greater than 10, the amine exists as a neutral base and the carboxyl as its conjugate base, so the alanine molecule has a net negative charge. At intermediate pH's the zwitterion concentration increases, and at a characteristic pH, called the **isoelectric point** (**pI**), the negatively and positively charged molecular species are present in equal concentration. This behavior is general for simple (difunctional) amino acids. Starting from a fully protonated state, the pK_a's of the acidic functions range from 1.8 to 2.4 for $-CO_2H$, and 8.8 to 9.7 for $-NH_3^{(+)}$. The isoelectric points range from 5.5 to 6.2. Titration curves show the neutralization of these acids by added base, and the change in pH during the titration.

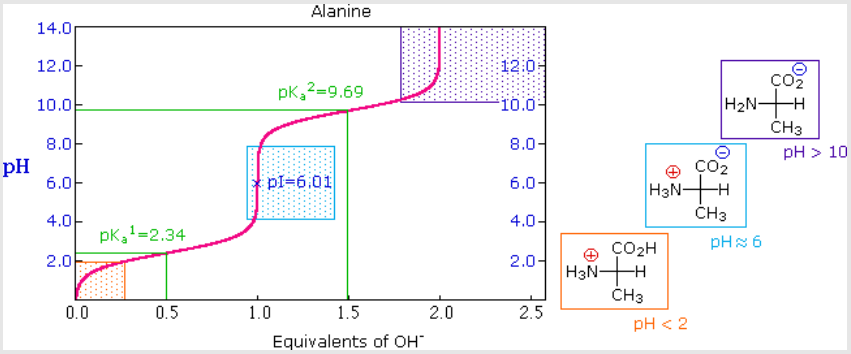


Figure **25.3.1**: Titration curves for many other amino acids may be examined at a useful site provided by The University of Virginia in Charlottesville.

The distribution of charged species in a sample can be shown experimentally by observing the movement of solute molecules in an electric field, using the technique of **electrophoresis** (Figure **25.3.2**). For such experiments an ionic buffer solution is incorporated in a solid matrix layer, composed of paper or a crosslinked gelatin-like substance. A small amount of the amino acid, peptide or protein sample is placed near the center of the matrix strip and an electric potential is applied at the ends of the strip, as shown in the following diagram. The solid structure of the matrix retards the diffusion of the solute molecules, which will remain where they are inserted, unless acted upon by the electrostatic potential.

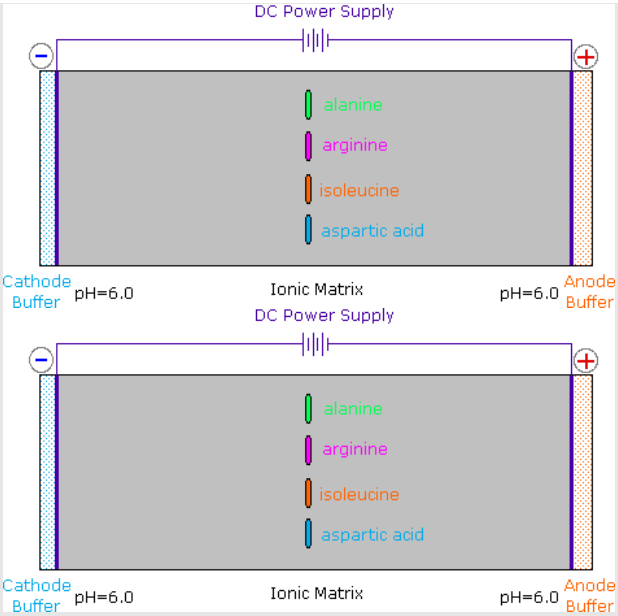
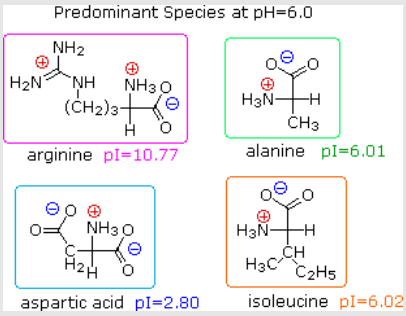


Figure **25.3.2**: In the example shown here, four different amino acids are examined simultaneously in a pH 6.00 buffered medium. To see the result of this experiment, click on the illustration. Note that the colors in the display are only a convenient reference, since these amino acids are colorless.

At pH 6.00 alanine and isoleucine exist on average as neutral zwitterionic molecules, and are not influenced by the electric field. Arginine is a basic amino acid. Both base functions exist as "onium" conjugate acids in the pH 6.00 matrix. The solute molecules of arginine therefore carry an excess positive charge, and they move toward the cathode. The two carboxyl functions in aspartic acid are both ionized at pH 6.00, and the negatively charged solute molecules move toward the anode in the electric field. Structures for all these species are shown to the right of the display.



It should be clear that the result of this experiment is critically dependent on the pH of the matrix buffer. If we were to repeat the electrophoresis of these compounds at a pH of 3.80, the aspartic acid would remain at its point of origin, and the other amino acids would move toward the cathode. Ignoring differences in molecular size and shape, the arginine would move twice as fast as the alanine and isoleucine because its solute molecules on average would carry a double positive charge.

As noted earlier, the titration curves of simple amino acids display two inflection points, one due to the strongly acidic carboxyl group (pK_a^1 = 1.8 to 2.4), and the other for the less acidic ammonium function (pK_a^2 = 8.8 to 9.7). For the 2º-amino acid proline, pK_a^2 is 10.6, reflecting the greater basicity of 2º-amines.

Table **25.3.1**: pKa Values of Polyfunctional Amino Acids

Amino Acid	α-CO_2H pK_a^1	α-NH_3 pK_a^2	Side Chain pK_a^3	pI
Arginine	2.1	9.0	12.5	10.8
Aspartic Acid	2.1	9.8	3.9	3.0
Cysteine	1.7	10.4	8.3	5.0
Glutamic Acid	2.2	9.7	4.3	3.2
Histidine	1.8	9.2	6.0	7.6
Lysine	2.2	9.0	10.5	9.8
Tyrosine	2.2	9.1	10.1	5.7

Some amino acids have additional acidic or basic functions in their side chains. These compounds are listed in Table **25.3.1**. A third pK_a, representing the acidity or basicity of the extra function, is listed in the fourth column of the table. The pI's of these amino acids (last column) are often very different from those noted above for the simpler members. As expected, such compounds display three inflection points in their titration curves, illustrated by the titrations of arginine and aspartic acid (Figure\ (\PageIndex{3}\)). For each of these compounds four possible charged species are possible, one of which has no overall charge. Formulas for these species are written to the right of the titration curves, together with the pH at which each is expected to predominate. The very high pH required to remove the last acidic proton from arginine reflects the exceptionally high basicity of the guanidine moiety at the end of the side chain.

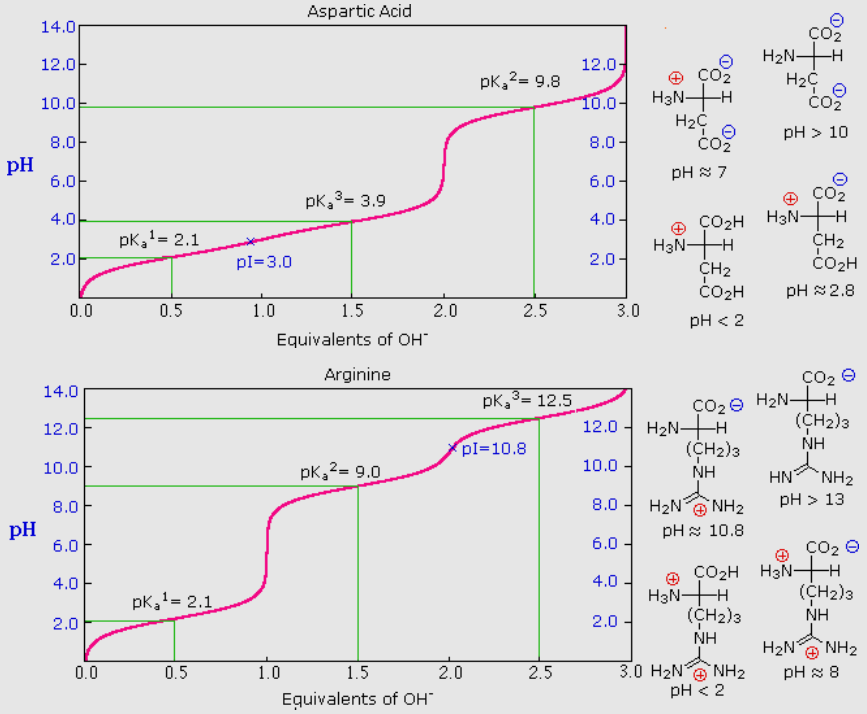


Figure **25.3.3**

THE ISOELECTRIC POINT

The isoelectric point, **pI**, is the pH of an aqueous solution of an amino acid (or peptide) at which the molecules on average have no net charge. In other words, the positively charged groups are exactly balanced by the negatively charged groups. For simple amino acids such as alanine, the pI is an average of the pK_a's of the carboxyl (2.34) and ammonium (9.69) groups. Thus, the pI for alanine is calculated to be: (2.34 + 9.69)/2 = 6.02, the experimentally determined value. If additional acidic or basic groups are present as side-chain functions, the pI is the average of the pK_a's of the two most similar acids. To assist in determining similarity we define two classes of acids. The first consists of acids that are neutral in their protonated form (e.g. CO_2H & SH). The second includes acids that are positively charged in their protonated state (e.g. $-NH_3^+$). In the case of aspartic acid, the similar acids are the alpha-carboxyl function (pK_a = 2.1) and the side-chain carboxyl function (pK_a = 3.9), so pI = (2.1 + 3.9)/2 = 3.0. For arginine, the similar acids are the guanidinium species on the side-chain (pK_a = 12.5) and the alpha-ammonium function (pK_a = 9.0), so the calculated pI = (12.5 + 9.0)/2 = 10.75

CONTRIBUTORS AND ATTRIBUTIONS

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25.4: SYNTHESIS OF AMINO ACIDS

Objectives

After completing this section, you should be able to

1. outline, by means of equations, how a racemic mixture of given amino acid can be prepared from a carboxylic acid using reactions you studied earlier in the course.
2. a. outline, by means of equations, the preparation of a given amino acid by the amidomalonate synthesis.
   b. identify the amino acid formed from using a given alkyl halide in an amidomalonate synthesis.
   c. identify the alkyl halide needed to produce a given amino acid by the amidomalonate synthesis.
3. describe, by means of equations, how an α-keto acid can be transformed to an amino acid by reductive amination.
4. a. describe a general method for resolving a racemic mixture of a given amino acid.
   b. provide a brief example of how a biological method may be employed to resolve a racemic mixture of a given amino acid.
   c. show the enantioselective preparation of an amino acid from the corresponding *Z* enamido acid.

Key Terms

Make certain that you can define, and use in context, the key terms below.

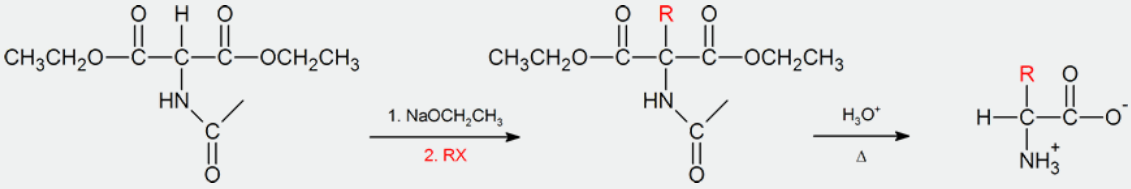
- amidomalonate synthesis
- enantioselective synthesis
- racemic mixture

Study Notes

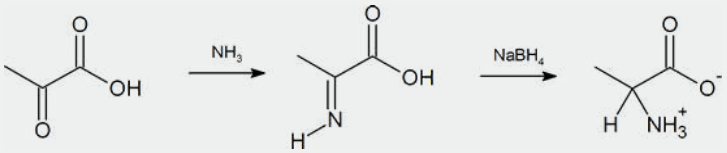
Do not be alarmed by the number of methods to synthesize amino acids described in this section.You have seen many of these reactions in previous sections and should already be familiar with the approaches discussed here.

To fulfill the requirements of Objective 1, review the Hell-Volhard-Zelinskii reaction (Section 22.4) and the Gabriel phthalimide synthesis (Section 24.6).

The **amidomalonate synthesis** is a simple variation of the malonic ester synthesis (Section 22.7). A base abstracts a proton from the alpha carbon, which is then alkylated with an alkyl halide. Then both the hydrolysis of the esters and the amide protecting group under aqueous acidic conditions generates the α-amino acid.

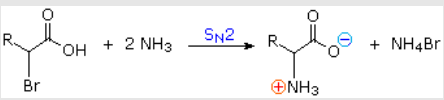


Another method of getting to the α-amino acid is by **reductive amination** of the α-keto acid which you have also previously encountered (Section 24.6).

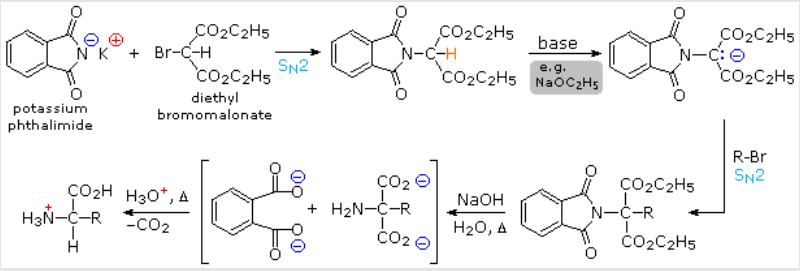


SYNTHESIS OF A-AMINO ACIDS

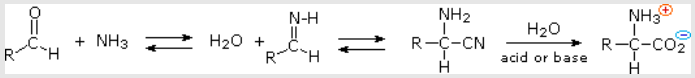
1) Amination of alpha-bromocarboxylic acids, illustrated by the following equation, provides a straightforward method for preparing alpha-aminocarboxylic acids. The bromoacids, in turn, are conveniently prepared from carboxylic acids by reaction with Br_2 + PCl_3. Although this direct approach gave mediocre results when used to prepare simple amines from alkyl halides, it is more effective for making amino acids, thanks to the reduced nucleophilicity of the nitrogen atom in the product. Nevertheless, more complex procedures that give good yields of pure compounds are often chosen for amino acid synthesis.



2) By modifying the nitrogen as a phthalimide salt, the propensity of amines to undergo multiple substitutions is removed, and a single clean substitution reaction of 1º- and many 2º-alkylhalides takes place. This procedure, known as the Gabriel synthesis, can be used to advantage in aminating bromomalonic esters, as shown in the upper equation of the following scheme. Since the phthalimide substituted malonic ester has an acidic hydrogen (colored orange), activated by the two ester groups, this intermediate may be converted to an ambident anion and alkylated. Finally, base catalyzed hydrolysis of the phthalimide moiety and the esters, followed by acidification and thermal decarboxylation, produces an amino acid and phthalic acid (not shown).

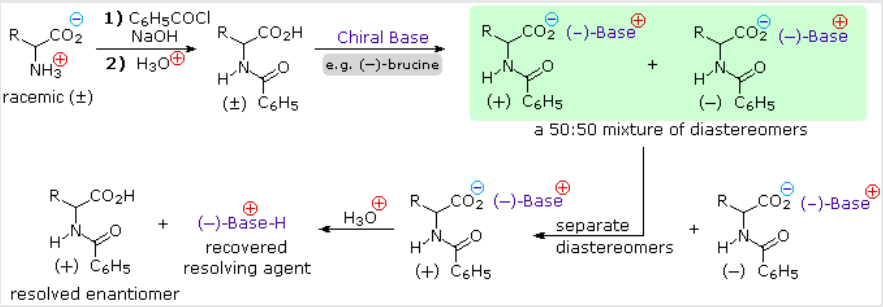


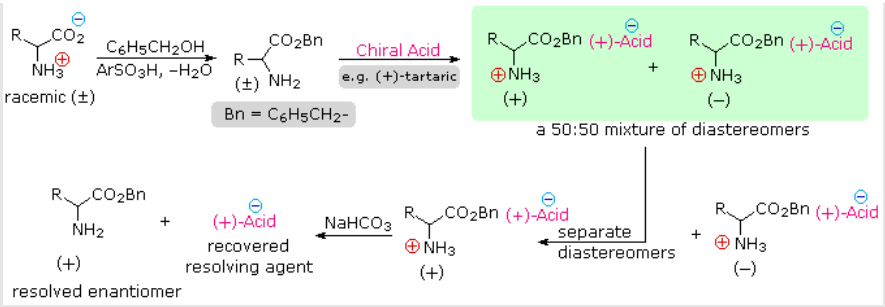
3) An elegant procedure, known as the **Strecker synthesis**, assembles an alpha-amino acid from ammonia (the amine precursor), cyanide (the carboxyl precursor), and an aldehyde. This reaction (shown below) is essentially an imino analog of cyanohydrin formation. The alpha-amino nitrile formed in this way can then be hydrolyzed to an amino acid by either acid or base catalysis.



4) Resolution The three synthetic procedures described above, and many others that can be conceived, give racemic amino acid products. If pure **L** or **D** enantiomers are desired, it is necessary to resolve these racemic mixtures. A common method of resolving racemates is by diastereomeric salt formation with a pure chiral acid or base. This is illustrated for a generic amino acid in the following diagram. Be careful to distinguish charge symbols, shown in colored circles, from optical rotation signs, shown in parenthesis.

In the initial display, the carboxylic acid function contributes to diastereomeric salt formation. The racemic amino acid is first converted to a benzamide derivative to remove the basic character of the amino group. Next, an ammonium salt is formed by combining the carboxylic acid with an optically pure amine, such as brucine (a relative of strychnine). The structure of this amine is not shown, because it is not a critical factor in the logical progression of steps. Since the amino acid moiety is racemic and the base is a single enantiomer (levorotatory in this example), an equimolar mixture of diastereomeric salts is formed (drawn in the green shaded box). Diastereomers may be separated by crystallization, chromatography or other physical manipulation, and in this way one of the isomers may be isolated for further treatment, in this illustration it is the (+):(-) diastereomer. Finally the salt is broken by acid treatment, giving the resolved (+)-amino acid derivative together with the recovered resolving agent (the optically active amine). Of course, the same procedure could be used to obtain the (-)-enantiomer of the amino acid.





Since amino acids are amphoteric, resolution could also be achieved by using the basic character of the amine function. For this approach we would need an enantiomerically pure chiral acid such as tartaric acid to use as the resolving agent. This alternative resolution strategy will be illustrated. Note that the carboxylic acid function is first esterified, so that it will not compete with the resolving acid.

Resolution of aminoacid derivatives may also be achieved by enzymatic discrimination in the hydrolysis of amides. For example, an aminoacylase enzyme from pig kidneys cleaves an amide derivative of a natural L-amino acid much faster than it does the D-enantiomer. If the racemic mixture of amides shown in the green shaded box above is treated with this enzyme, the L-enantiomer (whatever its rotation) will be rapidly converted to its free zwitterionic form, whereas the D-enantiomer will remain largely unchanged. Here, the diastereomeric species are transition states rather than isolable intermediates. This separation of enantiomers, based on very different rates of reaction, is called **kinetic resolution**.

ENANTIOSELECTIVE SYNTHESIS

Till now all of the synthetic routes to α-amino acids we have discussed yield a racemic mixture. Once produced one could resolve the mixture to obtain pure **L** or **D** enantiomers. However, enantioselective synthetic methods to produce pure compounds directly are being developed. For instance, several catalysts are now available for reduction of C=C to expose enantiopure amino acids. A good example is the industrial synthesis of L-DOPA, a drug used in the treatment of Parkinson's disease. W.S. Knowles shared the 2001 Nobel Price with R. Noyori and K.B. Sharpless for their contributions in the area of asymmetric catalytic reductions**.** Knowles developed several chiral phosphine–metal catalysts for asymmetric reductions. The rhodium(I) catalyst shown, which is complexed by large organic ligands, facilitates production of almost pure L-DOPA.

CONTRIBUTORS AND ATTRIBUTIONS

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25.5: PEPTIDES AND PROTEINS

Objectives

After completing this section, you should be able to

1. a. show, by means of a diagram, how two different amino acid residues can be combined to give two different dipeptides.
   b. draw the structure of a relatively simple peptide, given its full or abbreviated name and the structures of the appropriate amino acids.
   c. draw, or name, the six possible isomeric tripeptides that can be formed by combining three different amino acid residues (amino acid units) of given structure.
2. account for the fact that there is restricted rotation about the C—N bonds in peptides.
3. illustrate the formation of a disulfide linkage between two cysteine residues, and show how such bonds can link together two separate peptide chains or can provide a bridge between two cysteine residues present in a single peptide molecule.

Key Terms

Make certain that you can define, and use in context, the key terms below.

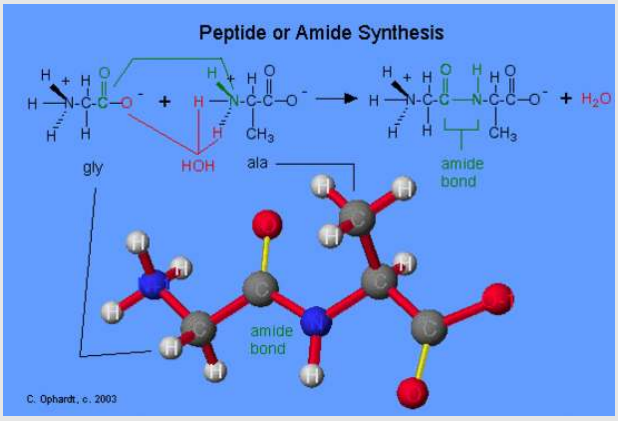
- C-terminal amino acid
- N-terminal amino acid
- peptides
- residues

Study Notes

If necessary, review the discussion of the delocalization of the nitrogen lone-pair electrons in amides that was presented in Section 24.3. Similarly, you may wish to refer back to Section 18.8 to review the interconversion of thiols and disulfides.

PEPTIDE BOND FORMATION OR AMIDE SYNTHESIS

The formation of peptides is nothing more than the application of the **amide synthesis reaction**. By convention, the amide bond in the peptides should be made in the order that the amino acids are written. The amine end (N terminal) of an amino acid is always on the left, while the acid end (C terminal) is on the right. The reaction of glycine with alanine to form the dipeptide glyclalanine is written as shown in the graphic on the left. Oxygen (red) from the acid and hydrogens (red) on the amine form a water molecule. The carboxyl oxygen (green) and the amine nitrogen (green) join to form the amide bond.



If the order of listing the amino acids is reversed, a different dipeptide is formed such as alaninylglycine.

Exercise \PageIndex1

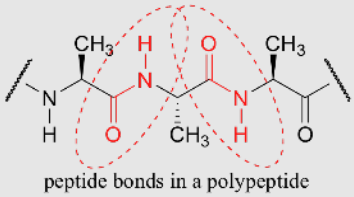
Write the reactions for:

a. ala + gly ---> Answer graphic

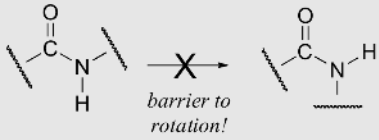
b. phe + ser ----> Answer graphic

RESONANCE CONTRIBUTORS FOR THE PEPTIDE BONDS

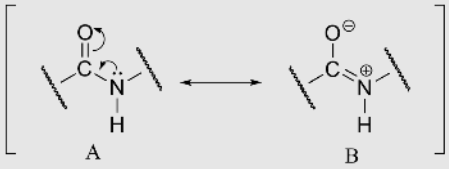
A consideration of resonance contributors is crucial to any discussion of the amide functional group. One of the most important examples of amide groups in nature is the ‘peptide bond’ that links amino acids to form polypeptides and proteins.



Critical to the structure of proteins is the fact that, although it is conventionally drawn as a single bond, the C-N bond in a peptide linkage has a significant barrier to rotation, almost as if it were a double bond.



This, along with the observation that the bonding around the peptide nitrogen has trigonal planar geometry, strongly suggests that the nitrogen is sp^2-hybridized. An important resonance contributor has a C=N double bond and a C-O single bond, with a separation of charge between the oxygen and the nitrogen.



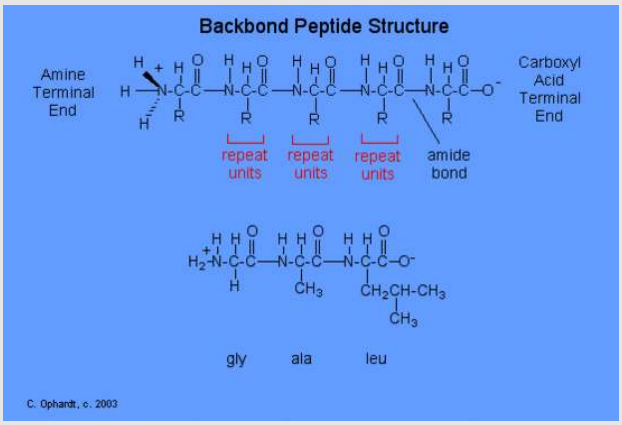
Although B is a minor contributor due to the separation of charges, it is still very relevant in terms of peptide and protein structure – our proteins would simply not fold up properly if there was free rotation about the peptide C-N bond.

BACKBONE PEPTIDE OR PROTEIN STRUCTURE

The structure of a peptide can be written fairly easily without showing the complete amide synthesis reaction by learning the structure of the "backbone" for peptides and proteins.

The peptide backbone consists of repeating units of "N-H 2, CH, C double bond O; N-H 2, CH, C double bond O; etc. See the graphic on the left .

After the backbone is written, go back and write the specific structure for the side chains as represented by the "R" as gly-ala-leu for this example. The amine end (N terminal) of an amino acid is always on the left (gly), while the acid end (C terminal) is on the right (leu).



Exercise \PageIndex2

Write the tripeptide structure for val-ser-cys. First write the "backbone" and then add the specific side chains.

Solution

 Answer graphic

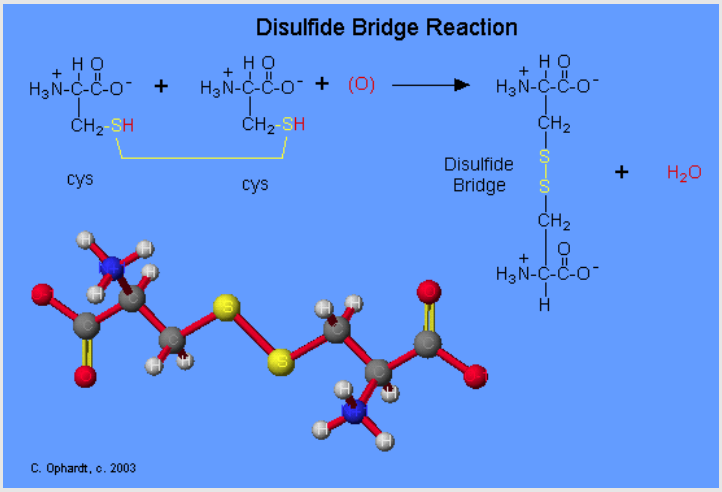
QUES. Write the structure for the tripeptide:

2 a) glu-cys-gly ---> Answer graphic

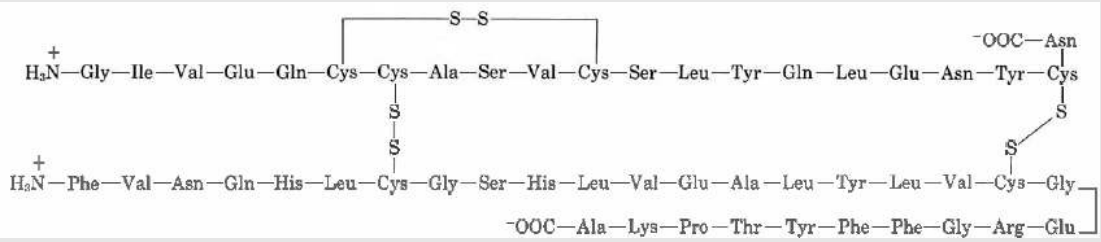
2 b) phe-tyr-asn ---> Answer graphic

DISULFIDE BRIDGES AND OXIDATION-REDUCTION

The amino acid cysteine undergoes oxidation and reduction reactions involving the -SH (sulfhydryl group). The oxidation of two sulfhydryl groups results in the formation of a **disulfide bond** by the removal of two hydrogens. The **oxidation** of two cysteine amino acids is shown in the graphic. An unspecified oxidizing agent (O) provides an oxygen which reacts with the hydrogen (red) on the -SH group to form water. The sulfurs (yellow) join to make the **disulfide bridge**. This is an important bond to recognize in protein tertiary structure. The reduction of a disulfide bond is the opposite reaction which again leads to two separate cysteine molecules. Remember that reduction is the addition of hydrogen.



Cysteine residues in the the peptide chain can form a loop buy forming the disulfide bond (—S—S—), while cysteine residues in different peptide chains can actually link what were otherwise separate chains. Insulin was the first protein whose amino acid sequence was determined. This pioneering work, completed in 1953 after some 10 years of effort, earned a Nobel Prize for British biochemist Frederick Sanger (born 1918). He found the primary structure to comprise of two chains linked by two cysteine disulfide bridges. Also note the first peptide chain possesses an internal loop.



Insulin

CONTRIBUTORS AND ATTRIBUTIONS

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Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

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

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25.6: AMINO ACID ANALYSIS OF PEPTIDES

Objectives

After completing this section, you should be able to describe, briefly, how the identity and amounts of each amino acid residue present in a peptide of unknown structure may be determined.

Key Terms

Make certain that you can define, and use in context, the key term below.

- amino acid analyzer

Study Notes

You need not memorize the reaction between ninhydrin and an *α*-amino acid.

ION-EXCHANGE CHROMATOGRAPHY

When a protein is to be analyzed, it is first heated with acid to hydrolyse all the peptide bonds. When such a mixture of amino acids is to be purified and estimated quantitatively, ion-exchange chromatography is the technique of choice. Fully automated amino acid analyzers are now available, which are equipped with a solvent pump to deliver the required buffer(s) in a programmed manner. There is a column, filled with Dowex 50 resin (Fig 26.5.1). This solid support is made up of polymeric beads. Chemically speaking they are polymers bearing arylsulfonic acid groups. The cation exchange resin helps in the separation of amino acids. In a typical run (Fig 26.5.2), the eluent is a buffer. The pH value of the buffer could be varied as step elution or as gradient elution. The chromatogram shown in Fig 26.5.2 is a chromatogram run with gradient elution technique, using **ninhydrin** as the post column treatment. The detector is a UV detector scanning the wavelengths 570 nm and 440 nm.

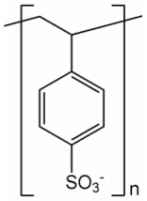


Fig 26.5.1: A Cation Rasin like Dowex 50 is a polymeric bead bearing aryl sulfonic acid groups

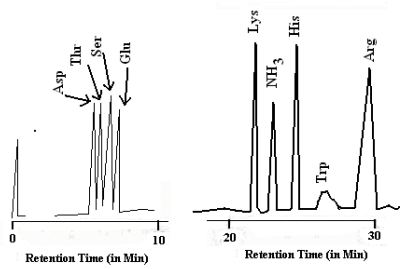
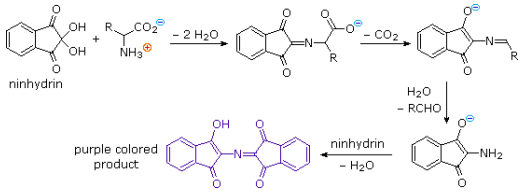


Fig 26.5.2: Some typical chromatograms from an amino acid analyzer

THE NINHYDRIN REACTION

Alpha-amino acids show reactivity at their the carboxylic acid and amine sites typical of those functional groups. In addition to these common reactions of amines and carboxylic acids, common alpha-amino acids, except proline, undergo a unique reaction with the triketohydrindene hydrate known as ninhydrin. Among the products of this unusual reaction (shown on the left below) is a purple colored imino derivative, which provides as a useful color test for these amino acids, most of which are colorless. A common application of the ninhydrin test is the visualization of amino acids in paper chromatography. As shown in the graphic on the right, samples of amino acids or mixtures thereof are applied along a line near the bottom of a rectangular sheet of paper (the baseline). The bottom edge of the paper is immersed in an aqueous buffer, and this liquid climbs slowly toward the top edge. As the solvent front passes the sample spots, the compounds in each sample are carried along at a rate which is characteristic of their functionality, size and interaction with the cellulose matrix of the paper. Some compounds move rapidly up the paper, while others may scarcely move at all. The ratio of the distance a compound moves from the baseline to the distance of the solvent front from the baseline is defined as the retardation (or retention) factor R_f. Different amino acids usually have different R_f's under suitable conditions. In the example on the right, the three sample compounds (1, 2 & 3) have respective R_f values of 0.54, 0.36 & 0.78.



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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. R Balaji Rao (Department of Chemistry, Banaras Hindu University, Varanasi) as part of Information and Communication Technology

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25.7: PEPTIDE SEQUENCING- THE EDMAN DEGRADATION

Objectives

After completing this section, you should be able to

1. describe how an Edman degradation is used to determine the sequence of the amino acid residues in peptides containing up to 20 such residues.
2. describe, briefly, how the procedure is modified to deal with peptides and proteins containing more than 20 amino acid residues.
3. write a detailed mechanism for the Edman degradation.
4. determine the structure of a peptide, given a list of the fragments that are produced by a partial acid hydrolysis.
5. determine the structure of a peptide, given a list of the fragments that are produced when the peptide is cleaved by a specific enzyme and the details of the types of bonds cleaved by that enzyme.
6. predict the fragments that would be produced when a peptide of known structure is cleaved by a specific enzyme, given sufficient information about the types of bonds that are cleaved by the enzyme in question.

Key Terms

Make certain that you can define, and use in context, the key term below.

- Edman degradation

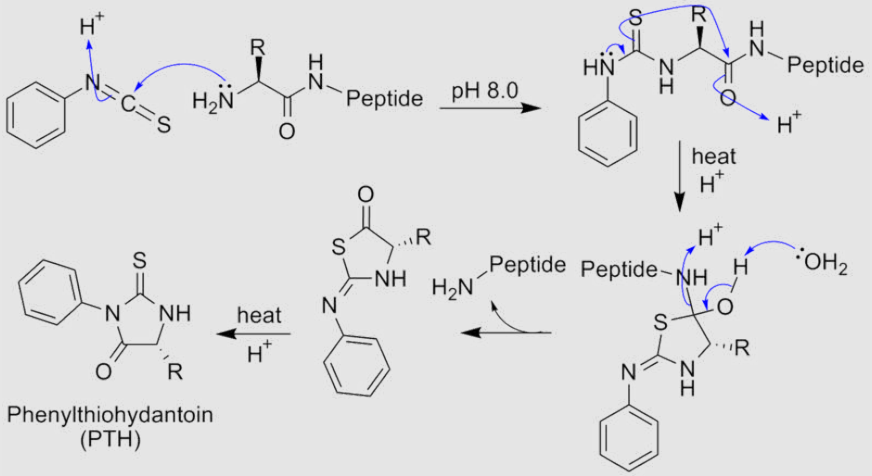
Study Notes

The reagent used in the Edman degradation is phenyl isothiocyanate. You may find it helpful to review the relationship between cyanates, isocyanates, thiocyanates and isothiocyanates.

R–O–C≡N	cyanate (such compounds do not exist)
R–N=C=O	isocyanate
R–S–C≡N	thiocyanate
R–N=C=S	isothiocyanate

You need not memorize the specific peptide bonds that are broken by the enzymes trypsin and chymotrypsin.

Edman degradation is the process of purifying protein by sequentially removing one residue at a time from the amino end of a peptide. To solve the problem of damaging the protein by hydrolyzing conditions, Pehr Edman created a new way of labeling and cleaving the peptide. Edman thought of a way of removing only one residue at a time, which did not damage the overall sequencing. This was done by adding Phenyl isothiocyanate, which creates a phenylthiocarbamoyl derivative with the N-terminal. The N-terminal is then cleaved under less harsh acidic conditions, creating a cyclic compound of phenylthiohydantoin PTH-amino acid. This does not damage the protein and leaves two constituents of the peptide. This method can be repeated for the rest of the residues, separating one residue at a time.



Edman degradation is very useful because it does not damage the protein. This allows sequencing of the protein to be done in less time. Edman sequencing is done best if the composition of the amino acid is known. As we saw in Section 26.5, to determine the composition of the amino acid, the peptide must be hydrolyzed. This can be done by denaturing the protein and heating it and adding HCl for a long time. This causes the individual amino acids to be separated, and they can be separated by ion exchange chromatography. They are then dyed with ninhydrin and the amount of amino acid can be determined by the amount of optical absorbance. This way, the composition but not the sequence can be determined

SEQUENCING LARGER PROTEINS

Larger proteins cannot be sequenced by the Edman sequencing because of the less than perfect efficiency of the method. A strategy called divide and conquer successfully cleaves the larger protein into smaller, practical amino acids. This is done by using a certain chemical or enzyme which can cleave the protein at specific amino acid residues. The separated peptides can be isolated by chromatography. Then they can be sequenced using the Edman method, because of their smaller size.

In order to put together all the sequences of the different peptides, a method of overlapping peptides is used. The strategy of divide and conquer followed by Edman sequencing is used again a second time, but using a different enzyme or chemical to cleave it into different residues. This allows two different sets of amino acid sequences of the same protein, but at different points. By comparing these two sequences and examining for any overlap between the two, the sequence can be known for the original protein.

For example, trypsin can be used on the initial peptide to cleave it at the carboxyl side of arginine and lysine residues. Using trypsin to cleave the protein and sequencing them individually with Edman degradation will yield many different individual results. Although the sequence of each individual cleaved amino acid segment is known, the order is scrambled. Chymotrypsin, which cleaves on the carboxyl side of aromatic and other bulky nonpolar residues, can be used. The sequence of these segments overlap with those of the trypsin. They can be overlapped to find the original sequence of the initial protein. However, this method is limited in analyzing larger sized proteins (more than 100 amino acids) because of secondary hydrogen bond interference. Other weak intermolecular bonding such as hydrophobic interactions cannot be properly predicted. Only the linear sequence of a protein can be properly predicted assuming the sequence is small enough.

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25.8: PEPTIDE SYNTHESIS

Objectives

After completing this section, you should be able to

1. describe why it is necessary to protect certain amino and carboxyl groups during the synthesis of a peptide.
2. describe, using appropriate equations, how carboxyl groups are protected by ester formation and amino groups are protected by the formation of their *tert*-butoxycarbonyl amide derivatives.
3. write a detailed mechanism for the formation of a peptide link between an amino acid with a protected amino group and an amino acid with a protected carboxyl group using dicyclohexylcarbodiimide.
4. outline the five steps required in order to form a dipeptide from two given amino acids.

In order to synthesize a peptide from its component amino acids, two obstacles must be overcome. The first of these is statistical in nature, and is illustrated by considering the dipeptide Ala-Gly as a proposed target. If we ignore the chemistry involved, a mixture of equal molar amounts of alanine and glycine would generate four different dipeptides. These are: **Ala-Ala, Gly-Gly, Ala-Gly & Gly-Ala**. In the case of tripeptides, the number of possible products from these two amino acids rises to eight. Clearly, some kind of selectivity must be exercised if complex mixtures are to be avoided.

The second difficulty arises from the fact that carboxylic acids and 1º or 2º-amines do not form amide bonds on mixing, but will generally react by proton transfer to give salts (the intermolecular equivalent of zwitterion formation).

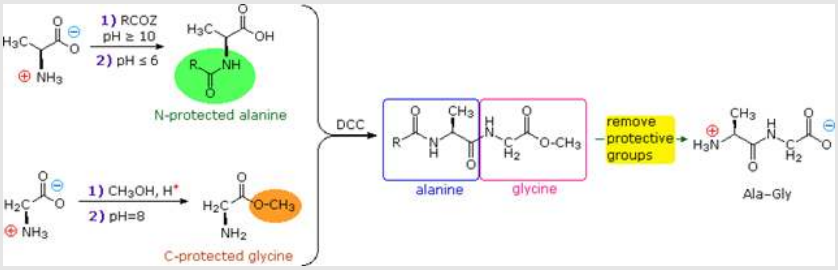
From the perspective of an organic chemist, peptide synthesis requires selective acylation of a free amine. To accomplish the desired amide bond formation, we must first deactivate all extraneous amine functions so they do not compete for the acylation reagent. Then we must selectively activate the designated carboxyl function so that it will acylate the one remaining free amine. Fortunately, chemical reactions that permit us to accomplish these selections are well known.

First, the basicity and nucleophilicity of amines are substantially reduced by amide formation. Consequently, the acylation of amino acids by treatment with acyl chlorides or anhydrides at pH > 10, as described earlier, serves to protect their amino groups from further reaction.

Second, acyl halide or anhydride-like activation of a specific carboxyl reactant must occur as a prelude to peptide (amide) bond formation. This is possible, provided competing reactions involving other carboxyl functions that might be present are precluded by preliminary ester formation. Remember, esters are weaker acylating reagents than either anhydrides or acyl halides, as noted earlier.

Finally, dicyclohexylcarbodiimide (DCC) effects the dehydration of a carboxylic acid and amine mixture to the corresponding amide under relatively mild conditions. The structure of this reagent and the mechanism of its action have been described. Its application to peptide synthesis will become apparent in the following discussion.

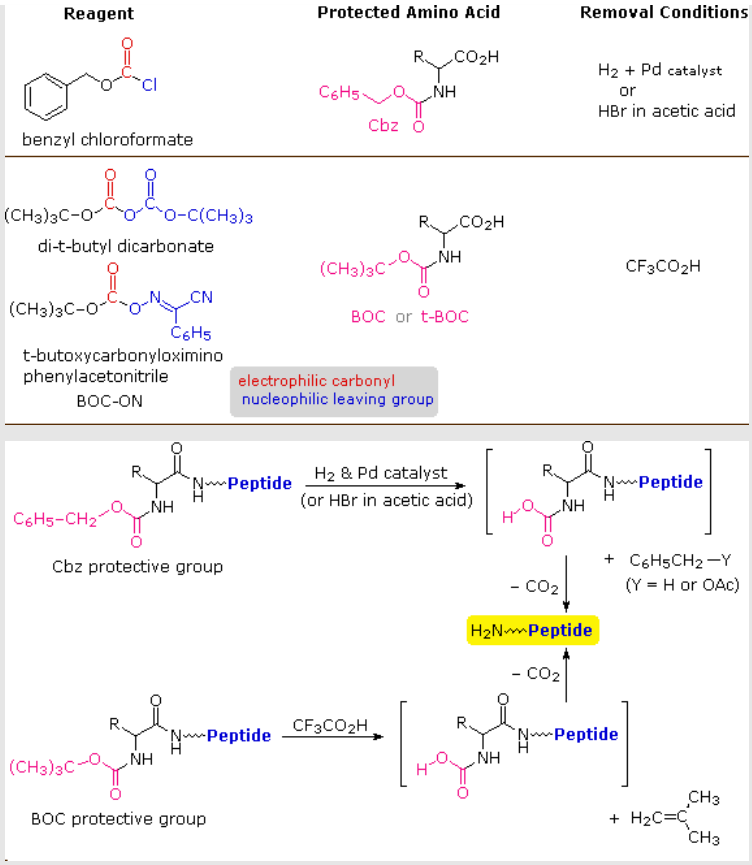
The strategy for peptide synthesis, as outlined here, should now be apparent. The following example shows a selective synthesis of the dipeptide Ala-Gly.



An important issue remains to be addressed. Since the N-protective group is an amide, removal of this function might require conditions that would also cleave the just formed peptide bond. Furthermore, the harsh conditions often required for amide hydrolysis might cause extensive racemization of the amino acids in the resulting peptide. This problem strikes at the heart of our strategy, so it is important to give careful thought to the design of specific N-protective groups. In particular, three qualities are desired:

1. The protective amide should be easy to attach to amino acids.
2. The protected amino group should not react under peptide forming conditions.
3. The protective amide group should be easy to remove under mild conditions.

A number of protective groups that satisfy these conditions have been devised; and two of the most widely used, **carbobenzoxy** (Cbz) and **t-butoxycarbonyl** (BOC or t-BOC), are described here.



The reagents for introducing these N-protective groups are the acyl chlorides or anhydrides shown in the left portion of the above diagram. Reaction with a free amine function of an amino acid occurs rapidly to give the "protected" amino acid derivative shown in the center. This can then be used to form a peptide (amide) bond to a second amino acid. Once the desired peptide bond is created the protective group can be removed under relatively mild non-hydrolytic conditions. Equations showing the protective group removal will be displayed above by are shown above. Cleavage of the reactive benzyl or tert-butyl groups generates a common carbamic acid intermediate (HOCO-NHR) which spontaneously loses carbon dioxide, giving the corresponding amine. If the methyl ester at the C-terminus is left in place, this sequence of reactions may be repeated, using a different N-protected amino acid as the acylating reagent. Removal of the protective groups would then yield a specific tripeptide, determined by the nature of the reactants and order of the reactions.

CONTRIBUTORS AND ATTRIBUTIONS

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

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25.9: AUTOMATED PEPTIDE SYNTHESIS- THE MERRIFIELD SOLID-PHASE TECHNIQUE

Objectives

After completing this section, you should be able to describe, briefly, the Merrifield solid-phase technique for the synthesis of polypeptides.

Key Terms

Make certain that you can define, and use in context, the key term below.

- solid-phase method (solid-phase synthesis)

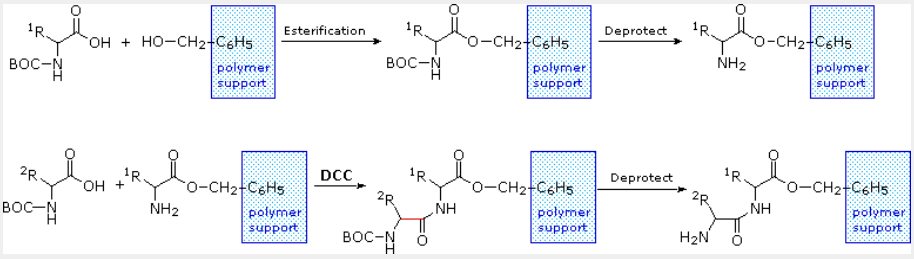
Study Notes

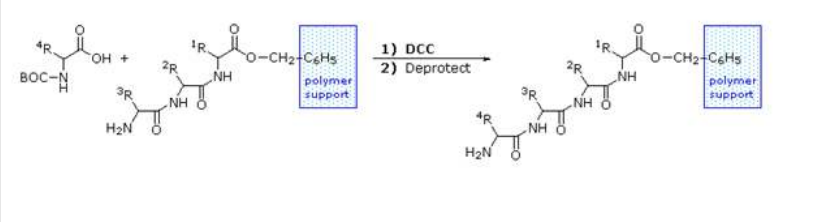
The solid-phase used in this method is a polymer support. You will not be examined on the details of the Merrifield solid-phase method; however, you should be prepared to write a couple of paragraphs describing this important process.

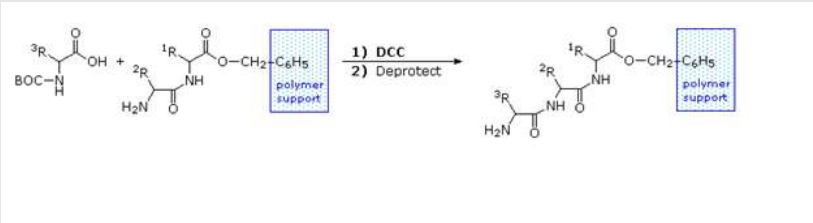
For his work on the synthesis of peptides, Bruce Merrifield was awarded the 1984 Nobel Prize in chemistry.

The synthesis of a peptide of significant length (e.g. ten residues) by this approach requires many steps, and the product must be carefully purified after each step to prevent unwanted cross-reactions. To facilitate the tedious and time consuming purifications, and reduce the material losses that occur in handling, a clever modification of this strategy has been developed. This procedure, known as the **Merrifield Synthesis** after its inventor R. Bruce Merrifield, involves attaching the C-terminus of the peptide chain to a polymeric solid, usually having the form of very small beads. Separation and purification is simply accomplished by filtering and washing the beads with appropriate solvents. The reagents for the next peptide bond addition are then added, and the purification steps repeated. The entire process can be automated, and peptide synthesis machines based on the Merrifield approach are commercially available. A series of equations illustrating the Merrifield synthesis may be viewed below. The final step, in which the completed peptide is released from the polymer support, is a simple benzyl ester cleavage. This is not shown in the display.

The Merrifield Peptide Synthesis







Two or more moderately sized peptides can be joined together by selective peptide bond formation, provided side-chain functions are protected and do not interfere. In this manner good sized peptides and small proteins may be synthesized in the laboratory. However, even if chemists assemble the primary structure of a natural protein in this or any other fashion, it may not immediately adopt its native

secondary, tertiary and quaternary structure. Many factors, such as pH, temperature and inorganic ion concentration influence the conformational coiling of peptide chains. Indeed, scientists are still trying to understand how and why these higher structures are established in living organisms.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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25.10: LEVELS OF PROTEIN STRUCTURE

Objectives

After completing this section, you should be able to

1. discuss, with reference to a suitable example (either given or of your own choice), the structure of proteins, paying particular attention to distinguishing between the primary, secondary, tertiary and quaternary structure.
2. describe the α-helical secondary structure displayed by many proteins.
3. describe the β-pleated-sheet structure displayed by many proteins.

Key Terms

Make certain that you can define, and use in context, the key terms below.

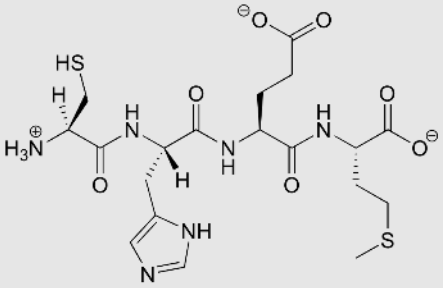
- α helix
- β pleated sheet
- primary structure
- quaternary structure
- secondary structure
- tertiary structure

Study Notes

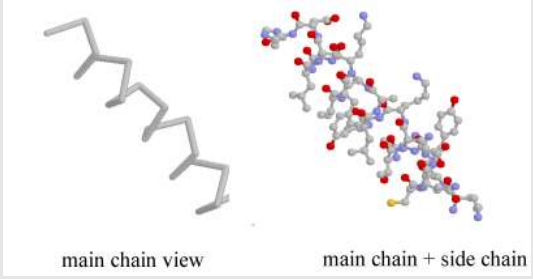
Note that in a diagram of the α-helical structure of a protein, the C-terminal of the protein is at the bottom of the diagram and the N-terminal is at the top. In an α helix, such as the one shown in Figure 26.9.1, the bulky R groups are all found on the outside of the helix, where they have the most room.

THE FOUR LEVELS OF PROTEIN STRUCTURE

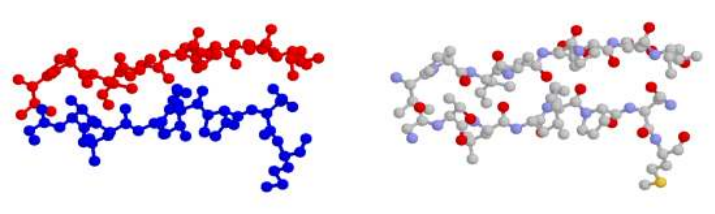
Protein structure can be discussed at four distinct levels. A protein's **primary structure** is two-dimensional - simply the sequence of amino acids in the peptide chain. Below is a Lewis structure of a short segment of a protein with the sequence CHEM (cysteine - histidine - glutamate - methionine)



Secondary structure is three-dimensional, but is a local phenomenon, confined to a relatively short stretch of amino acids. For the most part, there are three important elements of secondary structure: helices, beta-sheets, and loops. In a helix, the main chain of the protein adopts the shape of a clockwise spiral staircase, and the side chains point out laterally.

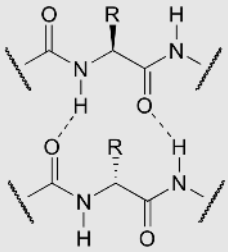


In a beta-sheet (or beta-strand) structure, two sections of protein chain are aligned side-by-side in an extended conformation. The figure below shows two different views of the same beta-sheet: in the left-side view, the two regions of protein chain are differentiated by color.



Loops are relatively disordered segments of protein chain, but often assume a very ordered structure when in contact with a second protein or a smaller organic compound.

Both helix and the beta-sheet structures are held together by very specific hydrogen-bonding interactions between the amide nitrogen on one amino acid and the carbonyl oxygen on another. The hydrogen bonding pattern in a section of a beta-strand is shown below.



hydrogen bonding in a β-strand

Secondary structure refers to the shape of a folding protein due exclusively to hydrogen bonding between its backbone amide and carbonyl groups. Secondary structure does not include bonding between the R-groups of amino acids, hydrophobic interactions, or other interactions associated with tertiary structure. The two most commonly encountered secondary structures of a polypeptide chain are α-helices and beta-pleated sheets. These structures are the first major steps in the folding of a polypeptide chain, and they establish important topological motifs that dictate subsequent tertiary structure and the ultimate function of the protein.

A-HELICES

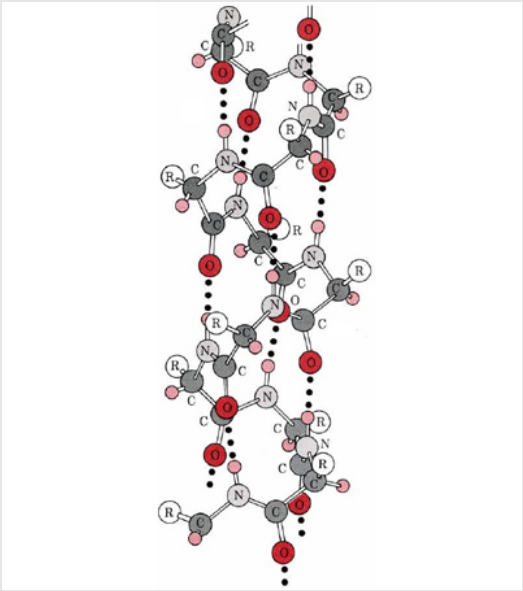
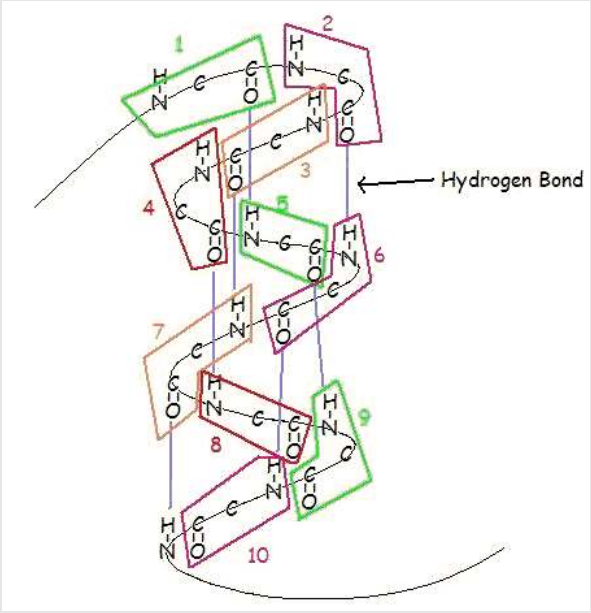


Figure: *Ball-and-stick model of the α helix. Hydrogen bonds are shown as dotted bonds. Note that R groups extend almost perpendicular from the axis.*

An α-helix is a right-handed coil of amino-acid residues on a polypeptide chain, typically ranging between 4 and 40 residues. This coil is held together by hydrogen bonds between the oxygen of C=O on top coil and the hydrogen of N-H on the bottom coil. Such a hydrogen bond is formed exactly every 4 amino acid residues, and every complete turn of the helix is only 3.6 amino acid residues. This regular pattern gives the α-helix very definite features with regards to the thickness of the coil and the length of each complete turn along the helix axis.

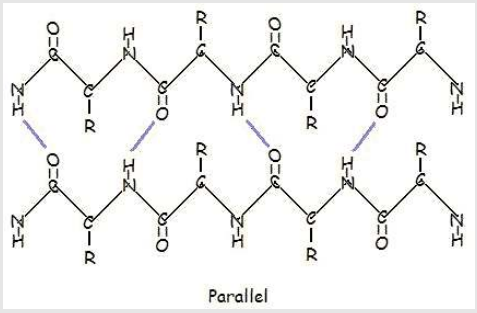
The structural integrity of an α-helix is in part dependent on correct steric configuration. Amino acids whose R-groups are too large (tryptophan, tyrosine) or too small (glycine) destabilize α-helices. Proline also destabilizes α-helices because of its irregular geometry; its R-group bonds back to the nitrogen of the amide group, which causes steric hindrance. In addition, the lack of a hydrogen on Proline's nitrogen prevents it from participating in hydrogen bonding.

Another factor affecting α-helix stability is the total dipole moment of the entire helix due to individual dipoles of the C=O groups involved in hydrogen bonding. Stable α-helices typically end with a charged amino acid to neutralize the dipole moment.

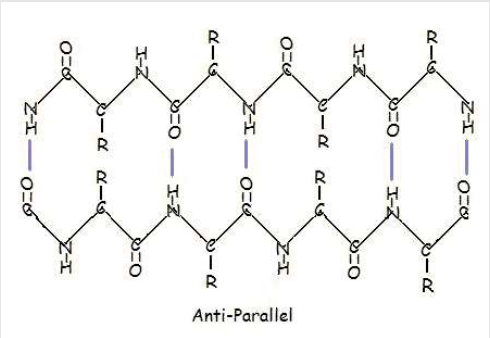


BETA-PLEATED SHEETS

This structure occurs when two (or more, e.g. ψ-loop) segments of a polypeptide chain overlap one another and form a row of hydrogen bonds with each other. This can happen in a parallel arrangement:



Or in anti-parallel arrangement:



Parallel and anti-parallel arrangement is the direct consequence of the directionality of the polypeptide chain. In anti-parallel arrangement, the C-terminus end of one segment is on the same side as the N-terminus end of the other segment. In parallel arrangement, the C-terminus end and the N-terminus end are on the same sides for both segments. The "pleat" occurs because of the

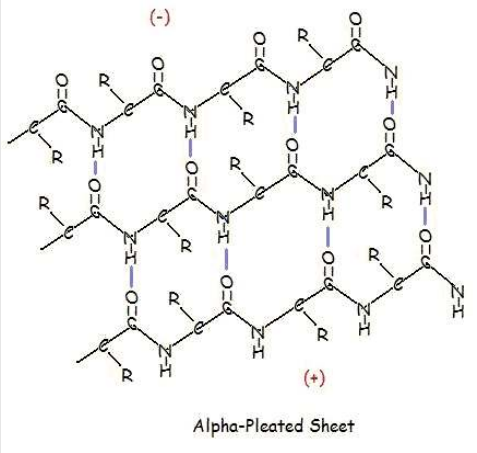
alternating planes of the peptide bonds between amino acids; the aligned amino and carbonyl group of each opposite segment alternate their orientation from facing towards each other to facing opposite directions.

The parallel arrangement is less stable because the geometry of the individual amino acid molecules forces the hydrogen bonds to occur at an angle, making them longer and thus weaker. Contrarily, in the anti-parallel arrangement the hydrogen bonds are aligned directly opposite each other, making for stronger and more stable bonds.

Commonly, an anti-parallel beta-pleated sheet forms when a polypeptide chain sharply reverses direction. This can occur in the presence of two consecutive proline residues, which create an angled kink in the polypeptide chain and bend it back upon itself. This is not necessary for distant segments of a polypeptide chain to form beta-pleated sheets, but for proximal segments it is a definite requirement. For short distances, the two segments of a beta-pleated sheet are separated by 4+2n amino acid residues, with 4 being the minimum number of residues.

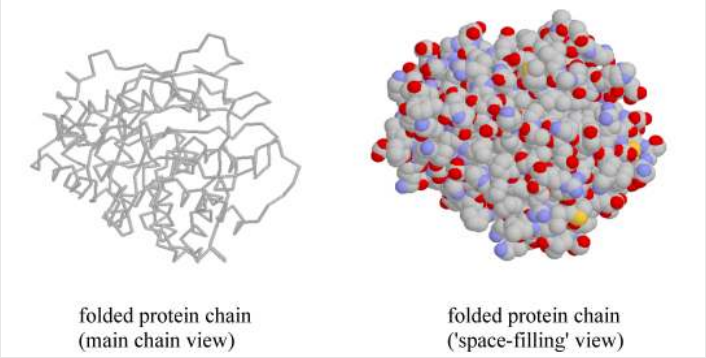
A-PLEATED SHEETS

A similar structure to the beta-pleated sheet is the α-pleated sheet. This structure is energetically less favorable than the beta-pleated sheet, and is fairly uncommon in proteins. An α-pleated sheet is characterized by the alignment of its carbonyl and amino groups; the carbonyl groups are all aligned in one direction, while all the N-H groups are aligned in the opposite direction. The polarization of the amino and carbonyl groups results in a net dipole moment on the α-pleated sheet. The carbonyl side acquires a net negative charge, and the amino side acquires a net positive charge.



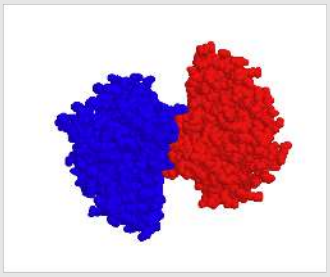
Alpha-Pleated Sheet

A protein's **tertiary structure** is the shape in which the entire protein chain folds together in three-dimensional space, and it is this level of structure that provides protein scientists with the most information about a protein's specific function.

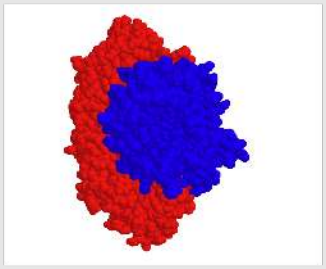

folded protein chain (main chain view)

folded protein chain ('space-filling' view)

While a protein's secondary and tertiary structure is defined by how the protein chain folds together, **quaternary structure** is defined by how two or more folded protein chains come together to form a 'superstructure'. Many proteins consist of only one protein chain, or **subunit**, and thus have no quaternary structure. Many other proteins consist of two identical subunits (these are called homodimers) or two non-identical subunits (these are called heterodimers).

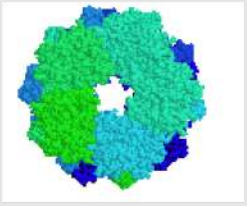


a homodimer

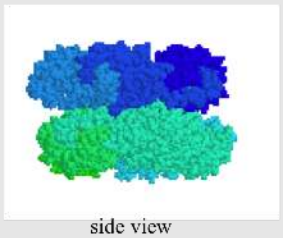


a heterodimer

Quaternary structures can be quite elaborate: below we see a protein whose quaternary structure is defined by ten identical subunits arranged in two five-membered rings, forming what can be visualized as a 'double donut' shape (this is fructose 1,6-bisphosphate aldolase):



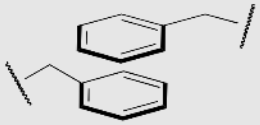
top view



side view

THE MOLECULAR FORCES THAT HOLD PROTEINS TOGETHER

The question of exactly how a protein 'finds' its specific folded structure out of the vast number of possible folding patterns is still an active area of research. What *is* known, however, is that the forces that cause a protein to fold properly and to remain folded are the same basic noncovalent forces that we talked about in chapter 2: ion-ion, ion-dipole, dipole-dipole, hydrogen bonding, and hydrophobic (van der Waals) interactions. One interesting type of hydrophobic interaction is called 'aromatic stacking', and occurs when two or more planar aromatic rings on the side chains of phenylalanine, tryptophan, or tyrosine stack together like plates, thus maximizing surface area contact.



Hydrogen bonding networks are extensive within proteins, with both side chain and main chain atoms participating. Ionic interactions often play a role in protein structure, especially on the protein surface, as negatively charged residues such as aspartate interact with positively-charged groups on lysine or arginine.

One of the most important ideas to understand regarding tertiary structure is that *a protein, when properly folded, is polar on the surface and nonpolar in the interior*. It is the protein's surface that is in contact with water, and therefore the surface must be hydrophilic in order for the whole structure to be soluble. If you examine a three dimensional protein structure you will see many charged side chains (e.g. lysine, arginine, aspartate, glutamate) and hydrogen-bonding side chains (e.g. serine, threonine, glutamine, asparagine) exposed on the surface, in direct contact with water. Inside the protein, out of contact with the surrounding water, there tend to be many more hydrophobic residues such as alanine, valine, phenylalanine, etc. If a protein chain is caused to come unfolded (through exposure to heat, for example, or extremes of pH), it will usually lose its solubility and form solid precipitates, as the hydrophobic residues from the interior come into contact with water. You can see this phenomenon for yourself if you pour a little bit of vinegar (acetic acid) into milk. The solid clumps that form in the milk are proteins that have come unfolded due to the sudden acidification, and precipitated out of solution.

In recent years, scientists have become increasing interested in the proteins of so-called 'thermophilic' (heat-loving) microorganisms that thrive in hot water environments such as geothermal hot springs. While the proteins in most organisms (including humans) will rapidly unfold and precipitate out of solution when put in hot water, the proteins of thermophilic microbes remain completely stable, sometimes even in water that is just below the boiling point. In fact, these proteins typically only gain full biological activity when in appropriately hot water - at room-temperature they act is if they are 'frozen'. Is the chemical structure of these thermostable proteins somehow unique and exotic? As it turns out, the answer to this question is 'no': the overall three-dimensional structures of

thermostable proteins look very much like those of ‘normal’ proteins. The critical difference seems to be simply that thermostable proteins have more extensive networks of noncovalent interactions, particularly ion-ion interactions on their surface, that provides them with a greater stability to heat. Interestingly, the proteins of ‘psychrophilic’ (cold-loving) microbes isolated from pockets of water in arctic ice show the opposite characteristic: they have far fewer ion-ion interactions, which gives them greater flexibility in cold temperatures but leads to their rapid unfolding in room temperature water.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Ed Vitz (Kutztown University), John W. Moore (UW-Madison), Justin Shorb (Hope College), Xavier Prat-Resina (University of Minnesota Rochester), Tim Wendorff, and Adam Hahn.

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25.11: ENZYMES AND COENZYMES

Objectives

After completing this section, you should be able to

1. describe the catalytic role of an enzyme in a biochemical reaction.
2. give an example of one fat-soluble and one water-soluble vitamin.

Key Terms

Make certain that you can define, and use in context, the key term below.

- coenzyme
- cofactor
- enzyme
- substrate
- vitamin

Study Notes

You should have a general knowledge of the function of enzymes, but you need not memorize specific names or the classification system.

A **catalyst** is any substance that increases the *rate* or speed of a chemical reaction without being changed or consumed in the reaction. **Enzymes** are biological catalysts, and nearly all of them are proteins. In addition, enzymes are highly specific in their action; that is, each enzyme catalyzes only one type of reaction in only one compound or a group of structurally related compounds. The compound or compounds on which an enzyme acts are known as its **substrates**. Enzymes are classified by reaction type into six categories show in Table **25.11.1**.

Table **25.11.1**: ***Classes of Enzymes***

Class	Type of Reaction Catalyzed	Examples
oxidoreductases	oxidation-reduction reactions	Dehydrogenases catalyze oxidation-reduction reactions involving hydrogen and reductases catalyze reactions in which a substrate is reduced.
transferases	transfer reactions of groups, such as methyl, amino, and acetyl	Transaminases catalyze the transfer of amino group, and kinases catalyze the transfer of a phosphate group.
hydrolases	hydrolysis reactions	Lipases catalyze the hydrolysis of lipids, and proteases catalyze the hydrolysis of proteins
lyases	reactions in which groups are removed without hydrolysis or addition of groups to a double bond	Decarboxylases catalyze the removal of carboxyl groups.
isomerases	reactions in which a compound is converted to its isomer	Isomerases may catalyze the conversion of an aldose to a ketose, and mutases catalyze reactions in which a functional group is transferred from one atom in a substrate to another.
ligases	reactions in which new bonds are formed between carbon and another atom; energy is required	Synthetases catalyze reactions in which two smaller molecules are linked to form a larger one.

Enzyme-catalyzed reactions occur in at least two steps. In the first step, an enzyme molecule (E) and the substrate molecule or molecules (S) collide and react to form an intermediate compound called the *enzyme-substrate* (E–S) *complex* (Equation 25.11.1). This

step is reversible because the complex can break apart into the original substrate or substrates and the free enzyme. Once the E–S complex forms, the enzyme is able to catalyze the formation of product (P), which is then released from the enzyme surface (Equation 25.11.2):

$$S + E \rightleftharpoons E\text{–}S \tag{25.11.1}$$

$$E\text{–}S \rightarrow P + E \tag{25.11.2}$$

Hydrogen bonding and other electrostatic interactions hold the enzyme and substrate together in the complex. The structural features or functional groups on the enzyme that participate in these interactions are located in a cleft or pocket on the enzyme surface. This pocket, where the enzyme combines with the substrate and transforms the substrate to product is called the active site of the enzyme (Figure 25.11.1).

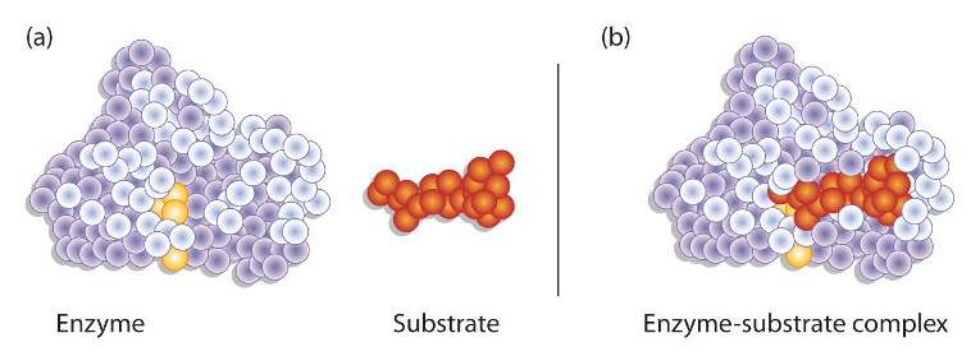


Figure* 25.11.1*: *Substrate Binding to the Active Site of an Enzyme. The enzyme dihydrofolate reductase is shown with one of its substrates: $NADP^+$ (a) unbound and (b) bound. The $NADP^+$ (shown in red) binds to a pocket that is complementary to it in shape and ionic properties.*

The active site possesses a unique conformation (including correctly positioned bonding groups) that is complementary to the structure of the substrate, so that the enzyme and substrate molecules fit together in much the same manner as a key fits into a tumbler lock. In fact, an early model describing the formation of the enzyme-substrate complex was called the lock-and-key model (Figure 25.11.2). This model portrayed the enzyme as conformationally rigid and able to bond only to substrates that exactly fit the active site.

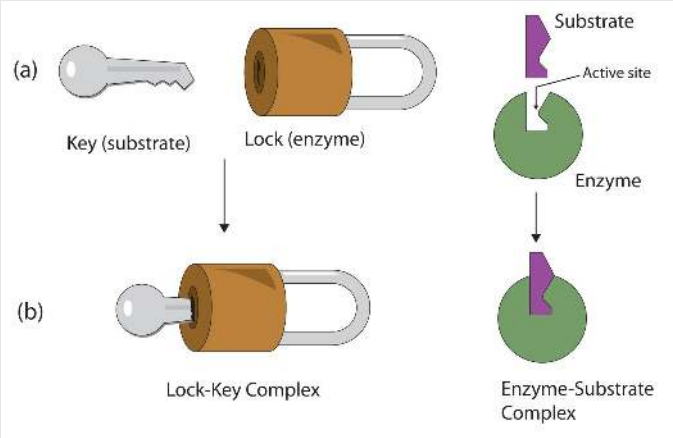


Figure 25.11.2: The Lock-and-Key Model of Enzyme Action. (a) Because the substrate and the active site of the enzyme have complementary structures and bonding groups, they fit together as a key fits a lock. (b) The catalytic reaction occurs while the two are bonded together in the enzyme-substrate complex.

Working out the precise three-dimensional structures of numerous enzymes has enabled chemists to refine the original lock-and-key model of enzyme actions. They discovered that the binding of a substrate often leads to a large conformational change in the enzyme, as well as to changes in the structure of the substrate or substrates. The current theory, known as theinduced-fit model, says that enzymes can undergo a change in conformation when they bind substrate molecules, and the active site has a shape complementary to that of the substrate only after the substrate is bound, as shown for hexokinase in Figure 25.11.3. After catalysis, the enzyme resumes its original structure.

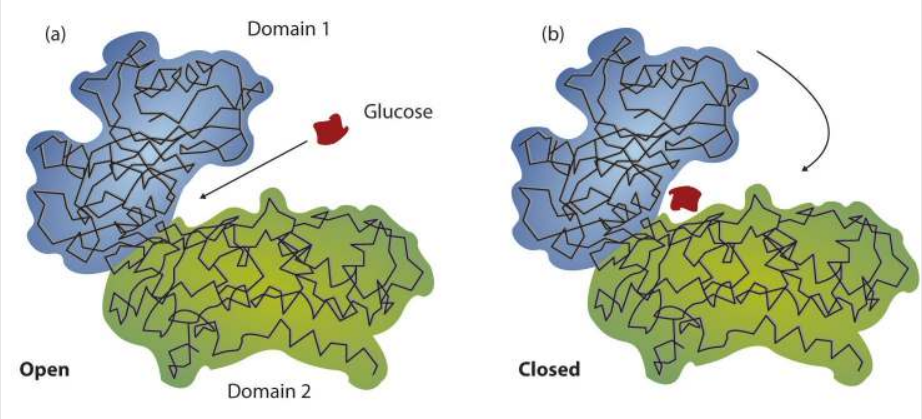


Figure **25.11.3**: The Induced-Fit Model of Enzyme Action. (a) The enzyme hexokinase without its substrate (glucose, shown in red) is bound to the active site. (b) The enzyme conformation changes dramatically when the substrate binds to it, resulting in additional interactions between hexokinase and glucose.

The structural changes that occur when an enzyme and a substrate join together bring specific parts of a substrate into alignment with specific parts of the enzyme's active site. Amino acid side chains in or near the binding site can then act as acid or base catalysts, provide binding sites for the transfer of functional groups from one substrate to another or aid in the rearrangement of a substrate. The participating amino acids, which are usually widely separated in the primary sequence of the protein, are brought close together in the active site as a result of the folding and bending of the polypeptide chain or chains when the protein acquires its tertiary and quaternary structure. Binding to enzymes brings reactants close to each other and aligns them properly, which has the same effect as increasing the concentration of the reacting compounds.

Example 25.11.1

a. What type of interaction would occur between an OH group present on a substrate molecule and a functional group in the active site of an enzyme?
b. Suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you just identified.

Solution

a. An OH group would most likely engage in hydrogen bonding with an appropriate functional group present in the active site of an enzyme.
b. Several amino acid side chains would be able to engage in hydrogen bonding with an OH group. One example would be asparagine, which has an amide functional group.

Exercise 25.11.1

a. What type of interaction would occur between an COO^- group present on a substrate molecule and a functional group in the active site of an enzyme?
b. Suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you just identified.

ENZYME COFACTORS AND VITAMINS

Many enzymes are simple proteins consisting entirely of one or more amino acid chains. Other enzymes contain a nonprotein component called a **cofactor** that is necessary for the enzyme's proper functioning. There are two types of cofactors: inorganic ions [e.g., zinc or Cu(I) ions] and organic molecules known as coenzymes. Most **coenzymes** are vitamins or are derived from vitamins.

Vitamins are organic compounds that are essential in very small (trace) amounts for the maintenance of normal metabolism. They generally cannot be synthesized at adequate levels by the body and must be obtained from the diet. The absence or shortage of a vitamin may result in a vitamin-deficiency disease. In the first half of the 20th century, a major focus of biochemistry was the identification, isolation, and characterization of vitamins. Despite accumulating evidence that people needed more than just carbohydrates, fats, and proteins in their diets for normal growth and health, it was not until the early 1900s that research established the need for trace nutrients in the diet.

Table **25.11.2**: Fat-Soluble Vitamins and Physiological Functions

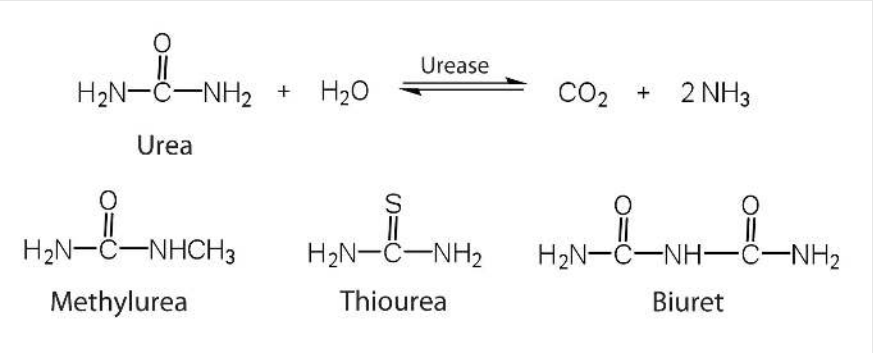
Vitamin	Physiological Function	Effect of Deficiency
vitamin A (retinol)	formation of vision pigments; differentiation of epithelial cells	night blindness; continued deficiency leads to total blindness
vitamin D (cholecalciferol)	increases the body's ability to absorb calcium and phosphorus	osteomalacia (softening of the bones); known as rickets in children
vitamin E (tocopherol)	fat-soluble antioxidant	damage to cell membranes
vitamin K (phylloquinone)	formation of prothrombin, a key enzyme in the blood-clotting process	increases the time required for blood to clot

Because organisms differ in their synthetic abilities, a substance that is a vitamin for one species may not be so for another. Over the past 100 years, scientists have identified and isolated 13 vitamins required in the human diet and have divided them into two broad categories: the *fat-soluble vitamins* (Table **25.11.2**), which include vitamins A, D, E, and K, and the *water-soluble vitamins*, which are the B complex vitamins and vitamin C (Table **25.11.3**). All fat-soluble vitamins contain a high proportion of hydrocarbon structural components. There are one or two oxygen atoms present, but the compounds as a whole are nonpolar. In contrast, water-soluble vitamins contain large numbers of electronegative oxygen and nitrogen atoms, which can engage in hydrogen bonding with water. Most water-soluble vitamins act as coenzymes or are required for the synthesis of coenzymes. The fat-soluble vitamins are important for a variety of physiological functions.

Table **25.11.3**: ***Water-Soluble Vitamins and Physiological Functions***

Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
vitamin B_1 (thiamine)	thiamine pyrophosphate	decarboxylation reactions	beri-beri
vitamin B_2 (riboflavin)	flavin mononucleotide or flavin adenine dinucleotide	oxidation-reduction reactions involving two hydrogen atoms	—
vitamin B_3 (niacin)	nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide phosphate	oxidation-reduction reactions involving the hydride ion (H^-)	pellagra
vitamin B_6 (pyridoxine)	pyridoxal phosphate	variety of reactions including the transfer of amino groups	—
vitamin B_{12} (cyanocobalamin)	methylcobalamin or deoxyadenoxylcobalamin	intramolecular rearrangement reactions	pernicious anemia
biotin	biotin	carboxylation reactions	—
folic acid	tetrahydrofolate	carrier of one-carbon units such as the formyl group	anemia
pantothenic Acid	coenzyme A	carrier of acyl groups	—
vitamin C (ascorbic acid)	none	antioxidant; formation of collagen, a protein found in tendons, ligaments, and bone	scurvy

One characteristic that distinguishes an enzyme from all other types of catalysts is its *substrate specificity*. An inorganic acid such as sulfuric acid can be used to increase the reaction rates of many different reactions, such as the hydrolysis of disaccharides, polysaccharides, lipids, and proteins, with complete impartiality. In contrast, enzymes are much more specific. Some enzymes act on a single substrate, while other enzymes act on any of a group of related molecules containing a similar functional group or chemical bond. Some enzymes even distinguish between D- and L-stereoisomers, binding one stereoisomer but not the other. Urease, for example, is an enzyme that catalyzes the hydrolysis of a single substrate—urea—but not the closely related compounds methyl urea, thiourea, or biuret. The enzyme carboxypeptidase, on the other hand, is far less specific. It catalyzes the removal of nearly any amino acid from the carboxyl end of any peptide or protein.



Enzyme specificity results from the uniqueness of the active site in each different enzyme because of the identity, charge, and spatial orientation of the functional groups located there. It regulates cell chemistry so that the proper reactions occur in the proper place at the proper time. Clearly, it is crucial to the proper functioning of the living cell.

CONCEPT REVIEW EXERCISES

1. Distinguish between the lock-and-key model and induced-fit model of enzyme action.
2. Which enzyme has greater specificity—urease or carboxypeptidase? Explain.

ANSWERS

1. The lock-and-key model portrays an enzyme as conformationally rigid and able to bond only to substrates that exactly fit the active site. The induced fit model portrays the enzyme structure as more flexible and is complementary to the substrate only after the substrate is bound.
2. Urease has the greater specificity because it can bind only to a single substrate. Carboxypeptidase, on the other hand, can catalyze the removal of nearly any amino acid from the carboxyl end of a peptide or protein.

TAKEAWAYS

- A substrate binds to a specific region on an enzyme known as the active site, where the substrate can be converted to product.
- The substrate binds to the enzyme primarily through hydrogen bonding and other electrostatic interactions.
- The induced-fit model says that an enzyme can undergo a conformational change when binding a substrate.
- Enzymes exhibit varying degrees of substrate specificity.

EXERCISES

1. What type of interaction would occur between each group present on a substrate molecule and a functional group of the active site in an enzyme?
   a. COO^-
   b. NH_3^+
   c. OH
   d. $CH(CH_3)_2$
2. What type of interaction would occur between each group present on a substrate molecule and a functional group of the active site in an enzyme?
   a. SH
   b. NH_2
   c. C_6H_5
   d. COO^-
3. For each functional group in Exercise 1, suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you identified.
4. For each functional group in Exercise 2, suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you identified.

ANSWERS

1. a. ionic bonding (salt bridge)
   b. ionic bonding (salt bridge)
   c. hydrogen bonding
   d. dispersion forces

2. a. disulfide bridge
b. H-bond because we can infer this amino group is part of an amide since it is not ionized
c. London dispersion
d. salt bridge (ionic bonding)

3. a. The amino acid has a positively charged side chain capable of forming salt bridges: histidine or arginine or lysine.
   b. The amino acid has a negatively charged side chain capable of forming salt bridges; aspartic acid or glutamic acid.
   c. The amino acid has a polar side chain capable of engaging in hydrogen bonding: serine or threonine or tyrosine or asparagine or glutamine or cysteine.
   d. The amino acid has a nonpolar side chain with London dispersion forces: alanine or valine or phenylalanine or leucine or isoleucine or methionine or tryptophan or proline or glycine.

4. a. The amino acid can form a disulfide bridge: cysteine OR the amino acid has a polar side chain capable of engaging in hydrogen bonding: serine or threonine or tyrosine or asparagine or glutamine

b. The amino acid has a polar side chain capable of engaging in hydrogen bonding: serine or threonine or tyrosine or asparagine or glutamine or cysteine.

c. The amino acid has a nonpolar side chain with London dispersion forces: alanine or valine or phenylalanine or leucine or isoleucine or methionine or tryptophan or proline or glycine.

d. The amino acid has a positively charged side chain capable of forming salt bridges: histidine or arginine or lysine.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

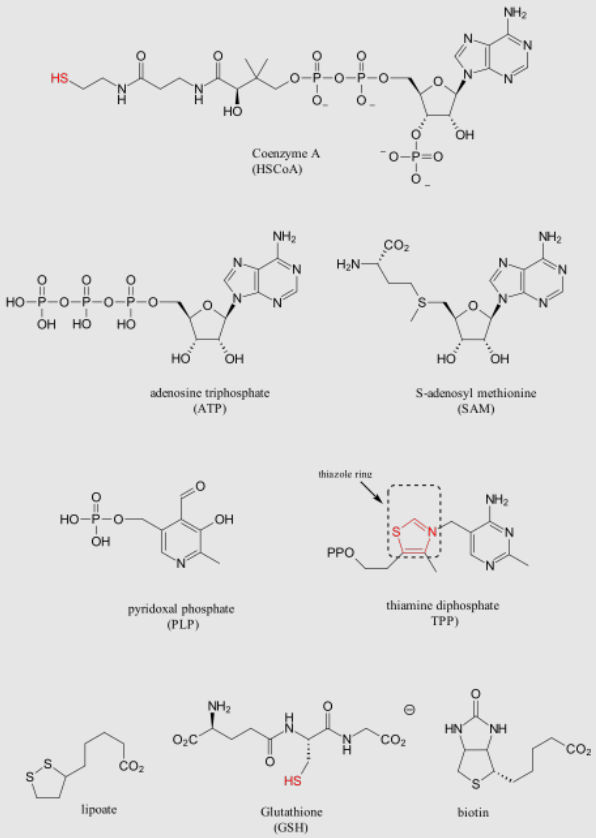
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25.12: HOW DO ENZYMES WORK?

Objectives

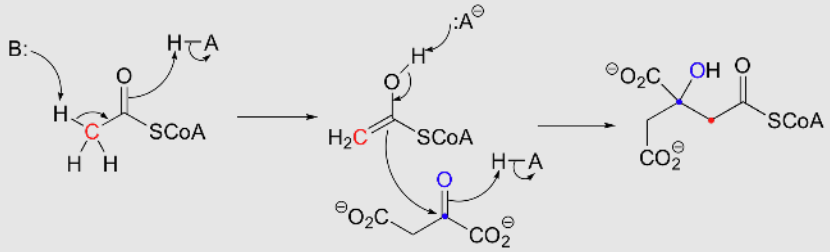
After completing this section, you should be able to

1. describe and explain the general function of an enzyme like citrate synthase in a reaction.
2. identify the structures of ten common coenzymes.

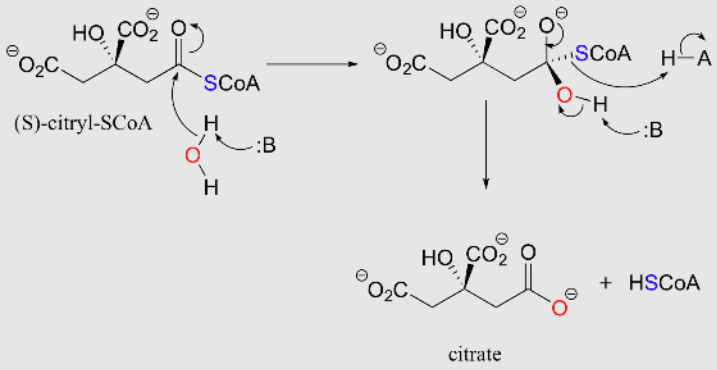


OXALOACETATE TO CITRATE CATALYZED BY CITRATE SYNTHASE

Citrate synthase is a protein with 433 amino acids with various functional groups that can react with substrates. This enzyme catalyzes oxaloacetate to eventually produce citrate as part of the citric acid (Krebs) cycle. In the first step of the citric acid (Krebs) cycle, acetyl CoA condenses with oxaloacetate to form (S)-citryl CoA. The carboxylate group of an aspartic acid (B:) on citrate synthase removes the acidic alpha proton on acetyl CoA, while a histidine site (H-A) donates a proton to form the enol. Then a second histidine site (H-A) protonates the carbonyl oxygen of oxaloacetate, while the carbon of the carbonyl is attacked by the enol. Simultaeously, that first histidine ($:A^-$) deprotonates the acetyl CoA enol. (S)-citryl CoA is generated.



The acyl group of a thioester of (S)-citryl CoA can be transferred to a water molecule in a hydrolysis reaction to converting (S)-citryl CoA to citrate. Again histidine sites on citrate synthase are an integral part of the mechanism and assist with removal and addition of protons.



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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CHAPTER OVERVIEW

26: LIPIDS

26.1: Introduction
26.2: Waxes, Fats, and Oils
26.3: Saponification of Fats and Oils; Soaps and Detergents
26.4: Phospholipids
26.5: Prostaglandins and other Eicosanoids
26.6: Terpenes and Terpenoids
26.7: Steroids
26.8: Biosynthesis of Steroids

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26.1: INTRODUCTION

Objectives

After completing this section, you should be able to identify fats and steroids as being examples of lipids.

Key Terms

Make certain that you can define, and use in context, the key term below.

- lipid

Lipids are not defined by the presence of specific functional groups, as carbohydrates are, but by a physical property—solubility. Compounds isolated from body tissues are classified as lipids if they are more soluble in organic solvents, such as dichloromethane, than in water. By this criterion, the lipid category includes not only **fats and oils**, which are esters of the trihydroxy alcohol glycerol and fatty acids, but also compounds that incorporate functional groups derived from phosphoric acid, carbohydrates, or amino alcohols, as well as **steroid compounds** such as cholesterol. The diagram below presents one scheme for classifying the various kinds of lipids.

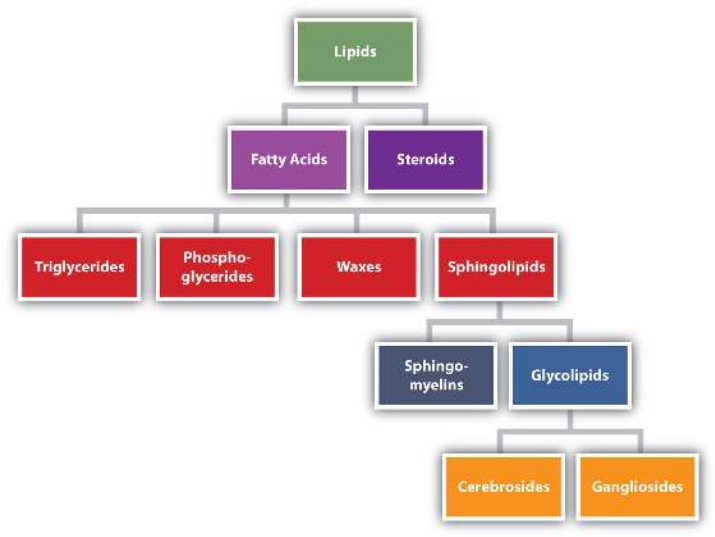


Figure: *Lipid Organization Based on Structural Relationships*

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- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

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26.2: WAXES, FATS, AND OILS

Objectives

After completing this section, you should be able to

1. identify waxes as being mixtures of long-chain esters, and write the general structure for such compounds.
2. identify fats and oils as being triacylglycerols, and write a general structure for such compounds.
3. relate the physical properties of animal fats and vegetable oils to their structures.
4. predict the behaviour of a given fat or oil when it is subjected to some of the more common reactions discussed in previous units; examples would include hydrolysis, reduction and ozonolysis.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- fat
- fatty acids
- triacylglycerols

Study Notes

You are not expected to memorize the trivial names or formulas of the fatty acids listed in Table 27.1. The systematic names for these compounds are shown in the tables below.

Saturated Fatty Acids

Table 27.1 Systematic names of some common saturated fatty acids

Trivial Name	Systematic Name
lauric acid	dodecanoic acid
myristic acid	tetradecanoic acid
palmitic acid	hexadecanoic acid
stearic acid	octadecanoic acid
arachidic acid	eicosanoic acid

Unsaturated Fatty Acids

Table 27.2 Systematic names of some common unsaturated fatty acids

Trivial Name	Systematic Name
palmitoleic acid	(*Z*)-9-hexadecenoic acid
oleic acid	(*Z*)-9-octadecenoic acid
ricinoleic acid	(*Z*)-12-hydroxy-9-octadecenoic acid
linoleic acid	(*Z*,*Z*)-9,12-octadecadienoic acid
linolenic acid	(*Z*,*Z*,*Z*)-9,12,15-octadecatrienoic acid
arachidonic acid	(*Z*,*Z*,*Z*,*Z*)-5,8,11,14-eicosatetraenoic acid

The systematic names in these tables may be somewhat unfamiliar, but they are derived in exactly the same way as the names of the simpler carboxylic acids that we discussed in Chapter 20. You may wish to review the alkane names (Section 3.2) and the *E*,*Z* system (Section 7.5) to satisfy yourself that you understand how these names originate.

In many older textbooks, the term “fatty acid” is used to describe all carboxylic acids, not only those that are obtained from the hydrolysis of triacylglycerols.

Fats play an important role in human nutrition, and most people are aware of the desirability of limiting their dietary intake of saturated fats, as these compounds have been associated with heart disease. Unsaturated fats are generally considered to be much more desirable from the point of view of good health. Notice that all the fatty acids derived from naturally occurring fats have a *Z* (i.e., cis) configuration.

Linoleic acid is an “essential” nutrient; that is, it cannot be made by the body in sufficient quantity to meet our physiological needs, and must be obtained from food. A deficiency in linoleic acid results in skin problems and liver abnormalities. Historically,

linolenic and arachidonic acids were also thought to be essential nutrients, but recent research suggests that they can be synthesized in the body if sufficient linoleic acid is present.

Waxes are esters of fatty acids with long chain monohydric alcohols (one hydroxyl group). Natural waxes are often mixtures of such esters, and may also contain hydrocarbons. The formulas for three well known waxes are given below, with the carboxylic acid moiety colored red and the alcohol colored blue.

Spermaceti	Beeswax	Carnuba wax
$CH_3(CH_2)_{14}CO_2$-$(CH_2)_{15}CH_3$	$CH_3(CH_2)_{24}CO_2$-$(CH_2)_{29}CH_3$	$CH_3(CH_2)_{30}CO_2$-$(CH_2)_{33}CH_3$

Waxes are widely distributed in nature. The leaves and fruits of many plants have waxy coatings, which may protect them from dehydration and small predators. The feathers of birds and the fur of some animals have similar coatings which serve as a water repellent. Carnuba wax is valued for its toughness and water resistance.

Triglycerides are esters of fatty acids and a trifunctional alcohol - glycerol (IUPAC name is 1,2,3-propantriol). The properties of fats and oils follow the same general principles as already described for the fatty acids. The important properties to be considered are: melting points and degree of unsaturation from component fatty acids. Since glycerol has three alcohol functional groups, three fatty acids must react to make three ester functional groups. The three fatty acids may or may not be identical. In fact, three different fatty acids may be present. The synthesis of a triglyceride is another application of the ester synthesis reaction. To write the structure of the triglyceride you must know the structure of glycerol and be given or look up the structure of the fatty acid in the table.

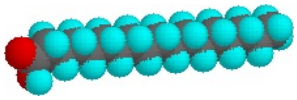
The common fats and oils including fatty acid content are listed below.

glycerides					
Fat or Oil	Saturated		Unsaturated		
	Palmitic	Stearic	Oleic	Linoleic	Other
Animal Origin					
Butter	29	9	27	4	31
Lard	30	18	41	6	5
Beef	32	25	38	3	2
Vegetable Origin					
Corn oil	10	4	34	48	4
Soybean	7	3	25	56	9
Peanut	7	5	60	21	7
Olive	6	4	83	7	-

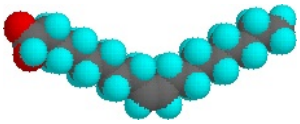
Saturated Fatty Acids		
Formula	Common Name	Melting Point
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 °C
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 °C
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 °C
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 °C
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 °C

Unsaturated Fatty Acids		
Formula	Common Name	Melting Point
$CH_3(CH_2)_5CH=CH(CH_2)_7CO_2H$	palmitoleic acid	0 °C
$CH_3(CH_2)_7CH=CH(CH_2)_7CO_2H$	oleic acid	13 °C
$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linoleic acid	-5 °C
$CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linolenic acid	-11 °C
$CH_3(CH_2)_4(CH=CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 °C

The higher melting points of the saturated fatty acids reflect the uniform rod-like shape of their molecules. The cis-double bond(s) in the unsaturated fatty acids introduce a kink in their shape, which makes it more difficult to pack their molecules together in a stable repeating array or crystalline lattice. The trans-double bond isomer of oleic acid, known as elaidic acid, has a linear shape and a melting point of 45 ºC (32 ºC higher than its cis isomer). The shapes of stearic and oleic acids are displayed in the models below.

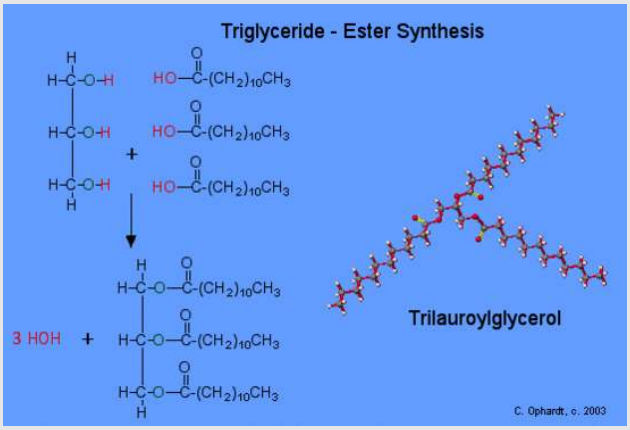


Stearic acid



Oleic acid

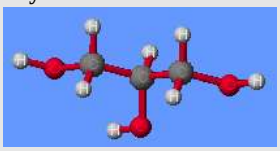
Two polyunsaturated fatty acids, linoleic and linolenic, are designated "essential" because their absence in the human diet has been associated with health problems, such as scaley skin, stunted growth and increased dehydration. These acids are also precursors to the prostaglandins, a family of physiologically potent lipids present in minute amounts in most body tissues.



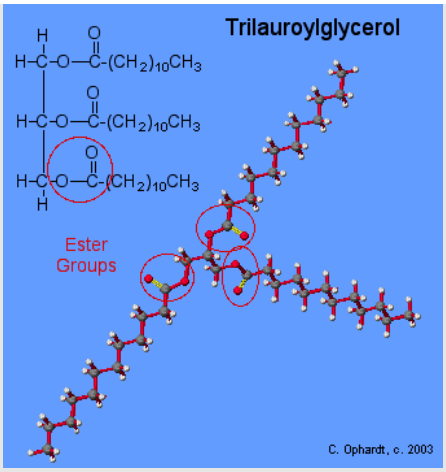
SYNTHESIS OF A TRIGLYCERIDE

Since glycerol, (IUPAC name is 1,2,3-propantriol), has three alcohol functional groups, three fatty acids must react to make three ester functional groups. The three fatty acids may or may not be identical. In fact, three different fatty acids may be present. nThe synthesis of a triglyceride is another application of the ester synthesis reaction. To write the structure of the triglyceride you must know the structure of glycerol and be given or look up the structure of the fatty acid in the table - find lauric acid.

Glycerol



The simplified reaction reveals the process of breaking some bonds and forming the ester and the by product, water. Refer to the graphic on the left for the synthesis of **trilauroylglycerol**. First, the -OH (red) bond on the acid is broken and the -H (red) bond on the alcohol is also broken. Both join to make HOH, a water molecule. Secondly, the oxygen of the alcohol forms a bond (green) to the acid at the carbon with the double bond oxygen. This forms the ester functional group. This process is carried out three times to make three ester groups and three water molecules.



As might be expected from the properties of the fatty acids, fats have a predominance of saturated fatty acids, and oils are composed largely of unsaturated acids. Thus, the melting points of triglycerides reflect their composition, as shown by the following examples. Natural mixed triglycerides have somewhat lower melting points, the melting point of lard being near 30 º C, whereas olive oil melts near -6 º C. Since fats are valued over oils by some Northern European and North American populations, vegetable oils are extensively converted to solid triglycerides (e.g. Crisco) by partial hydrogenation of their unsaturated components. Some of the remaining double bonds are isomerized (to trans) in this operation. These saturated and trans-fatty acid glycerides in the diet have been linked to long-term health issues such as atherosclerosis.



Triglycerides having three identical acyl chains, such as tristearin and triolein (above), are called "simple", while those composed of different acyl chains are called "mixed". If the acyl chains at the end hydroxyl groups (1 & 3) of glycerol are different, the center carbon becomes a chiral center and enantiomeric configurations must be recognized.

The hydrogenation of vegetable oils to produce semisolid products has had unintended consequences. Although the hydrogenation imparts desirable features such as spreadability, texture, "mouth feel," and increased shelf life to naturally liquid vegetable oils, it introduces some serious health problems. These occur when the cis-double bonds in the fatty acid chains are not completely saturated in the hydrogenation process. The catalysts used to effect the addition of hydrogen isomerize the remaining double bonds to their trans configuration. These unnatural trans-fats appear to to be associated with increased heart disease, cancer, diabetes and obesity, as well as immune response and reproductive problems.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Charles Ophardt, Professor Emeritus, Elmhurst College; Virtual Chembook

26.2: Waxes, Fats, and Oils is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

26.3: SAPONIFICATION OF FATS AND OILS; SOAPS AND DETERGENTS

Learning Objectives

After completing this section, you should be able to

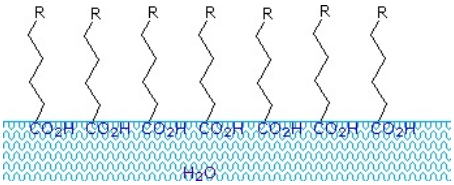
1. a. write an equation to represent the formation of a soap.
   b. identify the structure of the fat required to produce a given soap.
   c. identify the structure of a soap, given the structure of the fat from which it is produced.
2. describe the mechanism by which soaps exert their cleansing action.
3. give a chemical explanation of the problems encountered when carboxylate soaps are used in hard-water areas, and explain how they may be overcome by the use of sulphonate detergents.

Key Terms

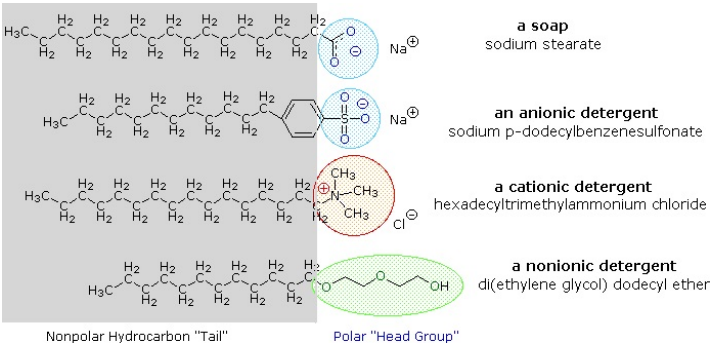
Make certain that you can define, and use in context, the key terms below.

- hydrophilic
- lipophilic (hydrophobic)
- amphiphilic
- micelles

Carboxylic acids and salts having alkyl chains longer than eight carbons exhibit unusual behavior in water due to the presence of both hydrophilic (CO_2) and hydrophobic (alkyl) regions in the same molecule. Such molecules are termed **amphiphilic** (Gk. amphi = both) or **amphipathic**. Fatty acids made up of ten or more carbon atoms are nearly insoluble in water, and because of their lower density, float on the surface when mixed with water. Unlike paraffin or other alkanes, which tend to puddle on the waters surface, these fatty acids spread evenly over an extended water surface, eventually forming a monomolecular layer in which the polar carboxyl groups are hydrogen bonded at the water interface, and the hydrocarbon chains are aligned together away from the water. This behavior is illustrated in the diagram on the right. Substances that accumulate at water surfaces and change the surface properties are called **surfactants**.

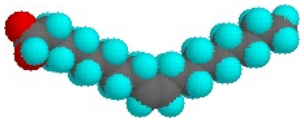


Alkali metal salts of fatty acids are more soluble in water than the acids themselves, and the amphiphilic character of these substances also make them strong surfactants. The most common examples of such compounds are soaps and detergents, four of which are shown below. Note that each of these molecules has a nonpolar hydrocarbon chain, the "tail", and a polar (often ionic) "head group". The use of such compounds as cleaning agents is facilitated by their surfactant character, which lowers the surface tension of water, allowing it to penetrate and wet a variety of materials.



Very small amounts of these surfactants dissolve in water to give a random dispersion of solute molecules. However, when the concentration is increased an interesting change occurs. The surfactant molecules reversibly assemble into polymolecular aggregates called micelles. By gathering the hydrophobic chains together in the center of the micelle, disruption of the hydrogen bonded structure of liquid

water is minimized, and the polar head groups extend into the surrounding water where they participate in hydrogen bonding. These micelles are often spherical in shape, but may also assume cylindrical and branched forms, as illustrated on the right. Here the polar head group is designated by a blue circle, and the nonpolar tail is a zig-zag black line.

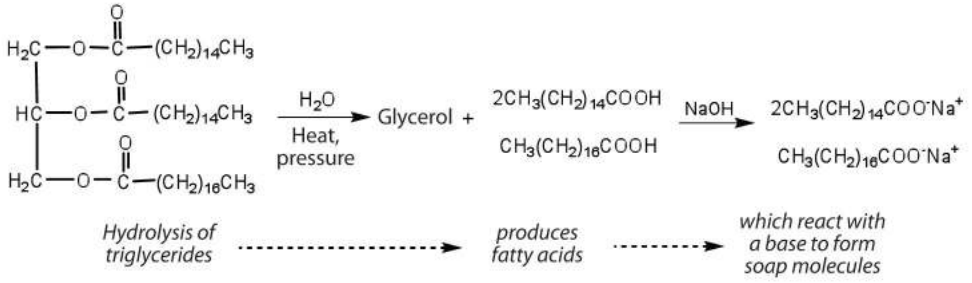


The oldest amphiphilic cleaning agent known to humans is soap. Soap is manufactured by the base-catalyzed hydrolysis (saponification) of animal fat (see below). Before sodium hydroxide was commercially available, a boiling solution of potassium carbonate leached from wood ashes was used. Soft potassium soaps were then converted to the harder sodium soaps by washing with salt solution. The importance of soap to human civilization is documented by history, but some problems associated with its use have been recognized. One of these is caused by the weak acidity (pKa ca. 4.9) of the fatty acids. Solutions of alkali metal soaps are slightly alkaline (pH 8 to 9) due to hydrolysis. If the pH of a soap solution is lowered by acidic contaminants, insoluble fatty acids precipitate and form a scum. A second problem is caused by the presence of calcium and magnesium salts in the water supply (hard water). These divalent cations cause aggregation of the micelles, which then deposit as a dirty scum.

These problems have been alleviated by the development of synthetic amphiphiles called detergents (or syndets). By using a much stronger acid for the polar head group, water solutions of the amphiphile are less sensitive to pH changes. Also the sulfonate functions used for virtually all anionic detergents confer greater solubility on micelles incorporating the alkaline earth cations found in hard water. Variations on the amphiphile theme have led to the development of other classes, such as the cationic and nonionic detergents shown above. Cationic detergents often exhibit germicidal properties, and their ability to change surface pH has made them useful as fabric softeners and hair conditioners. These versatile chemical "tools" have dramatically transformed the household and personal care cleaning product markets over the past fifty years

CHEMICAL REACTIONS OF FATS AND OILS

Fats and oils can participate in a variety of chemical reactions—for example, because triglycerides are esters, they can be hydrolyzed in the presence of an acid, a base, or specific enzymes known as lipases. The hydrolysis of fats and oils in the presence of a base is used to make soap and is called saponification. Today most soaps are prepared through the hydrolysis of triglycerides (often from tallow, coconut oil, or both) using water under high pressure and temperature [700 lb/in^2 (~50 atm or 5,000 kPa) and 200°C]. Sodium carbonate or sodium hydroxide is then used to convert the fatty acids to their sodium salts (soap molecules):



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- *The Basics of General, Organic, and Biological Chemistry* by David W. Ball, John W. Hill, and Rhonda J. Scott.

26.3: Saponification of Fats and Oils; Soaps and Detergents is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

26.4: PHOSPHOLIPIDS

Learning Objectives

After completing this section, you should be able to

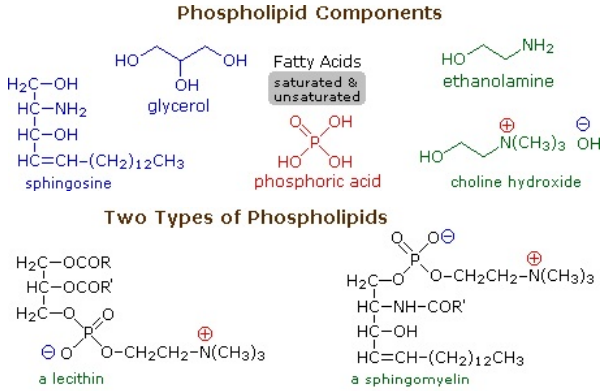
1. draw the general structure of a phosphoglyceride.
2. describe the occurrence and importance of phosphoglycerides in plant and animal tissues.

Key Terms

Make certain that you can define, and use in context, the key terms below.

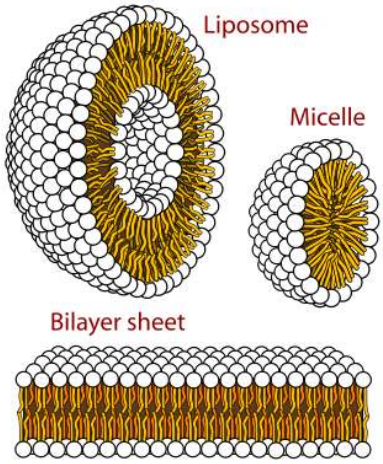
- phosphoglyceride
- phospholipid

Phospholipids are the main constituents of cell membranes. They resemble the triglycerides in being ester or amide derivatives of glycerol or sphingosine with fatty acids and phosphoric acid. The phosphate moiety of the resulting phosphatidic acid is further esterified with ethanolamine, choline or serine in the phospholipid itself. The following diagram shows the structures of some of these components. Clicking on the diagram will change it to display structures for two representative phospholipids. Note that the fatty acid components (R & R') may be saturated or unsaturated.



As ionic amphiphiles, phospholipids aggregate or self-assemble when mixed with water, but in a different manner than the soaps and detergents. Because of the two pendant alkyl chains present in phospholipids and the unusual mixed charges in their head groups, micelle formation is unfavorable relative to a bilayer structure. If a phospholipid is smeared over a small hole in a thin piece of plastic immersed in water, a stable planar bilayer of phospholipid molecules is created at the hole. As shown in the following diagram, the polar head groups on the faces of the bilayer contact water, and the hydrophobic alkyl chains form a nonpolar interior. The phospholipid molecules can move about in their half the bilayer, but there is a significant energy barrier preventing migration to the other side of the bilayer.

This bilayer membrane structure is also found in aggregate structures called **liposomes**. Liposomes are microscopic vesicles consisting of an aqueous core enclosed in one or more phospholipid layers. They are formed when phospholipids are vigorously mixed with water. Unlike micelles, liposomes have both aqueous interiors and exteriors.



A cell may be considered a very complex liposome. The bilayer membrane that separates the interior of a cell from the surrounding fluids is largely composed of phospholipids, but it incorporates many other components, such as cholesterol, that contribute to its structural integrity. Protein channels that permit the transport of various kinds of chemical species in and out of the cell are also important components of cell membranes.

The interior of a cell contains a variety of structures (organelles) that conduct chemical operations vital to the cells existence. Molecules bonded to the surfaces of cells serve to identify specific cells and facilitate interaction with external chemical entities. The sphingomyelins are also membrane lipids. They are the major component of the myelin sheath surrounding nerve fibers. Multiple Sclerosis is a devastating disease in which the myelin sheath is lost, causing eventual paralysis.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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26.5: PROSTAGLANDINS AND OTHER EICOSANOIDS

LEARNING OBJECTIVES

After completing this section, you should be able to

- describe the general structure of the prostaglandins, and identify a prostaglandin from a given list of organic structures.
- identify at least two important biological functions of prostaglandins.

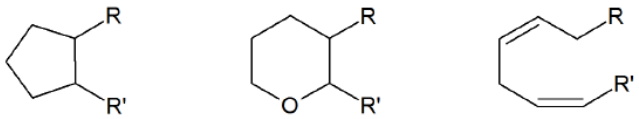
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

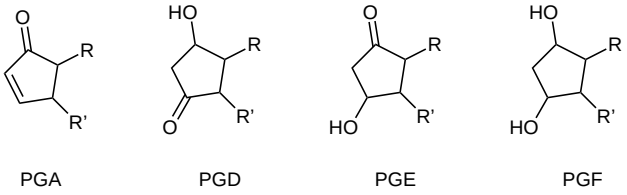
- eicosanoid
- prostaglandin

EICOSANOIDS

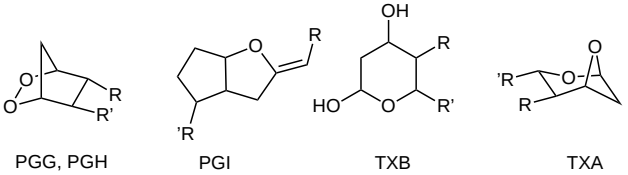
The members of this group of structurally related natural hormones have an extraordinary range of biological effects. They can lower gastric secretions, stimulate uterine contractions, lower blood pressure, influence blood clotting and induce asthma-like allergic responses. Because their genesis in body tissues is tied to the metabolism of the essential fatty acid arachadonic acid (5,8,11,14-eicosatetraenoic acid) they are classified as **eicosanoids**. Many properties of the common drug aspirin result from its effect on the cascade of reactions associated with these hormones. Eicosanoids include prostaglandins, leukotrienes, and thromboxanes.



Eicosanoids are primarily named off the ring system present in the molecule prostaglandin (PG), thromboxane (TX), leukotriene (LT). Common substitution patterns on the ring system are indicated with a letter in the name. Also, the number of double bonds in the molecule is indicated with a subscript number.

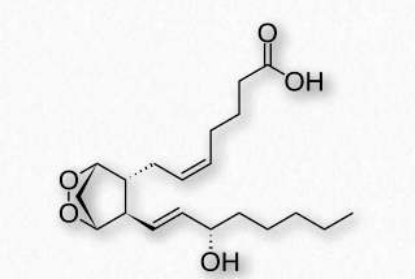


Prostaglandin structures for PGA, PGD, PGE and PGF



Structures for prostaglandins PGG, PGH and PGI and thromboxanes TXA and TXB

Thus the molecule PGH_2 means that it has the prostaglandin ring system with a type H Substitution pattern. The subscript 2 indicated that the molecule contains two double bonds.



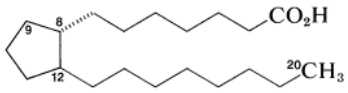
Prostaglandin PGH_2

PROSTAGLANDINS

Prostaglandins were first discovered and isolated from human semen in the 1930s by Ulf von Euler of Sweden. Thinking they had come from the prostate gland, he named them prostaglandins. It has since been determined that they exist and are synthesized in virtually every cell of the body. Prostaglandins, are like hormones in that they act as chemical messengers, but do not move to other sites, but work right within the cells where they are synthesized.

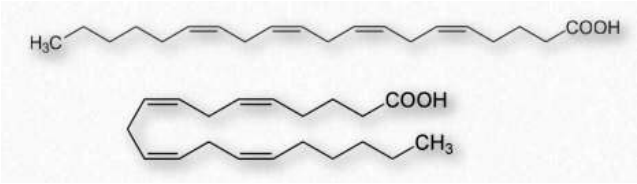
Prostaglandins are found in low concentrations distributed in a large number of organs, tissues, and body fluids of mammals. They exhibit a broad spectrum of physiological activity and are remarkably potent. Their precise biological role is not entirely clear, but they are known to induce strong contractions of smooth muscle tissue (lungs, uterus) and to lower blood pressure and sodium levels. Prostaglandins also have been implicated in the control of pituitary hormones released from the hypothalamus, and in the incidence of "pain" as a response to fever and inflammation. In fact, the analgesic property of aspirin possibly may result from the inhibition of prostaglandin biosynthesis

Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring and are based upon prostanoic acid, which is a C20 fatty acid in which there is a cyclopentane ring formed by connecting the C8 and C12 positions.



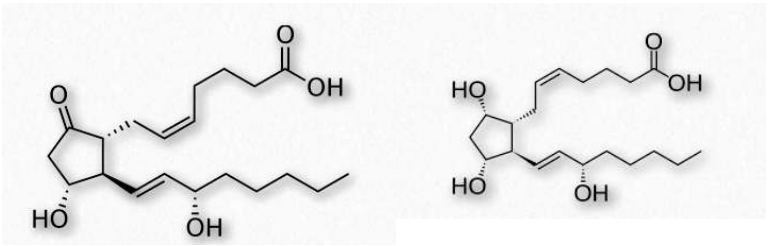
prostanoic acid

They are biochemically synthesized from the fatty acid, arachidonic acid. The unique shape of the arachidonic acid caused by a series of cis double bonds helps to put it into position to make the five member ring of the prostaglandin.



Arachidonic acid

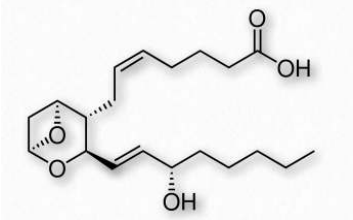
There are a variety of functional groups present in prostaglandin structures. The can have one, two, or three double bonds. On the five member ring there may also be double bonds, a ketone, or alcohol groups. Some typical structures are shown below.



Prostaglandin E2 (left) and Prostaglandin $F_{2\alpha}$ (Right)

THROMBOXANES

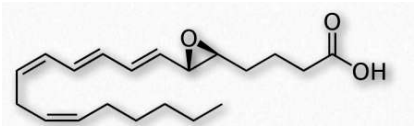
Thromboxanes play roles in clot formation and named for their role in thrombosis. They are potent vasoconstrictors and facilitate platelet aggregation. They are synthesized in platelets, as well. The anti-clotting effects of aspirin have their roots in the inhibition of synthesis of PGH2, which is the precursor of the thromboxanes. The most common thromboxanes are A2 (Figure 2.217) and B2.



Thromboxane $A2_2$

LEUKOTRIENES

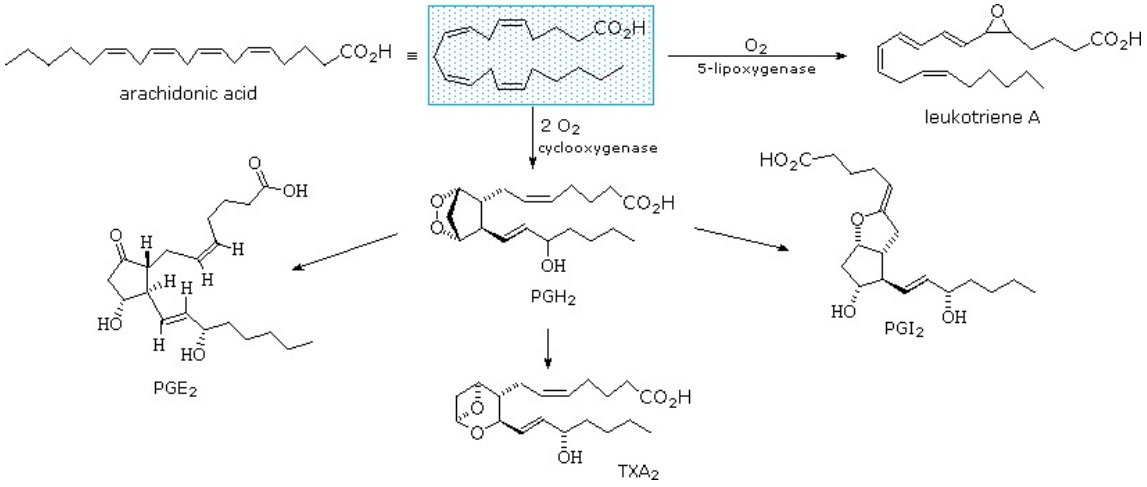
Another group of eicosanoid compounds are the leukotrienes (Figure 2.219). Like prostaglandins, leukotrienes are made from arachidonic acid. The enzyme catalyzing their formation is a dioxygenase known as arachidonate 5-lipoxygenase. Leukotrienes are involved in regulating immune responses. They are found in leukocytes and other immunocompetent cells, such as neutrophils, monocytes, mast cells, eosinophils, and basophils. Leukotrienes are associated with production of histamines and prostaglandins, which act as mediators of inflammation. Leukotrienes also trigger contractions in the smooth muscles of the bronchioles. When overproduced, they may pay a role in asthma and allergic reactions. Some treatments for asthma aim at inhibiting production or action of leukotrienes.



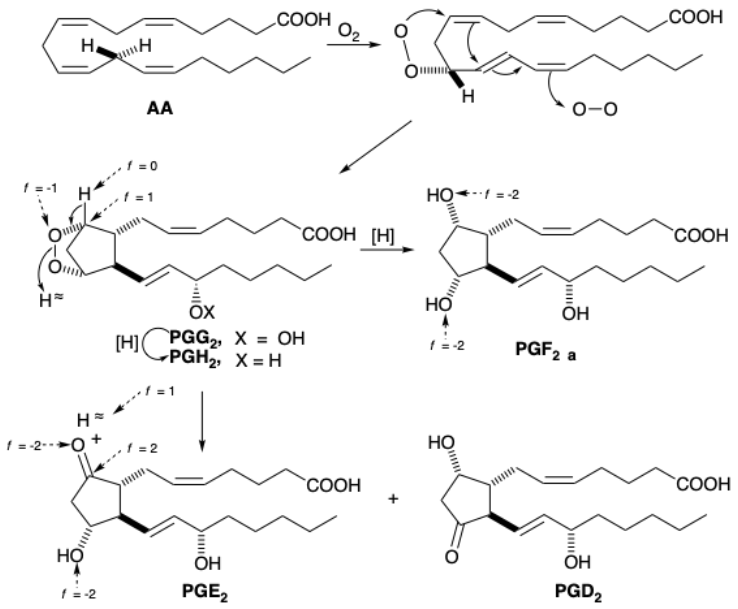
Leukotriene A_4 (LTA_4)

EICOSANOID BIOSYNTHESIS

The biosynthesis of eicosanoids begins with the reaction of arachidonic acid with $\mathbf{O_2}$ which can be catalyzed by two different cyclooxygenase enzymes (COX-1 & COX-2).



In nature, prostaglandins arise by an oxidative cyclization of poly-unsaturated twenty-carbon fatty acids, which begins with enantiospecific removal of the L-hydrogen atom of the prochiral methylene group at C-13 coupled with enantiospecific introduction of oxygen at the allylic C-15 position. Subsequent cyclization and termination by addition of a second molecule of oxygen leads to a 15-hydroperoxy bicyclic peroxide (PGG), that is reduced to a 15-hydroxy bicyclic peroxide (PGH). These intermediates, known as prostaglandin endoperoxides, have been isolated and shown to yield prostaglandins. Reduction of the peroxy bridge gives PGF, while disproportionation gives β-hydroxy ketones PGE and PGD. The carbons in prostaglandins are numbered one to twenty starting at the carboxyl carbon and following the numbering system of the biosynthetic precursor fatty acids.



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26.6: TERPENES AND TERPENOIDS

Objectives

After completing this section, you should be able to

1. identify a terpene from a given list of organic structures.
2. analyse the structure of a given terpene in terms of the isoprene rule.
3. classify a given terpene structure according to the number of isoprene units present; that is, determine whether a given terpene is a monoterpene, sesquiterpene, diterpene, etc.
4. identify and draw the structure of the precursors of isopentenyl diphosphate: (*R*) mevalonate or 1-deoxy-D-xylulose 5-phosphate.

Key Terms

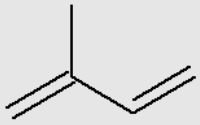
Make certain that you can define, and use in context, the key terms below.

- isoprene rule
- terpenoid
- terpene

Study Notes

You are not expected to memorize all the details of the synthetic mechanisms for terpenoids. However, you should know the overall general synthetic pathway illustrated under "Terpenoid Biosynthesis." As you read through the details of these mechanisms, realize that they may be complex, but they are based on experimental evidence. You should also note the important role of enzymes in many natural systems transformations. Finally, you will recognize that essentially, individual steps are often reactions you have already encountered in previous sections.

The terpenoids (aka isoprenoids) are a large (estimated 60% of known natural products) and diverse group of lipids derived from five-carbon isoprene units assembled in thousands of combinations. Technically a terpenoid contains oxygen, while a terpene is a hydrocarbon. Often the two terms are used to refer collectively to both groups.



isoprene

ISOPRENE RULE

Compounds classified as terpenes constitute what is arguably the largest and most diverse class of natural products. A majority of these compounds are found only in plants, but some of the larger and more complex terpenes (e.g. squalene & lanosterol) occur in animals. Terpenes incorporating most of the common functional groups are known, so this does not provide a useful means of classification. Instead, the number and structural organization of carbons is a definitive characteristic. Terpenes may be considered to be made up of isoprene (more accurately isopentane) units, an empirical feature known as the isoprene rule. Because of this, terpenes usually have $5n$ carbon atoms (n is an integer), and are subdivided as follows:

Classification	Isoprene Units	Carbon Atoms
monoterpenes	2	C_{10}
sesquiterpenes	3	C_{15}
diterpenes	4	C_{20}
sesterterpenes	5	C_{25}
triterpenes	6	C_{30}

Isoprene itself, a C_5H_8 gaseous hydrocarbon, is emitted by the leaves of various plants as a natural byproduct of plant metabolism. Next to methane it is the most common volatile organic compound found in the atmosphere. Examples of C10 and higher terpenes,

representing the four most common classes are shown in the following diagrams. Most terpenes may be structurally dissected into isopentane segments. How this is done can be seen in the diagram directly below.

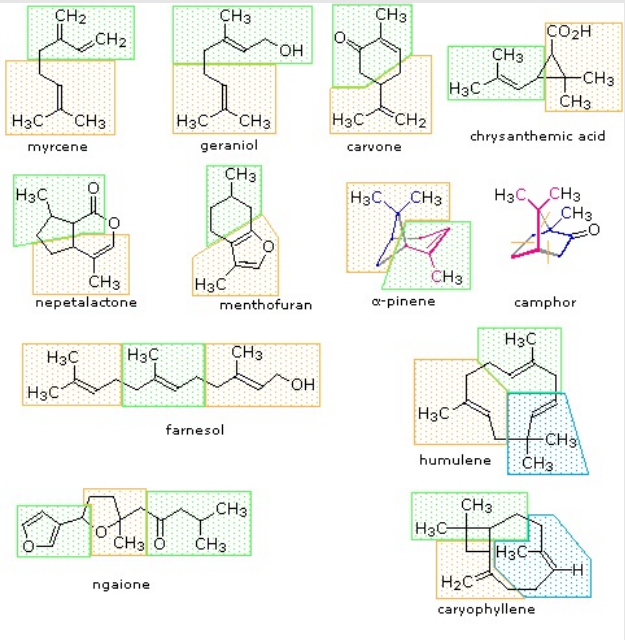


Figure 27.5.1: Monoterpenes and sesquiterpenes

The isopentane units in most of these terpenes are easy to discern, and are defined by the shaded areas. In the case of the monoterpene camphor, the units overlap to such a degree it is easier to distinguish them by coloring the carbon chains. This is also done for alpha-pinene. In the case of the triterpene lanosterol we see an interesting deviation from the isoprene rule. This thirty carbon compound is clearly a terpene, and four of the six isopentane units can be identified. However, the ten carbons in center of the molecule cannot be dissected in this manner. Evidence exists that the two methyl groups circled in magenta and light blue have moved from their original isoprenoid locations (marked by small circles of the same color) to their present location. This rearrangement is described in the biosynthesis section. Similar alkyl group rearrangements account for other terpenes that do not strictly follow the isoprene rule.

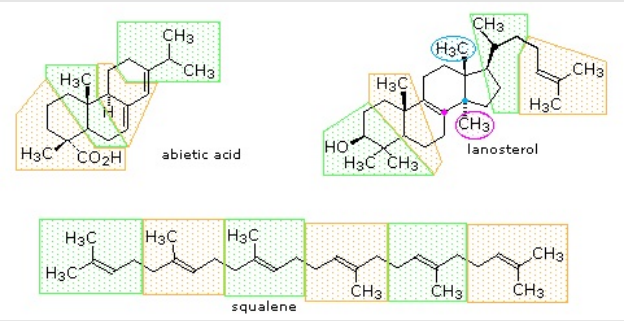
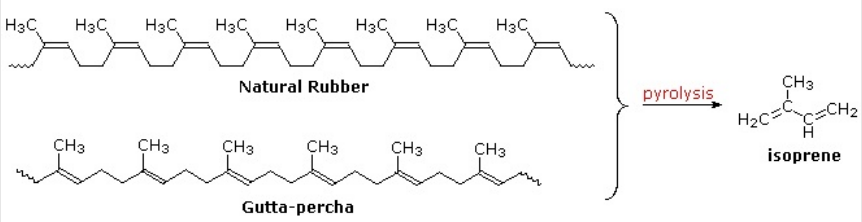


Figure 27.5.2: Triterpenes

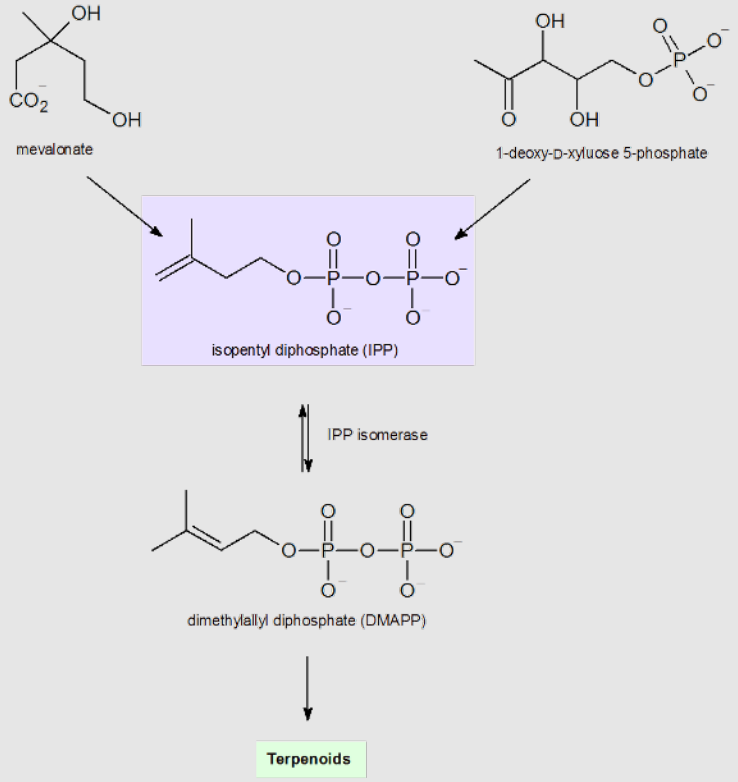
Polymeric isoprenoid hydrocarbons have also been identified. Rubber is undoubtedly the best known and most widely used compound of this kind. It occurs as a colloidal suspension called latex in a number of plants, ranging from the dandelion to the rubber tree (*Hevea brasiliensis*). Rubber is a polyene, and exhibits all the expected reactions of the C=C function. Bromine, hydrogen chloride and hydrogen all add with a stoichiometry of one molar equivalent per isoprene unit. Ozonolysis of rubber generates a mixture of levulinic acid ($CH_3COCH_2CH_2CO_2H$) and the corresponding aldehyde. Pyrolysis of rubber produces the diene isoprene along with other products.



The double bonds in rubber all have a Z-configuration, which causes this macromolecule to adopt a kinked or coiled conformation. This is reflected in the physical properties of rubber. Despite its high molecular weight (about one million), crude latex rubber is a soft, sticky, elastic substance. Chemical modification of this material is normal for commercial applications. Gutta-percha (structure above) is a naturally occurring E-isomer of rubber. Here the hydrocarbon chains adopt a uniform zig-zag or rod like conformation, which produces a more rigid and tough substance. Uses of gutta-percha include electrical insulation and the covering of golf balls.

TERPENOID BIOSYNTHESIS

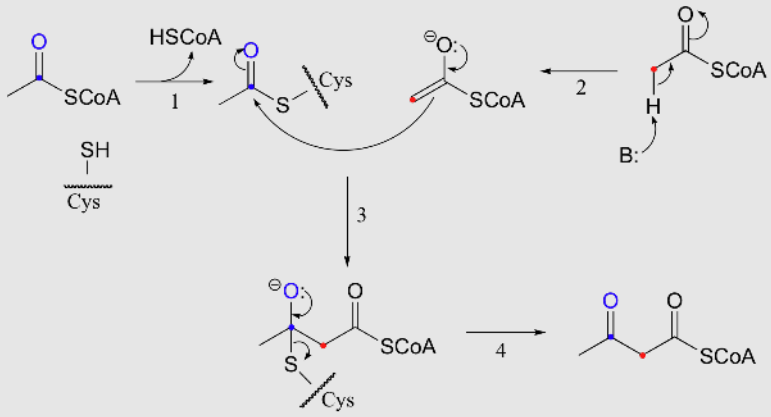
While we can identify isoprene units within a terpenoid structure and use that in its classification, the building block for terpenoid synthesis in nature is isopentenyl diphosphate (formerly called isopentenyl pyrophosphate and abbreviated IPP). There are two major routes to the synthesis of IPP; namely (1) the mevalonate pathway and (2) the 1-deoxyxylulose pathway.



MEVALONATE PATHWAY

Step 1 - Claisen Condensation

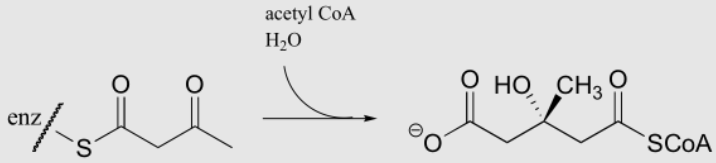
An early step in the biosynthesis of cholesterol and other ‘isoprenoid’ compounds is a Claisen condensation between two acetyl CoA molecules. An initial trans-thioesterase process transfers the acetyl group of the first acetyl CoA to an enzymatic cysteine (Reaction 1). In the Claisen condensation phase of the reaction, the alpha-carbon of a second acetyl CoA is deprotonated, forming an enolate (Reaction 2).



The enolate carbon attacks the electrophilic thioester carbon, forming a tetrahedral intermediate (Reaction 3) which quickly collapses to expel the cysteine thiol (Reaction 4) and produce acetoacetyl CoA.

Step 2 - **Aldol Condensation**

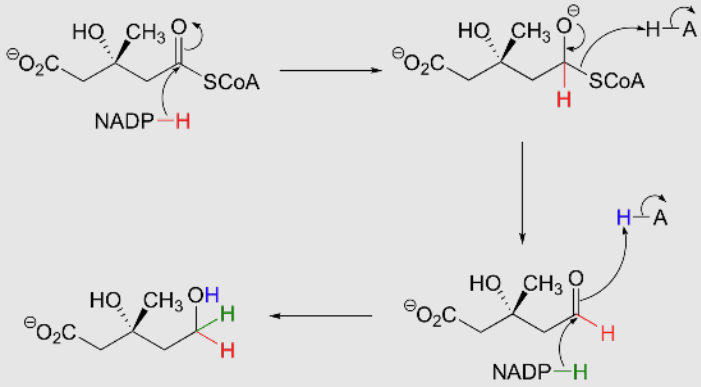
Acetyl CoA then reacts with the acetoacetyl CoA in an aldol-like addition. Subsequent hydrolysis produces (3*S*)-3-hydroxy-3-methylglutaryl CoA (HMG-CoA).



Generating HMG-CoA

Step 3 - **Reduction of the Thioester**

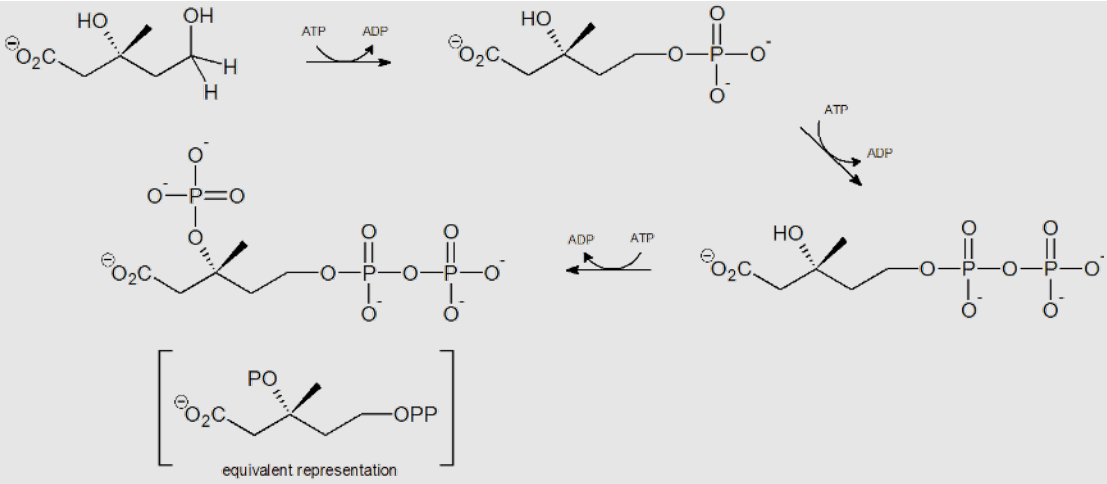
The thioester is reduced first to an aldehyde, then to a primary alcohol by two equivalents of NADPH producing (*R*)-mevalonate. The enzyme catalyzing this reaction is the target of the statin family of cholesterol-lowering drugs.



Generating (*R*)-Mevalonate

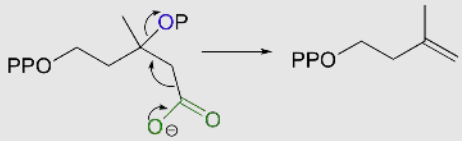
Step 4 - **Mevalonate Phosphorylation**

Two phsophorylations by adenosine triphosphate (ATP) occur at the terminal hydroxyl/phosphorus group through nucleophilic substitution, followed by a third ATP phosphorylation of the tertiary hydroxyl group.



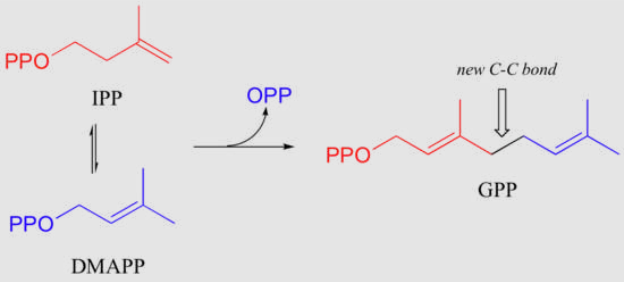
Step 5 - **Decarboxylation**

Finally isopentenyl diphosphate (IPP), the 'building block' for all isoprenoid compounds, is formed from a decarboxylation-elimination reaction.

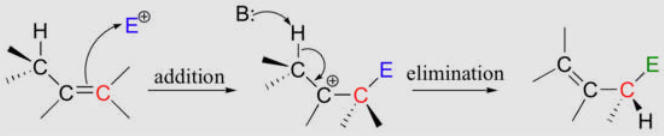


CONVERSION OF IPP TO TERPENOIDS

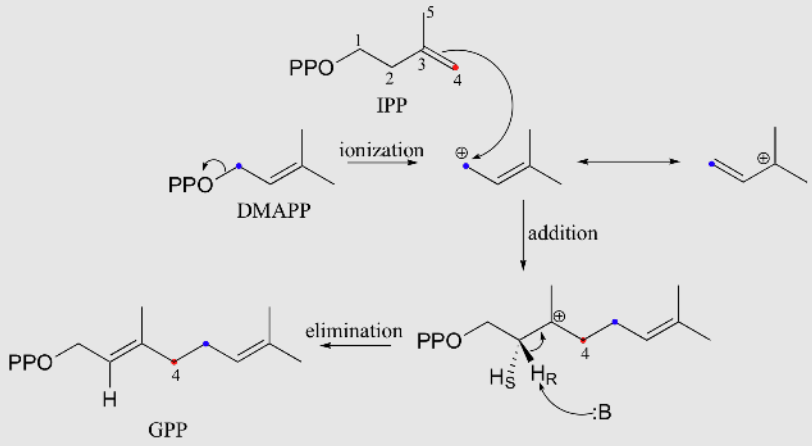
The electrophilic double bond isomerization catalyzed by IPP isomerase is a highly reversible reaction, with an equilibrium IPP:DMAPP ratio of about 6:1. In the next step of isoprenoid biosynthesis, the two five-carbon isomers condense to form a 10-carbon isoprenoid product called geranyl diphosphate (GPP).



This is a nice example of an electrophilic addition/elimination mechanism:

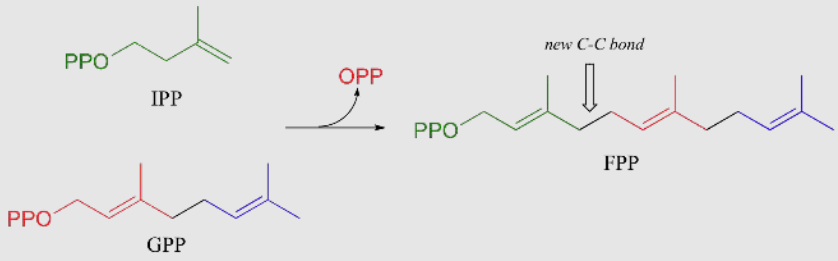


The first step is ionization of the electrophile - in other words, the leaving group departs and a carbocation intermediate is formed. In this case, the pyrophosphate group on DMAPP is the leaving group, and the electrophilic species is the resulting allylic carbocation.

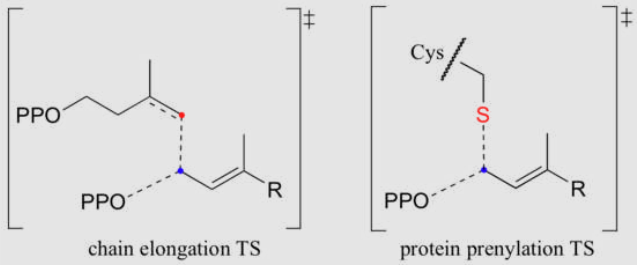


In the condensation (addition) step, the C_3-C_4 double bond in IPP attacks the positively-charged C_1 of DMAPP, resulting in a new carbon-carbon bond and a second carbocation intermediate, this time at a tertiary carbon. In the elimination phase, proton abstraction leads to re-establishment of a double bond in the GPP product. Notice that the enzyme specifically takes the *pro-R* proton in this step.

To continue the chain elongation process, another IPP molecule can then condense, in a very similar reaction, with C_1 of geranyl diphosphate to form a 15-carbon product called farnesyl diphosphate (FPP).

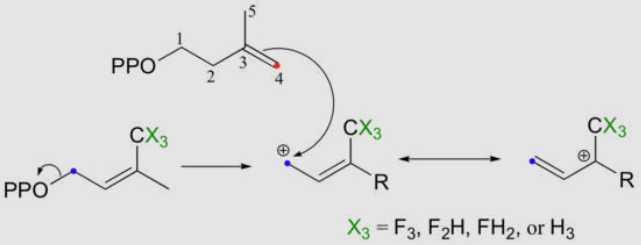


How do we know that these are indeed S_N1-like mechanisms with carbocation intermediates, rather than concerted S_N2-like mechanisms? First of all, recall that the question of whether a substitution is dissociative (S_N1-like) or associative (S_N2-like) is not always clear-cut - it could be somewhere in between, like the protein prenyltransferase reaction. The protein prenyltransferase reaction and the isoprenoid chain elongation reactions are very similar: the electrophile is the same, but in the former the nucleophile is a thiolate, while in the latter the nucleophile is a pi bond.



This difference in the identity of the nucleophilic species would lead one to predict that the chain elongation reaction has more S_N1-like character than the protein prenylation reaction. A thiolate is a very powerful nucleophile, and thus is able to *push* the pyrophosphate leaving group off, implying some degree of S_N2 character. The electrons in a pi bond, in contrast, are only weakly nucleophilic, and thus need to be *pulled* in by a powerful electrophile - *ie*. a carbocation.

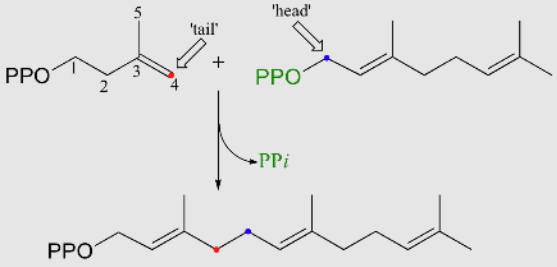
So it makes perfect sense that the chain elongation reaction should more S_N1-like than S_N2-like. Is this in fact the case? We know how to answer this question experimentally - just run the reaction with fluorinated DMAPP or GPP substrates and observe how much the fluorines slow things down.



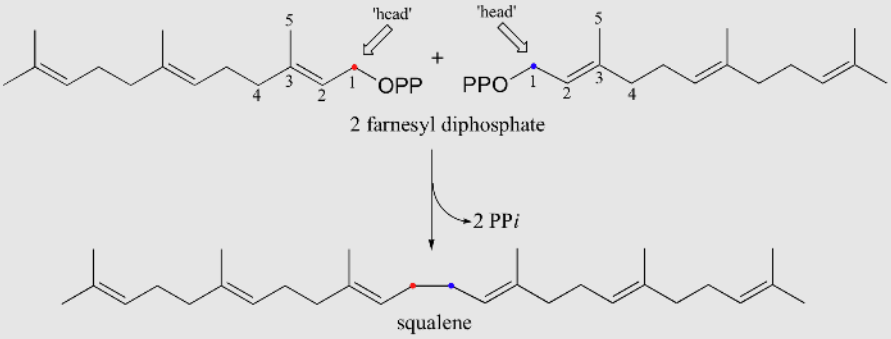
If the reaction is S_N1-like, the electron-withdrawing fluorines should destabilize the allylic carbocation intermediate and thus slow the reaction down considerably. If the mechanism is S_N2-like, the fluorine substitutions should not have a noticeable effect, because a carbocation intermediate would not be formed. When this experiment was performed with FPP synthase, the results were dramatic: the presence of a single fluorine slowed down the rate of the reaction by a factor of about 60, while two and three fluorines resulted in a reaction that was 500,000 and 3 million times slower, respectively (*J. Am. Chem. Soc.* **1981**, *103*, 3926.) These results strongly suggest indicate the formation of a carbocation intermediate in an S_N1-like displacement.

In this section, we will briefly examine the reaction catalyzed by an enzyme called squalene synthase, an important enzymatic transformation that involves some very interesting and unusual electrophilic additions, rearrangements, and reactive intermediates. This particular enzyme is also of interest because it represents a potential new target for cholesterol-lowering drugs.

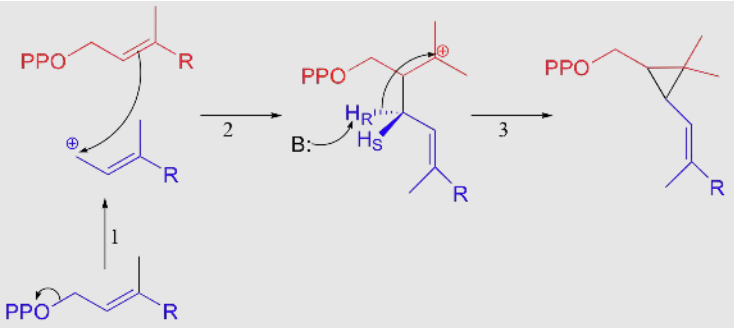
Cholesterol, as we discussed earlier in this chapter, is derived from a 30-carbon isoprenoid molecule called squalene. Squalene, in turn, is derived from the condensation of two molecules of farnesyl diphosphate (FPP), a 15-carbon isoprenoid. You may recall that FPP is the product of the C_4 to C_1, or 'head to tail' electrophilic condensation of isoprenoid chains:



The condensation of two molecules of FPP to form squalene, however, is something different: this is a 'head to head' condensation, where C_1 of the first molecule forms a bond to C_1 of the second. The chemistry involved is quite a bit more complicated.

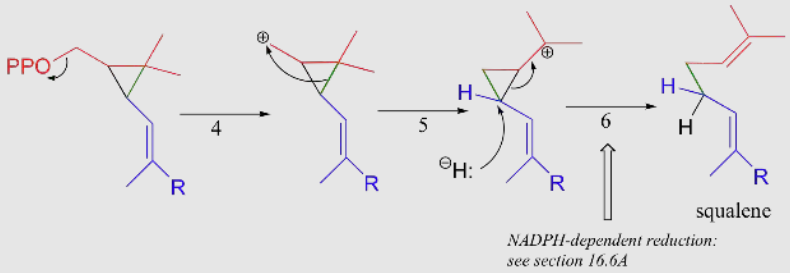


The first two steps are familiar: first, the pyrophosphate on one FPP molecule leaves (step 1), resulting in an allylic carbocation that is attacked by the C_2-C_3 π bond of the second molecule (step 2).

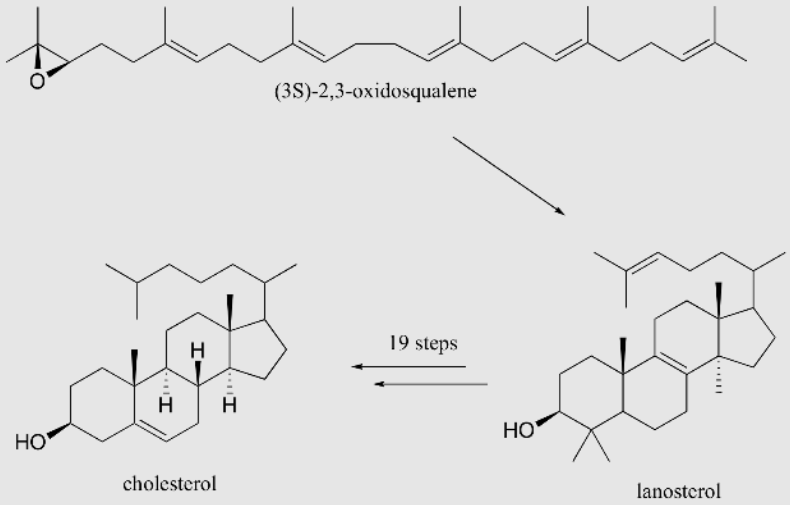


This results in a new carbon-carbon bond between the two FPP molecules, but with incorrect C_1 to C_2 connectivity (remember, the overall reaction is a C_1 to C_1 condensation). In step 3, a proton is abstracted and the electrons from the broken C-H bond bridge across a 2-carbon gap to form a cyclopropyl intermediate.

In the second stage of squalene synthesis, the second pyrophosphate group leaves, generating a cyclopropylcarbinyl cation (step 4). Because this is a primary carbocation, you probably are wondering about how stable it could be (and thus how likely an intermediate). As it turns out, such carbocations are remarkably stable, due to favorable interactions between the empty orbital and orbitals on the three-membered ring (the level of bonding theory needed to really understand this idea is beyond the scope of this text, but you may learn about it if you take a class in advanced organic chemistry). What occurs next is an alkyl shift leading to a tertiary carbocation (step 5).



Discussion of the final step (step 6) will need to be put off - this is a reduction with a hydride nucleophile derived from a coenzyme called NADPH. Although this may seem like an extremely convoluted (and perhaps unlikely!) mechanism, there is much experimental evidence to back it up.



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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26.7: STEROIDS

Objectives

After completing this section, you should be able to

1. draw the tetracyclic ring system on which the structure of all steroids is based.
2. identify the occurrence and biological roles of at least two common steroids.
3. sketch the stereochemical conformation of a steroid, given an adequate wedge-and-broken line structure, and determine whether the ring substituents in such a compound occupy axial or equatorial positions.
4. construct a molecular model of a steroid, given a suitable written description or a wedge-and-broken line structure from which to work.

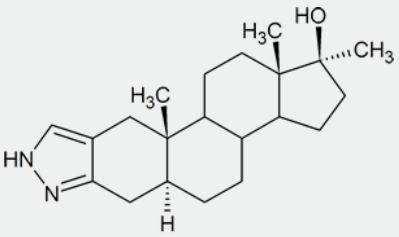
Key Terms

Make certain that you can define, and use in context, the key term below.

- steroid

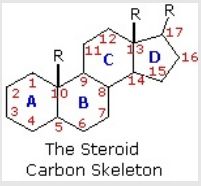
Study Notes

Since the 1988 Olympic Games in Seoul, even individuals who have no interest in chemistry or sport have heard the word "steroid" and are aware that some athletes use these substances to enhance their athletic abilities. Stanozolol, the substance which Canadian sprinter, Ben Johnson, was found to have used, has the structure shown below:



stanozolol

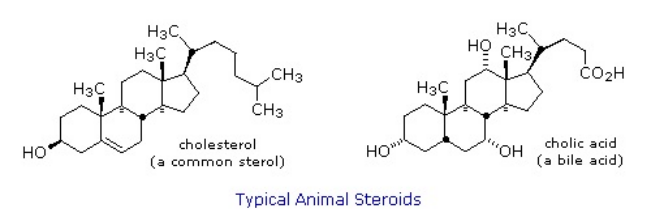
The important class of lipids called **steroids** are actually metabolic derivatives of terpenes, but they are customarily treated as a separate group. Steroids may be recognized by their tetracyclic skeleton, consisting of three fused six-membered and one five-membered ring, as shown in the diagram to the right. The four rings are designated A, B, C & D as noted, and the peculiar numbering of the ring carbon atoms (shown in red) is the result of an earlier misassignment of the structure. The substituents designated by R are often alkyl groups, but may also have functionality. The R group at the A:B ring fusion is most commonly methyl or hydrogen, that at the C:D fusion is usually methyl. The substituent at C-17 varies considerably, and is usually larger than methyl if it is not a functional group. The most common locations of functional groups are C-3, C-4, C-7, C-11, C-12 & C-17. Ring A is sometimes aromatic. Since a number of tetracyclic triterpenes also have this tetracyclic structure, it cannot be considered a unique identifier.



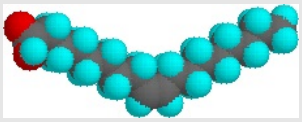
The Steroid Carbon Skeleton

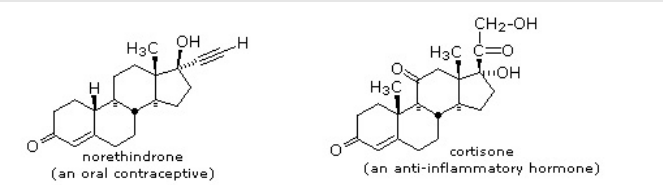
Steroids are widely distributed in animals, where they are associated with a number of physiological processes. Examples of some important steroids are shown in the following diagram. Norethindrone is a synthetic steroid, all the other examples occur naturally. A common strategy in pharmaceutical chemistry is to take a natural compound, having certain desired biological properties together with undesired side effects, and to modify its structure to enhance the desired characteristics and diminish the undesired. This is sometimes accomplished by trial and error.

The generic steroid structure drawn above has seven chiral stereocenters (carbons 5, 8, 9, 10, 13, 14 & 17), which means that it may have as many as 128 stereoisomers. With the exception of C-5, natural steroids generally have a single common configuration. This is shown in the last of the toggled displays, along with the preferred conformations of the rings.

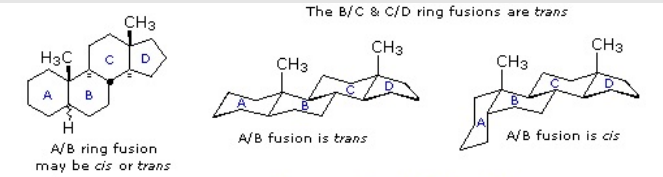


Typical Animal Steroids





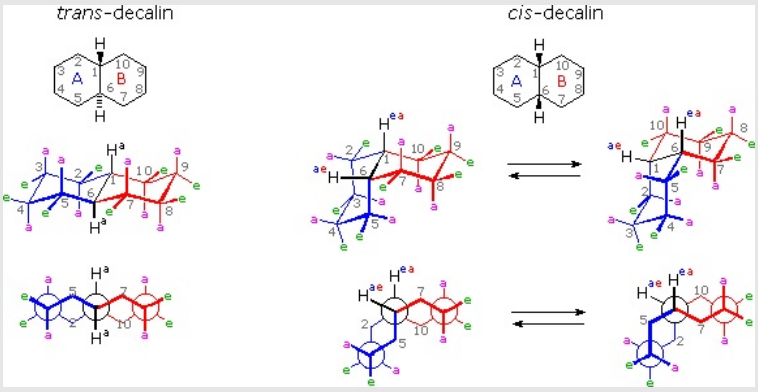
Medicinally Useful Steroids

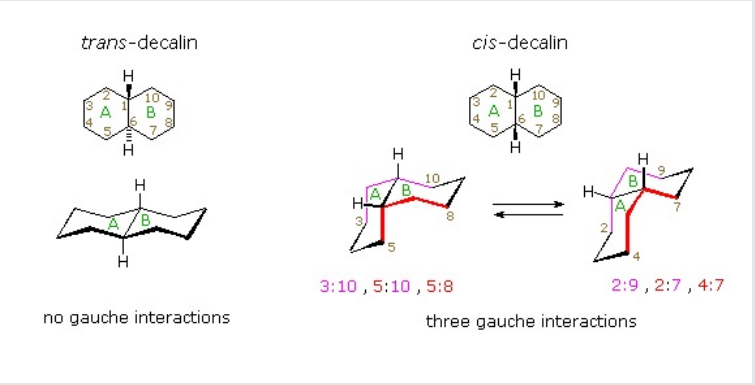


Common Steroid Conformations

Chemical studies of the steroids were very important to our present understanding of the configurations and conformations of six-membered rings. Substituent groups at different sites on the tetracyclic skeleton will have axial or equatorial orientations that are fixed because of the rigid structure of the trans-fused rings. This fixed orientation influences chemical reactivity, largely due to the greater steric hindrance of axial groups versus their equatorial isomers. Thus an equatorial hydroxyl group is esterified more rapidly than its axial isomer.

It is instructive to examine a simple bicyclic system as a model for the fused rings of the steroid molecule. Decalin, short for decahydronaphthalene, exists as cis and trans isomers at the ring fusion carbon atoms. Planar representations of these isomers are drawn at the top of the following diagram, with corresponding conformational formulas displayed underneath. The numbering shown for the ring carbons follows IUPAC rules, and is different from the unusual numbering used for steroids. For purposes of discussion, the left ring is labeled A (colored blue) and the right ring B (colored red). In the conformational drawings the ring fusion and the angular hydrogens are black.



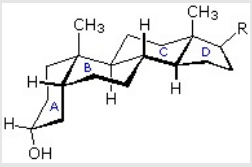


The trans-isomer is the easiest to describe because the fusion of the A & B rings creates a rigid, roughly planar, structure made up of two chair conformations. Each chair is fused to the other by equatorial bonds, leaving the angular hydrogens (Ha) axial to both rings. Note that the bonds directed above the plane of the two rings alternate from axial to equatorial and back if we proceed around the rings from C-1 to C-10 in numerical order. The bonds directed below the rings also alternate in a complementary fashion.

Conformational descriptions of cis- decalin are complicated by the fact that two energetically equivalent fusions of chair cyclohexanes are possible, and are in rapid equilibrium as the rings flip from one chair conformation to the other. In each of these all chair conformations the rings are fused by one axial and one equatorial bond, and the overall structure is bent at the ring fusion. In the conformer on the left, the red ring (B) is attached to the blue ring (A) by an axial bond to C-1 and an equatorial bond to C-6 (these terms refer to ring A substituents). In the conformer on the right, the carbon bond to C-1 is equatorial and the bond to C-6 is axial. Each of the angular hydrogens (Hae or Hea) is oriented axial to one of the rings and equatorial to the other. This relationship reverses when double ring flipping converts one cis-conformer into the other.

Cis-decalin is less stable than trans-decalin by about 2.7 kcal/mol (from heats of combustion and heats of isomerization data). This is due to steric crowding (hindrance) of the axial hydrogens in the concave region of both cis-conformers, as may be seen in the model display activated by the following button. This difference is roughly three times the energy of a gauche butane conformer relative to its anti conformer. Indeed three gauche butane interactions may be identified in each of the cis-decalin conformations, as will be displayed by clicking on the above conformational diagram. These gauche interactions are also shown in the model.

Steroids in which rings A and B are fused cis, such as the example on the right, do not have the sameconformational mobility exhibited by cis-decalin. The fusion of ring C to ring B in a trans configuration prevents ring B from undergoing a conformational flip to another chair form. If this were to occur, ring C would have to be attached to ring B by two adjacent axial bonds directed 180º apart. This is too great a distance to be bridged by the four carbon atoms making up ring C. Consequently, the steroid molecule is locked in the all chair conformation shown here. Of course, all these steroids and decalins may have one or more six-membered rings in a boat conformation. However the high energy of boat conformers relative to chairs would make such structures minor components in the overall ensemble of conformations available to these molecules.



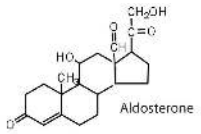
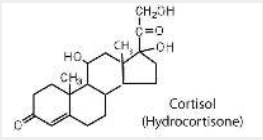
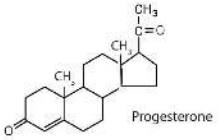
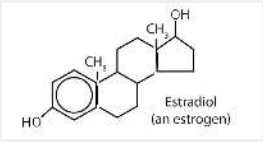
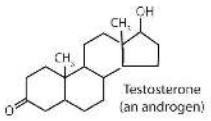
STEROID HORMONES

Hormones are chemical messengers that are released in one tissue and transported through the circulatory system to one or more other tissues. One group of hormones is known as steroid hormones because these hormones are synthesized from cholesterol, which is also a steroid. There are two main groups of steroid hormones: adrenocortical hormones and sex hormones.

The adrenocortical hormones, such as aldosterone and cortisol (Table 17.3), are produced by the adrenal gland, which is located adjacent to each kidney. Aldosterone acts on most cells in the body, but it is particularly effective at enhancing the rate of reabsorption of sodium ions in the kidney tubules and increasing the secretion of potassium ions and/or hydrogen ions by the tubules. Because the concentration of sodium ions is the major factor influencing water retention in tissues, aldosterone promotes water retention and reduces urine output. Cortisol regulates several key metabolic reactions (for example, increasing glucose production and mobilizing fatty acids and amino acids). It also inhibits the inflammatory response of tissue to injury or stress. Cortisol and its analogs are

therefore used pharmacologically as immunosuppressants after transplant operations and in the treatment of severe skin allergies and autoimmune diseases, such as rheumatoid arthritis.

Table 17.3 Representative Steroid Hormones and Their Physiological Effects

Hormone	Effect
 Aldosterone	regulates salt metabolism; stimulates kidneys to retain sodium and excrete potassium
 Cortisol (Hydrocortisone)	stimulates the conversion of proteins to carbohydrates
 Progesterone	regulates the menstrual cycle; maintains pregnancy
 Estradiol (an estrogen)	stimulates female sex characteristics; regulates changes during the menstrual cycle
 Testosterone (an androgen)	stimulates and maintains male sex characteristics

The sex hormones are a class of steroid hormones secreted by the gonads (ovaries or testes), the placenta, and the adrenal glands. Testosterone and androstenedione are the primary male sex hormones, or *androgens*, controlling the primary sexual characteristics of males, or the development of the male genital organs and the continuous production of sperm. Androgens are also responsible for the development of secondary male characteristics, such as facial hair, deep voice, and muscle strength. Two kinds of sex hormones are of particular importance in females: progesterone, which prepares the uterus for pregnancy and prevents the further release of eggs from the ovaries during pregnancy, and the estrogens, which are mainly responsible for the development of female secondary sexual characteristics, such as breast development and increased deposition of fat tissue in the breasts, the buttocks, and the thighs. Both males and females produce androgens and estrogens, differing in the amounts of secreted hormones rather than in the presence or absence of one or the other.

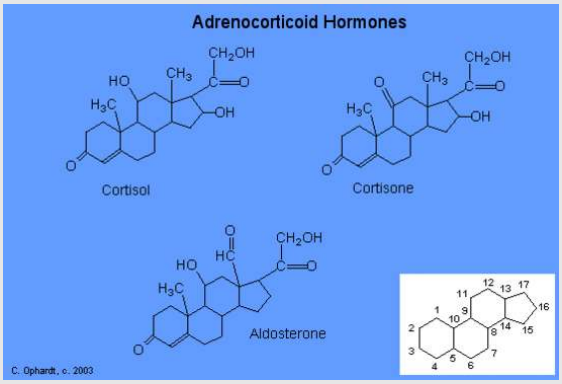
Sex hormones, both natural and synthetic, are sometimes used therapeutically. For example, a woman who has had her ovaries removed may be given female hormones to compensate. Some of the earliest chemical compounds employed in cancer chemotherapy were sex hormones. For example, estrogens are one treatment option for prostate cancer because they block the release and activity of testosterone. Testosterone enhances prostate cancer growth. Sex hormones are also administered in preparation for sex-change operations, to promote the development of the proper secondary sexual characteristics. Oral contraceptives are synthetic derivatives of the female sex hormones; they work by preventing ovulation.

ADRENOCORTICOID HORMONES

The adrenocorticoid hormones are products of the adrenal glands ("adrenal" means adjacent to the renal (kidney). The most important mineralocrticoid is **aldosterone**, which regulates the reabsorption of sodium and chloride ions in the kidney tubules and increases the loss of potassium ions. Aldosterone is secreted when blood sodium ion levels are too low to cause the kidney to retain sodium ions. If sodium levels are elevated, aldosterone is not secreted, so that some sodium will be lost in the urine. Aldosterone also controls swelling in the tissues.

Cortisol, the most important glucocortinoid, has the function of increasing glucose and glycogen concentrations in the body. These reactions are completed in the liver by taking fatty acids from lipid storage cells and amino acids from body proteins to make glucose and glycogen.

In addition, cortisol and its ketone derivative, **cortisone**, have the ability to inflammatory effects. Cortisone or similar synthetic derivatives such as prednisolone are used to treat inflammatory diseases, rheumatoid arthritis, and bronchial asthma. There are many side effects with the use of cortisone drugs, so there use must be monitored carefully.



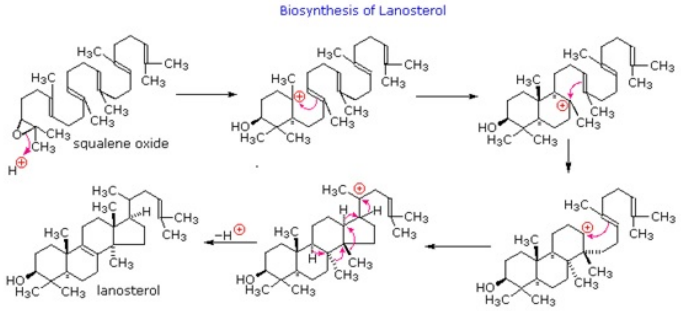
CONTRIBUTORS AND ATTRIBUTIONS

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- Prof. Steven Farmer (Sonoma State University)
- Charles Ophardt, Professor Emeritus, Elmhurst College; Virtual Chembook

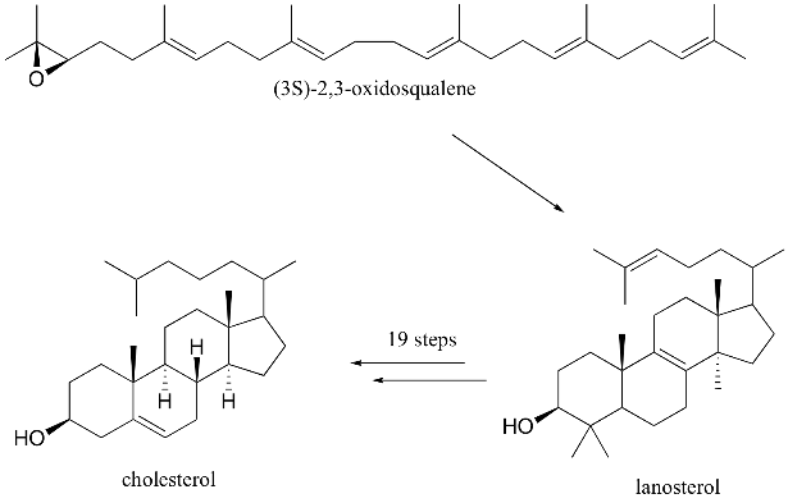
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26.8: BIOSYNTHESIS OF STEROIDS

On the diagram below, the series of cation-like cyclizations and rearrangements, known as the Stork-Eschenmoser hypothesis, is shown, which were identified in the biosynthesis of the triterpene lanosterol. Lanosterol is a precursor in the biosynthesis of steroids. This takes place by metabolic removal of three methyl groups and degradation of the side chain.

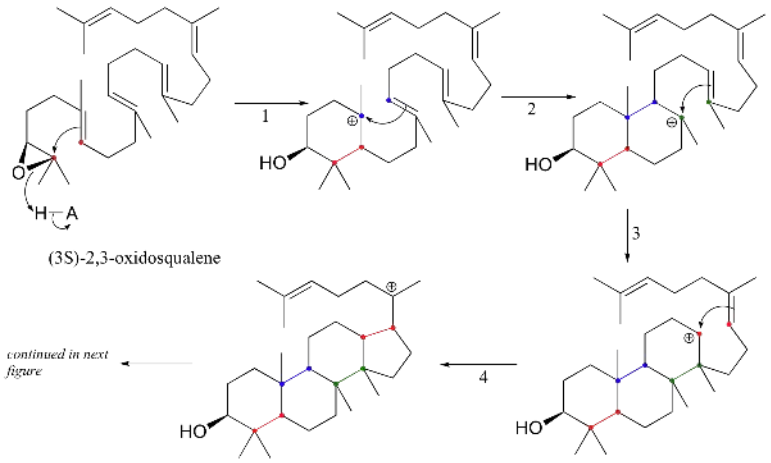


Rearrangements are particularly important in carbocation-intermediate reactions in which isoprenoid molecules cyclize to form complex multi-ring structures. One of the key steps in the biosynthesis of cholesterol is the electrophilic cyclization of oxidosqualene to form a steroid called lanosterol.

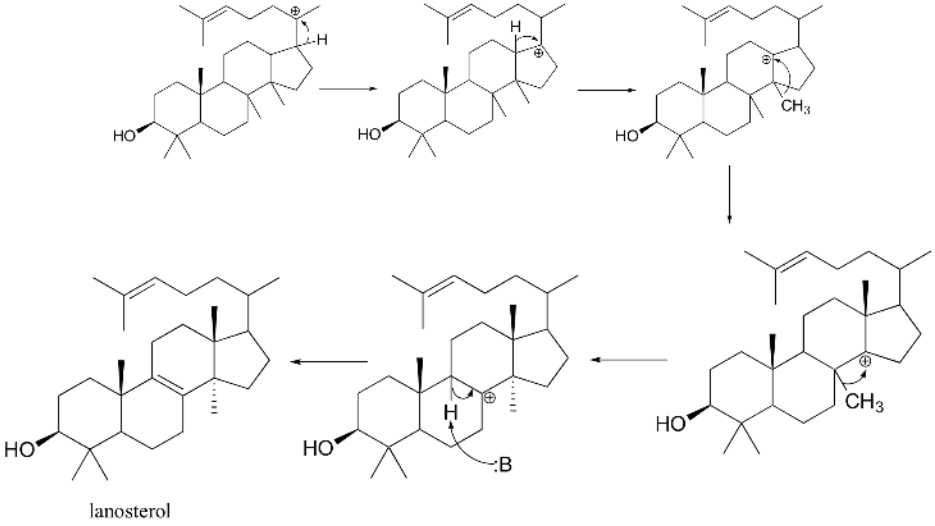


This fascinating reaction has two phases. The first phase, in which the actual cyclization takes place, is a series of electrophilic addition steps. The second phase is a series of hydride and methyl shifts. There is some argument about whether these processes occur in a stepwise fashion (with discreet carbocation intermediates) or in a concerted manner. For the sake of clarity, we will show the reaction proceeding stepwise.

The cyclization phase begins with attack by pi electrons on an epoxide electrophile (step 1 - review epoxide ring-opening reactions in section 8.6B).



Steps 2, 3, and 4 are simply successive attacks by pi electrons on the carbocation generated by the previous attack. The overall result of this electrophilic cascade is the opening of the epoxide ring, and closure of three six-membered and one five-membered ring. Next comes the rearrangement phase of the reaction. which is a series of two hydride shifts and two methyl shifts, followed by a proton abstraction which finally quenches the positive charge to form lanosterol.



CONTRIBUTORS AND ATTRIBUTIONS

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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CHAPTER OVERVIEW

27: NUCLEIC ACIDS

27.1: Nucleotides and Nucleic Acids
27.2: DNA Base Pairs
27.3: DNA Replication
27.4: Transcription of DNA
27.5: Translation of RNA- Protein Biosynthesis
27.6: DNA Sequencing
27.7: Polymerase Chain Reactions

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27.1: NUCLEOTIDES AND NUCLEIC ACIDS

Objectives

After completing this section, you should be able to

1. outline the relationship between nucleic acids, nucleotides and nucleosides.
2. identify, in general terms, the enzymatic hydrolysis products of nucleosides.
3. explain the structural difference between the sugar components of DNA and RNA.
4. identify by name the four heterocyclic amine bases found in deoxyribonucleotides.
5. identify by name the four heterocyclic amine bases found in ribonucleotides.
6. draw the general structure of a nucleotide and a nucleoside.
7. indicate the nitrogen atom by which a given purine or pyrimidine base attaches to the sugar component in nucleotides and nucleosides.
8. sketch a section of nucleic acid to show how the nucleotide units are joined together.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- deoxyribonucleic acid (DNA)
- nucleosides nucleotides
- ribonucleic acid (RNA)

Study Notes

The five bases that are found in nucleotides are often represented by their initial letter: adenine, A; guanine, G; cytosine, C; thymine, T; and uracil, U. Note that A, G, C and T occur in DNA; A, G, C and U occur in RNA. You are not required to memorize the structures of these bases, but you must know how each one bonds to the sugar unit in a nucleotide.

To fulfill Objective 6, you should be able to reproduce the figure below.

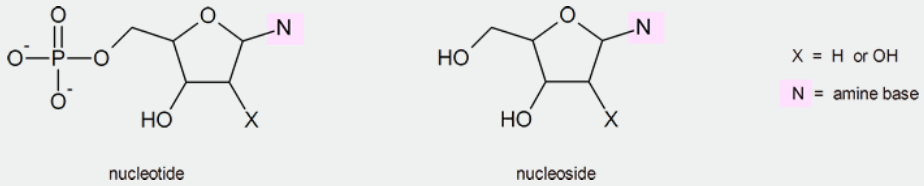
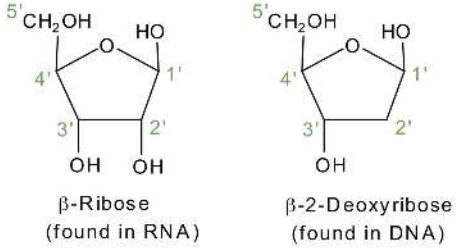


Figure **27.1.2** The Pyrimidine and Purine Nucleotides below.

The repeating, or monomer, units that are linked together to form nucleic acids are known as nucleotides. The deoxyribonucleic acid (DNA) of a typical mammalian cell contains about 3×10^9 nucleotides. Nucleotides can be further broken down to phosphoric acid (H_3PO_4), a pentose sugar (a sugar with five carbon atoms), and a nitrogenous base (a base containing nitrogen atoms).

$$\text{nucleic acids} \xrightarrow[\text{down into}]{\text{can be broken}} \text{nucleotides} \xrightarrow[\text{down into}]{\text{can be broken}} H_3PO_4 + \text{nitrogen base} + \text{pentose sugar} \tag{28.1.1}$$

If the pentose sugar is ribose, the nucleotide is more specifically referred to as a *ribonucleotide*, and the resulting nucleic acid is ribonucleic acid (RNA). If the sugar is 2-deoxyribose, the nucleotide is a *deoxyribonucleotide*, and the nucleic acid is DNA.



The nitrogenous bases found in nucleotides are classified as pyrimidines or purines. Pyrimidines are heterocyclic amines with two nitrogen atoms in a six-member ring and include uracil, thymine, and cytosine. Purines are heterocyclic amines consisting of a pyrimidine ring fused

to a five-member ring with two nitrogen atoms. Adenine and guanine are the major purines found in nucleic acids (Figure **27.1.1**).

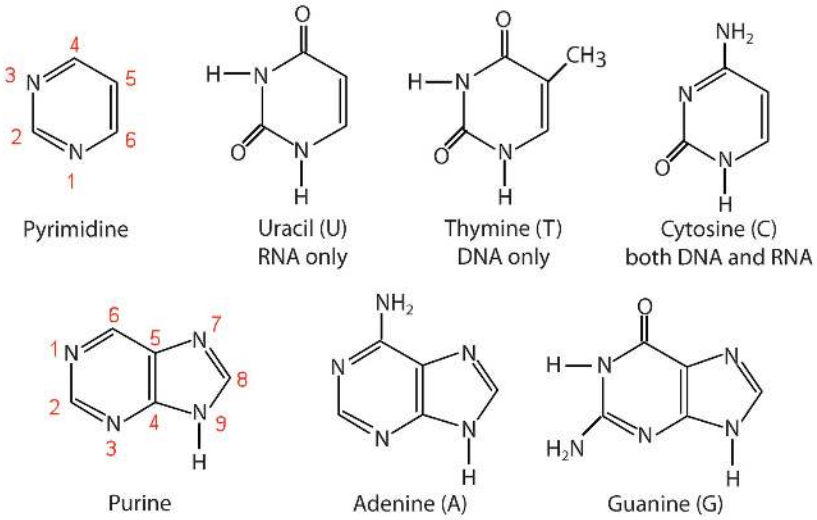


Figure **27.1.1**: The Nitrogenous Bases Found in DNA and RNA

The formation of a bond between C1′ of the pentose sugar and N1 of the pyrimidine base or N9 of the purine base joins the pentose sugar to the nitrogenous base. In the formation of this bond, a molecule of water is removed. Table 28.1.1 summarizes the similarities and differences in the composition of nucleotides in DNA and RNA.

Example 27.1.1

The numbering convention is that primed numbers designate the atoms of the pentose ring, and unprimed numbers designate the atoms of the purine or pyrimidine ring.

Table **27.1.1**: Composition of Nucleotides in DNA and RNA

Composition	DNA	RNA
purine bases	adenine and guanine	adenine and guanine
pyrimidine bases	cytosine and thymine	cytosine and uracil
pentose sugar	2-deoxyribose	ribose
inorganic acid	phosphoric acid (H_3PO_4)	H_3PO_4

The names and structures of the major ribonucleotides and one of the deoxyribonucleotides are given in Figure **27.1.2**.

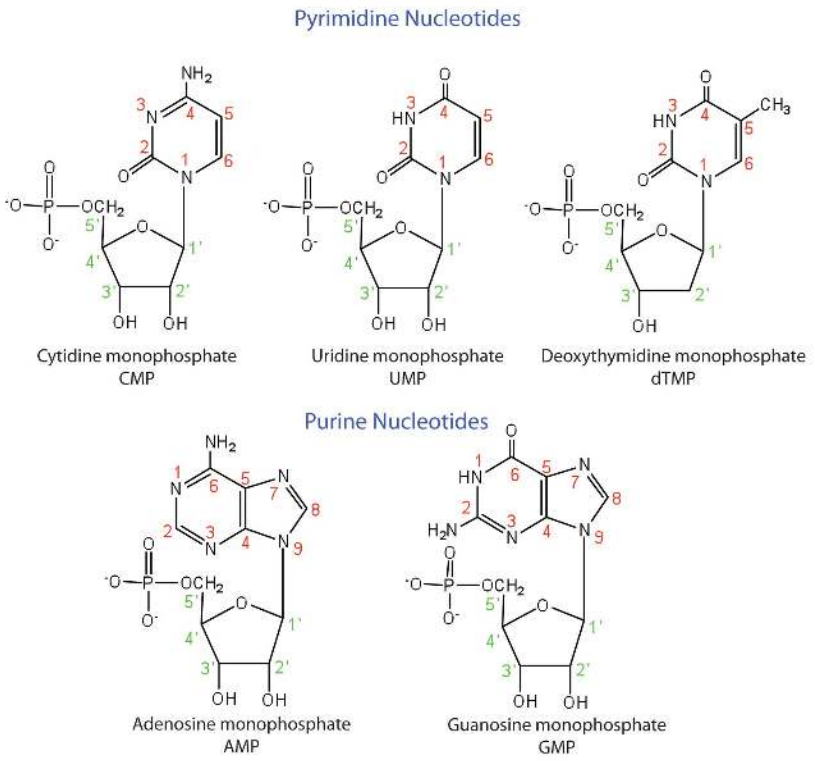


Figure **27.1.2** The Pyrimidine and Purine Nucleotides

Apart from being the monomer units of DNA and RNA, the nucleotides and some of their derivatives have other functions as well. Adenosine diphosphate (ADP) and adenosine triphosphate (ATP), shown in Figure **27.1.3**, have a role in cell metabolism. Moreover, a number of coenzymes, including flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide (NAD^+), and coenzyme A, contain adenine nucleotides as structural components.

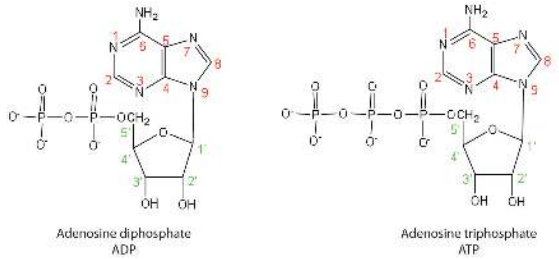


Figure **27.1.3**: Structures of Two Important Adenine-Containing Nucleotides

PRIMARY STRUCTURE OF NUCLEIC ACIDS

Nucleotides are joined together through the phosphate group of one nucleotide connecting in an ester linkage to the OH group on the third carbon atom of the sugar unit of a second nucleotide. This unit joins to a third nucleotide, and the process is repeated to produce a long nucleic acid chain (Figure 28.1.4). The backbone of the chain consists of alternating phosphate and sugar units (2-deoxyribose in DNA and ribose in RNA). The purine and pyrimidine bases branch off this backbone.

Note

Each phosphate group has one acidic hydrogen atom that is ionized at physiological pH. This is why these compounds are known as nucleic *acids*.

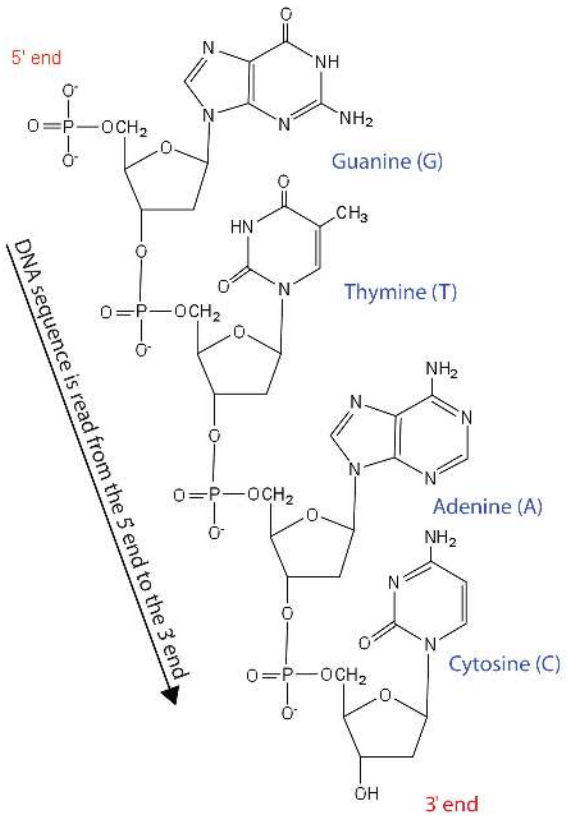


Figure **27.1.4**: Structure of a Segment of DNA. A similar segment of RNA would have OH groups on each C2′, and uracil would replace thymine.

Like proteins, nucleic acids have a primary structure that is defined as the sequence of their nucleotides. Unlike proteins, which have 20 different kinds of amino acids, there are only 4 different kinds of nucleotides in nucleic acids. For amino acid sequences in proteins, the convention is to write the amino acids in order starting with the N-terminal amino acid. In writing nucleotide sequences for nucleic acids, the convention is to write the nucleotides (usually using the one-letter abbreviations for the bases, shown in Figure 28.1.4) starting with the nucleotide having a free phosphate group, which is known as the 5′ end, and indicate the nucleotides in order. For DNA, a lowercase *d* is often written in front of the sequence to indicate that the monomers are deoxyribonucleotides. The final nucleotide has a free OH group on the 3′ carbon atom and is called the *3′ end*. The sequence of nucleotides in the DNA segment shown in Figure 28.1.4 would be written 5′-dG-dT-dA-dC-3′, which is often further abbreviated to dGTAC or just GTAC.

CONCEPT REVIEW EXERCISES

1. Identify the three molecules needed to form the nucleotides in each nucleic acid.
   a. DNA
   b. RNA
2. Classify each compound as a pentose sugar, a purine, or a pyrimidine.
   a. adenine
   b. guanine
   c. deoxyribose
   d. thymine
   e. ribose
   f. cytosine

ANSWERS

1. a. nitrogenous base (adenine, guanine, cytosine, and thymine), 2-deoxyribose, and H_3PO_4
   b. nitrogenous base (adenine, guanine, cytosine, and uracil), ribose, and H_3PO_4
2. a. purine

b. purine
c. pentose sugar
d. pyrimidine
e. pentose sugar
f. pyrimidine

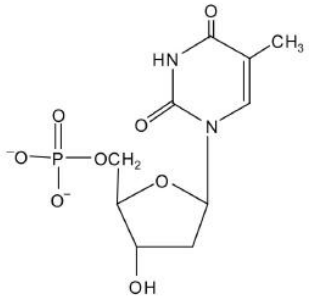
KEY TAKEAWAYS

- Nucleotides are composed of phosphoric acid, a pentose sugar (ribose or deoxyribose), and a nitrogen-containing base (adenine, cytosine, guanine, thymine, or uracil).
- Ribonucleotides contain ribose, while deoxyribonucleotides contain deoxyribose.

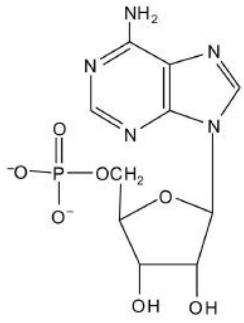
EXERCISES

1. What is the sugar unit in each nucleic acid?
   a. RNA
   b. DNA
2. Identify the major nitrogenous bases in each nucleic acid.
   a. DNA
   b. RNA
3. For each structure, circle the sugar unit and identify the nucleotide as a ribonucleotide or a deoxyribonucleotide.

a.

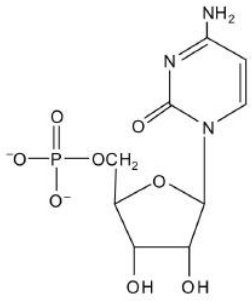


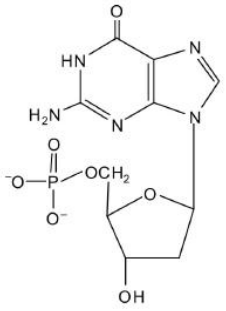
b.



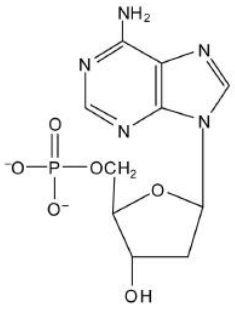
4. For each structure, circle the sugar unit and identify the nucleotide as a ribonucleotide or a deoxyribonucleotide.

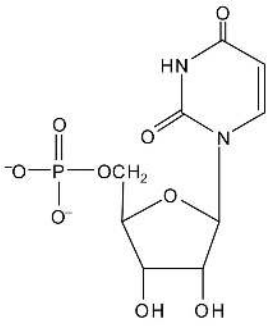
a.



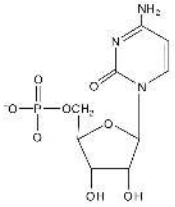
b. 

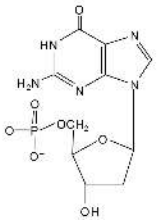
5. For each structure, circle the nitrogenous base and identify it as a purine or pyrimidine.

a. 

b. 

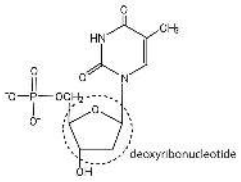
6. For each structure, circle the nitrogenous base and identify it as a purine or pyrimidine.

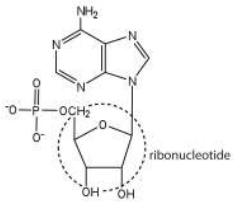
a. 

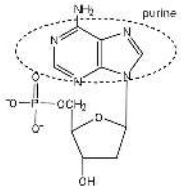
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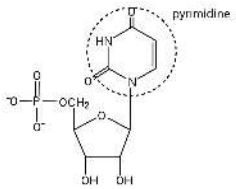
ANSWERS

1. a. ribose
   b. deoxyribose

3. a. 

b. 

a. 

b. 

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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27.2: DNA BASE PAIRS

Objectives

After completing this section, you should be able, given the necessary Kekulé structures, to show how hydrogen bonding can occur between thymine and adenine, and between guanine and cytosine; and to explain the significance of such interactions to the primary and secondary structures of DNA.

Study Notes

Watson and Crick received the Nobel Prize in 1962 for elucidating the structure of DNA and proposing the mechanism for gene reproduction. Their work rested heavily on X-ray crystallographic work done on RNA and DNA by Franklin and Wilkins. Wilkins shared the Nobel Prize with Watson and Crick, but Franklin had been dead four years at the time of the award (you cannot be awarded the Nobel Prize posthumously).

The history of Watson and Crick's proposed DNA model is controversial and a travesty of scientific ethics. Rosalind Franklin was deeply involved in the determination of the structure of DNA, and had collected numerous diffraction patterns. Watson attended a departmental colloquium at King's College given by Franklin, and came into possession of an internal progress report she had written. Both departmental colloquia and progress reports are merely methods of discussion between colleagues; works presented in these fora are not considered by scientists to be "published" works, and therefore are not in the public domain. Watson and Crick not only were aware of Franklin's work, but used her unpublished data, presented in confidence within her own college.

The final blow came about a year after the colloquium. Watson visited Wilkins at King's College, and Wilkins inexplicably handed over Franklin's diffraction photographs without her consent. Had Franklin's work not been secretly taken from her, she might quite possibly have solved the DNA structure before Watson and Crick, who at the time did not yet have their own photographs. This is truly one of the sadder episodes of questionable scientific ethics and discovery that I have ever encountered.

References

Kass-Simon, G., and P. Farnes. Women of Science: Righting the Record. Bloomington, IN: Indiana University Press, 1990.

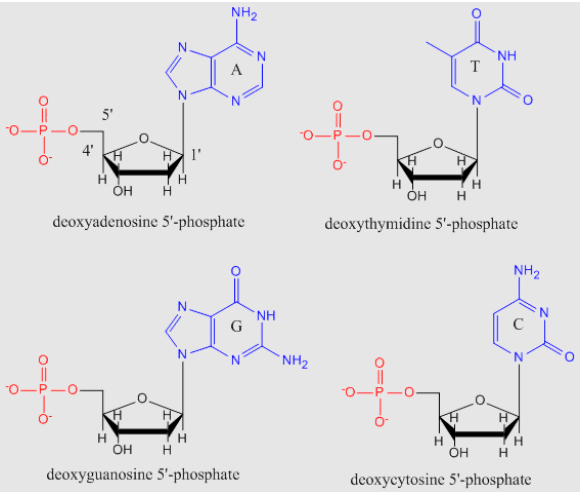
Maddox, B. Rosalind Franklin: The Dark Lady of DNA. New York: HarperCollins, 2002.

INTERMOLECULAR FORCES IN NUCLEIC ACIDS

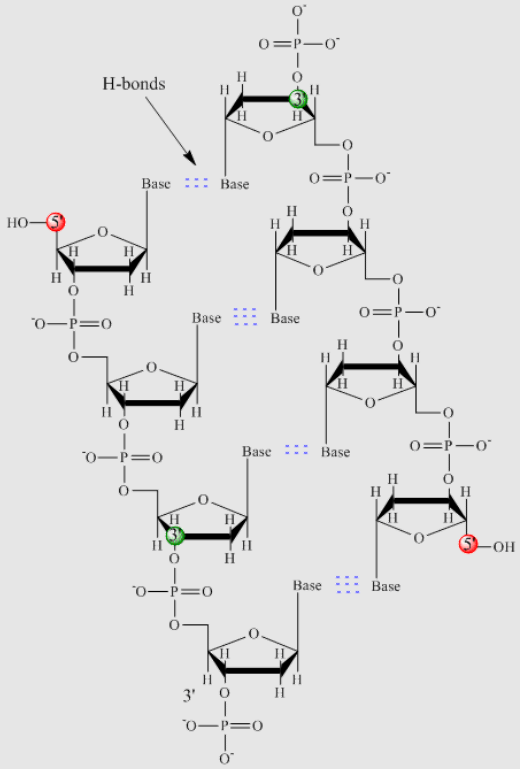
The nucleic acids RNA and DNA are involved in the storage and expression of genetic information in a cell. Both are polymers of monomeric nucleotides. DNA exists in the cell as double-stranded helices while RNA typically is a single-stranded molecule which can fold in 3D space to form complex secondary (double-stranded helices) and tertiary structures in a fashion similar to proteins. The complex 3D structures formed by RNA allow it to perform functions other than simple genetic information storage, such as catalysis. Hence most scientists believe that RNA preceded both DNA and proteins in evolution as it can both store genetic information and catalyze chemical reactions.

DNA

DNA is a polymer, consisting of monomers call deoxynucleotides. The monomer contains a simple sugar (deoxyribose, shown in black below), a phosphate group (in red), and a cyclic organic R group (in blue) that is analogous to the side chain of an amino acid.

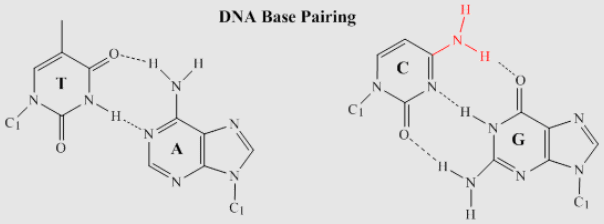


Only four bases are used in DNA (in contrast to the 20 different side chains in proteins) which we will abbreviate, for simplicity, as A, G, C and T. They are bases since they contain amine groups that can accept protons. The polymer consists of a sugar - phosphate - sugar - phosphate backbone, with one base attached to each sugar molecule. As with proteins, the DNA backbone is polar but also charged. It is a polyanion. The bases, analogous to the side chains of amino acids, are predominately polar. Given the charged nature of the backbone, you might expect that DNA does not fold to a compact globular (spherical) shape, even if positively charged cations like Mg bind to and stabilize the charge on the polymer. Instead, DNA exists usually as a double-stranded (ds) structure with the sugar-phosphate backbones of the two different strands running in opposite directions (5'-3' and the other 3'-5'). The strands are held together by hydrogen bonds between bases on complementary strands. Hence like proteins, DNA has secondary structure but in this case, the hydrogen bonds are not within the backbone but between the "side chain" bases on opposing strands. It is actually a misnomer to call dsDNA a molecule, since it really consists of two different, complementary strands held together by hydrogen bonds. A structure of ds-DNA showing the opposite polarity of the strands is shown below.



In double stranded DNA, the guanine (G) base on one strand can form three H-bonds with a cytosine (C) base on another strand (this is called a GC base pair). The thymine (T) base on one strand can form two H-bonds with an adenine (A) base on the other strand (this is called an AT base pair). Double-stranded DNA has a regular geometric structure with a fixed distance between the two backbones. This

requires the bases pairs to consists of one base with a two-ring (bicyclic) structure (these bases are called purines) and one with a single ring structure (these bases are called pyrimidines). Hence a G and A or a T and C are not possible base pair partners.



A and T base pair through Hydrogen bonds

G and C base pair through Hydrogen bonds

Double stranded DNA varies in length (number of sugar-phosphate units connected), base composition (how many of each set of bases) and sequence (the order of the bases in the backbone). The following links provide interactive Jmol models of dsDNA made by Angel Herráez, Univ. de Alcalá (Spain) and Eric Martz.

- Jmol model of ds-DNA with base pairs and H-bonds
- Jmol model of DNA strands and helical backbone
- Jmol model of DNA ends and parallelisms

Chromosomes consist of one dsDNA with many different bound proteins. The human genome has about 3 billion base pairs of DNA. Therefore, on average, each single chromosome of a pair has about 150 million base pairs and lots of proteins bound to it. dsDNA is a highly charged molecule, and can be viewed, to a first approximation, as a long rod-like molecule with a large negative charge. It is a polyanion. This very large molecule must somehow be packed into a small nucleus of a tiny cell. In complex (eukaryotic) cells, this packing problem is solved by coiling DNA around a core complex of four different pairs (eight proteins total) of histone proteins (H2A, H2B, H3, and H4) which have net positive charges. The histone core complex with dsDNA wound around approximately 2.5 times is called the nucleosome.

Jmol model of the nucleosome

DNA can adopt two other types of double-helical forms. The one discovered by Watson and Crick and found in most textbooks is called B-DNA. Depending on the actual DNA sequence and the hydration state of the DNA, it can be coaxed to form two other types of double-stranded helices, Z and A DNA. The A form is much more open then the B form.

The 3.2 billion base pairs of DNA in humans contains about 24,000 short stretches (genes) that encode different proteins. These genes are interspersed among DNA that helps determining if the gene is decoded into RNA molecules (see below) and ultimately into proteins. For a particular gene to be activated (or "turned on"), specific proteins must bind to the region of a particular gene. How can binding proteins find specific binding targets among the vast number of base pairs that to a first approximation have a repetitive sugar-phosphate-base repeat? The Jmol below shows how specificity can be achieved. When DNA winds into a double helix through base-pairs between AT and GC, hydrogen bond donors (amide Hs) and acceptors (Os) on the bases that are not used in intrastrand base pairing,are still available in the major and minor grove of the ds-DNA helix (see Jmol below). Unique base pair sequences will display unique patterns of H bond donors and acceptors in the major grove. These donors/acceptors can be recognized by specific DNA binding proteins which on binding can lead to gene activation.

- Jmol model of dsDNA showing unique H bond donors and acceptors in the major grove

CONTRIBUTORS AND ATTRIBUTIONS

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- Prof. Steven Farmer (Sonoma State University)
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- (Henry Jakubowski)

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27.3: DNA REPLICATION

Objectives

After completing this section, you should be able to describe, very briefly, the replication of DNA.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- replication
- semiconservative replication

Study Notes

Notice that the objective for this section requires only that you be able to describe the replication process briefly.

New cells are continuously forming in the body through the process of cell division. For this to happen, the DNA in a dividing cell must be copied in a process known as replication. The complementary base pairing of the double helix provides a ready model for how genetic replication occurs. If the two chains of the double helix are pulled apart, disrupting the hydrogen bonding between base pairs, each chain can act as a *template*, or pattern, for the synthesis of a new complementary DNA chain.

The nucleus contains all the necessary enzymes, proteins, and nucleotides required for this synthesis. A short segment of DNA is "unzipped," so that the two strands in the segment are separated to serve as templates for new DNA. DNA polymerase, an enzyme, recognizes each base in a template strand and matches it to the complementary base in a free nucleotide. The enzyme then catalyzes the formation of an ester bond between the 5′ phosphate group of the nucleotide and the 3′ OH end of the new, growing DNA chain. In this way, each strand of the original DNA molecule is used to produce a duplicate of its former partner (Figure 28.3.1). Whatever information was encoded in the original DNA double helix is now contained in each replicate helix. When the cell divides, each daughter cell gets one of these replicates and thus all of the information that was originally possessed by the parent cell.

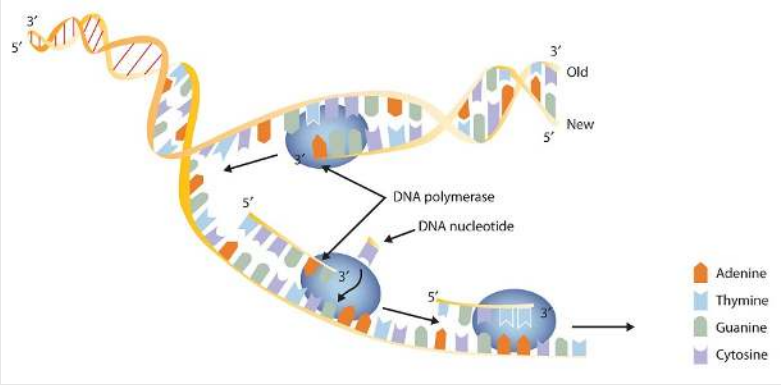


Figure: A Schematic Diagram of DNA Replication. DNA replication occurs by the sequential unzipping of segments of the double helix. Each new nucleotide is brought into position by DNA polymerase and is added to the growing strand by the formation of a phosphate ester bond. Thus, two double helixes form from one, and each consists of one old strand and one new strand, an outcome called *semiconservative replications*. (This representation is simplified; many more proteins are involved in replication.)

Example

A segment of one strand from a DNA molecule has the sequence 5′-TCCATGAGTTGA-3′. What is the sequence of nucleotides in the opposite, or complementary, DNA chain?

Solution

Knowing that the two strands are antiparallel and that T base pairs with A, while C base pairs with G, the sequence of the complementary strand will be 3′-AGGTACTCAACT-5′ (can also be written as TCAACTCATGGA).

Exercise

A segment of one strand from a DNA molecule has the sequence 5′-CCAGTGAATTGCCTAT-3′. What is the sequence of nucleotides in the opposite, or complementary, DNA chain?

What do we mean when we say information is encoded in the DNA molecule? An organism's DNA can be compared to a book containing directions for assembling a model airplane or for knitting a sweater. Letters of the alphabet are arranged into words, and these words direct the individual to perform certain operations with specific materials. If all the directions are followed correctly, a model airplane or sweater is produced.

In DNA, the particular sequences of nucleotides along the chains encode the directions for building an organism. Just as *saw* means one thing in English and *was* means another, the sequence of bases CGT means one thing, and TGC means something different. Although there are only four letters—the four nucleotides—in the genetic code of DNA, their sequencing along the DNA strands can vary so widely that information storage is essentially unlimited.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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27.4: TRANSCRIPTION OF DNA

Objectives

After completing this section, you should be able to

1. describe, very briefly, how RNA is synthesized in the nucleus of the cell by transcription of DNA.
2. identify the important structural differences between DNA and DNA.
3. given the appropriate Kekulé structures, show how uracil can form strong hydrogen bonds to adenine.
4. identify the base sequence in RNA that would be complementary to a given base sequence in DNA.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- messenger RNA
- RNA polymerase
- ribosomal RNA
- transcription
- transfer RNA

Study Notes

"Messenger RNA" (mRNA) carries the genetic information from the DNA in the nucleus to the cytoplasm where protein synthesis occurs. The code carried by mRNA is read by "transfer RNA" (tRNA) in a process called translation (see Section 28.5).

"Ribosomal RNA" (rRNA) is the term used to describe the RNA molecules which, together with proteins, make up the ribosomes on which proteins are synthesized.

For the hereditary information in DNA to be useful, it must be "expressed," that is, used to direct the growth and functioning of an organism. The first step in the processes that constitute DNA expression is the synthesis of RNA, by a template mechanism that is in many ways analogous to DNA replication. Because the RNA that is synthesized is a complementary copy of information contained in DNA, RNA synthesis is referred to as transcription.

There are three key differences between replication and transcription: (1) RNA molecules are much shorter than DNA molecules; only a portion of one DNA strand is copied or transcribed to make an RNA molecule. (2) RNA is built from ribonucleotides rather than deoxyribonucleotides. (3) The newly synthesized RNA strand does not remain associated with the DNA sequence it was transcribed from.

The DNA sequence that is transcribed to make RNA is called the *template strand*, while the complementary sequence on the other DNA strand is called the *coding* or *informational strand*. To initiate RNA synthesis, the two DNA strands unwind at specific sites along the DNA molecule. Ribonucleotides are attracted to the uncoiling region of the DNA molecule, beginning at the 3′ end of the template strand, according to the rules of base pairing. Thymine in DNA calls for adenine in RNA, cytosine specifies guanine, guanine calls for cytosine, and adenine requires uracil. RNA polymerase—an enzyme—binds the complementary ribonucleotide and catalyzes the formation of the ester linkage between ribonucleotides, a reaction very similar to that catalyzed by DNA polymerase (Figure 28.4.1). Synthesis of the RNA strand takes place in the 5′ to 3′ direction, antiparallel to the template strand. Only a short segment of the RNA molecule is hydrogen-bonded to the template strand at any time during transcription. When transcription is completed, the RNA is released, and the DNA helix reforms. The nucleotide sequence of the RNA strand formed during transcription is identical to that of the corresponding coding strand of the DNA, except that U replaces T.

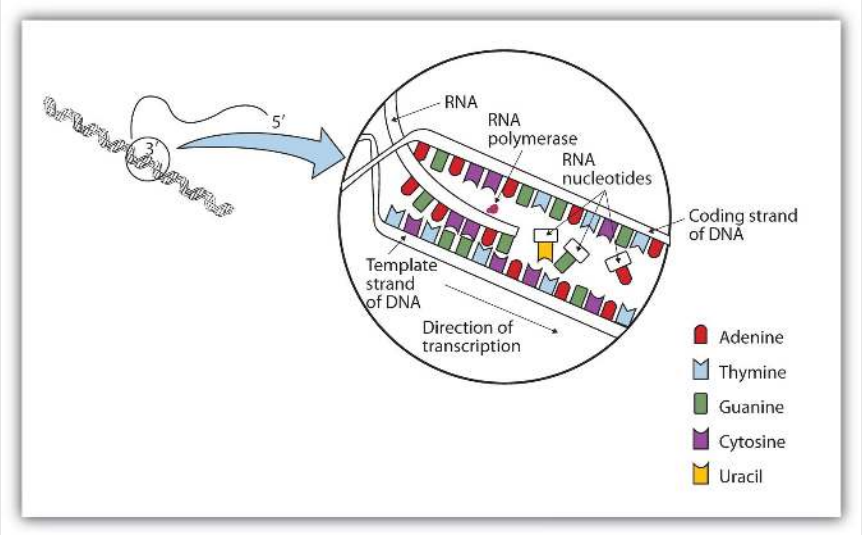


Figure: **A Schematic Diagram of RNA Transcription from a DNA Template**. The representation of RNA polymerase is proportionately much smaller than the actual molecule, which encompasses about 50 nucleotides at a time.

Example

A portion of the template strand of a gene has the sequence 5′-TCCATGAGTTGA-3′. What is the sequence of nucleotides in the RNA that is formed from this template?

Solution

Four things must be remembered in answering this question: (1) the DNA strand and the RNA strand being synthesized are antiparallel; (2) RNA is synthesized in a 5′ to 3′ direction, so transcription begins at the 3′ end of the template strand; (3) ribonucleotides are used in place of deoxyribonucleotides; and (4) thymine (T) base pairs with adenine (A), A base pairs with uracil (U; in RNA), and cytosine (C) base pairs with guanine (G). The sequence is determined to be 3′-AGGUACUCAACU-5′ (can also be written as 5′-UCAACUCAUGGA-3′).

Exercise

A portion of the template strand of a gene has the sequence 5′-CCAGTGAATTGCCTAT-3′. What is the sequence of nucleotides in the RNA that is formed from this template?

Three types of RNA are formed during transcription: *messenger RNA* (mRNA), *ribosomal RNA* (rRNA), and *transfer RNA* (tRNA). These three types of RNA differ in function, size, and percentage of the total cell RNA (Table 28.4.1). mRNA makes up only a small percent of the total amount of RNA within the cell, primarily because each molecule of mRNA exists for a relatively short time; it is continuously being degraded and resynthesized. The molecular dimensions of the mRNA molecule vary according to the amount of genetic information a given molecule contains. After transcription, which takes place in the nucleus, the mRNA passes into the cytoplasm, carrying the genetic message from DNA to the ribosomes, the sites of protein synthesis. Elsewhere, we shall see how mRNA directly determines the sequence of amino acids during protein synthesis.

Table: Properties of Cellular RNA in Escherichia coli

Type	Function	Approximate Number of Nucleotides	Percentage of Total Cell RNA
mRNA	codes for proteins	100–6,000	~3
rRNA	component of ribosomes	120–2900	83
tRNA	adapter molecule that brings the amino acid to the ribosome	75–90	14

Ribosomes are cellular substructures where proteins are synthesized. They contain about 65% rRNA and 35% protein, held together by numerous noncovalent interactions, such as hydrogen bonding, in an overall structure consisting of two globular particles of unequal size.

Molecules of tRNA, which bring amino acids (one at a time) to the ribosomes for the construction of proteins, differ from one another in the kinds of amino acid each is specifically designed to carry. A set of three nucleotides, known as a codon, on the mRNA

determines which kind of tRNA will add its amino acid to the growing chain. Each of the 20 amino acids found in proteins has at least one corresponding kind of tRNA, and most amino acids have more than one.

The two-dimensional structure of a tRNA molecule has three distinctive loops, reminiscent of a cloverleaf (Figure 28.4.2). On one loop is a sequence of three nucleotides that varies for each kind of tRNA. This triplet, called the anticodon, is complementary to and pairs with the codon on the mRNA. At the opposite end of the molecule is the acceptor stem, where the amino acid is attached.

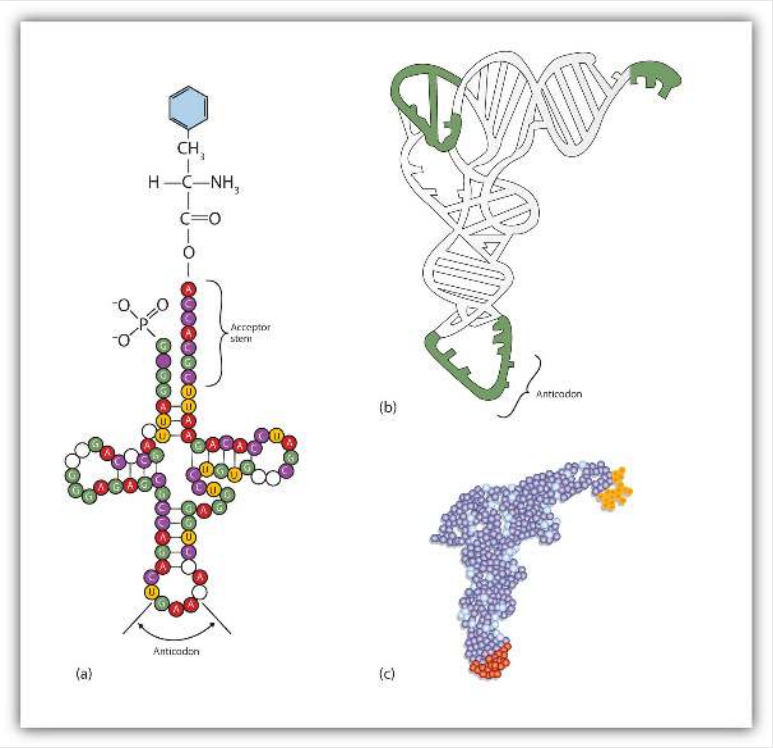


Figure : Transfer RNA (a) In the two-dimensional structure of a yeast tRNA molecule for phenylalanine, the amino acid binds to the acceptor stem located at the 3′ end of the tRNA primary sequence. (The nucleotides that are not specifically identified here are slightly altered analogs of the four common ribonucleotides A, U, C, and G.) (b) In the three-dimensional structure of yeast phenylalanine tRNA, note that the anticodon loop is at the bottom and the acceptor stem is at the top right. (c) This shows a space-filling model of the tRNA.

CONTRIBUTORS AND ATTRIBUTIONS

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- Prof. Steven Farmer (Sonoma State University)

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27.5: TRANSLATION OF RNA- PROTEIN BIOSYNTHESIS

Objectives

After completing this section, you should be able to describe, very briefly, the roles of messenger RNA and transfer RNA in the biosynthesis of proteins.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- anticodon
- codon
- translation

Study Notes

As in the preceding section, you should not be too concerned about trying to memorize details. The objective requires you to have a general understanding of the roles played by mRNA and tRNA in the biosynthesis of proteins, and that you be able to describe this process.

One of the definitions of a gene is as follows: a segment of deoxyribonucleic acid (DNA) carrying the code for a specific polypeptide. Each molecule of messenger RNA (mRNA) is a transcribed copy of a gene that is used by a cell for synthesizing a polypeptide chain. If a protein contains two or more different polypeptide chains, each chain is coded by a different gene. We turn now to the question of how the sequence of nucleotides in a molecule of ribonucleic acid (RNA) is translated into an amino acid sequence.

How can a molecule containing just 4 different nucleotides specify the sequence of the 20 amino acids that occur in proteins? If each nucleotide coded for 1 amino acid, then obviously the nucleic acids could code for only 4 amino acids. What if amino acids were coded for by groups of 2 nucleotides? There are 4^2, or 16, different combinations of 2 nucleotides (AA, AU, AC, AG, UU, and so on). Such a code is more extensive but still not adequate to code for 20 amino acids. However, if the nucleotides are arranged in groups of 3, the number of different possible combinations is 4^3, or 64. Here we have a code that is extensive enough to direct the synthesis of the primary structure of a protein molecule.

The *genetic code* can therefore be described as *the identification of each group of three nucleotides and its particular amino acid*. The sequence of these triplet groups in the mRNA dictates the sequence of the amino acids in the protein. Each individual three-nucleotide coding unit, as we have seen, is called a *codon*.

Protein synthesis is accomplished by orderly interactions between mRNA and the other ribonucleic acids (transfer RNA [tRNA] and ribosomal RNA [rRNA]), the ribosome, and more than 100 enzymes. The mRNA formed in the nucleus during transcription is transported across the nuclear membrane into the cytoplasm to the ribosomes—carrying with it the genetic instructions. The process in which the information encoded in the mRNA is used to direct the sequencing of amino acids and thus ultimately to synthesize a protein is referred to as *translation*.

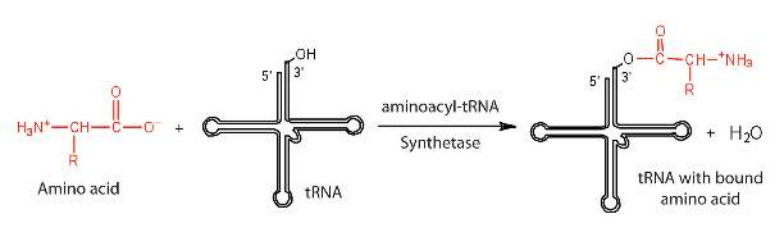
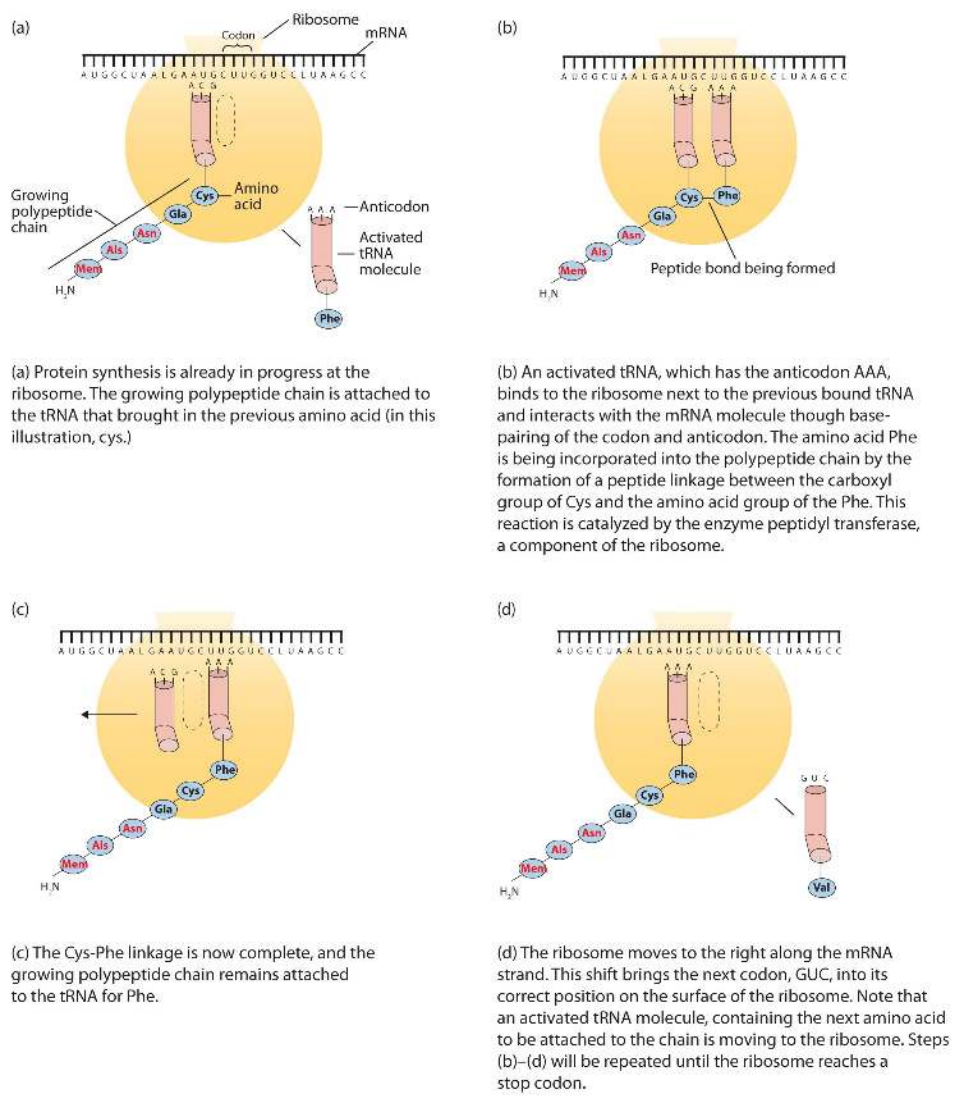


Figure: Binding of an Amino Acid to Its tRNA

Before an amino acid can be incorporated into a polypeptide chain, it must be attached to its unique tRNA. Each tRNA molecule has an **anticodon** for the amino acid it carries. An anticodon is a sequence of 3 bases, and is complementary to the codon for an amino acid. For example, the amino acid lysine has the codon AAG, so the anticodon is UUC. Therefore, lysine would be carried by a tRNA molecule with the anticodon UUC. Wherever the codon AAG appears in mRNA, a UUC anticodon on a tRNA temporarily binds to the codon. This crucial process requires an enzyme known as aminoacyl-tRNA synthetase (Figure 28.5.1). There is a specific aminoacyl-tRNA synthetase for each amino acid. This high degree of specificity is vital to the incorporation of the correct amino acid into a protein. After the amino acid molecule has been bound to its tRNA carrier, protein synthesis can take place. Figure 28.5.2 depicts a schematic stepwise representation of this all-important process.



(a) Protein synthesis is already in progress at the ribosome. The growing polypeptide chain is attached to the tRNA that brought in the previous amino acid (in this illustration, cys.)

(b) An activated tRNA, which has the anticodon AAA, binds to the ribosome next to the previous bound tRNA and interacts with the mRNA molecule though base-pairing of the codon and anticodon. The amino acid Phe is being incorporated into the polypeptide chain by the formation of a peptide linkage between the carboxyl group of Cys and the amino acid group of the Phe. This reaction is catalyzed by the enzyme peptidyl transferase, a component of the ribosome.

(c) The Cys-Phe linkage is now complete, and the growing polypeptide chain remains attached to the tRNA for Phe.

(d) The ribosome moves to the right along the mRNA strand. This shift brings the next codon, GUC, into its correct position on the surface of the ribosome. Note that an activated tRNA molecule, containing the next amino acid to be attached to the chain is moving to the ribosome. Steps (b)–(d) will be repeated until the ribosome reaches a stop codon.

Figure: The Elongation Steps in Protein Synthesis

Early experimenters were faced with the task of determining which of the 64 possible codons stood for each of the 20 amino acids. The cracking of the genetic code was the joint accomplishment of several well-known geneticists—notably Har Khorana, Marshall Nirenberg, Philip Leder, and Severo Ochoa—from 1961 to 1964. The genetic dictionary they compiled, summarized in Figure 28.5.3, shows that 61 codons code for amino acids, and 3 codons serve as signals for the termination of polypeptide synthesis (much like the period at the end of a sentence). Notice that only methionine (AUG) and tryptophan (UGG) have single codons. All other amino acids have two or more codons.

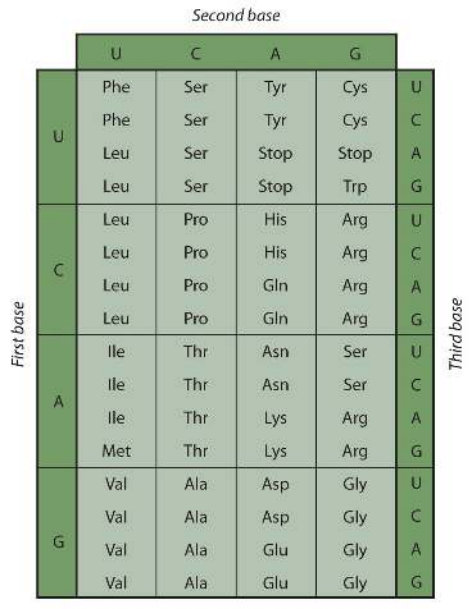


Figure: **The Genetic Code**

Example

A portion of an mRNA molecule has the sequence 5′-AUGCCACGAGUUGAC-3′. What amino acid sequence does this code for?

Solution

Use the Genetic Code Figure above to determine what amino acid each set of three nucleotides (codon) codes for. Remember that the sequence is read starting from the 5′ end and that a protein is synthesized starting with the N-terminal amino acid. The sequence 5′-AUGCCACGAGUUGAC-3′ codes for met-pro-arg-val-asp.

Exercise

A portion of an RNA molecule has the sequence 5′-AUGCUGAAUUGCGUAGGA-3′. What amino acid sequence does this code for?

Further experimentation threw much light on the nature of the genetic code, as follows:

1. The code is virtually universal; animal, plant, and bacterial cells use the same codons to specify each amino acid (with a few exceptions).
2. The code is “degenerate”; in all but two cases (methionine and tryptophan), more than one triplet codes for a given amino acid.
3. The first two bases of each codon are most significant; the third base often varies. This suggests that a change in the third base by a mutation may still permit the correct incorporation of a given amino acid into a protein. The third base is sometimes called the “wobble” base.
4. The code is continuous and nonoverlapping; there are *no* nucleotides between codons, and adjacent codons do not overlap.
5. The three termination codons are read by special proteins called release factors, which signal the end of the translation process.
6. The codon AUG codes for methionine and is also the initiation codon. Thus methionine is the first amino acid in each newly synthesized polypeptide. This first amino acid is usually removed enzymatically before the polypeptide chain is completed; the vast majority of polypeptides do not begin with methionine.

CONCEPT REVIEW EXERCISES

1. What are the roles of mRNA and tRNA in protein synthesis?
2. What is the initiation codon?
3. What are the termination codons and how are they recognized?

ANSWERS

1. mRNA provides the code that determines the order of amino acids in the protein; tRNA transports the amino acids to the ribosome to incorporate into the growing protein chain.

2. AUG
3. UAA, UAG, and UGA; they are recognized by special proteins called release factors, which signal the end of the translation process.

KEY TAKEAWAYS

- In translation, the information in mRNA directs the order of amino acids in protein synthesis.
- A set of three nucleotides (codon) codes for a specific amino acid.

EXERCISES

1. Write the anticodon on tRNA that would pair with each mRNA codon.
   a. 5′-UUU-3′
   b. 5′-CAU-3′
   c. 5′-AGC-3′
   d. 5′-CCG-3′
2. Write the codon on mRNA that would pair with each tRNA anticodon.
   a. 5′-UUG-3′
   b. 5′-GAA-3′
   c. 5′-UCC-3′
   d. 5′-CAC-3′
3. The peptide hormone oxytocin contains 9 amino acid units. What is the minimum number of nucleotides needed to code for this peptide?
4. Myoglobin, a protein that stores oxygen in muscle cells, has been purified from a number of organisms. The protein from a sperm whale is composed of 153 amino acid units. What is the minimum number of nucleotides that must be present in the mRNA that codes for this protein?
5. Use Figure 28.5.3to identify the amino acids carried by each tRNA molecule in Exercise 1.
6. Use Figure 28.5.3to identify the amino acids carried by each tRNA molecule in Exercise 2.
7. Use Figure 28.5.3to determine the amino acid sequence produced from this mRNA sequence: 5′-AUGAGCGACUUUGCGGGAUUA-3′.
8. Use Figure 28.5.3to determine the amino acid sequence produced from this mRNA sequence: 5′-AUGGCAAUCCUCAAACGCUGU-3′

ANSWERS

1. a. 3′-AAA-5′
   b. 3′-GUA-5′
   c. 3′-UCG-5′
   d. 3′-GGC-5′
3. 27 nucleotides (3 nucleotides/codon)
5. 1a: phenyalanine; 1b: histidine; 1c: serine; 1d: proline
7. met-ser-asp-phe-ala-gly-leu

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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27.6: DNA SEQUENCING

We will discuss one method of reading the sequence of DNA. This method, developed by Sanger won him a second Nobel prize. To sequence a single stranded piece of DNA, the complementary strand is synthesized. Four different reaction mixtures are set up. Each contain all 4 radioactive deoxynucleotides (dATP, dCTP, dGTP, dTTP) required for the reaction and DNA polymerase. In addition, dideoxyATP (ddATP) is added to one reaction tube The dATP and ddATP attach randomly to the growing 3' end of the complementary stranded. If ddATP is added no further nucleotides can be added after since its 3' end has an H and not a OH. That's why they call it dideoxy. The new chain is terminated.. If dATP is added, the chain will continue to grow until another A needs to be added. Hence a whole series of discreet fragments of DNA chains will be made, all terminated when ddATP was added. The same scenario occurs for the other 3 tubes, which contain dCTP and ddCTP, dTTP and ddTTP, and dGTP and ddGTP respectively. All the fragments made in each tube will be placed in separate lanes for electrophoresis, where the fragments will separate by size.

DIDEXOYNUCLEOTIDES

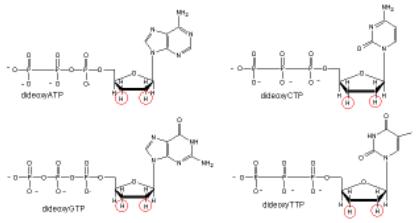


Figure: Didexoynucleotides

$$t = \frac{0.9\lambda}{\sqrt{B_M^2 - B_S^2}\cos\theta}$$

Example

You will pretend to sequence a single stranded piece of DNA as shown below. The new nucleotides are added by the enzyme DNA polymerase to the primer, GACT, in the 5' to 3' direction. You will set up 4 reaction tubes, Each tube contains all the dXTP's. In addition, add ddATP to tube 1, ddTTP to tube 2, ddCTP to tube 3, and ddGTP to tube 4. For each separate reaction mixture, determine all the possible sequences made by writing the possible sequences on one of the unfinished complementary sequences below. Cut the completed sequences from the page, determine the size of the polynucleotide sequences made, and place them as they would migrate (based on size) in the appropriate lane of a imaginary gel which you have drawn on a piece of paper. Lane 1 will contain the nucleotides made in tube 1, etc. Then draw lines under the positions of the cutout nucleotides to represent DNA bands in the gel. Read the sequence of the complementary DNA synthesized. Then write the sequence of the ssDNA that was to be sequenced.

- 5' T C A A C G A T C T G A 3' (STAND TO SEQUENCE)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)

Since the DNA fragments have no detectable color, they can not be directly visualized in the gel. Alternative methods are used. In the one described above, radiolabeled ddXTP's where used. Once the sequencing gel is run, it can be dried and the bands visualized by radioautography (also called autoradiography). A place of x-ray film is placed over the dried gel in a dark environment. The radiolabeled bands will emit radiation which will expose the x-ray film directly over the bands. The film can be developed to detect the bands. In a newer technique, the primer can be labeled with a flourescent dye. If a different dye is used for each reaction mixture, all the reaction mixtures can be run in one lane of a gel. (Actually only one reaction mix containing all the ddXTP's together need be performed.) The gel can then be scanned by a laser, which detects fluorescence from the dyes, each at a different wavelength.

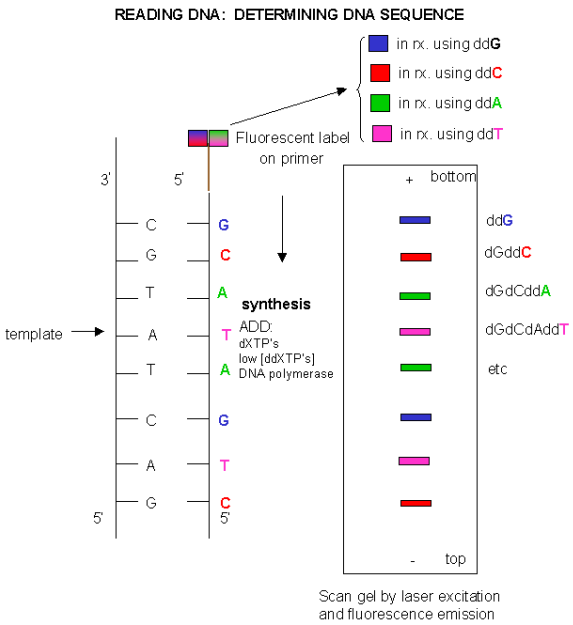
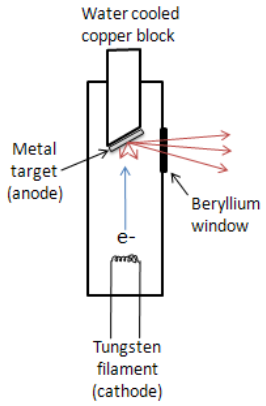


Figure: DNA sequencing using different fluorescent primers for each ddXTP reaction

One recent advance in sequencing allows for real-time determination of a sequence. The four deoxynucleotides are each labeled with a different fluorphore on the 5' phosphate (not the base as above). A tethered DNA polymerase elongates the DNA on a template, releasing the fluorophore into solution (i.e. the fluorophore is not incorporated into the DNA chain). The reaction takes place in a visualization chamber called a zero mode waveguide which is a cylindrical metallic chamber with a width of 70 nm and a volume of 20 zeptoliters (20 x 10-21 L). It sits on a glass support through which laser illumination of the sample is achieved. Given the small volume, non-incorporated fluorescently tagged deoxynucleotides diffuse in and out in the microsecond timescale. When a deoxynucleotide is incorporated into the DNA, its residence time is in the millisecond time scale. This allows for prolonged detection of fluorescence which give a high signal to noise ratio. This method might bring the cost of sequencing the human genome down from the initial billion dollar range to $100.



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27.7: POLYMERASE CHAIN REACTIONS

In the mid 80's a new method was developed to copy (amplify) DNA in a test tube. It doesn't require a plasmid or a virus. It just requires a DNA fragment, some primers (small polynucleotides complementary to sections of DNA on each strand and straddling the section of DNA to be amplified. Just add to this mixture dATP, dCTP, dGTP, dTTP, and a heat stable DNA polymerase from the organism Thermophilus aquaticus (which lives in hot springs), and off you go. The mixture is first heated to a temperature which will cause the DsDNA strands to separate. The temperature is cooled allowing a large stoichimetric excess of the primers to anneal to the ssDNA. The heat stable Taq polymerase (from Thermophilus aquaticus) polymerizes DNA from the primers. The temperature is raised again, allowing dsDNA strand separation. On cooling the primers anneal again to the original and newly synthesized DNA from the last cycle and synthesis of DNA occurs again. This cycle is repeated as shown in the diagram. This chain reaction is called the polymerase chain reaction (PCR). The target DNA synthesized is amplified a million times in 20 cycles, or a billion times in 30 cycles, which can be done in a few hours.

***Figure**: Copying DNA in the test tube - the polymerase chain reaction (PCR)*

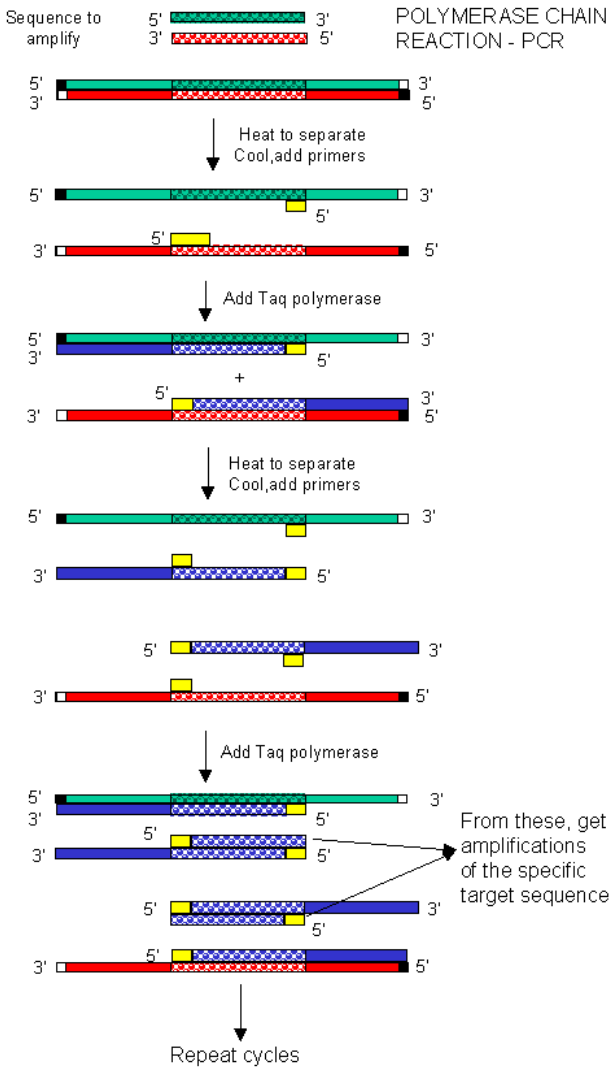
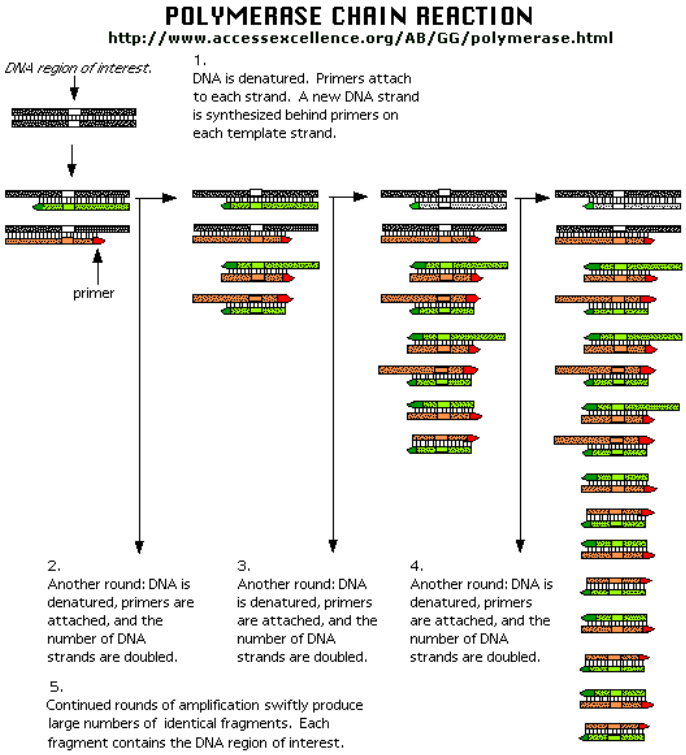


Figure: Another View of PCR



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