ATHABASCA UNIVERSITY CHEMISTRY 360 ORGANIC CHEMISTRY II



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Licensing

*A detailed breakdown of this resource's licensing can be found in **Back Matter/Detailed Licensing**.*

CHAPTER OVERVIEW

CHAPTER 17: ALCOHOLS AND PHENOLS

LEARNING OBJECTIVES

When you have completed Chapter 17, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design a multi-step synthesis using any of the reactions introduced in this chapter, together with any number of the reactions discussed in *Chemistry 350*.
3. solve "road-map" problems that require a knowledge of the chemistry of alcohols and phenols, in addition to the chemistry of the other classes of compounds discussed in *Chemistry 350*.
4. define, and use in context, the key terms introduced in this chapter.

In this chapter, we examine the chemistry of the alcohol family of compounds. Alcohols can undergo a wide variety of reactions, and because of this reactivity and because they can be prepared in a number of different ways, alcohols occupy an important position in organic chemistry.

The discussion begins with an outline of the nomenclature of alcohols and phenols. We review the physical properties of these compounds, and discuss methods used to obtain the lower members of the series on an industrial scale. A detailed discussion of the laboratory preparation of alcohols follows, with particular emphasis on those methods that involve either the reduction of a carbonyl compound or the use of a Grignard reagent.

Certain reactions of alcohols were discussed in previous chapters. In this chapter, we concentrate on the oxidation of alcohols to carbonyl compounds. We also introduce the concept of protecting a sensitive functional group during an organic synthesis. The discussion then turns to the uses of phenols, their preparation and their chemical reactivity.

Infrared, nuclear magnetic resonance and mass spectroscopy each can provide valuable information about alcohols and phenols, and we illustrate the application of these techniques to the identification of unknown alcohols and phenols with a number of examples.

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17.0 INTRODUCTION

Objectives

After completing this section, you should be able to

1. describe the structural differences among alcohols, phenols and enols.
2. write equations describing the industrial preparation of the two simplest alcohols: methanol and ethanol.

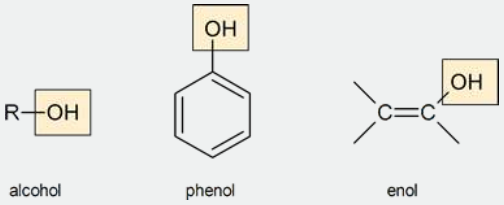
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- alcohol
- enol
- phenol

STUDY NOTES

Alcohols and phenols are organic compounds with at least one hydroxyl group attached to a saturated or an aryl carbon, respectively. Enols are a related third class of compounds, with the hydroxyl group attached to a vinylic carbon. We will discuss enols in more detail in Chapter 22.



alcohol phenol enol

The reading correctly points out the toxicity of methanol, and describes the adverse effects of its consumption. These effects have not been exaggerated; you may recall reading about the deaths of six residents of Peerless Lake, Alberta, in 1986, 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."

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 labelled "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.

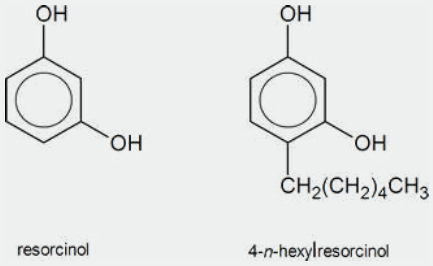
A third commonly encountered alcohol, isopropyl alcohol ("rubbing alcohol" or 2-propanol), is also toxic. It has the ability to kill germs and has a temporary lubricating effect during the rubbing process. Unlike methanol, 2-propanol is not absorbed through the skin; therefore it poses less of a health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

The use of alcohols as fuels is well established. In 2010, the Canadian federal government joined several of the provinces in requiring that all gasoline must include an average of five per cent ethanol. Some gasoline producers, notably Husky/Mohawk, average ten per cent ethanol content in their products. Some especially modified vehicles can use fuel that consists of 85 per cent ethanol (E85).

A phenol is an organic compound in which a hydroxyl group is directly bonded to one of the carbon atoms of an aromatic ring.

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.

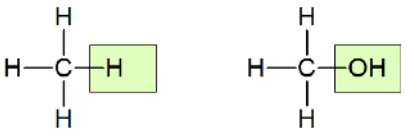
Phenol itself was rather strong for these purposes—it burns healthy tissue—and substitutes were eventually found. One such substitute, used today in throat lozenges and mouthwashes, is 4-*n*-hexylresorcinol.



resorcinol 4-*n*-hexylresorcinol

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:



methane methanol

The name, too, is derived from the name methane by replacing the final *e* with *ol* (for alcoh*ol*). The general formula for an alcohol may be written as R—OH, where R represents the hydrocarbon (alkane) portion of the molecule and is called an **alkyl group**. In methanol, R is the methyl group CH_3.

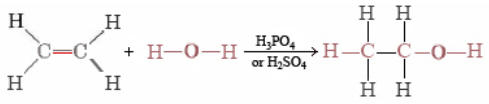
Methanol is also called wood alcohol because it can be obtained by heating wood in the absence of air, a process called **destructive distillation**. Methanol vapor given off when the wood is heated can be condensed to a liquid by cooling below its boiling point of 65°C. The effect of polarity and especially hydrogen bonding due to the OH group is evident when this is compared with the temperature of –85°C at which ethane, C_2H_6, boils. Both molecules contain 18 electrons and are nearly the same size, and so London forces should be about the same, but the OH group in one methanol molecule can form strong hydrogen bonds with an OH in another molecule. Methanol is an important industrial chemical—nearly 3×10^{10} kg was produced worldwide in 2003[1]. Some was made by destructive distillation, but most was synthesized from hydrogen and carbon monoxide:

$$2\,H_2\,(g) + CO\,(g) \longrightarrow CH_3OH\,(l) \qquad (1)$$

This reaction is carried out at pressures several hundred times normal atmospheric pressure, using metal oxides as catalysts. Methanol is mainly used to make other compounds from which plastics are manufactured, but some is consumed as fuel in jet engines and racing cars. Methanol is also a component of nonpermanent antifreeze and automobile windshield-washer solvent.

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.)

Ethanol can also be synthesized by adding H_2O to ethene, obtained during petroleum refining:



This is a typical example of an **addition reaction**. The H and OH from H_2O are added to the ethene molecule and held there by electrons made available when one-half of the double bond breaks.

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. Methanol also produces intoxication but is much more poisonous than ethanol—it can cause blindness and death. Denatured alcohol is ethanol to which methanol or some other poison has

been added, making it unfit for human consumption. Most of the ethanol not used in alcoholic beverages is denatured because in that form its sale is taxed at a much lower rate.

PHENOLS

Compounds in which a hydroxyl group is bonded to an aromatic ring are called phenols. 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. A corresponding difference in reactivity was observed in comparing aryl halides, such as bromobenzene, with alkyl halides, such as butyl bromide and tert-butyl chloride. Thus, nucleophilic substitution and elimination reactions were common for alkyl halides, but rare with aryl halides. This distinction carries over when comparing alcohols and phenols, so for all practical purposes substitution and/or elimination of the phenolic hydroxyl group does not occur.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- 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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17.1 NAMING ALCOHOLS AND PHENOLS

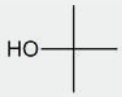
Objectives

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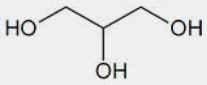
1. identify an alcohol as being primary, secondary or tertiary, given its structure, its IUPAC name or its trivial name.
2. write the IUPAC name of an alcohol or phenol given its Kekulé, condensed or shorthand structure.
3. draw the structure of an alcohol or phenol given its IUPAC name.
4. identify a number of commonly occurring alcohols (e.g., benzyl alcohol, *tert*-butyl alcohol) by their trivial names.

STUDY NOTES

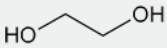
The following are common names of some alcohols (with IUPAC name).



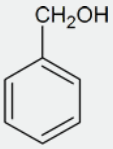
tert-butyl alcohol
(2-methyl-2-propanol)



gycerol
(1,2,3-propanetriol)



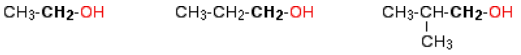
ethylene glycol
(1,2-ethanediol)



benzyl alcohol
(phenylmethanol)

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:

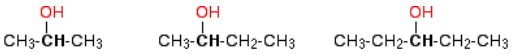


ethanol propan-1-ol 2-methylpropan-1-ol

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 CH2 group holding the -OH group. There is an exception to this. Methanol, CH3OH, 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:



propan-2-ol butan-2-ol pentan-3-ol

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:



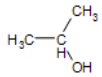
2-methylpropan-2-ol 2-methylbutan-2-ol

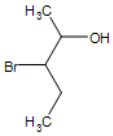
NAMING ALCOHOLS

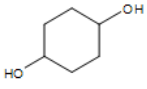
1. Find the longest chain containing the hydroxy group (OH). If there is a chain with more carbons than the one containing the OH group it will be named as a subsitutent.
2. Place the OH on the lowest possible number for the chain. With the exception of carbonyl groups such as ketones and aldehydes, the alcohol or hydroxy groups have first priority for naming.
3. When naming a cyclic structure, the -OH is assumed to be on the first carbon unless the carbonyl group is present, in which case the later will get priority at the first carbon.
4. When multiple -OH groups are on the cyclic structure, number the carbons on which the -OH groups reside.
5. Remove the final **e** from the parent alkane chain and add **-ol**. When multiple alcohols are present use **di, tri,** et.c before the **ol,** after the parent name. ex. 2,3-hexan**diol.** If a carbonyl group is present, the -OH group is named with the prefix "hydroxy," with the carbonyl group attached to the parent chain name so that it ends with **-al** or **-one.**

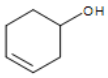
Examples

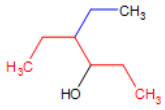
Ethan**e**: CH_3CH_3 ----->Ethan**ol**:  (the alcohol found in beer, wine and other consumed sprits)

Secondary alcohol:  2-propanol

Other functional groups on an alcohol:  3-bromo-2-pentanol

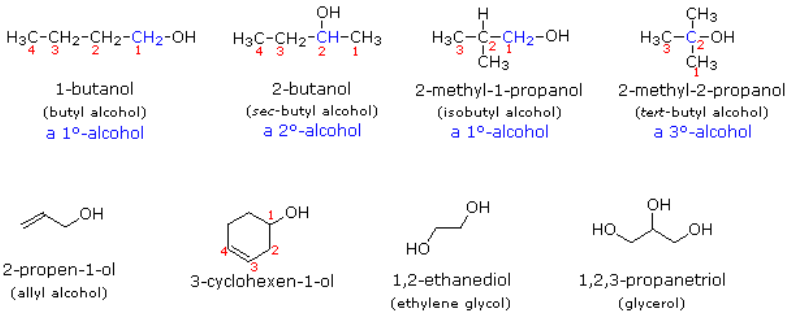
Cyclic alcohol (two -OH groups):  cyclohexan-1,4-diol

Other functional group on the cyclic structure:  3-hex**ene**ol (the alkene is in **bold** and indicated by numbering the carbon closest to the alcohol)

A complex alcohol:  4-ethyl-3hexanol (the parent chain is in red and the substituent is in blue)

In the IUPAC system of nomenclature, functional groups are normally designated in one of two ways. The presence of the function may be indicated by a characteristic suffix and a location number. This is common for the carbon-carbon double and triple bonds which have the respective suffixes **-ene** and **-yne**. Halogens, on the other hand, do not have a suffix and are named as substituents, for example: $(CH_3)_2C{=}CHCHClCH_3$ is 4-chloro-2-methyl-2-pentene.

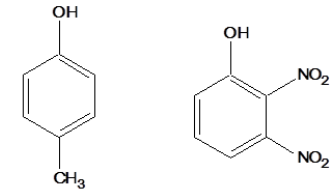
Alcohols are usually named by the first procedure and are designated by an **-ol** suffix, as in ethanol, CH_3CH_2OH (note that a locator number is unnecessary on a two-carbon chain). On longer chains the location of the hydroxyl group determines chain numbering. For example: $(CH_3)_2C{=}CHCH(OH)CH_3$ is 4-methyl-3-penten-2-ol. Other examples of IUPAC nomenclature are shown below, together with the common names often used for some of the simpler compounds. For the mono-functional alcohols, this common system consists of naming the **alkyl group** followed by the word **alcohol**. Alcohols may also be classified as primary, **1°**, secondary, **2°**, and tertiary, **3°**, in the same manner as alkyl halides. This terminology refers to alkyl substitution of the carbon atom bearing the hydroxyl group (colored blue in the illustration).



Many functional groups have a characteristic suffix designator, and only one such suffix (other than "-ene" and "-yne") may be used in a name. When the hydroxyl functional group is present together with a function of higher nomenclature priority, it must be cited and located by the prefix **hydroxy** and an appropriate number. For example, lactic acid has the IUPAC name 2-hydroxypropanoic acid.

NAMING PHENOLS

Phenols are named using the rules for aromatic compounds discussed in Section 15.1 Note! that *-phenol* is used rather than *-benzene*.



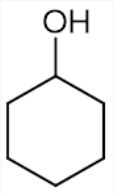
EXERCISES

? EXERCISE 17.1.1

Indicate if the following molecules are 1º, 2º, or 3º alcohols:

1)

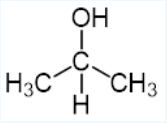
a)



b) $(CH_3)_3COH$

c) $CH_3CH_2CH_2OH$

d)



Answer

1)

a) Secondary

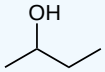
b) Tertiary

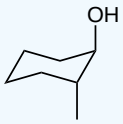
c) Primary

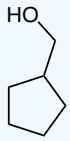
d) Secondary

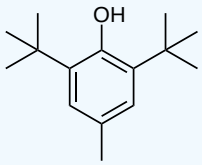
EXERCISE 17.1.2

Give IUPAC names for the following structures.

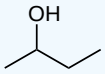




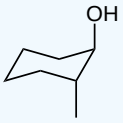




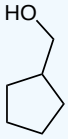
Answer



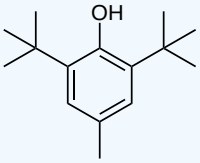
butan-2-ol



(1*R*, 2*R*)-2-mthylcyclohexan-1-ol



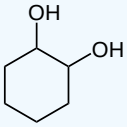
cyclopentylmethanol

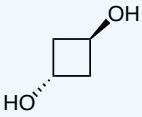


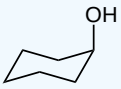
2,6-di-tert-butyl-4-methylphenol

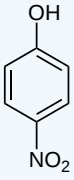
EXERCISE 17.1.3

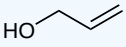
Name the following structures.







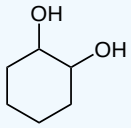




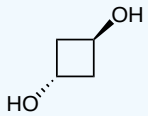


Answer

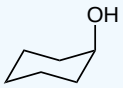
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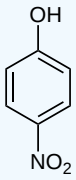
cyclohexane-1,2,-diol



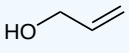
trans-cyclobutane-1,3-diol



cyclohexanol



4-nitrophenol



prop-2-en-1-ol



cycloproanol

EXERCISE 17.1.4

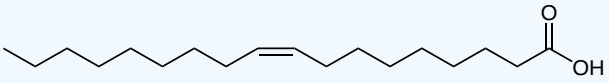
Draw and name all the alcohol isomers of C_3H_9O

Answer

Add texts here. Do not delete this text first.

EXERCISE 17.1.5

Oleic acid, a commonly occurring fatty acid in vegetable oils, has the following structure. Name the compound, making sure to give the correct alkene geometry.

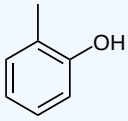


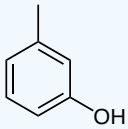
Answer

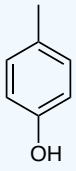
(9Z)-Octadec-9-enoic acid

EXERCISE 17.1.6

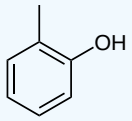
Creosols are naturally occurring compounds used building blocks for many molecules, they occur as three different isomers. Name each of the following isomers.



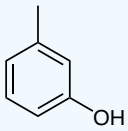




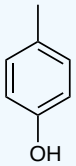
Answer



2-methylphenol



3-methylphenol

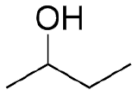


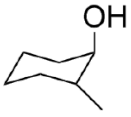
4-methylphenol

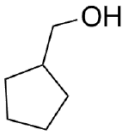
QUESTIONS

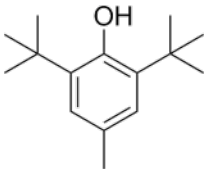
Q17.1.1

Give IUPAC names for the following structures.

(a) 

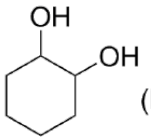
(b) 

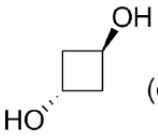
Indicate stereochemistry (c) 

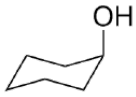
(d) 

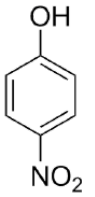
Q17.1.2

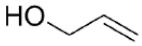
Name the following structures.

(a) 

(b) 

(c) 

(d) 

(e) 

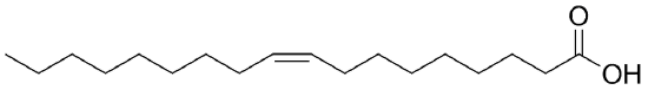
(f) 

Q17.1.3

Draw and name all the alcohol isomers of C_3H_9O

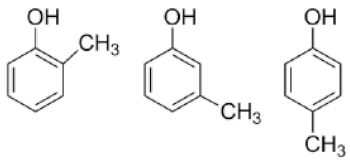
Q17.1.4

Oleic acid, a commonly occurring fatty acid in vegetable oils, has the following structure. Name the compound, making sure to give the correct alkene geometry.



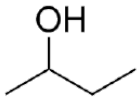
Q17.1.5

Creosols are naturally occurring compounds used building blocks for many molecules, they occur as three different isomers. Name each of the following isomers.

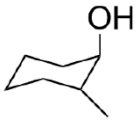


SOLUTIONS

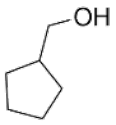
S17.1.1



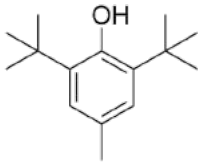
(a) butan-2-ol



(b) (1*R*,2*R*)-2-methylcyclohexan-1-ol



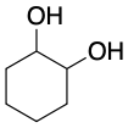
(c) cyclopentylmethanol (d)



2,6-di-*tert*-butyl-4-methylphenol

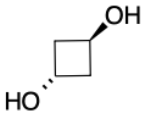
S17.1.2

(a)



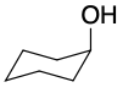
cycohexane-1,2-diol

(b)



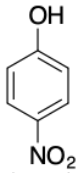
trans-cyclobutane-1,3-diol

(c)



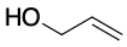
cyclohexanol

(a)



4-nitrophenol

(b)



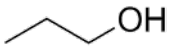
prop-2-en-1-ol

(c)



cyclopropanol

S17.1.3



propan-1-ol

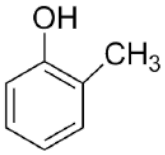


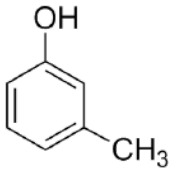
propan-2-ol or, 1-propanol and 2-propanol

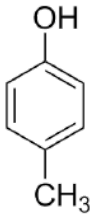
S17.1.4

(9*Z*)-Octadec-9-enoic acid

S17.1.5







2-methyphenol 3-methylphenol 4-methylphenol

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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17.2 PROPERTIES OF ALCOHOLS AND PHENOLS

Objectives

After completing this section, you should be able to

1. explain why the boiling points of alcohols and phenols are much higher than those of alkanes, ethers, etc., of similar molecular mass.
2. discuss the factors that are believed to determine the acidity of alcohols and phenols.
3. list a given series of alcohols or phenols in order of increasing or decreasing acidity.
4. explain the difference in acidity between two given alcohols or phenols.
5. explain why phenols are more acidic than alcohols.
6. explain, in terms of inductive and resonance effects, why a given substituted phenol is more or less acidic than phenol itself.
7. write equations for the reactions of given alcohols and phenols with strong bases, such as sodium hydride and sodium amide.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- acid ionization constant (K_a)
- alkoxide ion (RO^-)
- phenoxide ion (ArO^-)

STUDY NOTES

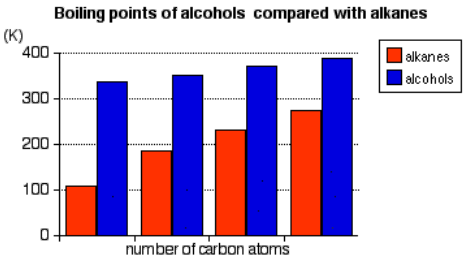
You may wish to review the concept of hydrogen bonding, which should have been discussed in your first-year general chemistry course.

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.



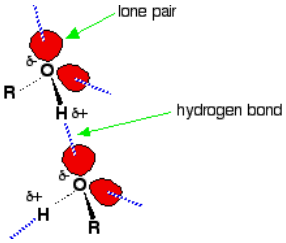
Notice that:

- The boiling point of an alcohol is always significantly higher than that of the analogous alkane.
- 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

- **Boiling points of the alcohols**: Hydrogen bonding is not the only intermolecular force alcohols experience. There are also van der Waals dispersion forces and dipole-dipole interactions. The hydrogen bonding and dipole-dipole interactions are much the same for all alcohols, but dispersion forces increase as the alcohols get bigger. These attractions get stronger as the molecules get longer and have more electrons. This increases the sizes of the temporary dipoles formed. This is why the boiling points increase as the number of carbon atoms in the chains increases. It takes more energy to overcome the dispersion forces, and thus the boiling points rise.
- **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:

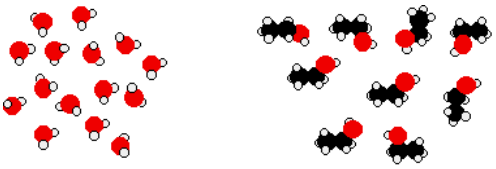


Ethanol is a longer molecule, and the oxygen atom brings with it an extra 8 electrons. Both of these increase the size of the van der Waals dispersion forces, and subsequently the boiling point. A more accurate measurement of the effect of the hydrogen bonding on boiling point would be a comparison of 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

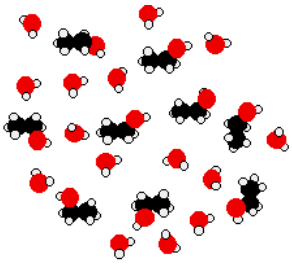
Small alcohols are completely soluble in water; mixing the two in any proportion generates a single solution. However, solubility decreases as the length of the hydrocarbon chain in the alcohol increases. At four carbon atoms and beyond, the decrease in solubility is noticeable; a two-layered substance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



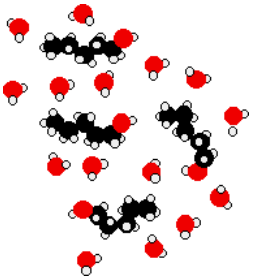
Both of these are held together mainly by hydrogen bonding.

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.

ACID/BASE PROPERTIES 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:

$$C_2H_5OH + Na^{\oplus}NH_2^{\ominus} \rightleftharpoons C_2H_5O^{\ominus}Na^{\oplus} + NH_3$$

sodium amide (sodamide) — sodium ethoxide

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

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

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 (Equation 15-1) lies more on the side of ROH and OHe as R is changed from primary to secondary to tertiary; therefore, tert-butyl alcohol is considered less acidic than ethanol:

$$ROH + OH^- \rightleftharpoons RO^- + HOH \qquad (1)$$

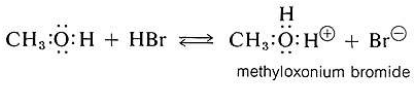
However, in the gas phase the order of acidity is reversed, and the equilibrium position for Equation 15-1 lies increasingly on the side of ROGas R is changed from primary to secondary to tertiary, terf-Butyl alcohol is therefore more acidic than ethanol in the gas phase. This seeming contradiction appears more reasonable when one considers what effect solvation (or the lack of it) has on equilibria expressed by Equation 15-1. In solution, the larger anions of alcohols, known as 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:

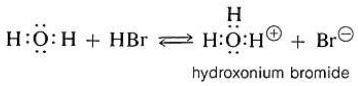
$CH_3O^{\ominus}$ methoxide — $C_2H_5O^{\ominus}$ ethoxide — $(CH_3)_2CHO^{\ominus}$ isopropoxide — $(CH_3)_3CO^{\ominus}$ *tert*-butoxide

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. (Also see Section 11-8A, which deals with the somewhat similar situation encountered with respect to the relative acidities of ethyne and water.)

CHEMICAL REACTIONS OF ALCOHOLS INVOLVING THE O-H BOND OF COMPOUNDS WITH BASIC PROPERTIES

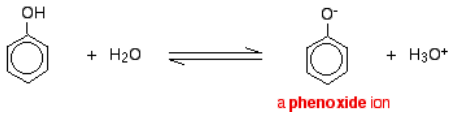
Alcohols are bases similar in strength to water and accept protons from strong acids. An example is the reaction of methanol with hydrogen bromide to give methyloxonium bromide, which is analogous to the formation of hydroxonium bromide with hydrogen bromide and water:



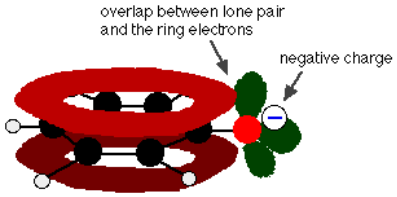


ACIDITY OF PHENOL

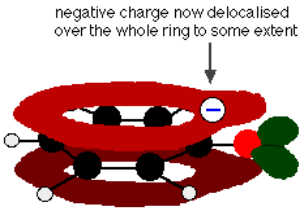
Compounds like alcohols and phenol which contain an -OH group attached to a hydrocarbon are very weak acids. Alcohols are so weakly acidic that, for normal lab purposes, their acidity can be virtually ignored. However, phenol is sufficiently acidic for it to have recognizably acidic properties - even 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:



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.

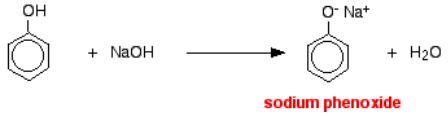


Spreading the charge around makes the ion more stable than it would be if all the charge remained on the oxygen. However, oxygen is the most electronegative element in the ion and the delocalized electrons will be drawn towards it. That means that there will still be a lot of charge around the oxygen 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.

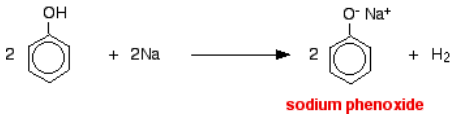
The resonance stabilization in these two cases is very different. An important principle of resonance is that charge separation diminishes the importance of canonical contributors to the resonance hybrid and reduces the overall stabilization. The contributing structures to the phenol

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.



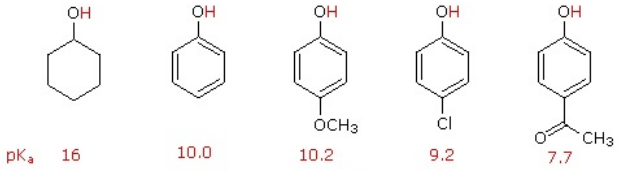
In this reaction, the hydrogen ion has been removed by the strongly basic hydroxide ion in the sodium hydroxide solution.

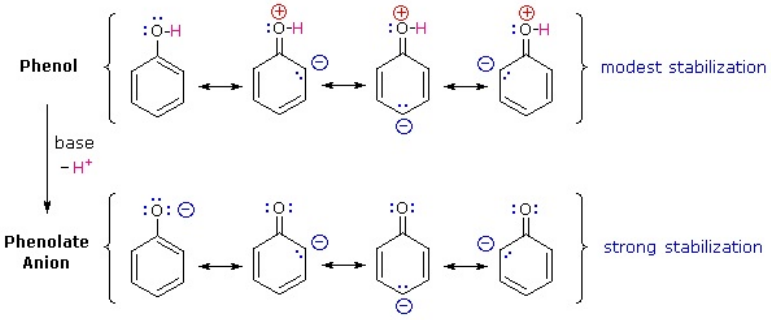
Acids react with the more reactive metals to give hydrogen gas. Phenol is no exception - the only difference is the slow reaction because phenol is such a weak acid. Phenol is warmed in a dry tube until it is molten, and a small piece of sodium added. There is some fizzing as hydrogen gas is given off.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

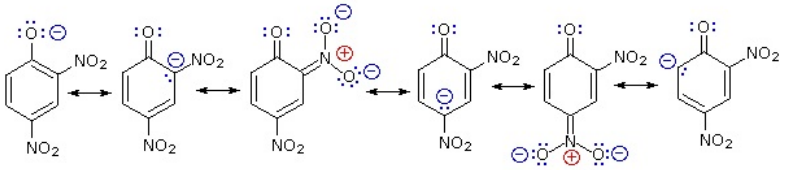


ACIDITY OF SUBSTITUTED PHENOLS

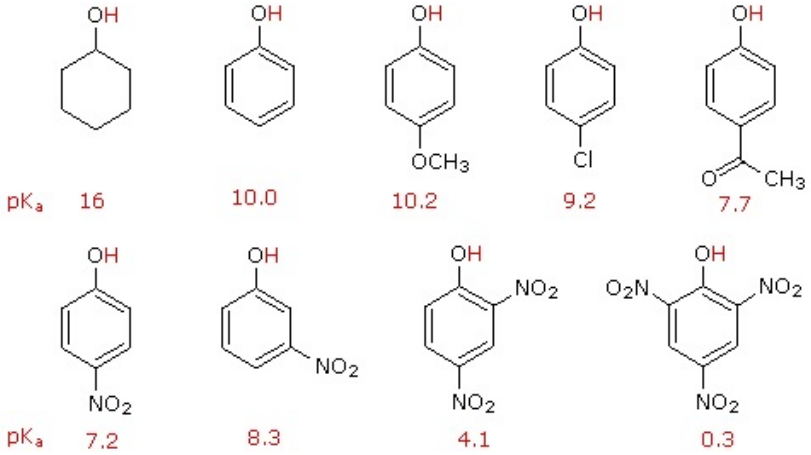
Substitution of the hydroxyl hydrogen atom is even more facile with phenols, which are roughly a million times more acidic than equivalent alcohols. This phenolic acidity is further enhanced by electron-withdrawing substituents ortho and para to the hydroxyl group, as displayed in the following diagram. 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.





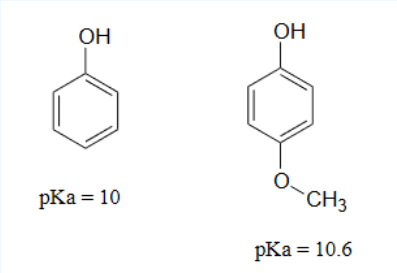


Resonance Stabilization of Phenolate by *ortho* and *para* Nitro Substituents



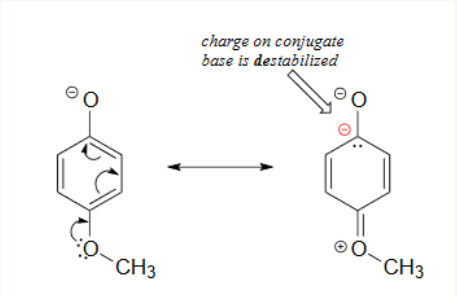
WORKED EXAMPLE 17.2.1

Using resonance structures, please explain why 4-methoxyphenol is less acidic than phenol.



Answer

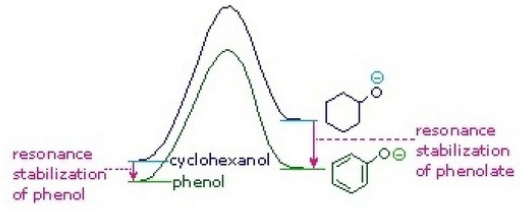
The methoxy group is an electron-donating group by resonance. A resonance contributor can be drawn in which a formal negative charge is placed on the carbon adjacent to the negatively-charged phenolate oxygen.



Because of like-charge repulsion, this destabilizes the negative charge on the phenolate oxygen, making the corresponding phenol less acidic.

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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.

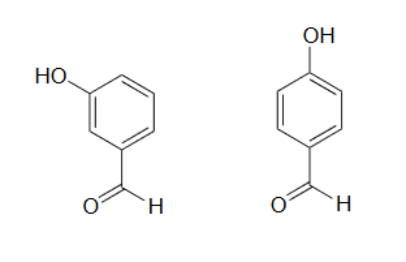


The resonance stabilization in these two cases is very different. An important principle of resonance is that charge separation diminishes the importance of canonical contributors to the resonance hybrid and reduces the overall stabilization. The contributing structures to the phenol hybrid all suffer 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.

EXERCISES

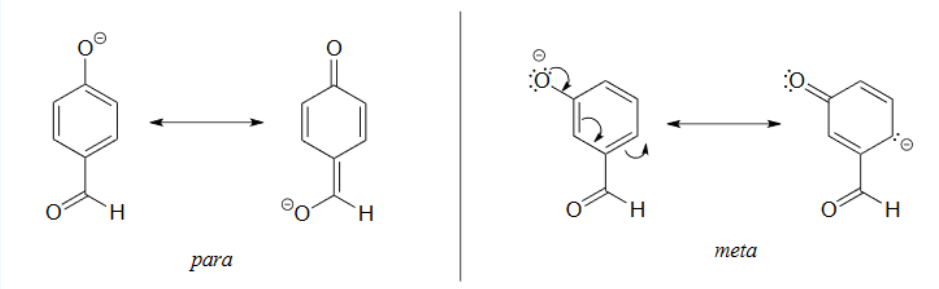
? EXERCISE 17.2.1

The position of the electron-withdrawing substituent relative to the phenol hydroxyl is very important in terms of its effect on acidity. Which of the two substituted phenols below is more acidic? Use resonance drawings to explain your answer.



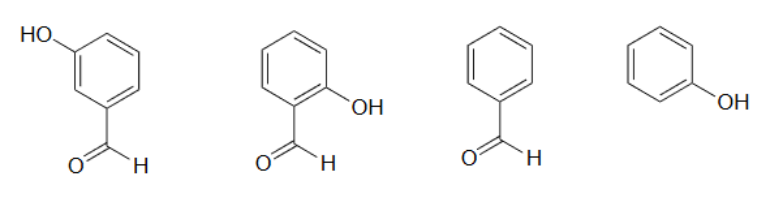
Answer

The para-subsituted phenol is more acidic, because the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. This is not possible when the aldehyde group is in the meta position.



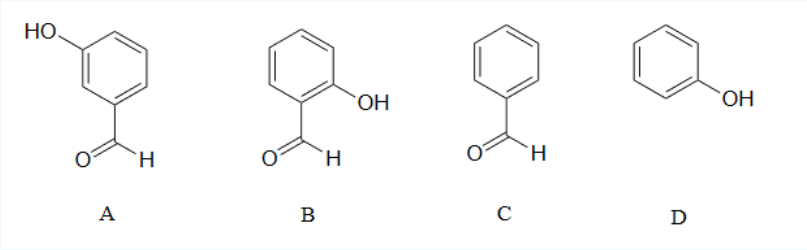
EXERCISE 17.2.2

Rank the four compounds below from most acidic to least.



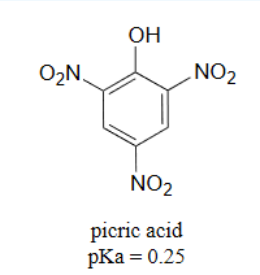
Answer

Compound B is the strongest acid due to electron-withdrawing resonance effects-the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. Compound A is the 2nd strongest acid -while the negative charge on the conjugate base cannot be delocalized to the aldehyde oxygen due to the *meta*-position, the aldehyde none the less has a stabilizing, electron-withdrawing inductive effect. Compound D is ranked #3 -it is phenol, and does not have any electron-withdrawing substituents on the ring as do B and A. Compound C is the least acidic -neither the phenyl group nor the aldehyde are even slightly acidic.



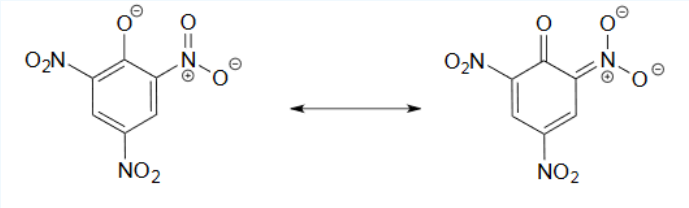
EXERCISE 17.2.3

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



Answer

The negative charge on the conjugate base of picric acid can be delocalized to oxygen atoms on all threeof the nitro groups. One such resonance contributor is shown below. This extensive delocalization means that the conjugate base is very stable, and the conjugate acid is thus a very strong acid.



EXERCISE 17.2.4

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

a) Butan-1-ol or pentan-1-ol

b) Phenol or cyclohexanol

c) Octan-1,3-diol or octan-1-ol

d) 1-Chlorohexane or hexan-1-ol

5) Predict which compound has the higher boiling point and explain your reasoning.

a) Water or ethanol

b) Butan-1-ol or octan-1-ol

c) Hexan-2-ol or hexan-2-one

Answer

a) 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.

b) 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.

c) 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.

d) 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.

5) a) 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.

b) 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.

c) Since hexan-1-ol can H-bond, it has a higher boiling point than hexan-2-one, which cannot H-bond.

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)

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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17.3 PREPARATION OF ALCOHOLS: A REVIEW

Objectives

After completing this section, you should be able to describe in detail the methods of preparing alcohols and diols, which you encountered in previous chapters.

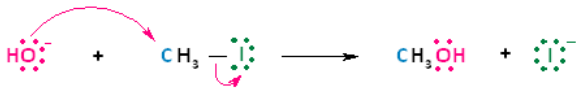
STUDY NOTES

If necessary, you should review Sections 8.4 and 8.5 describing direct hydration of alkenes, and Section 8.7 describing preparation of cis and trans diols from alkenes. Section 8.7 also gives more details on the formation of the respective osmate and epoxide intermediates of these reactions.

ALCOHOLS ARE PREPARED BY S_N2 REACTION

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.

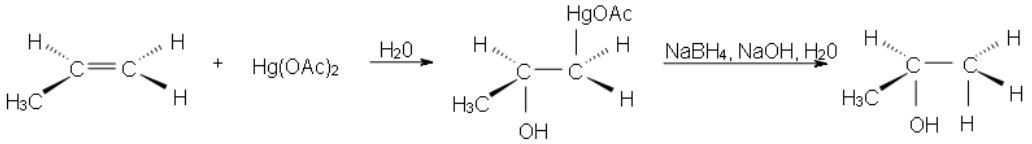
Example #1



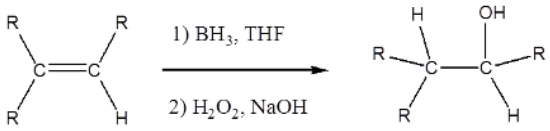
ALCOHOLS FROM ALKENES

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.



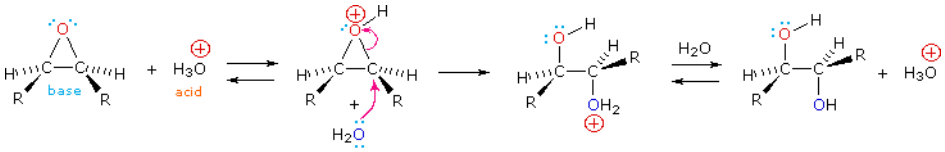
Hydroboration-Oxidation is a two step pathway used to produce alcohols. The reaction proceeds in an Anti-Markovnikov manner, where the hydrogen (from BH_3 or BHR_2) attaches to the more substituted carbon and the boron attaches to the least substituted carbon in the alkene bouble bond. Furthermore, the 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.



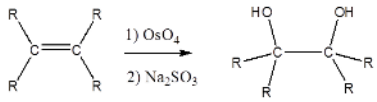
DIOLS FROM ALKENES

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.



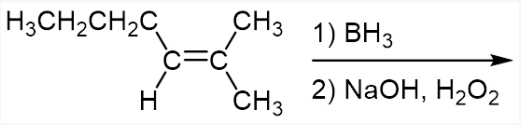
The reaction with OsO_4 is a concerted process that has a cyclic intermediate and no rearrangements. Vicinal syn dihydroxylation complements the epoxide-hydrolysis sequence which constitutes an *anti* dihydroxylation of an alkene. When an alkene reacts with osmium tetroxide, stereocenters can form in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

EXERCISE

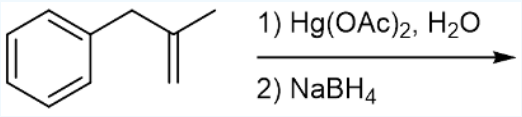
EXERCISE 17.3.1

1) Predict the products of the following reactions:

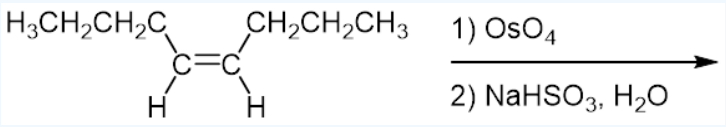
a)



b)



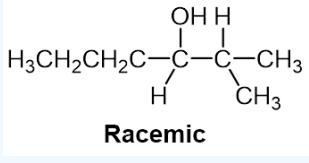
c)



Answer

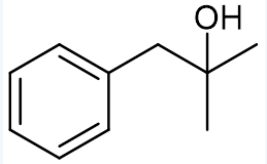
1)

a)

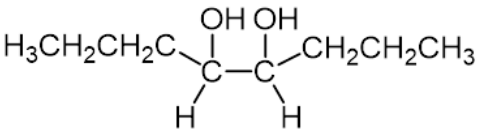


Racemic

b)



c)



Meso

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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17.4 ALCOHOLS FROM CARBONYL COMPOUNDS: REDUCTION

Objectives

After completing this section, you should be able to

1. determine whether a given reaction should be classified as an oxidation or a reduction.
2. write an equation to represent the reduction of an aldehyde or ketone using sodium borohydride or lithium aluminum hydride.
   a. discuss the relative advantages and disadvantages of using sodium borohydride or lithium aluminum hydride to reduce aldehydes or ketones to alcohols.
   b. identify the product formed from the reduction of a given aldehyde or ketone.
   c. identify the aldehyde or ketone that should be used to produce a given alcohol in a reduction reaction.
   d. identify the best reagent to carry out the reduction of a given aldehyde or ketone.
3. write an equation to represent the reduction of an ester or a carboxylic acid to an alcohol.
   a. identify the product formed from the reduction of a given ester or carboxylic acid.
   b. identify the esters or carboxylic acids that could be reduced to form a given alcohol.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- (organic) oxidation
- (organic) reduction

STUDY NOTES

In your course in first-year general chemistry, you probably discussed oxidation-reduction reactions in terms of the transfer of electrons and changes in oxidation numbers (oxidation states). In organic chemistry, it is often more convenient to regard reduction as the gain of hydrogen or loss of oxygen, and oxidation as the gain of oxygen or the loss of hydrogen. There is no contradiction in using these various definitions. For example, when hydrogen is added across the double bond of ethene to reduce it to ethane, the oxidation number of the doubly bonded carbon atoms decreases from −II to −III. Similarly, when 2-propanol



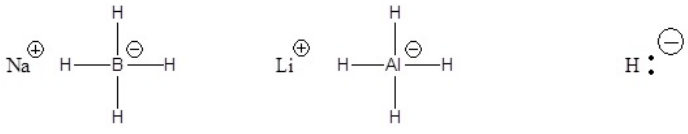
is oxidized to acetone



hydrogen is removed from the compound and the oxidation number of the central carbon atom increases from 0 to +II. If necessary, review the concept of oxidation number.

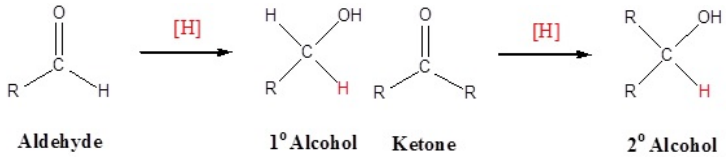
REDUCTION OF ALDEHYDES AND KETONES

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.



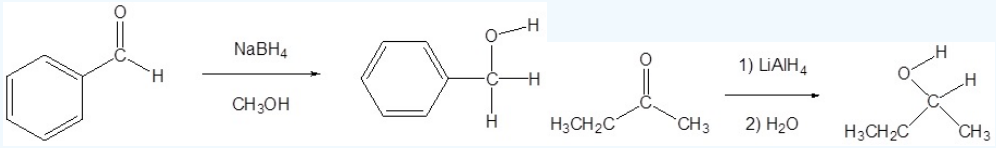
Sodium Borohydride **Lithium Aluminum Hydride** **Hydride Nucleophile**

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



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.

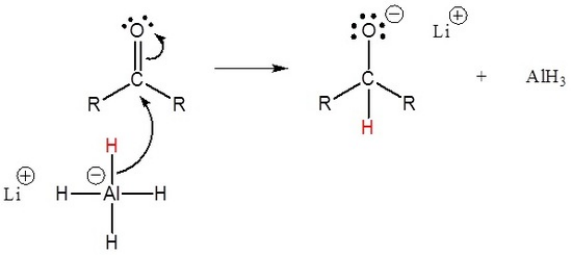
EXAMPLE 17.4.1



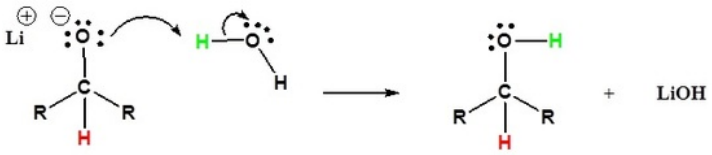
MECHANISM

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 attack by the hydride anion

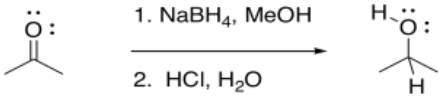


2) The alkoxide is protonated



BIOLOGICAL REDUCTION

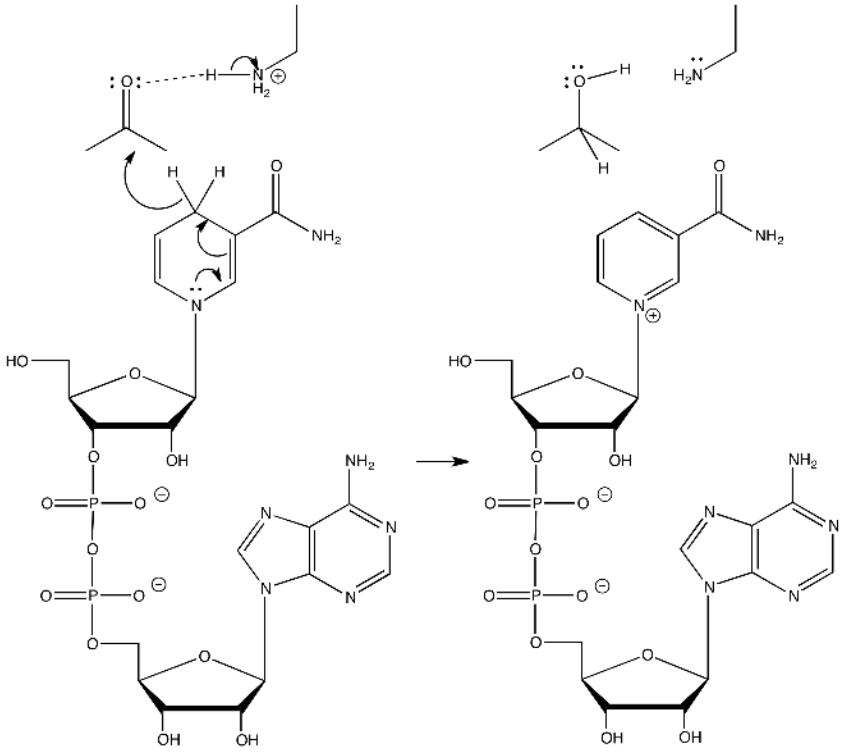
Addition to a carbonyl by a semi-anionic hydride, such as $NaBH_4$, results in conversion of the carbonyl compound to an alcohol. The hydride from the BH_4^- anion acts as a nucleophile, adding H^- to the carbonyl carbon. A proton source can then protonate the oxygen of the resulting alkoxide ion, forming an alcohol.



Formally, that process is referred to as a reduction. Reduction generally means a reaction in which electrons are added to a compound; the compound that gains electrons is said to be reduced. Because hydride can be thought of as a proton plus two electrons, we can think of conversion of a ketone or an aldehyde to an alcohol as a two-electron reduction. An aldehyde plus two electrons and two protons becomes an alcohol.

Aldehydes, ketones and alcohols are very common features in biological molecules. Converting between these compounds is a frequent event in many biological pathways. However, semi-anionic compounds like sodium borohydride don't exist in the cell. Instead, a number of biological hydride donors play a similar role.

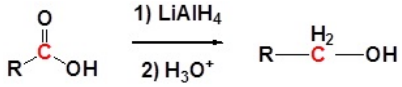
NADH is a common biological reducing agent. NADH is an acronym for nicotinamide adenine dinucleotide hydride. Insetad of an anionic donor that provides a hydride to a carbonyl, NADH is actually a neutral donor. It supplies a hydride to the carbonyl under very specific circumstances. In doing so, it forms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



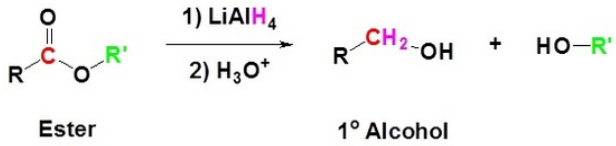
NADH NAD+

REDUCTION OF CARBOXYLIC ACIDS AND ESTERS

Carboxylic acids can be converted to 1º 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.

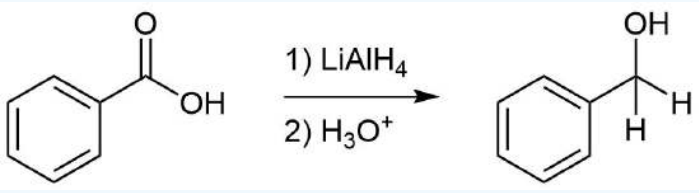


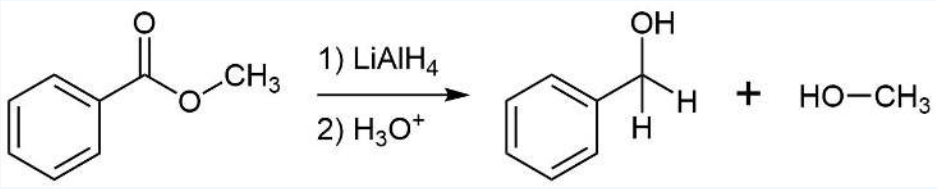
Esters can be converted to 1º alcohols using $LiAlH_4$, while sodium borohydride (***$NaBH_4$***) is not a strong enough reducing agent to perform this reaction.



Ester **1° Alcohol**

EXAMPLE 17.4.2

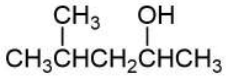




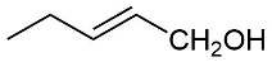
WORKED EXAMPLE 17.4.1

How would you prepare the following molecules using a hydride reduction?

a)



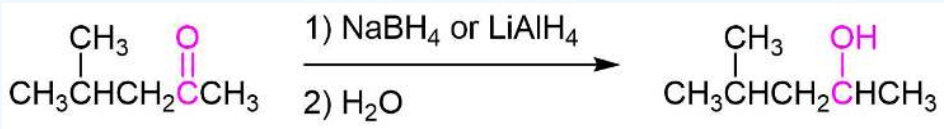
b)



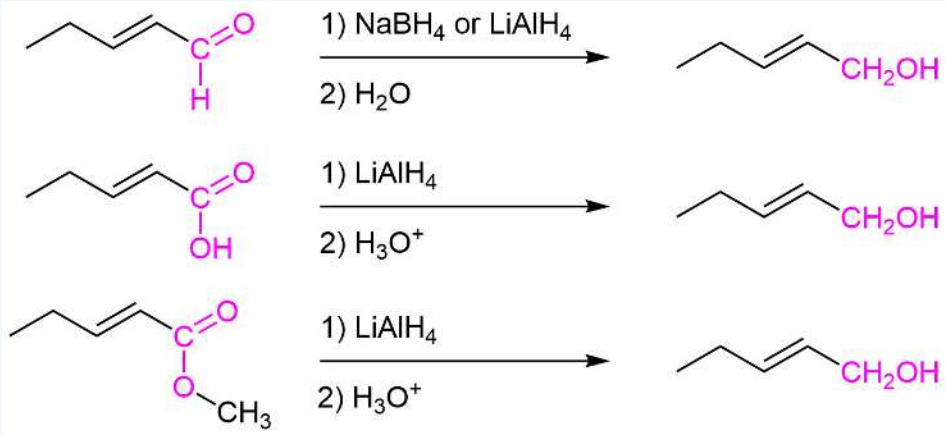
Answer

Analysis: The first step is to note if the target molecule is a 1° or 2° alcohol. Primary alcohols can be made by the hydride reduction of an aldehyde, carboxylic acid, or ester while secondary alcohols are made by the reduction of ketones. A 3° alcohol cannot be made by a hydride reduction. Also, it is important to remember than aldehydes and ketones can be reduced by both $NaBH^4$ and $LiAlH_4$ whereas carboxylic acids and ester can only be reduced by $LiAlH_4$.

a) Because the target molecule is a secondary alcohol the starting material must be a ketone.



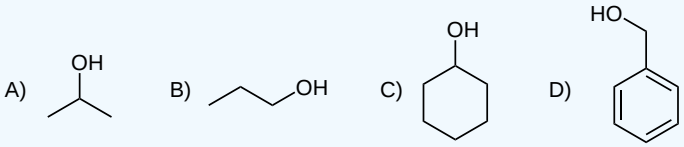
b) Because the target molecule is a primary alcohol the starting material could be an aldehyde, a carboxylic acid, or an ester.



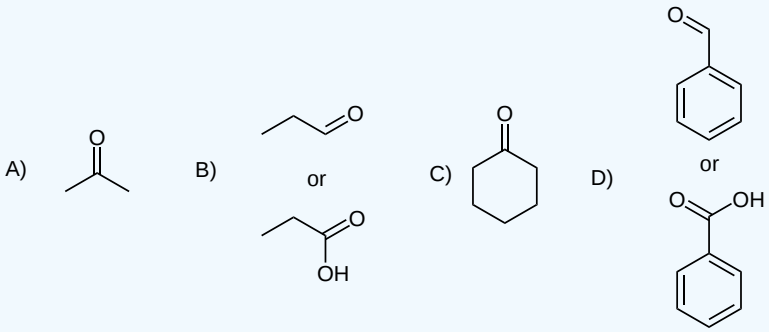
EXERCISES

EXERCISE 17.4.1

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

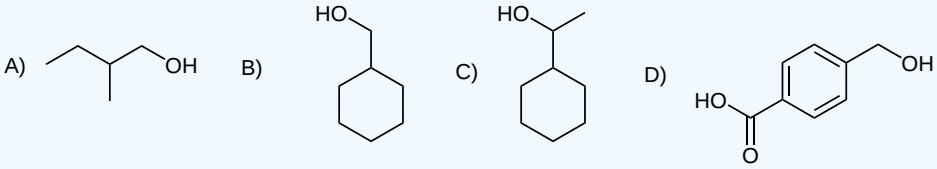


Answer



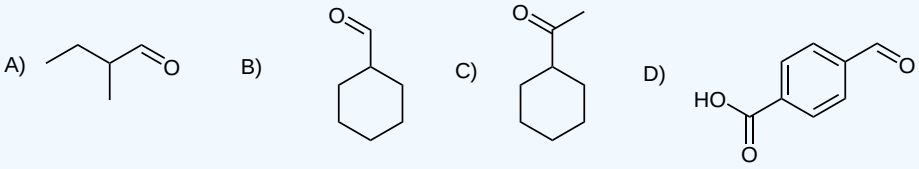
EXERCISE 17.4.2

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



Answer

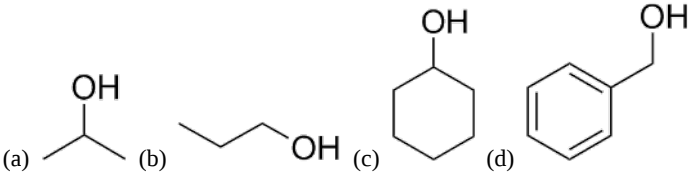
Note: $NaBH_4$ is only a strong enough reducing agent to reduce ketones and aldehydes.



QUESTIONS

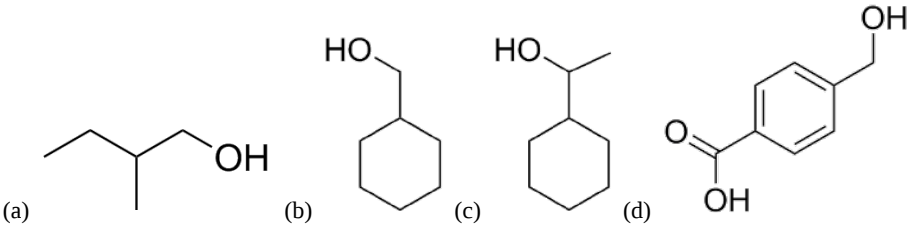
Q17.4.1

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



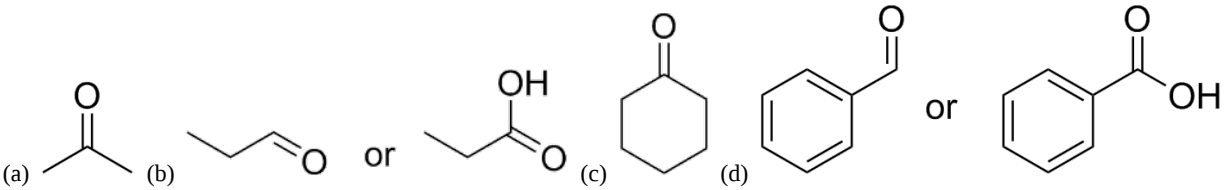
Q17.4.2

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



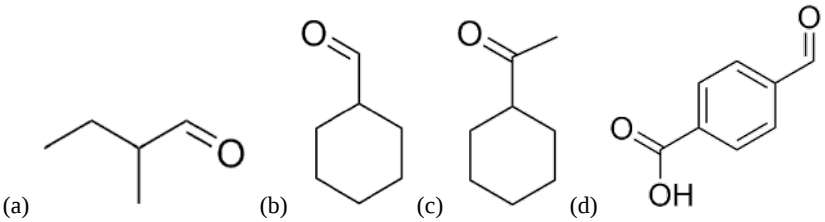
SOLUTIONS

S17.4.1



S17.4.2

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)

17.4 Alcohols from Carbonyl Compounds: Reduction is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

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17.5 ALCOHOLS FROM REACTION OF CARBONYL COMPOUNDS - GRIGNARD REAGENTS

Objectives

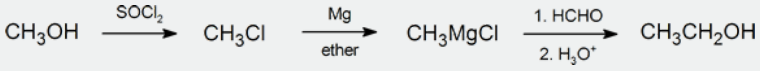
After completing this section, you should be able to

1. write an equation to illustrate the formation of a Grignard reagent.
2. write a general equation to represent the reaction of an aldehyde or ketone with a Grignard reagent.
3. write the detailed mechanism for the reaction of an aldehyde or ketone with a Grignard reagent.
4. identify the product formed from the reaction of a given aldehyde or ketone with a given Grignard reagent.
5. identify the carbonyl compound, the Grignard reagent, or both, needed to prepare a given alcohol.
6. write the equation to describe the reaction of an ester with a Grignard reagent.
7. identify the product formed from the reaction of a given ester with a given Grignard reagent.
8. discuss the limitations of Grignard reagent formation, and determine whether a given compound can be used to form such a reagent.

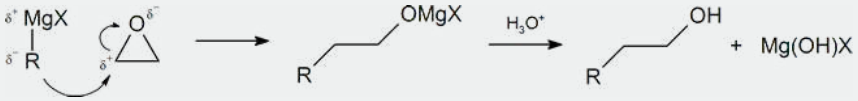
STUDY NOTES

Before you begin this section, you may wish to review Section 10.6 which discusses the formation of Grignard reagents.

Grignard reagents are among the most frequently used reagents in organic synthesis. They react with a wide variety of substrates; however, in this section, we are concerned only with those reactions that produce alcohols. Notice that in a reaction involving a Grignard reagent, not only does the functional group get changed, but the number of carbon atoms present also changes. This fact provides us with a useful method for ascending a homologous series. For example:



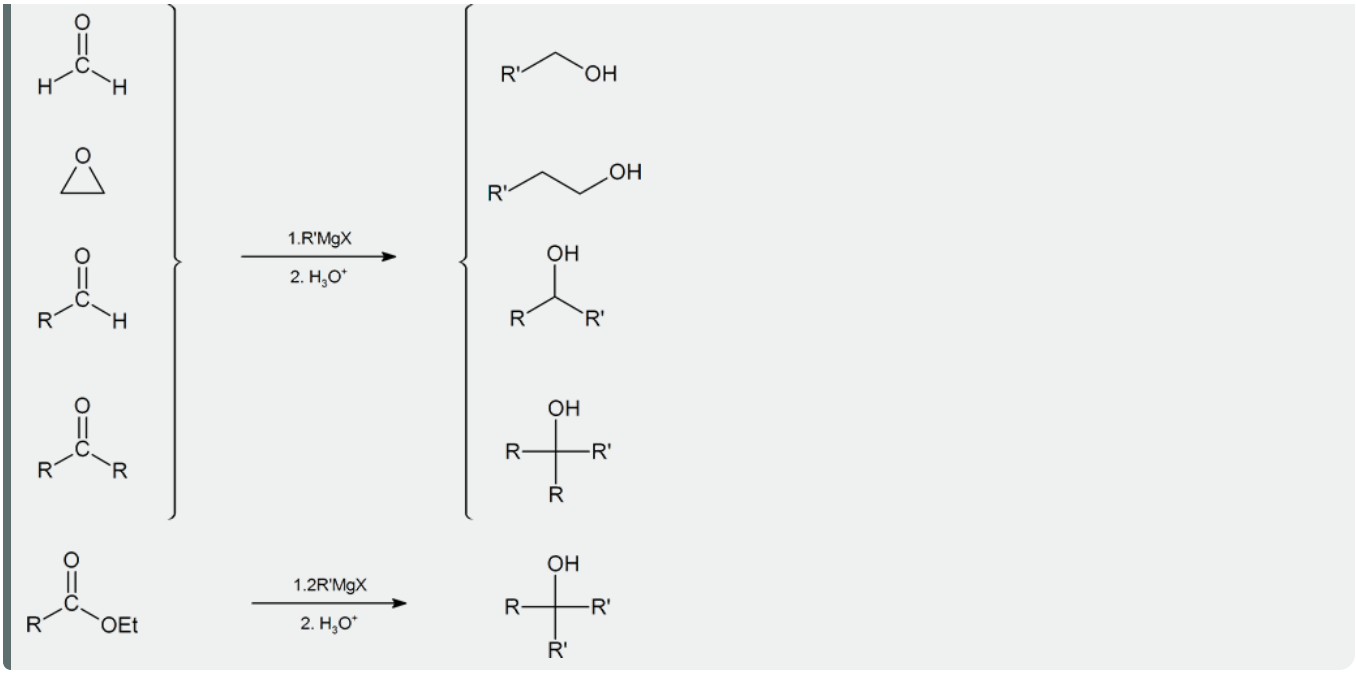
One important route for producing an alcohol from a Grignard reagent has been omitted from the discussion in the reading. It involves the reaction of the Grignard reagent with ethylene oxide to produce a primary alcohol containing two more carbon atoms than the original Grignard reagent.



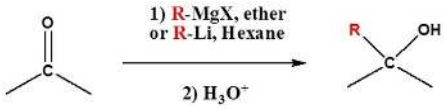
As mentioned in the reading, both organolithium and Grignard reagents are good nucleophiles. They also act as strong bases in the presence of acidic protons such as $-CO_2H$, $-OH$, $-SH$, $-NH$ and terminal alkyne groups. Not only do acidic protons interfere with the nucleophilic attack on the carbonyl of these organometallic reagents, if the starting materials possess any acidic protons, reagents cannot be generated in the first place. They are also the reason these reactions must be carried out in a water-free environment.

Another limitation of preparing Grignard and organolithium reagents is that they cannot already contain a carbonyl group (or other electrophilic multiple bonds like C═N C≡N, N═O S═O) because it would simply react with itself.

A summary of the methods used to prepare alcohols from Grignard reagents is provided below.

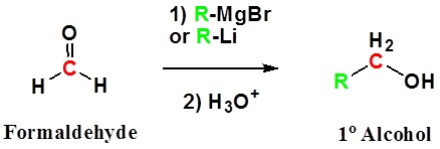


Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. The basic reaction involves the nucleophilic attack of the carbanionic carbon in the organometallic reagent with the electrophilic carbon in the carbonyl to form alcohols.

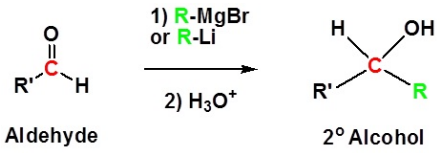


Both Grignard and Organolithium Reagents will perform these reactions

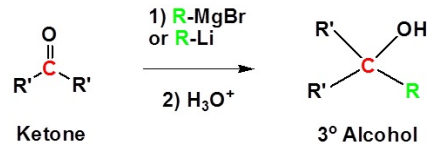
Addition to formaldehyde gives 1o alcohols



Addition to aldehydes gives 2° alcohols

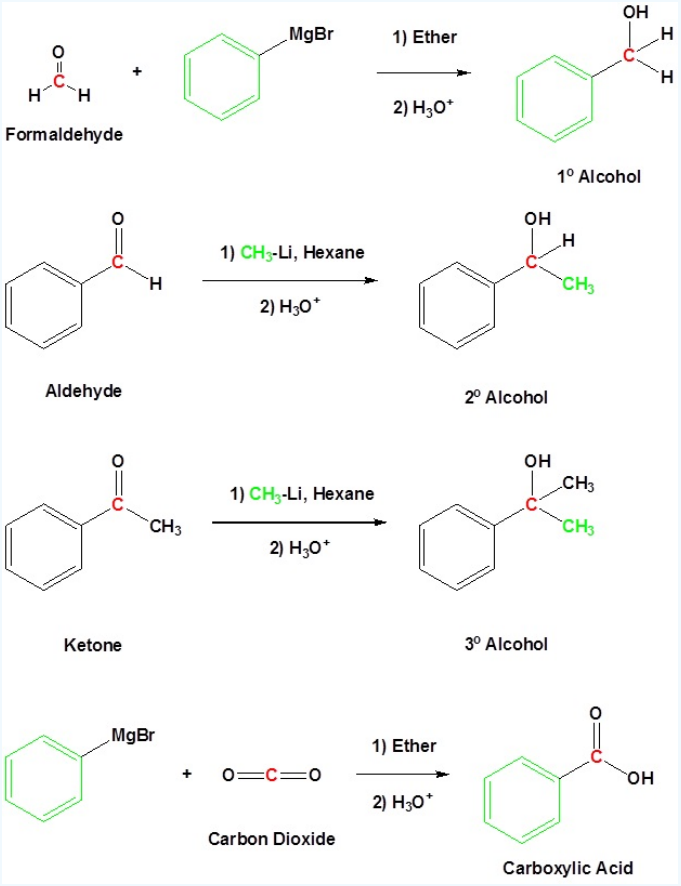


Addition to ketones gives 3o alcohols



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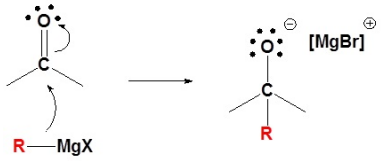
EXAMPLE 17.5.1



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 attack



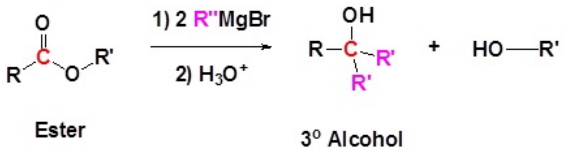
2) Protonation



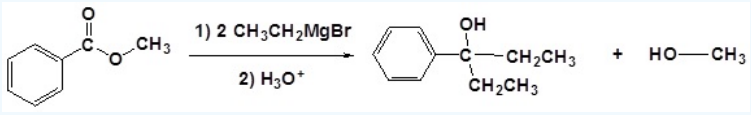
GRIGNARD REAGENTS CONVERT ESTERS TO 3° ALCOHOLS

In effect, the Grignard reagent adds twice.

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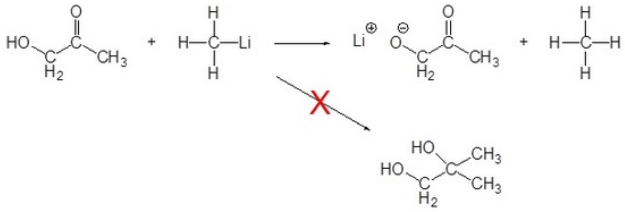


EXAMPLE 17.5.2



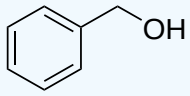
LIMITATION OF ORGANOMETALLIC REAGENTS

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.



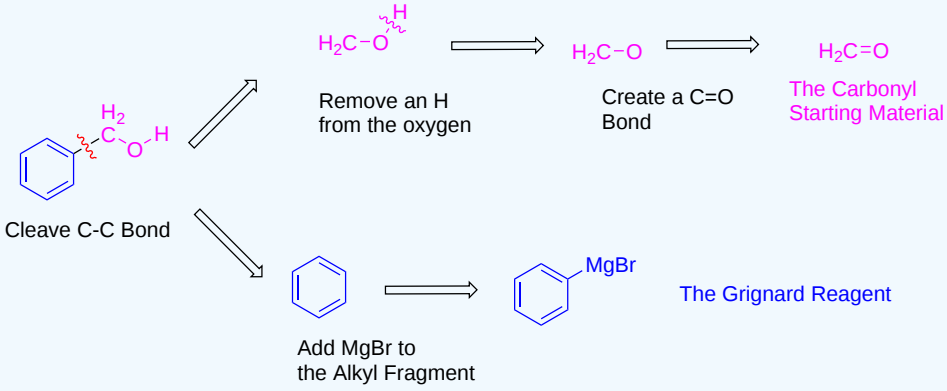
WORKED EXAMPLE 17.5.1

What reagents are required to make the following molecule using a Grignard Reaction?



Answer

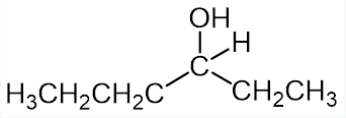
Analysis: Because the target molecule is a 1o alcohol there is only one C-C bond which can be cleaved to generate possible starting materials. The only possible reagents which would provide the target molecule would be formaldehyde and phenylmagnesium bromide.



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WORKED EXAMPLE 17.5.2

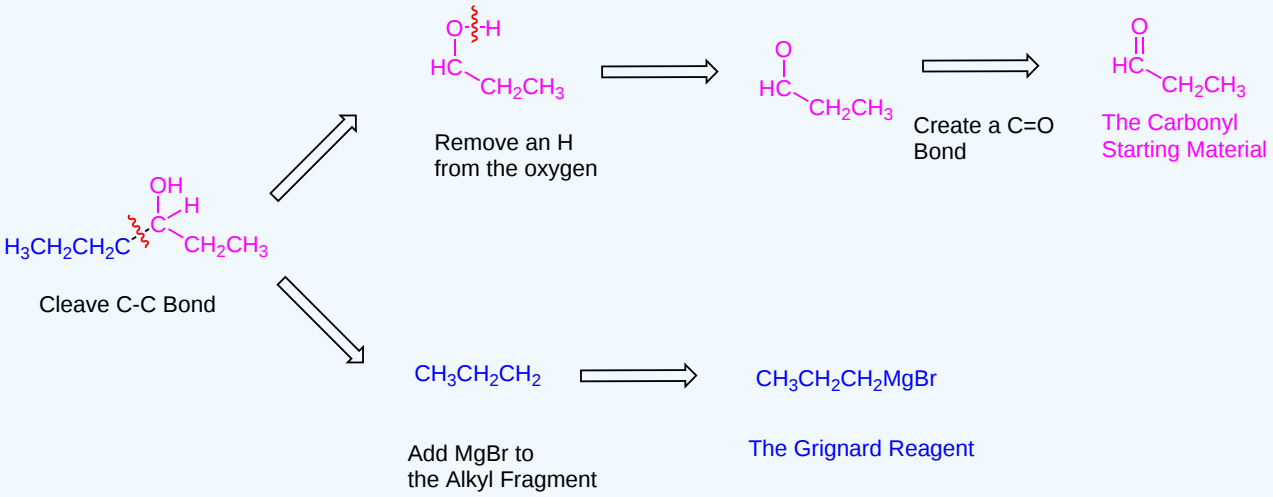
What reagents are required to make the following molecule using a Grignard Reaction?



Answer

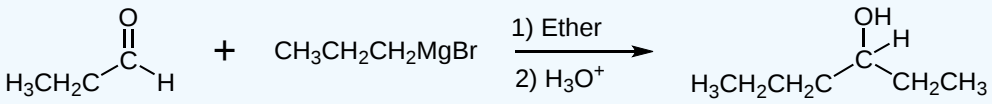
Analysis: Because the target molecule is an asymmetrical 2° alcohol there are two different C-C bond cleavage points. Each of these will provide a unique set of reagents which should be considered in terms of their reactivity and availability.

Pathway 1)

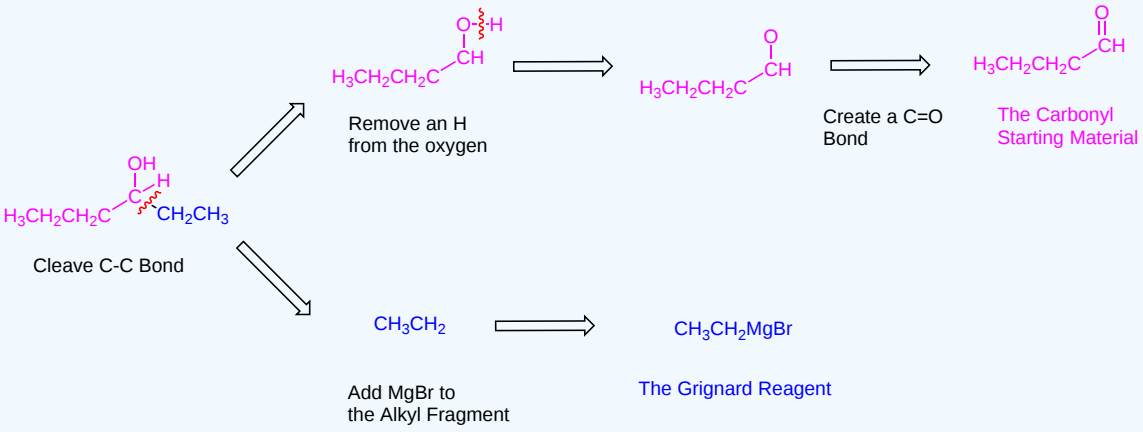


Pathway 1 synthesis)

Pathway 1 shows that propanal and propylmagnesium bromide can be reacted to create the target molecule.



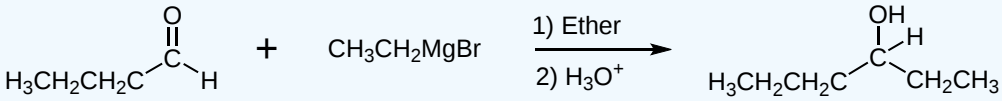
Pathway 2)



Pathway 2 synthesis)

Pathway 2 shows that butanal and ethylmagnesium bromide can be reacted to create the target molecule.

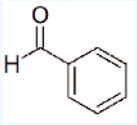
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EXERCISES

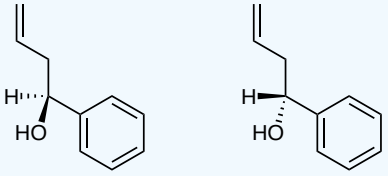
EXERCISE 17.5.1

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.



Answer

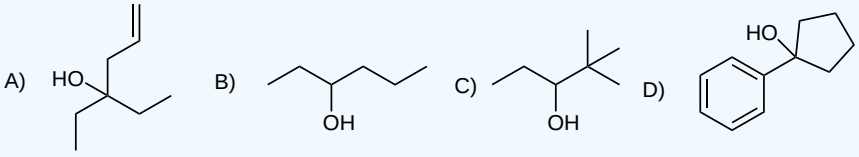
The result would be a racemic mixture of the following.



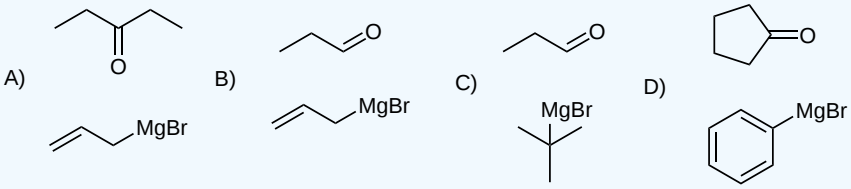
(*S*)-enantiomer (*R*)-enantiomer

EXERCISE 17.5.2

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

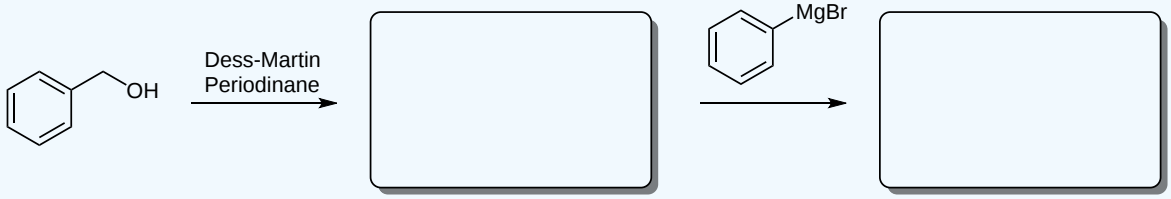


Answer

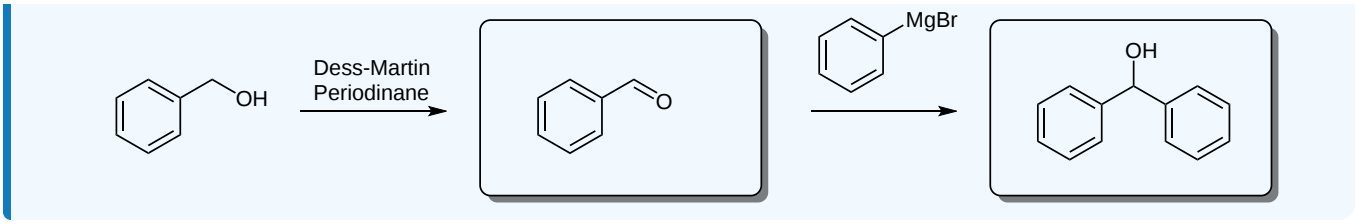


EXERCISE 17.5.3

Fill in the blanks of the following reaction scheme.



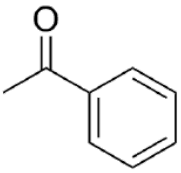
Answer



QUESTIONS

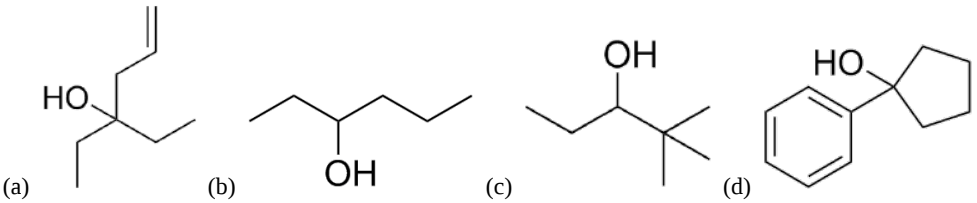
Q17.5.1

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.



Q17.5.2

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



Q17.5.3

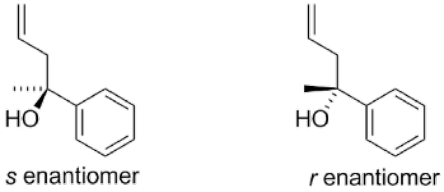
Fill in the blanks of the following reaction scheme.



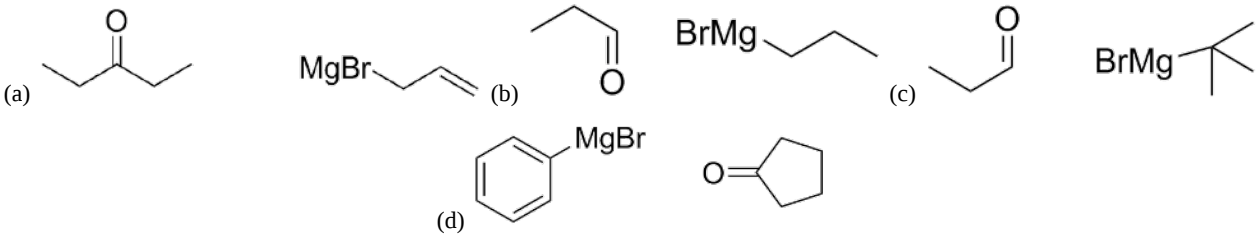
SOLUTIONS

S17.5.1

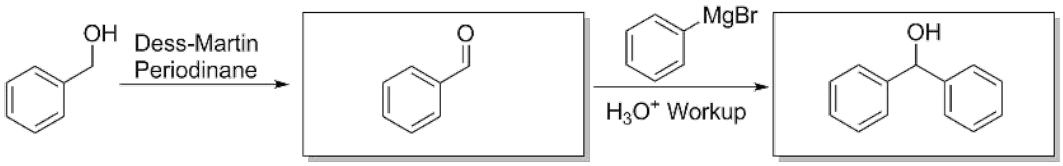
The result would be a racemic mixture of the following.



S17.5.2



S17.5.3



CONTRIBUTORS AND ATTRIBUTIONS

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

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17.6 REACTIONS OF ALCOHOLS

Objectives

After completing this section, you should be able to:

1. discuss the reactions of alcohols that have been introduced in previous units. These reactions include:
    a. conversion of alcohols into alkyl halides.
    b. conversion of alcohols into tosylates.
    c. dehydration of alcohols to yield alkenes.
    d. conversion of alcohols into esters.

STUDY NOTES

As you read through Section 17.6 you should be prepared to turn back to those earlier sections in which some of the reactions of alcohols were discussed:

- dehydration to alkenes—Section 8.1.
- conversion to alkyl halides—Section 10.5.

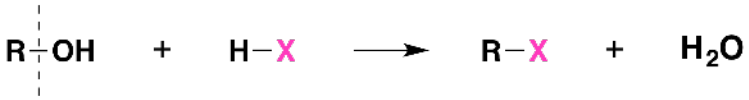
You may also wish to review the discussion of acidity constants, which can be found in Section 2.8.

Remember that when an alcohol reacts with tosyl chloride to form a tosylate, it is the O—H bond of the alcohol that is broken, not the C—O bond. This means that the absolute configuration of the carbon atom attached to the hydroxyl group remains unchanged throughout the reaction. The reading illustrates how this fact can be exploited to control the stereochemistry in an organic synthesis.

Finally, the reading shows the production of an ester from an alcohol and and an acid chloride. In Section 21.3 we will discuss the Fischer esterification, a famous reaction that uses an alcohol and a carboxylic acid to form the ester.

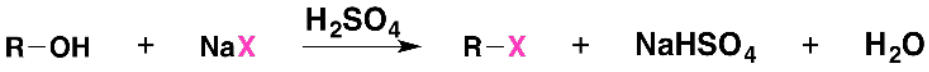
CONVERSION OF ALCOHOLS INTO ALKYL HALIDES

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).

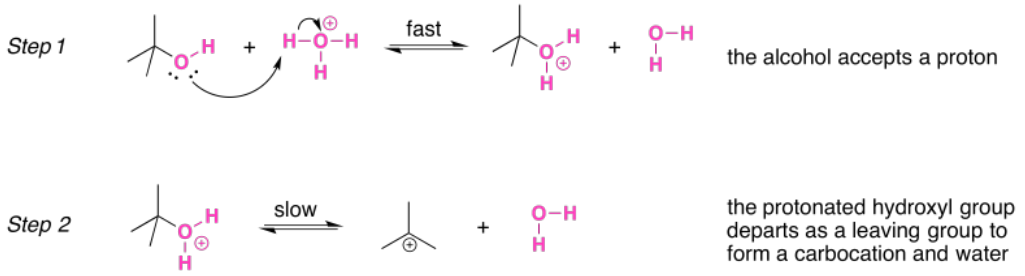
The reaction is acid catalyzed. Alcohols react with the strongly acidic hydrogen halides HCl, HBr, and HI, but they do not react with nonacidic NaCl, NaBr, or NaI. Primary and secondary alcohols can be converted to alkyl chlorides and bromides by allowing them to react with a mixture of a sodium halide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



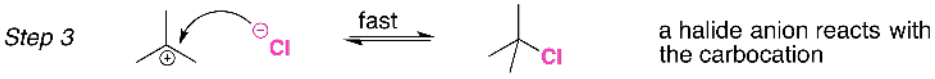
MECHANISMS OF THE REACTIONS OF ALCOHOLS WITH HX

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 (\)H_2O_), which makes the dissociation step of the S_N1 mechanism more favorable.



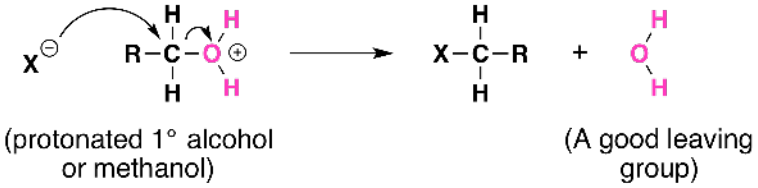
In step 3, the carbocation reacts with a nucleophile (a halide ion) to complete the substitution.



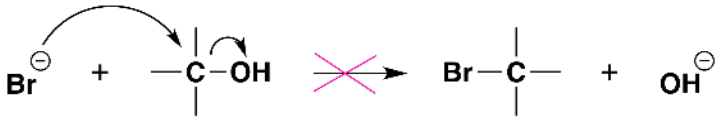
When we convert an alcohol to an alkyl halide, we carry out the reaction in the presence of acid and in the presence of halide ions, and not at elevated temperature. Halide ions are good nucleophiles (they are much stronger nucleophiles than water), and since halide ions are present in high concentration, 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:



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:

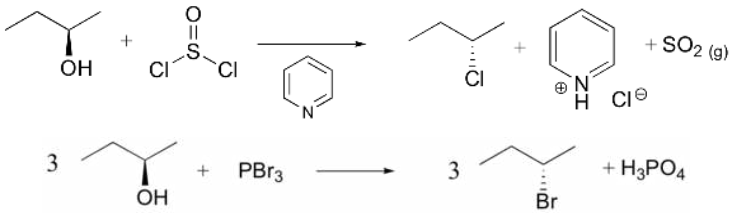


We can see now why the reactions of alcohols with hydrogen halides are acid-promoted.

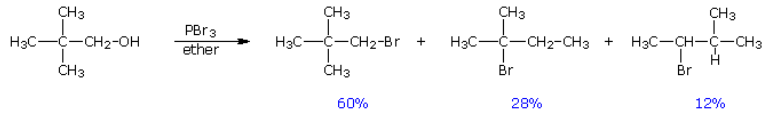
Carbocation rearrangements are extremely common in organic chemistry reactions are are defined as the movement of a carbocation from an unstable state to a more stable state through the use of various structural reorganizational "shifts" within the molecule. Once the carbocation has shifted over to a 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 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.

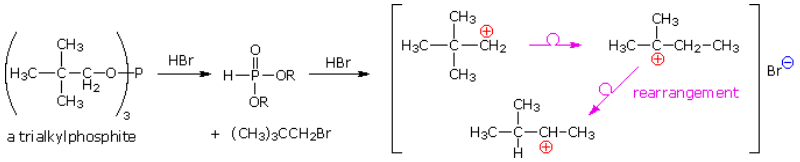
Synthetic organic chemists, when they want to convert an alcohol into a better leaving group, have several methods to choose from. One common strategy is to convert the alcohol into an alkyl chloride or bromide, using thionyl chloride or phosphorus tribromide:



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.

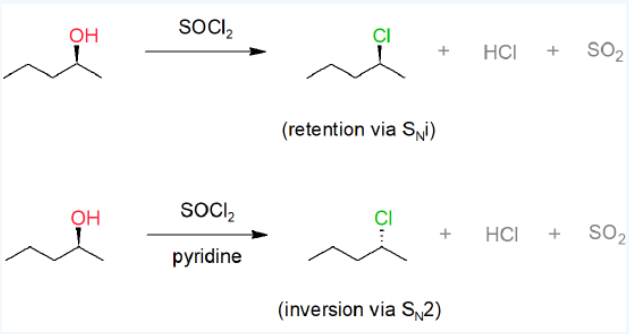


Below, an abbreviated mechanism for the reaction is displayed. The initially formed trialkylphosphite ester may be isolated if the HBr byproduct is scavenged by base. In the presence of HBr a series of acid-base and S_N2 reactions take place, along with the transient formation of carbocation intermediates. 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 **S_Ni** reaction (nucleophilic substitution internal). The carbocation partner in the ion pair may also rearrange. 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 17.6.1: CONVERSION OF ALCOHOLS TO ALKYL CHLORIDES

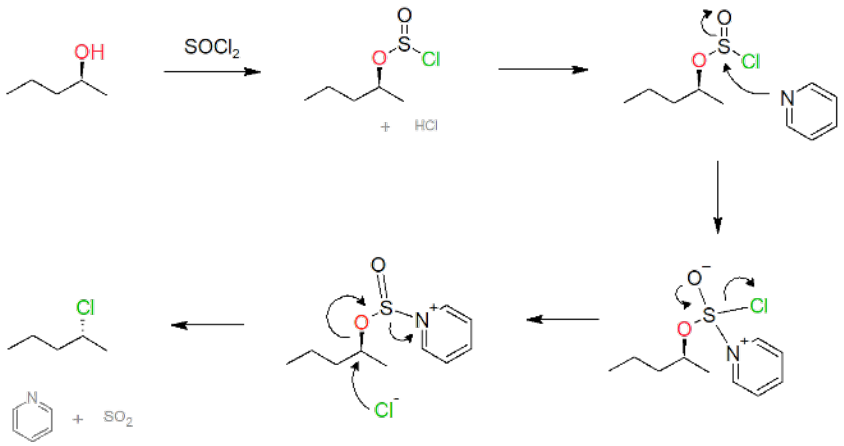


There's one important thing to note here: see the difference in stereochemistry? It's been inverted in the presence of pyridine.

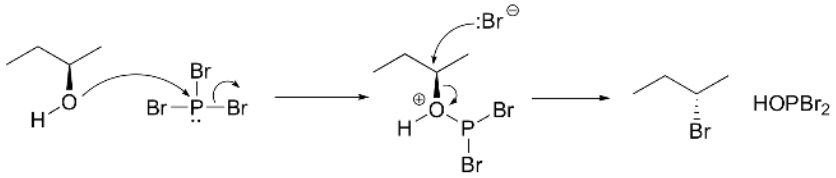
MECHANISMS

The S_Ni mechanism that leads to retention of stereochemistry is a rare process and beyond this chemistry course. You are not responsible for those details.

The reaction in pyridine proceeds through a backside attack (S_N2), there is inversion of configuration at the carbon



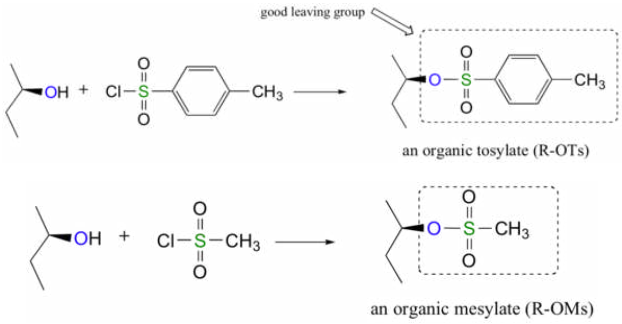
The PBr_3 reaction is thought to involve two successive S_N2-like steps:



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

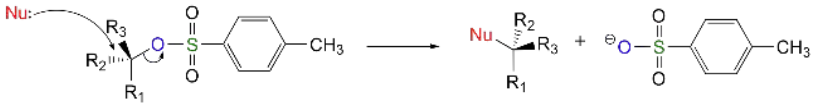
CONVERSION OF ALCOHOLS INTO TOSYLATES

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

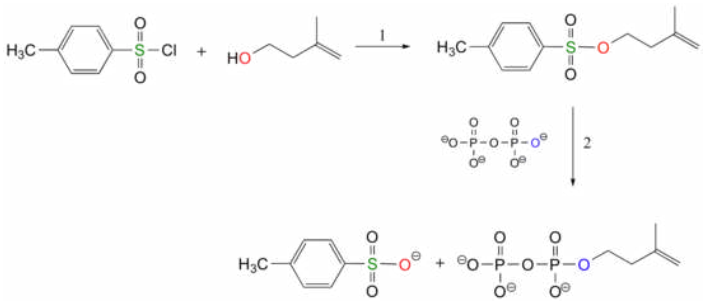


Notice, though, that unlike the halogenation reactions above, conversion of an alcohol to a tosylate or mesylate proceeds with retention of configuration at the electrophilic carbon.

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

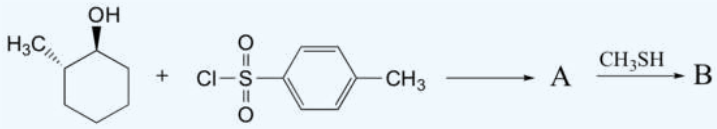


The laboratory synthesis of isopentenyl diphosphate - the 'building block' molecule used by nature for the construction of isoprenoid molecules such as cholesterol and b-carotene - was accomplished by first converting the alcohol into an organic tosylate (step 1), then displacing the tosylate group with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

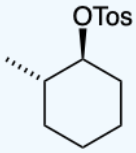


EXAMPLE 17.6.2

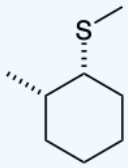
Predict the structures of A and B in the following reaction:



A. The tosylate is formed with retained stereochemistry.

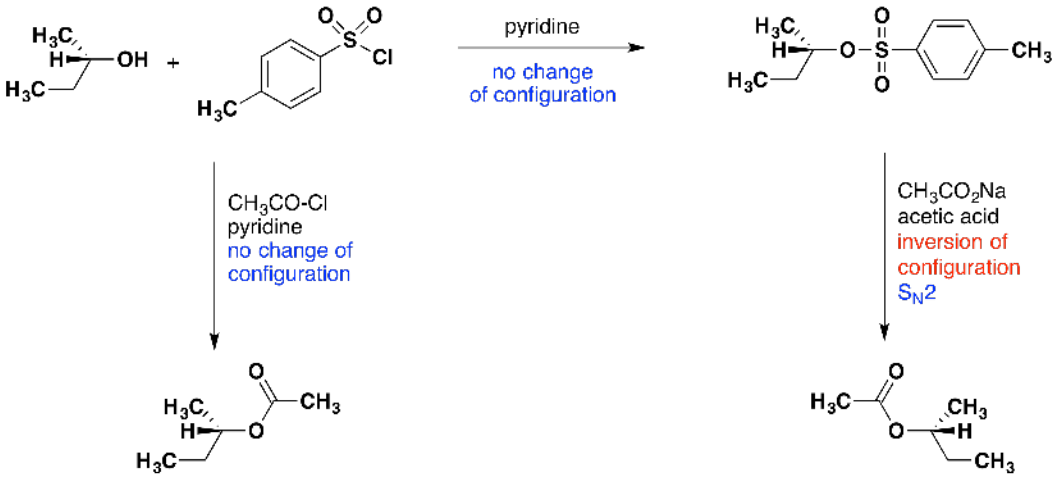


B. The thioether is formed with inverted stereochemistry.



The importance of sulfonate esters as intermediates in many substitution reactions cannot be overstated. A rigorous proof of the configurational inversion that occurs at the substitution site in S_N2 reactions makes use of such reactions. An example of such a proof is displayed below.

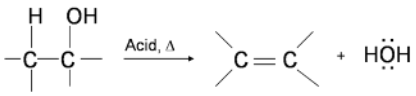
INVERSION PROOF



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DEHYDRATION OF ALCOHOLS TO YIELD ALKENES

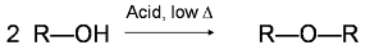
One way to synthesize alkenes is by dehydration of alcohols, a process in which alcohols undergo E1 or E2 mechanisms to lose water and form a double bond. The dehydration reaction of alcohols to generate alkene proceeds by heating the alcohols in the presence of a strong acid, such as sulfuric or phosphoric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



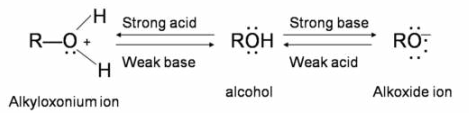
The required range of reaction temperature decreases with increasing substitution of the hydroxy-containing carbon:

- 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 both as 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 $^{+}OH_2$ (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.



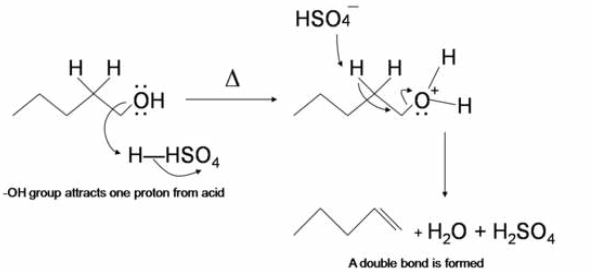
MECHANISM FOR THE DEHYDRATION OF ALCOHOL INTO ALKENE

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 nucleophile) then attacks 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 reaction is ranked as the following

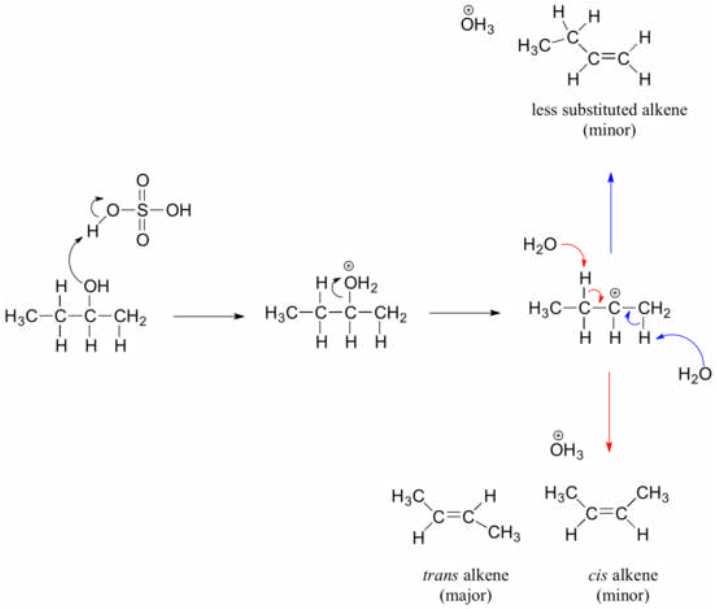
Methanol < primary < secondary < tertiary

Primary alcohol dehydrates through the E2 mechanism. Oxygen donates two electrons to a proton from sulfuric acid H_2SO_4, forming an alkyloxonium ion. Then the nucleophile HSO_4^- back-side attacks one adjacent hydrogen and the alkyloxonium ion leaves in a concerted process, making a double bond.



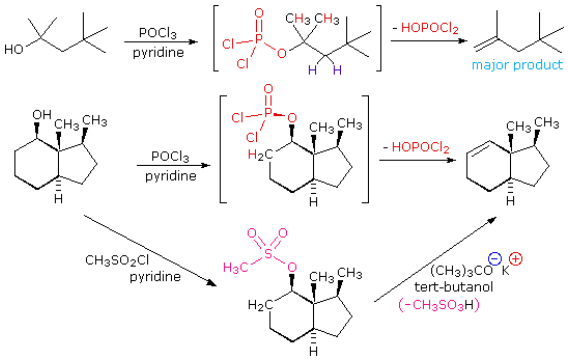
Secondary and tertiary alcohols dehydrate through the E1 mechanism. Similarly to the reaction above, secondary and tertiary –OH protonate to form alkyloxonium ions. However, in this case the ion leaves first and forms a carbocation as the reaction intermediate. The water molecule (which is a stronger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

DEHYDRATION REACTION OF SECONDARY ALCOHOL



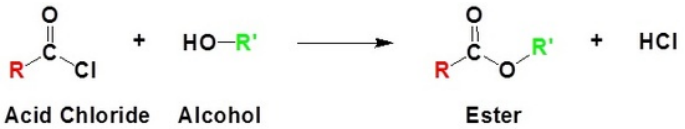
The dehydration mechanism for a tertiary alcohol is analogous to that shown above for a secondary alcohol.

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 $POCl_3$ method, which works well in this case because S_N2 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.

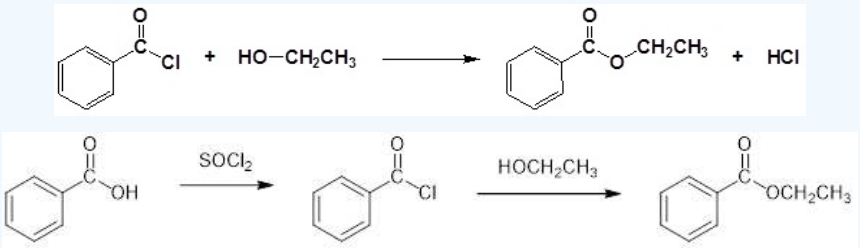


CONVERSION OF ALCOHOLS INTO ESTERS

Acid chlorides react with alcohols to form esters



EXAMPLE 17.6.3



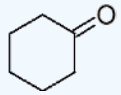
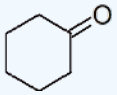
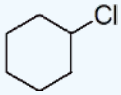
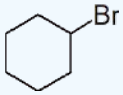
EXERCISES

EXERCISE 17.6.1

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

(A) CrO_3, H_2SO_4, H_2O (B) Dess-Martin Periodinane (C) $SOCl_2$ (D) PBr_3

Answer

A)  B)  C)  D) 

EXERCISE 17.6.2

Starting with cyclohexanol, describe how you would prepare the following?

(A) cyclohexyl acetate (B) 1-allylcyclohexan-1-ol (C) cyclohexene (D) ethoxycyclohexane

Answer

A) This can be seen as a transesterification, acid and some other ester would be needed to form cyclohexylacetate

B) First, oxidize the alcohol to a ketone, take for example Dess-Martin Periodinane, then use an allyl grignard to form 1-allylcyclohexan-1-ol

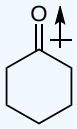
C) Alcohols can dehydrate to form alkenes under acidic conditions, so using anhydrous acid and heat would yield cyclohexene

D) The alcohol can also be a nucleophile, perform a halogen substitution, using 1-X ethane, to yield ethoxycyclohexane

EXERCISE 17.6.3

In cyclohexanone, a ketone, indicate the polarity of the bond between oxygen and carbon.

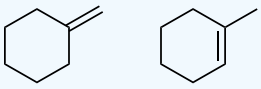
Answer



Oxygen is more electronegative than carbon creating the polar bond. This is the basis for the carbon's electrophilicity.

EXERCISE 17.6.4

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

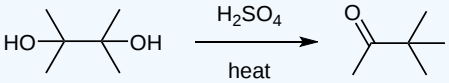


Answer

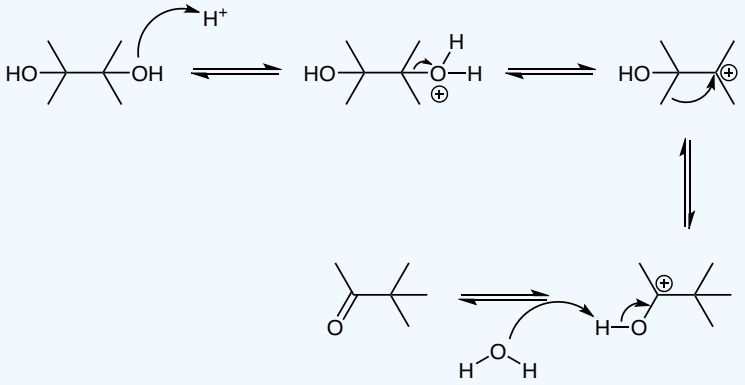
The more substituted alkene is favored, as more substituted alkenes are relatively lower in energy.

EXERCISE 17.6.5

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

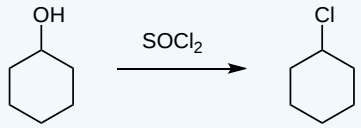


Answer

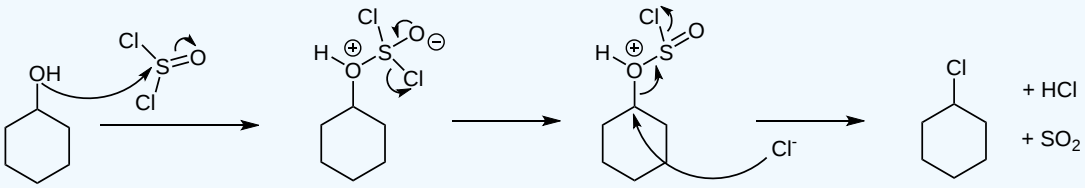


EXERCISE 17.6.6

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

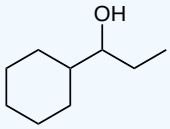


Answer



EXERCISE 17.6.7

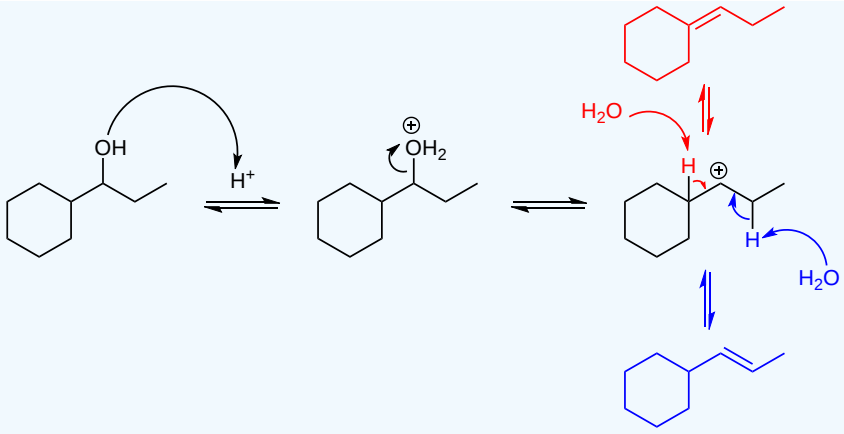
Draw an arrow pushing mechanism for the acid catalyzed dehydration of the following alcohol, make sure to draw both potential mechanisms. Assume no rearrangement for the first two product mechanisms. Which of these two would likely be the major product? If there was a rearrangement, draw the expected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



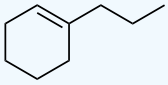
Answer

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

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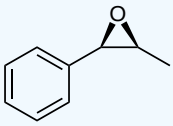


Note the secondary carbocation adjacent a tertiary carbon center, if there were a hydride transfer (rearrangement) to form a tertiary carbocation the following would be the major product. The minor product being the same product as the one formed from the red arrows.



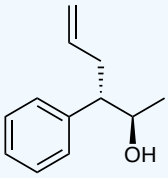
EXERCISE 17.6.8

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 S_N2 electrophiles.



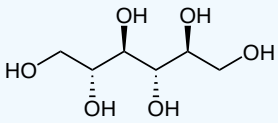
Answer

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EXERCISE 17.6.9

As seen in the previous example, there are many examples of chiral compounds containing alcohols. One common example of these are sugars, is the given the following sugar, allitol, also chiral?



Answer

This compound actually has a plane of symmetry, the plane parallel to the carbon chain/backbone. So, it is not chiral, also called a meso compound.

QUESTIONS

Q17.6.1

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

(a) CrO_3, H_2SO_4, H_2O (b) Dess-Martin Periodinane (c) $SOCl_2$ (d) NaH and 1-bromoethane (e) PBr_3

Q17.6.2

Starting with cyclohexanol, describe how you would prepare the following?

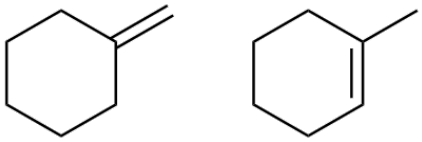
(a) cyclohexyl acetate (b) 1-allylcyclohexan-1-ol (c) cyclohexene (d) ethoxycyclohexane

Q17.6.3

In cyclohexanone, a ketone, indicate the polarity of the bond between oxygen and carbon.

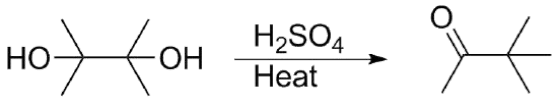
Q17.6.4

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



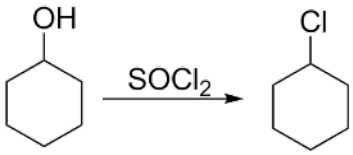
Q17.6.5

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



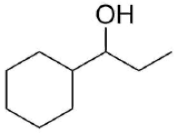
Q17.6.6

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



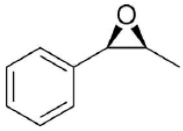
Q17.6.7

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.



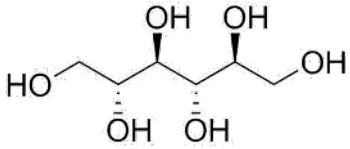
Q17.6.8

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.



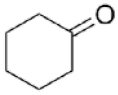
Q17.6.9

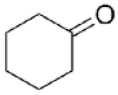
As seen in the previous example, there are many examples of chiral compounds containing alcohols. One common example of these are sugars, is the given the following sugar, allitol, also chiral?

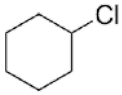


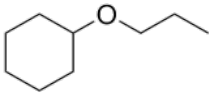
SOLUTIONS

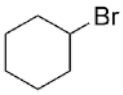
S17.6.1

(a) 

(b) 

(c) 

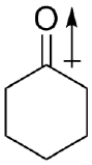
(d) 

(e) 

S17.6.2

a. This can be seen as a transesterification, acid and some other ester would be needed to form cyclohexylacetate
b. First, oxidize the alcohol to a ketone, take for example Dess-Martin Periodinane, then use an allyl grignard to form 1-allylcyclohexan-1-ol
c. Alcohols can dehydrate to form alkenes under acidic conditions, so using anhydrous acid and heat would yield cyclohexene
d. The alcohol can also be a nucleophile, perform a halogen substitution, using 1-X ethane, to yield ethoxycyclohexane

S17.6.3



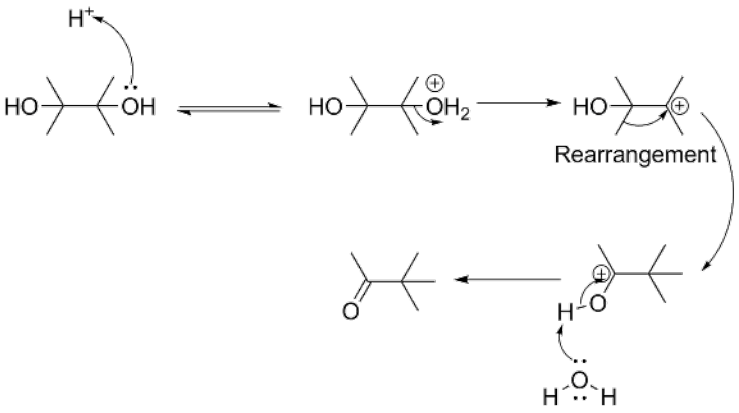
Oxygen is more electronegative than carbon creating the polar bond. This is the basis for the carbon's electrophilicity.

S17.6.4

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

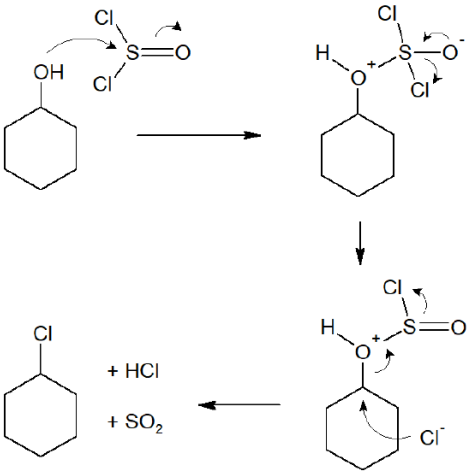
S17.6.5

This is also known as the Pinacol rearrangement.

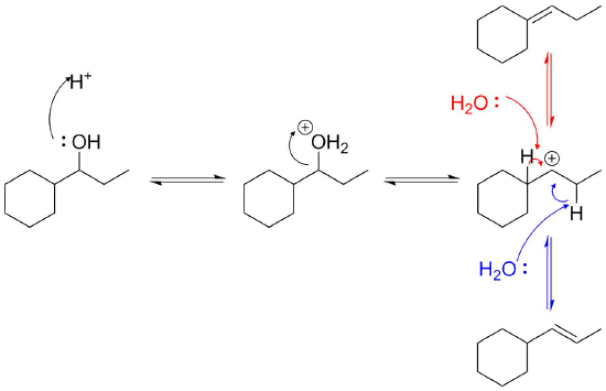


Note how the carbocation after the rearrangement is resonance stabilized by the oxygen

S17.6.6

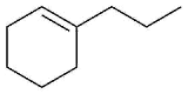


S17.6.7

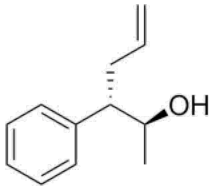


The major product of this mechanism would be the more highly substituted alkene, or the product formed from the red arrows.

Note the secondary carbocation adjacent a tertiary carbon center, if there were a hydride transfer (rearrangement) to form a tertiary carbocation the following would be the major product. The minor product being the same product as the one formed from the red arrows.



S17.6.8



S17.6.9

This compound actually has a plane of symmetry, the plane parallel to the carbon chain/backbone. So, it is not chiral, also called a meso compound.

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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17.7 OXIDATION OF ALCOHOLS

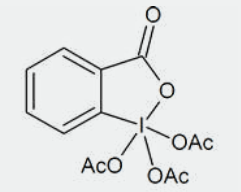
Objectives

After completing this section, you should be able to:

1. write an equation to represent the oxidation of an alcohol.
2. identify the reagents that may be used to oxidize a given alcohol.
3. identify the specific reagent that is used to oxidize primary alcohols to aldehydes rather than to carboxylic acids.
4. identify the product formed from the oxidation of a given alcohol with a specified oxidizing agent.
5. identify the alcohol needed to prepare a given aldehyde, ketone or carboxylic acid by simple oxidation.
6. write a mechanism for the oxidation of an alcohol using a chromium(VI) reagent.

STUDY NOTES

The reading mentions that 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.



Dess–Martin periodinane (DMP)

This page looks at the oxidation of alcohols using acidified sodium or potassium dichromate(VI) solution. This reaction is used to make aldehydes, ketones and carboxylic acids, and as a way of distinguishing between primary, secondary and tertiary alcohols.

OXIDIZING THE DIFFERENT TYPES OF ALCOHOLS

The oxidizing agent used in these reactions is normally 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:

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

OXIDIZING AGENTS

- $K_2C_r2O_7$ potassium dichromate
- CrO_3 Chromium Trioxide

Both of these are used along with H_2SO_4, H_2O

- 1° alcohol → Carboxylic acid
- 2° alcohol → Ketone
- 3° alcohol → No reaction

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:

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

The more usual simplified version looks like this:

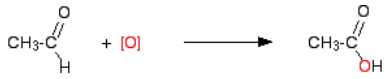
$$CH_3CH_2OH + 2[O] \rightarrow CH_3COOH + H_2O \quad (17.7.2)$$

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

$$CH_3CH_2OH + [O] \rightarrow CH_3CHO + H_2O \quad (17.7.3)$$

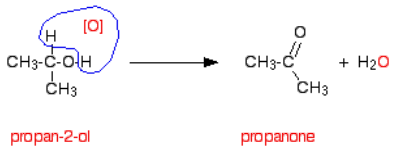
$$CH_3CHO + [O] \rightarrow CH_3COOH \quad (17.7.4)$$

This is what is happening in the second stage:



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:

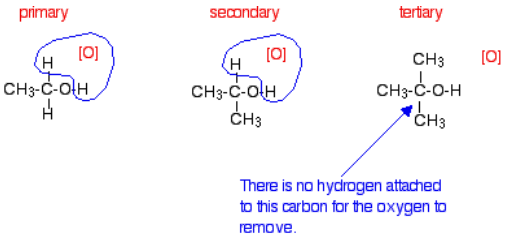


If you look back at the second stage of the primary alcohol reaction, you will see that an oxygen "slotted in" between the carbon and the hydrogen in the aldehyde group to produce the carboxylic acid. In this case, there is no such hydrogen - and the reaction has nowhere further to go.

TERTIARY ALCOHOLS

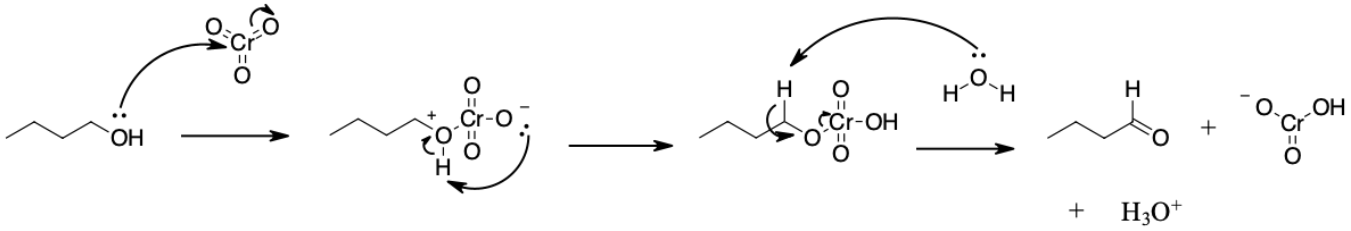
Tertiary alcohols are not oxidized by acidified sodium or potassium dichromate(VI) solution - there is no reaction whatsoever. If you look at what is happening with primary and secondary alcohols, you will see that the oxidizing agent is removing the hydrogen from the -OH group, and a hydrogen from the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



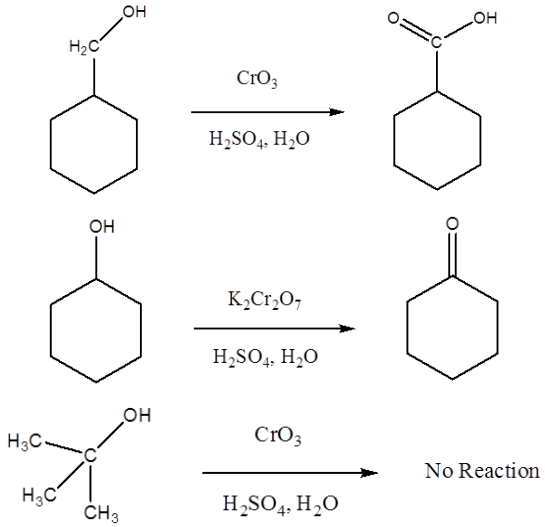
MECHANISM

During this reaction mechanism the chromium atom is being reduced from Cr(VI) in the CrO_3 starting material to Cr(IV) in the H_2CrO_3 product. Also, notice the the C=O bond is formed in the third step of the mechanism through an E2 reaction. Although E2 reaction are generally know for forming C=C double bonds thought the elimination of a halide leaving group, in this case they are use to generate a C=O through the elimination of a reduced metal as a leaving group.



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EXAMPLES



FORMATION OF ALDEHYDES USING PCC

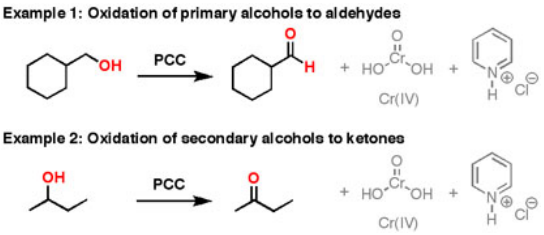
Pyridinium chlorochromate (PCC) is a milder version of chromic acid.



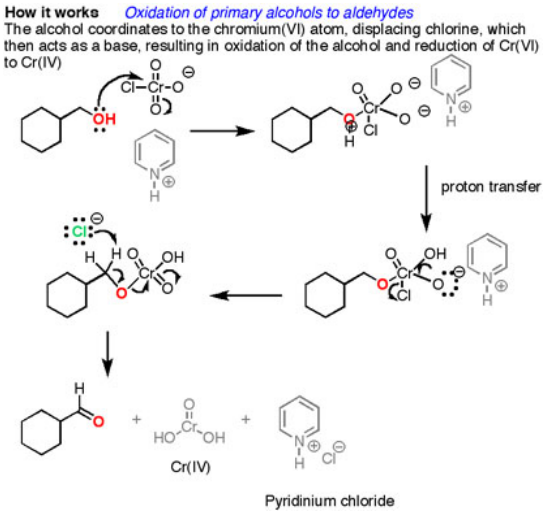
PCC (Pyridinium Chlorochromate)

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.



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.



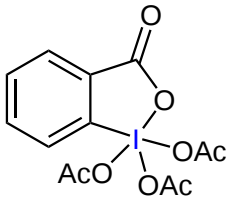
The first step is attack of oxygen on the chromium to form the Cr-O bond. Secondly, a proton on the (now positive) OH is transferred to one of the oxygens of the chromium, possibly through the intermediacy of the pyridinium salt. A chloride ion is then displaced, in a reaction reminiscent of a 1,2 elimination 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.

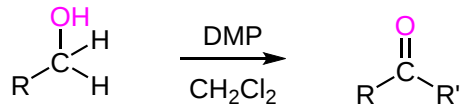
OXIDATION OF 1^{O} ALCOHOLS WITH DESS-MARTIN PERIODINANE (DMP) TO FORM ALDEHYDES

PCC is being replaced in laboratories by **Dess-Martin periodinane (DMP)** in dichloromethane solvent, which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous conditions (lower reaction temperature and a nonacidic medium). DMP is named after Daniel Dess and James Martin, who developed it in 1983.

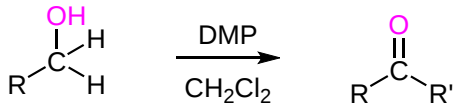


Dess-Martin periodinane (DMP)

GENERAL REACTIONS

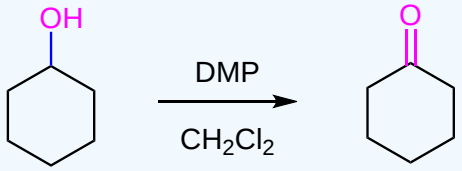


2° Alcohol **Ketone**

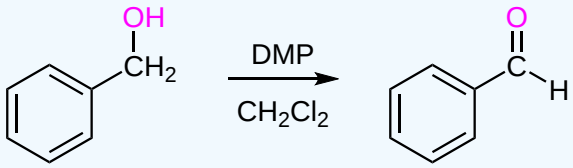


2° Alcohol **Ketone**

EXAMPLE 1



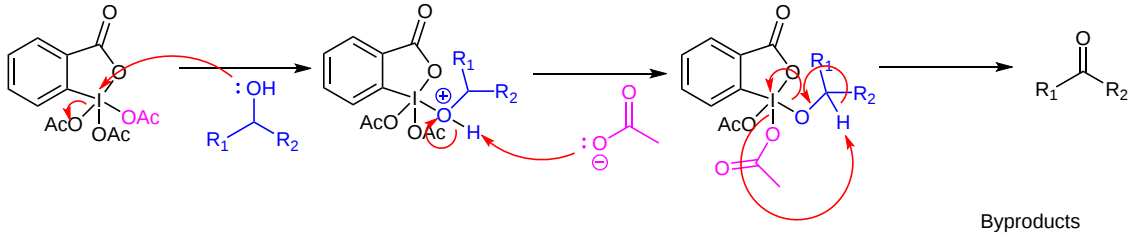
Oxidation of Cyclohexanol to Cyclohexanone



Oxidation of Benzyl Alcohol to Benzaldehyde

MECHANISM

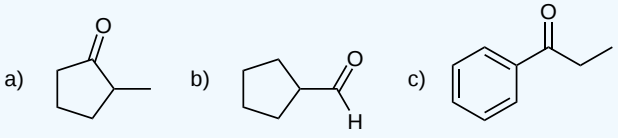
The first step of the mechanism involves the reactant alcohol attacking the Iodine (V) atom and eliminating an acetate (Ac^-) leaving group to form a periodinate intermediate. The next step is a concerted E2-like reaction where a hydrogen is removed from the alcohol, the C=O bond is formed, an acetate group is eliminated from the iodine atom, and the iodine (V) atom gains two electrons to be reduced to iodine (III).



EXERCISES

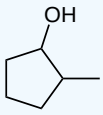
EXERCISE 17.7.1

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

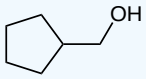


Answer

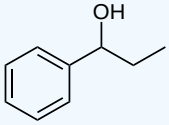
a) Any oxidant capable of oxidizing an alcohol to a ketone would work, such as the Jones reagent (CrO_3, H_2SO_4, H_2O), PCC, or Dess-Martin periodinane.



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



c) 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.



? EXERCISE 17.7.2

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

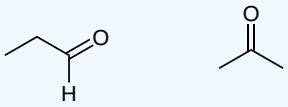
Answer



? EXERCISE 17.7.3

Show the products of the oxidation of 1-propanol and 2-propanol with Dess-Martin periodinane.

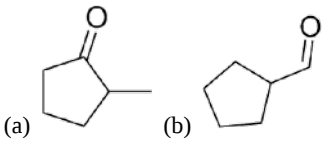
Answer



QUESTIONS

Q17.7.1

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

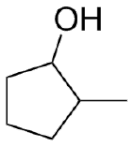


Q17.7.2

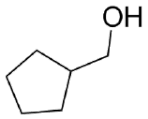
Show the products of the oxidation of 1-propanol and 2-propanol with chromic acid in aqueous solution.

SOLUTIONS

S17.7.1

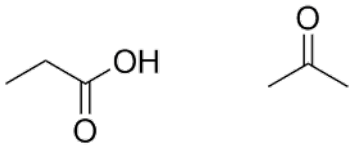
(a) 

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.

(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.

S17.7.2



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
- Jim Clark (Chemguide.co.uk)

James Ashenhurst (MasterOrganicChemistry.com)

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17.8 PROTECTION OF ALCOHOLS

Objectives

After completing this section, you should be able to:

1. explain what is meant by “protecting” a functional group during an organic synthesis.
2. describe one common method for protecting the hydroxy group of an alcohol, and give an example of its use (e.g., in the preparation of a Grignard reagent).

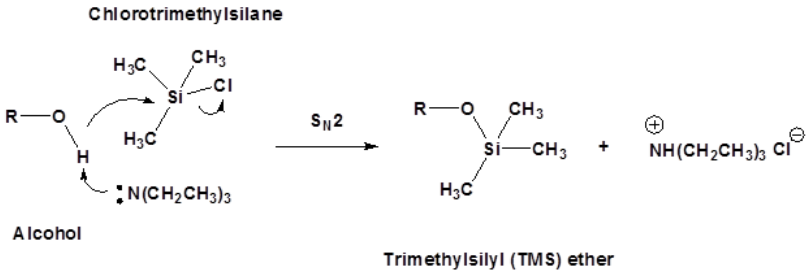
Often during the synthesis of complex molecules on functional group in a molecule interferes with an intended reaction on a second functional group on the same molecule. An excellent example is the fact that a Grignard reagent can't be prepared from halo alcohol because the C-Mg bond is not compatible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

When situations like this occurs chemists circumvent eh problem by protecting the interfering functional group. Functional group protection involves three steps:

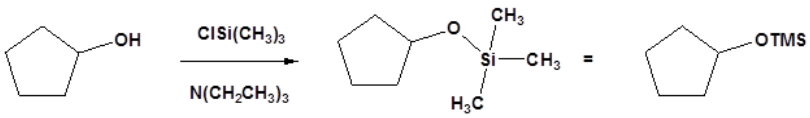
1. Blocking the interfering functionality by introducing a protecting group.
2. Performing the intended reaction.
3. Removing the protecting group and reforming the original functional group.

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.

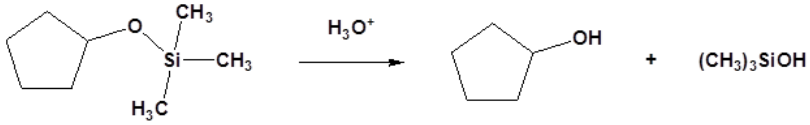
GENERAL REACTION



EXAMPLE

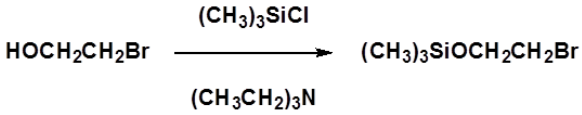


The silyl ether protecting group can be removed by reaction with an aqueous acid or the fluoride ion.

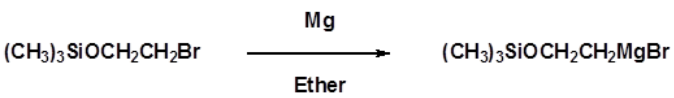


By utilizing a protecting group a Grignard reagent can be formed and reacted on a halo alcohol.

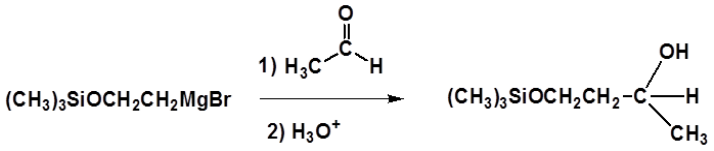
1) Protect the Alcohol



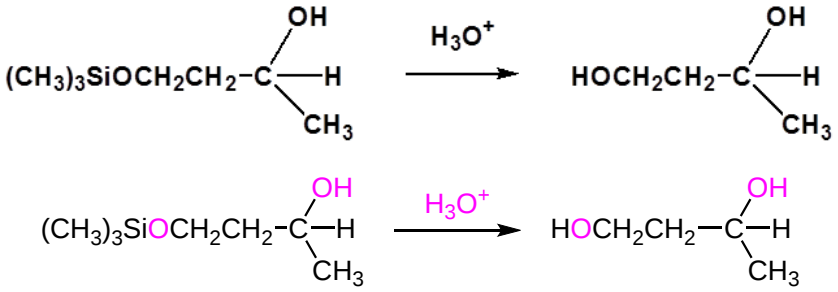
2) Form the Grignard Reagent



3) Perform the Grignard Reaction



4) Deprotection

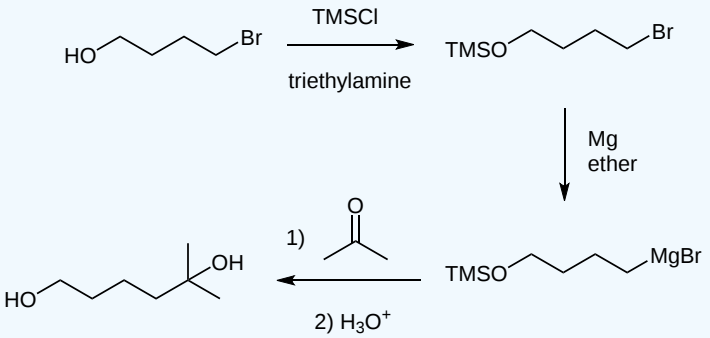


EXERCISE

? EXERCISE 17.8.1

Propose a multiple-step synthesis to transform 4-bromo-1-butanol into 2-methylhexane-2,6-diol.

Answer



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

Prof. Steven Farmer (Sonoma State University)

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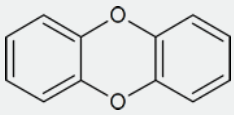
17.9 PHENOLS AND THEIR USES

Objectives

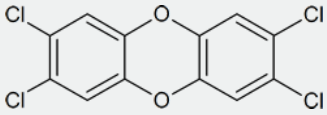
After completing this section, you should be able to describe two methods that can be used to obtain phenol on an industrial scale.

STUDY NOTES

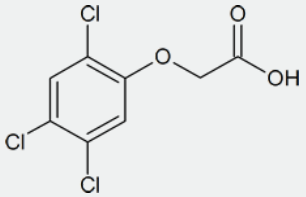
One substance that has become symbolic of the struggle between industrial development and environmental protection is dioxin. The name dioxin is used to refer to a family of compounds having a basic structure in which two benzene rings are joined by two oxygen atoms:

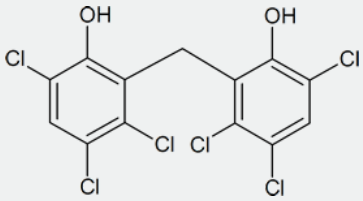


However, media references to dioxin are usually in connection with 2,3,7,8-tetrachlorodibenzo- *p*-dioxin, or TCDD:

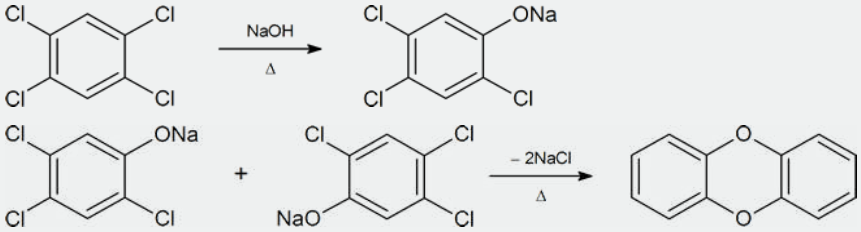


TCDD is a by-product formed in the manufacture of trichlorophenol, an intermediate in the production of the herbicide 2,4,5-T (one of the ingredients of the infamous Agent Orange), in the manufacture of hexachlorophene, by pulp and paper mills that use chlorine to produce white paper, and as a result of the incineration of municipal refuse.





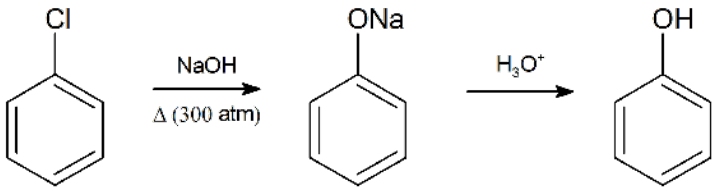
The equation given below shows how 2,3,7,8-tetrachlorodibenzo- *p*-dioxin is formed during the manufacture of 2,4,5-trichlorophenol, an intermediate produced in the synthesis of 2,4,5-T. The process involves the reaction of 1,2,4,5-tetrachlorobenzene with base at a temperature of about 160°C.



The possible hazards presented by dioxin first became apparent in 1957, when some German workers involved in the manufacture of 2,4,5-T developed chloracne—a skin condition resembling acne. The precise toxicological effects of dioxin on humans is open to debate, but as little as 0.6 mg per kg of body weight will kill 50% of guinea pigs injected with TCDD within a specified time.

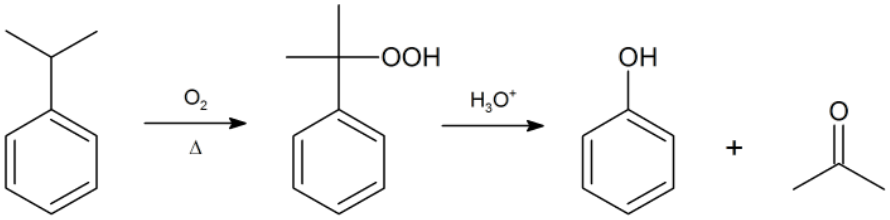
DOW'S PROCESS

An early commercial preparation of phenol in the late 19th and early 20th century was by the hydrolysis of chlorobenzene with strong base to produce a sodium phenoxide intermediate, which affords phenol upon acidification.



CUMENE PROCESS

Developed in the 1940s and currently responsible for most industrial phenol production this process involves isopropylbenzene—commonly known as cumene. Treatment of cumene with oxygen in air generates 2-hydroperoxypropan-2-ylbenzene (cumene hydroperoxide) through a radical pathway. When hydrolyzed in acidic medium the peroxide intermediate produces phenol and acetone, which are both valuable chemical products.



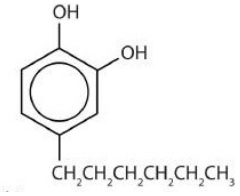
TO YOUR HEALTH: PHENOLS AND US

Phenols are widely used as antiseptics (substances that kill microorganisms on living tissue) and as disinfectants (substances intended to kill microorganisms on inanimate objects such as furniture or floors). The first widely used antiseptic was phenol. Joseph Lister used it for antiseptic surgery in 1867. Phenol is toxic to humans, however, and can cause severe burns when applied to the skin. In the bloodstream, it is a systemic poison—that is, one that is carried to and affects all parts of the body. Its severe side effects led to searches for safer antiseptics, a number of which have been found.



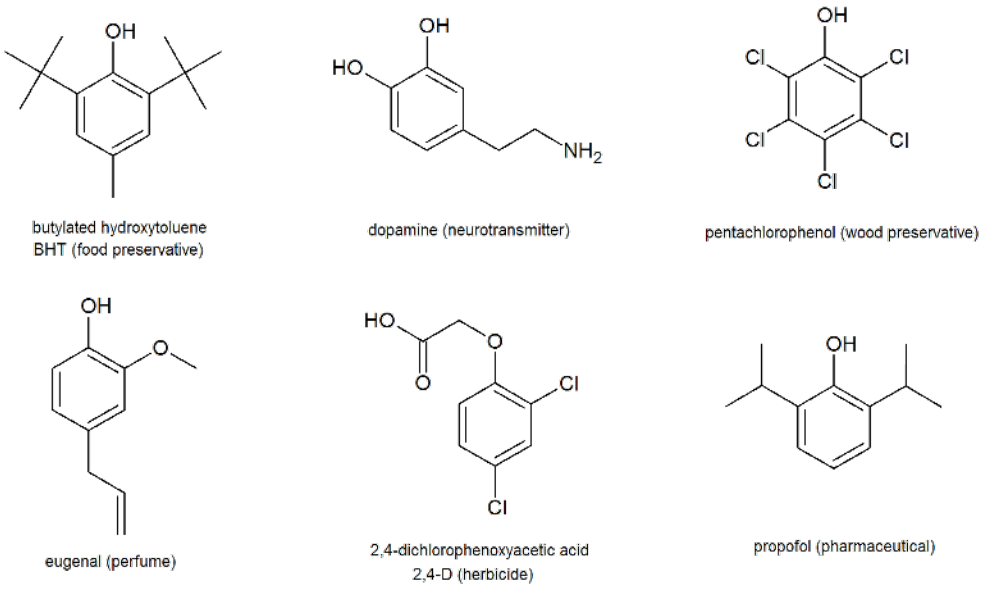
An operation in 1753, painted by Gaspare Traversi, of a surgery before antiseptics were used.

One safer phenolic antiseptic is 4-hexylresorcinol (4-hexyl-1,3-dihydroxybenzene; resorcinol is the common name for 1,3-dihydroxybenzene, and 4-hexylresorcinol has a hexyl group on the fourth carbon atom of the resorcinol ring). It is much more powerful than phenol as a germicide and has fewer undesirable side effects. Indeed, it is safe enough to be used as the active ingredient in some mouthwashes and throat lozenges.



The compound 4-hexylresorcinol is mild enough to be used as the active ingredient in antiseptic preparations for use on the skin.

In addition to acting as an antiseptic, phenol is also a useful precursor in many chemical syntheses to produce pharmaceuticals, food preservatives, polymers, resins and adhesives. Phenolics are also present in a number of biological systems and natural products such as neurotransmitters, flavouring agents, and vitamins to name a few.



BISPHENOL A

In the United States, single-serve bottled water is the fastest growing beverage of choice. However, drinking tap water creates less pollution and uses less energy and natural resources than transporting and manufacturing plastic water bottles. Unlike soda and other carbonated beverages, there is no deposit on water bottles and therefore fewer are recycled by consumers. Nationally, only 10% of plastic water bottles are recycled creating large quantites of waste. Many water bottles are apolycarbonate plastic made of Bisphenol A (BPA).

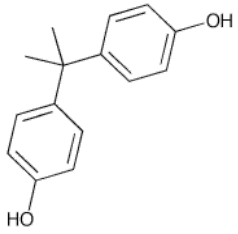


Figure 1: *Bisphenol A*

BPA was first synthesized by Thomas Zincke of the University of Marburg, Germany in 1905. Zincke did not propose uses for BPA however scientists discovered the many uses of BPA in 1953. Polycarbonate plastics became a commonly used commercial product in the 1950's.

BPA was created from a condensation reaction of phenol and acetone with hydrogen chloride, an acid catalyst, and a promoter such as methyl mercaptan. Once formed by this reaction, BPA is washed with water, neutralized with calcium hydroxide and distilled under vacuum. BPA can also be purified further by distillation and extractive crystallisation. Higher purity BPA is used to make polycarbonate plastics while the lower purity BPA is used to make Epoxy Resin. BPA's IUPAC name is 4,4'-dihydroxy-2,2,-diphenylpropane. It's chemical formula is $C_{15}H_{16}O_2$. The production of BPA produces H_2O (see image below) and therefore requires a condensation reaction for production.

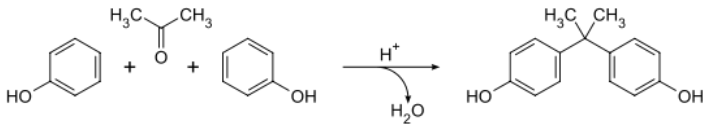


Figure 2 *The production of BPA*

A concern with the use of BPA in water bottles is the potential for leaching into the water which is then consumed. When BPA is present in in the human body, it mimics the hormone estrogen and is capable of binding to estrogen receptors. In doing so, it changes the genes in the body that are expressed which triggers changes in hormone concentration, enzyme function and protein synthesis.

Using plastic water bottles that contain BPA is damaging both to the environment and human health. A green alternative to the use of plastic water bottles is filtered tap water carried in refillable stainless steel containers.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
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17.10 REACTIONS OF PHENOLS

Objectives

After completing this section, you should be able to:

1. explain why phenols and phenoxide ions are very reactive towards electrophilic aromatic substitution (see Section 16.4 of the textbook).
2. write an equation to illustrate the oxidation of a phenol or an arylamine to a quinone, and identify the reagents used to oxidize phenols.
3. write an equation to illustrate the reduction of a quinone to a hydroquinone, and identify the reagents used to reduce quinones.
4. describe, briefly, the biological importance of the redox properties of quinones.

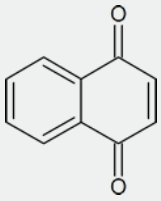
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

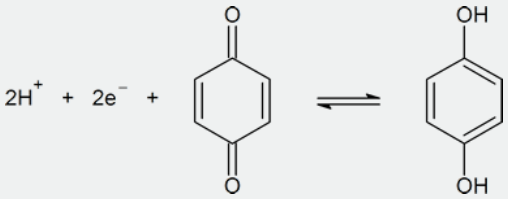
- hydroquinone
- quinone
- ubiquinone

STUDY NOTES

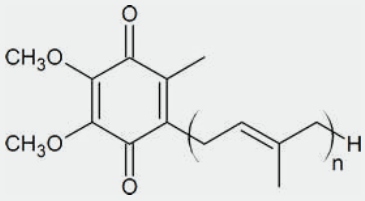
"Quinone" is a term used to describe cyclohexadiendiones in general, and *p*-benzoquinone in particular. In addition to benzene, other aromatic systems also give rise to quinones; for example, 1,4-naphthoquinone



"Hydroquinones" are produced by the reduction of quinones according to the following half-reaction:



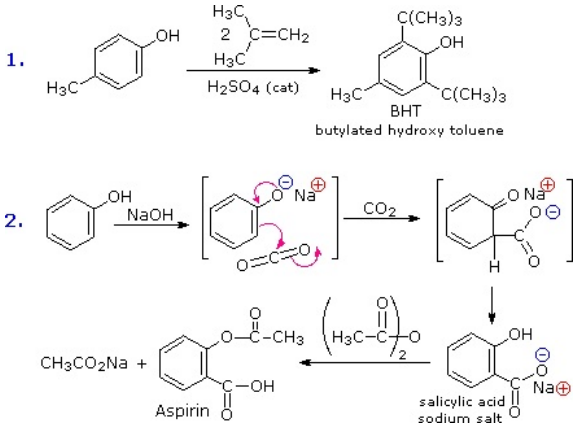
"Ubiquinones" are naturally occurring quinones whose role is to transfer a pair of electrons from one substance to another in enzyme-catalyzed reactions. Ubiquinones are also called coenzymes Q.



ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS

The facility with which the aromatic ring of phenols and phenol ethers undergoes electrophilic substitution has been noted. Two examples are shown in the following diagram. The first shows the Friedel-Crafts synthesis of the food preservative BHT from para-cresol. The second reaction is interesting in that it further demonstrates the delocalization of charge that occurs in the phenolate anion. Carbon dioxide is a weak electrophile and normally does not react with aromatic compounds; however, the negative charge concentration on the phenolate ring enables the carboxylation reaction shown in the second step. The sodium salt of salicylic acid is the major product, and the preference for

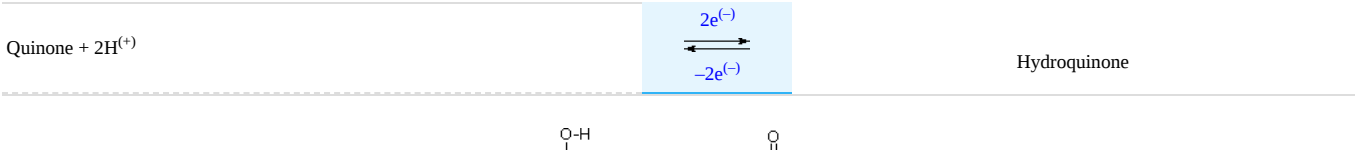
ortho substitution may reflect the influence of the sodium cation. This is called the **Kolbe-Schmidt reaction**, and it has served in the preparation of aspirin, as the last step illustrates.

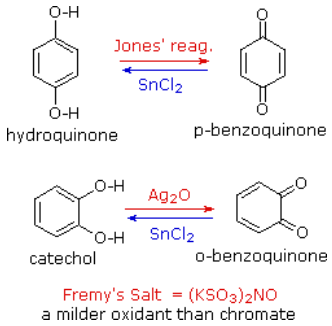


OXIDATION OF PHENOLS: QUINONES

Phenols are rather easily oxidized despite the absence of a hydrogen atom on the hydroxyl bearing carbon. Among the colored products from the oxidation of phenol by chromic acid is the dicarbonyl compound **para-benzoquinone** (also known as 1,4-benzoquinone or simply quinone); an ortho isomer is also known. These compounds are easily reduced to their dihydroxybenzene analogs, and it is from these compounds that quinones are best prepared. Note that meta-quinones having similar structures do not exist. The redox equilibria between the dihydroxybenzenes hydroquinone and catechol and their quinone oxidation states are so facile that milder oxidants than chromate (Jones reagent) are generally preferred.

One such oxidant is **Fremy's salt**, shown on the right. Reducing agents other than stannous chloride (e.g. $NaBH_4$) may be used for the reverse reaction. The position of the quinone-hydroquinone redox equilibrium is proportional to the square of the hydrogen ion concentration, as shown by the following half-reactions (electrons are colored blue). The electrode potential for this interconversion may therefore be used to measure the pH of solutions.

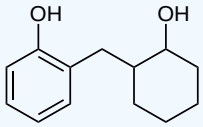




EXERCISES

? EXERCISE 17.10.1

Predict the major product if the following reagents/reagents were used. No reaction is also a possible answer.

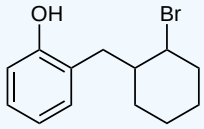


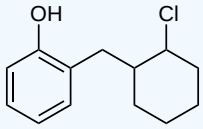
a. 1 equivalent of PBr_3

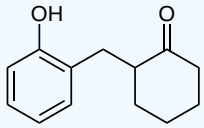
https://chem.libretexts.org/@go/page/90947

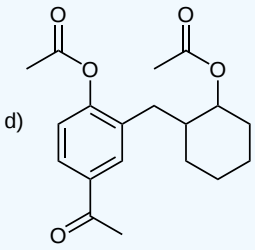
b. 1 equivalent of $SOCl_2$
c. Dess–Martin periodinane
d. 3 equivalents of acetyl chloride and $AlCl_3$ as a catalyst
e. Heat and H_2SO_4 (assume the phenol does not act as a nucleophile in this case)

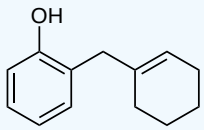
Answer

a) 

b) 

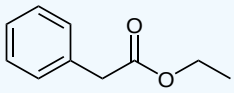
c) 

d) 

e) 

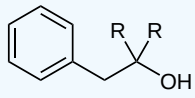
EXERCISE 17.10.2

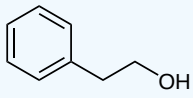
Predict the major product if the following reagents/conditions were used. No reaction is also a possible answer.



a. 2 equivalents of RMgBr and H_3O^+ work-up
b. $LiAlH_4$ and H_3O^+ work-up
c. $NaBH_4$ and H_3O^+ work-up

Answer

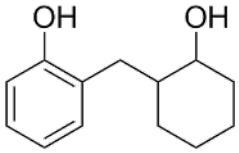
a) 

b) 

QUESTIONS

Q17.10.1

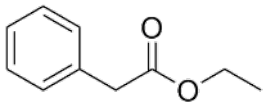
Predict the major product if the following reagents/reagents were used. No reaction is also a possible answer.



(a) 1 equivalent of PBr_3 (b) 1 equivalent of $SOCl_2$ (c) Dess–Martin periodinane (d) 3 equivalents of acetyl chloride and $AlCl_3$ as a catalyst (e) Heat and H_2SO_4 (assume the phenol does not act as a nucleophile in this case)

Q17.10.2

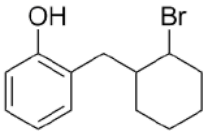
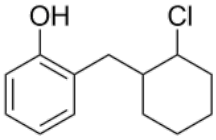
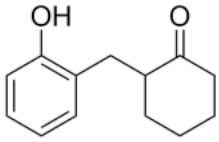
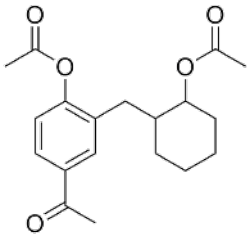
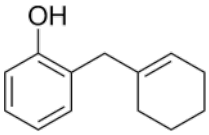
Predict the major product if the following reagents/conditions were used. No reaction is also a possible answer.



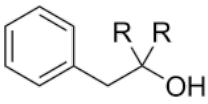
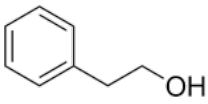
(a) 2 equivalents of RMgBr and H_3O^+ work-up (b) $LiAlH_4$ and H_3O^+ work-up (c) $NaBH_4$ and H_3O^+ work-up

SOLUTIONS

S17.10.1

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

S17.10.2

(a)  (b)  (c) No reaction. $NaBH_4$ is milder oxidant than $LiAlH_4$. It typically only reduces ketones and aldehydes.

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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17.11 SPECTROSCOPY OF ALCOHOLS AND PHENOLS

Objectives

After completing this section, you should be able to:

1. identify the two most prominent absorptions seen in the infrared spectra of alcohols and phenols.
2. describe the characteristic feature of the proton NMR spectra of alcohols and phenols.
   a. explain how deuterium oxide (D_2O) can be used to assist in the identification of the signal caused by the presence of the O—H proton in the ^1H NMR spectrum of an alcohol.
   b. predict the general form (i.e., number of peaks, approximate chemical shifts, and splitting pattern) of the proton NMR of a given alcohol or phenol.
3. describe the two most common initial fragmentations in the mass spectra of alcohols.
4. use spectral data (infrared, NMR, mass spectroscopy) to assist in the identification of an unknown alcohol or phenols. You may use tables of characteristic absorptions as an aid to accomplishing this objective.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- alpha cleavage
- dehydration

STUDY NOTES

The ^1H NMR chemical shifts for phenols are not particularly distinctive. However, one expects the —OH signal to be in the 4–7 ppm range, while the aromatic protons (see Section 15.7) are expected to be found at 7–8 ppm.

In a mass spectrometer, alcohols fragment in two characteristic ways: alpha cleavage and dehydration. From the equation showing H-Y elimination, you can see that the dehydration of an alcohol in a mass spectrometer is essentially the same as the dehydration of an alcohol in a normal chemical reaction. “Alpha cleavage” refers to the breaking of the bond between the oxygen-bearing carbon atom and one of the neighbouring carbons.

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.

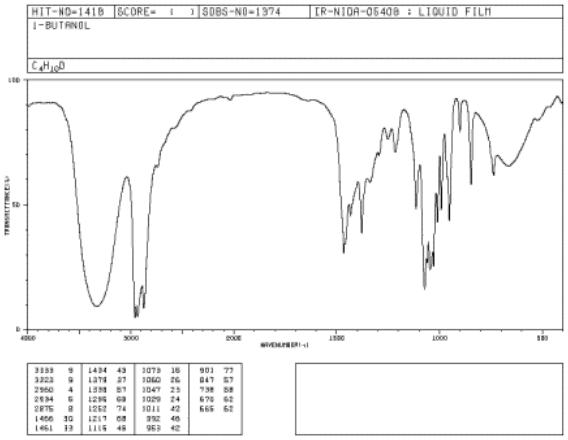


Figure IR8. IR spectrum of 1-butanol. Source: SDBSWeb : http://riodb01.ibase.aist.go.jp/sdbs/

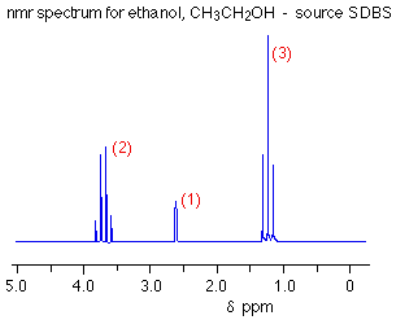
(National Institute of Advanced Industrial Science and Technology of Japan, 14 July 2008)

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 EDIT SECTION

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:



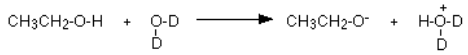
- The Nuffield Data Book quotes 2.0 - 4.0, but the Nuffield text book shows a peak at about 5.4.
- The OCR Data Sheet for use in their exams quotes 3.5 - 5.5.
- A reliable degree level organic chemistry text book quotes1.0 - 5.0, but then shows an NMR spectrum for ethanol with a peak at about 6.1.
-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



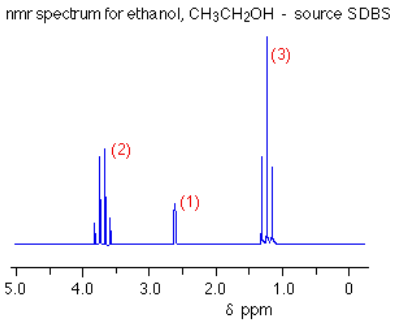
Deuterium atoms don't produce peaks in the same region of an NMR spectrum as ordinary hydrogen atoms, and so the peak disappears. You might wonder what happens to the positive ion in the first equation and the OD^- in the second one. These get lost into the normal equilibrium which exists wherever you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

$$2D_2O \rightleftharpoons D_3O^+ + OH^-$$

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.

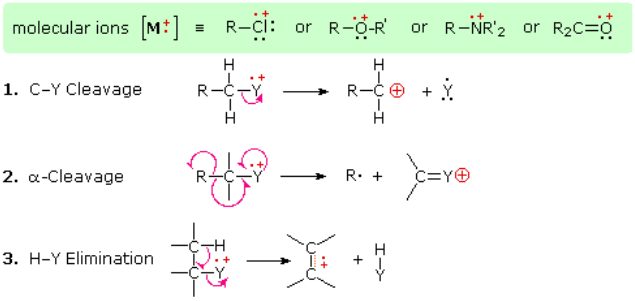


The left-hand cluster of peaks is due to the CH_2 group. It is a quartet because of the 3 hydrogens on the next door CH_3 group. You can ignore the effect of the -OH hydrogen. Similarly, the -OH peak in the middle of the spectrum is a singlet. It hasn't turned into a triplet because of the influence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

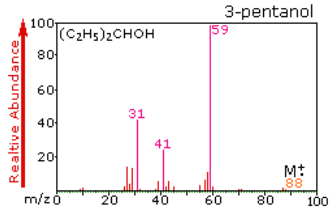
MASS SPECTRA FRAGMENTATION PATTERNS EDIT SECTION

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.

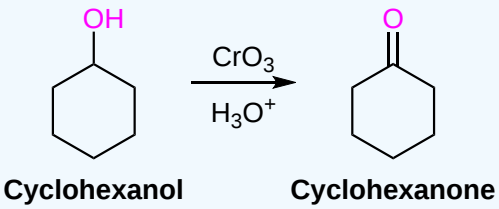


EXERCISES

https://chem.libretexts.org/@go/page/90948

EXERCISE 17.11.1

Assume that you have just converted cyclohexanol into cyclohexanone. How would you use IR spectroscopy to tell if the conversion was successful? What changes would you expect to see between the starting material and the product?



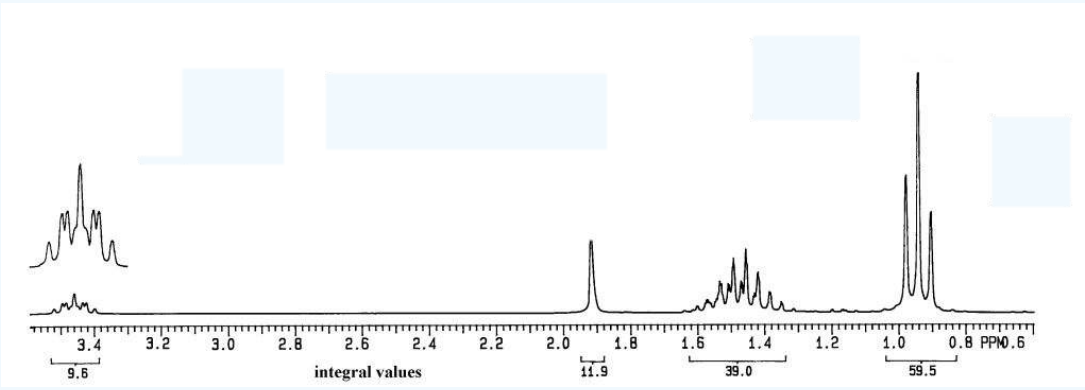
Cyclohexanol **Cyclohexanone**

Answer

The cyclohexanol starting material would have a distinctive O-H stretch between 3300 and 3400 cm^{-1}. If the conversion were successful this peak would not be present in the product. Also, the IR spectrum of the product would have a strong C=O stretch between 1700 and 1800 cm^{-1}.

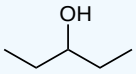
EXERCISE 17.11.2

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.



Answer

3-Pentanol



EXERCISE 17.11.3

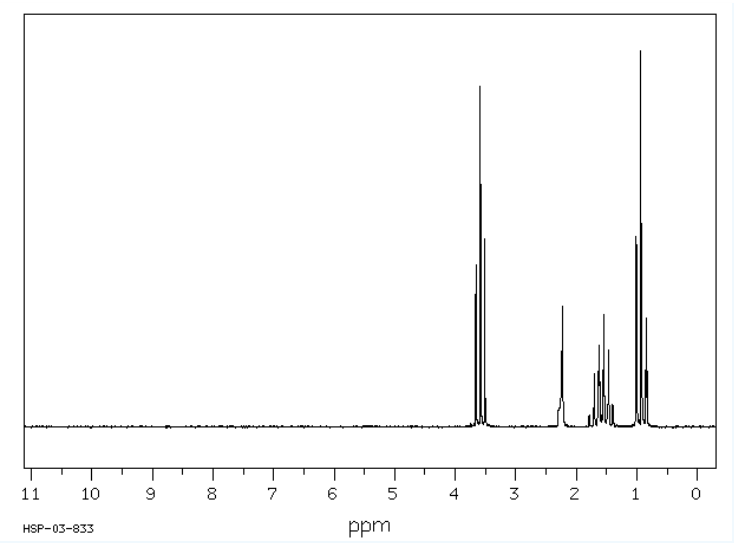
How would you expect the NMR spectrum show in the previous question change if D_2O was added to the NMR sample tube?

Answer

The -OH peak at 1.9 ppm would disappear due to deuterium exchange.

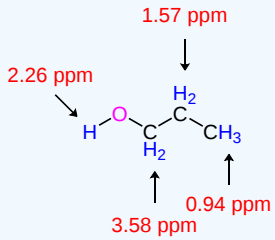
EXERCISE 17.11.4

From mass spectroscopy analysis it was determined that a compound has the general formula C_3H_8O. Given the following ^1H NMR spectrum, draw the structure. 0.94 (tr, 3H); 1.57 (mult, 2H); 2.26 (s, 1H); 3.58 (tr, 2H)



Answer

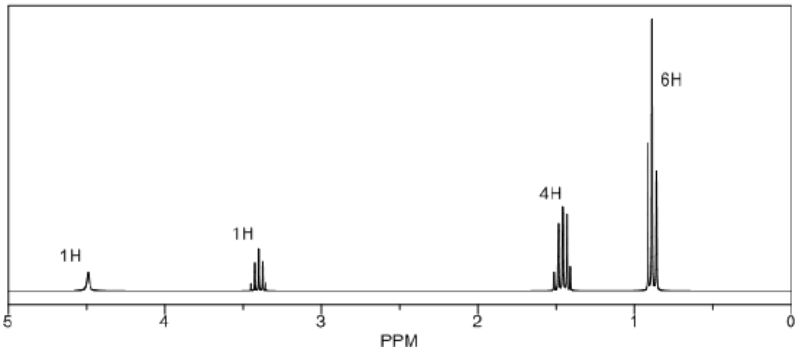
1-Propanol



QUESTIONS

Q17.11.1

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.

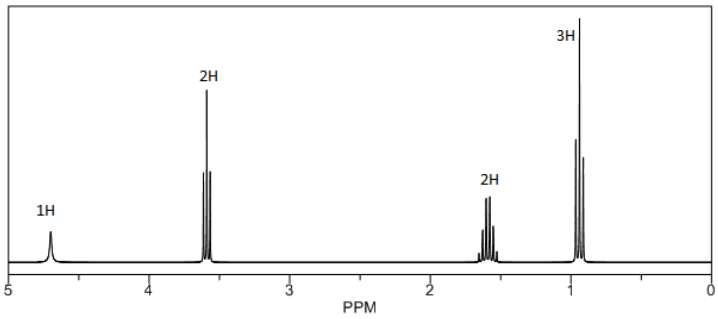


Q17.11.2

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.

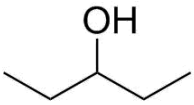
Q17.11.3

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.



SOLUTIONS

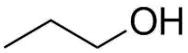
S17.11.1



S17.11.2

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.

S17.11.3

1-propanol 

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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17.S: ALCOHOLS AND PHENOLS (SUMMARY)

CONCEPTS & VOCABULARY

17.0 Introduction

- Alcohols have hydroxide groups (OH) bonded to an sp^3 carbon.
- Enols have a hydroxide bonded to an sp^2 carbon that is not part of an aromatic ring, a vinyl carbon.
- Phenols have a hydroxide bonded to an sp^2 carbon that is part of an aromatic ring, an aryl carbon.

17.1 Naming Alcohols and Phenols

- Alcohols can be described as methyl, primary, secondary or tertiary, based on the number of alkyl groups attached to the carbon bonded to OH.
- Alcohols are named following IUPAC rules, by dropping the -e of an alkane and replacing with -ol.

17.2 Properties of Alcohols and Phenols

- Alcohols, enols and phenols all have significantly higher boiling points than alkanes, due to hydrogen bonding.
- Small alcohols are soluble in water.
- Alcohols are amphoteric, they act as an acid when reacting with bases and as a base when reacting with acids.
- Phenols are more acidic than alcohols due to resonance delocalization of the negative charge in the phenoxide conjugate base.
- Substituent groups on an aromatic ring that withdraw electron density increase the acidity of phenols, while substituent groups that donate electron density decrease acidity of phenols.

17.3 Preparation of Alcohols: A Review

- Alcohols can be prepared from alkyl halides by reacting with hydroxide.
- Alcohols can be prepared from alkenes by reaction with acid/water or oxymercuration to form the more substituted alcohol.
- Alcohols can be prepared from alkenes by hydroboration/oxidation to form the less substituted alcohol.
- Diols can be prepared from alkenes by first forming an epoxide, then ring opening the epoxide to form an anti-diol.
- Diols can be prepared from alkenes by reacting with osmium tetraoxide, then reducing off the osmium to form syn-diols.

17.4 Alcohols from Carbonyl Compounds: Reduction

- Organic reduction can be defined by increasing the number of bonds to hydrogen.
- Aldehydes and ketones can be reduced to alcohols with several different hydride donor reagents.
- NADH is an example of a biological reducing agent, which donates a hydride to carbonyl groups, reducing them to an alcohol.
- Carboxylic acids and esters can be reduced to alcohols with a strong reducing agent such as lithium aluminum hydride $LiAlH_4$.

17.5 Alcohols from Carbonyl Compounds: Grignard Reaction

- One of the most important organometallic groups of molecules are Grignard reagents, which are alkyl magnesium halides.
- Grignard reagents, like other organometallic compounds, include a nucleophilic alkyl group that can react with many different electrophiles.
- Grignard reagents will add to aldehydes and ketones forming alcohol products.
- Grignard reagents will add twice to ester molecules, forming alcohol products.
- Grignard reagents are strong bases, therefore the will not undergo nucleophilic addition reactions with molecules that have protons that are even slightly acidic such as: alcohols, carboxylic acids, alkynes, and amines or amides that have an N-H bond.

17.6 Reactions of Alcohols

- Alcohols can be converted into alkyl halides directly by reaction with strong hydrogen halides. This works best for 3° alcohols.
- Conversion of 1° and 2° alcohols into alkyl halides commonly use thionyl chloride ($SOCl_2$) or phosphorus tribromide (PBr_3).
- To activate an alcohol in order to make the hydroxide a good leaving group, tosylates (toluenesulfonates) and mesylates (methanesulfonates) can be formed.
- Alcohols can be dehydrated by heating in strong acid solution to form an alkene.
- Alcohols react with acid chlorides to form esters.

17.7 Oxidation of Alcohols

- Primary and secondary alcohols can be oxidized with various chromium reagents, while tertiary alcohols are not.
- Secondary alcohols are oxidized to ketones.
- Primary alcohols are oxidized to carboxylic acids using chromium trioxide or dichromate compounds.

- Primary alcohols can be stopped in their oxidation at aldehydes by reacting with pyridinium chlorochromate or Dess-Martin periodinane.

17.8 Protection of Alcohols

- Protection of a functional group is useful when that functional group may interfere with an intended reaction.
- Protection converts a functional group into a non-interfering derivative molecule through a reaction that can be easily reversed to remove the protecting group.
- Protection consists of a series of reactions that include protect, perform intended reactions, and deprotect.
- Alcohols can be protected as silyl ethers by reacting with chlorotrialkyl silanes.

17.9 Phenols and Their Uses

- Phenols can be prepared from chlorobenzene or isopropylbenzene.
- Phenol and phenol derivatives (such as resorcinol) are used as germicides and antiseptics.
- Bisphenol A (BPA) has controversially been used to create polycarbonate plastics such as water bottles.

17.10 Reactions of Phenols

- Phenols can react with strong electrophiles (such as in Friedel-Crafts reactions).
- Phenols react with strong oxidizing agents including Jones reagent or silver oxide to form quinones.

17.11 Spectroscopy of Alcohols and Phenols

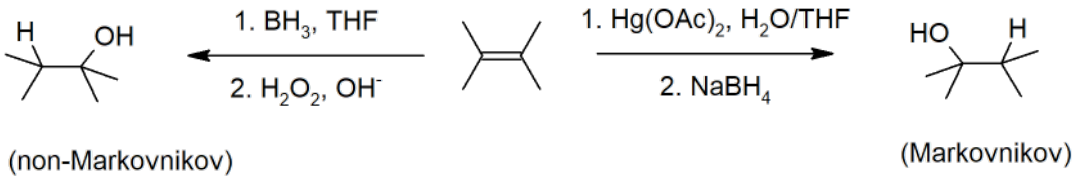
- Alcohols are among the most identifiable functional groups in infrared spectroscopy due to the strong, wide absorbance around 3400 cm^{-1}.
- Alcohol peaks are much more difficult to recognize in ^1H NMR, since OH hydrogens are relatively reactive and can exchange with hydrogens from the solvent, they are often weak absorptions without strong, sharp peaks.
- Hydroxide protons are not split in ^1H NMR.
- Loss of hydroxide in mass spectroscopy can lead to loss of a fragment with 17 m/z.

SKILLS TO MASTER

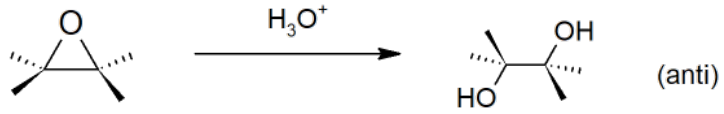
- Skill 17.1 Identify types of alcohols.
- Skill 17.2 Name molecules with hydroxide groups using IUPAC rules.
- Skill 17.3 Describe properties related to intermolecular forces (including hydrogen bonding).
- Skill 17.4 Explain acid-base properties of alcohols and phenols.
- Skill 17.5 Describe how additional functional groups affect the acidity of phenols.
- Skill 17.6 Draw mechanisms to form alcohols from alkyl halides.
- Skill 17.7 Draw mechanisms to form alcohols from alkenes.
- Skill 17.8 Draw mechanisms to form alcohols by reduction reactions.
- Skill 17.9 Draw mechanisms to form alcohols by reaction of carbonyl compounds with Grignard reagents (and other organometallics).
- Skill 17.10 Draw mechanisms for conversion of alcohols to alkyl halides.
- Skill 17.11 Draw mechanisms for conversion of alcohols to tosylates.
- Skill 17.12 Draw mechanisms for dehydration of alcohols to alkenes.
- Skill 17.13 Draw mechanisms for conversion of alcohols to esters.
- Skill 17.14 Draw mechanisms for oxidation of alcohols to aldehydes, ketones, and carboxylic acids.
- Skill 17.15 Write out syntheses that incorporate protection and deprotection of alcohols.
- Skill 17.16 Identify presence of alcohols by IR, NMR and MS.

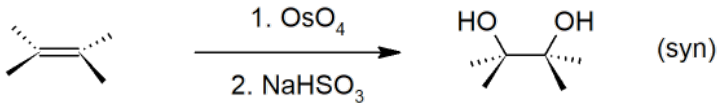
SUMMARY OF REACTIONS

Alcohol Preparation (Hydrolysis)

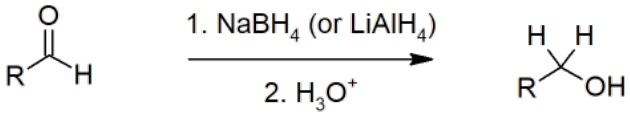


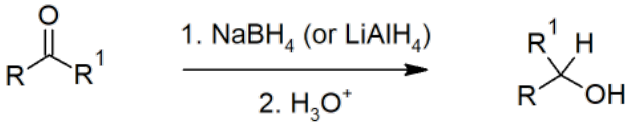
(non-Markovnikov) (Markovnikov)

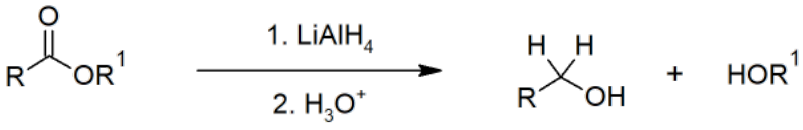


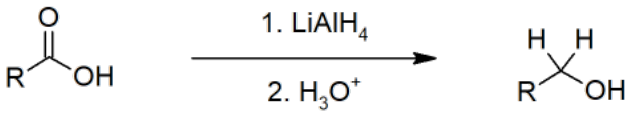


Alcohol Preparation (Reducing the Carbonyl)

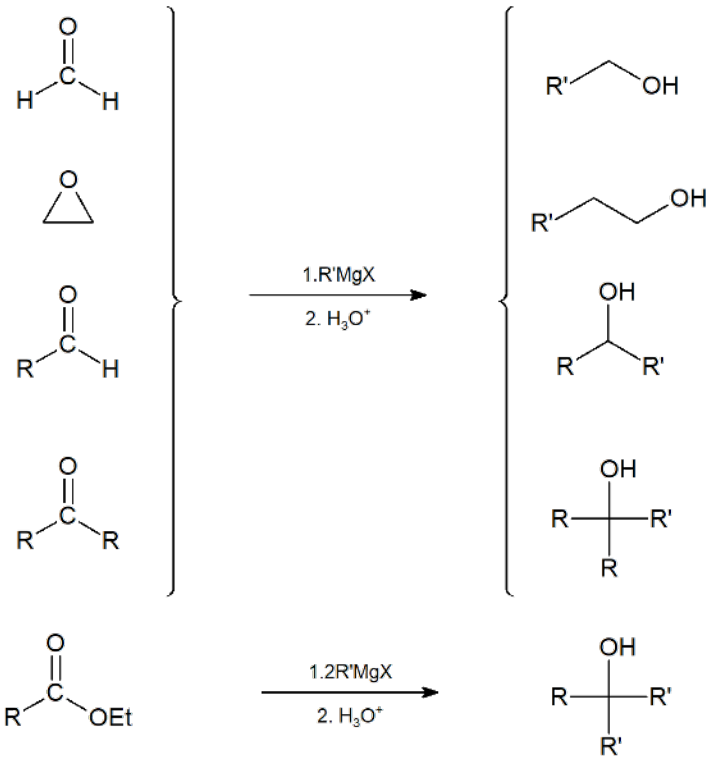




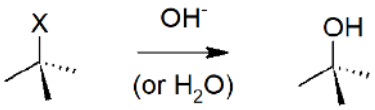




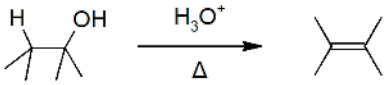
Alcohol Preparation (Grignard Additions)

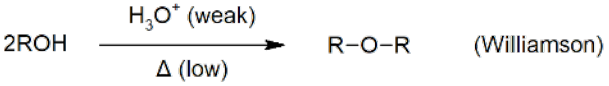


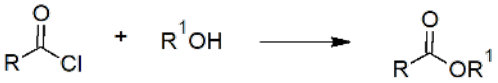
Alcohol Preparation (from Organohalide)

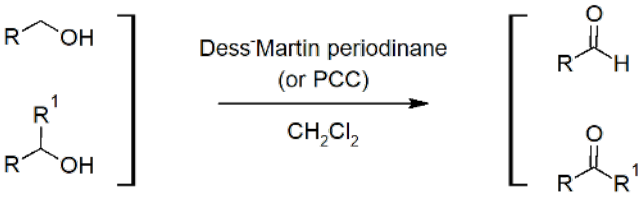


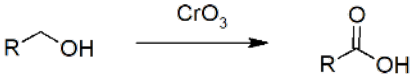
Alcohol Reactions



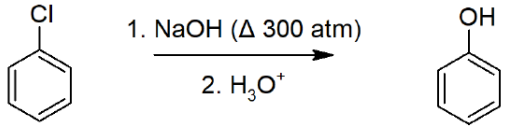


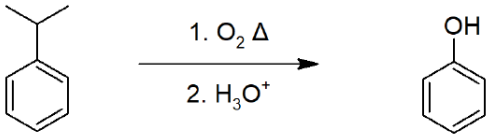






Phenol Preparation





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CHAPTER OVERVIEW

CHAPTER 18: ETHERS AND EPOXIDES; THIOLS AND SULFIDES

LEARNING OBJECTIVES

When you have completed Chapter 18, you should be able to:

1. fulfill all of the detailed objectives listed under each individual section.
2. design a multi-step synthesis using one or more of the reactions introduced in this chapter, along with any number of the reactions you have studied to date.
3. solve “road-map” problems that may require a knowledge of the chemistry of ethers, epoxides, thiols and sulfides, in addition to any of the material you have studied up to this point in organic chemistry.
4. define, and use in context, the key terms introduced in this chapter.

We shall begin in a very traditional manner, with a discussion of the nomenclature of ethers. We will then describe how ethers may be prepared in the laboratory, and discuss the relative inertness of these compounds. A discussion of the chemistry of cyclic ethers follows, with particular emphasis on the preparation and reactions of epoxides—cyclic ethers containing a three-membered ring. We will then introduce crown ethers—compounds that consist of large rings containing several oxygen atoms—and the spectroscopic properties of ethers. The unit will close with a description of the chemistry of thiols and sulfides, the sulfur-containing analogues of alcohols and ethers.

18.0 Introduction
18.1 Names and Properties of Ethers
18.2 Synthesis of Ethers
18.3 Reactions of Ethers: Acidic Cleavage
18.4 Reactions of Ethers - Claisen Rearrangement
18.5 Cyclic Ethers: Epoxides
18.6 Reactions of Epoxides: Ring-opening
18.7 Crown Ethers
18.8 Thiols and Sulfides
18.9 Spectroscopy of Ethers
Chapter 18 - Affix: A Preview of Carbonyl Compounds
18.S: Ethers and Epoxides; Thiols and Sulfides (Summary)

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18.0 INTRODUCTION

Objectives

After completing this section, you should be able to use the terms “ether,” “diethyl ether ” and “ethyl ether ” appropriately in context.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

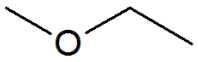
- ether (R—O—R′)
- sulfide (R—S—R′)
- thiol (R—S—H)

STUDY NOTES

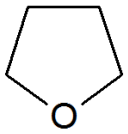
As defined in the textbook, an “ether” is a substance with the general formula (R—O—R′) where R and R′are alkyl, aryl, vinyl or allyl groups. However, the word “ether” is also commonly used to refer to the specific compound, $CH_3—CH_2—O—CH_2—CH_3$, which is correctly called “diethyl ether.” Further confusion can arise because some chemists refer to “diethyl ether ” as “ethyl ether.” In this course, “ether ” will be used to refer to the class of compounds with the structure (R—O—R′); diethyl ether will refer to the compound, $CH_3—CH_2—O—CH_2—CH_3$; and “ethyl ether ” will not be used.

ETHERS AND EPOXIDES

While the general formula for ethers is R-O-R′, keep in mind that there also cyclic ethers like tetrahydrofuran (a common organic solvent) or even epoxides which you first encounter in Section 8.7 in synthesizing diols from alkenes.



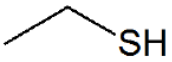
ethyl methyl ether



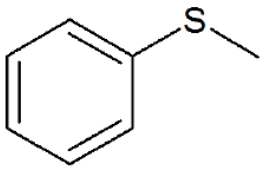
tetrahydrofuran

THIOLS AND SULFIDES

Thiols (thio alcohols or mercaptans) and sulfides (thioethers) are the sulfur analogues of alcohols and ethers and have the general formulas of R-S-H and R-S-R′, respectively.



ethanethiol



methyl phenyl sulfide

CONTRIBUTORS AND ATTRIBUTIONS

Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

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18.1 NAMES AND PROPERTIES OF ETHERS

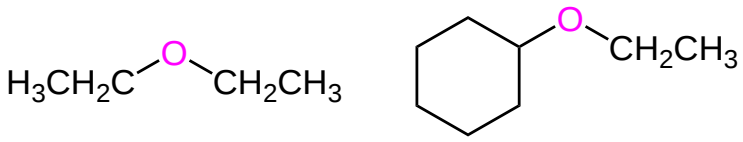
Objectives

After completing this section, you should be able to:

1. write two acceptable names for a simple dialkyl ether, given its Kekulé, shorthand or condensed structure.
2. name a complicated ether by the IUPAC system, given its Kekulé, shorthand or condensed structure.
3. draw the Kekulé, condensed or shorthand structure of an ether, given an acceptable name.
4. explain why the boiling point of an ether is generally higher than that of an alkane of similar molecular mass.

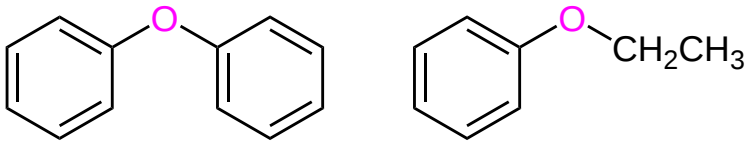
STRUCTURE OF ETHERS

Ethers are a class of organic compounds that contain an sp^3 hybridized oxygen between two alkyl groups and have the formula R-O-R'. these compounds are used in dyes, perfumes, oils, waxes and other industrial uses. Aliphatic ethers have no aryl groups directly attached to the ether oxygen.



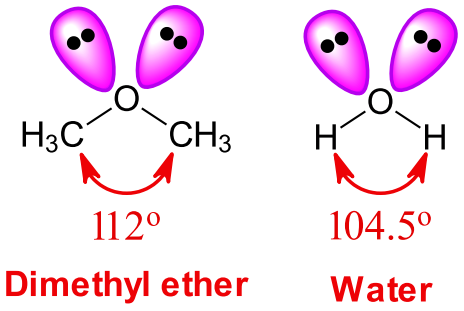
Examples of Aliphatic Ethers

Aromatic ethers have at least one aryl ring directly attached to the ether oxygen. In aryl ethers, the lone pair elections on oxygen are conjugated with the aromatic ring which significantly changes the properties of the ether.

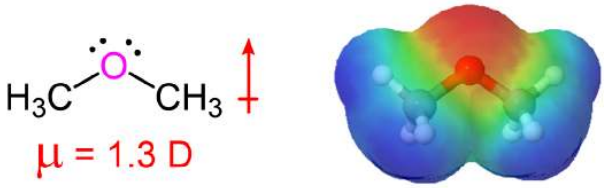


Example of Aromatic Ethers

The sp^3 hybridization of oxygen gives ethers roughly the same geometry as alcohols and water. The R-O-R' bond angle is close to what is expected in a tetrahedral geometry. The bond angle of dimethyl ether is 112º which is larger than the H-O-H bond angle in water (104.5º) due to the steric repulsion of the methyl groups.



The presence of an electronegative oxygen atom gives ethers a small dipole moment.



COMPARISONS OF PHYSICAL PROPERTIES OF ALCOHOLS AND ETHERS

Ethers, unlike alcohols, have no hydrogen atom on the oxygen atom (that is, no OH group). Therefore, there is no intermolecular hydrogen bonding between ether molecules, which makes their boiling points much lower than an alcohol with similar mass. Despite the presence of a small dipole moment, ethers have boiling points that about the same alkanes of comparable molar mass. (Table 18.1.2).

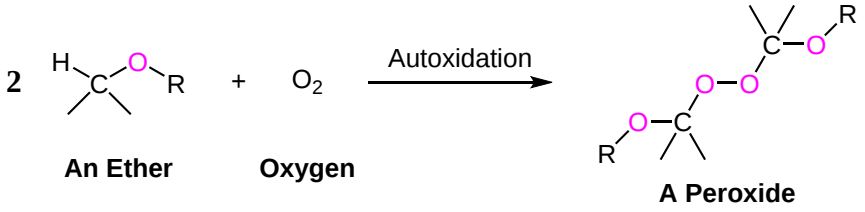
Table 18.1.2 Comparison of Boiling Points of Alkanes, Alcohols, and Ethers

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

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).

PEROXIDE FORMATION

Many ethers can react with oxygen to form explosive peroxide compounds n a free radical process called autoxidation. For this reason ethers should not be stored for long periods of time and should not be stored in glass bottles. The danger is particularly acute when ether solutions are distilled to near dryness. The hydroperoxides can become more concentrated during a distillation because they tend to have a slightly higher boiling point than the corresponding ether. Before performing an ether distillation great care should be taken to test for the presence of peroxides.

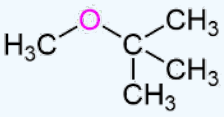


An Ether **Oxygen** **A Peroxide**

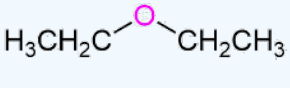
NAMING ETHERS

When no other functional group is present, simple ethers are often given common functional class names. Both alkyl groups attached to the oxygen atom are named as substituents (in alphabetical order) and then the word *ether* is added. The common names for alkyl substituents discussed in **Section 3.3** are often used.

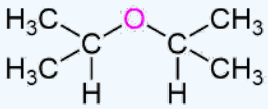
EXAMPLE 18.1.1



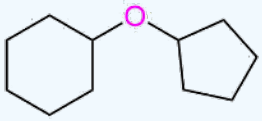
Methyl *tert*-butyl ether



Diethyl ether



Diisopropyl ether



Cyclohexyl cyclopentyl ether

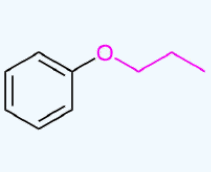
IUPAC nomenclature for ethers should be used for complicated ethers, compounds with more than one ether linkage, and compounds where other functional groups are present with an ether. In these cases, an RO group of the ether is named as an alkoxy substituent.

Common alkoxy substituents are given names derived from their alkyl component. The suffix *-yl* is replaced with *-oxy*. (Table 18.1.1):

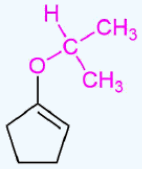
Table 18.1.1: Common Alkyl and Alkoxy Groups

Alkyl Group	Name	Alkoxy Group	Name
CH_3–	Methyl	CH_3O–	Methoxy
CH_3CH_2–	Ethyl	CH_3CH_2O–	Ethoxy
$(CH_3)_2CH$–	Isopropyl	$(CH_3)_2CHO$–	Isopropoxy
$(CH_3)_3C$–	tert-Butyl	$(CH_3)_3CO$–	tert-Butoxy
C_6H_5–	Phenyl	C_6H_5O–	Phenoxy

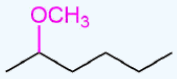
EXAMPLE 18.1.2



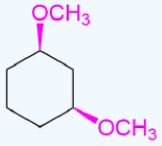
Propoxybenzene



1-Isopropoxycyclopentene



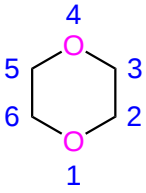
2-Methoxyhexane



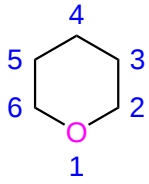
***Cis*-1,3-Dimethoxycyclohexane**

CYCLIC ETHERS

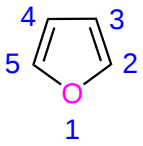
In cyclic ethers are a type of heterocycle with one or more oxygens located in the ring. Many cyclic ethers have common names and are often used as solvents due to their inert nature. These ring structures are often found in biological molecules such as sugars and DNA. The rings are numbered so that an oxygen gets position 1.



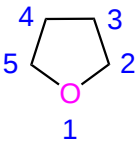
Dioxane



Tetrahydropyran

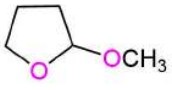


Furan

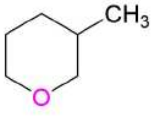


Tetrahydrofuran

Example 18.1.3



2-Methoxytetrahydrofuran



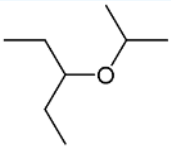
3-Methyltetrahydropyran

EXERCISE

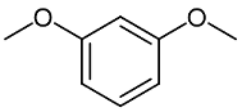
EXERCISE 18.1.1

Please name the following ethers:

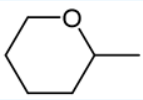
a)



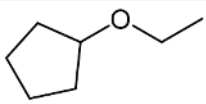
b)



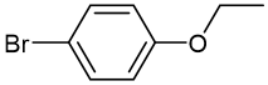
c)



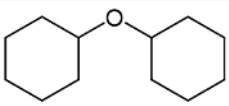
d)



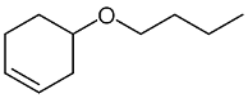
e)



f)



g)



Answers

a) 3-Isopropoxypentane

b) 1,3-Dimethoxybenzene

c) 2-Methyltetrahydropyran

d) Cyclopentyl ethyl ether

e) 1-bromo-4-ethoxybenzene

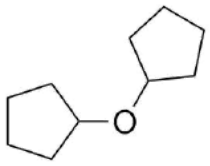
f) Dicyclohexyl ether

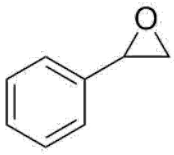
g) 4-Butoxycyclohexene

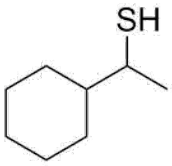
QUESTIONS

Q18.1.1

Give the IUPAC name for the following chemical structures.

(a) 

(b) 

(c) 

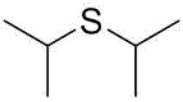
Q18.1.2

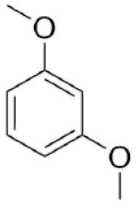
Draw structures of the following.

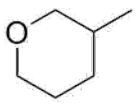
(a) 3-isopropoxypentane (b) 1-(4-chlorophenoxy)-3-methylbenzene (c) 2-(tert-butoxy)-2-methylpropane

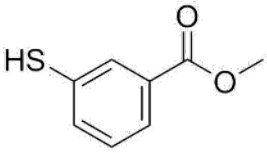
Q18.1.3

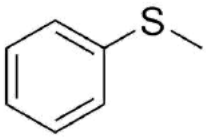
Name the following ethers and sulfides.

(a) 

(b) 

(c) 

(d) 

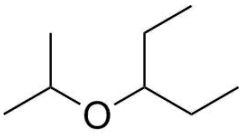
(e) 

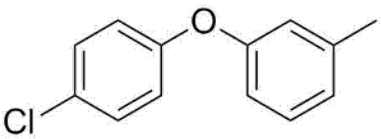
SOLUTIONS

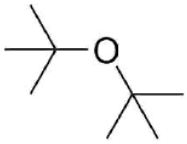
S18.1.1

(a) oxydicyclopentane (b) 2-phenyloxirane (c) 1-cyclohexylethane-1-thiol

S18.1.2

(a) 

(b) 

(c) 

S18.1.3

(a) diisopropylsulfide (b) 1,3-dimethoxybenzene (c) 2-Methyltetrahydro-2H-pyran (d) methyl 3-sulfanylbenzoate (e) methyl(phenyl)sulfide

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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18.2 SYNTHESIS OF ETHERS

Objectives

After completing this section, you should be able to:

1. write an equation to illustrate the industrial preparation of simple symmetrical ethers.
2. write an equation to illustrate the Williamson synthesis of ethers.
   a. identify the ether obtained from the reaction of a given alkyl halide with a given alkoxide ion.
   b. identify the reagents needed to prepare a given ether through a Williamson synthesis.
   c. identify the limitations of the Williamson synthesis, and make the appropriate choices when deciding how best to synthesize a given ether.
   d. write an equation to describe the formation of an alkoxide from an alcohol.
   e. identify silver(I) oxide as a reagent which can be used in a Williamson synthesis.
3. write an equation to show how an ether can be prepared by the alkoxymercuration-demercuration of an alkene.
   a. identify the product formed from the alkoxymercuration-demercuration of a given alkene.
   b. identify the alkene, the reagents, or both, needed to prepare a given ether by the alkoxymercuration-demercuration process.
   c. write the detailed mechanism of the reaction between an alkene, an alcohol and mercury(II) trifluoroacetate.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- alkoxymercuration
- oxymercuration
- Williamson ether synthesis

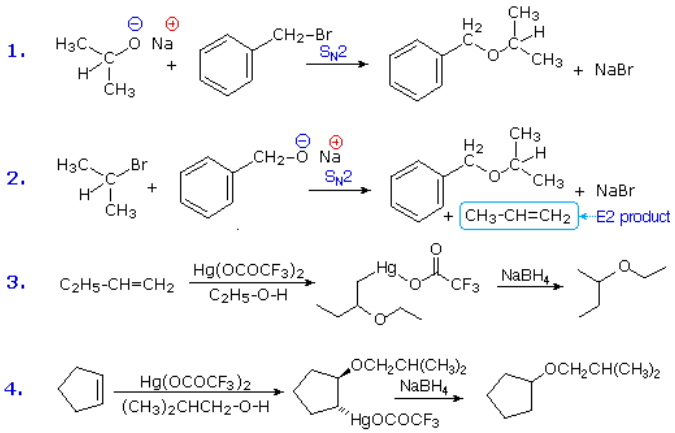
STUDY NOTES

We studied oxymercuration as a method of converting an alkene to an alcohol in Section 8.4. “Alkoxymercuration” is a very similar process, except that we are now converting an alkene into an ether. The two processes are compared below.

In	oxymercuration	alkoxymercuration
we react an	alkene	alkene
with	water	an alcohol
in the presence of	$Hg(O_2CCH_3)_2$	$Hg(O_2CCF_3)_2$
followed by treatment with	$NaBH_4$	$NaBH_4$
to produce an	alcohol	ether

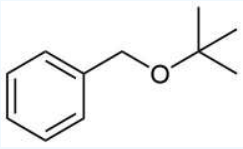
Review the mechanism of the oxymercuration reaction in Section 8.4, paying particular attention to the regiochemistry and the stereochemistry of the reaction. The mechanism is identical to alkoxymercuration.

Ethers are usually prepared from alcohols or their conjugate bases. One important procedure, known as the **Williamson Ether Synthesis**, proceeds by an S_N2 reaction of an alkoxide nucleophile with an alkyl halide. Reactions #1 and #2 below are two examples of this procedure. When applied to an unsymmetrical ether, as in this case, there are two different combinations of reactants are possible. Of these one is usually better than the other. Since alkoxide anions are strong bases, the possibility of a competing E2 elimination must always be considered. Bearing in mind the factors that favor substitution over elimination, a 1°-alkyl halide should be selected as a preferred reactant whenever possible. Thus, reaction #1 gives a better and cleaner yield of benzyl isopropyl ether than does reaction #2, which generates considerable elimination product.



? WORKED EXAMPLE 18.2.1

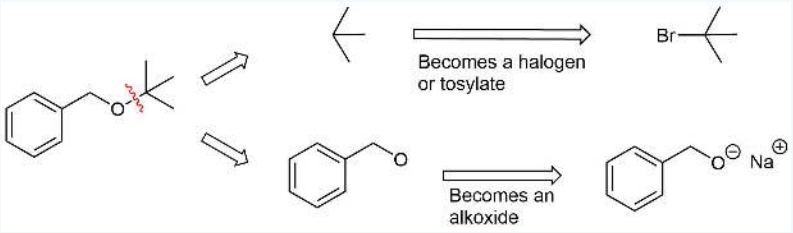
How would you prepare the following molecule using a Williamson Ether Synthesis?



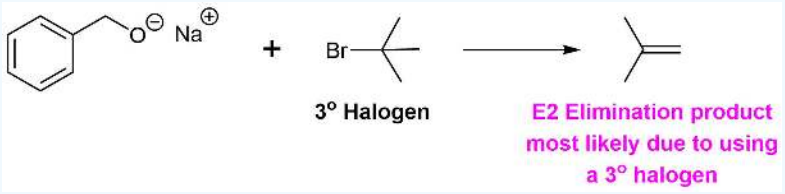
Answer

Analysis: The ether is asymmetrical so each of the C-O bonds can be broken to create a different set of possible reactants. After cleavage of the C-O bond, pathway 1 shows a 3º halogen as the starting material. This reaction will most likely not be effective due to alkoxides reacting with 3º halogens to preferable form an alkenes by E2 elimination. Pathway 2 shows a 1º halogen as a starting material which is favorable for S_N2 reactions.

Pathway 1

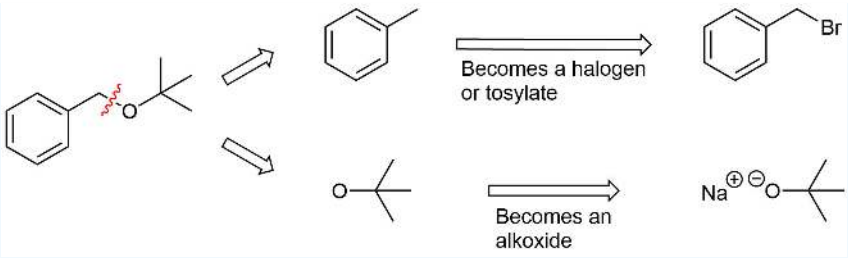


Solution 1

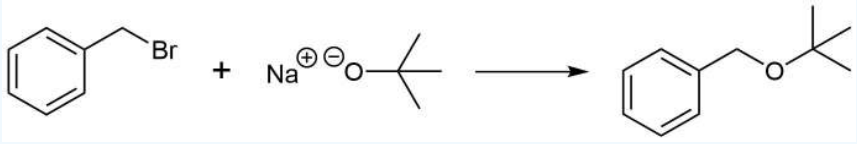


Pathway 2

https://chem.libretexts.org/@go/page/90953



Solution 2



A second general ether synthesis, **alkoxymercuration**, is patterned after the oxymercuration reaction. Reactions #3 and #4 are examples of this two-step procedure. Note that the alcohol reactant is used as the solvent, and a trifluoroacetate mercury (II) salt is used in preference to the acetate (trifluoroacetate anion is a poorer nucleophile than acetate). The mechanism of alkoxymercuration is similar to that of oxymercuration, with an initial anti-addition of the mercuric species and alcohol being followed by reductive demercuration.

Acid-catalyzed dehydration of small 1º-alcohols constitutes a specialized industrial method of preparing symmetrical ethers. As shown in the following two equations, the success of this procedure depends on the temperature. At 110º to 130 ºC an S_N2 reaction of the alcohol conjugate acid leads to an ether product.

$$2\,CH_3CH_2{-}OH + H_2SO_4 \xrightarrow{130\ ^\circ C} CH_3CH_2{-}O{-}CH_2CH_3 + H_2O \tag{18.2.1}$$

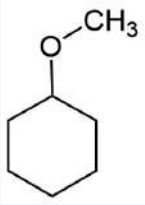
At higher temperatures (over 150 ºC) an E2 elimination takes place.

$$CH_3CH_2{-}OH + H_2SO_4 \xrightarrow{150\ ^\circ C} CH_2{=}CH_2 + H_2O \tag{18.2.2}$$

This reaction **cannot** be employed to prepare unsymmetrical ethers. It is because a mixture of products is likely to be obtained.

? WORKED EXAMPLE 18.2.2

How would you prepare the following molecule using a alkoxymercuration?

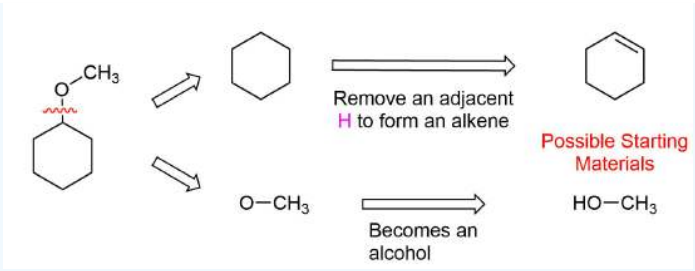


Answer

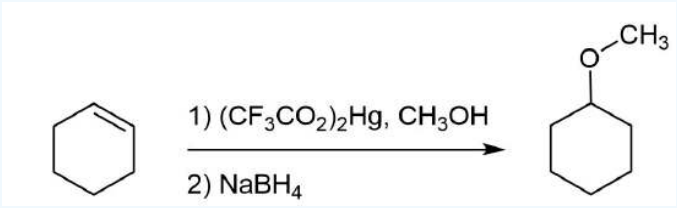
Analysis: The ether is symmetrical so each C-O bond of the ether can be cleaved to produce a set of starting materials for consideration. Pathway one shows a set of starting material which should work well for this reaction. The alcohol, methanol, can easily be used as a solvent. Although the alkene does not have a defined more and less substituted side, its symmetry will prevent a mixture of product from forming. The fragmentation for pathway 2 shows starting material which are not viable for this reaction. The alkyl fragment only has one carbon which cannot be used to form an alkene starting material. This means pathway 2 is not a viable method for the synthesis of the target molecule.

Pathway 1

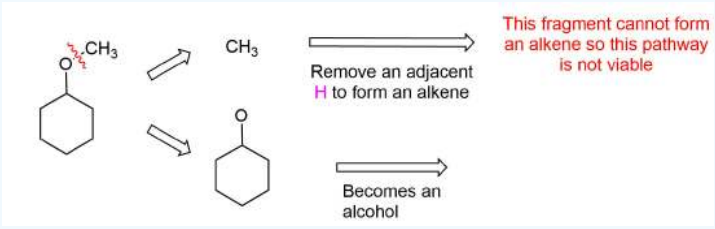
https://chem.libretexts.org/@go/page/90953



Solution 1



Pathway 2



EXERCISES

? EXERCISE 18.2.1

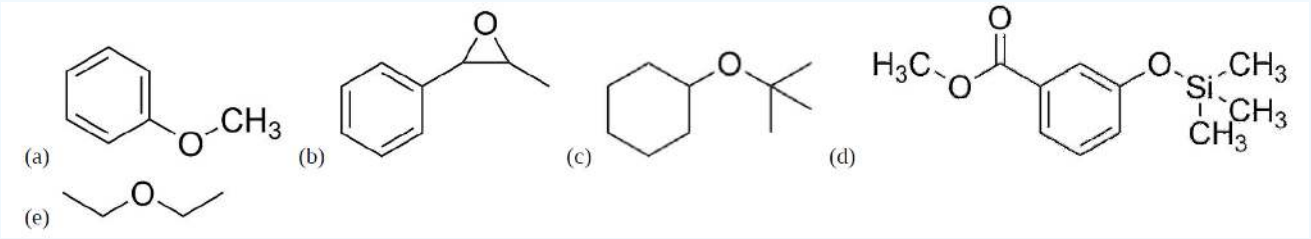
When preparing ethers using the Williamson ether synthesis, what factors are important when considering the nucleophile and the electrophile?

Answer

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

? EXERCISE 18.2.2

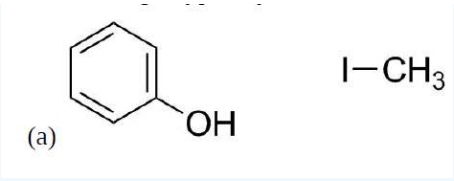
How would you synthesize the following ethers? Keep in mind there are multiple ways. The Williamson ether synthesis, alkoxymercuration of alkenes, and also the acid catalyzed substitution.

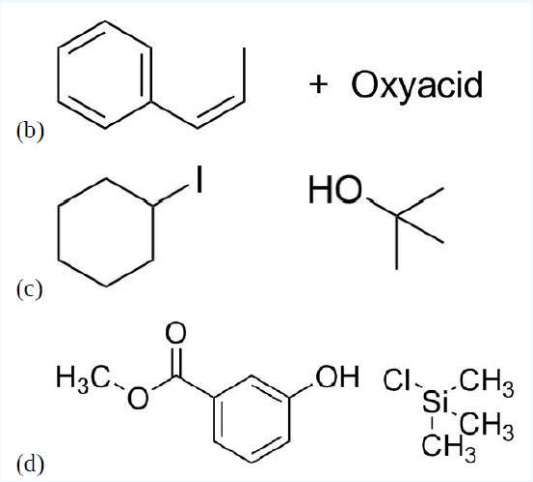


Answer

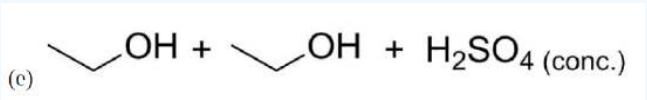
The Williamson ether syntheses require added catalytic base. Also, most of the halides can be interchanged, say for example for a -Br or a -Cl. Although, typically -I is the best leaving group.

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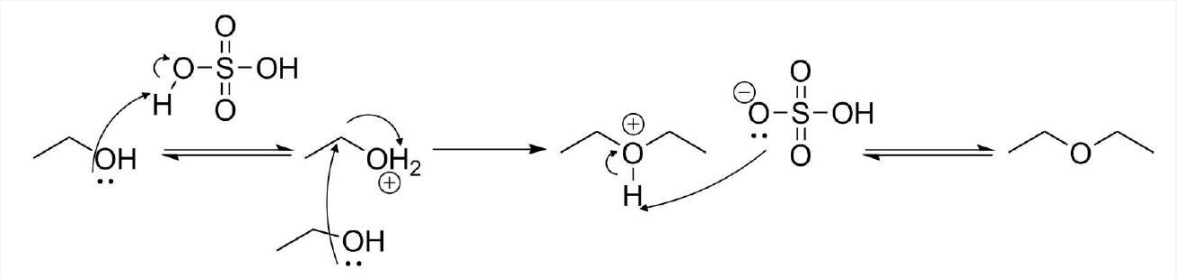
Note, there is only one ether (also called a silyl ether, and often used as an alcohol protecting group.) The other group is an ester.



EXERCISE 18.2.3

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

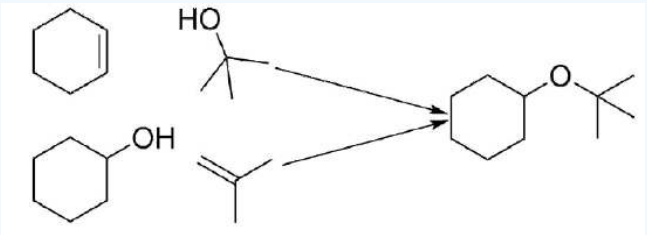
Answer



EXERCISE 18.2.4

t-Butoxycyclohexane can be prepared two different ways from an alkene and an alcohol, draw both possible reactions.

Answer



While both are possible, the top route is likely easier because both starting materials are a liquid.

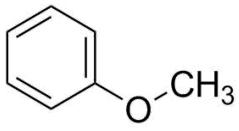
QUESTIONS

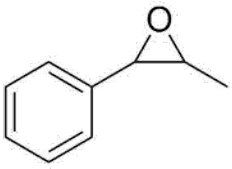
Q18.2.1

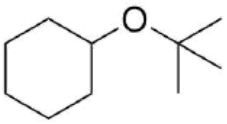
When preparing ethers using the Williamson ether synthesis, what factors are important when considering the nucleophile and the electrophile?

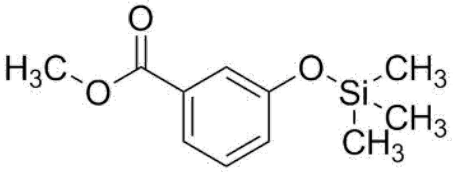
Q18.2.2

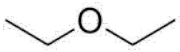
How would you synthesize the following ethers? Keep in mind there are multiple ways. The Williamson ether synthesis, alkoxymercuration of alkenes, and also the acid catalyzed substitution.

(a) 

(b) 

(c) 

(d) 

(e) 

Q18.2.3

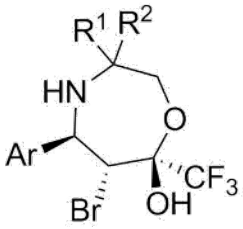
Draw the electron arrow pushing mechanism for the formation of diethyl ether in the previous problem.

Q18.2.4

Ether C from problem 26 can also be prepared from an alkene and an alcohol, draw these two. (There are two possibilities for the alcohol and alkene)

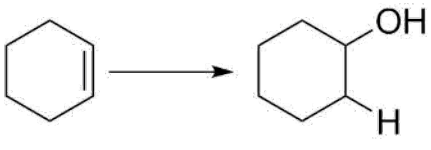
Q18.2.5

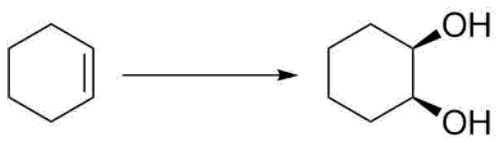
Epoxides are often formed intramolecularly. Take for example this large ring, in a publication from 2016 [*J. Org. Chem.*, **2016**, *81 (20)*, pp 10029–10034]. If subjected to base, what epoxide would be formed? (Include stereochemistry)

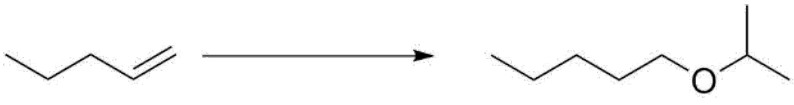


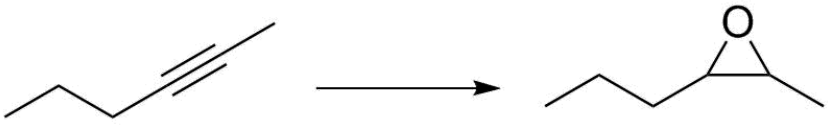
Q18.2.6

What reagents would you use to perform the following transformations?

(a) 

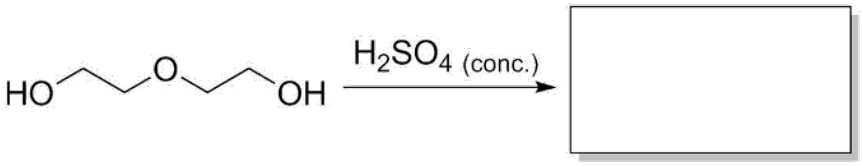
(b) 

(c) 

(d) 

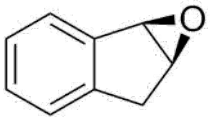
Q18.2.7

Predict the product of the following.



Q18.2.8

If the following epoxide were subjected to a general nucleophile, Nu, what would be the major product?



SOLUTIONS

S18.2.1

The nucleophile ideally should be very basic, yet not sterically hindered. This will minimize any elimination reactions from occuring. The electrophile should have the characteristics of a good Sn2 electrophile, preferably primary to minimize any elimination reactions from occuring.

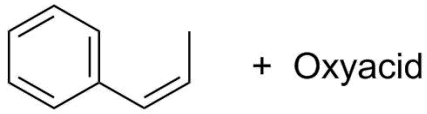
S18.2.2

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.

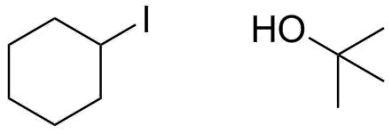
(a)



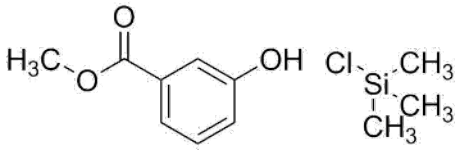
(b)



(c)

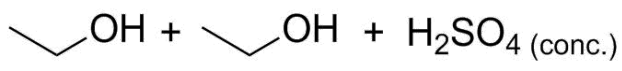


(d)

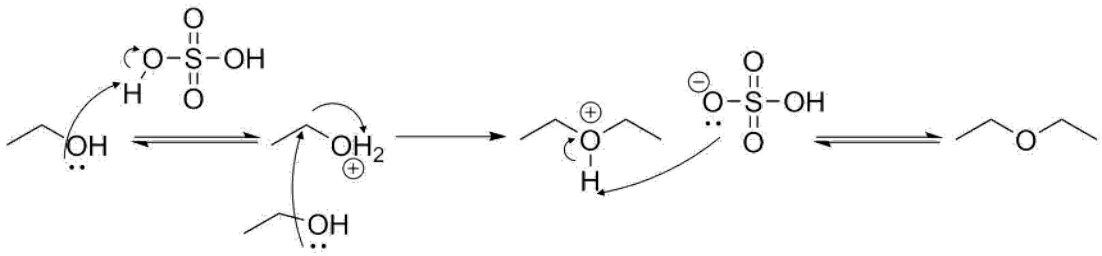


Note, there is only one ether (also called a silyl ether, and often used as an alcohol protecting group.) The other group is an ester.

(e)

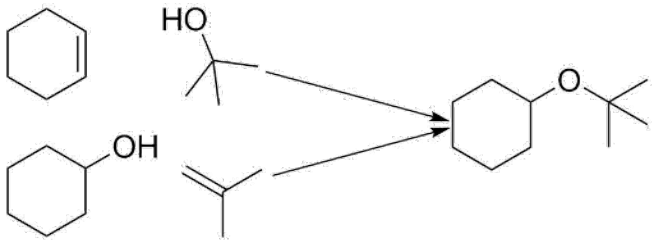


S18.2.3



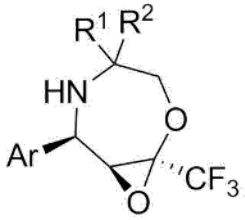
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S18.2.4



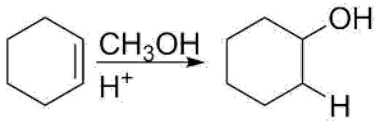
While both are possible, the top route is likely easier because both starting materials are a liquid.

S18.2.5

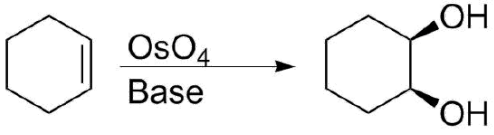


S18.2.6

(a)

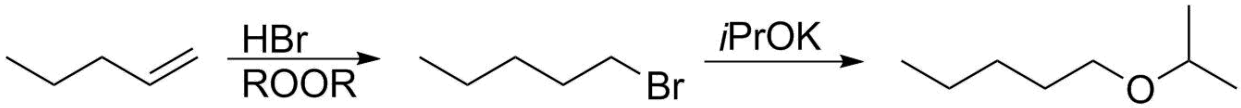


(b)



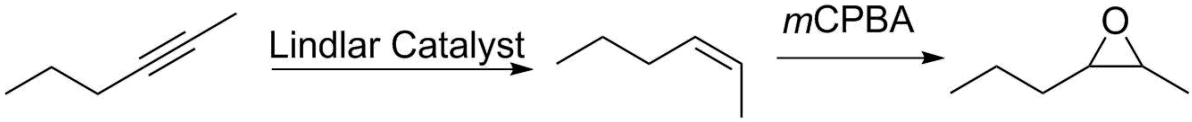
Note the cis addition

(c)



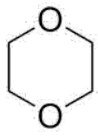
An oxidation to an alcohol through hydroboration, and subsequent substitution with 2-bromopropane could also work, but this route provides the least likelihood of an elimination reaction occurring.

(d)



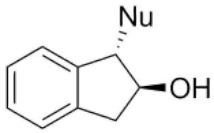
Lindlar's catalyst reduces alkynes to cis/Z alkenes. This stereochemistry is retained after epoxidation.

S18.2.7



The result is the production of dioxane, a common solvent.

S18.2.8



The regiochemistry is determined by the slight electron withdrawing effect of the adjacent benzene ring. The stereochemistry is determined by the stereospecific Sn2 mechanism.

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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18.3 REACTIONS OF ETHERS: ACIDIC CLEAVAGE

Objectives

After completing this section, you should be able to:

1. write an equation to illustrate the acidic cleavage of an ether.
2. identify the products formed when a given ether is cleaved by a strong acid.
3. identify the reagent needed to bring about cleavage of a given ether.
4. deduce the structure of an unknown ether, given the products of acidic cleavage of the ether.
5. write the detailed mechanism for the acidic cleavage of a given ether.

STUDY NOTES

There are a number of points in this section that require additional explanations.

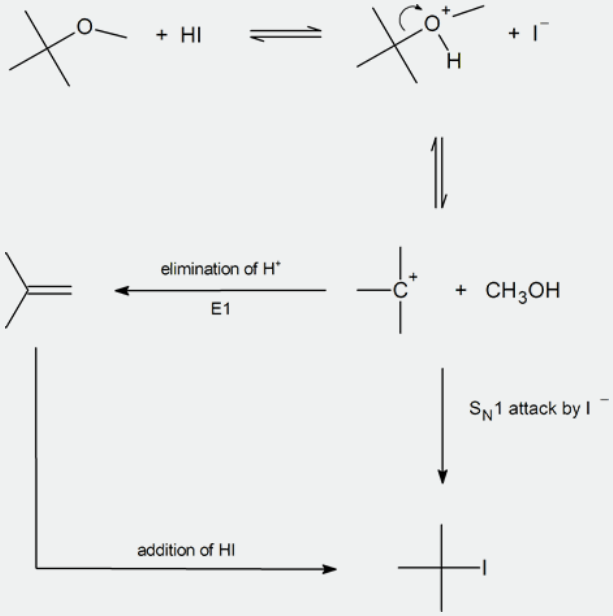
First, if an excess of HI (or HBr) is used in the cleavage reaction, the alcohol formed is converted by a nucleophilic substitution reaction to the appropriate alkyl halide:

$ROH + HI \rightarrow RI + H_2O$

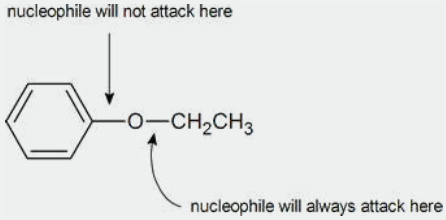
In view of this substitution, some textbooks simplify the overall cleavage process as:

$R{-}O{-}R' + 2HI \rightarrow RI + R'I + H_2O$

Second, we should consider in detail how certain ethers (those containing tertiary alkyl, benzyl or allyl groups) cleave by an S_N1 mechanism:

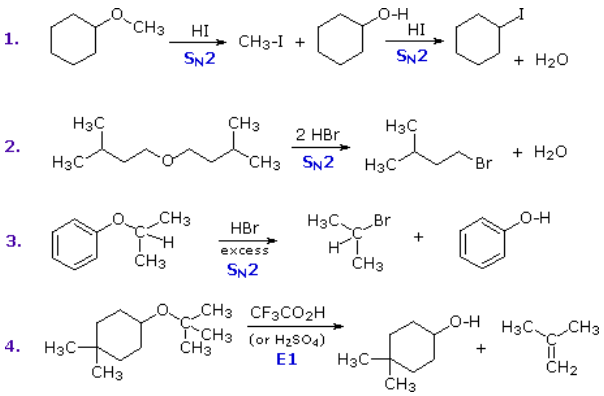


Finally, notice that an aryl alkyl ether will always produce a phenol and an alkyl halide, never an aryl halide and an alcohol. This is because we rarely see a nucleophile attacking an aromatic ring carbon in preference to an aliphatic carbon:



As phenols do not undergo nucleophilic substitution reactions, even if an excess of HX is used, the products from the cleavage of an aryl alkyl ether are a phenol and an alkyl halide. Diaryl ethers are not cleaved by acids.

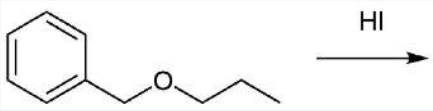
The most common reaction of ethers is cleavage of the C–O bond by strong acids. This may occur by S_N1 or E1 mechanisms for 3º-alkyl groups or by an S_N2 mechanism for 1º-alkyl groups. Some examples are shown in the following diagram. The conjugate acid of the ether is an intermediate in all these reactions, 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. The reaction shown here (#4) is the reverse of the tert-butyl ether preparation described earlier.

? WORKED EXAMPLE 18.3.1

Predict the products of the following reaction:



Answer

Analysis: When considering the acidic cleavage of ethers it is important to realize that S_N2, S_N1, or E1 reactions are possible depending on the conditions. First, identify if the ether has a substituent which can easily form a carbocation: tertiary, benzylic, or allylic substituents. If none of these substituents are present the reaction will most likely be S_N2. However, if one of the substituents is present the reaction will most likely be S_N1 or E1. Next, identify if the reaction conditions will allow for an E1 reaction. These are the presence of a tertiary alkyl substituent on the ether along with the use of a strong acid which has a poor nucleophile as a conjugate base. If this set of conditions is not present the reaction will most likely be S_N1.

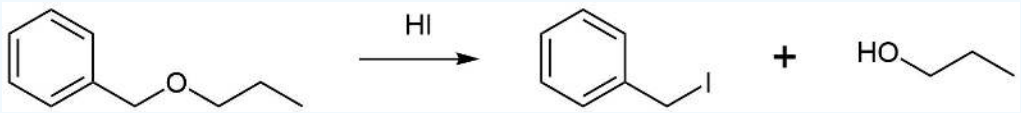
For a S_N2 reaction: The less hindered alkyl substituent of the ether will become a halogen. The other alkyl substituent will become an alcohol.

For a S_N1 reaction: The substituent which easily forms a carbocation will become a halogen and the other alkyl substituent will become an alcohol.

For an E1 reaction: The tertiary alkyl substutent will form an alkene and the other alkyl substiutent will become an alcohol.

For the reaction proposed above, the reactant contains a benzylic substituent so the reaction will most likely be S_N1. Consequently, the benzylic substituent will become and Iodide product and the propyl substituent will become an alcohol.

Solution

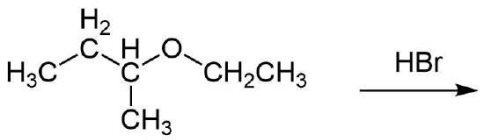


EXERCISES

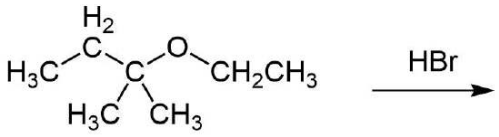
EXERCISE 18.3.1

Predict the product of the following reactions:

a)

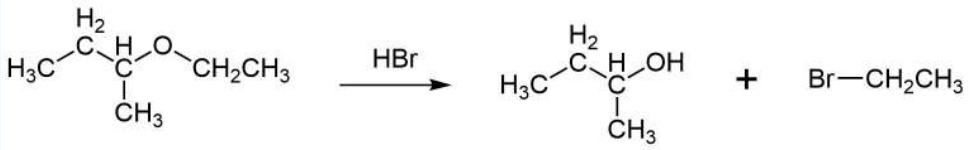


b)

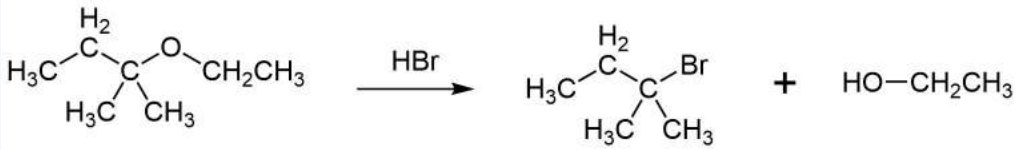


Answer

a)

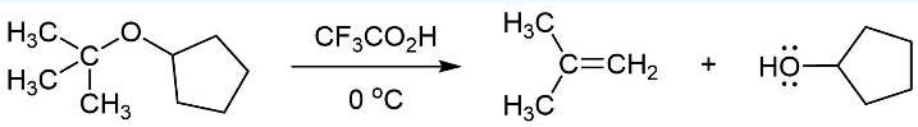


b)

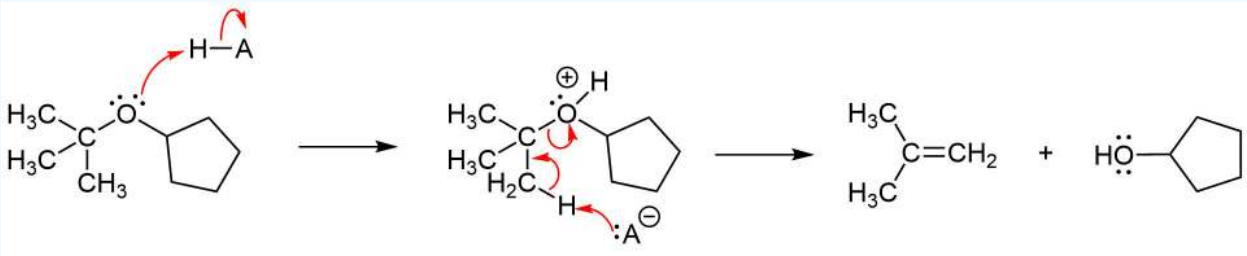


EXERCISE 18.3.2

Please draw the mechanism for the following reaction:



Answer



EXERCISE 18.3.3

Why is HCl less effective at cleaving ethers than HBr or HI?

Answer

HCl's conjugate base Cl^- is a poor nucleophile when compared to Br^- and I^-. The chloride anion is not a strong enough nucleophile to promote the acidic cleavage of ethers.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
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18.4 REACTIONS OF ETHERS - CLAISEN REARRANGEMENT

Objectives

After completing this section, you should be able to:

1. write an equation to represent the Claisen rearrangement of allyl phenyl ester.
2. account for the formation of a specific product from a Claisen rearrangement, without giving mechanistic details.

KEY TERMS

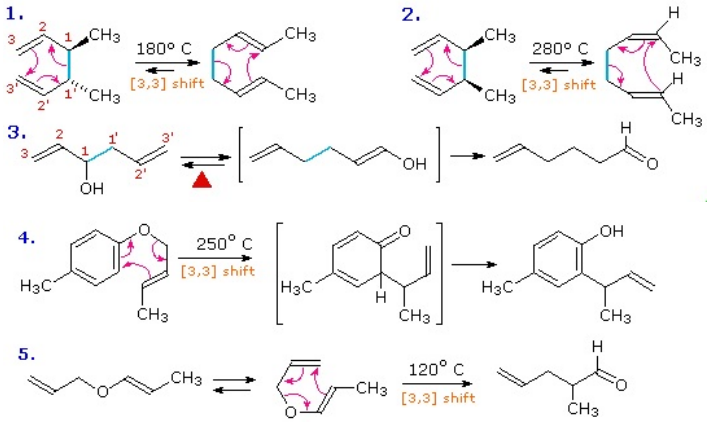
Make certain that you can define, and use in context, the key term below:

- Claisen rearrangement

COPE AND CLAISEN REARRANGEMENTS

The [3,3] sigmatropic rearrangement of 1,5-dienes or allyl vinyl ethers, known respectively as the Cope and Claisen rearrangements, are among the most commonly used sigmatropic reactions. Three examples of the Cope rearrangement are shown in the following diagram. Reactions 1 and 2 (top row) demonstrate the stereospecificity of this reaction. The light blue σ-bond joins two allyl groups, oriented so their ends are near each other. Since each allyl segment is the locus of a [1,3] shift, the overall reaction is classified as a [3,3] rearrangement. The three pink colored curved arrows describe the redistribution of three bonding electron pairs in the course of this reversible rearrangement. The diene reactant in the third reaction is drawn in an extended conformation. This molecule must assume a coiled conformation (as above) before the [3,3] rearrangement can take place. The product of this rearrangement is an enol which immediately tautomerizes to its keto form. Such variants are termed the oxy-Cope rearrangement, and are useful because the reverse rearrangement is blocked by rapid ketonization. If the hydroxyl substituent is converted to an alkoxide salt, the activation energy of the rearrangement is lowered significantly.

The degenerate or self-replicating Cope rearrangement has been a fascinating subject of research. For examples .



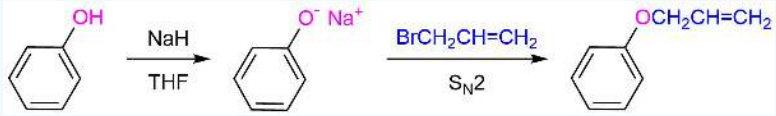
Two examples of the Claisen Rearrangement may be seen. Reaction 4 is the classic rearrangement of an allyl phenyl ether to an ortho-allyl phenol. The methyl substituent on the allyl moiety serves to demonstrate the bonding shift at that site. The initial cyclohexadienone product immediately tautomerizes to a phenol, regaining the stability of the aromatic ring. Reaction 5 is an aliphatic analog in which a vinyl group replaces the aromatic ring. In both cases three pairs of bonding electrons undergo a reorganization.

EXERCISES

? EXERCISE 18.4.1

Show how you could synthesize allyl phenyl ether from allyl bromide and phenol.

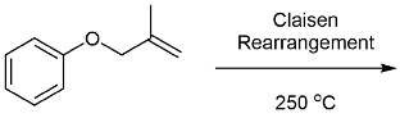
Answer



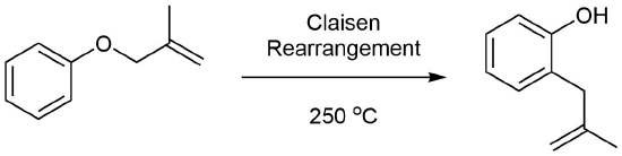
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EXERCISE 18.4.2

What would be the expected product of the following Claisen rearrangement?



Answer



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

18.4 Reactions of Ethers - Claisen Rearrangement is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

18.5 CYCLIC ETHERS: EPOXIDES

Objectives

After completing this section, you should be able to

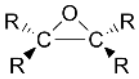
1. write an equation to describe the industrial preparation of ethylene oxide.
2. list two important industrial uses of ethylene oxide.
3. write an equation to describe the normal laboratory preparation of an epoxide.
4. identify the epoxide produced from the reaction of a given alkene with a peroxyacid.
5. identify the alkene, the reagent, or both, needed to prepare a given epoxide.
6. write an equation to describe the preparation of an epoxide from an alkene via a halohydrin.

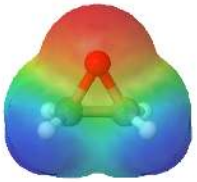
KEY TERMS

Make certain that you can define, and use in context, the key term below.

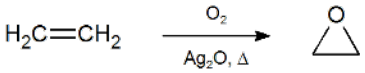
- epoxide (oxirane)

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. Epoxides behave differently than other ethers due to the strain created by the three-membered ring.



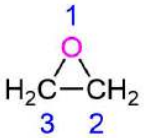


The most important and simplest epoxide is ethylene oxide which is prepared on an industrial scale by catalytic oxidation of ethylene by air. Ethylene oxide is used as an important chemical feedstock in the manufacturing of ethylene glycol, which is used as antifreeze, liquid coolant and solvent. In turn, ethylene glycol is used in the production of polyester and polyethylene terephthalate (PET) the raw material for plastic bottles.



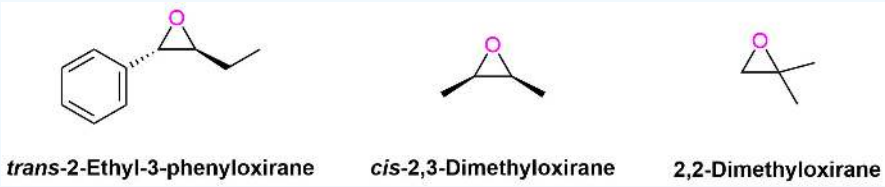
NOMENCLATURE OF EPOXIDES

The name ethylene oxide is not systematic but common. Epoxides are systematically named as an oxirane ring system much like the other cyclic ethers discussed in Section 18.1. The oxygen is numbered in the 1 position.



Oxirane

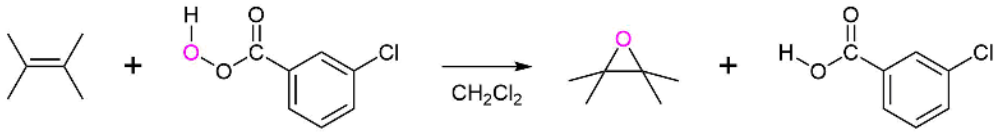
EXAMPLE 18.5.1



SYNTHESIS OF EPOXIDES

As discussed in Section 8-7, epoxides are typically prepared by the reaction of an alkene and a peroxycarboxylic acid (RCO_3H), such as *meta*-chloroperbenzoic acid (MCPBA). The peroxycarboxylic acid has the unique property of having an electropositive oxygen atom on the CO_3H 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 CO_3H group becomes CO_2H.

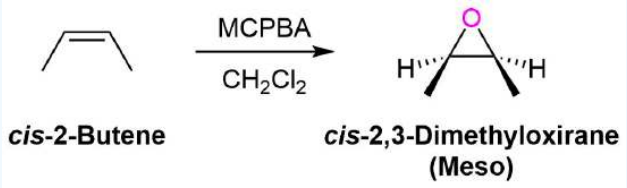
General Reaction

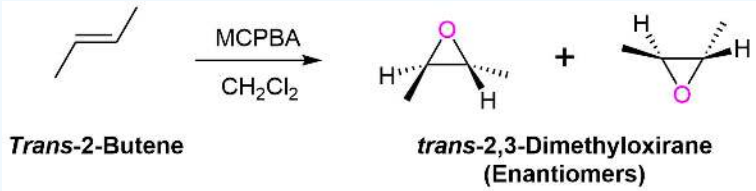


Stereochemical Consideration

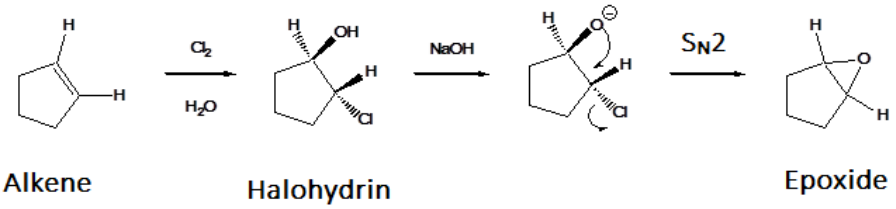
The oxygen addition to the alkene is a syn addition and is stereospecific. The substituents of a *cis*-alkene will appear in the *cis* configuration on the epoxide ring. Likewise, Substituents of a *trans*-alkene will appear in the *trans* configuration on the epoxide ring. During this reaction the sp^2 hybridized carbons of the alkene are converted to sp^3 hybridized carbons in the epoxide. Thus, there is the possibility of two new chiral carbons forming in the epoxide product. In most cases, epoxidation of an alkene will product a mixture of enantiomers in the product, due to the electrophilic oxygen being able to attack from above or below the plane of the alkene. One major exception is the epoxidation of symmetrical cis-alkene which produces a meso compound product.

EXAMPLE 18.5.2





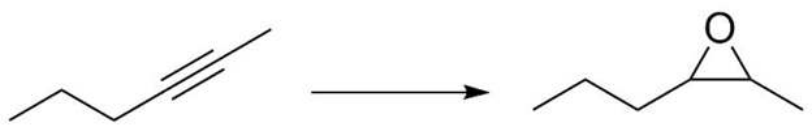
Treatment of an alkene with X_2 & H_2O creates a halohydrin (Section 8-3). When a halohydrin is treated with a base the alcohol is deprotonated to from an alkoxide. This causes an intramolecular Williamson ether synthesis to produce an epoxide along with the elimination of HX. Note, that this reaction generally forms a mixture of enantiomeric products unless a meso compound is produced.



EXERCISES

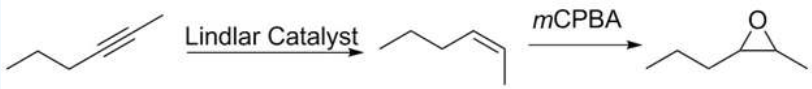
EXERCISE 18.5.1

What reagents would you use to perform the following transformation?



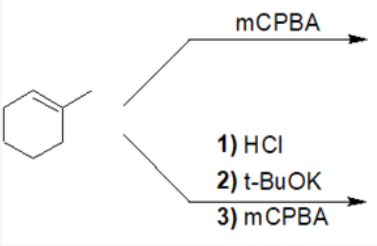
Answer

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

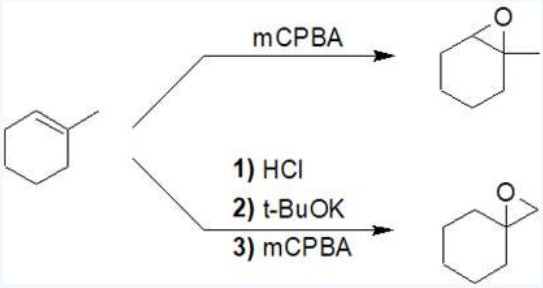


EXERCISE 18.5.2

Predict the products of the following reactions:



Answer



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."

18.5 Cyclic Ethers: Epoxides is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

18.6 REACTIONS OF EPOXIDES: RING-OPENING

Objectives

After completing this section, you should be able to

1. write an equation to describe the opening of an epoxide ring under mildly acidic conditions.
   a. identify the product formed from the hydrolysis of an epoxide.
   b. write the mechanism for the opening of an epoxide ring by an aqueous acid, paying particular attention to the stereochemistry of the product.
   c. identify the product formed when an epoxide ring is opened by a hydrogen halide under anhydrous conditions.
2. predict the major product from the acidic cleavage of a given unsymmetrical epoxide.
3. write an equation to illustrate the cleavage of an epoxide ring by a base.
   a. identify the product formed from the reaction of a given epoxide with given base.
   b. explain why epoxides are susceptible to cleavage by bases, whereas other cyclic ethers are not.

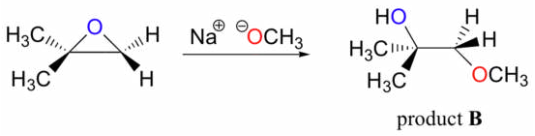
STUDY NOTES

In the discussion on base-catalyzed epoxide opening, the mechanism is essentially S_N2. While oxygen is a poor leaving group, the ring strain of the epoxide really helps to drive this reaction to completion. Indeed, larger cyclic ethers would not be susceptible to either acid-catalyzed or base-catalyzed cleavage under the same conditions because the ring strain is not as great as in the three-membered epoxide ring.

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

The nonenzymatic ring-opening reactions of epoxides provide a nice overview of many of the concepts we have seen already in this chapter. 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. 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 attack, leading to what we will refer to as product B:

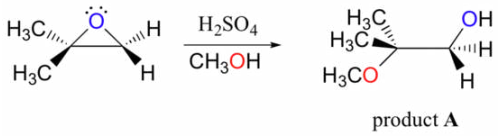
basic ring-opening:



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 attack. As a result, product A predominates.

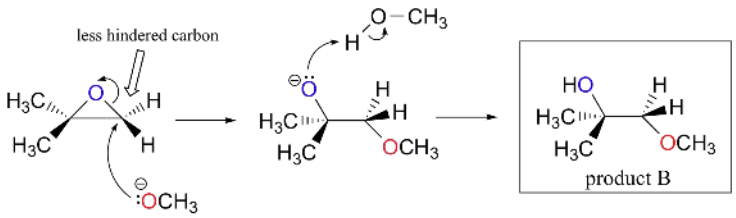
acidic ring-opening:



product **A**

These are both 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).

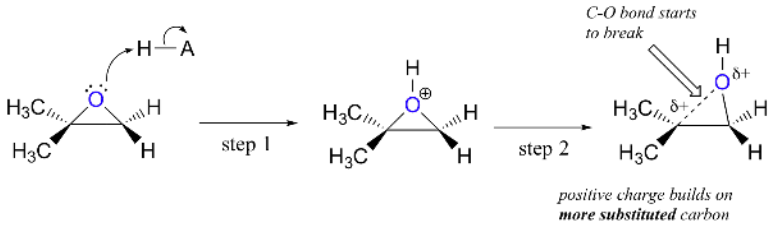
Let us examine the basic, S_N2 case first. The leaving group is an alkoxide anion, because there is no acid available to protonate the oxygen prior to ring opening. An alkoxide is a poor leaving group, and thus the ring is unlikely to open without a 'push' from the nucleophile.



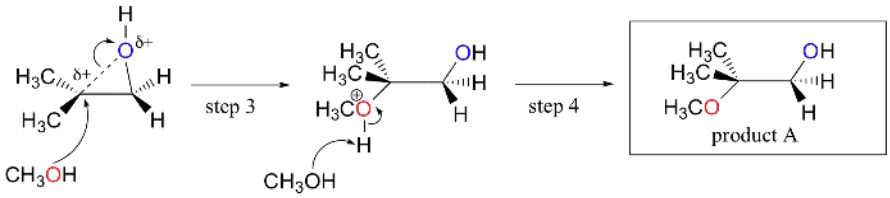
The nucleophile itself is potent: a deprotonated, negatively charged methoxide ion. When a nucleophilic substitution reaction involves a poor leaving group and a powerful nucleophile, it is very likely to proceed by an S_N2 mechanism.

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, nucleophilic attack takes place from the backside, resulting in inversion at the electrophilic carbon.

Probably the best way to depict the acid-catalyzed epoxide ring-opening reaction is as a hybrid, or cross, between an S_N2 and S_N1 mechanism. 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 the discussion from section 8.4B about carbocation stability).



Unlike in an S_N1 reaction, the nucleophile attacks the electrophilic carbon (step 3) before a complete carbocation intermediate has a chance to form.

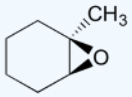


Attack takes place preferentially from the backside (like in an S_N2 reaction) because the carbon-oxygen bond is still to some degree in place, and the oxygen blocks attack from the front side. Notice, however, how the regiochemical outcome is different from the base-catalyzed reaction: in the acid-catalyzed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

EXAMPLE 18.6.1

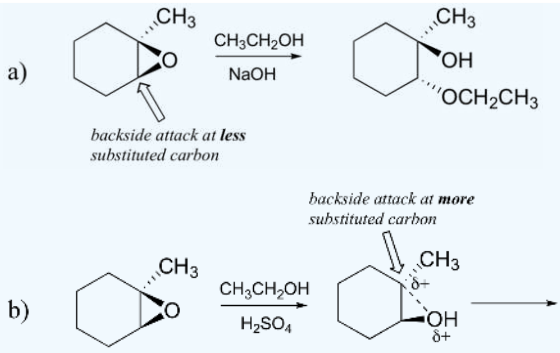
Predict the major product(s) of the ring opening reaction that occurs when the epoxide shown below is treated with:

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!*

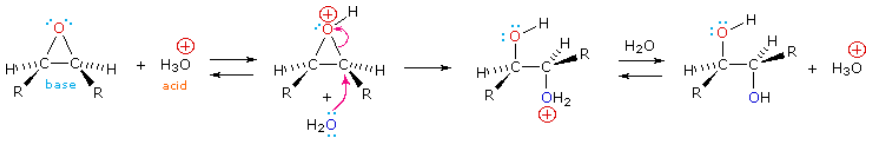
Answer



ANTI DIHYDROXYLATION

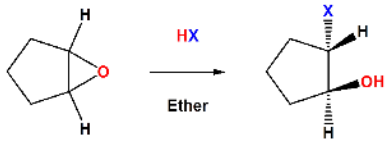
EDIT SECTION

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.

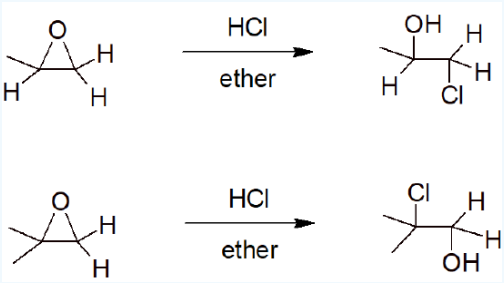


ADDITION OF HX

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 attack the less substituted carbon and an S_N2 like reaction. However, if one of the epoxide carbons is tertiary, the halogen anion will primarily attack the tertiary carbon in a S_N1 like reaction.



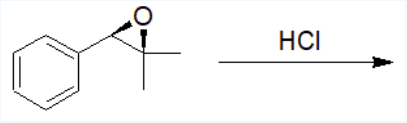
✔ EXAMPLE 18.6.2



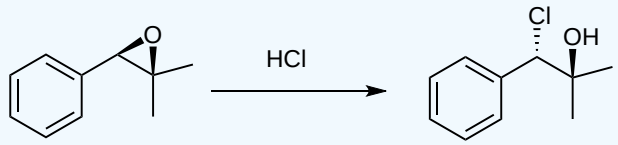
EXERCISES

? EXERCISE 18.6.1

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



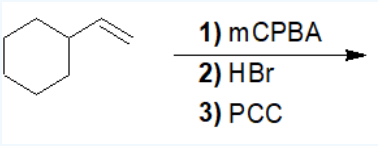
Answer



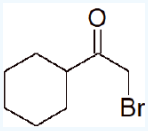
The ring side of the protonated epoxide intermediate will better stabilize a partial positive charge, so would be the more likely carbon for the chloride ion to attack.

EXERCISE 18.6.2

Predict the product of the following reaction.

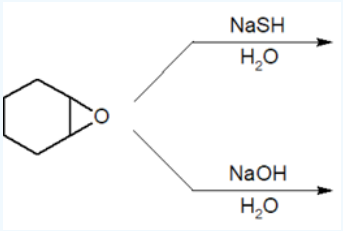


Answer

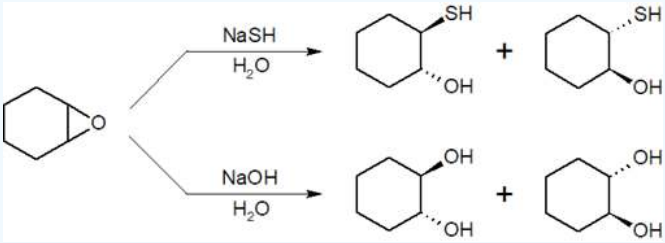


EXERCISE 18.6.3

Provide the final products of the following reactions.



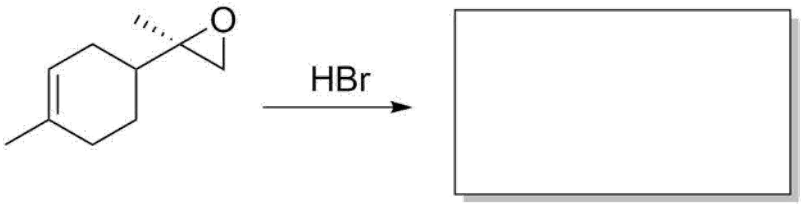
Answer



QUESTIONS

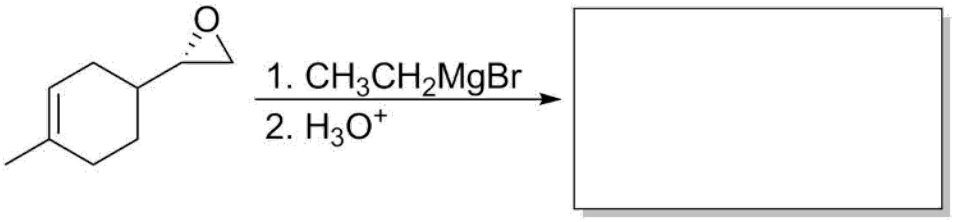
Q18.6.1

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



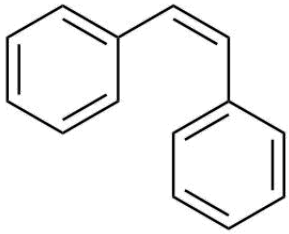
Q18.6.2

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



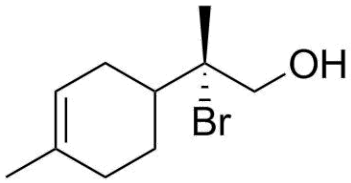
Q18.6.3

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?



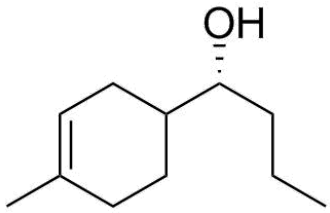
SOLUTIONS

S18.6.1



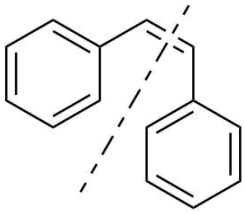
Note that the stereochemistry has been inverted

S18.6.2

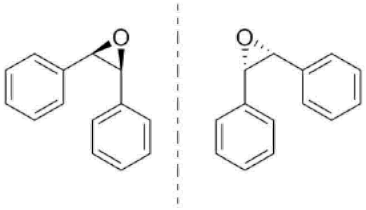


S18.6.3

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.

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

18.6 Reactions of Epoxides: Ring-opening is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

18.7 CROWN ETHERS

Objectives

After completing this section, you should be able to

1. write the normally accepted name for a crown ether, given its structure.
2. draw the structure of a crown ether, given its normally accepted name.
3. describe, briefly, the uses of crown ethers.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- crown ether

STUDY NOTES

A "crown ether " is a cyclic ether containing several (i.e., 4, 5, 6 or more) oxygen atoms. As we have indicated in the objectives above, a detailed knowledge of these compounds is not required in this course.

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.

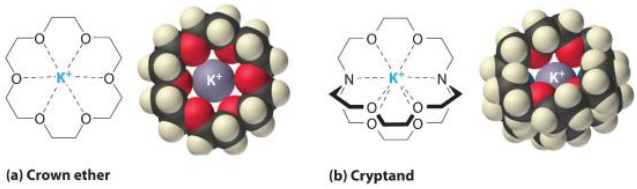


Figure 18.7.1: *Crown Ethers and Cryptands (a) The potassium complex of the crown ether 18-crown-6. Note how the cation is nestled within the central cavity of the molecule and interacts with lone pairs of electrons on the oxygen atoms. (b) The potassium complex of 2,2,2-cryptand, showing how the cation is almost hidden by the cryptand. Cryptands solvate cations via lone pairs of electrons on both oxygen and nitrogen atoms.*



Figure 18.7.2: Effect of a Crown Ether on the Solubility of $KMnO_4$ 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, $KMnO_4$ 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.

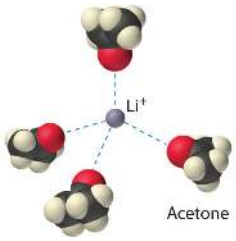


Figure 18.7.3: *Ion–Dipole Interactions in the Solvation of Li^+ Ions by Acetone, a Polar Solvent*

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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18.8 THIOLS AND SULFIDES

Objectives

After completing this section, you should be able to

1. 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

Note: All of these terms are defined in the "Study Notes," below.

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

STUDY NOTES

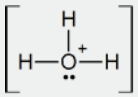
The chemistry of sulfur-containing organic compounds is often omitted from introductory organic chemistry courses. However, we have included a short section on these compounds, not for the sake of increasing the amount of material to be digested, but because much of the chemistry of these substances 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.

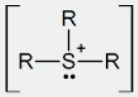
(Organic) sulfides have the structure R—S—R′, and are therefore the sulfur analogues of ethers. The nomenclature of sulfides can be easily understood if one understands the nomenclature of the corresponding ethers. Notice that the term "thio" is also used in inorganic chemistry. For example, SO_4^{2-} 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.

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:



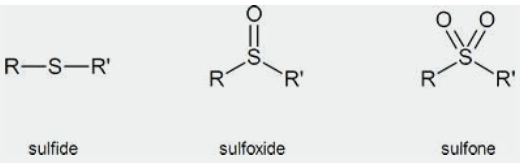
hydronium ion



trialkylsulfonium ion

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.



sulfide sulfoxide sulfone

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

Oxygen-containing Compound	Sulfur Analogue
ether, R—O—R′	sulfide, 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′, disulfide

Table 18.1 Comparison of compounds containing oxygen and sulfur

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

EDIT SECTION

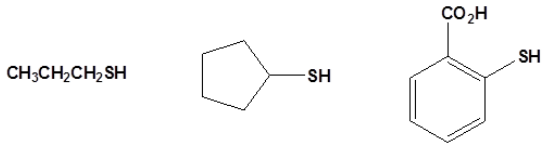
Oxygen assumes only two oxidation states in its organic compounds (–1 in peroxides and –2 in other compounds). Sulfur, on the other hand, is found in oxidation states ranging from –2 to +6, as shown in the following table (some simple inorganic compounds are displayed in orange).

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-R sulfite esters	SO_3 R-O–S(=O)(=O)–O-R sulfate esters

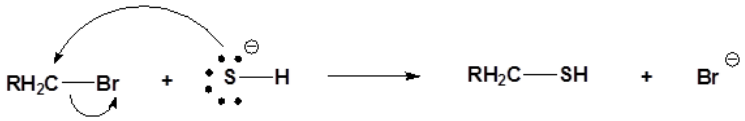
THIOLS

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.

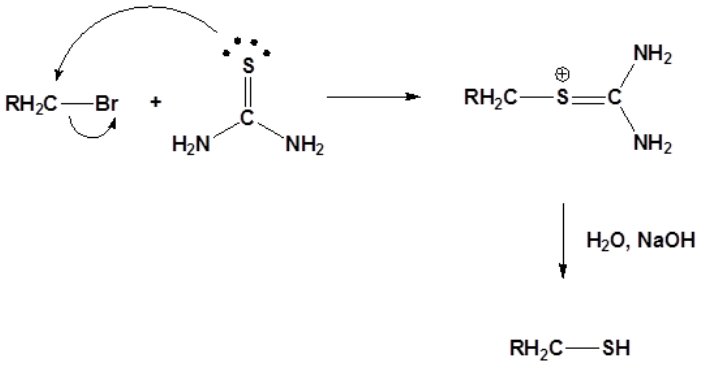


Propanethiol **Cyclopentanethiol** **o-Mercaptobenzoic acid**

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

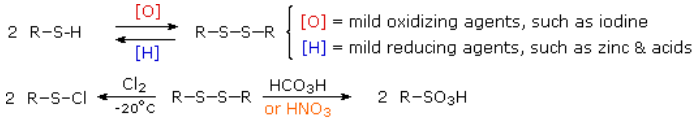


On problem with this reaction is that the thiol product can undergo a second S_N2 reaction with an additional alkyl halide to produce a sulfide side product. This problem can be solved by using thiourea, $(NH_2)_2C=S$, as the nucleophile. The reaction first produces an alkyl isothiourea salt and an intermediate.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



DISULFIDES

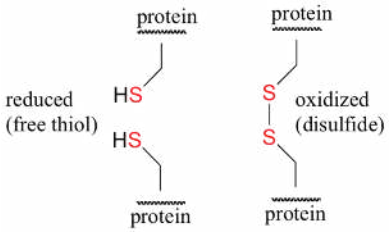
Oxidation of thiols and other sulfur compounds changes the oxidation state of sulfur rather than carbon. We see some representative sulfur oxidations in the following examples. In the first case, mild oxidation converts thiols to disufides. An equivalent oxidation of alcohols to peroxides is not normally 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.



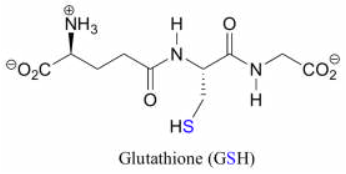
DISULFIDE BRIDGES IN PROTEINS

EDIT SECTION

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'.

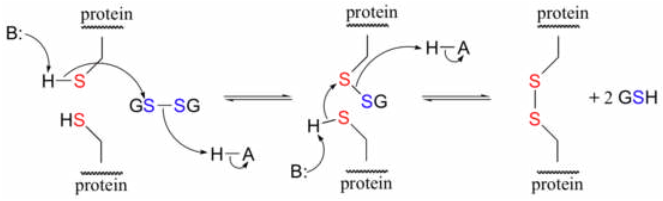


Glutathione (GSH)

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.

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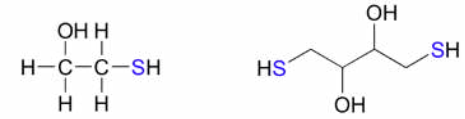


In its reduced (thiol) state, glutathione can reduce disulfides bridges in proteins through the reverse of the above reaction.

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.

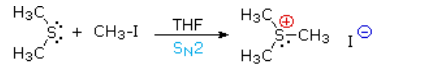


SULFIDES

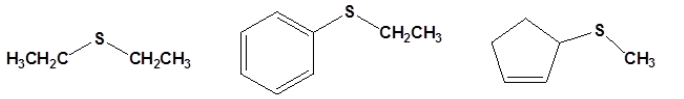
Sulfur analogs of ethers are called **sulfides**. The chemical behavior of sulfides contrasts with that of ethers in some important ways. Since hydrogen sulfide (H_2S) is a much stronger acid than water (by more than ten million fold), we expect, and find, thiols to be stronger acids than equivalent 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.

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

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 3°-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. 

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.

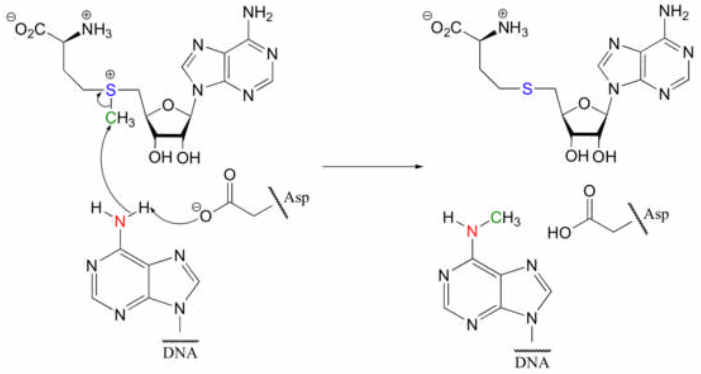


Diethyl sulfide Ethyl phenyl sulfide 3-(Methylthio)cyclopentene

SAM METHYLTRANSFERASES [EDIT SECTION]

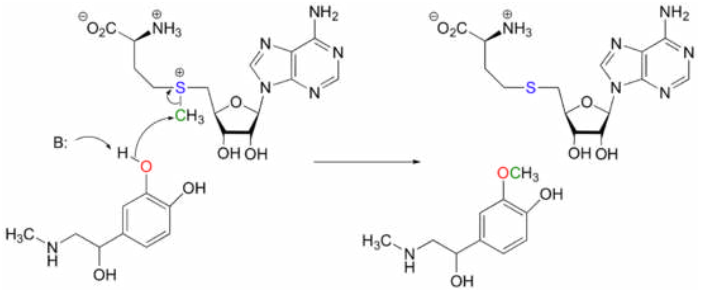
The most common example of sulfonium ions in a living organism is the reaction of S-Adenosylmethionine. Some of the most important examples of S_N2 reactions in biochemistry are those catalyzed by S-adenosyl methionine (SAM) – dependent methyltransferase enzymes. We have already seen, in chapter 6 and 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:

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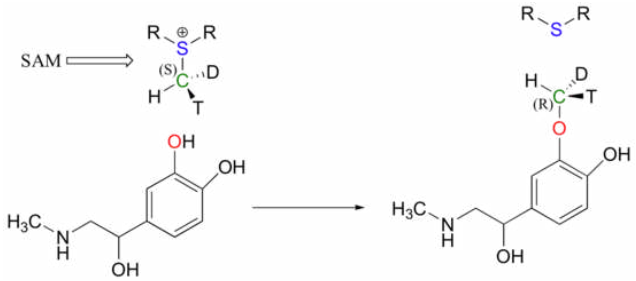
(*Nucleic Acids Res.* **2000**, *28*, 3950).

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



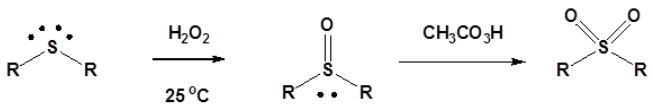
Notice that in this example, the attacking nucleophile is an alcohol rather than an amine (that's why the enzyme is called an O-methyltransferase). In both cases, though, a basic amino acid side chain is positioned in the active site in just the right place to deprotonate the nucleophilic group as it 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:

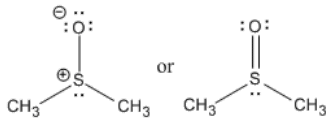


Here, the methyl group of SAM was made to be chiral by incorporating hydrogen isotopes tritium (^{3}H, T) and deuterium (^{2}H, D). The researchers determined that the reaction occurred with inversion of configuration, as expected for an S_N2 displacement (*J. Biol. Chem.* **1980,** *255*, 9124).

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.



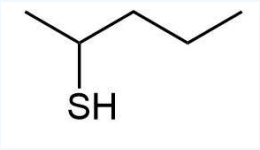
DMSO is a very polar, aprotic solvent

EXERCISES

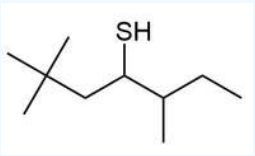
? EXERCISE 18.8.1

Give IUPAC names the following compounds:

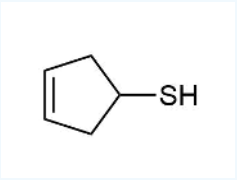
a)



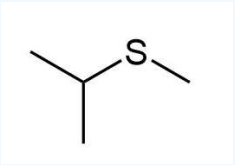
b)



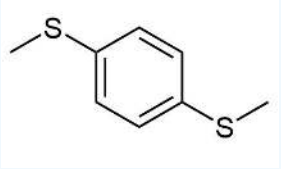
c)



d)

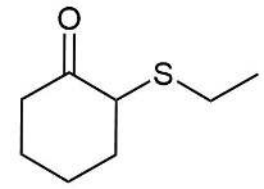


e)



f)

https://chem.libretexts.org/@go/page/90959



Answer

a) 2-Pentanethiol

b) 2,2,5-Trimethyl-4-heptanethiol

c) 3-Cyclopentene-1-thiol

d) Methyl isopropyl sulfide

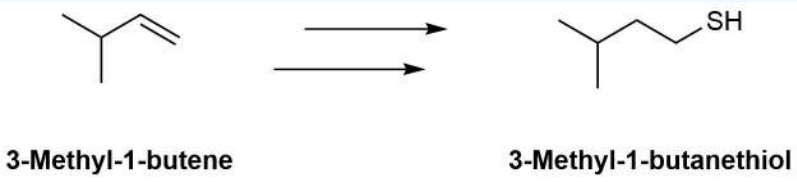
e) *p*-Di(methylthio)benzene

f) 2-(Ethylthio)cyclohexanone

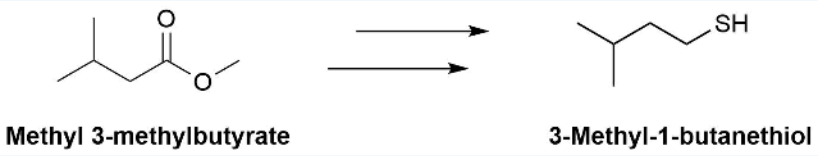
EXERCISE 18.8.2

The molecule 3-methyl-1-butanethiol has been shown to be one of the components of skunk spray. How would make the following conversions?

a)



b)



Answers

a) 1) HBr & Peroxides, 2) $(NH_2)_2C=S$, 3) NaOH & H_2O

b) 1) $LiAlH_4$, 2) H_3O^+, 3) PBr_3, 4) $(NH_2)_2C=S$, 5) NaOH & H_2O

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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18.9 SPECTROSCOPY OF ETHERS

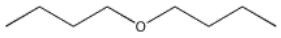
Objectives

After completing this section, you should be able to

1. use the ^{1}H NMR spectrum of an unknown ether or epoxide to determine its identity.
2. identify the approximate chemical shift expected for protons attached to the carbon atoms that are bonded to oxygen in an ether or an epoxide.

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.

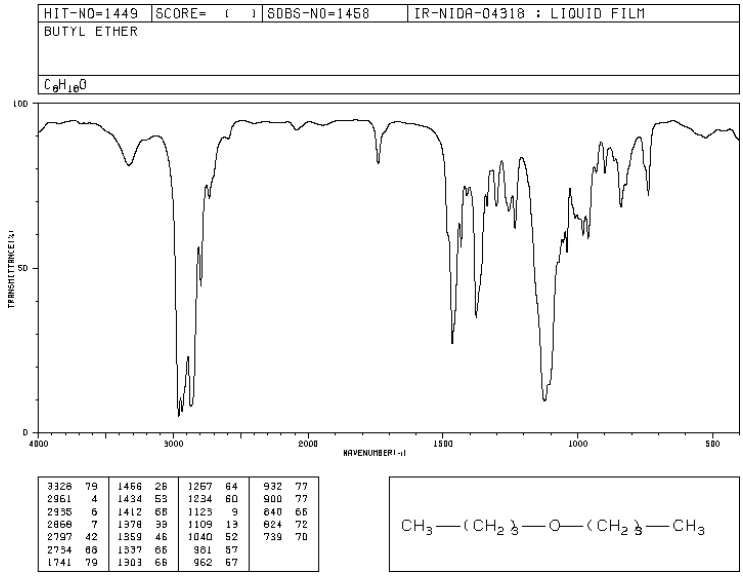
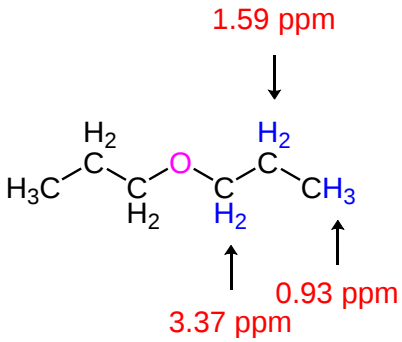


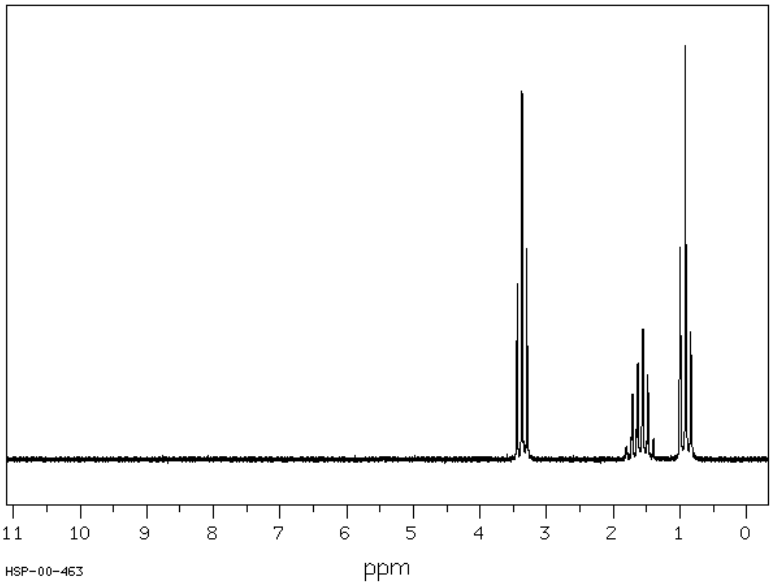
Figure IR7. *IR spectrum of dibutyl ether. Source: SDBSWeb: http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 30 March 2021)*

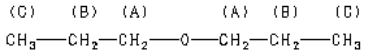
NMR SPECTROSCOPY

- 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)







CONTRIBUTORS AND ATTRIBUTIONS

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

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CHAPTER 18 - AFFIX: A PREVIEW OF CARBONYL COMPOUNDS

So far, in our survey of the oxygen-containing organic compounds, we have studied the chemistry of ethers and alcohols. Now we turn our attention to a much larger group of compounds—those containing a carbonyl group:



The variety of carbonyl compounds is so wide, and their chemistry so extensive, that we shall need the next five chapters to discuss them thoroughly. One advantage of this course is that we have divided up the discussion of carbonyl compounds so that this large amount of factual material can be studied in small, readily digestible blocks.

The purpose of this chapter is to provide a general outline of what is to follow in the next five chapters: the various types of carbonyl compounds are introduced, the nature of the carbonyl group is explained, and the four most common mechanisms by which carbonyl groups react are described in general terms.

CHAPTER OBJECTIVES

When you have completed this chapter, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. identify the various types of carbonyl compounds.
3. write the mechanism of each of the four general types of reactions discussed in the chapter.
4. define, and use in context, the key terms introduced in this chapter.

INTRODUCTION

OBJECTIVES

After completing this section, you should be able to give examples of the wide variety of biologically important, pharmaceutical and industrial compounds that contain one or more carbonyl groups.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- carbonyl group

STUDY NOTES

A “carbonyl group” consists of an sp^2-hybridized carbon atom that is joined to an oxygen atom by a double bond.

NATURAL OCCURRENCE OF ALDEHYDES AND KETONES

Aldehydes and ketones are widespread in nature and are often combined with other functional groups. Examples of naturally occurring molecules which contain a aldehyde or ketone functional group are shown in the following two figures. The compounds in the figure 1 are found chiefly in plants or microorganisms and those in the figure 2 have animal origins. Many of these molecular structures are chiral.

When chiral compounds are found in nature they are usually enantiomerically pure, although different sources may yield different enantiomers. For example, carvone is found as its levorotatory (R)-enantiomer in spearmint oil, whereas, caraway seeds contain the dextrorotatory (S)-enantiomer. In this case the change of the stereochemistry causes a drastic change in the perceived scent. Aldehydes and ketones are known for their sweet and sometimes pungent odors. The odor from vanilla extract comes from the molecule vanillin. Likewise, benzaldehyde provides a strong scent of almonds and is this author’s favorite chemical smell. Because of their pleasant fragrances aldehyde and ketone containing molecules are often found in perfumes. However, not all of the fragrances are pleasing. In particular, 2-Heptanone provides part of the sharp scent from blue cheese and (R)-Muscone is part of the musky smell from the Himalayan musk deer. Lastly, ketones show up in many important hormones such as progesterone (a female sex hormone) and testosterone (a male sex hormone). Notice how subtle differences in structure can cause drastic changes in biological activity. The ketone functionality also shows up in the anti-inflammatory steroid, Cortisone.

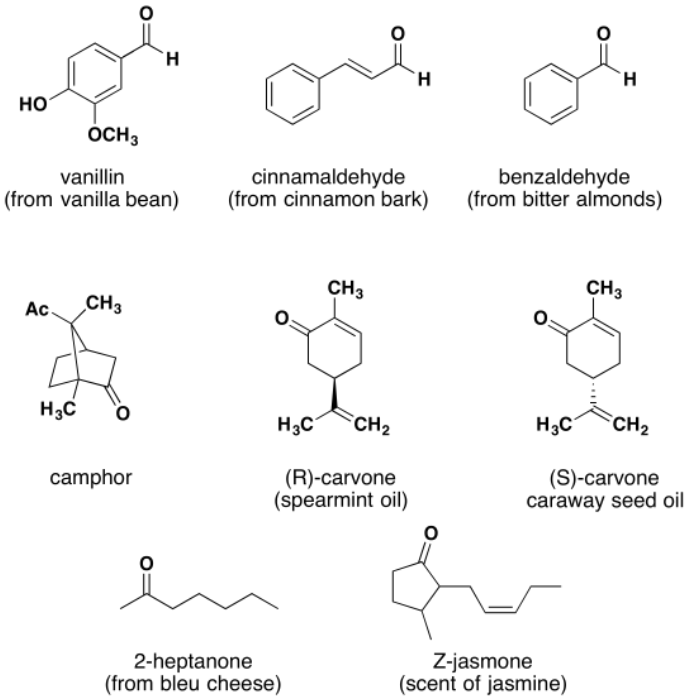


Figure 1. Aldehyde and ketone containing molecules isolated from plant sources.

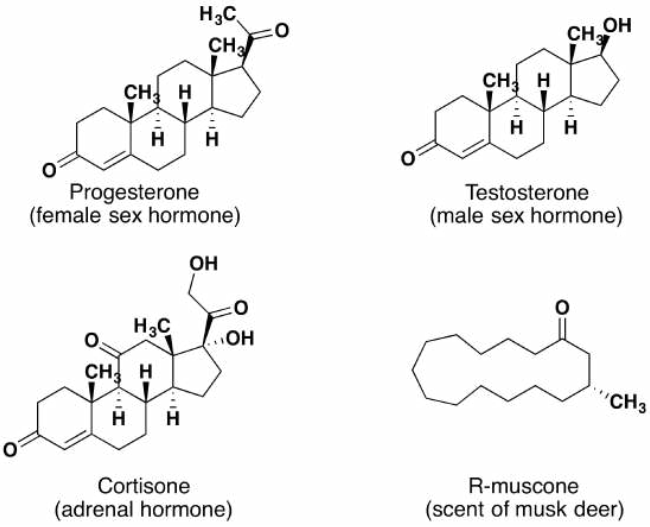


Figure 2. Aldehyde and ketone containing molecules isolated from animal sources.

CONTRIBUTORS AND ATTRIBUTIONS

Prof. Steven Farmer (Sonoma State University)

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

I KINDS OF CARBONYL COMPOUNDS

OBJECTIVES

After completing this section, you should be able to

1. identify the following types of compounds as containing carbonyl groups: aldehydes, ketones, carboxylic acids, acid chlorides, acid anhydrides, esters, lactones, amides and lactams.
2. identify the important difference between aldehydes and ketones, and the other types of compounds listed under Objective 1, above.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- acyl fragment or acyl group

STUDY NOTES

The idea of an “acyl group”

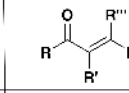
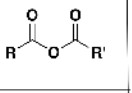


is not really new. Recall that in Chapter 16 we discussed the introduction of acyl groups into benzene rings by means of the Friedel-Crafts acylation reaction.

Note the use of the word “moiety” as an alternative to “group” or “fragment.”

Study the different types of carbonyl compounds listed in the table so that you can immediately recognize to which type a given compound belongs.

SOME CARBONYL COMPOUNDS

Compound	Aldehyde	Ketone	Formaldehyde	Carboxylic Acid	Ester	Amide	Enone	Acyl Halide	Acid Anhydride
Structure									
General Formula	RCHO	RCOR'	CH_2O	RCOOH	RCOOR'	RCONR'R''	RC(O)C(R')CR''R'''	RCOX	$(RCO)_2O$

One should also add to this list lactones (cyclic esters) and lactams (cyclic amides).

CONTRIBUTORS AND ATTRIBUTIONS

- Sharleen Agvateesiri

II NATURE OF THE CARBONYL GROUP

OBJECTIVES

After completing this section, you should be able to describe the electronic structure, polarity, and geometry of the carbonyl group.

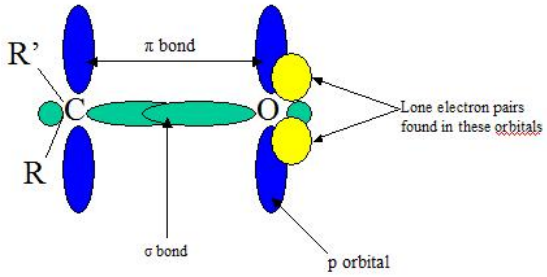
A carbonyl group is a chemically organic functional group composed of a carbon atom double-bonded to an oxygen atom --> [**C=O**] The simplest carbonyl groups are aldehydes and ketones usually attached to another carbon compound. These structures can be found in many aromatic compounds contributing to smell and taste.

INTRODUCTION

Before going into anything in depth be sure to understand that the **C=O** entity itself is known as the "Carbonyl group" while the members of this group are called "carbonyl compounds" --> **X**-C=O. The carbon and oxygen are usually sp^2 hybridized and planar.

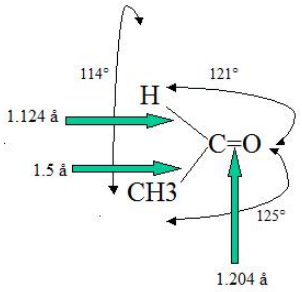
CARBONYL GROUP DOUBLE BONDS

The double bonds in alkenes and double bonds in carbonyl groups are VERY different in terms of reactivity. The C=C is *less* reactive due to C=O electronegativity attributed to the oxygen and its two lone pairs of electrons. One pair of the oxygen lone pairs are located in 2s while the other pair are in 2p orbital where its axis is directed perpendicular to the direction of the pi orbitals. The Carbonyl groups properties are directly tied to its electronic structure as well as geometric positioning. For example, the electronegativity of oxygen also polarizes the pi bond allowing the single bonded substituent connected to become electron withdrawing.



**Note: Both the pi bonds are in phase (top and botom blue ovals)*

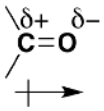
The double bond lengths of a carbonyl group is about 1.2 angstroms and the strength is about 176-179 kcal/mol). It is possible to correlate the length of a carbonyl bond with its polarity; the longer the bond meaing the lower the polarity. For example, the bond length in C=O is larger in acetaldehyde than in formaldehyde (this of course takes into account the inductive effect of CH_3 in the compound).



POLARIZATION

As discussed before, we understand that oxygen has two lone pairs of electrons hanging around. These electrons make the oxygen more electronegative than carbon. The carbon is then partially postive (electrophillic) and the oxygen partially negative (nucleophillic). The polarizability is denoted by a lowercase delta and a positive or negative superscript depending. For example, carbon would have d+ and oxygen delta^(-). The polarization of carbonyl groups also effects the boiling point of aldehydes and ketones to be higher than those of hydrocarbons in the same amount. The larger the carbonyl compound the less soluble it is in water. If the compound exceeds six carbons it then becomes insoluble.

**For more information about carbonyl solubility, look in the "outside links" section*



**Amides are the most stable of the carbonyl couplings due to the high-resonance stabilization between nitrogen-carbon and carbon-oxygen.*

CONTRIBUTORS AND ATTRIBUTIONS

- Sharleen Agvateesiri

III GENERAL REACTIONS OF CARBONYL COMPOUNDS

OBJECTIVES

After completing this section, you should be able to

1. list the four general reaction mechanisms that dominate the chemistry of carbonyl compounds.
2. discuss nucleophilic addition reactions of aldehydes and ketones (Chapter 19).
    a. write a general mechanism for nucleophilic addition to a carbonyl compound.
    b. write a detailed mechanism for the addition of a given nucleophile (e.g., a Grignard reagent) to an aldehyde or ketone.
3. discuss nucleophilic acyl substitution reactions of carboxylic acid derivatives (Chapter 21).
    a. write a general mechanism to illustrate nucleophilic acyl substitution reactions.

b. write a detailed mechanism for the reaction of a given carbonyl-containing compound with a given nucleophile through a nucleophilic acyl substitution.

4. discuss alpha substitution reactions (Chapter 22).
   a. write a general mechanism to illustrate alpha-substitution of a carbonyl compound through the formation of an enol or enolate anion.
   b. explain the stability and ease of formation of enolate anions.
   c. write the detailed mechanism for the formation of an alpha-substituted carbonyl compound from the overall reaction of a carbonyl compound with a primary alkyl halide.
5. discuss carbonyl condensation reactions (Chapter 23).
   a. write a general mechanism to illustrate the condensation reaction that can occur between two molecules of a carbonyl compound; for example, the reaction of two molecules of acetaldehyde to form one molecule of aldol.

KEY TERMS

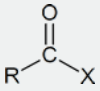
Note: All of these terms are defined in the "Study Notes," below.

- aldol reaction
- alkylation
- alpha substitution
- carbonyl condensation
- enol
- enolate anion
- nucleophilic acyl substitution
- nucleophilic addition reaction

STUDY NOTES

A "nucleophilic addition reaction" (of a carbonyl compound) involves the initial attack of a nucleophile on the slightly positive carbonyl-carbon atom to form a tetrahedral intermediate.

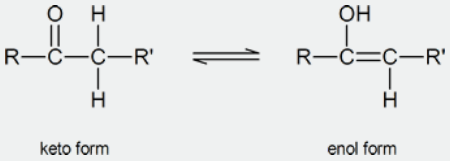
In a "nucleophilic acyl substitution reaction," a nucleophile attacks the carbonyl carbon of a carboxylic acid derivative



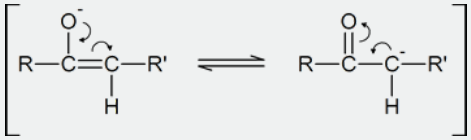
and initially produces a tetrahedral intermediate. The intermediate then reacts by expelling the leaving group, X, thereby forming a new carboxylic acid derivative.

In an "alpha substitution reaction" of a carbonyl compound, one of the hydrogen atoms attached to a carbon atom adjacent to the carbonyl group is removed and replaced by some other group.

Alpha substitution reactions of carbonyl compounds involve the "enol" form of the compound. Keto-enol tautomerism was briefly introduced in Section 9.4. Review this section if necessary.



As you can see from the above diagram, the enol form has a hydroxyl group attached to one of the s p2 -hybridized carbon atoms of a carbon-carbon double bond. Removal of the proton from the hydroxyl group produces a resonance-stabilized "enolate anion":

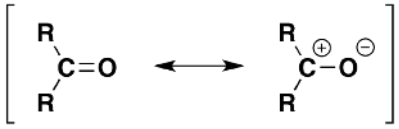


A "carbonyl condensation reaction" is one in which two carbonyl- containing molecules condense together (i.e., join together), often with the elimination of water. The reaction involves the formation of an enolate anion from one carbonyl-containing molecule, followed

by the subsequent nucleophilic attack by this enolate anion on the carbonyl carbon atom of the second molecule.

NUCLEOPHILIC ADDITION TO A CARBONYL GROUP

C=O is prone to additions and nucleophillic attack because or carbon's positive charge and oxygen's negative charge. The resonance of the carbon partial positive charge allows the negative charge on the nucleophile to attack the Carbonyl group and become a part of the structure and a positive charge (usually a proton hydrogen) attacks the oxygen. Just a reminder, the nucleophile is a good acid therefore "likes protons" so it will attack the side with a positive charge.



**Remember: due to the electronegative nature of oxygen the carbon is partially positive and oxygen is partially negative*

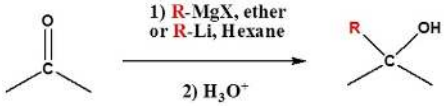


1 2 3

1. The Nucleophile (Nu) attacks the positively charged carbon and pushes one of the double bond electrons onto oxygen to give it a negative charge.
2. The Nucleophile is now a part of the carbonl structure with a negatively cahrged oxygen and a Na^+ "floating" around.
3. The negatively charged oxygen attacks the proton (H^+) to give the resulting product above.

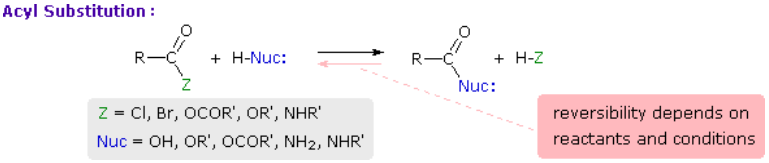
An Organometallic Example

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.

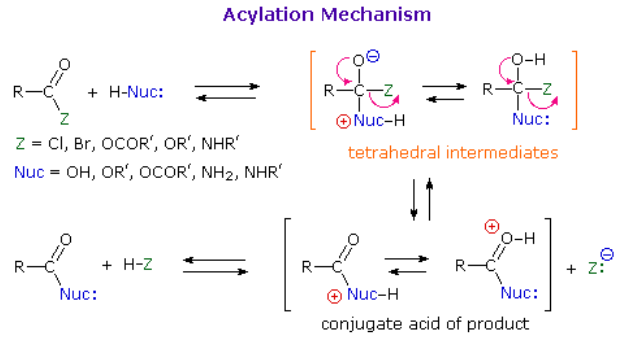


NUCLEOPHILIC ACYL SUBSTITUTION

This is probably the single most important reaction of carboxylic acid derivatives. The overall transformation is defined by the following equation, and may be classified either as **nucleophilic substitution at an acyl group** or as **acylation of a nucleophile**. For certain nucleophilic reagents the reaction may assume other names as well. If Nuc-H is water the reaction is often called **hydrolysis**, if Nuc–H is an alcohol the reaction is called **alcoholysis**, and for ammonia and amines it is called **aminolysis**.



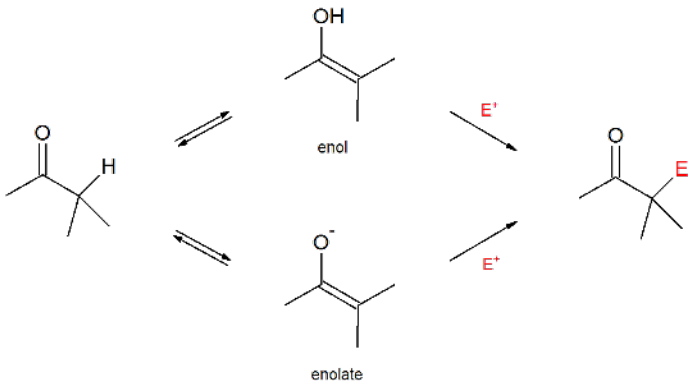
As illustrated in the following diagram, acylation reactions generally take place by an **addition-elimination process** in which a nucleophilic reactant bonds to the electrophilic carbonyl carbon atom to create a tetrahedral intermediate. This tetrahedral intermediate then undergoes an elimination to yield the products. In this two-stage mechanism bond formation occurs before bond cleavage, and the carbonyl carbon atom undergoes a hybridization change from sp^2 to sp^3 and back again. The facility with which nucleophilic reagents add to a carbonyl group was noted earlier for aldehydes and ketones.



Mechanism Toggle

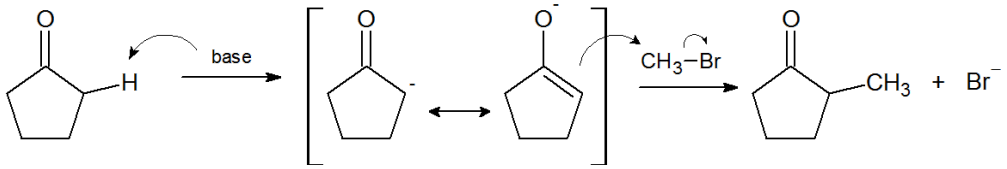
ALPHA-SUBSTITUTION REACTIONS

Now we will investigate reactions which occur a the carbon alpha to the carbonyl groups. These reactions involve two new nucleophilic species the enol and the enolate.



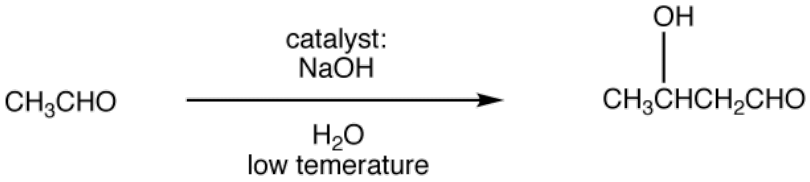
Note! The electrophile replaces the hydrogen on the alpha carbon.

The following is a specific example of this type of reaction. Here we methylate the carbon alpha to the carbonyl group through an enolate intermediate. The hydrogen on the alpha carbon is acidic because of the presence of the C=O group and is therefore preferentially abstracted by the base.



CARBONYL CONDENSATION REACTIONS

Enolizable aldehydes and enolizable ketones, in the presence of an acid or base catalyst usually in aqueous medium at low temperature, undergo a reaction, giving an aldol as the major product. This reaction is known as aldol reaction. The base-catalyzed aldol reaction, in which the catalyst is usually the hydroxide ion, is more common. Careful control of reaction temperature is critical because high temperatures promote aldol condensation. The optimum temperature depends on the nature of the aldehyde or ketone. Typically, heating the reaction mixture results in aldol condensation. For example:

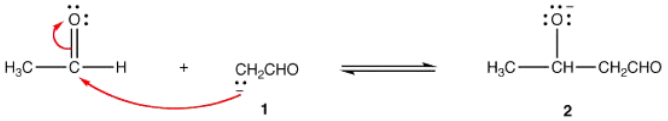


Mechanism:

Step 1: The hydroxide ion deprotanates the aldehyde reversibly.



Step 2: Enolate ion 1 adds to the unreacted aldehyde.



Step 3: Alkoxide ion 2 is protonated by water.



Since all three steps are reversible, the overall reaction is reversible and its equilibrium constant depends on the nature of the aldehyde or ketone. The reactions of aldehydes in which the α-carbon is a secondary carbon usually have large equilibrium constants; those of other aldehydes and ketones have small equilibrium constants. These observations suggest that the equilibrium constant of aldol reaction is sensitive to steric hindrance at the carbonyl carbon in the aldehyde or ketone.

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

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Sharleen Agvateesiri
- Gamini Gunawardena from the OChemPal site (Utah Valley University)
- Prof. Steven Farmer (Sonoma State University)

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18.S: ETHERS AND EPOXIDES; THIOLS AND SULFIDES (SUMMARY)

CONCEPTS & VOCABULARY

18.0 Introduction

- Ethers are molecules containing oxygen which is bonded to two carbon groups.
- Thiols are sulfur analogues of alcohols with an SH group instead of OH.
- Sulfides are sulfur analogues of ethers with sulfur bonded to two carbon groups instead of oxygen.

18.1 Names and Properties of Ethers

- Ether groups are named as alkoxy groups.
- Ethers do not have intramolecular hydrogen bonding (unlike alcohols), therefore ethers have significantly reduced intermolecular forces causing boiling points that are much lower than similar sized alcohols.

18.2 Preparing Ethers

- Alkoxymercuration can be used to prepare an ether from an alkene.

18.3 Reactions of Ethers: Acidic Cleavage

- The carbon-oxygen bonds of ethers can be cleaved with strong acids through either nucleophilic substitution or elimination reactions.

18.4 Reactions of Ethers: Claisen Rearrangement

- The Claisen rearrangement is a [3, 3] sigmatropic rearrangement reaction that converts aryl or enol ethers into carbonyl compounds (though the aromatic version rearranges into a phenol to re-establish aromaticity.

18.5 Cyclic Ethers: Epoxides

- Epoxides, also called oxiranes, have a three-membered ring structure with one oxygen and two carbon atoms.
- Epoxides can be formed from alkenes by reaction with peroxy acids (MCPBA for example).
- Epoxides can be formed from halohydrin molecules by reaction with a base, which causes an intramolecular Williamson ether synthesis.

18.6 Reactions of Epoxides: Ring Opening

- When epoxides are ring opened under basic conditions, they follow S_N2 mechanism leading to the nucleophile adding to the less substituted side of the epoxide.
- When epoxides are ring opened under acidic conditions, they follow S_N1 mechanism leading to the nucleophile adding to the more substituted side of the epoxide.
- When epoxides are ring opened in aqueous reactions, the result is an anti-diol.
- Halo acids can be added to epoxides to form anti-halohydrins.

18.7 Crown Ethers

- Crown ethers are cyclic ethers containing several oxygen atoms.
- Crown ethers are named by the number of total atoms in the ring, followed by the word crown and finally the number of oxygen atoms (18-crown-6 for example).

18.8 Thiols and Sulfides

- Thiols can be prepared from alkyl halides through reaction with hydrosulfide ion (SH^-) or through a more complicated series of reactions including thiourea.
- Thiols can be oxidized with mild oxidizing agents to form disulfides.
- Disulfide bridges link cysteine residues in protein structures.
- Sulfides are sulfur analogues of ether, though are much better nucleophiles with sulfur in place of oxygen.

18.9 Spectroscopy of Ethers

- Ethers show standard C-H stretches and bends in IR along with a strong C-O stretch around 1000 cm^{-1}.
- In ^1H NMR, hydrogens on carbons adjacent to the oxygen typically appear between 3.4-4.5 ppm.
- Hydrogens on carbons of an epoxide ring typically appear between 2.5-3.5 ppm in ^1H NMR.

18.10 Interchapter: A Preview of Carbonyl Chemistry

- Carbonyl groups are one of the most important features in organic chemistry and consist of a sp^2 carbon double-bonded to oxygen.
- Carbonyl groups are present in ~10 different functional groups.

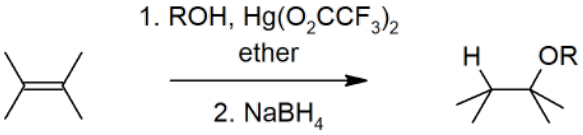
- Carbonyl groups are polarized with a partial positive charge on carbon and partial negative charge on oxygen. This makes the carbon atom an electrophile, while the oxygen can act as a nucleophile.
- Carbonyl groups can react through several mechanisms including nucleophilic addition and nucleophilic acyl substitution, alpha substitution and condensation.

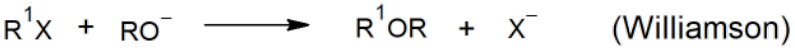
SKILLS TO MASTER

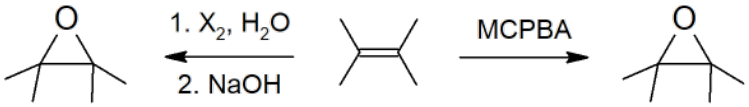
- Skill 18.1 Name ethers using common naming and IUPAC.
- Skill 18.2 Write reaction equations for preparation of ethers.
- Skill 18.3 Write mechanisms for reactions of ethers with strong halogen acids.
- Skill 18.4 Draw mechanisms for Cope and Claisen rearrangements.
- Skill 18.5 Draw mechanisms for ring-opening epoxides under acidic and basic conditions.
- Skill 18.6 Draw and name crown ethers.
- Skill 18.7 Explain how disulfide bridges contribute to protein structure.
- Skill 18.8 Give an example of S-adenosyl methionine activity in biological systems.
- Skill 18.9 Use IR and NMR spectra to identify ethers.

SUMMARY OF REACTIONS

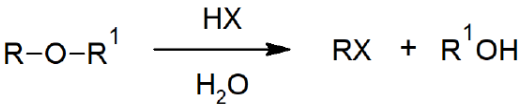
Ether and Epoxide Preparation

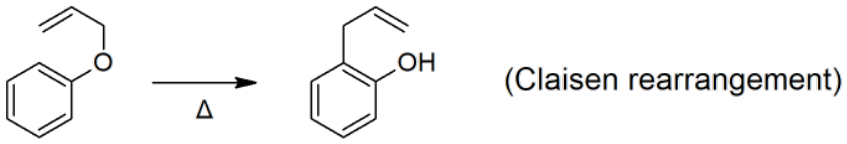


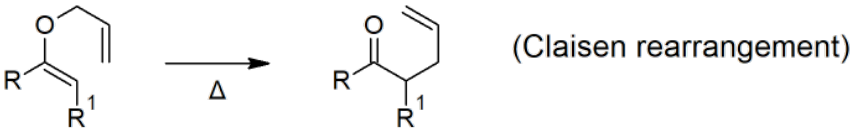




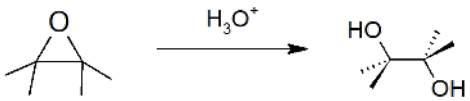
Ether Reactions

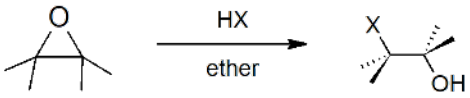


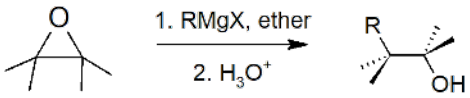


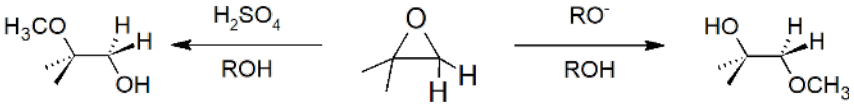


Epoxide Reactions

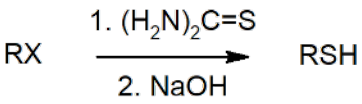


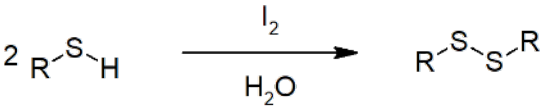


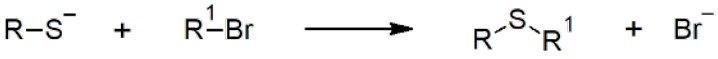


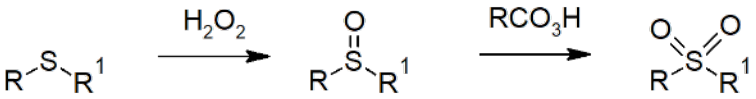


Sulfur Compound Reactions









18.S: Ethers and Epoxides; Thiols and Sulfides (Summary) is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

CHAPTER OVERVIEW

CHAPTER 19: ALDEHYDES AND KETONES: NUCLEOPHILIC ADDITION REACTIONS

Nucleophilic addition reactions were described in general terms in Chapter 18. In Chapter 19, we take a more detailed look at these reactions as we make a comprehensive study of the chemistry of aldehydes and ketones. Aldehydes and ketones are discussed together because their chemistry is very similar. However, as you work through the chapter, be sure to look for specific instances where the chemistry of these two classes of compounds differs.

As usual, we begin the chapter with a discussion of nomenclature. This introduction is followed by descriptions of the methods used to prepare aldehydes and ketones in the laboratory. You will notice that a number of these reactions have already appeared in previous units. Note that an important differences between aldehydes and ketones is the resistance of the latter to oxidation.

A large part of this chapter is concerned with the addition of various nucleophiles to the carbonyl group of aldehydes and ketones. In particular, we discuss the addition of a variety of nitrogen-containing compounds—alcohols and phosphorus ylides. Many of these reactions are important to chemists concerned primarily with the synthesis of new organic compounds.

We also describe the Cannizzaro reaction and conjugate addition to α, β-unsaturated carbonyl compounds. We mention the occurrence of nucleophilic addition reactions in biological systems, and conclude the unit with a look at the use of spectroscopic techniques in the analysis of aldehydes and ketones.

Chapter Objectives
19.1 Naming Aldehydes and Ketones
19.2 Preparing Aldehydes and Ketones
19.3 Oxidation of Aldehydes and Ketones
19.4 Nucleophilic Addition Reactions of Aldehydes and Ketones
19.5 Nucleophilic Addition of Water: Hydration
19.6 Nucleophilic Addition of HCN: Cyanohydrin Formation
19.7 Nucleophilic Addition of Grignard Reagents and Hydride Reagents: Alcohol Formation
19.8 Nucleophilic Addition of Amines: Imine and Enamine Formation
19.9 Nucleophilic Addition of Hydrazin - The Wolff-Kishner Reaction
19.10 Nucleophilic Addition of Alcohols: Acetal Formation
19.11 Nucleophilic Addition of Phosphorus Ylides: The Wittig Reaction
19.12 Biological Reductions
19.13 Conjugate Nucleophilic Addition to alpha, beta-unsaturated Aldehydes and Ketones
19.14 Spectroscopy of Aldehydes and Ketones
19.S: Aldehydes and Ketones (Summary)

Chapter 19: Aldehydes and Ketones: Nucleophilic Addition Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

CHAPTER OBJECTIVES

When you have completed Chapter 19, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design a multi-step synthesis in which you may have to use any of the reactions discussed in this chapter together with any number of reactions from previous chapters.
3. solve “road-map” problems that require a knowledge of the chemistry of aldehydes and ketones.
4. use evidence from any combination of infrared spectroscopy, nuclear magnetic resonance spectroscopy, mass spectroscopy and chemical reactions to determine the structure of an unknown aldehyde or ketone.
5. define, and use in context, the key terms introduced in this chapter.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

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19.1 NAMING ALDEHYDES AND KETONES

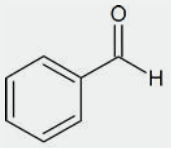
Objectives

After completing this section, you should be able to

1. provide the IUPAC name of an aldehyde or ketone, given its Kekulé, condensed or shorthand structure.
2. draw the structure of an aldehyde or ketone, given its IUPAC name.
3. draw the structure of the following aldehydes and ketones, given their trivial names: formaldehyde, acetaldehyde, benzaldehyde, acetone, acetophenone, benzophenone.

STUDY NOTES

We only use those trivial names listed under Objective 3, above. We use systematic names in all other cases. For example, the systematic name of the compound shown below is benzenecarbaldehyde, but it has the trivial name of benzaldehyde.



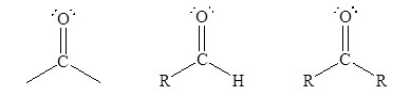
benzenecarbaldehyde
(benzaldehyde)

When naming unsaturated aldehydes and ketones, you must give the carbonyl group "priority" over the double bond when you are deciding which end of the carbon chain to begin numbering The carbonyl-carbon of an aldehyde will always be at the end of the carbon chain in an acyclic compound; and therefore numbering always starts at this carbon. It is for this reason, too, that the number "1" is not required when naming a compound such as 2-ethyl-4-methylpentanal.

The most potent and varied odors are aldehydes. Ketones are widely used as industrial solvents. Aldehydes and ketones contain the carbonyl group. Aldehydes are considered the most important functional group. They are often called the formyl or methanoyl group. Aldehydes derive their name from the *dehyd*ration of *al*cohols. Aldehydes contain the carbonyl group bonded to at least one hydrogen atom. Ketones contain the carbonyl group bonded to two carbon atoms.

INTRODUCTION

Aldehydes and ketones are organic compounds which incorporate a **carbonyl functional group**, C=O. The carbon atom of this group has two remaining bonds that may be occupied by hydrogen, alkyl or aryl substituents. If at least one of these substituents is hydrogen, the compound is an **aldehyde**. If neither is hydrogen, the compound is a **ketone**.

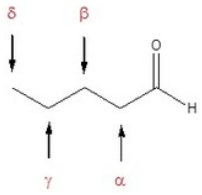


Carbonyl Group **Aldehyde** **Ketone**

NAMING ALDEHYDES

The IUPAC system of nomenclature assigns a characteristic suffix ***-al*** to aldehydes. For example, $H_2C=O$ is methan**al**, more commonly called formaldehyde. Since an aldehyde carbonyl group must always lie at the end of a carbon chain, it is always is given the #1 location position in numbering and it is not necessary to include it in the name. There are several simple carbonyl containing compounds which have common names which are retained by IUPAC.

Also, there is a common method for naming aldehydes and ketones. For aldehydes common parent chain names, similar to those used for carboxylic acids, are used and the suffix ***–aldehyde*** is added to the end. In common names of aldehydes, carbon atoms near the carbonyl group are often designated by Greek letters. The atom adjacent to the carbonyl function is alpha, the next removed is beta and so on.



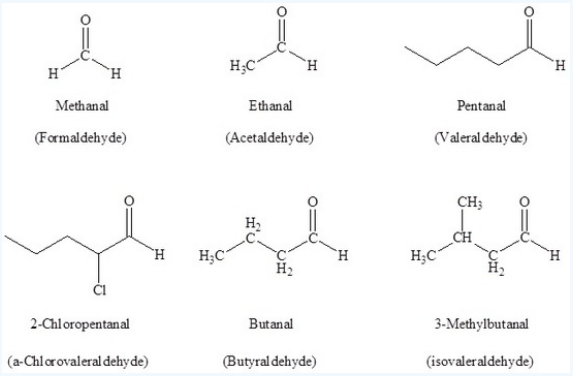
If the aldehyde moiety  (-CHO) is attached to a ring the suffix ***–carbaldehyde*** is added to the name of the ring. The carbon attached to this moiety will get the #1 location number in naming the ring.

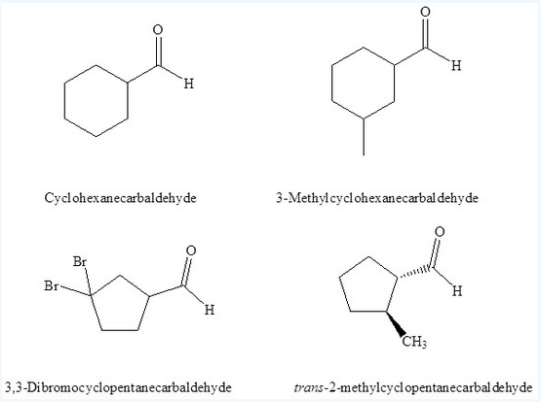
SUMMARY OF ALDEHYDE NOMENCLATURE RULES

1. Aldehydes take their name from their parent alkane chains. The ***-e*** is removed from the end and is replaced with ***-al***.
2. The aldehyde funtional group is given the #1 numbering location and this number is not included in the name.
3. For the common name of aldehydes start with the common parent chain name and add the suffix ***-aldehyde***. Substituent positions are shown with Greek letters.
4. When the -CHO functional group is attached to a ring the suffix ***-carbaldehyde*** is added, and the carbon attached to that group is C1.

EXAMPLE 19.1.1

The IUPAC system names are given on top while the common name is given on the bottom in parentheses.





NAMING KETONES

The IUPAC system of nomenclature assigns a characteristic suffix of **-one** to ketones. A ketone carbonyl function may be located anywhere within a chain or ring, and its position is usually given by a location number. Chain numbering normally starts from the end nearest the carbonyl group. Very simple ketones, such as propanone and phenylethanone do not require a locator number, since there is only one possible site for a ketone carbonyl function

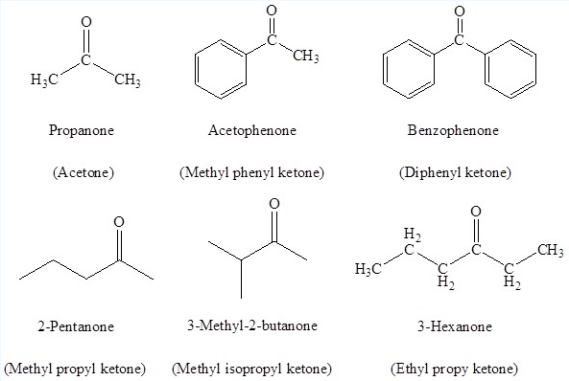
The common names for ketones are formed by naming both alkyl groups attached to the carbonyl then adding the suffix **-ketone**. The attached alkyl groups are arranged in the name alphabetically.

SUMMARY OF KETONE NOMENCLATURE RULES

1. Ketones take their name from their parent alkane chains. The ending ***-e*** is removed and replaced with ***-one***.
2. The common name for ketones are simply the **substituent groups listed alphabetically + *ketone*.**
3. Some common ketones are known by their generic names. Such as the fact that *propanone* is commonly referred to as *acetone*.

EXAMPLE 19.1.2

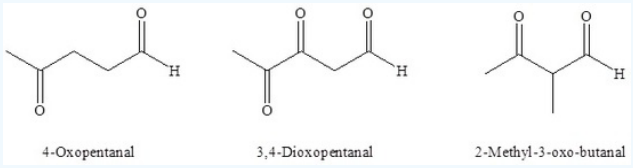
The IUPAC system names are given on top while the common name is given on the bottom in parentheses.



NAMING ALDEHYDES AND KETONES IN THE SAME MOLECULE

As with many molecules with two or more functional groups, one is given priority while the other is named as a substituent. Because aldehydes have a higher priority than ketones, molecules which contain both functional groups are named as aldehydes and the ketone is named as an **"oxo"** substituent. It is not necessary to give the aldehyde functional group a location number, however, it is usually necessary to give a location number to the ketone.

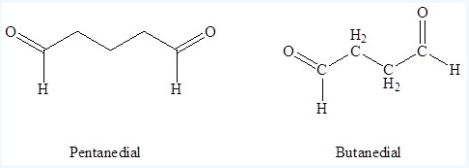
EXAMPLE 19.1.3



NAMING DIALDEHYDES AND DIKETONES

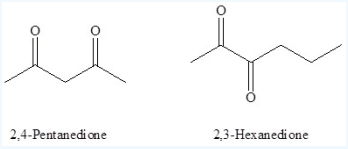
For dialdehydes the location numbers for both carbonyls are omitted because the aldehyde functional groups are expected to occupy the ends of the parent chain. The ending **–dial** is added to the end of the parent chain name.

EXAMPLE 19.1.4



For diketones both carbonyls require a location number. The ending **-dione** or **-dial** is added to the end of the parent chain.

✔ EXAMPLE 19.1.5

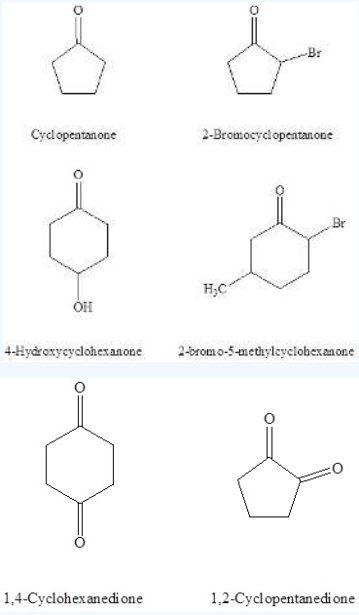


NAMING CYCLIC KETONES AND DIKETONES

In cyclic ketones the carbonyl group is assigned location position #1, and this number is not included in the name, unless more than one carbonyl group is present. The rest of the ring is numbered to give substituents the lowest possible location numbers. Remember the prefix **cyclo** is included before the parent chain name to indicate that it is in a ring. As with other ketones the **–e** ending is replaced with the **–one** to indicate the presence of a ketone.

With cycloalkanes which contain two ketones both carbonyls need to be given a location numbers. Also, an **–e** is not removed from the end but the suffix **–dione** is added.

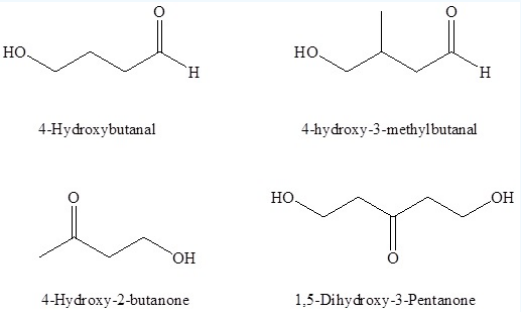
✔ EXAMPLE 19.1.6



NAMING CARBONYLS AND HYDROXYLS IN THE SAME MOLECULE

When and aldehyde or ketone is present in a molecule which also contains an alcohol functional group the carbonyl is given nomenclature priority by the IUPAC system. This means that the carbonyl is given the lowest possible location number and the appropriate nomenclature suffix is included. In the case of alcohols the **OH** is named as a **hydroxyl** substituent. However, the **l** in hydroxyl is generally removed.

EXAMPLE 19.1.7



NAMING CARBONYLS AND ALKENES IN THE SAME MOLECULE

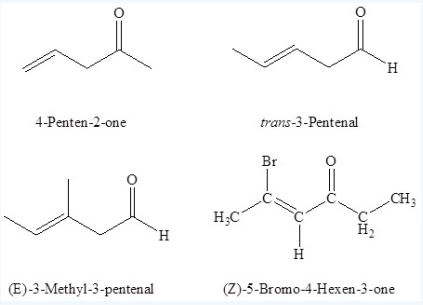
When and aldehyde or ketone is present in a molecule which also contains analkene functional group the carbonyl is given nomenclature priority by the IUPAC system. This means that the carbonyl is given the lowest possible location number and the appropriate nomenclature suffix is included.

When carbonyls are included with an alkene the following order is followed:

(Location number of the alkene)-(Prefix name for the longest carbon chain minus the **-ane** ending)-(an **-en** ending to indicate the presence of an alkene)-(the location number of the carbonyl if a ketone is present)-(either an **–one** or and **-anal** ending).

Remember that the carbonyl has priority so it should get the lowest possible location number. Also, remember that cis/tran or E/Z nomenclature for the alkene needs to be included if necessary.

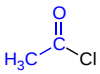
EXAMPLE 19.1.8



ALDEHYDES AND KETONES AS FRAGMENTS

- *Alkanoyl* is the common name of the fragment, though the older naming, *acyl*, is still widely used.
- *Formyl* is the common name of the fragment.
- *Acety* is the common name of the CH_3-C=O- fragment.

EXAMPLE 19.1.9



acetyl chloride



acetylaldehyde



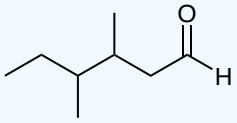
formyl fluoride

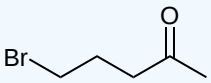
EXERCISES

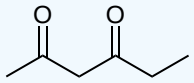
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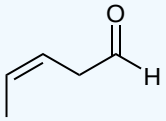
EXERCISE 19.1.1

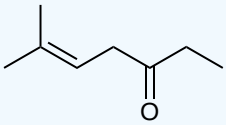
Give the IUPAC name for each compound:

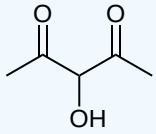
a) 

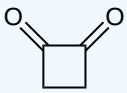
b) 

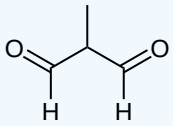
c) 

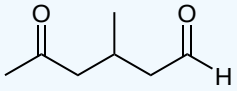
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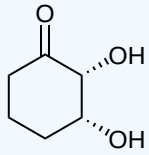
e) 

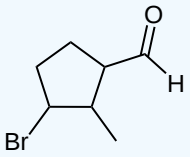
f) 

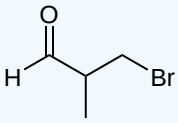
g) 

h) 

i) 

j) 

k) 

l) 

Answer

Add texts here. Do not delete this text first.

A) 3,4-dimethylhexanal

B) 5-bromo-2-pentanone

C) 2,4-hexanedione

D) *cis*-3-pentenal

E) 6-methyl-5-hepten-3-one

F) 3-hydroxy-2,4-pentanedione

G) 1,2-cyclobutanedione

H) 2-methyl-propanedial

I) 3-methyl-5-oxo-hexanal

J) *cis*-2,3-dihydroxycyclohexanone

K) 3-bromo-2-methylcyclopentanecarboaldehyde

L) 3-bromo-2-methylpropanal

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EXERCISE 19.1.2

Give the structure corresponding to each IUPAC name:

A) butanal

B) 2-hydroxycyclopentanone

C) 2,3-pentanedione

D) 1,3-cyclohexanedione

E) 3,4-dihydoxy-2-butanone

F) (E) 3-methyl-2-hepten-4-one

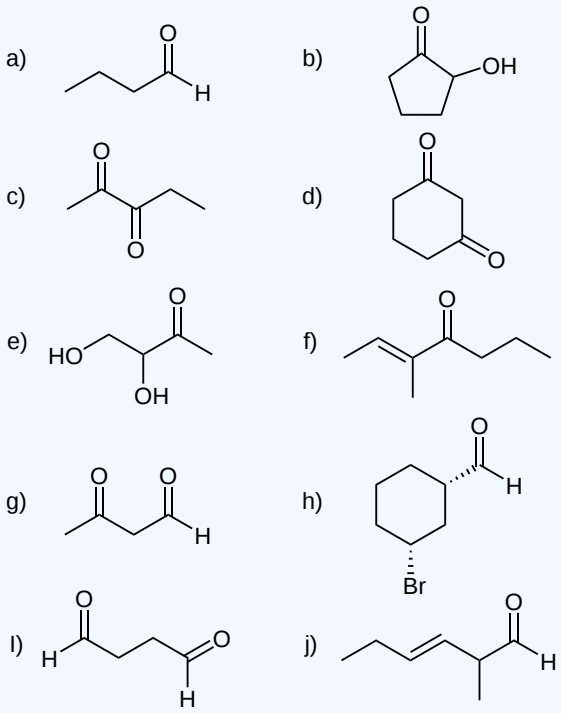
G) 3-oxobutanal

H) *cis*-3-bromocyclohexanecarboaldehyde

I) butanedial

J) *trans*-2-methyl-3-hexenal

Answer



REFERENCES

1. Vollhardt, K. Peter C., and Neil E. Schore. Organic Chemistry. 5th ed. New York: W.H. Freeman, 2007.
2. Zumdahl, Steven S., and Susan A. Zumdahl. Chemistry. 6th ed. Boston: Houghton Mifflin College Division, 2002.

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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19.2 PREPARING ALDEHYDES AND KETONES

Objectives

After completing this section, you should be able to

1. describe in detail the methods for preparing aldehydes discussed in earlier units (i.e., the oxidation of primary alcohols and the cleavage of alkenes).
2. write an equation to describe the reduction of an ester to an aldehyde.
   a. identify the product formed when a given ester is reduced with diisobutylaluminum hydride.
   b. identify the reagents and conditions used in the reduction of an ester to an aldehyde.
   c. identify the disadvantages of using diisobutylaluminum hydride to reduce an ester to an aldehyde.
3. describe in detail the methods for preparing ketones discussed in earlier units (i.e., the oxidation of secondary alcohols, the ozonolysis of alkenes, Friedel-Crafts acylation, and the hydration of terminal alkynes).
   a. write an equation to illustrate the formation of a ketone through the reaction of an acid chloride with a dialkylcopper lithium reagent.
   b. identify the ketone produced from the reaction of a given acid chloride with a specified dialkylcopper lithium reagent.
   c. identify the acid chloride, the dialkylcopper lithium reagent, or both, needed to prepare a specific ketone.

STUDY NOTES

You may wish to review the sections in which we discuss the oxidation of alcohols (17.7) and the cleavage of alkenes (8.8). A third method of preparing aldehydes is to reduce a carboxylic acid derivative; for example, to reduce an ester with diisobutylaluminum hydride (DIBAL-H).

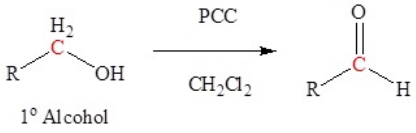
There are essentially five methods of preparing ketones in the laboratory. Four of them have been discussed in earlier sections:

1. the oxidation of a secondary alcohol—Section 17.7.
2. the ozonolysis of an alkene—Section 8.8.
3. Friedel-Crafts acylation—Section 16.3.
4. the hydration of a terminal alkyne—Section 9.4.

The "new" method we introduce in this section involves the reaction of an acid chloride with a diorganocopper reagent. The latter substances were discussed in Section 10.7, which you might now wish to review.

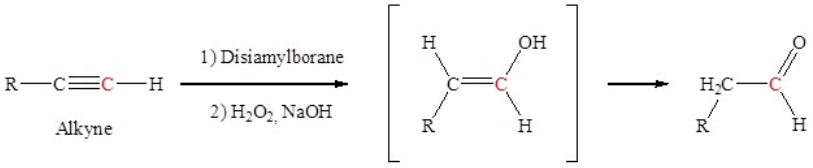
Aldehydes and ketones can be prepared using a wide variety of reactions. Although these reactions are discussed in greater detail in other sections, they are listed here as a summary and to help with planning multistep synthetic pathways. Please use the appropriate links to see more details about the reactions.

OXIDATION OF 1^{O} ALCOHOLS WITH PCC TO FORM ALDEHYDES



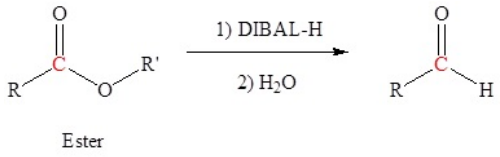
HYDRATION OF AN ALKYNE TO FORM ALDEHYDES

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.

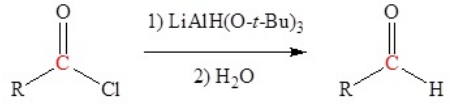


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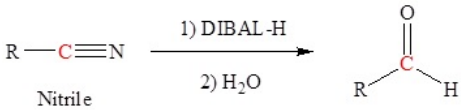
REDUCTION OF AN ESTER, ACID CHLORIDE OR NITRILE TO FORM ALDEHYDES



Ester



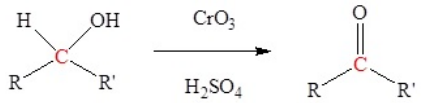
Acid Chloride



Nitrile

OXIDATION OF 2^{O} ALCOHOLS TO FORM KETONES

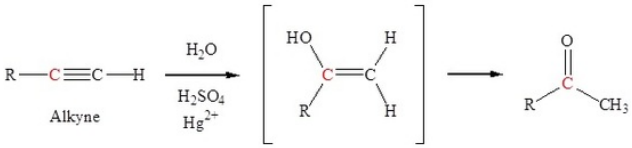
Typically uses Jones reagent (CrO_3 in H_2SO_4) but many other reagents can be used



2° Alcohol

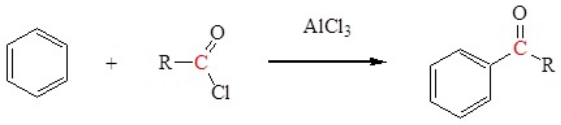
HYDRATION OF AN ALKYNE TO FORM KETONES

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.



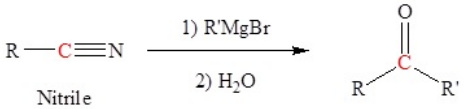
Alkyne

FRIEDEL-CRAFTS ACYLATION TO FORM A KETONE



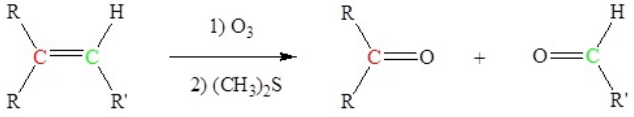
Acid Chloride

REACTION OF GRIGNARD REAGENTS WITH NITRILES TO FORM KETONES



Nitrile

ALKENES CAN BE CLEAVED USING OZONE (O_3) TO FORM ALDEHYDES AND/OR KETONES

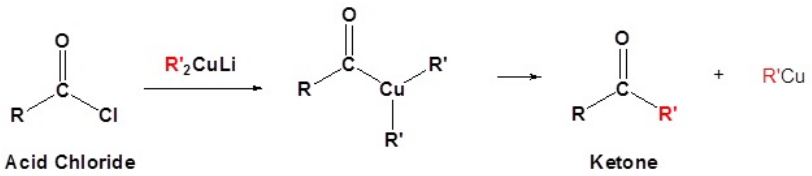


Alkene

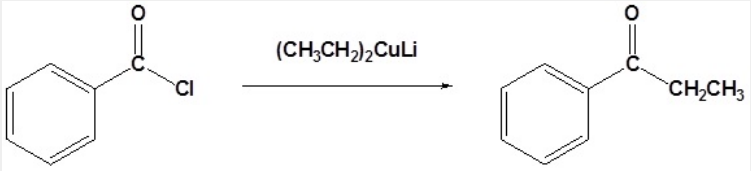
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This is an example of a Ozonolysis reaction.

ORGANOCUPRATE REAGENTS CONVERT ACID CHLORIDES TO KETONES



Example 1:



EXERCISE

? EXERCISE 19.2.1

What reagents would be required to prepare hexanal from the following starting materials?

(a) $CH_3CH_2CH_2CH_2CH_2CH_2OH$

(b) $CH_3CH_2CH_2CH_2CH_2CH{=}CH_2$

(c) $CH_3CH_2CH_2CH_2CO_2CH_3$

(d) $CH_3CH_2CH_2CH{=}CH_2$

Answer

(a) Dess–Martin periodinane or PCC in CH_2Cl_2

(b) 1. O_3, 2. Zn/H_3O^+

(c) 1. DIBAH 2. H_2O

(d) 1. BH_3 2. H_2O_2/NaOH; 2. Dess–Martin periodinane or PCC

CONTRIBUTORS AND ATTRIBUTIONS

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

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- **Organocuprate reagents convert acid chlorides to ketones** is licensed CC BY-NC-SA 4.0.

19.3 OXIDATION OF ALDEHYDES AND KETONES

Objectives

After completing this section, you should be able to

1. write an equation for the oxidation of an aldehyde using
   a. CrO_3/sulfuric acid.
   b. Tollens reagent.
2. explain the difference in structure which makes aldehydes susceptible to oxidation and ketones difficult to oxidize.
3. identify the carboxylic acid produced when a given aldehyde is oxidized.
4. identify the aldehyde, the oxidizing agent, or both, needed to prepare a given carboxylic acid.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- Tollens reagent

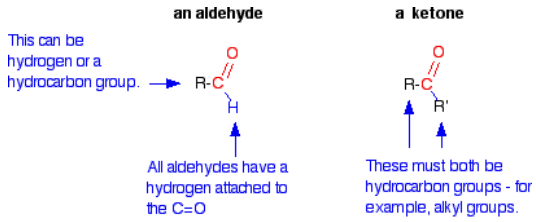
STUDY NOTES

An important difference between aldehydes and ketones is the ease with which the latter can be oxidized. Tollen's reagent is a classical organic laboratory technique to test for the presence of an aldehyde. The reagent consists of silver(I) ions dissolved in dilute ammonia. When the aldehyde is oxidized, the silver(I) ions are reduced to silver metal. When the reaction is carried out in a test-tube, the metallic silver is deposited on the walls of the tube, giving it a mirrorlike appearance. This characteristic accounts for the term "silver mirror test" which is applied when this reaction is used to distinguish between aldehydes and ketones—the latter, of course, do not react.

This page looks at ways of distinguishing between aldehydes and ketones using oxidizing agents such as acidified potassium dichromate(VI) solution, Tollens' reagent, Fehling's solution and Benedict's solution.

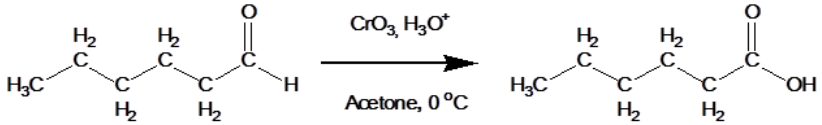
WHY DO ALDEHYDES AND KETONES BEHAVE DIFFERENTLY?

You will remember that the difference between an aldehyde and a ketone is the presence of a hydrogen atom attached to the carbon-oxygen double bond in the aldehyde. Ketones don't have that hydrogen.

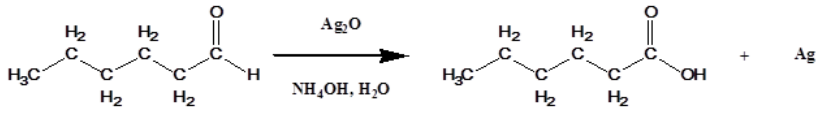


OXIDATION OF ALDEHYDES

The presence of that hydrogen atom makes aldehydes very easy to oxidize. Or, put another way, they are strong reducing agents. The most common reagent for this conversion is CrO_3 in aqueous acid. This reaction generally gives good yields at room temperature.

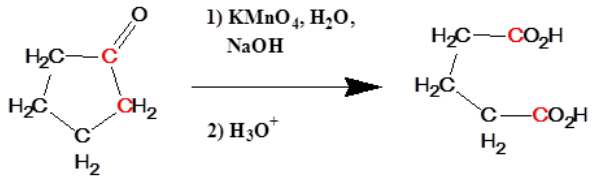


Unfortunately, the acid condition for the previous reaction can cause unwanted side reaction. If this problem occurs it can be rectified by using a solution of sliver oxide, Ag_2O, in aqueous ammonia, also called Tollens' reagent.



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Because ketones do not have that particular hydrogen atom, they are resistant to oxidation, and only very strong oxidizing agents like potassium manganate(VII) solution (potassium permanganate solution) oxidize ketones. However, they do it in a destructive way, breaking carbon-carbon bonds and forming two carboxylic acids.



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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19.4 NUCLEOPHILIC ADDITION REACTIONS OF ALDEHYDES AND KETONES

Objectives

After completing this section, you should be able to

1. give a general description of the nucleophilic addition reactions of aldehydes and ketones, identifying the two possible courses (or variations) that such reactions can take after the initial attack by the nucleophile.
2. explain why, in general, aldehydes undergo nucleophilic addition reactions more readily than do ketones, and determine which of two given aldehydes or ketones will react most readily in such reactions.

KEY TERMS

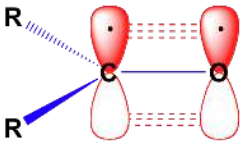
Make certain that you can define, and use in context, the key term below.

- nucleophilic addition reaction

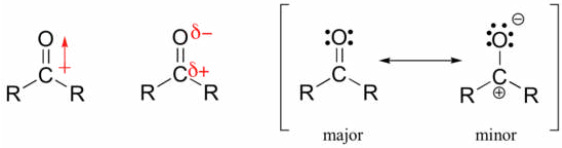
STUDY NOTES

We have already discussed electrophilic addition reactions at some length; now you will meet nucleophilic addition reactions for the first time. Nucleophilic addition reactions involve the initial attack of a nucleophile on the slightly positive carbon centre of the carbonyl group.

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.

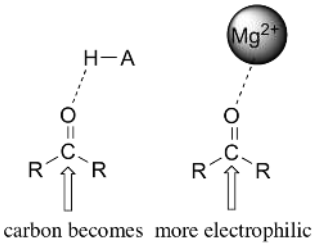


The carbon-oxygen double bond is polar: oxygen is more electronegative than carbon, so electron density is higher on the oxygen side of the bond and lower on the carbon side. Recall that bond polarity can be depicted with a dipole arrow, or by showing the oxygen as holding a partial negative charge and the carbonyl carbon a partial positive charge.



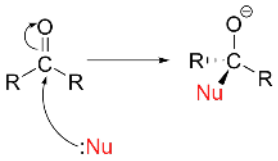
A third way to illustrate the carbon-oxygen dipole is to consider the two main resonance contributors of a carbonyl group: the major form, which is what you typically see drawn in Lewis structures, and a minor but very important contributor in which both electrons in the pbond are localized on the oxygen, 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.

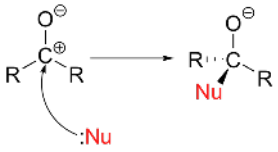


The same effect can also be achieved if a Lewis acid, such as a magnesium ion, is located near the carbonyl oxygen.

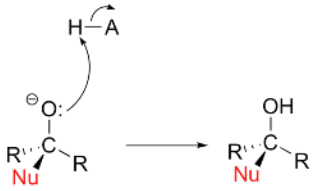
Unlike the situation in a nucleophilic substitution reaction, when a nucleophile attacks an aldehyde or ketone carbon there is no leaving group – the incoming nucleophile simply 'pushes' the electrons in the pi bond up to the oxygen.



Alternatively, if you start with the minor resonance contributor, you can picture this as an attack by a nucleophile on a carbocation.



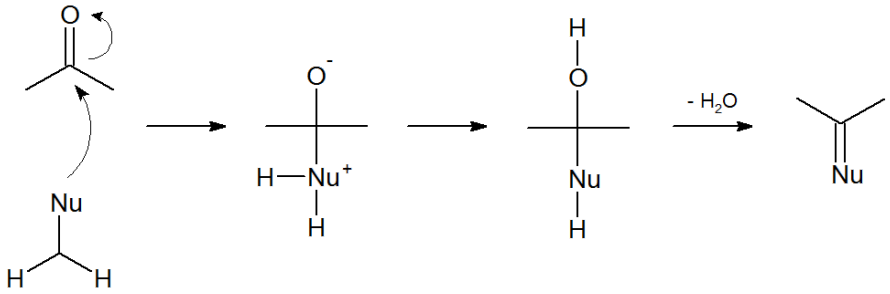
After the carbonyl is attacked by the nucleophile, the negatively charged oxygen has the capacity to act as a nucleophile. However, most commonly the oxygen acts instead as a base, abstracting a proton from a nearby acid group in the solvent or enzyme active site.



This very common type of reaction is called a **nucleophilic addition**.

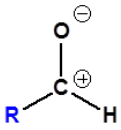
NUCLEOPHILIC ADDITION OF A NEUTRAL NUCLEOPHILE

This second variatation of the general nucleophilic addition the carbonyl oxygen is completely removed as water to from a C=Nu bond.

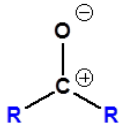


RELATIVE REACTIVITY OF CARBONYL COMPOUNDS TO NUCLEOPHILIC ADDITION

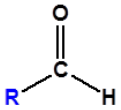
In general aldehydes are more reactive than ketones because of the lack of stabilizing alkly groups. The primary carbocation formed in the in the polarizing resonance structure of an aldehyde (discussed above) is less stable and therefore more reactive than the secondary carbocation formed by a ketone.



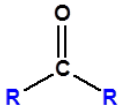
1° Carbocation
(Less Stable, More Reactive)



2° Carbocation
(MoreStable, Less Reactive)



Aldehyde
Less Stabilization
More Reactive



Ketone
Less Stabilization
More Reactive

CONTRIBUTORS AND ATTRIBUTIONS

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

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19.5 NUCLEOPHILIC ADDITION OF WATER: HYDRATION

Objectives

After completing this section, you should be able to

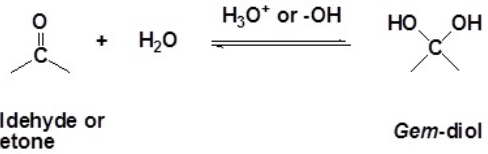
1. write the step-wise mechanism for the base-catalyzed hydration of an aldehyde or ketone.
2. write the step-wise mechanism for the acid-catalyzed hydration of an aldehyde or ketone.

KEY TERMS

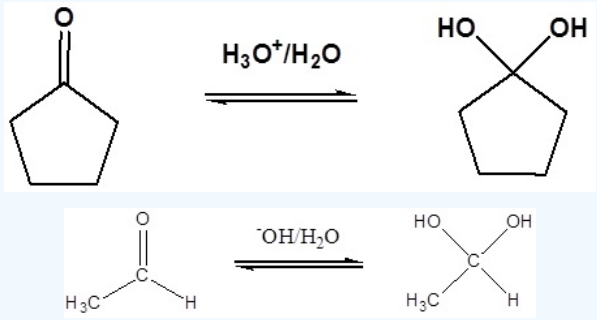
Make certain that you can define, and use in context, the key term below.

- geminal (gem) diol

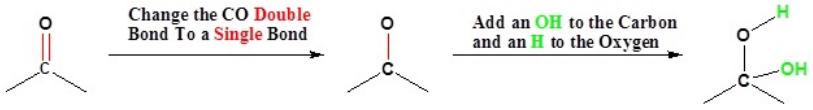
It has been demonstrated that water, in the presence of an acid or a base, adds rapidly to the carbonyl function of aldehydes and ketones establishing a reversible equilibrium with a **hydrate** (geminal-diol or *gem*-diol). The word germinal or gem comes from the Latin word for twin, *geminus*.



EXAMPLE 19.5.1

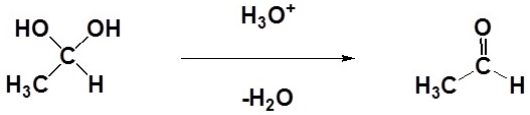


GOING FROM REACTANTS TO PRODUCTS SIMPLIFIED



REVERSIBILITY OF THE REACTION EDIT SECTION

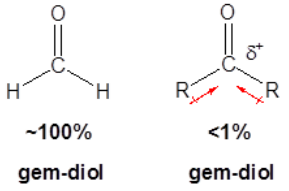
Isolation of *gem*-diols is difficult because the reaction is reversibly. Removal of the water during a reaction can cause the conversion of a gem-diol back to the corresponding carbonyl.

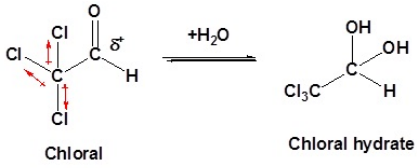


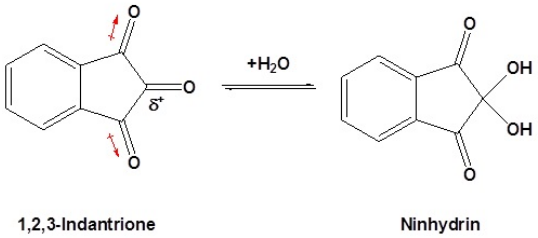
FACTORS AFFECTING THE *GEM*-DIOL EQUILIBRIUM EDIT SECTION

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. 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.





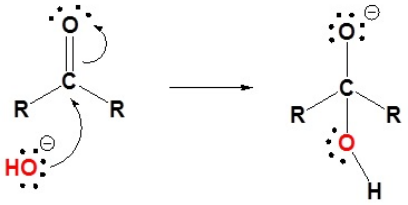


MECHANISM OF *GEM*-DIOL FORMATION

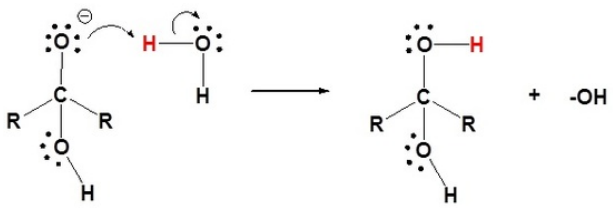
The mechanism is catalyzed by the addition of an acid or base. Note! This may speed up the reaction but is has not effect on the equilibriums discussed above. Basic conditions speed up the reaction because hydroxide is a better nucleophilic than water. Acidic conditions speed up the reaction because the protonated carbonyl is more electrophilic.

BASIC CONDITIONS

1) Nucleophilic attack by hydroxide

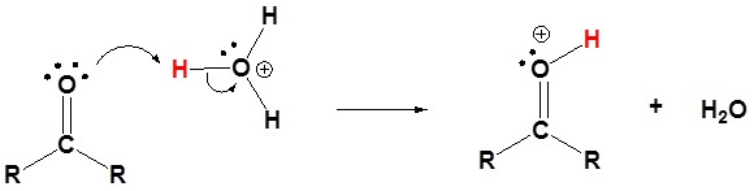


2) Protonation of the alkoxide

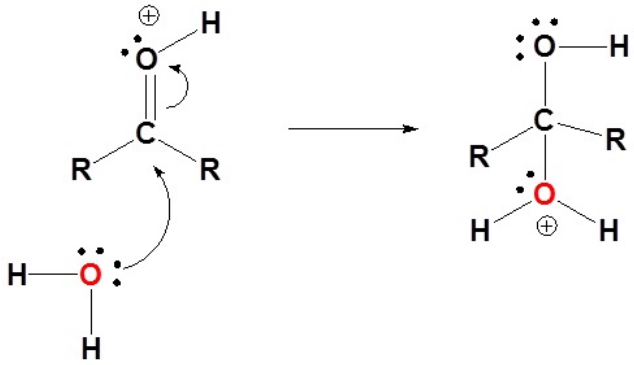


ACIDIC CONDITIONS

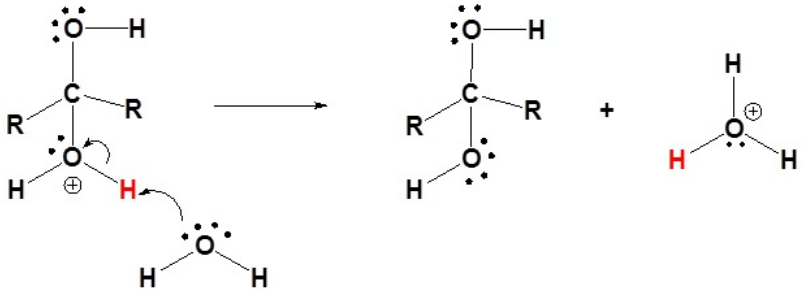
1) Protonation of the carbonyl



2) Nucleophilic attack by water



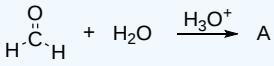
3) Deprotonation

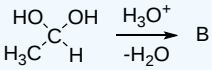


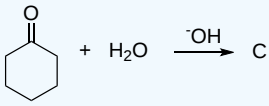
EXERCISES

? EXERCISE 19.5.1

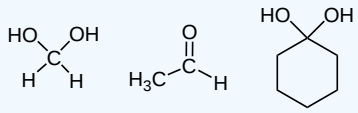
Draw the expected products of the following reactions.







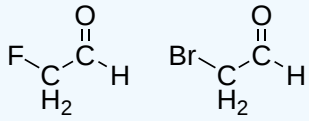
Answer



A B C

EXERCISE 19.5.2

Of the following pairs of molecules which would you expect to form a larger percentage of *gem*-diol at equilibrium? Please explain your answer.

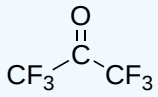


Answer

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.

EXERCISE 19.5.3

Would you expect the following molecule to form appreciable amount of *gem*-diol in water? Please explain your answer.



Answer

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 the alkyl group is dominated by the presence of six highly electronegative fluorines turning these into electron withdrawing groups.

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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19.6 NUCLEOPHILIC ADDITION OF HCN: CYANOHYDRIN FORMATION

Objectives

After completing this section, you should be able to

1. write an equation to describe the formation of a cyanohydrin from an aldehyde or ketone.
2. identify the cyanohydrin formed from the reaction of a given aldehyde or ketone with hydrogen cyanide.
3. identify the aldehyde or ketone, the reagents, or both, needed to prepare a given cyanohydrin.
4. write the detailed mechanism for the addition of hydrogen cyanide to an aldehyde or ketone.
5. write equations to represent the conversion of cyanohydrins to hydroxyamines and hydroxycarboxylic acids, and hence recognize the importance of cyanohydrin formation in organic synthesis.

a. identify the product formed when a given cyanohydrin is either reduced with lithium aluminum hydride or hydrolyzed with mineral acid.

b. identify the aldehyde or ketone, and other reagents needed to prepare a given α-hydroxyamine or α-hydroxycarboxylic acid.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- cyanohydrin

STUDY NOTES

For successful cyanohydrin formation it is important to have free cyanide ions available to react with the ketone or aldehyde. This can be achieved by using a salt (e.g. KCN or NaCN) or a silylated (e.g. Me_3SiCN) form of cyanide under acidic conditions or by using HCN with some base added to produce the needed CN^- nucleophile.

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).

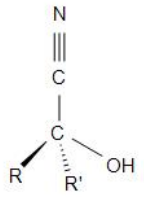
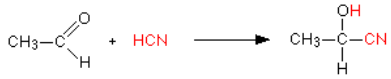
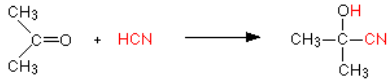


***Figure 19.6.1**: General structure of a cyanohydrin*

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:

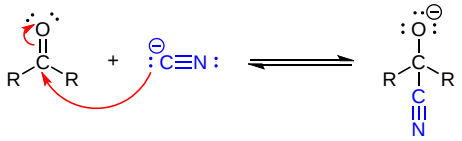


The reaction isn't normally done using hydrogen cyanide itself, because this is an extremely poisonous gas. Instead, the aldehyde or ketone is mixed with a solution of sodium or potassium cyanide in water to which a little sulphuric acid has been added. The pH of the solution is adjusted to about 4 - 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.

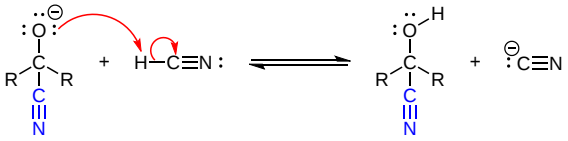
MECHANISM OF CYANOHYDRIN FORMATION

In the first step of the mechanism, the cyanide ion acts as a nucleophile and forms a C-C bond with the electrophillic carbonyl carbon. The two electrons in the carbonyl pi bond are pushed on to the electronegative oxygen forming a tetrahedral alkoxide ion intermediate. In the second step, the alkoxide ion is protonated by HCN which regenerates the cyanide ion.

STEP 1: NUCLEOPHILIC ATTACK



STEP 2: PROTONATION



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).

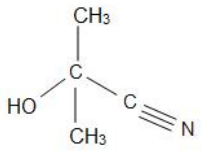


Figure 19.6.2: *Acetone cyanohydrins*

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.

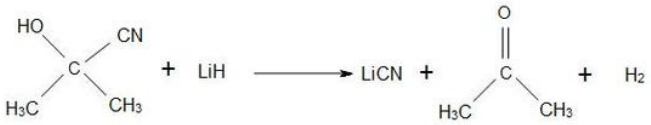
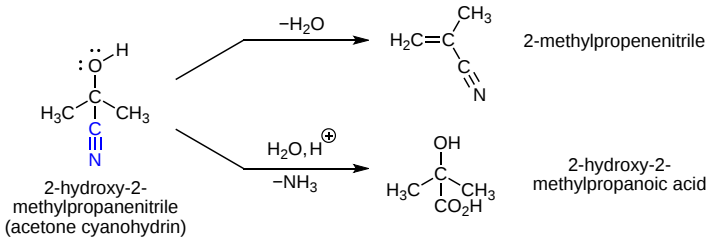
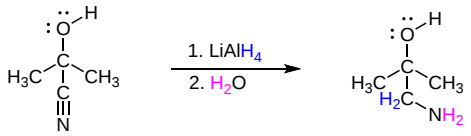


Figure 19.6.3: *Reduction of* Acetone cyanohydrins

FURTHER CHEMISTRY OF CYANOHYDRINS

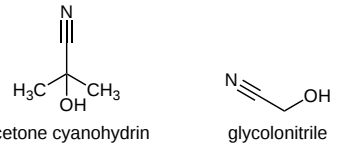
Cyanohydrin functional groups often prove useful because of the further chemistry that can be carried out due to the presence of a hydroxyl and a nitrile functionality. In particular, dehydration can convert the hydroxyl group into an alkene (Section 17.6). The nitrile can be converted into a carboxylic acid function group through reaction with a hot acidic aqueous solution (Section 20.7). Also, the nitrile can be reduced by the addition of $LiAlH_4$ to form a primary amine.





OTHER CYANOHYDRINS

Other interesting cyanohydrins are: **acetone cyanohydrin**, and **glycolonitrile**.

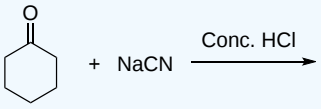


Acetone cyanohydrin has the structure, $(CH_3)_2C(OH)CN$, and is used in the production of methyl methacrylate (also known as acrylic). Glycolonitrile is an organic compound with the structural formula of $HOCH_2CN$, which is the simplest cyanohydrin that is derived by formaldehydes.

EXERCISE

? EXERCISE 19.6.1

What product is formed in this reaction?



Answer



CONTRIBUTORS AND ATTRIBUTIONS

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- Jim Clark (Chemguide.co.uk)

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19.7 NUCLEOPHILIC ADDITION OF GRIGNARD REAGENTS AND HYDRIDE REAGENTS: ALCOHOL FORMATION

Objectives

After completing this section, you should be able to:

1. write the equation to describe the nucleophilic addition reaction between a Grignard reagent and a carbonyl group.
2. write the general mechanism of nucleophilic addition of the “hydride ion” in the reduction of a carbonyl group.

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:-).

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**

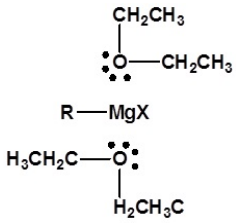
$$\mathrm{R_3C{-}X + 2\,Li \rightarrow R_3C{-}Li + LiX} \quad \textbf{(19.7 Nucleophilic Addition of Grignard Reagents and Hydride Reagents.1)}$$

- **A Grignard Regent**

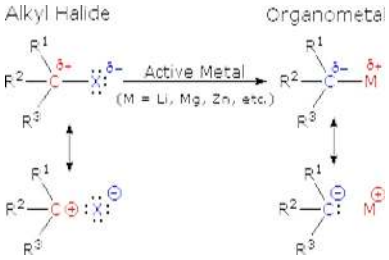
$$\mathrm{R_3C{-}X + Mg \rightarrow R_3C{-}MgX} \quad \textbf{(19.7 Nucleophilic Addition of Grignard Reagents and Hydride Reagents.2)}$$

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.

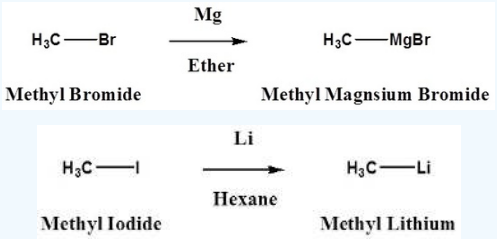
A suitable solvent must be used. For alkyl lithium formation pentane or hexane are usually used. Diethyl ether can also be used but the subsequent alkyl lithium reagent must be used immediately after preparation due to an interaction with the solvent. Ethyl ether or THF are essential for Grignard reagent 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.



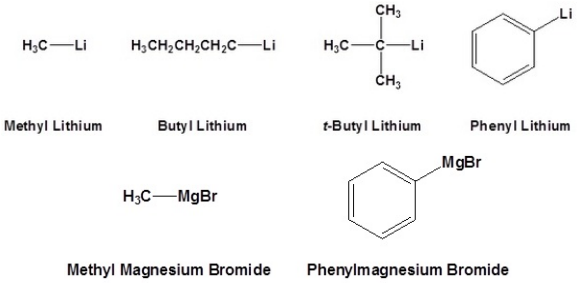
These reactions are obviously substitution reactions, but they cannot be classified as nucleophilic substitutions, as were the earlier reactions of alkyl halides. Because the functional carbon atom has been reduced, the polarity of the resulting functional group is inverted (an originally electrophilic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



✔ EXAMPLE 19.7.1

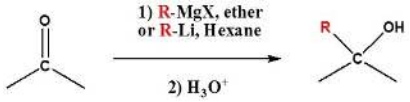


COMMON ORGANOMETALLIC REAGENTS



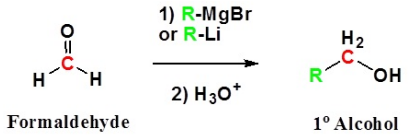
REACTION OF ORGANOMETALLIC REAGENTS WITH VARIOUS CARBONYLS

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.

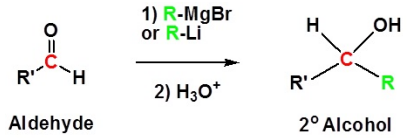


Both Grignard and Organolithium Reagents will perform these reactions

Addition to formaldehyde gives 1o alcohols



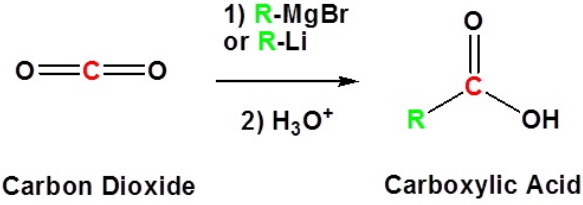
Addition to aldehydes gives 2° alcohols



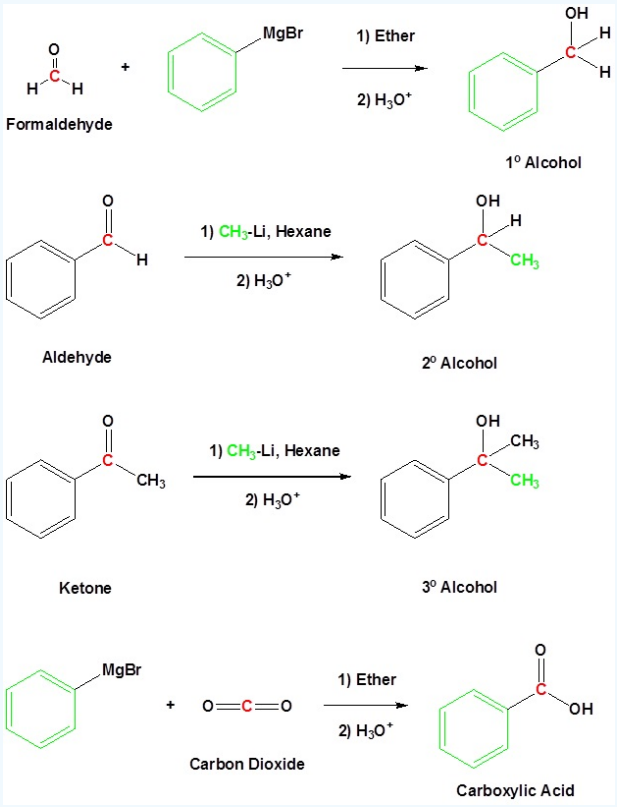
Addition to ketones gives 3o alcohols



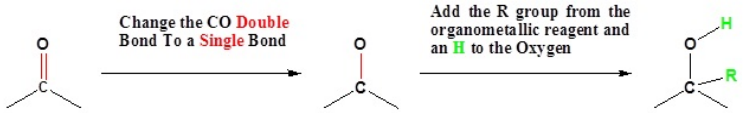
Addition to carbon dioxide (CO_2) forms a carboxylic acid



EXAMPLE 19.7.2



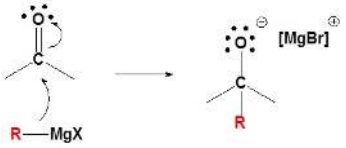
Going from Reactants to Products Simplified



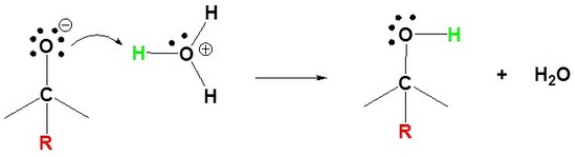
MECHANISM FOR THE ADDITION TO CARBONYLS

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

1) Nucleophilic attack

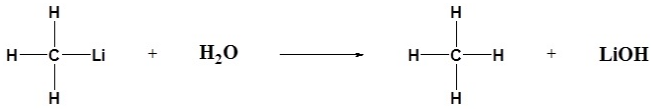


2) Protonation

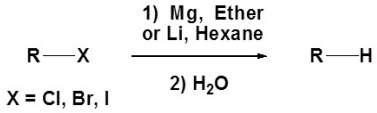


ORGANOMETALLIC REAGENTS AS BASES

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.



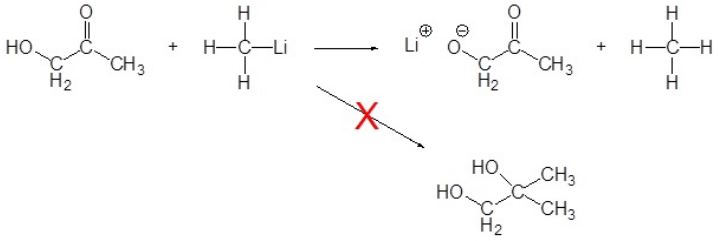
In fact, the reactivity of Grignard reagents and organolithium reagents can be exploited to create a new method for the conversion of halogens to the corresponding hydrocarbon (illustrated below). The halogen is converted to an organometallic reagent and then subsequently reacted with water to from an 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

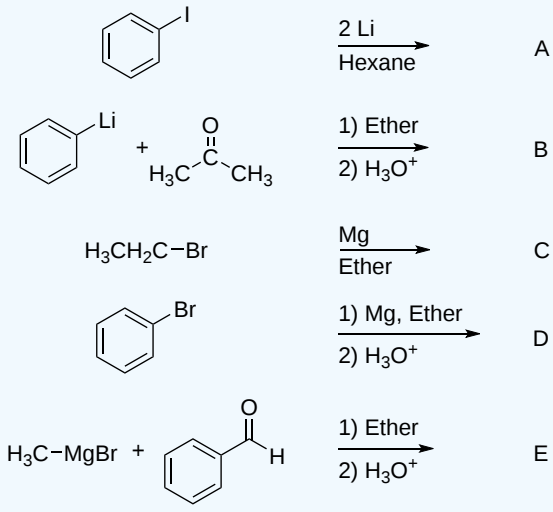
As discussed above, Grignard and organolithium reagents are powerful bases. Because of this they cannot be used as nucleophiles on compounds which contain acidic hydrogens. If they are used they will act as a base and deprotonate the acidic hydrogen rather than act as a nucleophile and attack the carbonyl.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



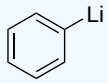
EXERCISES

? EXERCISE 19.7.1

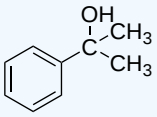
Please draw the products of the following reactions:



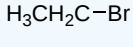
Answer



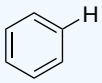
A



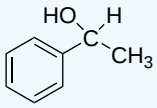
B



C



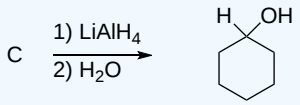
D

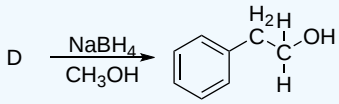


E

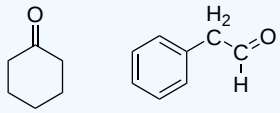
EXERCISE 19.7.2

Please draw the structure of the molecule which must be reacted to produce the product.





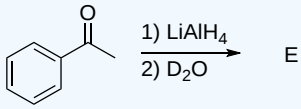
Answer



C D

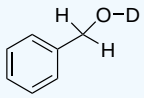
EXERCISE 19.7.3

Deuterium oxide (D_2O) is a form of water where the hydrogens have been replaced by deuteriums. For the following $LiAlH_4$ reduction the water typically used has been replaced by deuterium oxide. Please draw the product of the reaction and place the deuterium in the proper location. Hint! Look at the mechanism of the reaction.



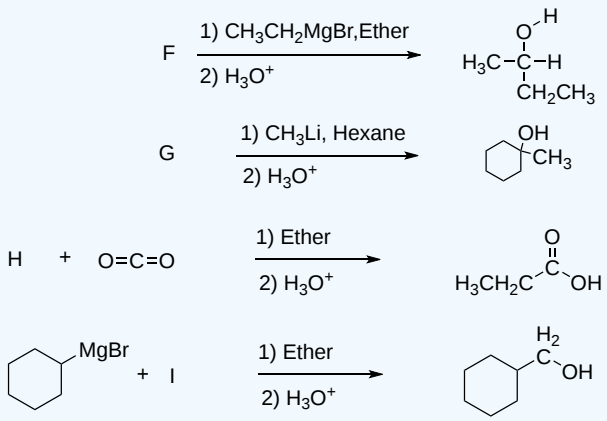
E

Answer

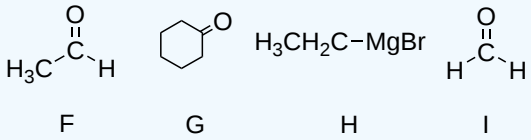


EXERCISE 19.7.4

Please indicate the starting material required to produce the product.

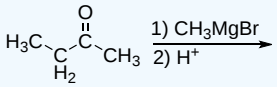


Answer



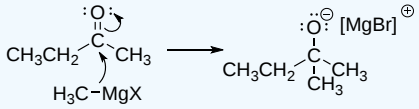
? EXERCISE 19.7.5

Please give a detailed mechanism and the final product of this reaction

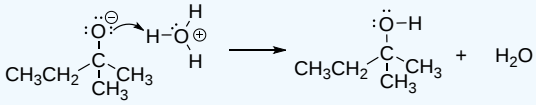


Answer

Nucleophilic attack



Protonation



CONTRIBUTORS AND ATTRIBUTIONS

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

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19.8 NUCLEOPHILIC ADDITION OF AMINES: IMINE AND ENAMINE FORMATION

Objectives

After completing this section, you should be able to

1. write equations to describe the reactions that occur between aldehydes or ketones and primary or secondary amines.
2. identify the product formed from the reaction of a given aldehyde or ketone with a given primary or secondary amine.
3. identify the aldehyde or ketone, the amine, or both, required in the synthesis of a given imine or enamine.
4. write the detailed mechanism for the reaction of an aldehyde or ketone with a primary amine.
5. write the detailed mechanism for the reaction of an aldehyde or ketone with a secondary amine.
6. explain why the rate of a reaction between an aldehyde or ketone and a primary or secondary amine is dependent on pH.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

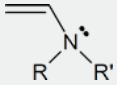
- 2,4-dinitrophenylhydrozone
- enamine
- imine

STUDY NOTES

An imine is a compound that contains the structural unit



An enamine is a compound that contains the structural unit



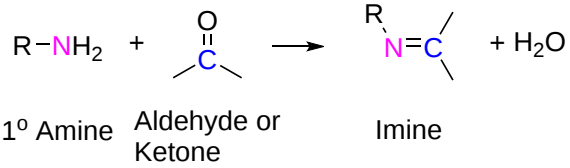
Both of these types of compound can be prepared through the reaction of an aldehyde or ketone with an amine.

You may have the opportunity to observe the reaction of an aldehyde and ketone with 2,4-dinitrophenylhydrazine (Brady's reagent) to form a 2,4-dinitrophenylhydrozone in the laboratory. This is a classical organic chemistry test to confirm the presence of a carbonyl group. The reaction produces very colourful and bright precipitates of yellow, orange and red.

If you can understand why the two reactions of imine and enamine formation are essentially identical, and can write a detailed mechanism for each one, you are well on the way to mastering organic chemistry. If you understand how and why these reactions occur, you can keep the amount of material that you need to memorize to a minimum.

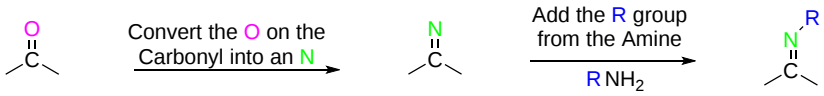
REACTION WITH PRIMARY AMINES TO FORM IMINES

The reaction of aldehydes and ketones with ammonia or 1°-amines forms imine derivatives, also known as Schiff bases (compounds having a C=N function). Water is eliminated in the reaction.

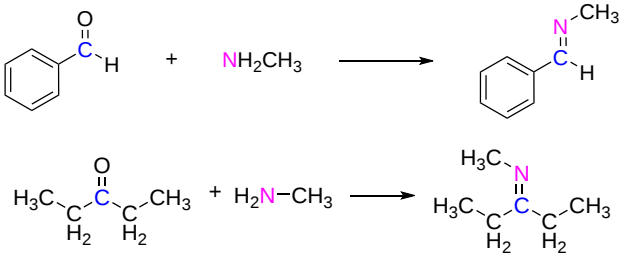


PREDICTING THE PRODUCTS OF AN IMINE FORMING REACTION

During imine formation, the carbonyl oxygen is completely removed. The nitrogen of the 1° amine reactant replaces the carbonyl oxygen to form the imine C=N bond. During the process the nitrogen of the 1° amine loses both of its hydrogens.



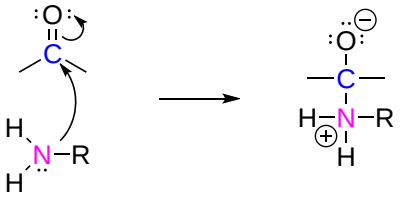
EXAMPLES OF IMINE FORMING REACTIONS



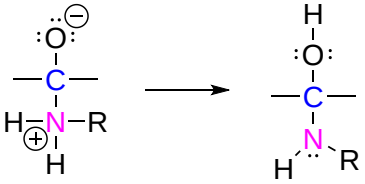
MECHANISM OF IMINE FORMATION

Imine formation is a reversible process that starts with the nucleophilic addition of a primary amine to the carbonyl group of an aldehyde or ketone. Next, a proton transfer forms a neutral amino alcohol called a carbinolamine. Acid protonation of the carbinolamine oxygen converts it into a better leaving group which is subsequently eliminated as water producing an iminium ion. Deprotonation of nitrogen gives the final imine product.

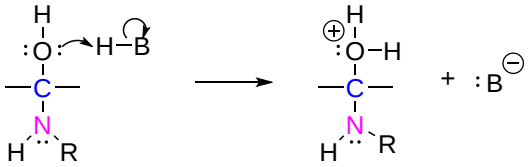
1) Nucleophilic addition



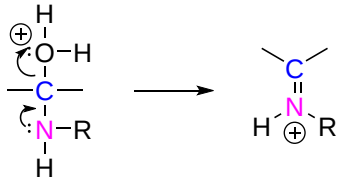
2) Protron transfer



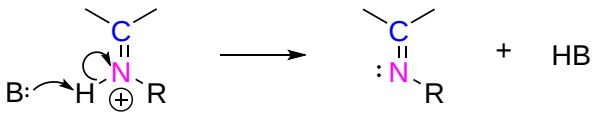
3) Protonation



4) Water is eliminated to form an iminium ion.

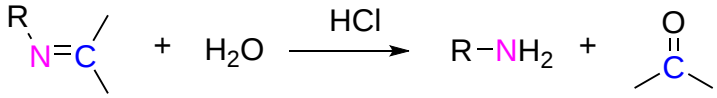


5) Deprotonation



REVERSIBILITY OF IMINE FORMING REACTIONS

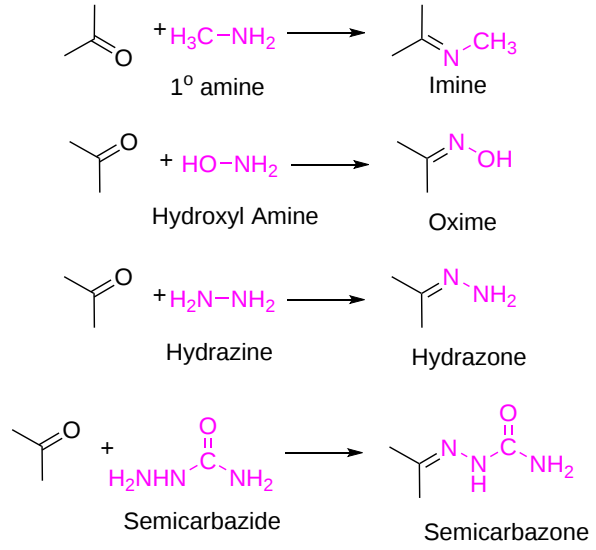
Imines can be hydrolyzed back to the corresponding 1° amine under acidic conditions.



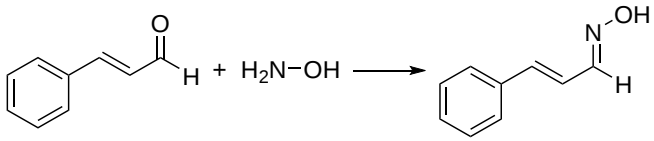
REACTIONS INVOLVING OTHER REAGENTS OF THE TYPE Y-NH_2

A wide variety of substances with $-NH_2$ groups can react with aldehydes and ketones by an addition-elimination sequence to yield compounds with a carbon-nitrogen double bond. 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 below, 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 Section 19.9.

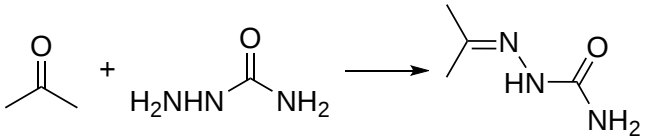
With the exception of unsubstituted hydrazones, these derivatives are easily prepared and are often crystalline solids - even when the parent aldehyde or ketone is a liquid. Since melting points can be determined more quickly and precisely than boiling points, derivatives such as these are useful for comparison and identification of carbonyl compounds. It should be noted that although semicarbazide has three nitrogen groups ($–NH_2$) only one of them is a reactive amine. The other two are similar to amides and are deactivated by resonance with the adjacent carbonyl group.



EXAMPLE



Cinnamaldehyde reacting with hydroxylamine to form cinnamaldehyde oxime

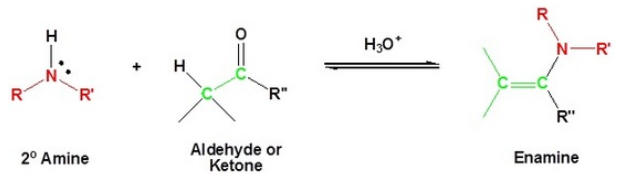


Acetone reacting with semicarbazide to form acetone semicarbazide

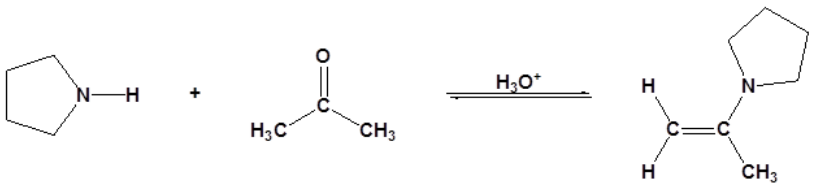
REACTION WITH SECONDARY AMINES TO FORM ENAMINES

Most aldehydes and ketones react with 2°-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.

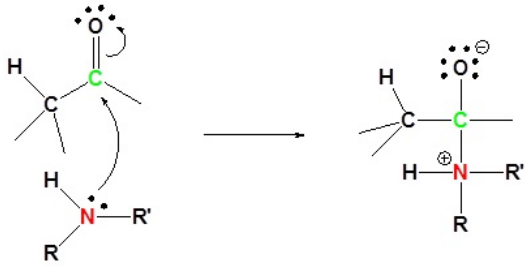


2° Amine | Aldehyde or Ketone | Enamine

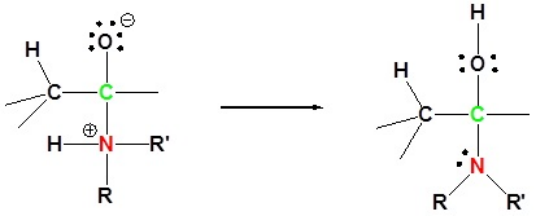


MECHANISM

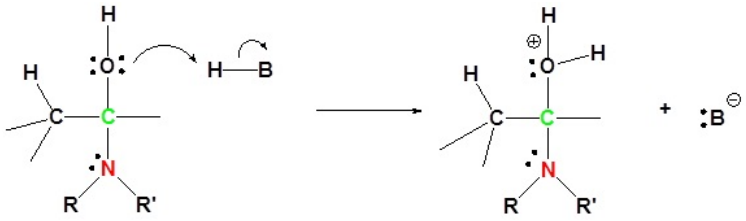
1) Nuleophilic attack



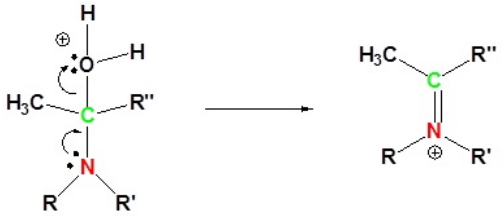
2) Proton transfer



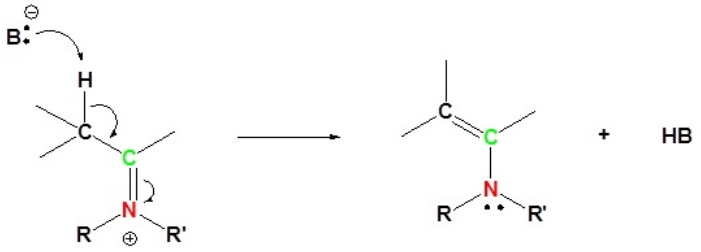
3) Protonation of OH



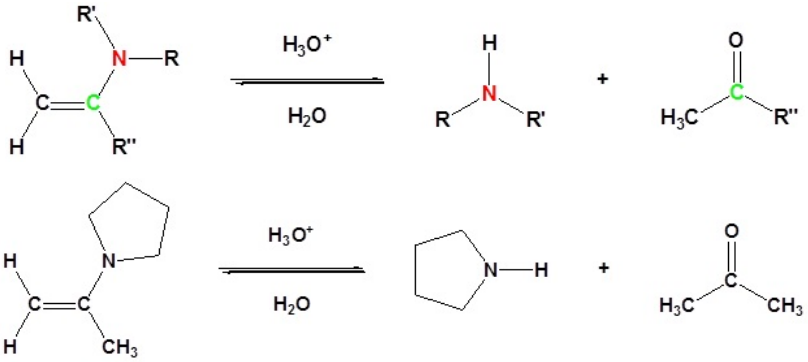
4) Removal of water



5) Deprotonation



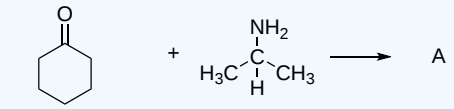
REVERSIBILITY OF ENAMINES

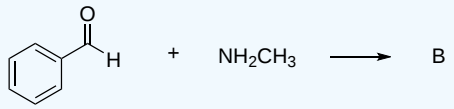


EXERCISES

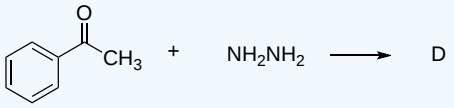
? EXERCISE 19.8.1

Please draw the products of the following reactions.

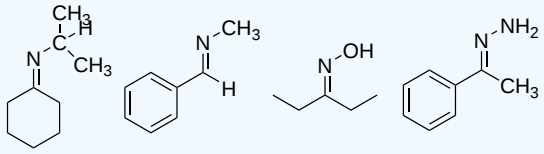








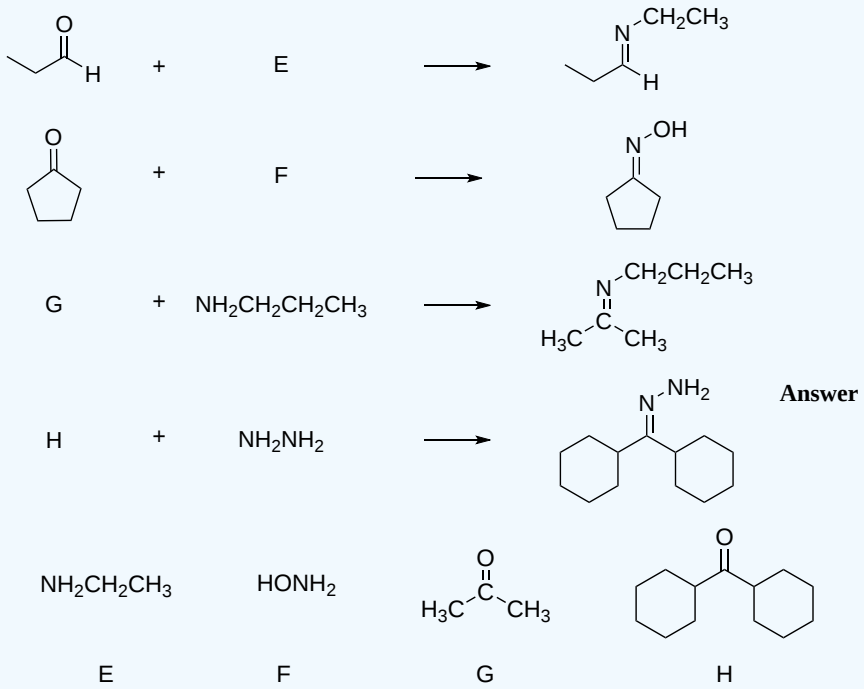
Answer



A B C D

? EXERCISE 19.8.2

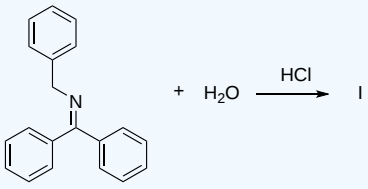
Please draw the structure of the reactant needed to produce the indicated product.



Answer

EXERCISE 19.8.3

Please draw the products of the following reaction.



Answer

CONTRIBUTORS AND ATTRIBUTIONS

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

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19.9 NUCLEOPHILIC ADDITION OF HYDRAZIN - THE WOLFF-KISHNER REACTION

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the Wolff-Kishner reduction of an aldehyde or ketone.
2. identify the product formed from the Wolff-Kishner reduction of a given aldehyde or ketone.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

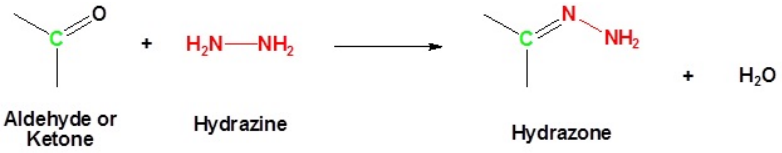
- Wolff-Kishner reduction

STUDY NOTES

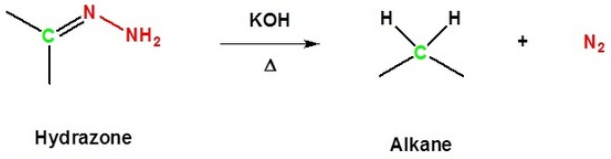
After studying this section, you can add yet another method of reducing organic compounds to your growing list of reduction reactions.

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.

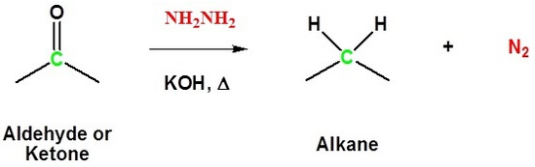
REACTION OF ALDEHYDES OR KETONES WITH HYDRAZINE PRODUCES A HYDRAZONE



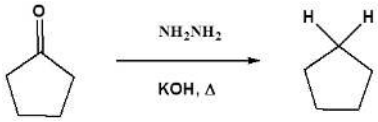
REACTION WITH A BASE AND HEAT CONVERTS A HYDRAZONE TO AN ALKANE



BOTH REACTIONS TOGETHER PRODUCES THE WOLFF-KISHNER REDUCTION



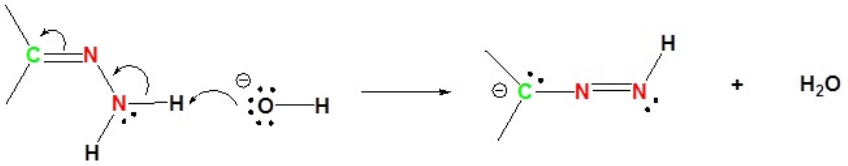
Example



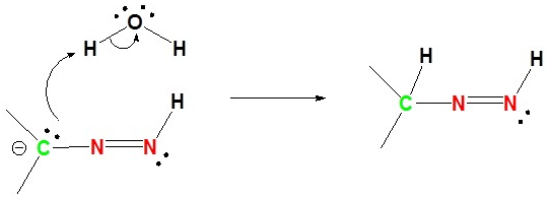
https://chem.libretexts.org/@go/page/90972

MECHANISM OF THE WOLFF-KISHNER REDUCTION

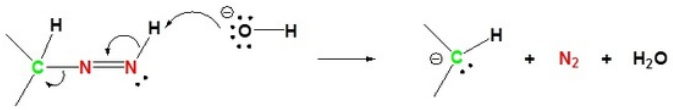
1) Deprotonation of Nitrogen



2) Protonation of the Carbon



3) Deprotonation of Nitrogen



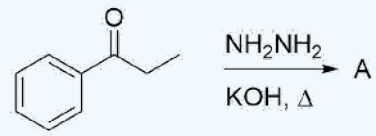
4) Protonation of Carbon

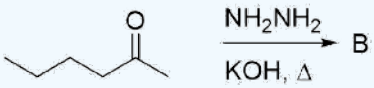


EXERCISE

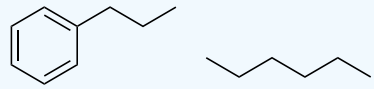
? EXERCISE 19.9.1

Please draw the products of the following reactions.





Answer



A B

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 ALCOHOLS: ACETAL FORMATION

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the formation of acetals.
2. identify the acetal formed from the reaction of a given aldehyde or ketone with a given alcohol.
3. identify the carbonyl compound, the alcohol, or both, needed to form a given acetal.
4. write a detailed mechanism for the reaction which occurs between an aldehyde or a ketone and an alcohol.
5. explain how an acid catalyst makes aldehydes and ketones more susceptible to attack by alcohols.
6. illustrate how the reversibility of the reaction between an aldehyde or a ketone and an alcohol can be used to protect a carbonyl group during an organic synthesis.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- acetal
- hemiacetal

STUDY NOTES

This section presents a second example of the use of a protecting group. [The first was in the discussion of alcohols, Section 17.8.] Because of the reactivity of hydroxy groups and carbonyl groups, we often need to protect such groups during organic syntheses. When you are designing multi-step syntheses as part of an assignment or examination question, you must always keep in mind the possibility that you may need to protect such groups to carry out the desired sequence of reactions successfully.

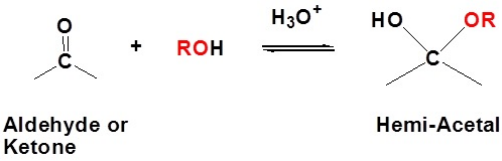
In this organic chemistry topic, we shall see how alcohols (R-OH) add to carbonyl groups. Carbonyl groups are characterized by a carbon-oxygen double bond. The two main functional groups that consist of this carbon-oxygen double bond are Aldehydes and Ketones.

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.

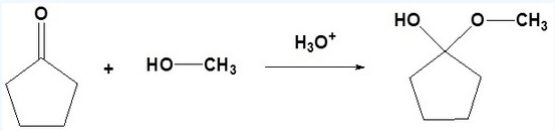
To achieve effective hemiacetal or acetal formation, two additional features must be implemented. First, an acid catalyst must be used because alcohol is a weak nucleophile; and second, the water produced with the acetal must be removed from the reaction by a process such as a molecular sieves or a **Dean-Stark 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.

FORMATION OF HEMIACETALS

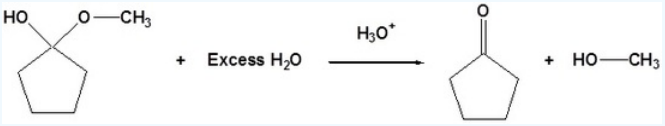


Aldehyde or Ketone **Hemi-Acetal**

EXAMPLE 19.10.1: FORMATION OF HEMIACETALS

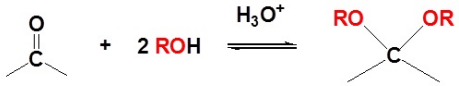


EXAMPLE 19.10.2: HEMIACETAL REVERSIBILITY



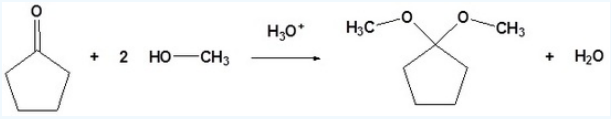
FORMATION OF ACETALS

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.

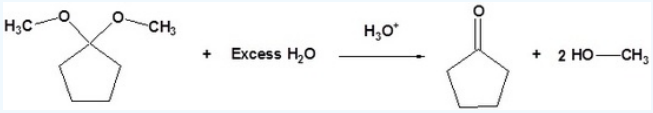


Aldehyde or Ketone **Acetal**

EXAMPLE 19.10.3: FORMATION OF ACETALS



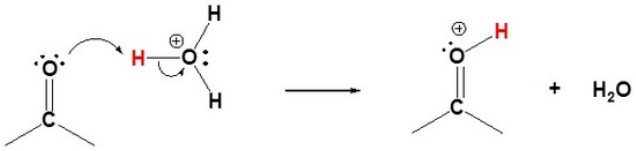
EXAMPLE 19.10.4: ACETAL REVERSIBILITY



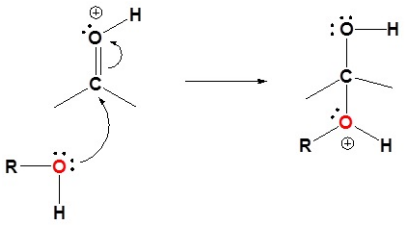
MECHANISM FOR HEMIACETAL AND ACETAL FORMATION

The mechanism shown here applies to both acetal and hemiacetal formation

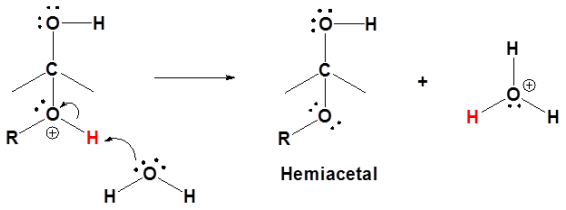
1) Protonation of the carbonyl



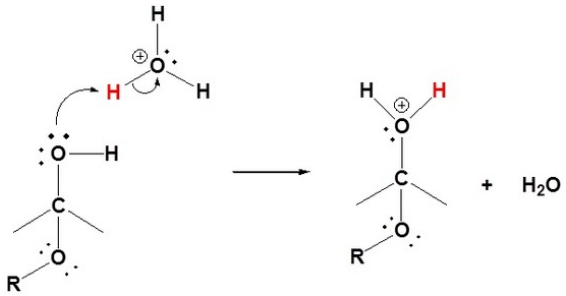
2) Nucleophilic attack by the alcohol



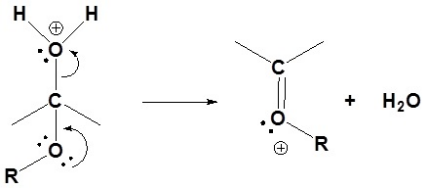
3) Deprotonation to form a hemiacetal



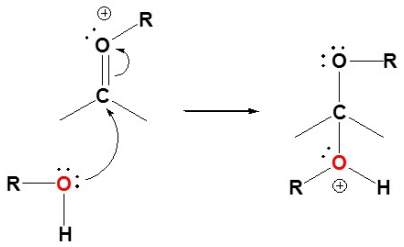
4) Protonation of the alcohol



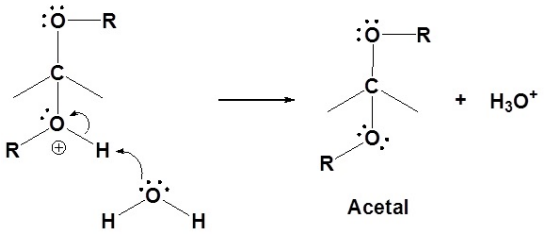
5) Removal of water



6) Nucleophilic attack by the alcohol



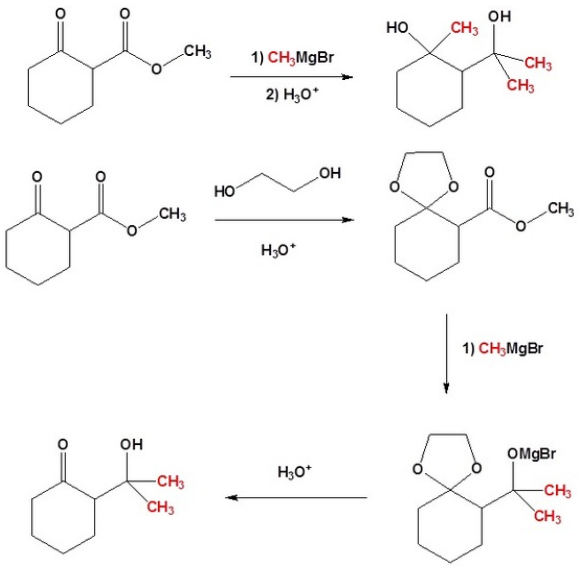
7) Deprotonation by water



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.

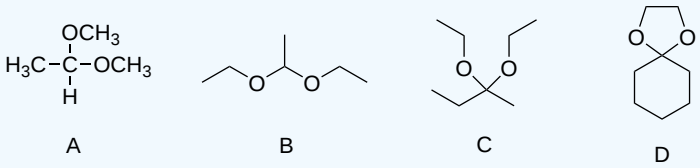
In the following example we would like a Grignard reagent to react with the ester and not the ketone. This cannot be done without a protecting group because Grignard reagents react with esters and ketones.



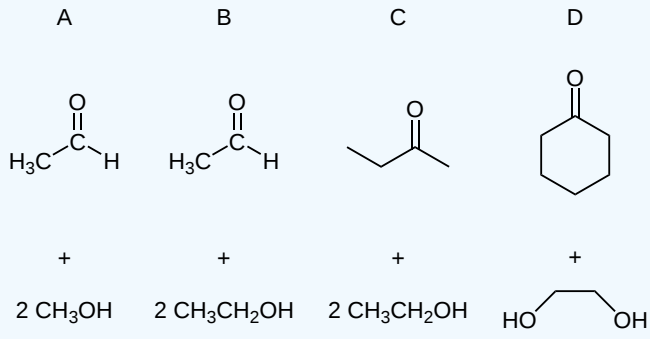
EXERCISES

? EXERCISE 19.10.1

For each acetal/ketal A-D in the figure below, specify the required aldehyde/ketone and alcohol starting materials.

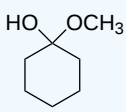


Answer

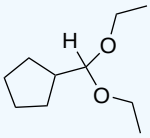


EXERCISE 19.10.2

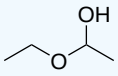
Categorize each of the following molecules as a hemiacetal, acetal, hydrate of an aldehyde, or hydrate of a ketone.



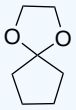
A



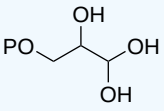
B



C



D



E

Answer

A - hemiacetal, B - acetal, C - hemiacetal, D - acetal, E - hydrate of an aldehyde

EXERCISE 19.10.3

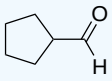
Specify the acetal that would form from a reaction between the given starting compounds.

a.



(2 Equivalents)

b.

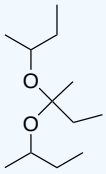


+ $HOCH_2CH_2OH$

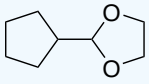
(1 Equivalent)

Answer

a)



b)



CONTRIBUTORS AND ATTRIBUTIONS

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

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19.11 NUCLEOPHILIC ADDITION OF PHOSPHORUS YLIDES: THE WITTIG REACTION

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the formation of an ylide (phosphorane).
2. write an equation to illustrate the reaction that takes place between an ylide and an aldehyde or ketone.
3. identify the alkene which results from the reaction of a given ylide with a given aldehyde or ketone.
4. identify the aldehyde or ketone, the ylide, or both, needed to prepare a given alkene by a Wittig reaction.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- betaine
- Wittig reaction
- ylide (phosphorane)

STUDY NOTES

The name triphenylphosphine is derived as follows: the compound PH_3 is called phosphine; replacing the three hydrogen atoms with phenyl groups therefore gives us triphenylphosphine.

Note the following series of IUPAC-accepted trivial names:

NH_3—ammonia

PH_3—phosphine

AsH_3—arsine

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.

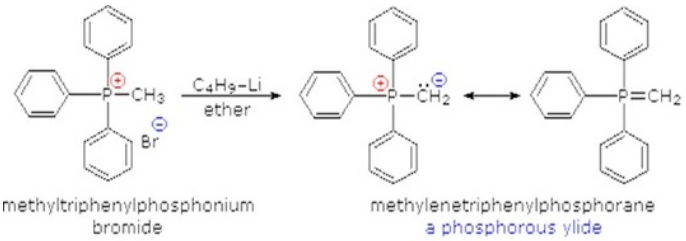
PREPARATION OF PHOSPHORUS YLIDES

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

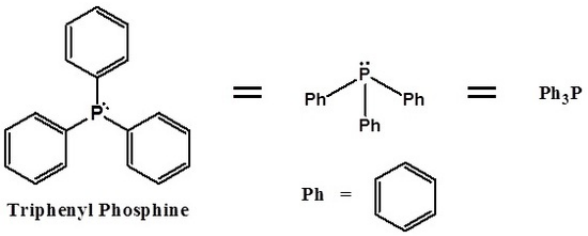
The stabilization of the carbanion provided by the phosphorus causes an increase in acidity (pKa ~35). Very strong bases, such as butyl lithium, are required for complete formation of ylides.



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.

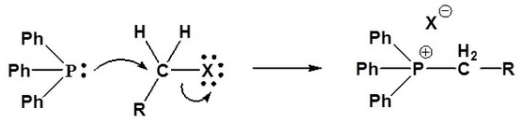
$$R_3P{=}CR'_2 \;+\; H_2O \longrightarrow R_3P{=}O \;+\; R'_2CH_2$$

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.

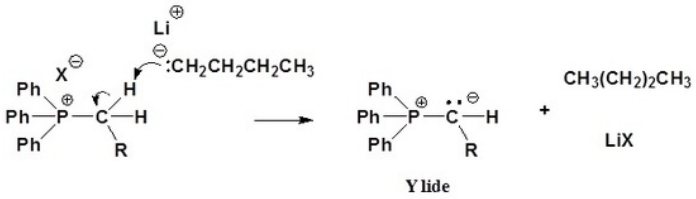


MECHANISM OF YLIDE FORMATION

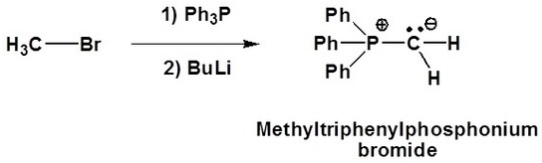
1) S_N2 reaction



2) Deprotonation

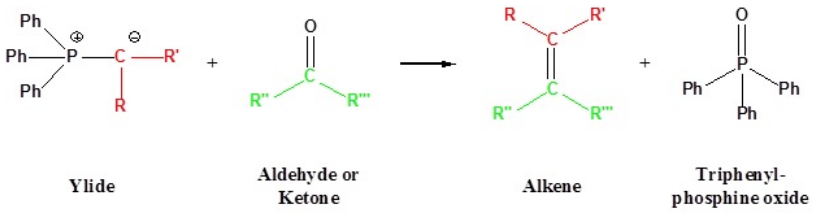


EXAMPLES OF YLIDE FORMATION

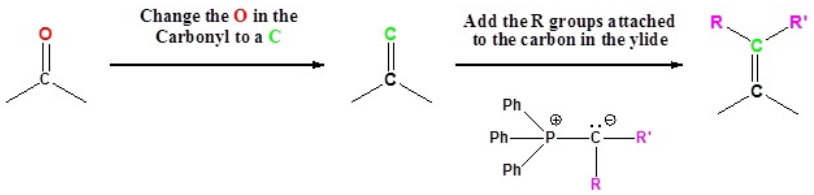


THE WITTIG REACTION

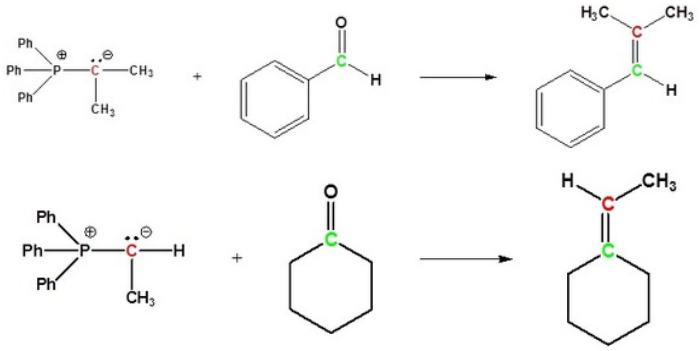
The most important use of ylides in synthesis comes from their reactions with aldehydes and ketones, which are initiated in every case by a covalent bonding of the nucleophilic alpha-carbon to the electrophilic carbonyl carbon. Ylides react to give substituted alkenes in a transformation called the Wittig 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.



Going from reactants to products simplified



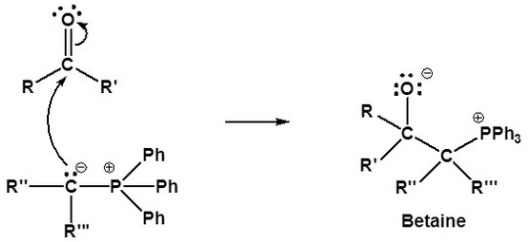
EXAMPLES OF THE WITTIG REACTION



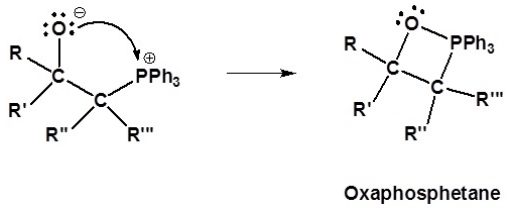
MECHANISM OF THE WITTIG REACTION

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.

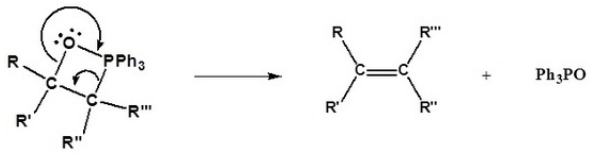
1) Nucleophillic attack on the carbonyl



2) Formation of a 4 membered ring

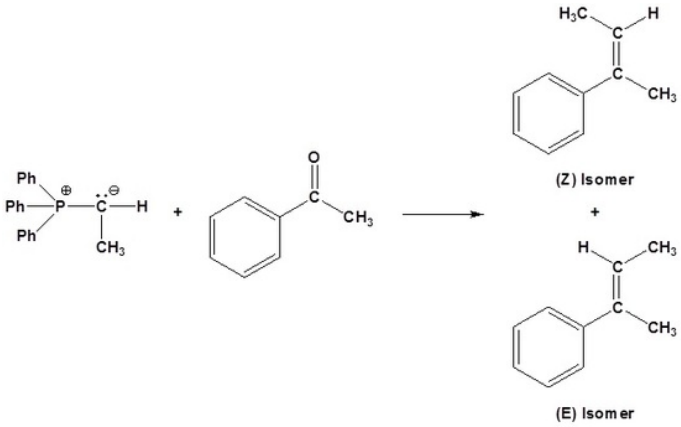


3) Formation of the alkene



LIMITATION OF THE WITTIG REACTION

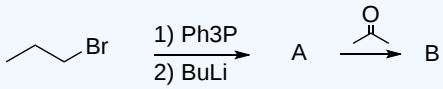
If possible both E and Z isomer of the double bond will be formed. This should be considered when planning a synthesis involving a Wittig Reaction.

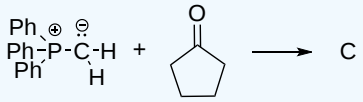


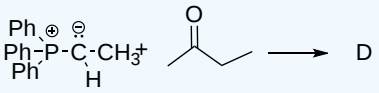
EXERCISES

? EXERCISE 19.11.1

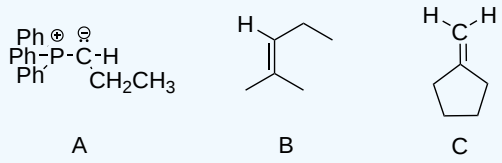
Draw the product of the following reactions.

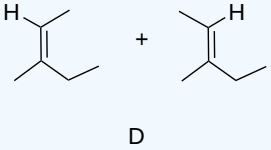






Answer

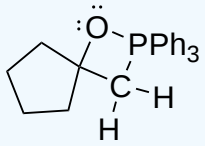




EXERCISE 19.11.2

Draw the structure of the oxaphosphetane which is made during the mechanism of the reaction given that produces product **C**.

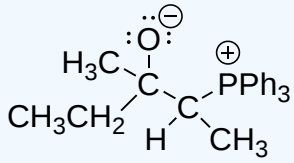
Answer



EXERCISE 19.11.3

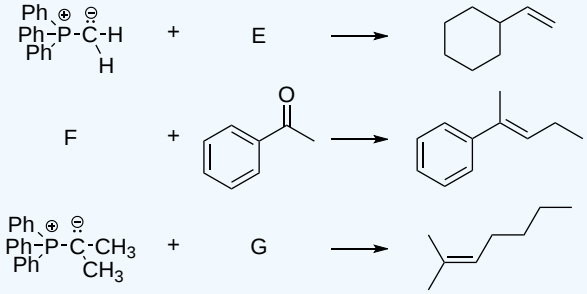
Draw the structure of the betaine which is made during the mechanism of the reaction given that produces product **D**.

Answer

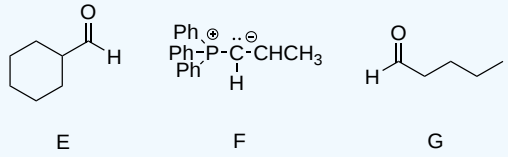


EXERCISE 19.11.4

Indicate the starting material required to produce the product in each reaction.



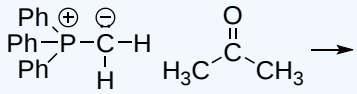
Answer



E F G

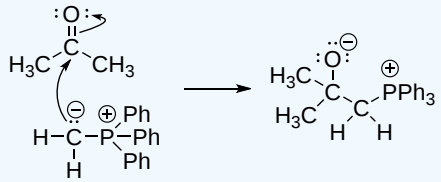
EXERCISE 19.11.5

Give a detailed mechanism and the final product of this reaction.

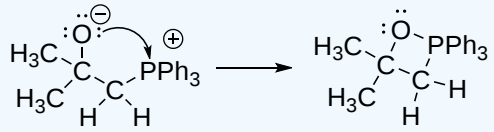


Answer

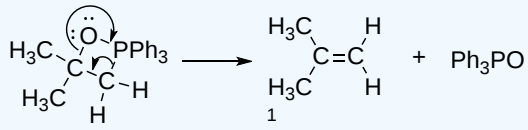
Nucleophillic attack on the carbonyl



Formation of a 4 membered ring



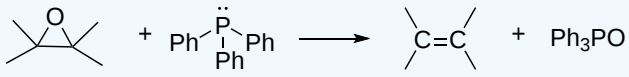
Formation of the alkene



1

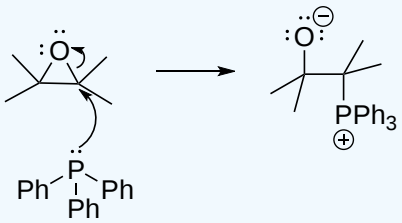
EXERCISE 19.11.6

It has been shown that reacting and epoxide with triphenylphosphine forms an alkene. Please propose a mechanism for this reaction. Review the section on epoxide reactions if you need help.

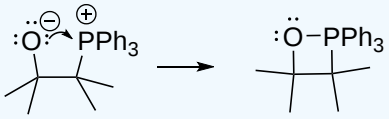


Answer

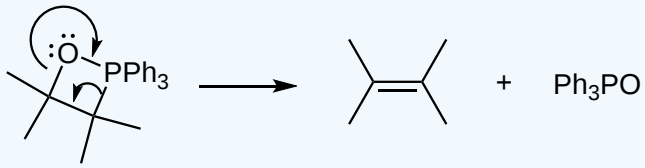
Nucleophillic attack on the epoxide



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)

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19.12 BIOLOGICAL REDUCTIONS

Objectives

After completing this section, you should be able to

1. determine whether or not a given aldehyde will undergo the Cannizzaro reaction.
2. write an equation to illustrate the Cannizzaro reaction.
3. identify the products formed when a given aldehyde undergoes a Cannizzaro reaction.
4. write the detailed mechanism of the Cannizzaro reaction.

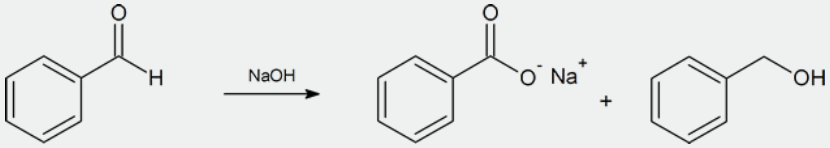
KEY TERMS

Make certain that you can define, and use in context, the key term below.

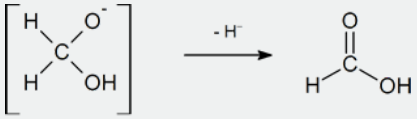
- Cannizzaro reaction

STUDY NOTES

In 1853 Stanislao Cannizzaro discovered that the base-induced disproportionation of an aldehyde resulted in a carboxylic acid (oxidation product) and an alcohol (reduction product).



Note that in the mechanism shown in the reading has an intermediate generated from methanal (formaldehyde) that effectively becomes a hydride (H^-) donor, which reduces a second molecule of methanal to methanol.

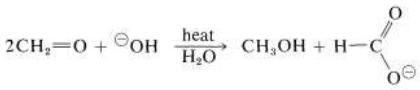


hydride donor

Carbonyl reductions are a part of important biological pathways in living organisms. Recall in Section 17.4 that NADH can donate H^- to reduce aldehydes and ketones. You may wish to review this section.

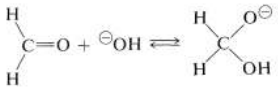
CANNIZZARO REACTION

A characteristic reaction of aldehydes without α hydrogens is the self oxidation-reduction they undergo in the presence of strong base. With methanal as an example,

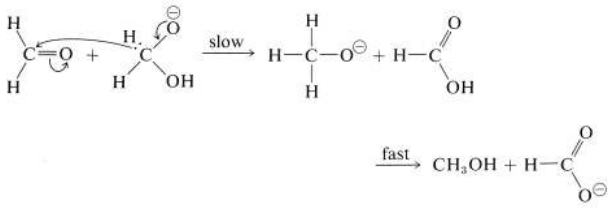


If the aldehyde has α hydrogens, other reactions usually occur more rapidly.

The mechanism of this reaction, usually called the **Cannizzaro reaction**,[4] combines many features of other processes studied in this chapter. The first step is reversible addition of hydroxide ion to the carbonyl group:



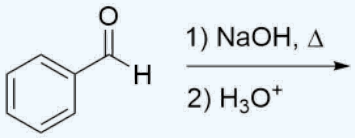
A hydrogen can be transferred as hydride ion to methanal from the hydroxyalkoxide ion, thereby reducing the methanal to methanol:



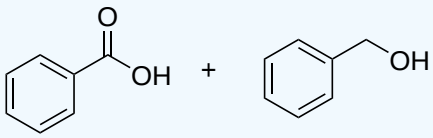
EXERCISE

? EXERCISE 19.12.1

Please draw the expected product(s) of the following reaction:



Answer



CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

16.5: Typical Carbonyl-Addition Reactions

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19.13 CONJUGATE NUCLEOPHILIC ADDITION TO ALPHA, BETA-UNSATURATED ALDEHYDES AND KETONES

Objectives

After completing this section, you should be able to

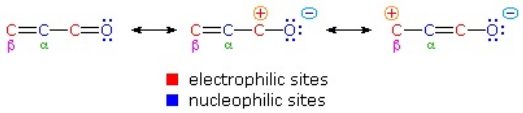
1. explain how the carbonyl group which is present in α, β-unsaturated aldehydes and ketones activates the carbon-carbon double bond so that it is susceptible to attack by nucleophiles.
2. write equations to illustrate the addition of amines, water and lithium diorganocopper reagents to α, β-unsaturated aldehydes and ketones.
3. identify the product formed from the reaction of a given primary or secondary amine with a given α, β-unsaturated aldehyde or ketone.
4. identify the aldehyde or ketone, the primary or secondary amine, or both, needed to prepare a given β-amino aldehyde or ketone.
5. identify the product formed from the reaction of an α, β-unsaturated aldehyde or ketone with water.
6. identify the product formed from the reaction of a given α, β-unsaturated aldehyde or ketone with a given lithium diorganocopper reagent.
7. identify the α, β-unsaturated aldehyde or ketone, the lithium diorganocopper reagent, or both, needed to prepare a given product through a conjugate addition reaction.

STUDY NOTES

At first this section may appear to contain a considerable amount of information, but you should realize that much of the material presented is really repetition. Essentially we see how three different nucleophilic reagents, primary and secondary amines, water and lithium diorganocoppers can add across a carbon-carbon double bond when the latter is conjugated to the carbonyl group of an aldehyde or ketone. Note that the first reagent can also react directly with the carbonyl group of an aldehyde or ketone when there is no conjugated carbon-carbon double bond present, but that the third reagent, lithium dialkylcopper, cannot do so.

You may be confused about the designation of the product from the conjugate addition to an α, β-unsaturated aldehyde or ketone as a 1,4 adduct. You can more clearly understand this name if you recognize that the proton added in the second step of the reaction first adds to the oxygen of the enolate ion to produce an enol. The latter then tautomerizes to the more stable keto form.

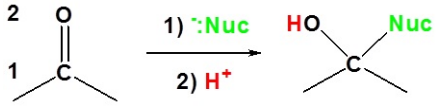
One of the largest and most diverse classes of reactions is composed of nucleophilic additions to a carbonyl group. Conjugation of a double bond to a carbonyl group transmits the electrophilic character of the carbonyl carbon to the beta-carbon of the double bond. These conjugated carbonyl are called enones or α, β unsaturated carbonyls. A resonance description of this transmission is shown below.



From this formula it should be clear that nucleophiles may attack either at the carbonyl carbon, as for any aldehyde, ketone or carboxylic acid derivative, or at the beta-carbon. These two modes of reaction are referred to as 1,2-addition and 1,4-addition respectively. A 1,4-addition is also called a conjugate addition.

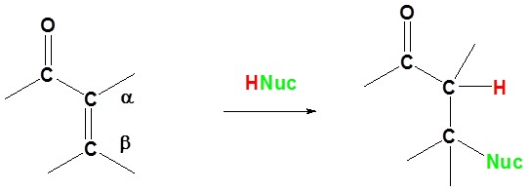
BASIC REACTION OF 1,2 ADDITION

Here the nucleophile adds to the carbon which is in the one position. The hydrogen adds to the oxygen which is in the two position.



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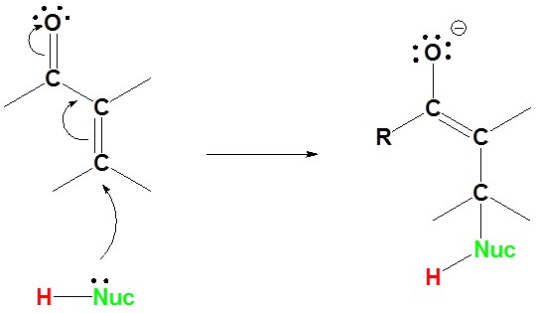
BASIC REACTION OF 1,4 ADDITION



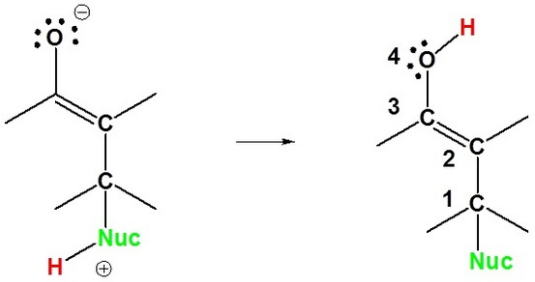
In 1,4 addition the Nucleophile is added to the carbon β to the carbonyl while the hydrogen is added to the carbon α to the carbonyl.

MECHANISM FOR 1,4 ADDITION

1) Nucleophilic attack on the carbon β to the carbonyl

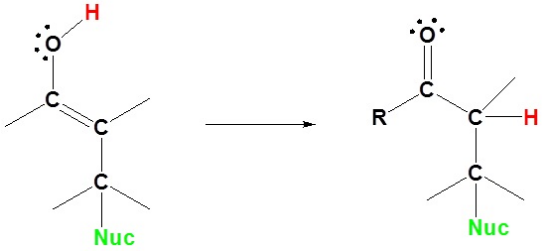


2) Proton Transfer

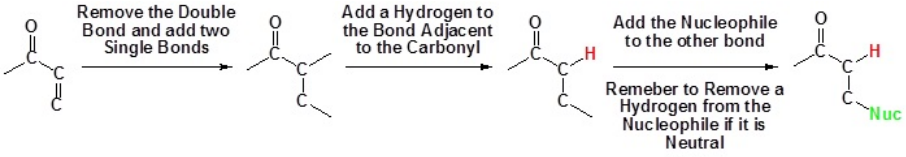


Here we can see why this addition is called 1,4. The nucleophile bonds to the carbon in the one position and the hydrogen adds to the oxygen in the four position.

3) Tautomerization



Going from reactant to products simplified



1,2 VS. 1,4 ADDITION

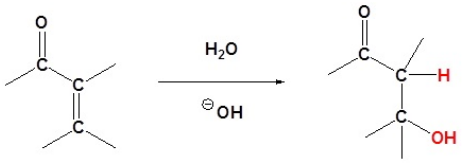
Whether 1,2 or 1,4-addition occurs depends on multiple variables but mostly it is determined by the nature of the nucleophile. During the addition of a nucleophile there is a competition between 1,2 and 1,4 addition products. If the nucleophile is a strong base, such as Grignard

reagents, both the 1,2 and 1,4 reactions are irreversible and therefor are under kinetic control. Since 1,2-additions to the carbonyl group are fast, we would expect to find a predominance of 1,2-products from these reactions.

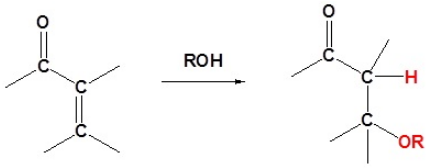
If the nucleophile is a weak base, such as alcohols or amines, then the 1,2 addition is usually reversible. This means the competition between 1,2 and 1,4 addition is under thermodynamic control. In this case 1,4-addition dominates because the stable carbonyl group is retained.

NUCLEOPHILES WHICH ADD 1,4 TO A, B UNSATURATED CARBONYLS

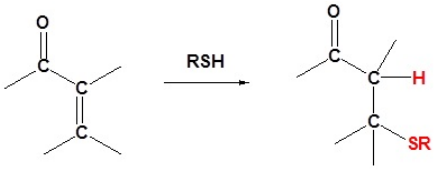
Water



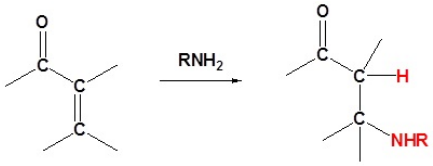
Alcohols



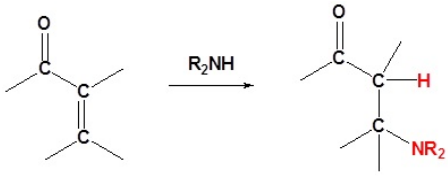
Thiols



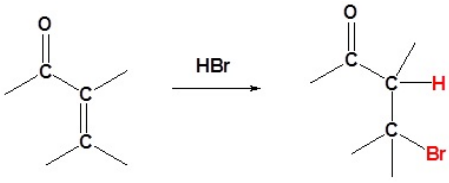
1° Amines



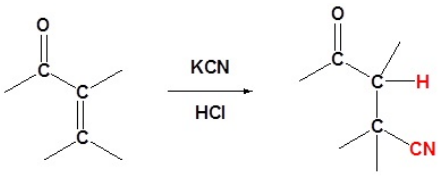
2° Amines



HBr



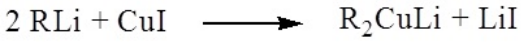
Cyanides



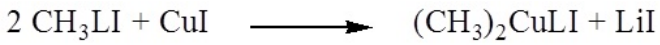
GILMAN REAGENTS

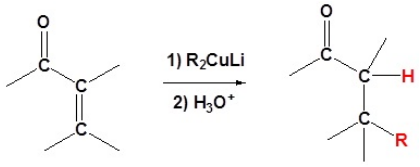
Another important reaction exhibited by organometallic reagents is metal exchange. Organolithium reagents react with cuprous iodide to give a lithium dimethylcopper reagent, which is referred to as a Gilman reagent. Gilman reagents are a source of carbanion like nucleophiles similar to Grignard and Organo lithium reagents. However, the reactivity of organocuprate reagents is slightly different and this difference will be exploited in different situations. In the case of α, β unsaturated carbonyls organocuprate reagents allow for an 1,4 addition of an alkyl group. As we will see later Grignard and Organolithium reagents add alkyl groups 1,2 to α, β unsaturated carbonyls

Organocuprate reagents are made from the reaction of organolithium reagents and CuI

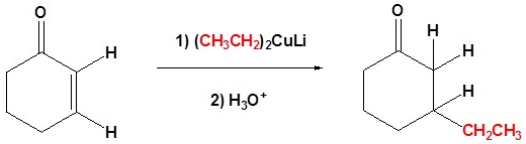


This acts as a source of $R:^-$



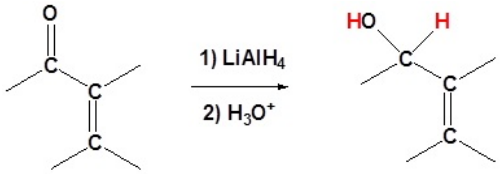


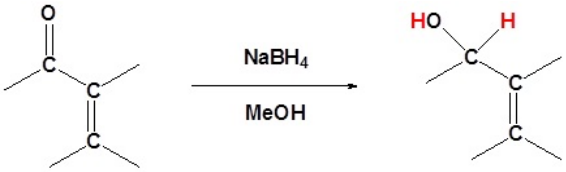
Example



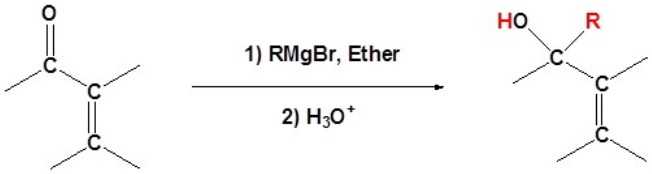
NUCLEOPHILES WHICH ADD 1,2 TO A, B UNSATURATED CARBONYLS

Metal Hydrides

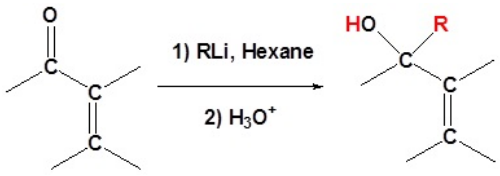




Grignard Reagents



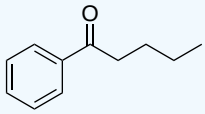
Organolithium Reagents



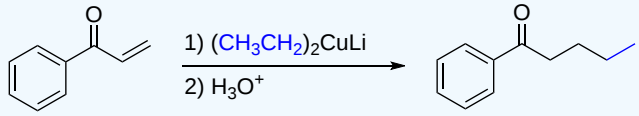
EXERCISES

EXERCISE 19.13.1

How would you make the following molecule using a 1,4 Conjugate Addition of a Gilman Reagen to a α, β Unsaturated Ketone?



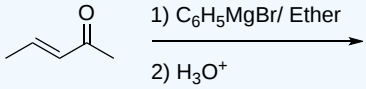
Answer



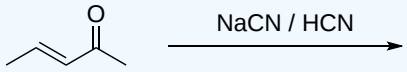
EXERCISE 19.13.2

Draw the bond-line structures for the products of the reactions below.

a)

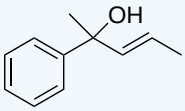


b)

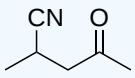


Answer

a)

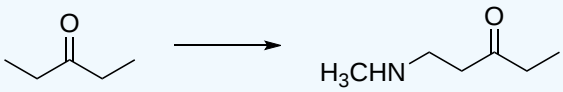


b)

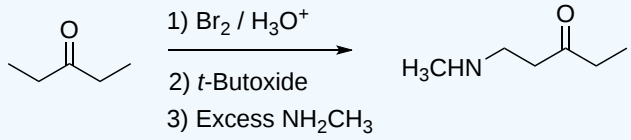


EXERCISE 19.13.3

Specify the reagents needed to perform the following chemical transformation.



Answer



CONTRIBUTORS AND ATTRIBUTIONS

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

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19.14 SPECTROSCOPY OF ALDEHYDES AND KETONES

Objectives

After completing this section, you should be able to

1. identify the region of the infrared spectrum in which the carbonyl absorption of aldehydes and ketones is found.
2. identify the region of the infrared spectrum in which the two characteristic C—H absorptions of aldehydes are found.
3. use a table of characteristic absorption frequencies to assist in the determination of the structure of an unknown aldehyde or ketone, given its infrared spectrum and other spectral or experimental data.
4. identify the region of a proton NMR spectrum in which absorptions caused by the presence of aldehydic protons and protons attached to the α-carbon atoms of aldehydes and ketones occur.
5. identify two important fragmentations that occur when aliphatic aldehydes and ketones are subjected to analysis by mass spectrometry.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- McLafferty rearrangement

STUDY NOTES

The appearance of a strong absorption at 1660–1770 cm^{-1} in the infrared spectrum of a compound is a clear indication of the presence of a carbonyl group. Although you need not remember the detailed absorptions it is important that you realize that the precise wavenumber of the infrared absorption can often provide some quite specific information about the environment of the carbonyl group in a compound. Notice how conjugation between a carbonyl group and a double bond (α, β-unsaturated aldehyde or ketone or aromatic ring) lowers the absorption by about 25–30 cm^{-1}.

You may wish to review the McLafferty rearrangement and the alpha cleavage in Section 12.3.

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.

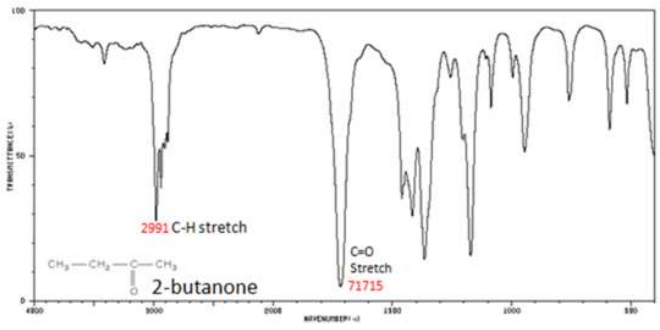


Figure 8. Infrared Spectrum of 2-Butanone

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.

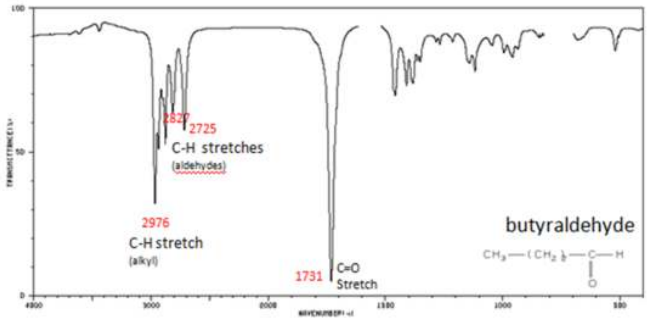
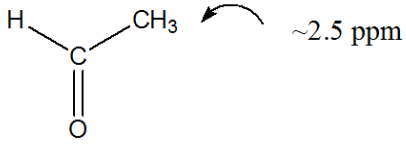


***Figure 9**. Infrared Spectrum of Butyraldehyde*

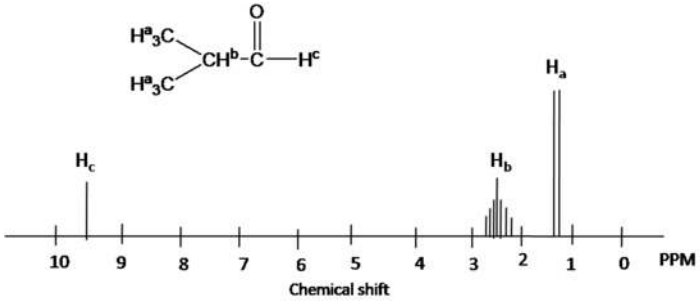
NMR SPECTRA

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).

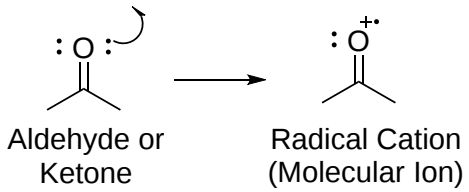


4) Splitting pattern is determined by (N+1) rule: Ha is split into two peaks by H_b(#of proton=1). H_b has the septet pattern by H_a (#of proton=6). H_c has one peak.(Note that H_c has doublet pattern by H_b due to vicinal proton-proton coupling.)

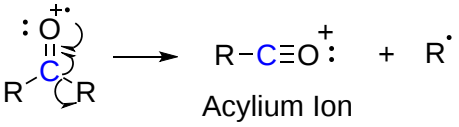
MASS SPECTRA

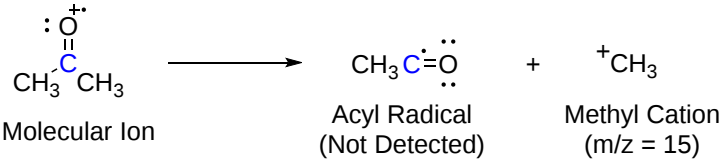
Aldehydes and ketones generally give moderately intense signals due to their molecular ions, M^+. Thus the determination of the molecular weight of a ketone by mass spectroscopy usually is not difficult. Furthermore, there are some characteristic fragmentation patterns that aid in structural identification. These are:

- Formation of the molecular ion:

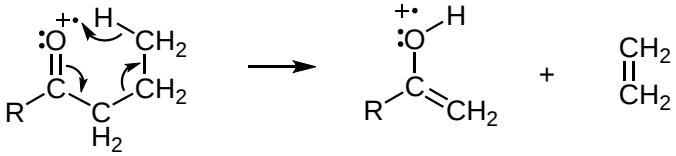


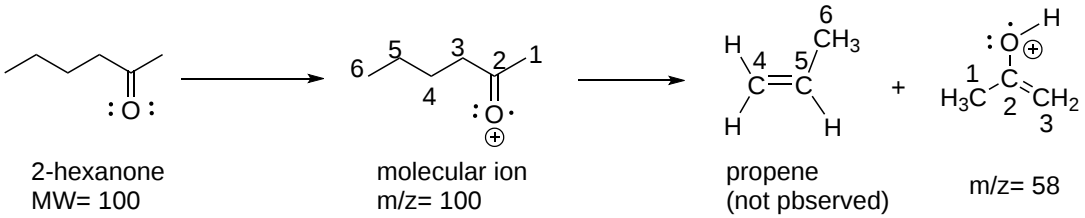
- *α cleavage to form an acylium ion. This is usually the base peak in the mass spectra.*



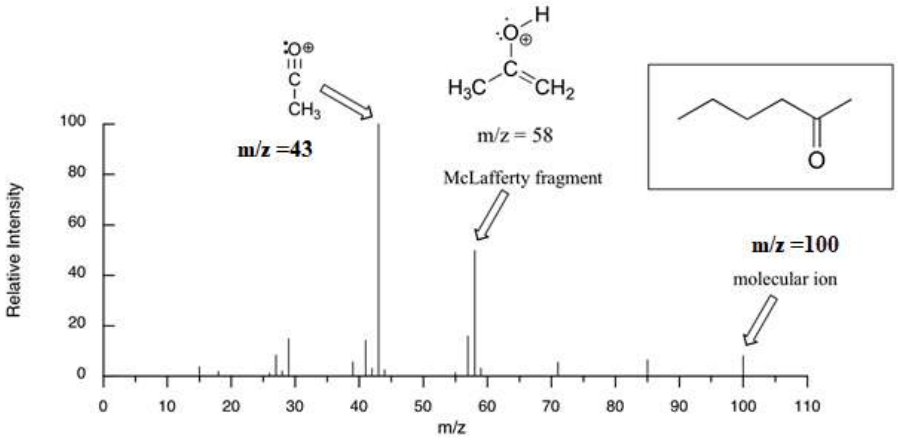


- *A common fragmentation pattern for larger carbonyl compounds is a transfer of γ hydrogen with β cleavage* called the **McLafferty rearrangement:**





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 an acylium ion formed after alpha cleavage is at m/z = 43. The molecular ion peak is at m/z =100.



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.S: ALDEHYDES AND KETONES (SUMMARY)

CONCEPTS & VOCABULARY

19.0 Chapter Objectives and Preview of Carbonyl Chemistry

- Aldehydes are carbonyl compounds with an R group and a hydrogen attached to the carbonyl carbon.
- Ketones are carbonyl compounds with two R groups attached to the carbonyl carbon.

19.1 Naming Aldehydes and Ketones

- Aldehydes are named following IUPAC rules with the standard ending -al.
- Ketones are named following IUPAC rules with the standard ending -one.
- Aldehydes have priority over ketones when both appear in the same molecule.

19.2 Preparing Aldehydes and Ketones

- Primary alcohols can be oxidized to aldehydes with PCC (pyridinium chlorochromate) or DMP (Dess-Martin Periodinane).
- Terminal alkynes can be hydrated to form aldehydes through hydroboration-oxidation reactions.
- Esters can be reduced to aldehydes with DIBAL-H.
- Acid chlorides can be reduced to aldehydes with hydrides.
- Nitriles can be reduced to aldehydes with DIBAL-H.
- Secondary alcohols can be oxidized to ketones with chromic acid/Jones reagent.
- Alkynes can be hydrated to form ketones.
- Aryl ketones can be formed by Friedel-Crafts acylation of aromatic rings.
- Nitriles can be reacted with Grignard reagents to form ketones.
- Alkenes can be cleaved with ozone to form aldehydes or ketones.
- Acid halides can be converted to ketones by reacting with Gilman reagents.

19.3 Oxidation of Aldehydes and Ketones

- Aldehydes can be oxidized more easily than ketones due to the aldehyde hydrogen.
- Jones reagent is a mixture of CrO_3 and aqueous acid.
- Aldehydes can be oxidized to carboxylic acids with chromium trioxide/Jones reagent.
- Ketones can undergo oxidative cleavage with very strong oxidizing agents such as potassium permanganate.
- Ketones can be oxidized to esters by peroxycarboxylic acids in a reaction known as Baeyer-Villiger oxidation.

19.4 Nucleophilic Addition Reactions of Aldehydes and Ketones

- Carbonyl bonds are polarized with a partial positive charge on the carbon making it an electrophile and a target for attack by nucleophiles.
- Neither aldehydes nor ketones have a good leaving group causing both to undergo nucleophilic addition reactions.
- Aldehydes are more reactive than ketones to nucleophilic addition reactions.

19.5 Nucleophilic Addition Reactions of Water: Hydration

- Gem-diols are molecules that have two hydroxide groups attached to the same carbon.
- Aldehydes and ketones can react with water under either acidic or basic conditions to form gem-diols.

19.6 Nucleophilic Addition Reactions of HCN: Cyanohydrin Formation

- Cyanohydrins are molecules with a cyanide and a hydroxide attached to the same carbon.
- Cyanohydrins can be formed from aldehydes or ketones by reacting with cyanide ion and a weak acid.

19.7 Nucleophilic Addition Reactions of Hydride and Grignard Reagents: Alcohol Formation

- Metal hydrides can reduce aldehydes and ketones to alcohols.
- Organometallic reagents include carbon bonds to metals which react similarly to carbanions.
- Grignard reagents (R-Mg-X) and organolithium compounds add to aldehydes and ketones to form alcohols.

19.8 Nucleophilic Addition of Amines: Imine and Enamine

- Imines are characterized by a carbon-nitrogen double bond.
- Reaction of aldehydes and ketones with primary amines can form imines.
- Reaction of aldehydes and ketones with secondary amines can form enamines.

19.9 Nucleophilic Addition of Hydrazine - The Wolff-Kishner Reaction

- Hydrazine will react with aldehydes and ketones to form hydrazones (similar to imine formation). Heating of the hydrazone with base converts it to an alkane.
- The combination of hydrazone formation and reduction (of aldehydes and ketones) is called the Wolff-Kishner reaction.

19.10 Nucleophilic Addition of Alcohols: Acetal Formation

- Hemiacetals have one hydroxide and one ether attached to a carbon.
- Acetals have two ethers attached to a carbon.
- Reaction of an aldehyde or ketone with an alcohol under acidic conditions forms a hemi-acetal. Continuation of the same reaction results in an acetal.
- Acetals can reform the aldehyde or ketone by reacting with acid.
- Acetals are useful as protecting groups due to the reversible nature of acetal formation.

19.11 Nucleophilic Addition of Phosphorun Ylides: The Wittig Reaction

- A molecule with positive and negative charges on adjacent atoms is called an ylide.
- Wittig reagents are organophosphorus ylides which can be drawn as a double bonded structure called a phosphorane.
- The Wittig reaction is used to convert an aldehyde or ketone into an alkene by reacting with an organophosphrous ylide.
- Oxaphosphetane intermediates containing a 4 membered ring including one oxygen and one phosphorus atom occur during the Wittig reaction.

19.12 Biological Reductions

- The Cannizzaro reaction allows an aldehyde to react with another like molecule in strong base to form one oxidized molecule (carboxylic acid) and one reduced molecule (alcohol).
- NADH, one of the most important biological reducing agents, uses a similar mechanism to the Cannizzaro reaction while reducing ketones in biological systems to alcohols while being converted to NAD^+.

19.13 Conjugate Nucleophilic Addition of alpha, beta-Unsaturated Aldehydes and Ketones

- α, β-unsaturated carbonyls have an alkene attached to the carbonyl carbon.
- Due to resonance delocalization, the β-carbon of an α, β-unsaturated carbonyl is electrophilic and will react with nucleophiles.
- α, β-unsaturated carbonyls can undergo 1,2 or 1,4 addition.
- 1,4 addition is also called conjugate addition.
- Lithium diorganocopper reagents are called Gilman reagents.
- Gilman reagents typically react with α, β-unsaturated carbonyls via conjugate addition.

19.14 Spectroscopy of Aldehydes and Ketones

- IR of aldehydes and ketones is defined strongly by the carbonyl stretching vibration.
- ^1H NMR of aldehydes show the aldehyde proton between 10 and 11 ppm as well as the protons on carbon adjacent to the carbonyl at about 2.5 ppm.
- ^1H NMR of ketones show the protons on carbon adjacent to the carbonyl at about 2.5 ppm.
- ^{13}C NMR of aldehydes and ketones show the carbonyl carbon at about 200 ppm.
- Mass spectra of aldehydes and ketones typically yield moderately intense molecular ions, M^+. They also can undergo some rearrangements that yield common fragmentation patterns.

SKILLS TO MASTER

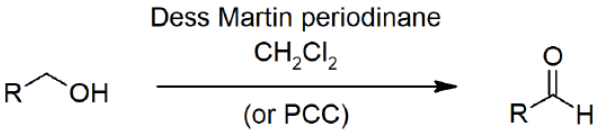
- Skill 19.1 Explain the relative reactivity of aldehydes vs. ketones to nucleophiles, based on carbonyl bond polarity.
- Skill 19.2 Name aldehydes and ketones using IUPAC rules.
- Skill 19.3 Draw the structure of an aldehyde or ketone from the IUPAC name.
- Skill 19.4 Interpret common names of aldehydes and ketones.
- Skill 19.5 Describe methods for preparing aldehydes and ketones.
- Skill 19.6 Draw mechanisms for oxidations of aldehydes and ketones.
- Skill 19.7 Explain general reactivity of aldehydes and ketones through the nucleophilic addition mechanism.
- Skill 19.8 Draw mechanisms for nucleophilic addition reactions to aldehydes and ketones including
  - Hydration
  - Cyanohydrin formation
  - Hydride Reduction

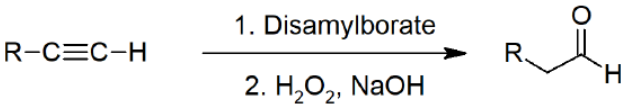
- Organometallic reactions
- Addition of amines
- Wolff-Kishner reaction
- Acetal formation
- Wittig reaction
- Cannizzaro reaction
- Conjugate addition

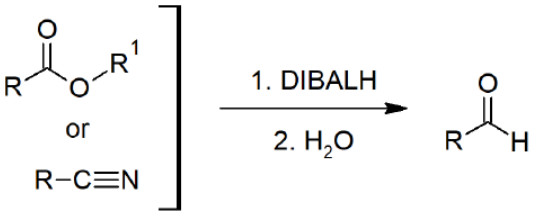
- Skill 19.9 Use IR, NMR and MS to identify aldehydes and ketones.

SUMMARY OF REACTIONS

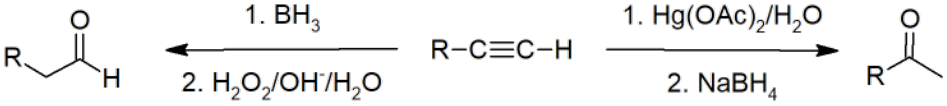
Aldehyde Preparation

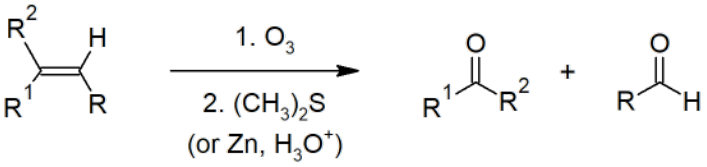




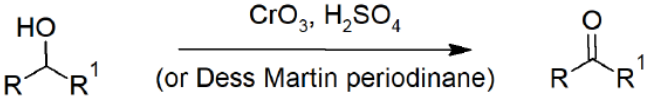


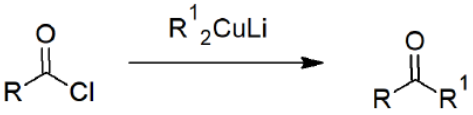
Aldehyde and Ketone Preparation

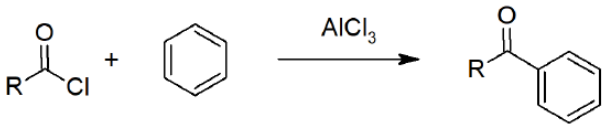


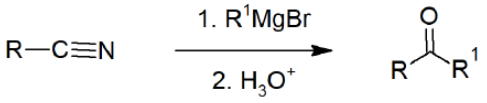


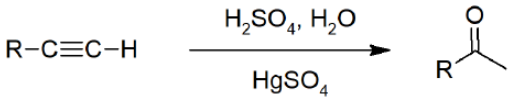
Ketone Preparation



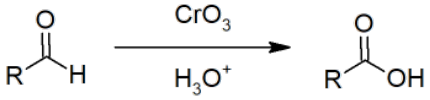


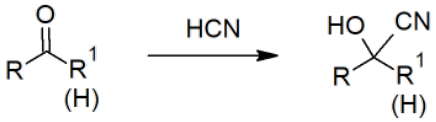


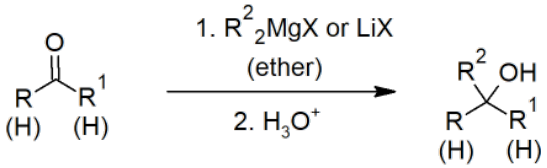


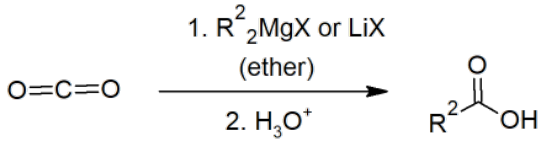


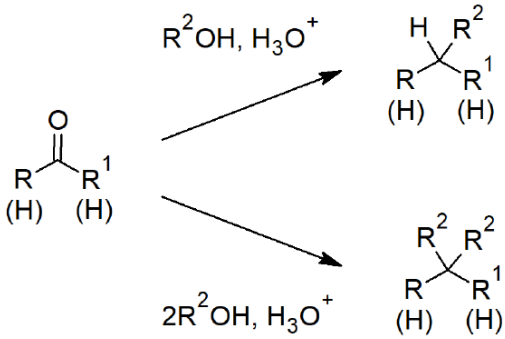
Aldehyde and Ketone Reactions

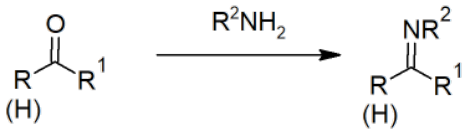


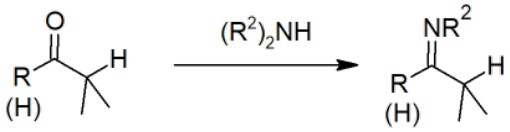


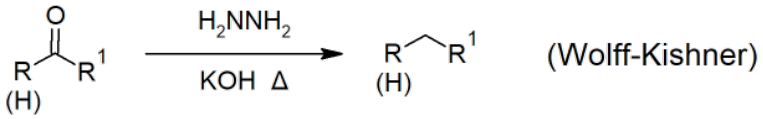


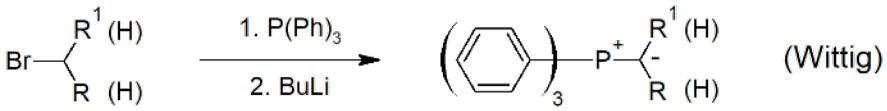


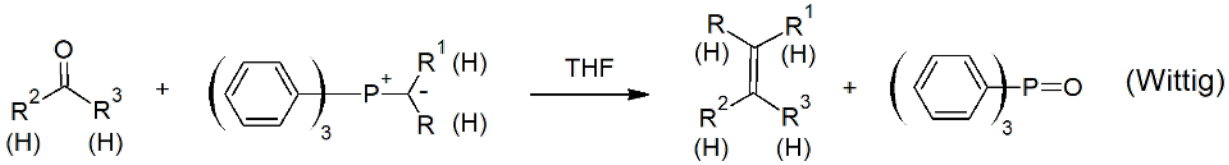


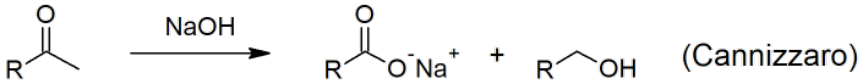




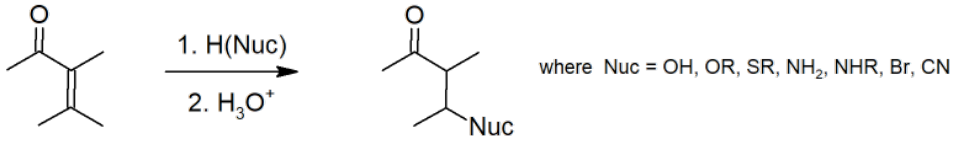


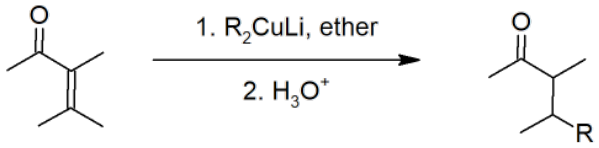






Conjugated Addition Reactions





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CHAPTER OVERVIEW

CHAPTER 20: CARBOXYLIC ACIDS AND NITRILES

This chapter presents a straightforward discussion of the chemistry of carboxylic acids (formerly called “fatty acids”) and nitriles. As usual, we begin with a description of how the compounds are named. We then consider the subtleties of their structure, and how these structural features influence physical properties, such as boiling point. We place considerable emphasis on the dissociation of carboxylic acids and the effect of substituents on acid strength.

We have already encountered a number of methods of preparing carboxylic acids. We shall review these methods, and learn about two additional procedures. The only reactions of carboxylic acids that we study in detail in this chapter are reduction and decarboxylation, although two other common reactions of carboxylic acids, alpha substitution and nucleophilic acyl substitution, will be described in later chapters.

We will then look at the formation of nitriles and their chemical reactivity; and our discussion of carboxylic acid and nitrile chemistry concludes with a look at the infrared and NMR spectra of these compounds, with emphasis on the characterization of carboxylic acids.

20: Carboxylic Acids and Nitriles

Chapter Objectives

20.0 Introduction

20.1 Naming Carboxylic Acids and Nitriles

20.2 Structure and Properties of Carboxylic Acids

20.3 Biological Acids and the Henderson-Hasselbalch Equation

20.4 Substituent Effects on Acidity

20.5 Preparing Carboxylic Acids

20.6 Reactions of Carboxylic Acids: An Overview

20.7 Chemistry of Nitriles

20.8 Spectroscopy of Carboxylic Acids and Nitriles

20.S: Carboxylic Acids and Nitriles (Summary)

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CHAPTER OVERVIEW

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CHAPTER OBJECTIVES

When you have completed Chapter 20, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design multi-step syntheses in which the reactions introduced in this chapter are used in conjunction with any of the reactions described in previous chapters.
3. solve road-map problems which require a knowledge of the chemistry of carboxylic acids.
4. define, and use in context, the key terms introduced in this chapter.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

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20.0 INTRODUCTION

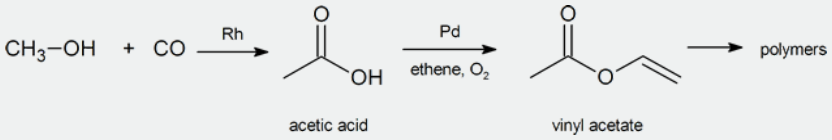
Objectives

After completing this section, you should be able to

1. list a number of naturally occurring carboxylic acids.
2. state one of the industrial uses of acetic acid.

STUDY NOTES

The global demand for acetic acid is about 6.5 million tonnes per year. A common industrial preparation of acetic acid is the catalytic oxidation of methanol with carbon monoxide. Much of the acetic acid produced is converted to vinyl acetate polymer and used in adhesives and paints.



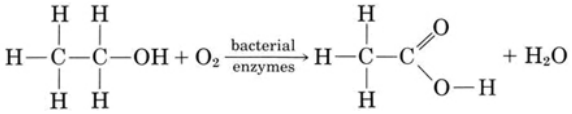
acetic acid vinyl acetate

Not only are carboxylic acids valuable, but they and their derivatives are useful starting materials for many synthetic products. Finally, carboxylic acids and their derivatives are also found in a variety of natural systems and important biological pathways.

CARBOXYLIC ACIDS

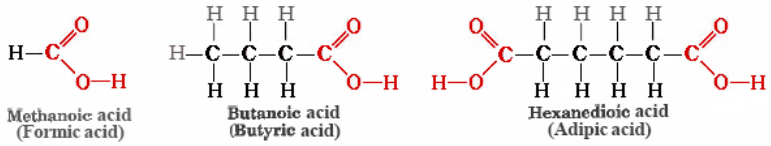
Serving wine usually involves a rather elaborate ceremony in which the host tastes the wine before pouring it for the guests. One reason for this is the possibility that the wine may have been spoiled by exposure to air.

Certain bacterial enzymes are capable of converting ethanol to ethanoic acid (acetic acid) when oxygen is present:



The same reaction occurs when cider changes into vinegar, which contains 4 to 5 percent acetic acid. Acetic acid gives vinegar its sour taste and pungent odor and can do the same thing to wine.

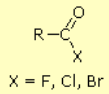
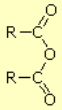
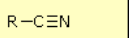
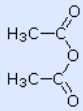
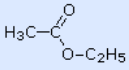
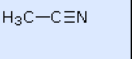
Acetic acid, CH_3COOH, is an example of the class of compounds called **carboxylic acids**, each of which contains one or more carboxyl groups, COOH. The general formula of a carboxylic acid is RCOOH. Some other examples are



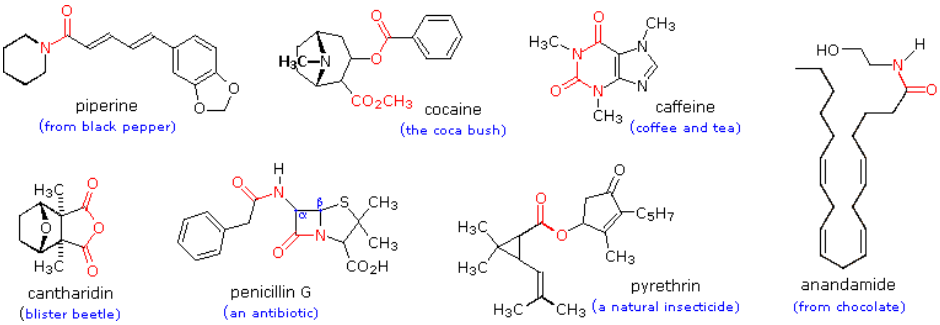
Formic acid (the name comes from Latin word *formica* meaning “ant“) is present in ants and bees and is responsible for the burning pain of their bites and stings. Butyric acid, a component of rancid butter and Limburger cheese, has a vile odor. Adipic acid is an example of a dicarboxylic acid—it has two functional groups—and is used to make nylon.

CARBOXYLIC ACID DERIVATIVES

Other functional group combinations with the carbonyl group can be prepared from carboxylic acids, and are usually treated as related derivatives. Five common classes of these **carboxylic acid derivatives** are listed in the following table. Although nitriles do not have a carbonyl group, they are included here because the functional carbon atoms all have the same oxidation state. The top row (yellow shaded) shows the general formula for each class, and the bottom row (light blue) gives a specific example of each. As in the case of amines, amides are classified as 1º, 2º or 3º, depending on the number of alkyl groups bonded to the nitrogen.

acyl halide	anhydride	ester	amide	nitrile
 X = F, Cl, Br or I			 R′ = H or alkyl	
 propanoyl chloride	 acetic anhydride	 ethyl acetate	 formamide	 acetonitrile

Functional groups of this kind are found in many kinds of natural products. Some examples are shown below with the functional group colored red. Most of the functions are amides or esters, cantharidin being a rare example of a natural anhydride. Cyclic esters are called **lactones**, and cyclic amides are referred to as **lactams**. Penicillin G has two amide functions, one of which is a β-lactam. The Greek letter locates the nitrogen relative to the carbonyl group of the amide.



CONTRIBUTORS

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- 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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- **Related Derivatives** by William Reusch is licensed CC BY-NC-SA 4.0.

20.1 NAMING CARBOXYLIC ACIDS AND NITRILES

Objectives

After completing this section, you should be able to

1. write the IUPAC name of a carboxylic acid, given its Kekulé, condensed or shorthand structure.
2. draw the condensed or shorthand structure of a carboxylic acid, given its IUPAC name.
3. draw the structure of the following carboxylic acids, given their trivial names: formic acid and acetic acid.
4. provide an acceptable name for a nitrile of given structure.
5. draw the condensed or shorthand structure of a nitrile, give either its trivial or IUPAC name.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- carboxylic acid
- nitrile

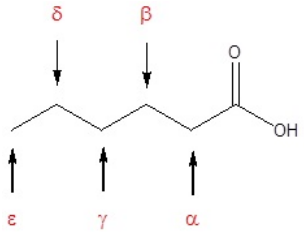
STUDY NOTES

You need not memorize all the trivial names listed in the table, just remember the two names identified in Objective 3, above.

CARBOXYLIC ACIDS, RCO_2H

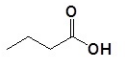
The IUPAC system of nomenclature assigns a characteristic suffix to these classes. The **–e** ending is removed from the name of the parent chain and is replaced **-anoic acid**. Since a carboxylic acid group must always lie at the end of a carbon chain, it is always is given the #1 location position in numbering and it is not necessary to include it in the name.

Many carboxylic acids are called by the common names. These names were chosen by chemists to usually describe a source of where the compound is found. In common names of aldehydes, carbon atoms near the carboxyl group are often designated by Greek letters. The atom adjacent to the carbonyl function is alpha, the next removed is beta and so on.

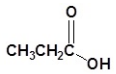


Formula	Common Name	Source	IUPAC Name	Melting Point	Boiling Point
HCO_2H	formic acid	ants (L. formica)	methanoic acid	8.4 ºC	101 ºC
CH_3CO_2H	acetic acid	vinegar (L. acetum)	ethanoic acid	16.6 ºC	118 ºC
$CH_3CH_2CO_2H$	propionic acid	milk (Gk. protus prion)	propanoic acid	-20.8 ºC	141 ºC
$CH_3(CH_2)_2CO_2H$	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

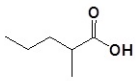
Example (Common Names Are in Red)



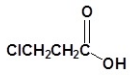
Butanoic acid
(Butyric Acid)



Propanoic acid
(Propionic Acid)



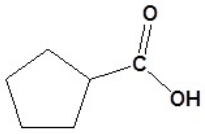
2-Methylpentanoic acid
(β-Methylvaleric acid)



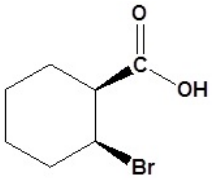
3-Chloropropanoic acid
(γ-Chloropropionic acid)

NAMING CARBOXYL GROUPS ADDED TO A RING

When a carboxyl group is added to a ring the suffix **-carboxylic acid** is added to the name of the cyclic compound. The ring carbon attached to the carboxyl group is given the #1 location number.

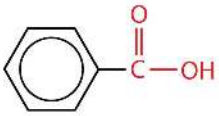


Cyclopentanecarboxylic acid



Cis-2-Bromocyclohexanecarboylic acid

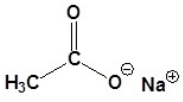
The acid with the carboxyl group attached directly to a benzene ring is called benzoic acid (C_6H_5COOH).



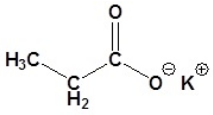
Benzoic acid

NAMING CARBOXYLATES

Salts of carboxylic acids are named by writing the name of the cation followed by the name of the acid with the **–ic acid** ending replaced by an **–ate** ending. This is true for both the IUPAC and Common nomenclature systems.



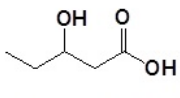
Sodium ethanoate
(Sodium Acetate)



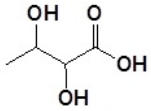
Potassium Propanoate
(Potassium propionate)

NAMING CARBOXYLIC ACIDS WHICH CONTAIN OTHER FUNCTIONAL GROUPS

Carboxylic acids are given the highest nomenclature priority by the IUPAC system. This means that the carboxyl group is given the lowest possible location number and the appropriate nomenclature suffix is included. In the case of molecules containing carboxylic acid and alcohol functional groups the OH is named as a hydroxyl substituent. However, the **l** in hydroxyl is generally removed.

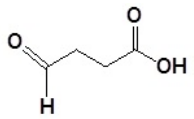


3-Hydroxypentanoic acid

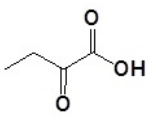


2,3-Dihydroxybutanoic acid

In the case of molecules containing a carboxylic acid and aldehydes and/or ketones functional groups the carbonyl is named as a "Oxo" substituent.

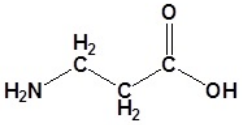


4-Oxobutanoic acid

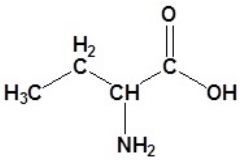


2-Oxobutanoic acid

In the case of molecules containing a carboxylic acid an amine functional group the amine is named as an "amino" substituent.



3-Aminopropanoic acid

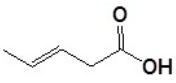


2-Aminobutanoic acid

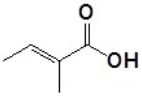
When carboxylic acids are included with an alkene the following order is followed:

(Location number of the alkene)-(Prefix name for the longest carbon chain minus the -ane ending)-(an –enoic acid ending to indicate the presence of an alkene and carboxylic acid)

Remember that the carboxylic acid has priority so it should get the lowest possible location number. Also, remember that cis/tran or E/Z nomenclature for the alkene needs to be included if necessary.



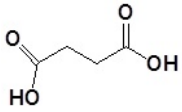
Trans-3-pentenoic acid



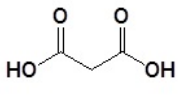
(E)-2-Methyl-2-butenoic acid

NAMING DICARBOXYLIC ACIDS

For dicarboxylic acids the location numbers for both carboxyl groups are omitted because both functional groups are expected to occupy the ends of the parent chain. The ending **–dioic acid** is added to the end of the parent chain.



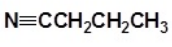
Butanedioic acid



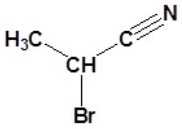
Propanedioic acid

NAMING NITRILES

Name the parent alkane (include the carbon atom of the nitrile as part of the parent) followed with the word -nitrile. The carbon in the nitrile is given the #1 location position. It is not necessary to include the location number in the name because it is assumed that the functional group will be on the end of the parent chain.

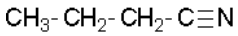


Butane nitrile



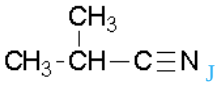
2-Bromopropane nitrile

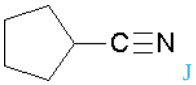
Cycloalkanes are followed by the word -carbonitrile. The substituent name is cyano.



- 1-butanenitrile or 1-cyanopropane

Try to name the following compounds using these conventions



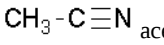


J

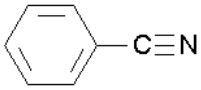
Try to draw structures for the following compounds

- butanedinitrile
- 2-methycyclohexanecarbonitrile

Some common names that you should know are...



acetonitrile



benzonitrile

Try to draw a structure for the following compound

- 2-methoxybenzonitrile

CONTRIBUTORS AND ATTRIBUTIONS

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

Richard Banks (Boise State University)

20.1 Naming Carboxylic Acids and Nitriles is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

20.2 STRUCTURE AND PROPERTIES OF CARBOXYLIC ACIDS

Objectives

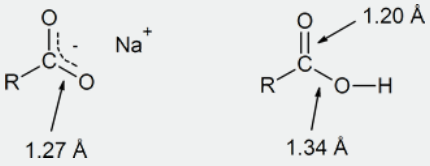
After completing this section, you should be able to

1. describe the geometry and electronic structure of a simple carboxylic acid; for example, acetic acid.
2. describe the hydrogen bonding that occurs between carboxylic acid molecules, and hence account for the relatively high boiling points of these compounds.
3. write an expression for the dissociation constant of a given carboxylic acid, and use it to calculate dissociation constants, percentage dissociation, etc.
4. identify carboxylic acids as being weaker acids than mineral acids, such as hydrochloric acid, but stronger acids than alcohols.
5. use the concept of resonance to explain why carboxylic acids are stronger acids than alcohols.
6. draw an orbital picture of a carboxylate anion to show the equivalence of the two oxygen atoms.
7. explain why the two carbon-oxygen bond lengths are identical in sodium carboxylate, but different in carboxylic acid.
8. write an equation for the reaction of a carboxylic acid with a base, such as sodium hydroxide.

STUDY NOTES

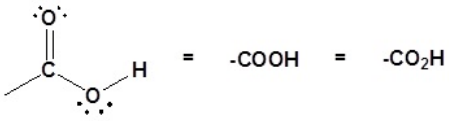
You might wish to review Sections 2.7, “Acids and Bases: The Brønsted-Lowry Definition” and 6.7, “Describing a Reaction: Equilibria, Rates, and Energy Changes” in conjunction with this section.

In the reading, the discussion of the role of resonance in the acidity of a carboxylic acid explains that the two carbon-oxygen bonds in the delocalized carboxylate anion are identical (both 1.27 Å). However, in the structure of a carboxylic acid the C—O bond (1.20 Å) is shorter than the C—OH bond (1.34 Å).



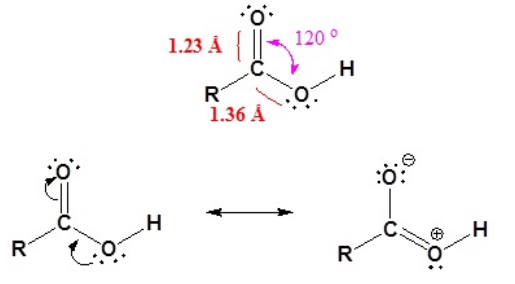
STRUCTURE OF THE CARBOXYL ACID GROUP

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.



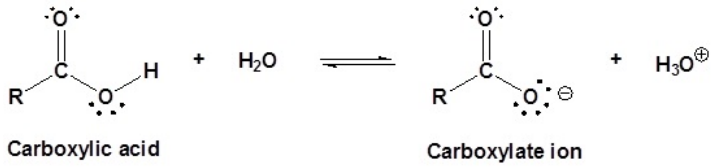
Carboxyl Group

The carbon and oxygen in the carbonyl are both sp2 hybridized which give a carbonyl group a basic trigonal shape. The hydroxyl oxygen is also sp2 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 will be discussed later.



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

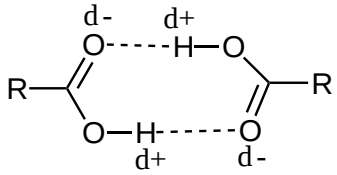
The table at the beginning of this page gave the melting and boiling points for a homologous group of carboxylic acids having from one to ten carbon atoms. The boiling points increased with size in a regular manner, but the melting points did not. Unbranched acids made up of an even number of carbon 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).

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

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.

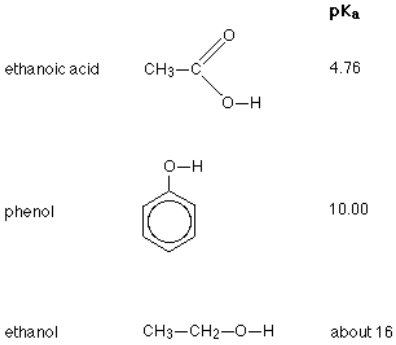


Intermolecular hydrogen bonding in carboxylic acids.

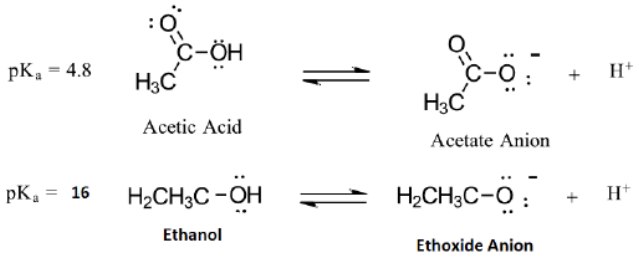
COMPARING THE STRENGTHS OF WEAK ACIDS

EDIT SECTION

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:



Remember - the smaller the number the stronger the acid. Comparing the other two to ethanoic acid, you will 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 findamental 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.

ACIDITY OF CARBOXYLIC ACIDS

The pK_a 's of some typical carboxylic acids are listed in the following table. When we compare these values with those of comparable alcohols, such as ethanol (pK_a = 16) and 2-methyl-2-propanol (pK_a = 19), it is clear that carboxylic acids are stronger acids by over ten powers of ten! Furthermore, electronegative substituents near the carboxyl group act to increase the acidity.

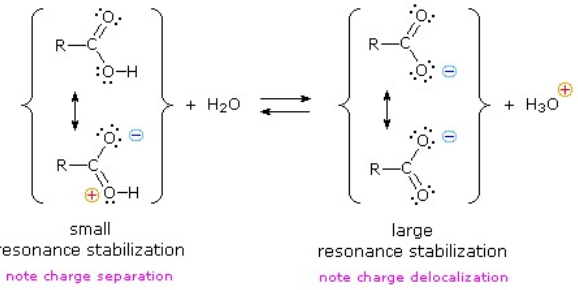
Compound	pK_a	Compound	pK_a
HCO_2H	3.75	$CH_3CH_2CH_2CO_2H$	4.82
CH_3CO_2H	4.74	$ClCH_2CH_2CH_2CO_2H$	4.53
FCH_2CO_2H	2.65	$CH_3CHClCH_2CO_2H$	4.05
$ClCH_2CO_2H$	2.85	$CH_3CH_2CHClCO_2H$	2.89
$BrCH_2CO_2H$	2.90	$C_6H_5CO_2H$	4.20
ICH_2CO_2H	3.10	$p\text{-}O_2NC_6H_4CO_2H$	3.45
Cl_3CCO_2H	0.77	$p\text{-}CH_3OC_6H_4CO_2H$	4.45

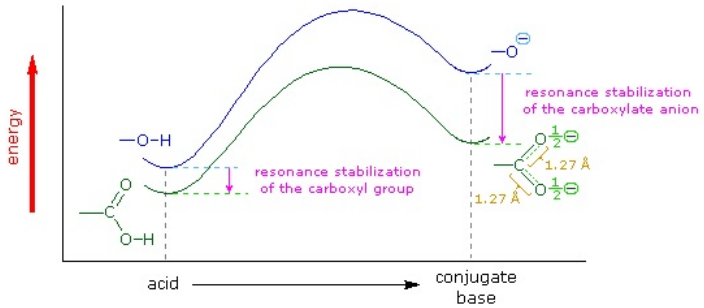
Why should the presence of a carbonyl group adjacent to a hydroxyl group have such a profound effect on the acidity of the hydroxyl proton? To answer this question we must return to the nature of acid-base equilibria and the definition of pK_a , illustrated by the general equations given below.

$$H\text{–}A + H_2O \rightleftharpoons H_3O^{\oplus} + A:^{\ominus} \qquad K_{eq} = \frac{[H_3O^{\oplus}]\,[A:^{\ominus}]}{[HA]\,[H_2O]}$$

$$K_a = \frac{[H_3O^{\oplus}]\,[A:^{\ominus}]}{[HA]} \qquad pK_a = -\log K_a = \log\left(\frac{1}{K_a}\right)$$

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.





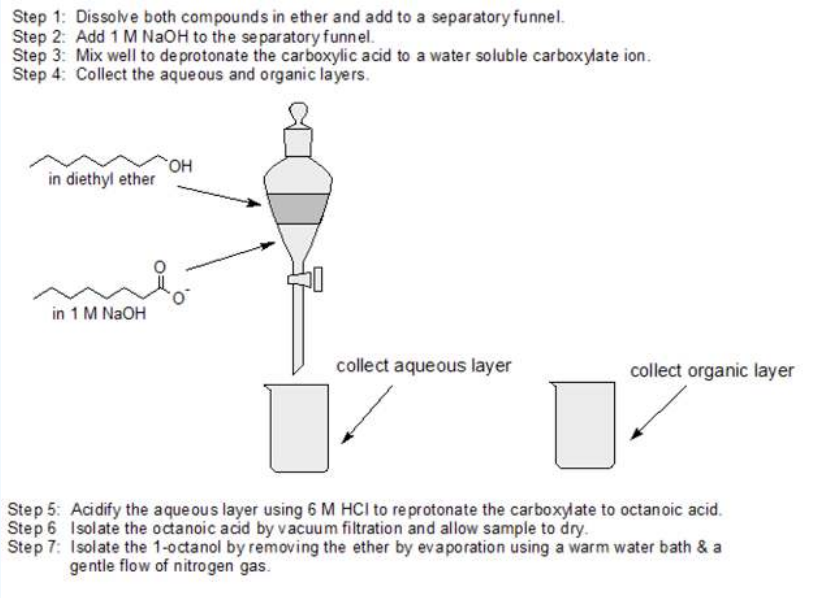
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EXERCISES

EXERCISE 20.2.1

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



EXERCISE 20.2.2

What percentage of propanoic acid (CH_3CH_2COOH) is dissociated into its conjugate base in a 0.20 M aqueous solution? $K_a = 1.32 \times 10^{-5}$

Answer

From the acid equilibrium expression we get that:

$[CH_3CH_2COO^-][H_3O^+]/[CH_3CH_2COOH] = K_a = 1.32 \times 10^{-5}$

$[X][X]/[0.20\ M - X] = 1.32 \times 10^{-5}$

Assume X is small compared to 0.20 M

$[X]^2/[0.20\ M] = 1.32 \times 10^{-5}$

$X = [CH_3CH_2COO^-] = 1.62 \times 10^{-3}$ M

$[CH_3CH_2COO^-] / [CH_3CH_2COOH] \times 100 = \%\text{Disassociation}$

1.62×10^{-3} M / 0.20 M X 100 = **0.812%**

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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20.3 BIOLOGICAL ACIDS AND THE HENDERSON-HASSELBALCH EQUATION

Objectives

After completing this section, you should be able to

1. identify the form that carboxylic acids take within living cells.
2. use the Henderson-Hasselbalch equation to calculate the percentages of dissociated and undissociated acids [A^-] and [HA] in a solution, given the pK_a value of the acid and the pH of the solution.
3. explain why cellular carboxylic acids are always referred to by the name of their anion.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- Henderson-Hasselbalch equation
- physiological pH

ORGANIC MOLECULES IN BUFFERED SOLUTION: THE HENDERSON-HASSELBALCH EQUATION

The environment inside a living cell, where most biochemical reactions take place, is an aqueous buffer with pH ~ 7 (or sometimes referred to as the physiological pH). Recall from your General Chemistry course that a buffer is a solution of a weak acid and its conjugate base. The key equation for working with buffers is the Henderson-Hasselbalch equation:

The Henderson-Hasselbalch equation:

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

The equation tells us that if our buffer is an equimolar solution of a weak acid and its conjugate base, the pH of the buffer will equal the pK_a of the acid (because the log of 1 is equal to zero). If there is more of the acid form than the base, then of course the pH of the buffer is lower than the pK_a of the acid.

The Henderson-Hasselbalch equation is particularly useful when we want to think about the protonation state of different biomolecule functional groups in a pH 7 buffer. When we do this, we are always assuming that the concentration of the biomolecule is small compared to the concentration of the buffer components. (The actual composition of physiological buffer is complex, but it is primarily based on phosphoric and carbonic acids.).

Imagine an aspartic acid residue located on the surface of a protein in a human cell. Being on the surface, the side chain is in full contact with the pH 7 buffer surrounding the protein. In what state is the side chain functional group: the protonated state (a carboxylic acid) or the deprotonated state (a carboxylate ion)?

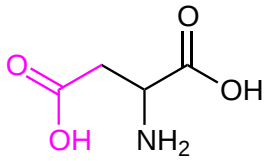


Figure 20.3.1: Aspartic acid with the carboxylic acid side-chain highlighted. (CC BY-SA 4.0; Layne Morsch via LibreTexts)

Using the Henderson-Hasselbalch equation, we fill in our values for the pH of the buffer and a rough pKa approximation of $pK_a = 5$ for the carboxylic acid functional group. Doing the math, we find that the ratio of carboxylate to carboxylic acid is about 100 to 1: the carboxylic acid is almost completely ionized (in the deprotonated state) inside the cell. This result extends to all other carboxylic acid groups you might find on natural biomolecules or drug molecules: in the physiological environment, carboxylic acids are almost completely deprotonated. Indeed, often cellular carboxylic acids are often referred to by the name of their anion. So rather than pyruvic acid, or acetic acid or lactic acid, it is pyruvate, acetate or lactate.

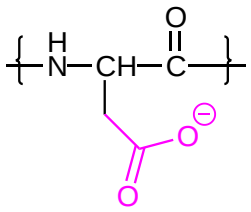


Figure 20.3.2: Aspartate (as part of a protein or polypeptide). (CC BY-SA 4.0; Layne Morsch via LibreTexts)

While we are most interested in the state of molecules at pH 7, the Henderson-Hasselbalch equation can of course be used to determine the protonation state of functional groups in solutions buffered to other pH levels. The exercise below provide some practice in this type of calculation.

EXERCISES

EXERCISE 20.3.1

What is the pH of an aqueous buffer solution that is 30 mM in acetic acid and 40 mM in sodium acetate? The pK_a of acetic acid is 4.8.

Solution

This is a direct application of the Henderson-Hasselbalch equation.

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

The ratio of base to acid is 40/30, or 1.33. Therefore, substituting these values and the pK_a results in

$$\begin{aligned} pH &= 4.8 + \log\left(\frac{40}{30}\right) \\ &= 4.8 + \log 1.33 \\ &= 4.8 + 0.125 \\ &= 4.9 \end{aligned}$$

EXERCISE 20.3.2

What is the ratio of acetate ion to neutral acetic acid when a small amount of acetic acid (pK_a = 4.8) is dissolved in a buffer of pH 2.8? pH 3.8? pH 4.8? pH 5.8? pH 6.8?

Answer

We use the Henderson-Hasselbalch equation and let the base to acid ratio be x.

For pH = 2.8:

$$2.8 = 4.8 + \log x$$

$x = 0.01 to 1$

- pH 3.8, the ratio is 0.10 to 1
- pH 4.8, the ratio is 1.0 to 1
- pH 5.8, the ratio is 10 to 1
- pH 6.8, the ratio is 100 to 1

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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20.4 SUBSTITUENT EFFECTS ON ACIDITY

Objectives

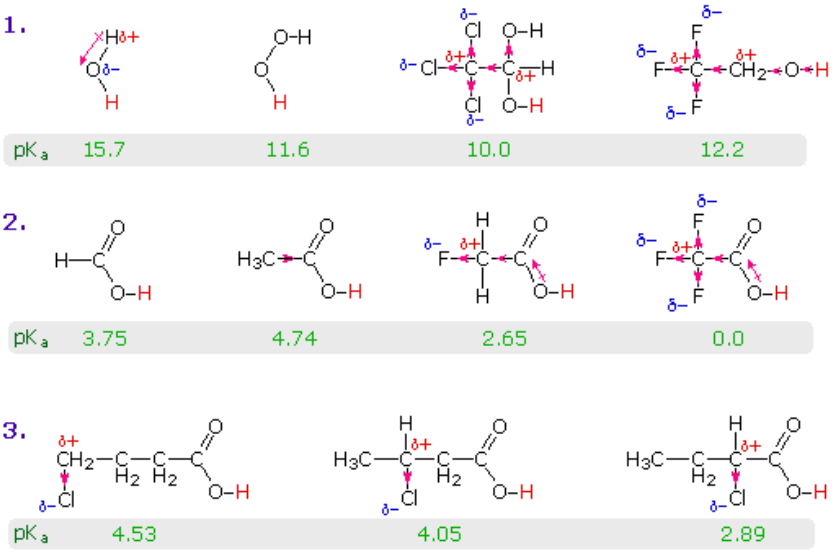
After completing this section, you should be able to

1. list a given series of carboxylic acids in order of increasing or decreasing acidity.
2. explain the difference in acidity between two or more given carboxylic acids.
3. arrange a series of substituted benzoic acids in order of increasing or decreasing acidity.
4. determine whether a given substituted benzoic acid will be more or less acidic than benzoic acid.
5. decide which of two or more substituted benzoic acids is the most acidic, and explain your decision on the basis of the electron-withdrawing or electron-releasing ability of the substituent.
6. use the K_a (or pK_a) of a substituted benzoic acid to predict the effect that the substituent has on the susceptibility of the benzene ring to electrophilic attack.

STUDY NOTES

You have already seen how the presence of an electron-withdrawing or electron-releasing group affects the stability of a positively charged carbocation. Now you see how these groups affect the stability of carboxylate anions, and in turn, determine the dissociation constant of a carboxylic acid.

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.

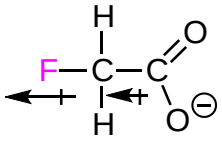


Water is less acidic than hydrogen peroxide because hydrogen is less electronegative than oxygen, and the covalent bond joining these atoms is polarized in the manner shown. Alcohols are slightly less acidic than water, due to the poor electronegativity of carbon, but chloral hydrate, $Cl_3CCH(OH)_2$, 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).

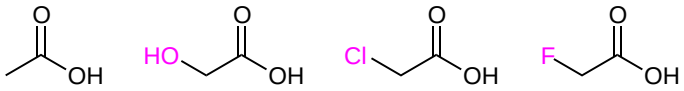
WITHDRAWING INDUCTIVE EFFECTS

A fluorine atom is more electronegative than a hydrogen atom, and thus it is able to 'induce', or 'pull' the electron density of covalent bonds towards itself. In the fluoroacetate anion, the electrons in the C-F covalent bond are pulled toward the fluorine giving the carbon a partial positive charge. The positively charged carbon, in turn, draws electron density away from the carboxylate anion, dispersing the charge, and creating a stabilizing effect. Stabilizing the carboxylate anion increases the acidity of the corresponding carboxylic acid. In this context, the fluorine substituent is acting as an **electron-withdrawing group**.



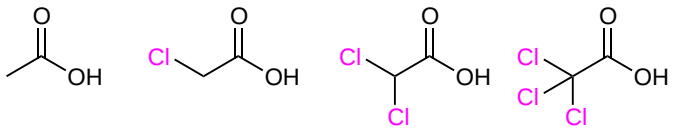
Fluoroacetate anion stabilized by electron withdrawing inductive effect of fluorine

A similar effect is seen when other electron-withdrawing groups are attached to $-CH_2CO_2H$. As the power of the electron-withdrawing group becomes stronger there is a corresponding drop in the pK_a of the carboxylic acid.



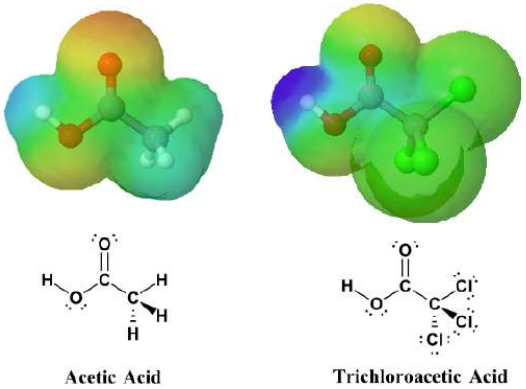
$pK_a = 4.8$ $pK_a = 3.9$ $pK_a = 2.8$ $pK_a = 2.6$

The presence of multiple electron-withdrawing groups compounds the inductive effect and continues to increase the acidity of the carboxylic acid. Dichloroacetic is a stronger acid than chloroacetic acid, and trichloroacetic acid is even stronger.



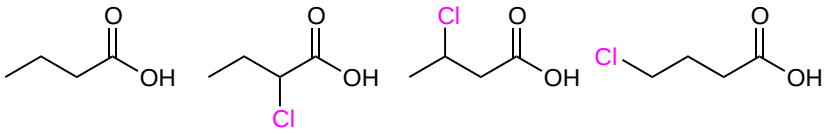
$pK_a = 4.8$ $pK_a = 2.8$ $pK_a = 1.3$ $pK_a = 0.64$

The inductive effects of chlorine be clearly seen when looking at the electrostatic potential maps of acetic acid (Left) and trichloroacetic acid (Right). The O-H bond in trichloroacetic acid is highly polarized, as shown by the dark blue color making it a much stronger acid than acetic acid.



Acetic Acid Trichloroacetic Acid

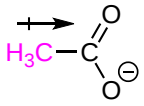
Because inductive effects are not transmitted effectively through covalent bonds, the acid-strengthening effect falls off rapidly as the number of sigma bonds between the carboxylic acid and the electron-withdrawing group increases. A distance of three sigma bonds almost completely eliminates chlorine's inductive effect in 4-chlorobutanoic acid, giving it a similar pK_a value to unsubstituted butanoic acid.



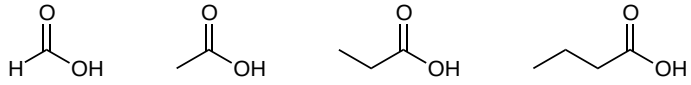
$pK_a = 4.8$ $pK_a = 2.8$ $pK_a = 4.0$ $pK_a = 4.5$

DONATING INDUCTIVE EFFECTS

Alkyl groups (hydrocarbons) are inductively electron-donating. In this case, the inductive effects pushes electron density onto the carboxylate anion, producing a destabilizing effect, decreasing the acidity of the carboxylic acid.



Lengthening the alkyl chain of a carboxylic acid can increase this inductive effect but it no longer decreases the acidity further after the chain is about three carbons long.

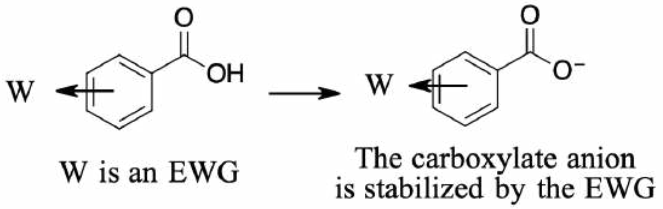


$pK_a = 3.75$ $pK_a = 4.76$ $pK_a = 4.87$ $pK_a = 4.82$

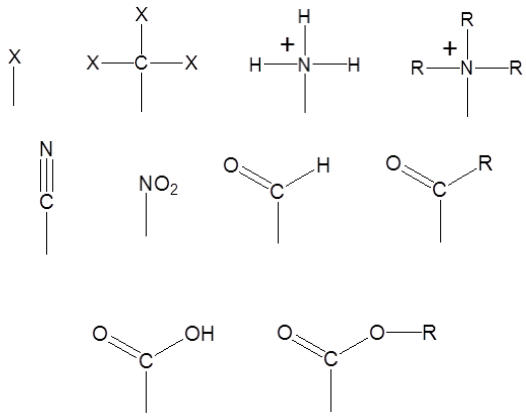
ACIDITY OF SUBSTITUTED BENZOIC ACIDS

ELECTRON-WITHDRAWING GROUPS

The conjugate base of benzoic acid is stabilized by electron-withdrawing groups (EWG). This makes the acid more acidic by delocalizing the charge of the carboxylate ion.

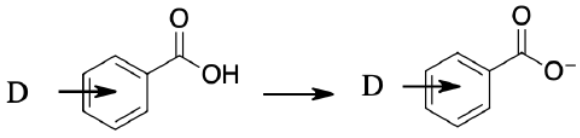


Electron-withdrawing groups deactivate the benzene ring to electrophilic attack and make benzoic acids more acidic.



ELECTRON-DONATING GROUPS

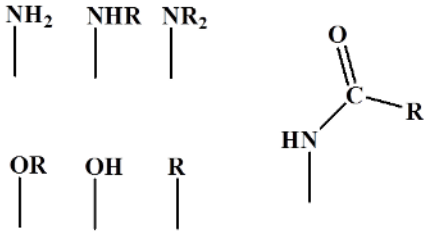
The conjugate base of benzoic acid is destabilized by electron-donating groups (EDG). This makes the acid less acidic by pushing more electron density toward the negative charge in the carboxylate.



D is an EDG

The carboxylate anion is destabilized by the EDG

Electron-donating groups activate the benzene ring to electrophilic attack and make benzoic acids less acidic.

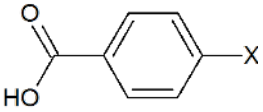


Several examples of electron donating groups.

CONTRIBUTORS

- Layne Morsch (University of Illinois Springfield)

Notice the trend in the following table where electron donating substituents (X) at the para position lead to weaker acids while those having more electron withdrawing groups, further down the table, generate stronger acids.

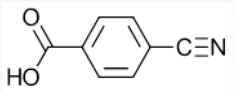


Dissociation Constants of *p*-Substituted Benzoic Acid

X	pK_a	
$—N(CH_3)_2$	6.03	weaker acid
$—NHCH_3$	5.04	
—OH	4.57	
$—OCH_3$	4.50	
$—C(CH_3)_3$	4.38	
—H	4.20	
—Cl	4.00	
—Br	3.96	
—CHO	3.77	
—CN	3.55	
$—NO_2$	3.43	stronger acid

EXAMPLE 20.4.1

The following molecule, *p*-cyanobenzoic acid, has a pK_a of 3.55. Does the cyano substituent activate or deactivate the aromatic ring towards electrophilic aromatic substitution?



p-cyanobenzoic acid

Solution

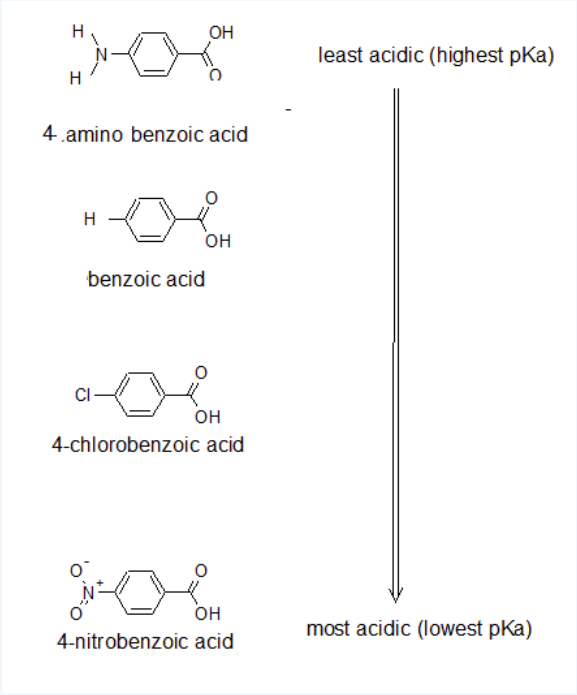
The pK_a of benzoic acid is 4.2 which means it is a weaker acid than *p*-cyanobenzoic acid. This this means that the cyano substituent is deactivating the ring.

EXERCISES

EXERCISE 20.4.1

Draw the bond-line structures and arrange the following compounds in order of increasing acidity: 4-nitrobenzoic acid; 4-aminobenzoic acid; 4-chlorobenzoic acid; and benzoic acid. Try to use the expected inductive effects of the substituents to determine the acidity rather than looking at the pK_a table.

Answer



EXERCISE 20.4.2

For the following pairs, which is expected to be the stronger acid? Explain your answer.

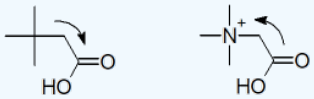
(a) $(CH_3)_3CCH_2CO_2H$ or $(CH_3)_3\overset{+}{N}CH_2CO_2H$

(b) $CH_3CH_2CO_2H$ or $CH_3\underset{OH}{\underset{|}{C}}HCO_2H$

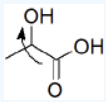
(c) $CH_3\overset{O}{\overset{\|}{C}}CO_2H$ or $CH_2{=}CHCO_2H$

Answer

a) Consider the inductive effects of the substituents attached to the carboxylic acid. The tert-butyl group is electron-donating which should decrease the acidity of the carboxylic acid. The trimethylammonium substituent is positively charged and can be a powerful electron-withdrawing substituent. This should increase the acidity of the carboxylic acid. The compound $(CH_3)_3NCH_2CO_2H$ is expected to be a stronger acid than $(CH_3)_3CCH_2CO_2H$. The acidity constants for these two compounds match the predictions.

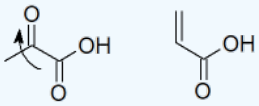


b) Having an electron-withdrawing hydroxyl group at the C-2 stabilizes the carboxylate ion of lactic acid through inductive effects.



This should make lactic acid more acidic than propanoic acid.

c) Due to the presence of a highly electronegative oxygen, the carbonyl group is expected to be more strongly electron-withdrawing than a carbon–carbon double bond. Thus, pyruvic acid should be a stronger acid than acrylic acid.



EXERCISE 20.4.3

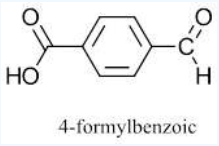
Oxalic acid is a dicarboxylic acid with two acidic protons. The first proton is much more acidic (pK_a = 1.20) than a typical carboxylic acid. However, Heptanedioic acid's first acidic proton has a pK_a much closer to that of a typical carboxylic acid. Explain these differences.

Answer

With oxalic acid one carboxyl group acts as an inductive electron-withdrawing group which increases the acidity of the other carboxylic acid. This inductive effect is only relevant with the two carboxyl groups are separated by only a few bonds. In heptanedioic acid, the carboxyl groups are separated by five carbon which effectively negates the inductive effect.

EXERCISE 20.4.4

The carboxylic acid of 4-formylbenzoic acid has a pK_a of 3.75. Is this molecule likely to be more reactive or less reactive than benzene toward electrophilic aromatic substitution?



4-formylbenzoic

Answer

Benzoic acid (pK_a = 4.2) has a higher pK_a and is less acidic than 4-formylbenzoic acid (pK_a = 3.75). This means that the formyl group is removing electrons from the aromatic ring making it deactivated toward electrophilic aromatic substitution.

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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20.5 PREPARING CARBOXYLIC ACIDS

Objectives

After completing this section, you should be able to

1. describe in detail the methods of preparing carboxylic acids discussed in previous chapters:
    a. the oxidation of alkylbenzenes.
    b. the oxidative cleavage of alkenes.
    c. the oxidation of primary alcohols and aldehydes.
2. discuss, in detail, the hydrolysis of nitriles:
    a. write an equation to illustrate the preparation of a carboxylic acid through nucleophilic attack by cyanide ion on an alkyl halide and hydrolysis of the nitrile which results.
    b. identify the carboxylic acid formed from the hydrolysis of a given nitrile, or from the reaction of a given alkyl halide with cyanide ion followed by hydrolysis of the resulting nitrile.
    c. identify the alkyl halide needed to prepare a given carboxylic acid by the formation and subsequent hydrolysis of a nitrile.
    d. identify the reagents needed to convert a given alkyl halide into a carboxylic acid containing one more carbon atom.
3. discuss, in detail, the carboxylation of Grignard reagents:
    a. write an equation describing the formation of a carboxylic acid from a Grignard reagent.
    b. identify the carboxylic acid obtained through the treatment of a given Grignard reagent with carbon dioxide followed by dilute acid.
    c. identify the Grignard reagent (or the alkyl halide required to form the Grignard reagent) that must be used to produce a given carboxylic acid by reaction with carbon dioxide.
    d. write the detailed mechanism for the formation of a carboxylic acid using a Grignard reagent.

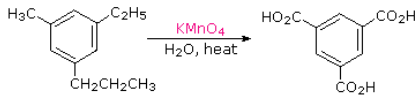
STUDY NOTES

Review the methods of obtaining carboxylic acids presented in earlier sections:

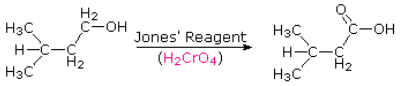
1. oxidation of aromatic compounds—Section 16.9.
2. oxidative cleavage of alkenes—Section 8.8.
3. oxidation of primary alcohols and aldehydes—Sections 17.7 and 19.3.

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.

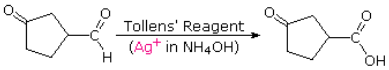
1. Oxidation of Arene Side-Chains



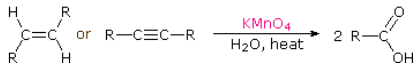
2. Oxidation of 1°-Alcohols



3. Oxidation of Aldehydes



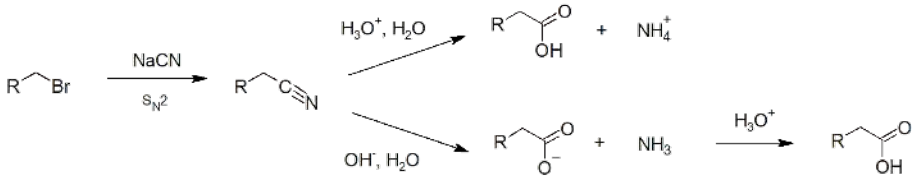
4. Oxidative Cleavage of Alkenes and Alkynes



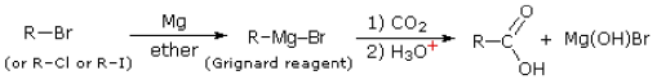
Two other useful procedures for preparing carboxylic acids involve hydrolysis of nitriles and carboxylation of organometallic intermediates. As shown in the following diagram, both methods begin with an organic halogen compound and the carboxyl group eventually replaces the halogen. Both methods require 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.

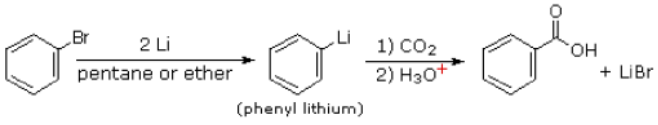
In the second procedure the electrophilic halide is first transformed into a strongly nucleophilic metal derivative, and this adds to carbon dioxide (an electrophile). The initial product is a salt of the carboxylic acid, which must then be released by treatment with strong aqueous acid.

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.

WORKED EXAMPLE 20.5.1

Thus far this chapter has discussed three main methods for the creation of a carboxylic acid functional group: the oxidation of a 1° alcohol, the carboxylation of a Grignard reagent, and the hydrolysis of a nitrile. Select one of these three methods to perform the following transformation. Briefly explain why the other two methods would be unsuccessful.

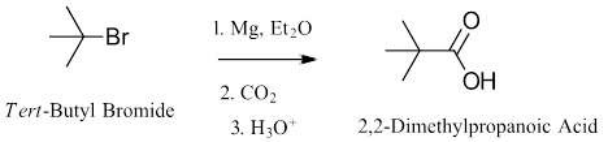
a) Tert-Butyl Bromide → 2,2-Dimethylpropanoic acid.

b) Benzyl Bromide → Benzoic Acid

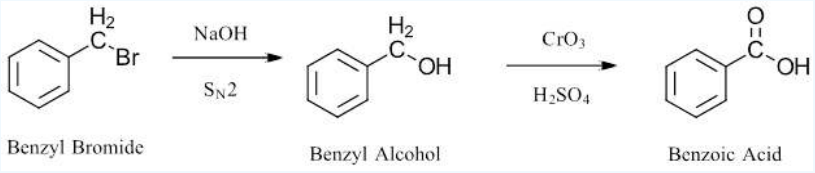
c) 3-Bromo-1-propanol → 4-Hydroxybutanoic acid

Solution

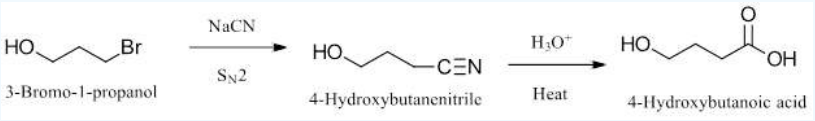
a) The product contains one more carbon than the reactant so the oxidation of a 1º alcohol would be an ineffective method. Also, the reactant contains a tertiary halide, so the S_N2 reaction required to form a nitrile would not be possible. The carboxylation of a Grignard reagent would be the most effective method because it allows for the addition of a carbon, it is not severely affected by the sterics of the tertiary halide, and there are no incompatible functional groups.



b) The product and reactant have the same number of carbons so both the carboxylation of a Grignard reagent and hydrolysis of a nitrile would be ineffective for this conversion. Benzyl bromide is a primary alkyl halide which can easily be converted to a primary alcohol by an S_N2 reaction with NaOH. Once formed, the primary alcohol can be converted to a carboxylic acid using an oxidation reaction.



c) The product contains one more carbon than the reactant so the oxidation of a primary alcohol would not be an effective method. Also, the carboxylation of a Grignard reagent would not be an effect method because the presence of an incompatible alcohol functional group in the reactant. The reactant contains a primary halogen which can readily be converted to a nitrile by an S_N2 reaction with NaCN. The resulting nitrile can be converted to a carboxylic acid through hydrolysis.

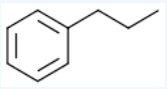


EXERCISES

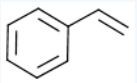
? EXERCISE 20.5.1

Show how the following molecules can be used to synthesize benzoic acid:

a)



b)



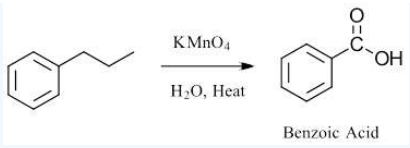
c)



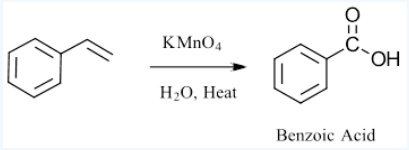
Answer

a)

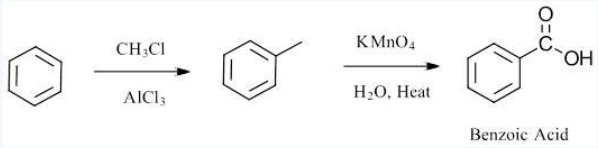
https://chem.libretexts.org/@go/page/90985



b)



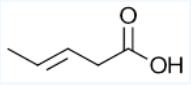
c)



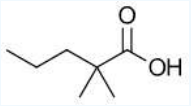
? EXERCISE 20.5.2

Please give the structure of the bromide required to make the following using the carboxylation of a Grignard reagent:

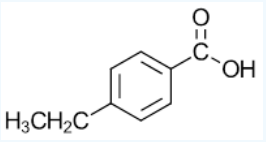
a)



b)

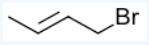


c)

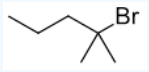


Answer

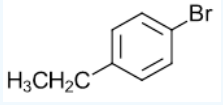
a)



b)



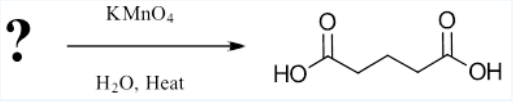
c)



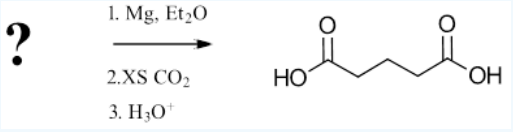
? EXERCISE 20.5.3

Please give the possible reactants for the following reactions:

a) There are at least four possible answers for question a.

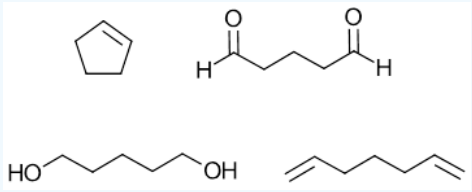


b)

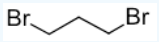


Answer

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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20.6 REACTIONS OF CARBOXYLIC ACIDS: AN OVERVIEW

Objectives

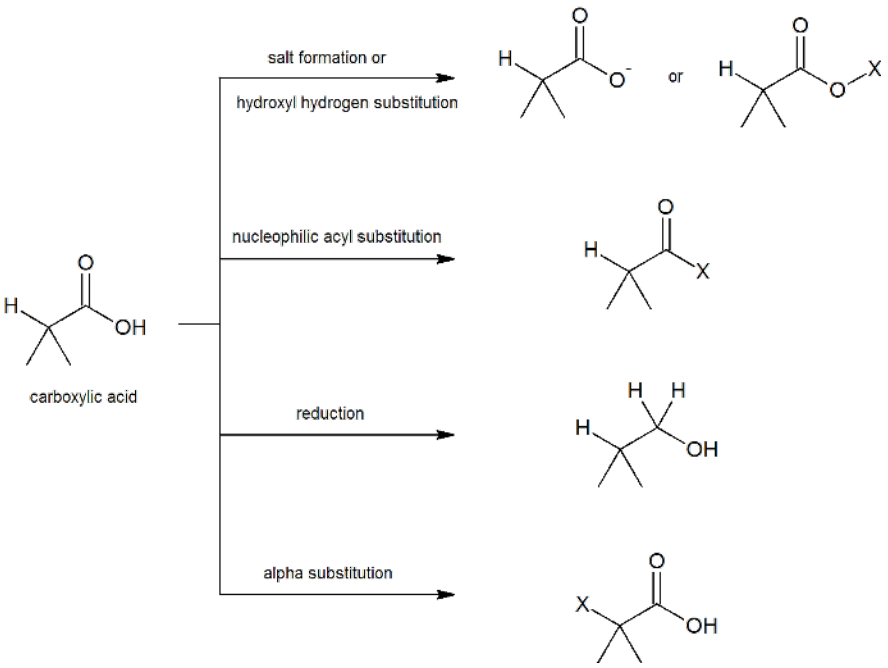
After completing this section, you should be able to identify the four types of reaction which a carboxylic acid can undergo.

STUDY NOTES

You may wish to review Section 17.4 which discusses reduction of carbonyl compounds to form alcohols and Sections 20.2–20.4 which highlights the acidity of carboxylic acids, which is important to salt formation and substitution of the hydroxyl hydrogen. Nucleophilic acyl substitution (Chapter 21) and alpha substitutions (Chapter 22) are discussed later in more detail.

FOUR CATEGORIES OF CARBOXYLIC ACID REACTIONS

The scheme summarizes some of the general reactions that carboxylic acids undergo.

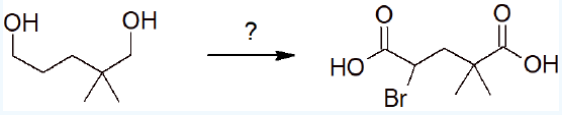


Four general reaction categories are represented here: (1) As carboxylic acid deprotonates quite readily, it is quite easy to form a carboxylate salt or to substitute the hydroxyl hydrogen. (2) The category of nucleophilic acyl substitution represents the substitution of the whole hydroxyl group, which 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.

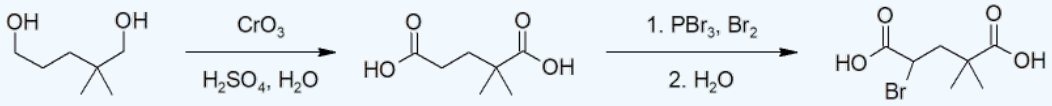
EXERCISES

EXERCISE 20.6.1

Show how the following transformation can be performed. Multiple steps may be required.

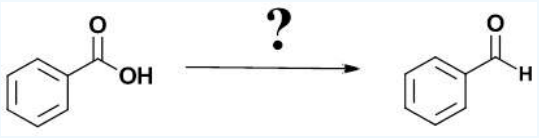


Answer

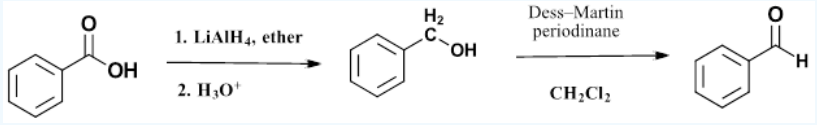


EXERCISE 20.6.2

Show how the following transformation can be performed. Multiple steps may be required.



Answer



CONTRIBUTORS AND ATTRIBUTIONS

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

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20.7 CHEMISTRY OF NITRILES

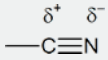
Objectives

After completing this section, you should be able to

1. discuss, in detail, the preparation of nitriles:
   a. write an equation to illustrate the formation of a nitrile by the nucleophilic attack of cyanide ion on an alkyl halide.
   b. write an equation to illustrate the formation of a nitrile by the dehydration of a primary amide.
   c. identify the product formed when a primary amide is treated with $SOCl_2$, P_2O_5, or $POCl_3$.
   d. identify the primary amide, the reagents, or both, needed to prepare a given nitrile by a dehydration reaction.
   e. write a detailed mechanism for the dehydration of a primary amide by thionyl chloride.
2. discuss, in detail, the reactions of nitriles:
   a. write an equation to describe the (acidic or basic) hydrolysis of a nitrile.
   b. write detailed mechanisms for the acidic and basic hydrolysis of nitriles.
   c. identify the products formed from the (acidic or basic) hydrolysis of a given nitrile.
   d. identify the nitrile, the reagents, or both, needed to obtain a given carboxylic acid from a hydrolysis reaction.
   e. write an equation to describe the reduction of a nitrile to give a primary amine.
   f. identify the product formed from the lithium aluminum hydride reduction of a given nitrile.
   g. identify the nitrile, the reagents, or both, needed to prepare a given amine by direct reduction.
   h. write a detailed mechanism for the reduction of a nitrile to a primary amine using lithium aluminum hydride.
   i. give an example of the reduction of a nitrile with diisobutylaluminum hydride.
   j. write an equation to illustrate the reaction of a nitrile with a Grignard reagent.
   k. identify the product formed from the reaction of a given nitrile with a given Grignard reagent.
   l. identify the nitrile, the Grignard reagent, or both, needed to prepare a given ketone.
   m. write a detailed mechanism for the reaction of a nitrile with a Grignard reagent.

STUDY NOTES

To be able to understand the driving force behind the reactions of nitriles, you must recognize the polarity of this group:

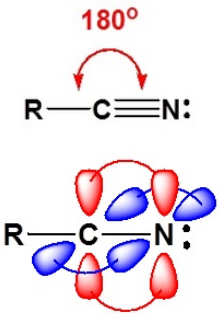


You can therefore expect to see similarities between the behaviour of the nitrile group and the similarly polarized carbonyl group:



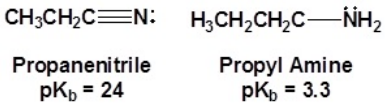
PROPERTIES OF NITRILES

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.



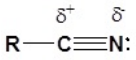
The lone pair electrons on the nitrogen are contained in a *sp* hybrid orbital which makes them much less basic and an amine. The 50% character of an *sp* hybrid orbital close to the nucleus and therefore less basic compared to other nitrogen containing compounds such as

amines.



Propanenitrile	Propyl Amine
$pK_b = 24$	$pK_b = 3.3$

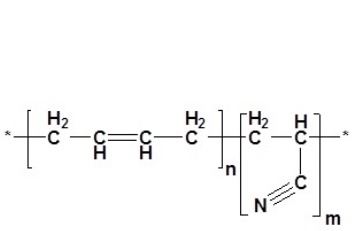
The presence of an electronegative nitrogen causes nitriles to be very polar molecules. Consequently, nitriles tend to have higher boiling points than molecules with a similar size.



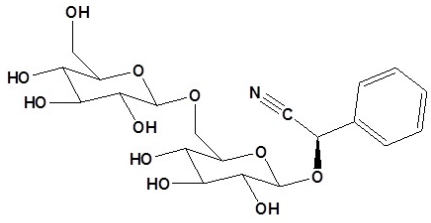
	Boiling Point
$CH_3CH_2C{\equiv}N$ Propanenitrile	96-98 °C
$CH_3CH_2C{\equiv}C{-}H$ Butyne	8.1 °C
$CH_3CH_2CH_2CH_3$ Butane	-1-1 °C

INTERESTING NITRILES

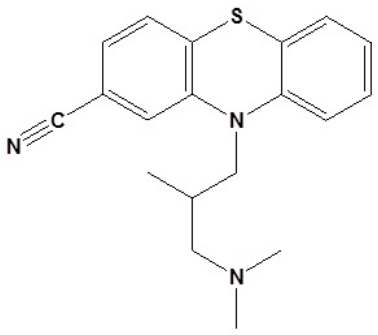
One of the most common occurrences of nitriles is in Nitrile rubber. Nitrile rubber is a synthetic copolymer of acrylonitrile and butadiene. This form of rubber is highly resistant to chemicals and is used to make protective gloves, hoses and seals.



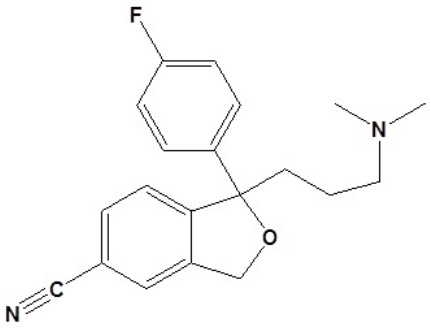
Nitrile Rubber



Amygdalin: Found in Bitter Almonds



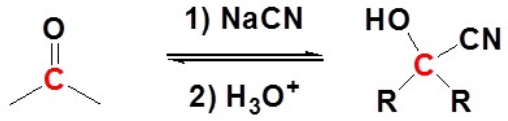
Cyamemazine: an antipsychotic



Citalopram: an antidepressant

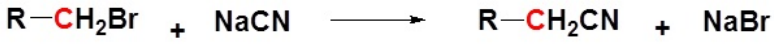
PREPARATION OF NITRILES

Addition of cyanide ($^-$:C≡N) to an aldehyde or ketone forms a cyanohydrin

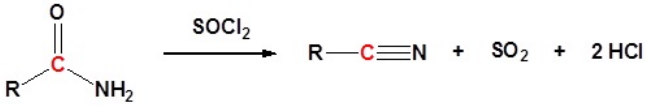


Aldehyde or Ketone — Cyanohydrin

Nitriles are formed by an S_N2 reaction between a bromide and sodium cyanide



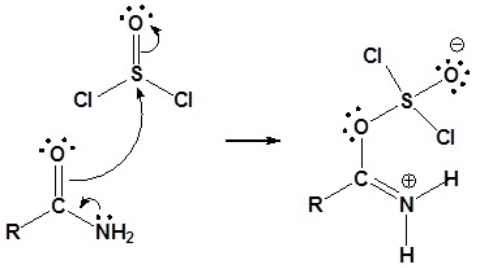
1° Amides can be converted to nitriles by dehydration with thionyl chloride (or other dehydrating agents like P_2O_5, or $POCl_3$).



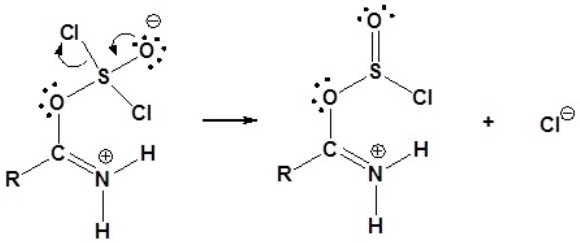
1° Amide — Nitrile

MECHANISM

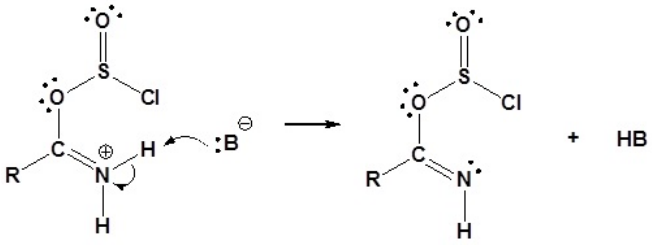
1) Nucleophilic attach on thionyl chloride



2) Leaving group removal

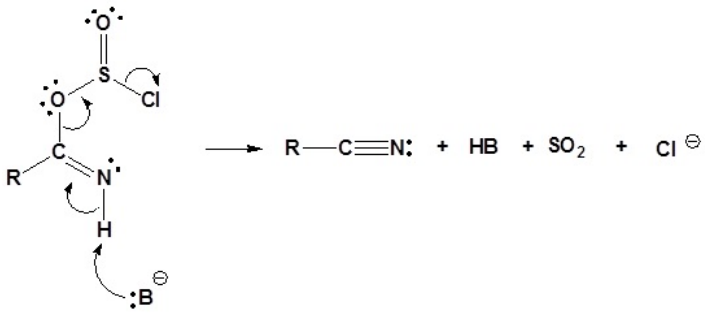


3) Deprotonation



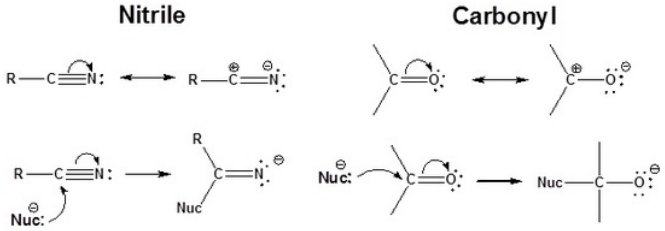
4) Leaving group removal

https://chem.libretexts.org/@go/page/90987

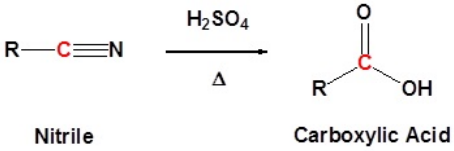


REACTIONS OF NITRILES

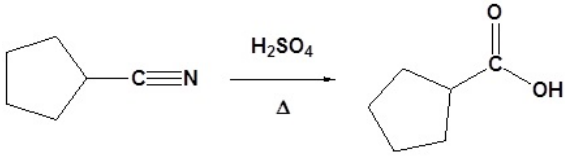
The carbon in a nitrile is electrophilic because a resonance structure can be drawn which places a positive charge on it. Because of this the triple bond of a nitrile accepts a nucleophile in a manner similar to a carbonyl.



Nitriles can be converted to carboxylic acid with heating in sulfuric acid. During the reaction an amide intermediate is formed.



EXAMPLE

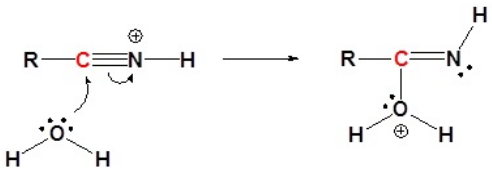


MECHANISM

1) Protonation

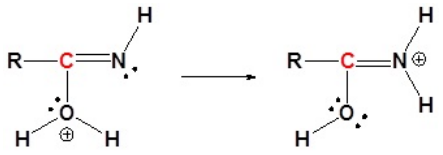


2) Nucleophilic attack by water

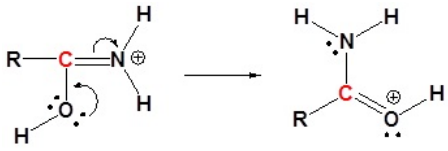


3) Proton Transfer

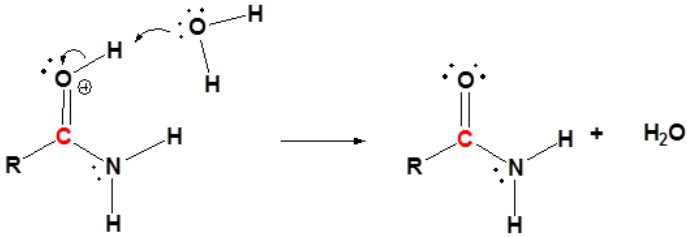
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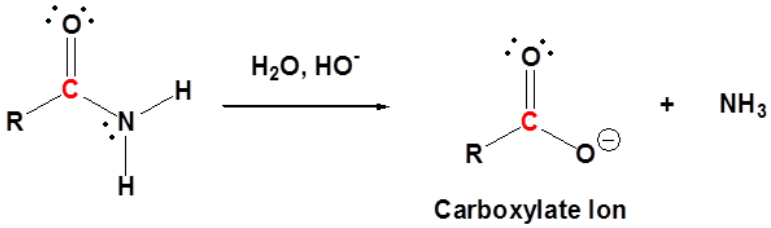
4) Resonance



5) Deprotonation



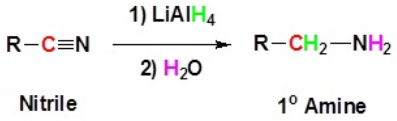
6) Further hydrolysis of the amide. This mechanism can be found in Section 21.7



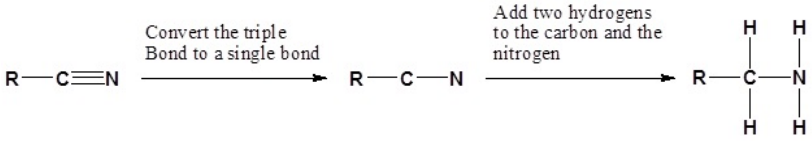
NITRILES CAN BE CONVERTED TO 1° AMINES BY REACTION WITH $LiALH_4$

During this reaction the hydride nucleophile attacks 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.

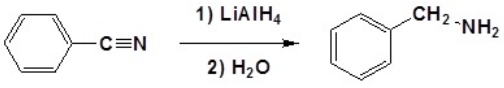
GENERAL REACTION



GOING FROM REACTANTS TO PRODUCTS SIMPLIFIED

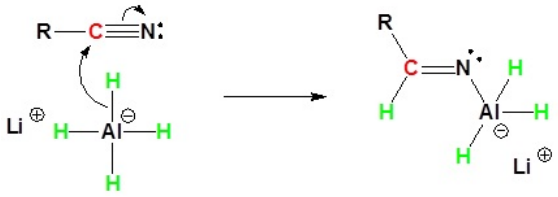


EXAMPLE

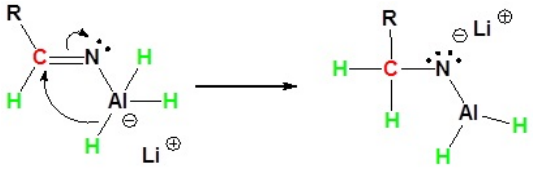


MECHANISM

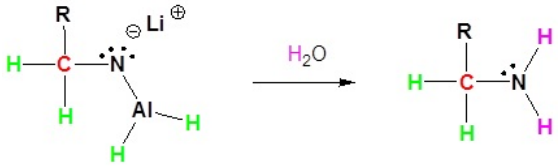
1) Nucleophilic Attack by the Hydride



2) Second nucleophilic attack by the hydride.



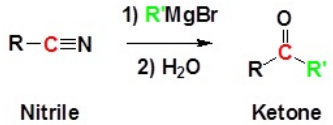
3) Protonation by addition of water to give an amine



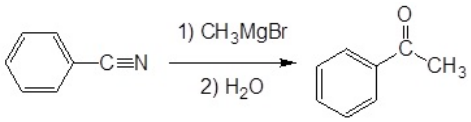
REACTION OF NITRILES WITH ORGANOMETALIIC REAGENTS

Grignard reagents can attack the electophillic carbon in a nitrile to form an imine salt. This salt can then be hydrolyzed to become a ketone.

GENERAL REACTION

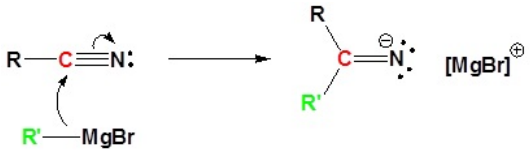


EXAMPLE

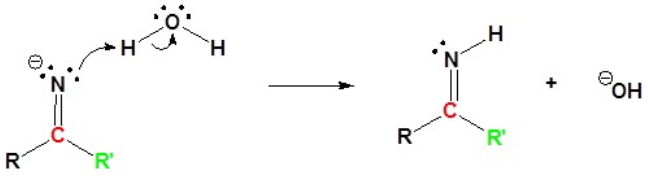


MECHANISM

1) Nucleophilic Attack by the Grignard Reagent

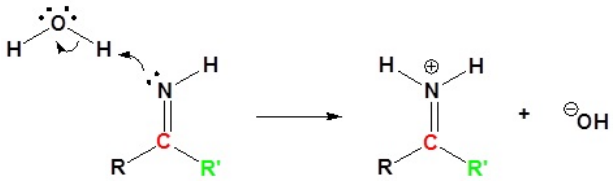


2) Protonation

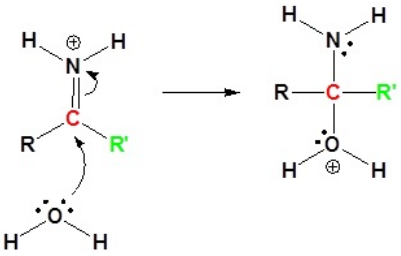


3) Protonation

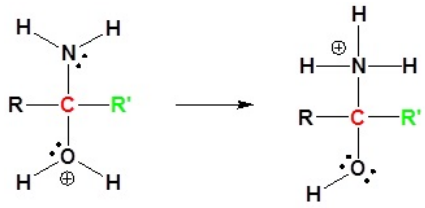
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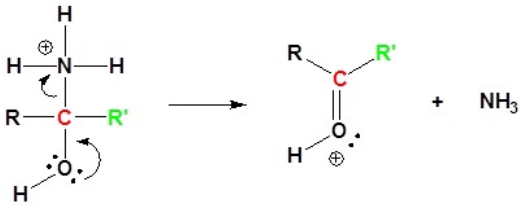
4) Nucleophilic attack by water



5) Proton Transfer



6) Leaving group removal



7) Deprotonation

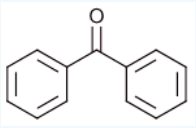


EXERCISES

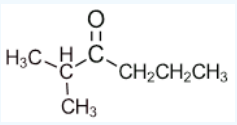
? EXERCISE 20.7.1

Show how the following compounds could be prepared from a nitrile:

a)

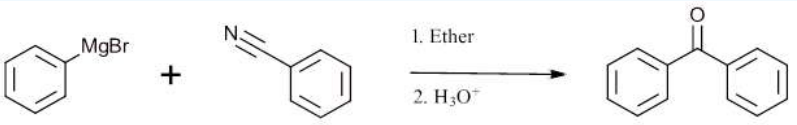


b)

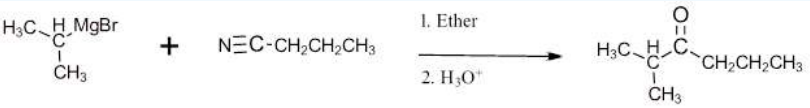


Answer

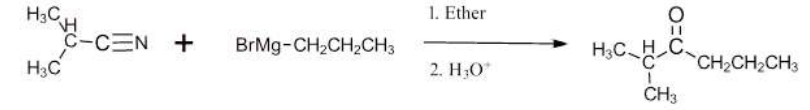
a)



b)



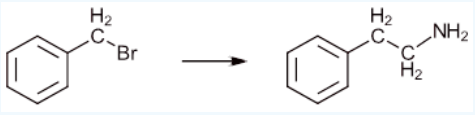
Or



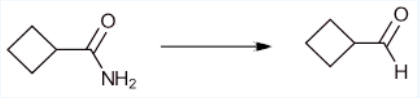
? EXERCISE 20.7.2

Show how the following transformations could be preformed:

a)

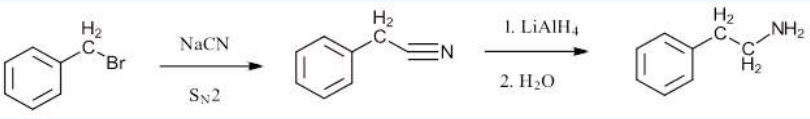


b)

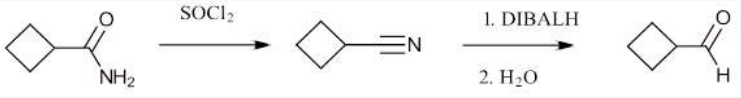


Answer

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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20.8 SPECTROSCOPY OF CARBOXYLIC ACIDS AND NITRILES

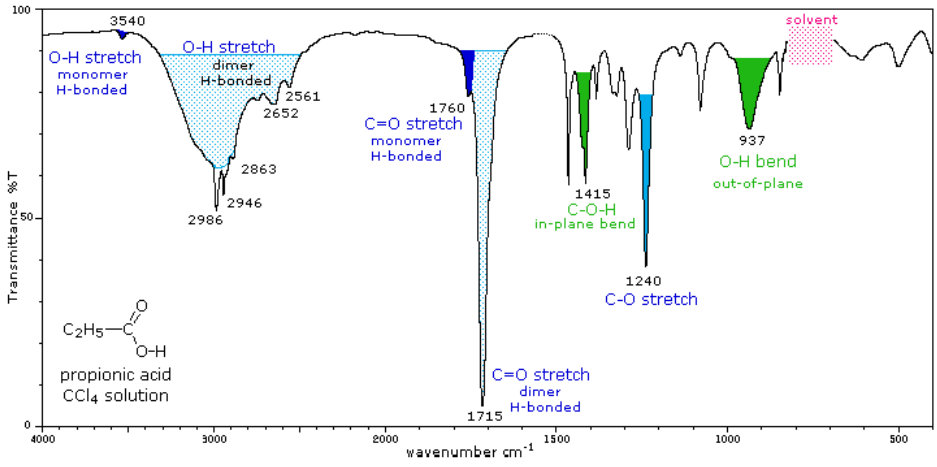
Objectives

After completing this section, you should be able to

1. identify the two characteristic infrared absorptions displayed by all carboxylic acids.
2. state the approximate ^{1}H NMR absorption of a carboxylic acid proton.
3. use infrared and NMR spectroscopy data to assist in the identification of an unknown carboxylic acid, with or without the assistance of a table of characteristic absorptions.

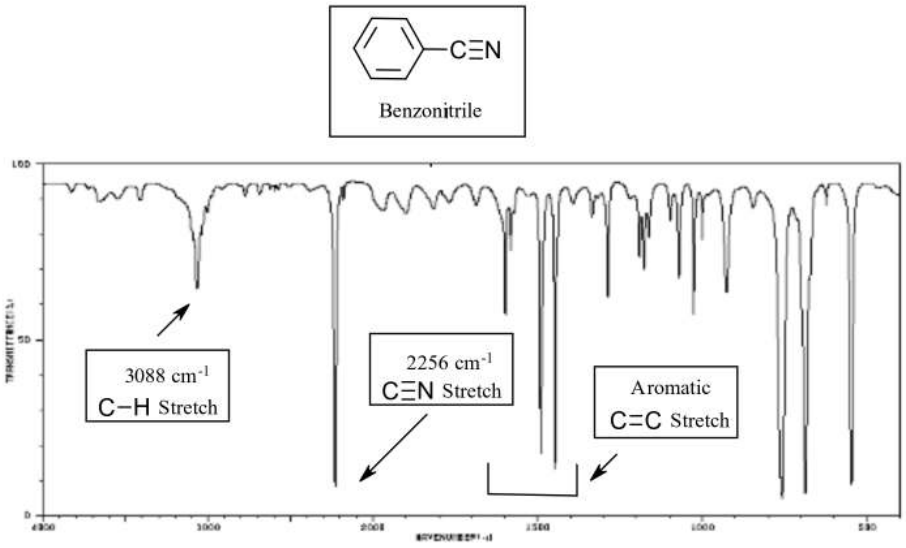
IR

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.



The Infrared Spectrum of Propanoic Acid

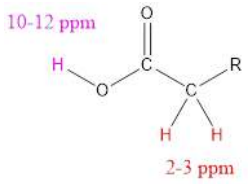
Nitriles show a distinctive absorption for the C-N triple bond which appear near 2250 cm^{-1}



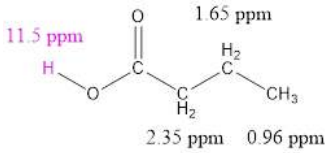
The Infrared Spectrum of Benzonitrile

^{1}H NUCLEAR MAGNETIC SPECTROSCOPY

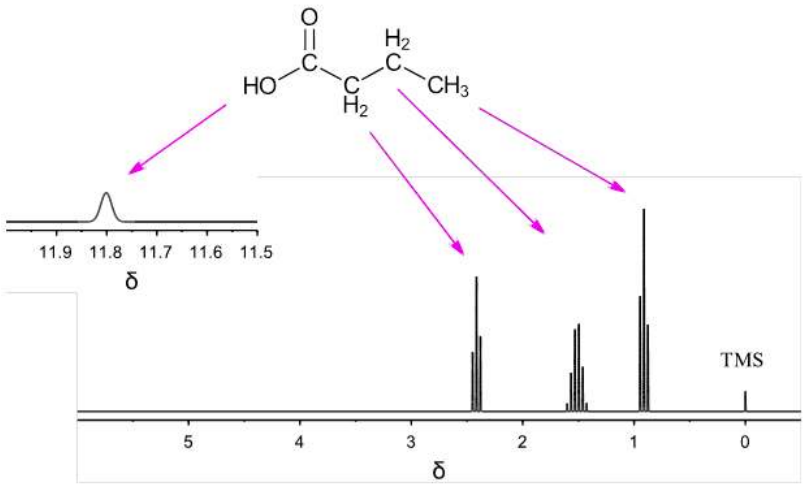
The acidic O-H protons of carboxylic acids are highly deshielded due to the electronegativity of oxygen and anisotropy from the C=O carbonyl bond. They tend to be among the least shielded protons appearing far downfield in the 10–12 ppm region which is considered distinctive for carboxylic acids. Due to hydrogen bonding the proton of a carboxylic acid often appears as a broad singlet and adding D_2O causes the signal to disappear due to hydrogen-deuterium exchange. Protons on carbons adjacent to a carboxylic acid absorb in the 2-3 ppm region. Some deshielding occurs due to the fact that the carbonyl oxygen is pulling electron density away from the carbonyl carbon which inductively pulls electron density away from the adjacent carbon.



The Typical ^{1}H Peaks for a Carboxylic Acid



The ^{1}H Peaks for Butanoic Acid



A ^{1}H NMR Spectra for Butanoic Acid

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

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20.S: CARBOXYLIC ACIDS AND NITRILES (SUMMARY)

CONCEPTS & VOCABULARY

20.0 Chapter Objectives and Introduction to Carboxylic Acids

- Carboxylic acids are defined as molecules that have a hydroxyl group bonded to a carbonyl group (RCOOH).
- Fatty acids are naturally occurring carboxylic acids that are important components of lipids.
- Fatty acids can either be saturated (all carbon-carbon bonds are single bonds) and unsaturated (one or more carbon-carbon double bonds).
- Several other functional groups can be prepared from carboxylic acids and are considered derivatives (acyl halides, anhydrides, esters, amides and nitriles).

20.1 Naming Carboxylic Acids and Nitriles

- Carboxylic acids are named following IUPAC rules with ending -oic acid.
- When carboxylic acids are named as an attachment to a ring, add -carboxylic acid to the name of the cyclic compound.
- Nitriles are named following IUPAC rules with the ending -nitrile or -carbonitrile.

20.2 Structure and Properties of Carboxylic Acids

- Carboxylic acids have trigonal planar shape around the carbonyl carbon and due to resonance structures, all the atoms of the functional group are co-planar.
- Conjugation in carboxylic acids increases acidity of the hydroxyl hydrogen compared to alcohols. The conjugate base (carboxylate) is stabilized by resonance.
- Carboxylic acids form hydrogen bonded dimers yielding higher boiling points than for other molecules of similar size.
- Small carboxylic acids are often soluble in water due to hydrogen bonding. Larger carboxylic acids are often slightly soluble in water, though when converted to a carboxylate salt by treating with base, become water soluble.

20.3 Biological Acids and the Henderson-Hasselbalch Equation

- Carboxylic acids are fully protonated in acidic solutions.
- Carboxylic acids are fully dissociated in basic solutions.
- The Henderson-Hasselbalch equation can be used to relate pH, pKa and ratio of concentrations of acid and conjugate base.

20.4 Substituent Effects on Acidity

- Withdrawing groups (through inductive or resonance effects) can stabilize carboxylates, increasing acidity of carboxylic acids.
- Donating groups (through inductive or resonance effects) destabilize carboxylates, decreasing acidity of carboxylic acids.
- Nearly all substituents in ortho positions increase acid strength whether donating or withdrawing, this is called the *ortho*-effect.

20.5 Preparing Carboxylic Acids

- Carboxylic acids can be prepared through oxidation of several functional groups including: 1° alcohols, aldehydes, alkyl arene side chains, and alkenes.
- Carboxylic acids can also be prepared by carboxylation of Grignard reagents and hydrolysis of nitriles.

20.6 Reactions of Carboxylic Acids: An Overview

- There are four main categories of carboxylic acid reactions:
  - Acid/base reaction (salt formation)
  - Nucleophilic acyl substitution
  - Reduction
  - Substitution alpha to the carbonyl

20.7 Chemistry of Nitriles

- Nitriles have linear geometry due to the *sp* hybrid orbitals on carbon and nitrogen.
- Nitriles are less basic than amines.
- Nitriles can be prepared from aldehydes, ketones, or amides.
- Nitriles react similarly to carbonyl compounds where nucleophiles will attack the carbon end of the nitrile.
- Nitriles can be hydrolyzed to carboxylic acids under basic or acidic conditions.
- Nitriles can be reduced to amines by hydride reduction.
- Nitriles can be converted to aldehyde by reaction with DIBALH.

- Nitriles can be converted to ketones by reaction with organometallic compounds.

20.8 Spectroscopy of Carboxylic Acids and Nitriles

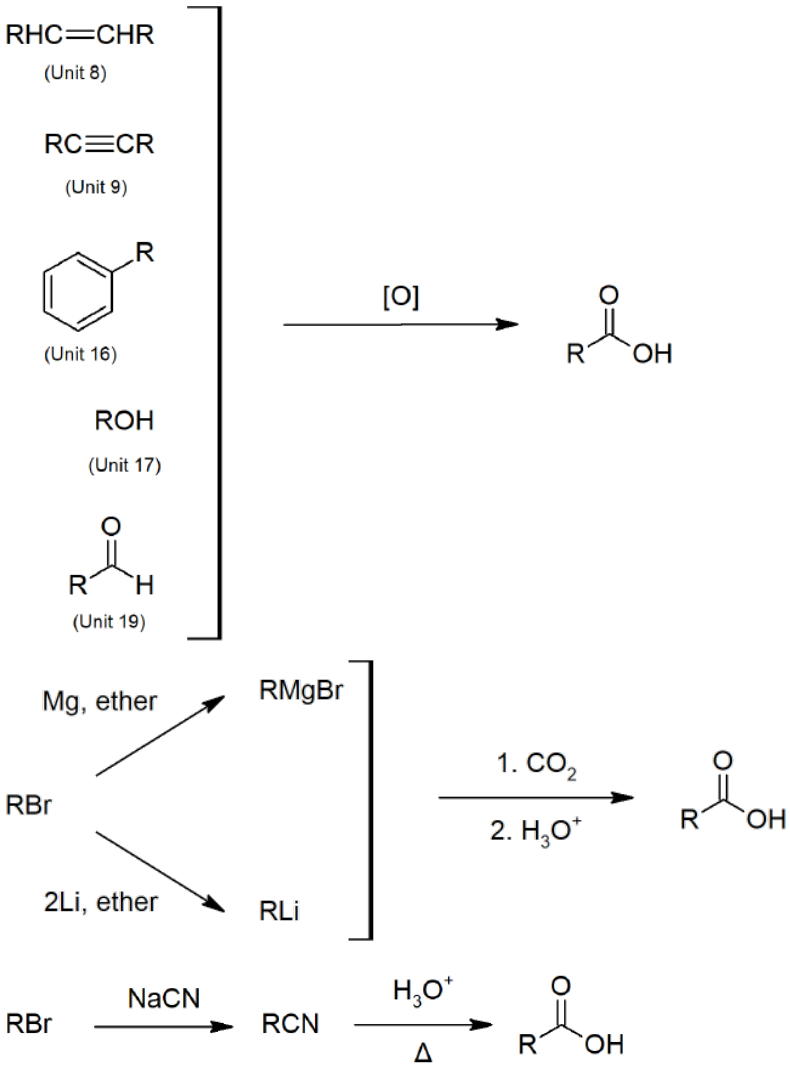
- IR of carboxylic acids typically show a very strong and broad OH stretch from about 2500 to 3300 cm^{-1} as well as a strong carbonyl stretch around 1710 cm^{-1}.
- ^{1}H NMR of carboxylic acids show the OH proton between 10-12 ppm as well as hydrogens on carbon adjacent to the carbonyl around 2-3 ppm.
- ^{13}C NMR of carboxylic acids show the carbonyl carbon at 160-180 ppm.
- Mass spectra of carboxylic acids often have fragments for OH (loss of 17) and COOH (loss of 45).
- The most identifying characteristic of IR of nitriles is the CN triple bond stretch which appears near 2250 cm^{-1}.
- ^{1}H NMR of nitriles show protons on the carbon next to the nitrile at around 2-3 ppm.
- ^{13}C NMR of nitriles show the nitrile carbon in the 115-120 ppm range.
- Mass spectra of nitriles will often not have a visible molecular ion, but instead exhibit a strong M-1 peak.

SKILLS TO MASTER

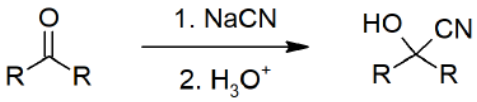
- Skill 20.1 Name carboxylic acids and nitriles using IUPAC rules.
- Skill 20.2 Draw the structure of carboxylic acids and nitriles from the IUPAC name.
- Skill 20.3 Describe the geometries and approximate bond angles of carboxylic acids and nitriles.
- Skill 20.4 Explain the acidity of carboxylic acids based on conjugate base stabilization.
- Skill 20.5 Explain physical properties of carboxylic acids.
- Skill 20.6 Describe the structure of carboxylic acids in buffered solutions.
- Skill 20.7 Use the Henderson-Hasselbach equation to relate pH, pK_a, and acid/conjugate base concentrations.
- Skill 20.8 Explain inductive effects on acidity.
- Skill 20.9 Explain relative acidity of aromatic acids.
- Skill 20.10 Draw mechanisms for preparing carboxylic acids including:
  - Oxidations
  - Carboxylation of Grignard reagents
  - Hydrolysis of Nitriles
- Skill 20.11 List the four categories of carboxylic acid reactions.
- Skill 20.12 Draw reactions for preparing nitriles including formation from:
  - aldehyde or ketone
  - 1° amide
- Skill 20.13 List general reactions of nitriles.
- Skill 20.14 Draw mechanisms for reactions of nitriles including:
  - Hydrolysis to acids (acidic and basic mechanisms)
  - Reduction to 1° amines
  - Conversion to aldehyde by reaction with DIBALH.
  - Conversion to ketones by reaction with organometallic compounds.
- Skill 20.15 Plan a synthesis of a ketone from a nitrile.
- Skill 20.16 Use IR, NMR and MS to identify carboxylic acids and nitriles.

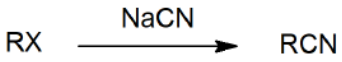
SUMMARY OF REACTIONS

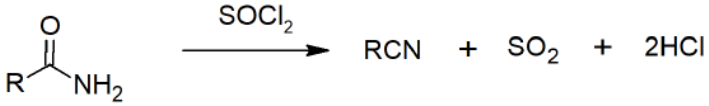
Carboxylic Acid Preparation



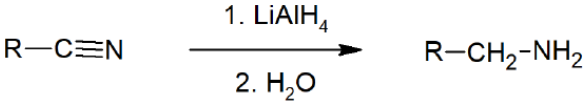
Nitrile Preparation

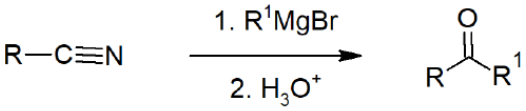






Reaction of Nitriles





CONTRIBUTOR

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Layne Morsch (University of Illinois Springfield)

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CHAPTER OVERVIEW

CHAPTER 21: CARBOXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL SUBSTITUTION REACTIONS

The compounds discussed in this chapter are all considered to be derived from carboxylic acids, and include acid halides, acid anhydrides, esters and amides (thioesters and acyl phosphates are also briefly mentioned). As you proceed through the chapter, you should be looking for similarities in behaviour among the various classes of compounds. These similarities can be readily understood once you appreciate the fact that, in most of their reactions, carboxylic acid derivatives react via the nucleophilic acyl substitution mechanism.

In this chapter, we describe the nomenclature of the various types of carboxylic acid derivatives, and explain the relative reactivity of these compounds in terms of resonance contributions to the ground state of each type of compound.

We describe the reactions of carboxylic acids, acid halides, acid anhydrides, esters, amides, polyamides and polyesters in detail, and discuss the biological importance of thiol esters briefly. The chapter concludes with a look at how infrared spectroscopy and NMR spectroscopy can be used in the identification of unknown carboxylic acid derivatives.

Chapter Objectives
21.0 Introduction
21.1 Naming Carboxylic Acid Derivatives
21.2 Nucleophilic Acyl Substitution Reactions
21.3 Nucleophilic Acyl Substitution Reactions of Carboxylic Acids
21.4 Chemistry of Acid Halides
21.5 Chemistry of Acid Anhydrides
21.6 Chemistry of Esters
21.7 Chemistry of Amides
21.8 Chemistry of Thioesters and Acyl Phosphates: Biological Carboxylic Acid Derivatives
21.9 Polyamides and Polyesters: Step-Growth Polymers
21.10 Spectroscopy of Carboxylic Acid Derivatives
21.S: Carboxylic Acid Derivatives (Summary)

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CHAPTER OBJECTIVES

When you have completed Chapter 21, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design multi-step syntheses in which the reactions introduced in this chapter are used in conjunction with any of the reactions described in previous chapters.
3. solve road-map problems that require a knowledge of the chemistry of carboxylic acid derivatives.
4. define, and use in context, any of the key terms introduced in this chapter.

CONTRIBUTORS AND ATTRIBUTIONS

Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

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21.0 INTRODUCTION

OBJECTIVES

After completing this section, you should be able to

1. identify, and give an example of
   a. an acid halide.
   b. an acid anhydride.
   c. an ester.
   d. an amide.
2. write the general form of a nucleophilic acyl substitution reaction.

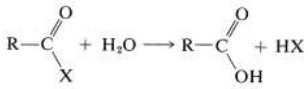
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- acyl derivative
- nucleophilic acyl substitution reaction

CARBOXYLIC ACID DERIVATIVES

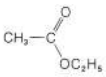
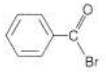
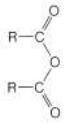
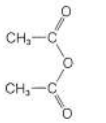
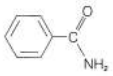
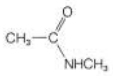
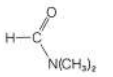
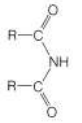
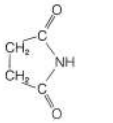
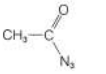
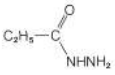
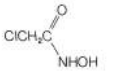
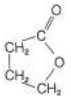
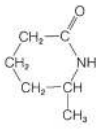
A **acyl derivative** (functional derivative) of a carboxylic acid is a substance formed by replacement of the hydroxyl group of the acid by some other group, **X**, such that it can be hydrolyzed back to the acid in accord with Equation 18-7:



(18-7)

By this definition, an amide, $\mathbf{RCONH_2}$, but not a ketone, $\mathbf{RCOCH_3}$, is a functional derivative of a carboxylic acid. Several derivatives of carboxylic acids are give in Table 1.

Table 1: *Functional Derivatives of Carboxylic Acids*

Derivative	Structure	Example: Structure	Example: Name
esters			ethyl ethanoate (ethyl acetate)
acyl halides	 X = F, Cl, Br, I		benzenecarbonyl bromide (benzoyl bromide)
anhydrides			ethanoic anhydride (acetic anhydride)
amides (primary)			benzenecarboxamide (benzamide)
amides (secondary and tertiary)			*N*-methylethanamide (*N*-methylacetamide)
			*N*,*N*-dimethylmethanamide (*N*,*N*-dimethylformamide)
imides			butanimide (azacyclopenta-2,5-dione, succinimide)
acyl azides			ethanoyl azide (acetyl azide)
hydrazides			diazanylethanone[a] (propionohydrazide)
hydroxamic acids			*N*-hydroxychloroethanamide (chloroacetylhydroxamic acid)
lactones (cyclic esters)	 most stable with $n = 3,4$		oxacyclopentan-2-one (γ-butyrolactone)
lactams (cyclic amides)	 most stable with $n = 3,4$		6-methylazacyclohexan-2-one (δ-caprolactam)

[a]This is a recommended but not widely used name. Without some thought, few organic chemists currently could write the proper structure that corresponds to it.

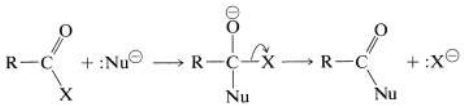
The common structural feature of the compounds listed in Table 3 is the acyl group **RCO–**. However, nitriles, **RC ≡ N**, often are considered to be acid derivatives, even though the acyl group is not present as such, because hydrolysis of nitriles leads to carboxylic acids:

$$\underset{\text{ethanenitrile (acetonitrile)}}{CH_3C{\equiv}N} + 2H_2O \xrightarrow{H^{\oplus}} \underset{\text{ethanoic acid (acetic acid)}}{CH_3COOH} + NH_3$$

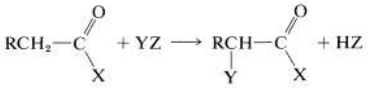
https://chem.libretexts.org/@go/page/90991

NUCLEOPHILIC ACYL SUBSTITUTION REACTION

The main type of reaction of carboxylic acid derivatives with which we now shall be concerned are the replacement of **X** by attack of a nucleophile $Nu^{\ominus}$ at the carbonyl carbon with subsequent cleavage of the **C–X** bond (Equation 18-8) or an nucleophilic acyl substitution reaction. Carboxylic acid derivatives can also undergo substitution at the α carbon facilitated by the carbonyl group (Equation 18-9):



(18-8)



(18-9)

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca 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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21.1 NAMING CARBOXYLIC ACID DERIVATIVES

Objectives

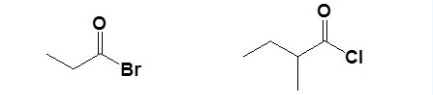
After completing this section, you should be able to

1. provide a satisfactory name for an acid halide of given structure.
2. draw the condensed or shorthand structure of an acid halide, given either its commonly used or systematic name.
3. provide a satisfactory name for an acid anhydride of given structure.
4. draw the condensed or shorthand structure of an acid anhydride, given either its trivial or IUPAC name.
5. provide an acceptable name for an amide of given structure.
6. draw the condensed or shorthand structure of an amide, given its trivial or IUPAC name.
7. provide an acceptable name for an ester of given structure.
8. draw the condensed or shorthand structure of an ester, given either its trivial or IUPAC name.
9. provide an acceptable name for a thioester of given structure.
10. draw the condensed or shorthand structure of a thioester, given its trivial or IUPAC name.
11. provide an acceptable name for an acyl phosphate.
12. draw the condensed or shorthand structure of an acyl phosphate, given either its trivial or IUPAC name.

NOMENCLATURE OF ACID HALIDES

The nomenclature of acid halides starts with the name of the corresponding carboxylic acid. The **–ic acid** ending is removed and replaced with the ending **-yl** followed by the name of the halogen with an **–ide** ending. This is true for both common and IUPAC nomenclature. The carbonyl carbon is given the #1 location number. It is not necessary to include the location number in the name because it is assumed that the functional group will be on the end of the parent chain.

✔ EXAMPLE 21.1.1



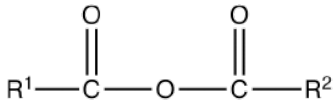
Propanoyl bromide (Propionyl bromide) 2-Methylbutanoyl chloride (2-Methylbutyryl chloride)

The acid anhydride functional group results when two carboxylic acids combine and lose water (anhydride = without water). Symmetrical acid anhydrides are named like carboxylic acids except the ending **-acid** is replaced with **-anhydride**. This is true for both the IUPAC and Common nomenclature.

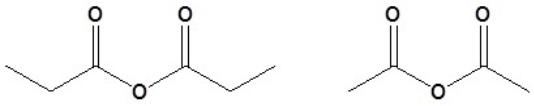
NOMENCLATURE OF ANHYDRIDES

SYMMETRICAL ANHYDRIDES

A symmetrical anhydride is a carboxylic acid anhydride that has the following general structural formula.



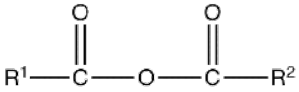
where R^1=R^2= hydrogen atoms, alkyl groups, aryl groups



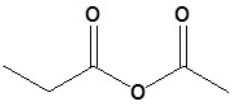
Propanoic anhydride (Propionic anhydride) Ethanoic anhydride (Acetic anhydride)

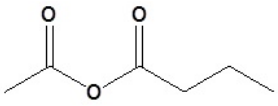
UNSYMMETRICAL ANHYDRIDES

A mixed or unsymmetrical anhydride is a carboxylic acid anhydride that has the following general structural formula.



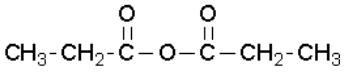
where $R^1 \neq R^2$, but are hydrogen atoms, alkyl groups, aryl groups. When naming unsymmetrical acid anhydrides, name both using alkanoic general method and then put the two names *alphabetically*. Hence, first name each component and alphabetically arranged them followed by spaces and then the word anhydride.



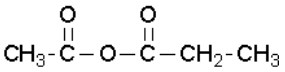


Ethanoic propanoic anhydride **Butanoic ethanoic anhydride**

(Acetic propionic anhydride) **(Acetic butyic anhydride)**

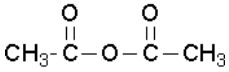


propanoic anhydride

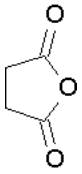


ethanoic propanoic anhydride

COMMON NAMES THAT YOU SHOULD KNOW



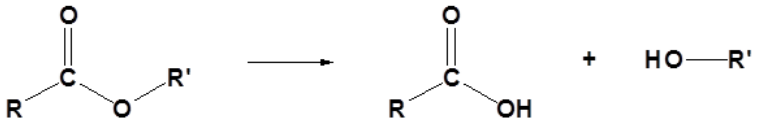
acetic anhydride (Try to name this anhydride by the proper name. J)



succinic anhydride (Try to name this anhydride by the proper name. J)

NOMENCLATURE OF ESTERS

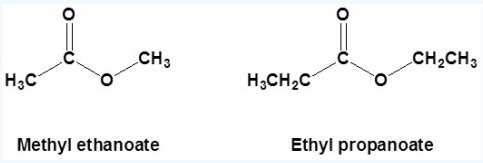
Esters are made from a carboxylic acid and an alcohol.



Ester **Carboxylic Acid** **Alcohol**

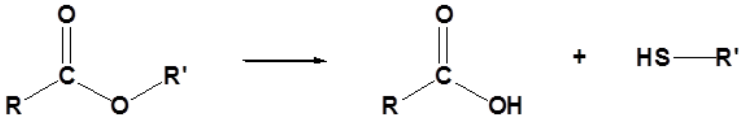
Esters are named as if the alkyl chain from the alcohol is a substituent. No number is assigned to this alkyl chain. This is followed by the name of the parent chain form the carboxylic acid part of the ester with an **–e** remove and replaced with the ending **–oate**.

EXAMPLE 21.1.2



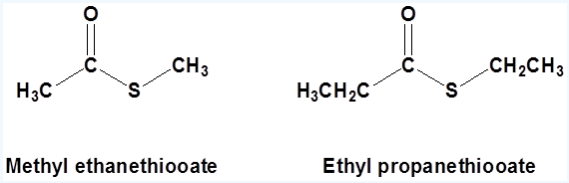
NOMENCLATURE OF THIOESTERS

Thiosters are made from a carboxylic acid and an thiol.



Thioesters are named as if the alkyl chain from the alcohol is a substituent. No number is assigned to this alkyl chain. This is followed by the name of the parent chain from the carboxylic acid part of the thioester named as an alkane with the ending **–thiooate**.

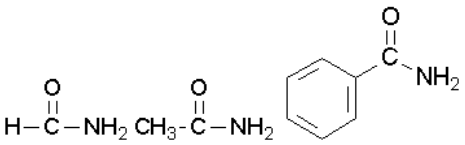
EXAMPLE 21.1.3



NOMENCLATURE OF AMIDES

PRIMARY AMIDES

Primary amides are named by changing the name of the acid by dropping the -oic acid or -ic acid endings and adding -amide. The carbonyl carbon is given the #1 location number. It is not necessary to include the location number in the name because it is assumed that the functional group will be on the end of the parent chain.

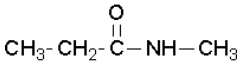


methanamide or formamide (left), ethanamide or acetamide (center) , benzamide (right)

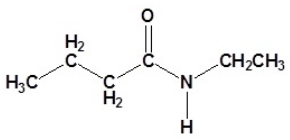


SECONDARY AMIDES

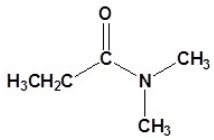
Secondary amides are named by using an upper case N to designate that the alkyl group is on the nitrogen atom. Alkyl groups attached to the nitrogen are named as substituents. The letter N is used to indicate they are attached to the nitrogen. Tertiary amides are named in the same way.



N-methylpropanamide



N-Ethylbutanamide

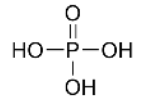


N,N-Dimethylpropanamide

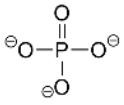
Name the parent alkane (include the carbon atom of the nitrile as part of the parent) followed with the word -nitrile. The carbon in the nitrile is given the #1 location position. It is not necessary to include the location number in the name because it is assumed that the functional group will be on the end of the parent chain.

NAMING PHOSPHATES

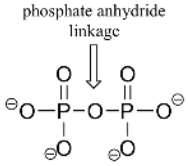
Phosphoryl groups are derivatives of phosphoric acid, a strong acid that is commonly used in the laboratory. The fully deprotonated conjugate base of phosphoric acid is called a phosphate ion, or inorganic phosphate (often abbreviated 'P_i'). When two phosphate groups are linked to each other, the linkage is referred to as a 'phosphate anhydride', and the ion is called 'inorganic pyrophosphate' (abbreviation PP_i).



phosphoric acid

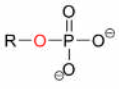


inorganic phosphate (P_i)

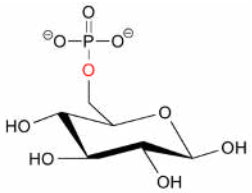


inorganic pyrophosphate (PP_i)

When a phosphate ion is attached to a carbon atom on an organic molecule, the chemical linkage is referred to as a phosphate ester, and the whole species is called an organic monophosphate. Glucose-6-phosphate is an example.

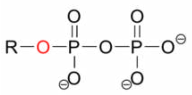


organic monophosphate

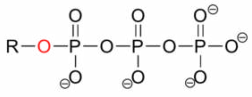


glucose-6-phosphate

If an organic molecule is linked to two or three phosphate groups, the resulting species are called organic diphosphates and organic triphosphates.

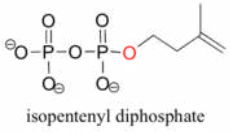


organic diphosphate
(ROPP)

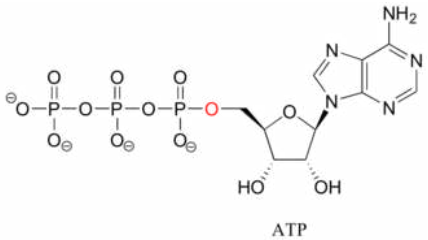


organic triphosphate
(ROPPP)

Isopententyl diphosphate and adenosine triphosphate (ATP) are good examples:

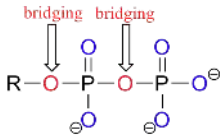


isopentenyl diphosphate

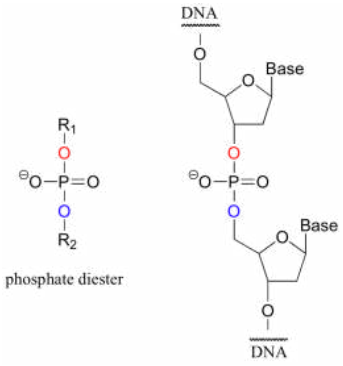


ATP

Oxygen atoms in phosphate groups are referred to either 'bridging' and 'non-bridging', depending on their position. An organic diphosphate has two bridging and five non-bridging oxygens.

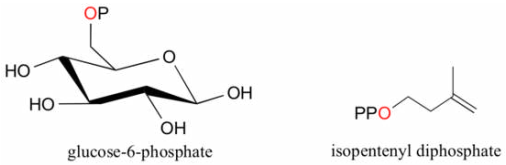


When a single phosphate is linked to two organic groups, the term 'phosphate diester' is used. The backbone of DNA is composed of phosphate diesters.



The term 'phosphoryl group' is a general way to refer to all of the phosphate-based groups mentioned in the paragraphs above.

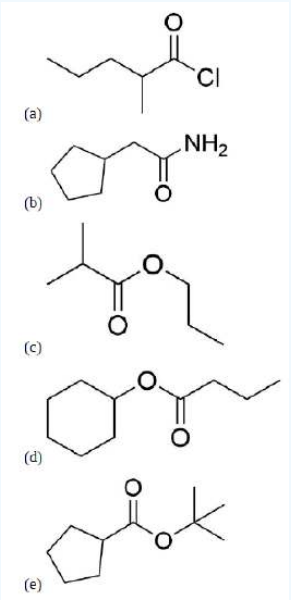
Recall (section 1.4A) that phosphate groups on organic structures are sometimes abbreviated simply as 'P', a convention that we will use throughout this text. For example, glucose-6-phosphate and isopentenyl diphosphate are often depicted as shown below. Notice that the 'P' abbreviation includes the oxygen atoms and negative charges associated with the phosphate groups.



EXERCISES

? EXERCISE 21.1.1

Name the following compounds using IUPAC conventions.



Answer

a) 2-methylpentanoyl chloride

b) 2-cyclopentylacetamide

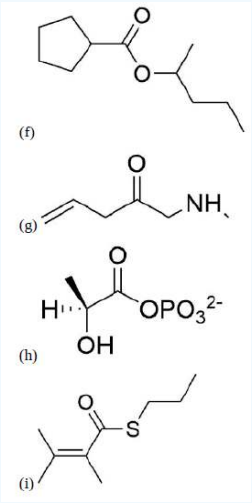
c) propyl 2-methylpropanoat

d) cyclohexylbutanoate

e) sec-butyl cyclopentanecarboxylate

EXERCISE 21.1.2

Name the following compounds using IUPAC conventions.



Answer

f) 1-methylbutylcyclopentane carboxylate

g) N-methyl-3-butenamide

h) (S)-2-hydroxypropanoyl phosphate

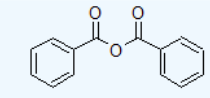
i) propyl 2,3-dimethyl-2-butenethioate

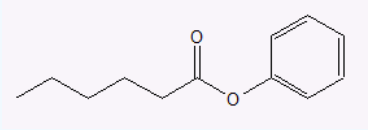
EXERCISE 21.1.3

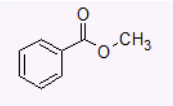
Draw structures corresponding to the following names:

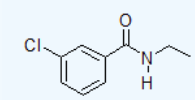
a. benzoic anhydride
b. phenyl hexanoate
c. methyl benzoate
d. 3-chloro-N-ethylbenzamide
e. pentanamide

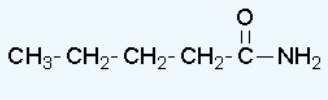
Answer

a. 

b. 

c. 

d. 

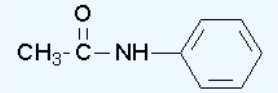
e. 

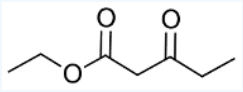
? EXERCISE 21.1.4

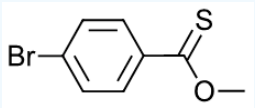
Draw structures corresponding to the following names:

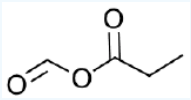
a. N-phenylethanamide
b. Ethyl 3-oxopentanoate
c. Methyl p-bromobenzenethioate
d. Formic propanoic anhydride
e. cis-2-Methylcyclopentanecarbonyl bromide

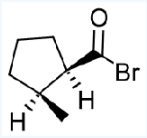
Answer

a. 

b. 

c. 

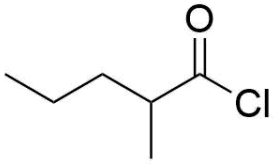
d. 

e. 

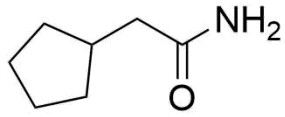
QUESTIONS

Q21.1.1

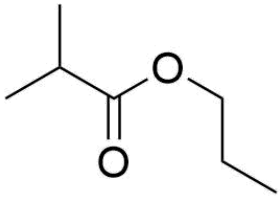
Name the following compounds using IUPAC conventions

(a) 

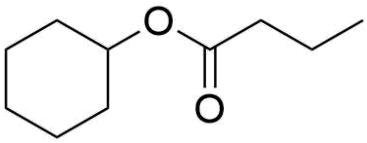
(b)



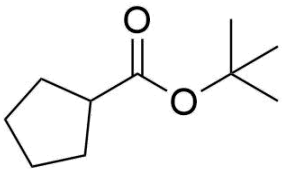
(c)



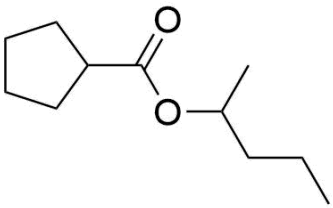
(d)



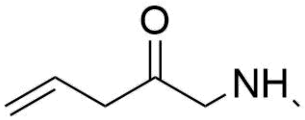
(e)



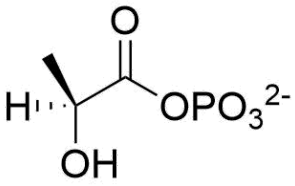
(f)



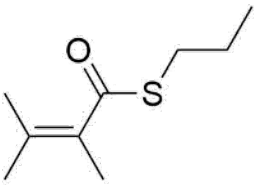
(g)



(h)



(i)



SOLUTIONS

S21.1.1

a. 3-methylpentanoyl chloride
b. 2-cyclopentylacetamide
c. propyl 2-methylpropanoate
d. cyclohexylbutanoate
e. tert-butyl cyclopentanecarboxylate

f. 1-methylbutylcyclopentane carboxylate
g. N-methyl-3-butenamide
h. (S)-2-hydroxypropanoyl phosphate
i. propyl 2,3-dimethyl-2-butenethioate

CONTRIBUTORS AND ATTRIBUTIONS

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

Richard Banks (Boise State University)

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21.2 NUCLEOPHILIC ACYL SUBSTITUTION REACTIONS

Objectives

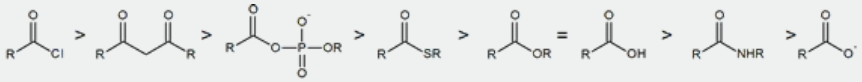
After completing this section, you should be able to

1. compare the reactions of carboxylic acid derivatives with nucleophiles to the reactions of aldehydes and ketones with nucleophiles.
2. arrange a given list of carboxylic acid derivatives in order of increasing or decreasing reactivity towards nucleophiles.
3. explain the difference in reactivity towards nucleophiles of two or more given carboxylic acid derivatives.
4. explain why esters and amides are commonly found in nature, but acid halides and acid anhydrides are not.

STUDY NOTES

The general nucleophilic acyl substitution reaction, and its mechanism, were discussed earlier in "III. General Reactions of Carbonyl Compounds." Review if necessary.

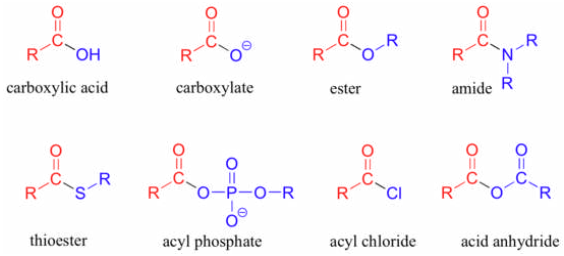
The reading describes the relative reactivities of "biologically relevant acyl groups." Both acid anhydrides and acid halides readily react with water and cannot exist for any length of time in living organisms. The following scheme illustrates the relative reactivities of most carboxylic acid derivatives that you will encounter.



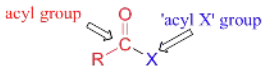
most reactive — least reactive

CARBOXYLIC ACID DERIVATIVES AND ACYL GROUPS

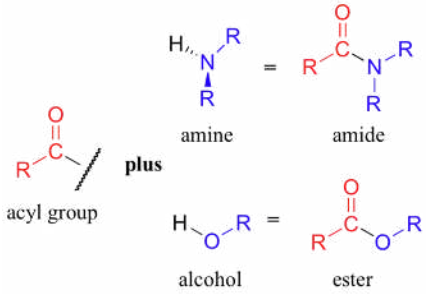
The functional groups that undergo nucleophilic acyl substitutions are called carboxylic acid derivatives: these include carboxylic acids themselves, carboxylates (deprotonated carboxylic acids), amides, esters, thioesters, and acyl phosphates. Two more examples of carboxylic acid derivatives which are less biologically relevant but important in laboratory synthesis are carboxylic acid anyhydrides and acid chlorides.



The carboxylic acid derivatives can be distinguished from aldehydes and ketones by the presence of a group containing an electronegative heteroatom - usually oxygen, nitrogen, or sulfur – bonded directly to the carbonyl carbon. You can think of a carboxylic acid derivative as having two sides. One side is the carbonyl group and the attached alkyl group: this is called an **acyl group** (in the specific case where R is a methyl group, the term **acetyl group** is used). One the other side is the heteroatom-containing group: in this text, we will sometimes refer to this component as the 'acyl X' group (this, however, is *not* a standard term in organic chemistry).



Notice that the acyl X groups are simply deprotonated forms of other functional groups: in an amide, for example, the acyl X group is an amine, while in an ester the acyl X group is an alcohol.



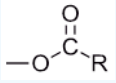
EXAMPLE 21.2.1

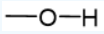
What is the 'Y' group in:

a. an acid anhydride?

b. a carboxylic acid?

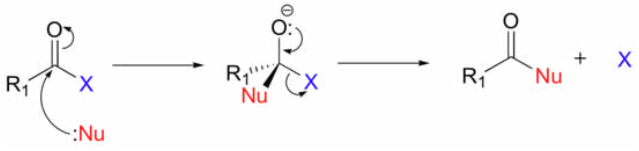
Answers

a. 

b. 

THE NUCLEOPHILIC ACYL SUBSTITUTION REACTION

The fact that the atom adjacent to the carbonyl carbon in carboxylic acid derivatives is an electronegative heteroatom – rather than a carbon like in ketones or a hydrogen like in aldehydes - is critical to understanding the reactivity of these functional groups. Just like in aldehydes and ketones, carboxylic acid derivatives are attacked from one side of their trigonal planar carbonyl carbon by a nucleophile, converting this carbon to tetrahedral (sp^3) geometry. In carboxylic acid derivatives, the acyl X group is a potential leaving group. What this means is that the tetrahedral product formed from attack of the nucleophile on the carbonyl carbon is not the product: it is a *reactive intermediate*. The tetrahedral intermediate rapidly collapses: the carbon-oxygen double bond re-forms, and the acyl X group is expelled.



Notice that in the product, the nucleophile becomes the new acyl X group. This is why this reaction type is called a nucleophilic acyl *substitution*: one acyl X group is substituted for another. For example, in the reaction below, one alcohol X group (3-methyl-1-butanol) is replaced by another alcohol X group (methanol), as one ester is converted to another.



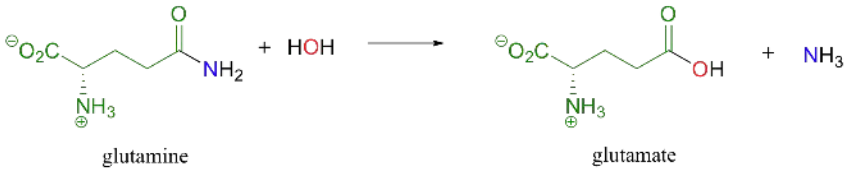
Another way of looking at this reaction is to picture the *acyl* group being transferred from one acyl X group to another: in the example above, the acetyl group is being transferred from 3-methyl-1-butanol to methanol. For this reason, nucleophilic acyl substitutions are also commonly referred to as **acyl transfer** reactions.

When the incoming nucleophile in an acyl substitution is a water molecule, the reaction is also referred to as an acyl hydrolysis. For example, the following reaction can be described as the hydrolysis of an ester (to form a carboxylic acid and an alcohol).

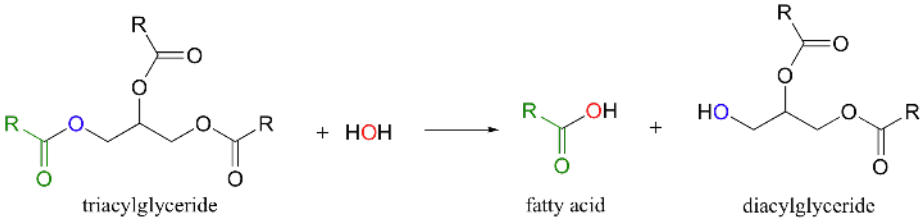


We could also describe this reaction as the transfer of an acyl group from an alcohol to a water molecule.

In a similar vein, the hydrolysis of an amide to form a carboxylic acid could be described as the transfer of an acyl group from ammonia (NH_3) to water.

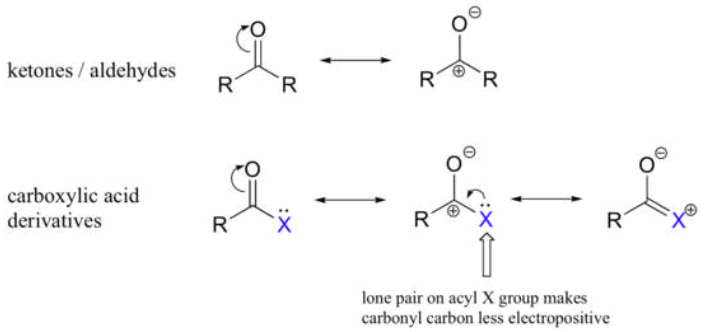


As we will see in later sections of this chapter the hydrolysis of esters and amides are particularly important reaction types in biochemical pathways. When your body digests the fat in a hamburger, for example, enzymes in your pancreas called lipases first catalyze ester hydrolysis reactions to free the fatty acids (we'll look more closely at this reaction in section 12.4D).

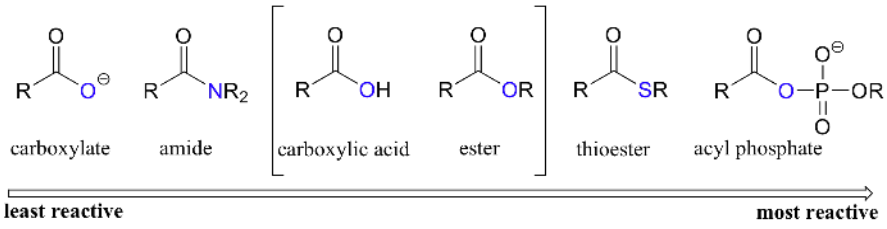


THE RELATIVE REACTIVITY OF CARBOXYLIC ACID DERIVATIVES

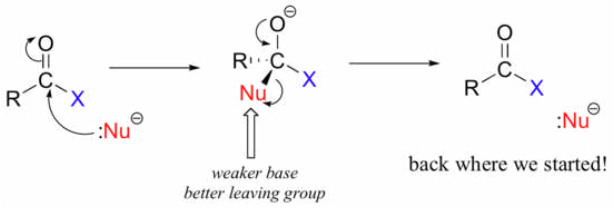
The relative reactivity of the carboxylic acid derivatives is an important concept to understand before entering into a detailed examination of nucleophilic acyl substitutions. As a general rule, the carbonyl carbon in an acyl group is less electrophilic than that in an aldehyde or ketone. This is because in carboxylic acid derivatives, the partial positive charge on the carbon is stabilized somewhat by resonance effects from the adjacent heteroatom.



Among the carboxylic acid derivatives, carboxylate groups are the least reactive towards nucleophilic acyl substitution, followed by amides, then esters and (protonated) carboxylic acids, thioesters, and finally acyl phosphates, which are the most reactive among the biologically relevant acyl groups.



The different reactivities of the functional groups can be understood by evaluating the basicity of the leaving group in each case - remember from section 8.5 that weaker bases are better leaving groups! A thioester is more reactive than an ester, for example, because a thiolate (RS^-) is a weaker base than an alkoxide (RO^-). In general, if the incoming nucleophile is a weaker base than the 'acyl X' group that is already there, the first nucleophilic step will simply reverse itself and we'll get the starting materials back:

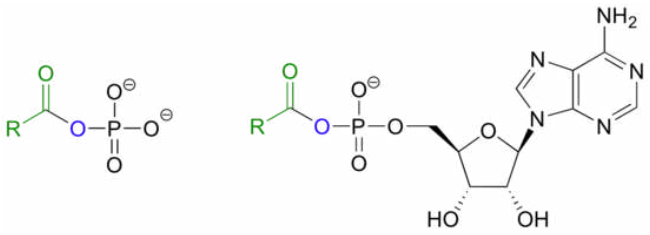


This is why it is not possible to *directly* convert an ester, for example, into a thioester by an acyl substitution reaction – this would be an uphill reaction.

Here's another way to think about the relative reactivites of the different carboxylic acid derivatives: consider the relative electrophilicity, or degree of partial positive charge, on the carbonyl carbon in each species. This depends on how much electron density the neighboring heteroatom on the acyl X group is able to donate: greater electron donation by the heteroatom implies lower partial positive charge on the carbonyl carbon, which in turn implies lower electrophilicity.

The negatively charged oxygen on the carboxylate group has lots of electron density to donate, thus the carbonyl carbon is not very electrophilic. In amides, the nitrogen atom is a powerful electron donating group by resonance - recall that the carbon-nitrogen bond in peptides has substantial double-bond character - thus amides are relatively unreactive. Amides *do* undergo acyl substitution reactions in biochemical pathways, but these reactions are inherently slow and the enzymes catalyzing them have evolved efficient strategies to lower the activation energy barrier.

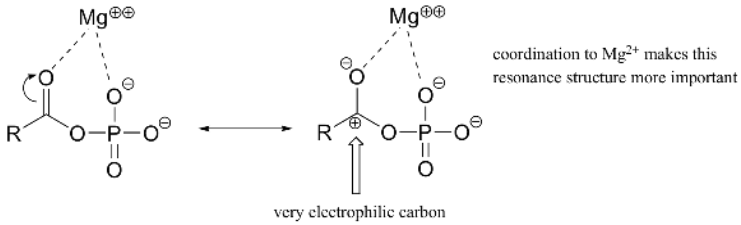
Carboxylic acids and esters are in the middle range of reactivity, while thioesters are somewhat more reactive. The most reactive of the carboxylic acid derivatives frequently found in biomolecules are the acyl phosphates. These are most often present in two forms: the simple acyl monophosphate, and the acyl-adenosine monophosphate.



acyl monophosphate

acyl adenosine monophosphate
(acyl AMP)

Both are highly reactive to acyl substitution reactions, and are often referred to as '**activated acyl groups**' or '**activated carboxylic acids**'. The high reactivity of acyl phosphates is due mainly to the ability to form complexes with magnesium ions.



The magnesium ion acts as a Lewis acid to accept electron density from the oxygen end of the acyl carbonyl bond, thus greatly increasing the degree of partial positive charge - and thus the electrophilicity - of the carbonyl carbon. The magnesium ion also balances negative charge on the phosphate, making it an excellent leaving group.

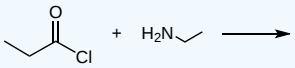
In our examination of acyl substitution reactions, we will start with the formation and reactions of the highly reactive acyl phosphates. We will then discuss how thioesters play a key role in the acyl substitution reactions of lipid metabolism. Finally, we will take a look at some important acyl substitution reactions involving esters, as well as the formation and cleavage of the amide linkages in the peptide bonds of proteins.

✔ WORKED EXAMPLE 21.2.1

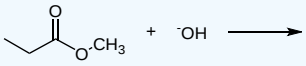
Draw the expected products of the following reactions:

a)

https://chem.libretexts.org/@go/page/90993

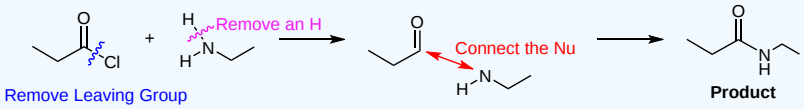


b)

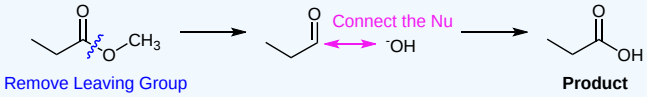


Solution

a) The nucleophile is neutral.



b) The nucleophile is negatively charged.

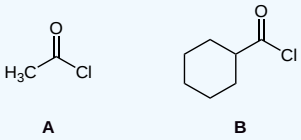


EXERCISES

? EXERCISE 21.2.1

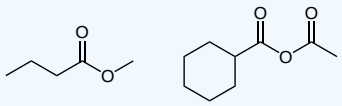
Which of the following compounds would be expected to be the most reactive towards nucleophilic acyl substitution? Briefly explain your answer.

a)



A **B**

b)



A **B**

Answer

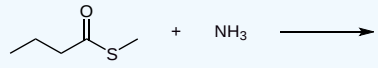
a) Compound A would expected to be the more reactive. For two compounds with the same carboxylic acid derivative group the one with the least steric crowding on the acyl side is typically the most reactive.

b) Compound B would be expected to be the more reactive. In general acid anhydrides are more reactive than ester.

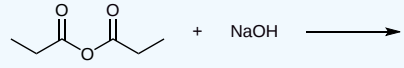
? EXERCISE 21.2.2

Draw the expected products of the following reactions:

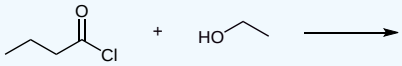
a)



b)

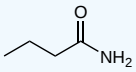


c)

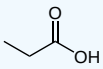


Answer

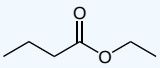
a)



b)



c)



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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21.3 NUCLEOPHILIC ACYL SUBSTITUTION REACTIONS OF CARBOXYLIC ACIDS

Objectives

After completing this section, you should be able to

1. write an equation to describe the formation of
   a. an acid chloride from a carboxylic acid.
   b. an ester from a carboxylic acid.
   c. an amide from a carboxylic acid.
   d. an alcohol from carboxylic acid.
2. write an equation to represent the formation of a cyclic anhydride from a dicarboxylic acid.
3. write the detailed mechanism for the reaction of a carboxylic acid with thionyl chloride.
4. identify the reagents necessary to convert a given carboxylic acid to a given acid chloride, ester, amide or alcohol.
5. identify the carboxylic acid required for a direct synthesis of a given acid chloride, amide, ester or alcohol.
6. write an equation to describe the formation of an ester through the nucleophilic attack of a carboxylate anion on an alkyl halide.
7. write a detailed mechanism for the Fischer esterification reaction.
8. describe the evidence from isotopic labelling experiments that is commonly cited to support the generally accepted mechanism of the Fischer esterification reaction.
9. explain why the direct conversion of a carboxylic acid to an amide can only be achieved with difficulty and at a high temperature.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- Fischer esterfication reaction

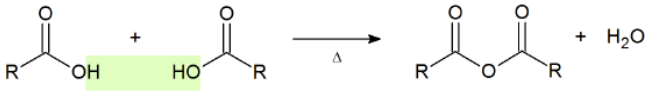
STUDY NOTES

If necessary, review the S_N2 reaction between a carboxylate anion and a primary alkyl halide (Sections 11.2 and 11.3).

You should recall that the oxygen-18 isotope, ^{18}O, has a nucleus containing eight protons and ten neutrons. Because it is non-radioactive, ^{18}O can be safely employed in the investigation of reaction mechanisms.

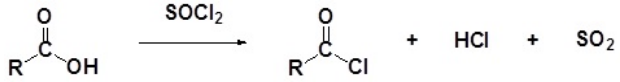
ACID ANHYDRIDE FORMATION

An acid anhydride (or just anhydride) is the product of formal condensation of two oxoacid molecules with the release of a water molecule. The most common anhydrides in organic chemistry are those derived from carboxylic acids at high temperatures to remove water.

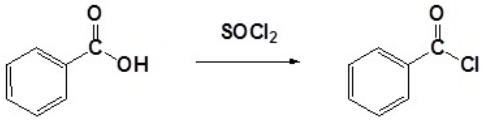


CARBOXYLIC ACIDS REACT WITH THIONYL CHLORIDE ($SOCl_2$) TO FORM ACID CHLORIDES

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.

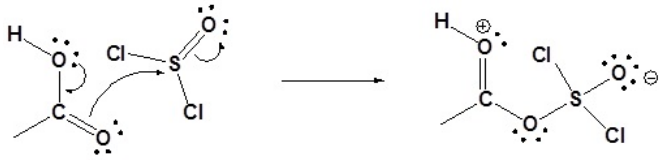


EXAMPLE

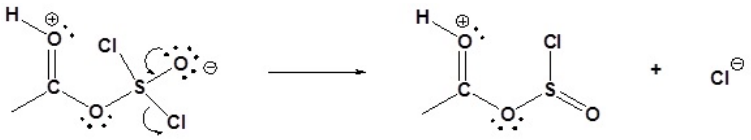


MECHANISM

1) Nucleophilic attack on Thionyl Chloride

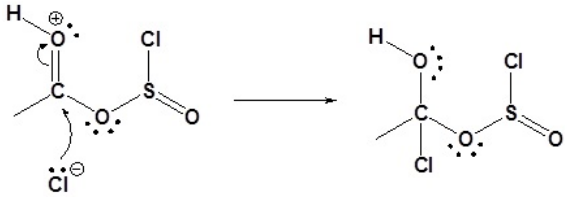


2) Removal of Cl leaving group

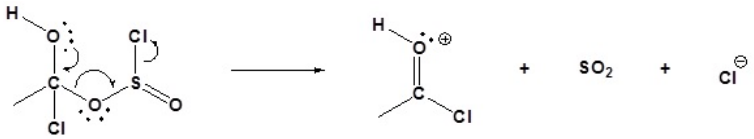


A Chlorosulfite

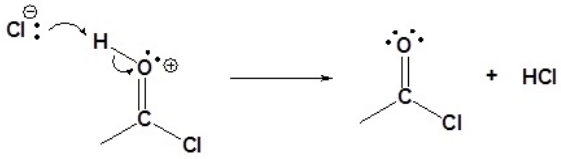
3) Nucleophilic attack on the carbonyl



4) Leaving group removal



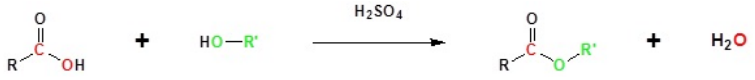
5) Deprotonation



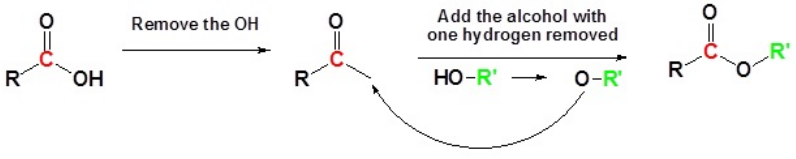
CARBOXYLIC ACIDS CAN REACT WITH ALCOHOLS TO FORM ESTERS IN A PROCESS CALLED FISCHER ESTERIFICATION

Usually the alcohol is used as the reaction solvent. An acid catalyst is required.

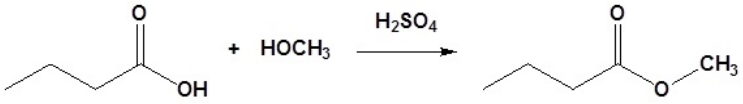
BASIC REACTION



GOING FROM REACTANTS TO PRODUCTS SIMPLIFIED

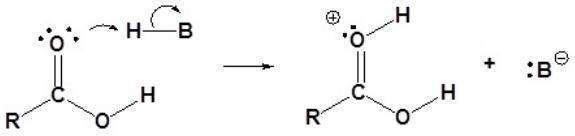


EXAMPLE

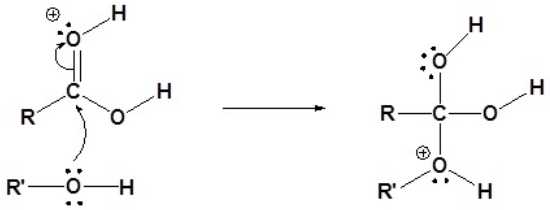


MECHANISM

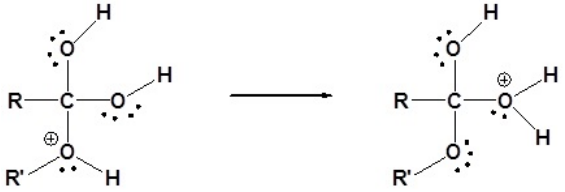
1) Protonation of the carbonyl by the acid. The carbonyl is now activated toward nucleophilic attack.



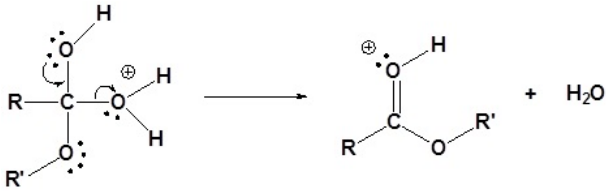
2) Nucleophilic attack on the carbonyl



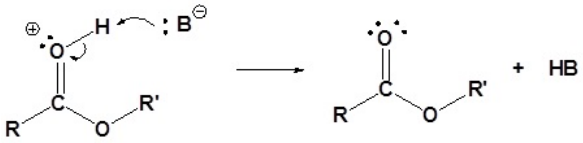
3) Proton transfer



4) Water leaves

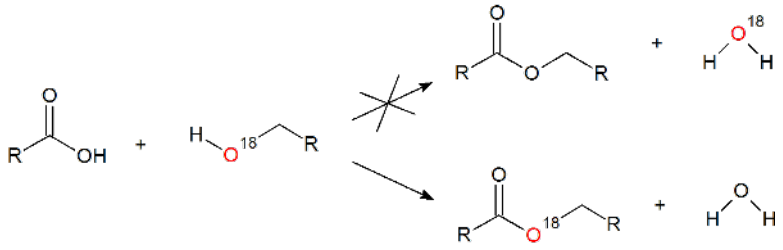


5) Deprotonation



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.

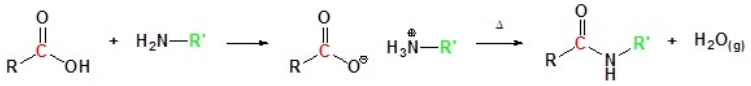


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CONVERSION OF CARBOXYLIC ACIDS TO AMIDES

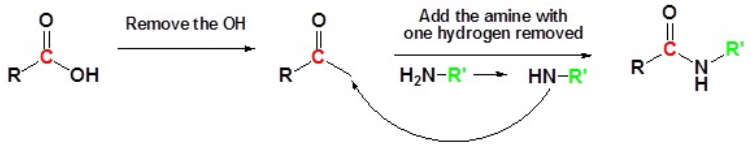
The direct reaction of a carboxylic acid with an amine would be expected to be difficult because the basic amine would deprotonate the carboxylic acid to form a highly unreactive carboxylate. However when the ammonium carboxylate salt is heated to a temperature above 100 ^{o}C water is driven off and an amide is formed.

GENERAL REACTION



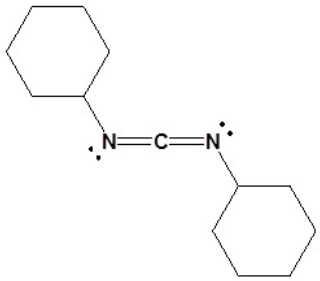
Ammonium Carboxylate Salt

GOING FROM REACTANTS TO PRODUCTS SIMPLY



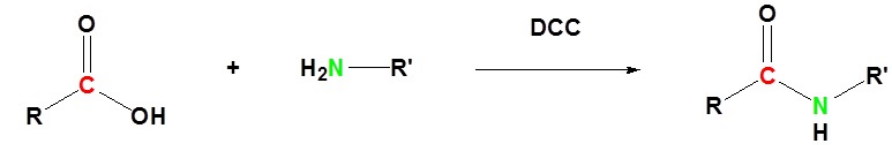
CONVERSION OF CARBOXYLIC ACIDS TO AMIDE USING DCC AS AN ACTIVATING AGENT

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. DCC induced coupling to form an amide linkage is an important reaction in the synthesis of peptides.



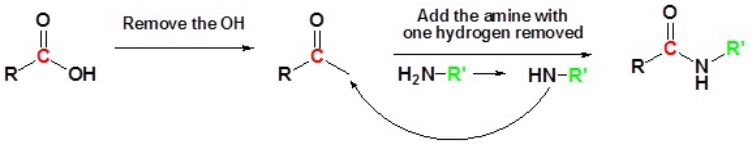
Dicyclohexylcarbodiimide (DCC)

BASIC REACTION



Carboxylic Acid Amine Amide

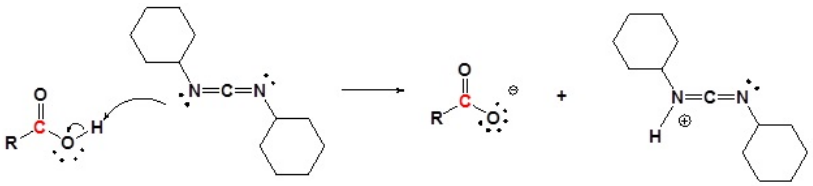
GOING FROM REACTANTS TO PRODUCTS SIMPLIFIED



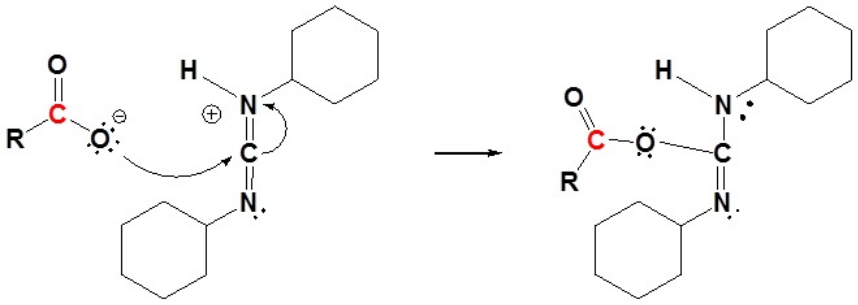
MECHANISM

1) Deprotonation

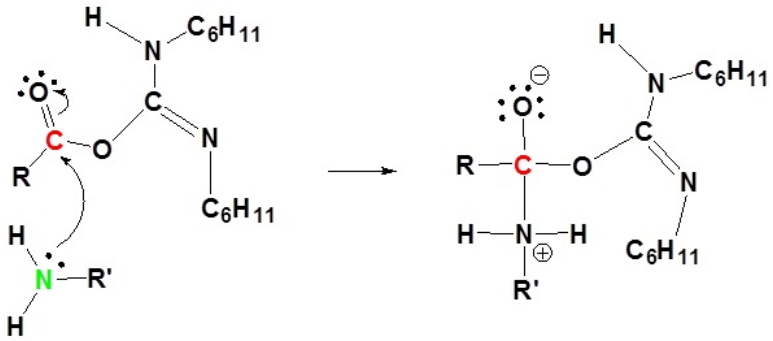
https://chem.libretexts.org/@go/page/90994



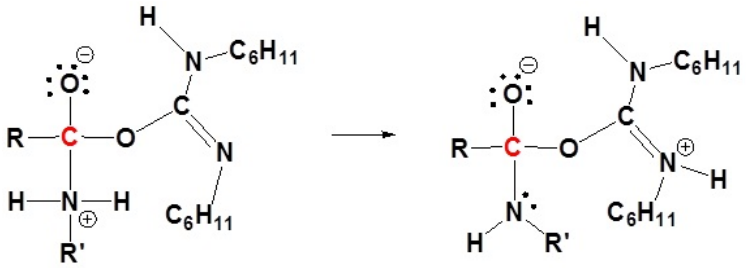
2) Nucleophilic attack by the carboxylate



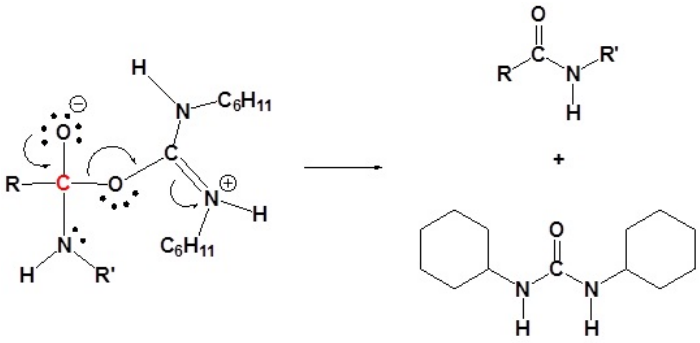
3) Nucleophilic attack by the amine



4) Proton transfer



5) Leaving group removal



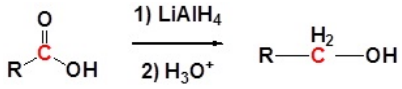
Dicyclohexylurea

https://chem.libretexts.org/@go/page/90994

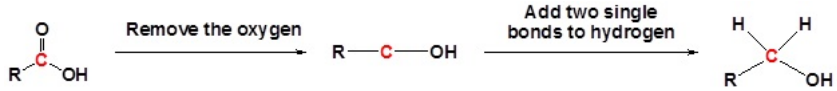
CARBOXYLIC ACIDS CAN BE CONVERTED TO 1^{O} ALCOHOLS USING LITHIUM ALUMINUM HYDRIDE ($LiAlH_4$)

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.

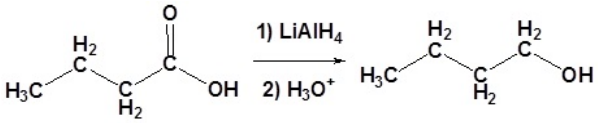
GENERAL REACTION



GOING FROM REACTANT TO PRODUCTS SIMPLIFIED

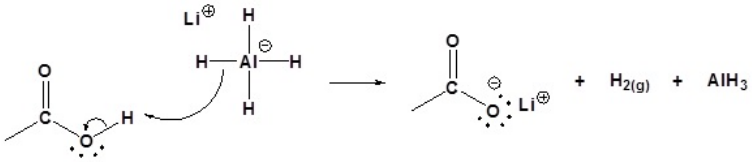


EXAMPLE

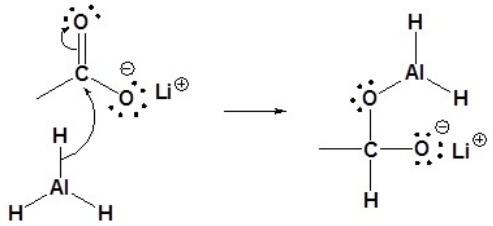


POSSIBLE MECHANISM

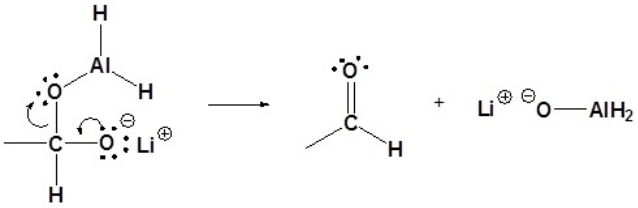
1) Deprotonation



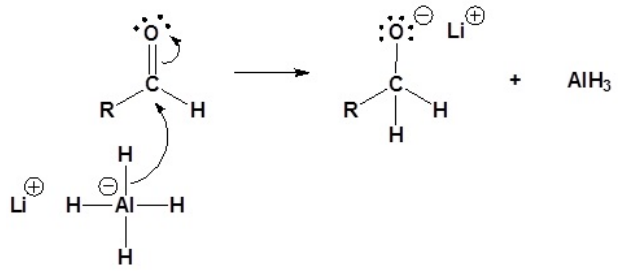
2) Nucleopilic attack by the hydride anion



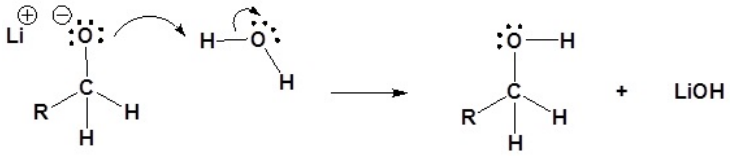
3) Leaving group removal



4) Nucleopilic attack by the hydride anion

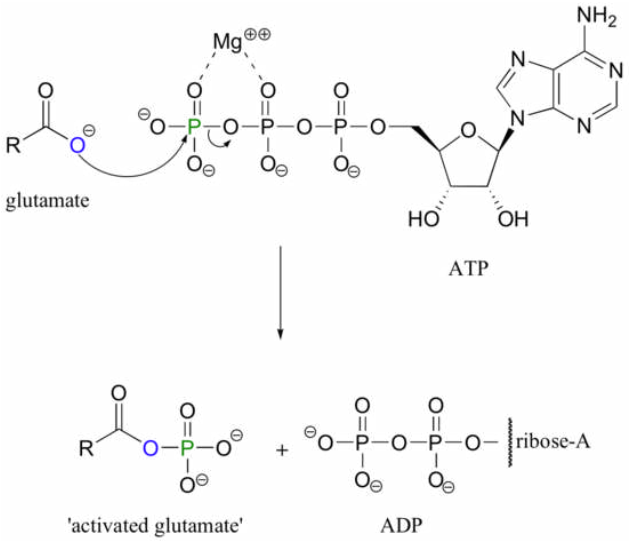


5) The alkoxide is protonated



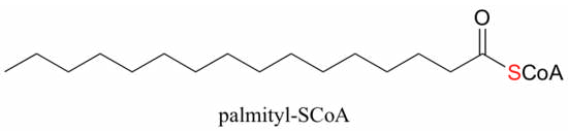
BIOLOGIC CONVERSION OF CARBOXYLIC ACIDS

In biological chemistry direct conversion of a carboxylic acid to an acyl derivative by nucleophilic acyl substitution does not occur. 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: phosphorylation of a carboxylate oxygen with ATP as the phosphate donor.

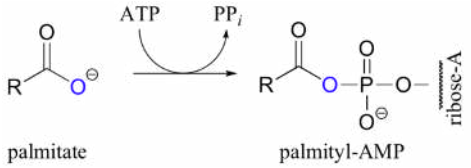


Note that this is just one of the many ways that ATP is used as a energy storage unit: in order to make a high energy acyl phosphate molecule from a low energy carboxylate, the cell must 'spend' the energy of one ATP molecule.

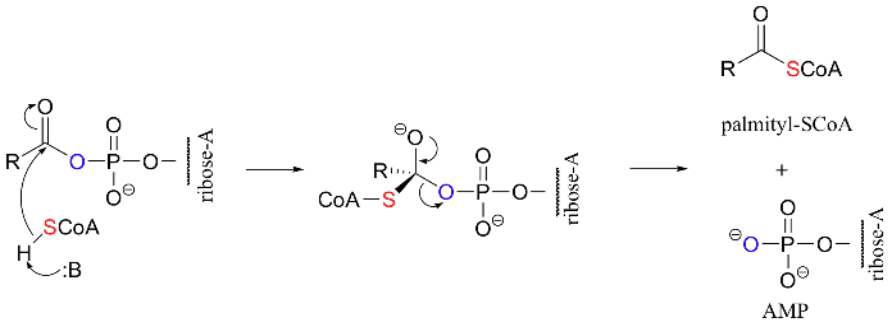
An excellent example of biological activated carboxylic acids is seed in the biosynthesis of fatty acids. In the biologically active form of fatty acids, the carboxylate groups have been converted to thioesters using coenzyme A. For example, the activated form of the C_{16} fatty acid palmitate is:



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 (section 12.2B).



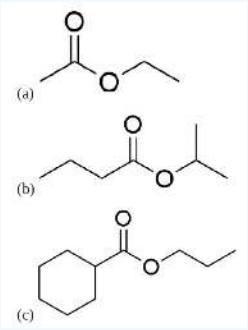
The activated acyl-AMP intermediate is then attacked by the thiol sulfur of coenzyme A, and the AMP group is expelled to form the fatty acyl CoA.



EXERCISES

? EXERCISE 21.3.1

How would you create the following esters from the corresponding acids?



Answer

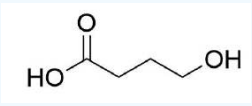
a) Acetic acid + ethanol

b) Butanoic acid + isopropanol

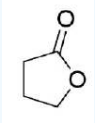
c) Cyclohexanecarboxylic acid + propanol

? EXERCISE 21.3.2

The following molecule is treated with acid and undergoes an intramolecular Fischer Esterification. Draw the product.



Answer

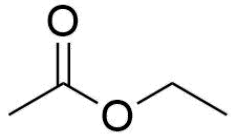


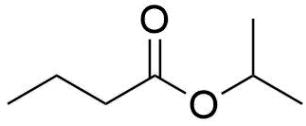
https://chem.libretexts.org/@go/page/90994

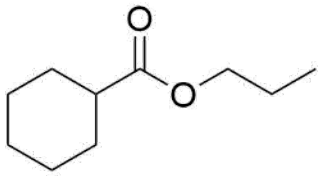
QUESTIONS

Q21.3.1

How would you create the following esters from the corresponding acids?

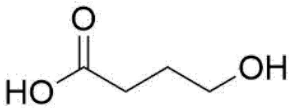
(a) 

(b) 

(c) 

Q21.3.2

The following molecule is treated with acid and undergoes an intramolecular Fischer Esterification. Draw the product.

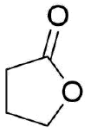


SOLUTIONS

S21.3.1

a. Acetic acid + ethanol
b. Butanoic acid + isopropanol
c. Cyclohexanecarboxylic acid + propanol

S21.3.2



CONTRIBUTORS AND ATTRIBUTIONS

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

21.3 Nucleophilic Acyl Substitution Reactions of Carboxylic Acids is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

21.4 CHEMISTRY OF ACID HALIDES

Objectives

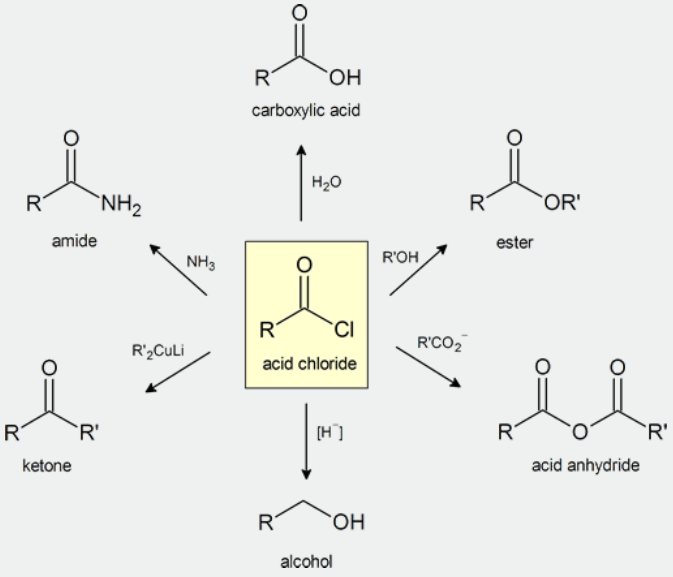
After completing this section, you should be able to

1. identify the reagent normally used to convert a carboxylic acid to an acid bromide.
2. write equations to show how an acid halide may be converted into each of the following: a carboxylic acid, an ester, an amide.
3. write a detailed mechanisms for the reaction of an acid halide with each of the following: water, an alcohol, ammonia, a primary or secondary amine.
4. identify the product formed when a given acid halide reacts with any of the following reagents: water, an alcohol, a primary or secondary amine.
5. identify the acid halide, the reagents, or both, needed to prepare a given carboxylic acid, ester or amide.
6. identify the product formed when a given acid halide reacts with water, a given alcohol, ammonia, or a given primary or secondary amine.
7. identify lithium aluminum hydride as a reagent for reducing acid halides to primary alcohols, and explain the limited practical value of this reaction.
8. identify the partial reduction of an acid halide using lithium tri-*tert*-butoxyaluminum to form an aldehyde.
9. write an equation to describe the formation of a tertiary alcohol by the reaction of an acid halide with a Grignard reagent.
10. write a detailed mechanism for the reaction of an acid halide with a Grignard reagent.
11. identify the product formed from the reaction of a given acid halide with a given Grignard reagent.
12. identify the acid halide, the Grignard reagent, or both, needed to prepare a given tertiary alcohol.
13. write an equation to illustrate the reaction of an acid halide with a lithium diorganocopper reagent.
14. identify the product formed from the reaction of a given acid halide with a given lithium diorganocopper reagent.
15. identify the acid halide, the lithium diorganocopper reagent, or both, that must be used to prepare a given ketone.

STUDY NOTES

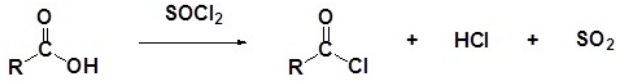
This figure provides a convenient general summary of a few of the reactions described in Section 21.4.

Note that $LiAlH_4$ is a common reagent for hydride [H^-] reduction of and acid chloride to an alcohol.

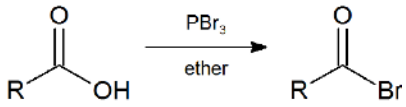


FORMATION OF ACID HALIDES

Carboxylic acids react with thionyl chloride ($SOCl_2$) to form acid chlorides. 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.

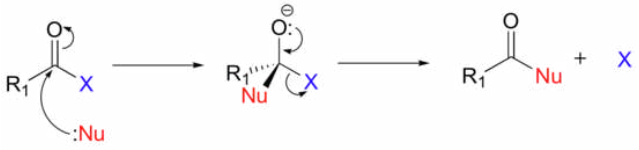


Earlier (Section 10.5) we saw that primary and secondary alcohols react with PBr_3 to afford the corresponding alkyl bromide. In a similar fashion acid bromides can be formed from the carboxylic acid.



NUCLEOPHILIC ACYL SUBSTITUTION MECHANISM

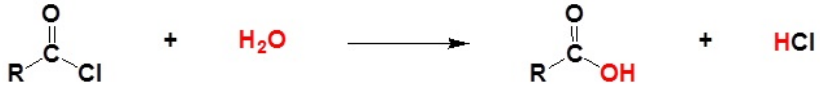
If you understand the mechanism of a typical nucleophilic acyl substitution, the reaction of an acyl halide with water, an alcohol or ammonia should not present you with any difficulty.



X = Cl, Br :Nu = H_2O, ROH, NH_2R, NHR_2 etc.

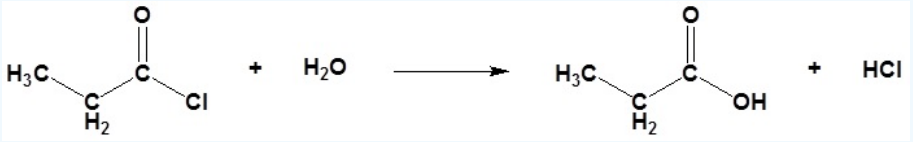
ACID CHLORIDES REACT WITH WATER TO FORM CARBOXYLIC ACIDS.

GENERAL REACTION



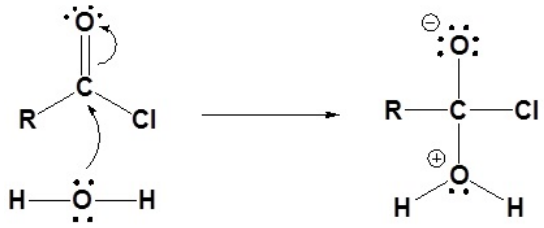
Acid Chloride **Carboxylic Acid**

EXAMPLE 21.4.1

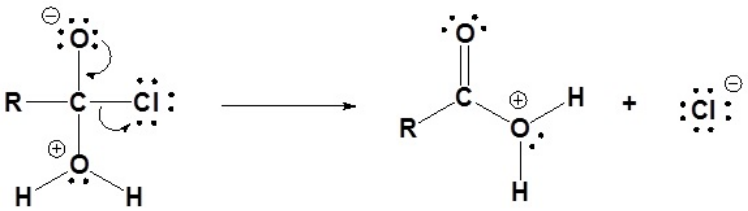


MECHANISM

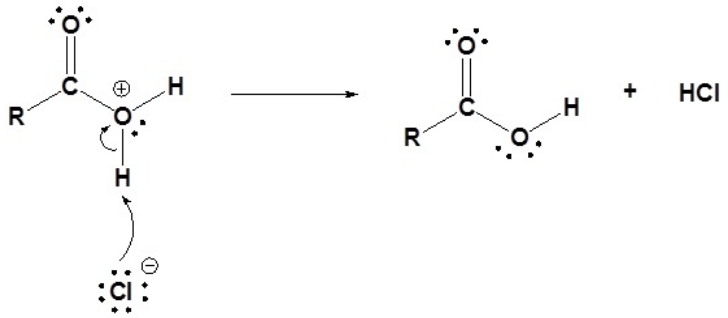
1) Nucleophilic attack by water



2) Leaving group is removed



3) Deprotonation



ACID CHLORIDES REACT WITH CARBOXYLIC ACIDS TO FORM ANHYDRIDES



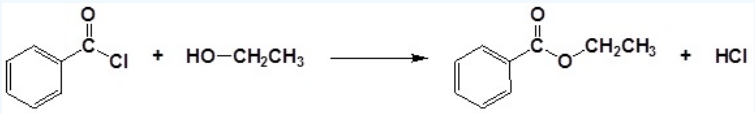
Acid Chloride Carboxylic Acid Acid Anhydride

ACID CHLORIDES REACT WITH ALCOHOLS TO FORM ESTERS

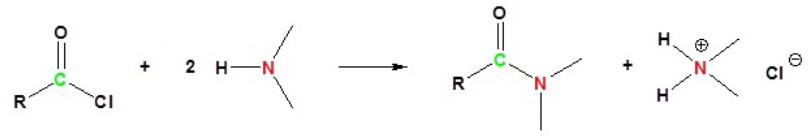


Acid Chloride Alcohol Ester

EXAMPLE 21.4.2



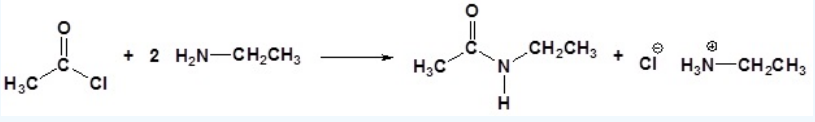
ACID CHLORIDES REACT WITH AMMONIA, 1^{O} AMINES AND 2^{O} AMINES TO FORM AMIDES.



Acid Chloride Amine Amide

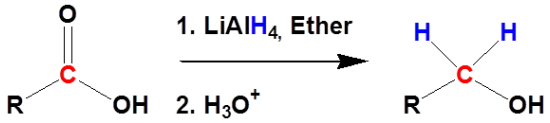
EXAMPLE 21.4.3



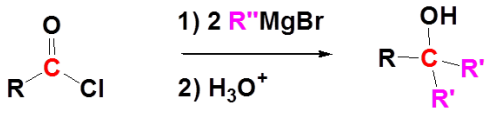


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ACID CHLORIDES CAN BE REDUCED TO FORM 1^{O} ALCOHOLS

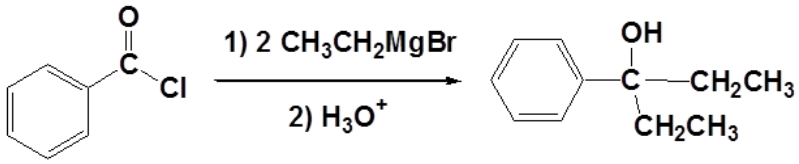


GRIGNARD REAGENTS CONVERT ACID CHLORIDE TO 3° ALCOHOLS

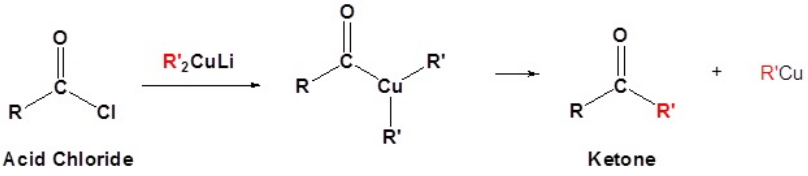


Acid Chloride

3° Alcohol



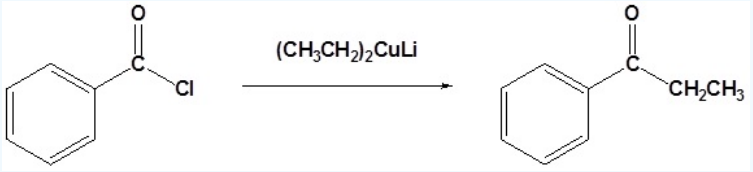
ORGANOCUPRATE REAGENTS CONVERT ACID CHLORIDES TO KETONES.



Acid Chloride

Ketone

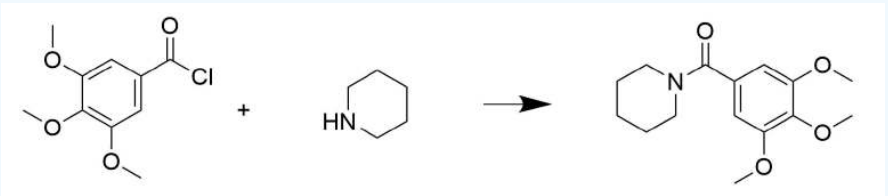
✔ EXAMPLE 21.4.4



EXERCISES

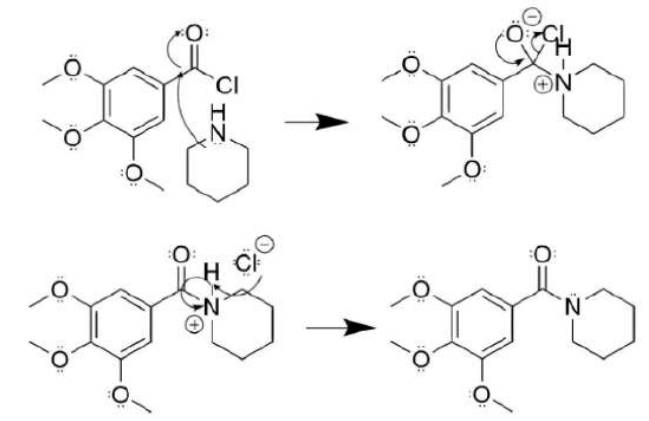
? EXERCISE 21.4.1

Draw the mechanism for the following reaction.



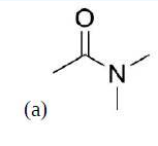
Answer

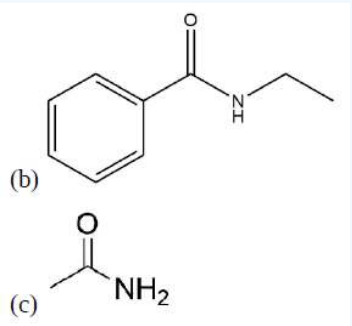
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? EXERCISE 21.4.2

Propose a synthesis of the following molecules from an acid chloride and an amide.





Answer

a) Acetyl chloride and dimethylamine

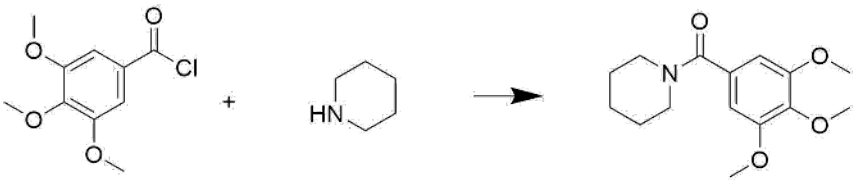
b) Benzoyl chloride and ethylamine

c) Acetyl chloride and ammonia

QUESTIONS

Q21.4.1

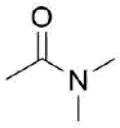
Draw the mechanism for the following reaction



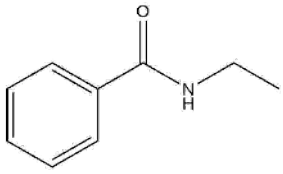
Q21.4.2

Propose a synthesis of the following molecules from an acid chloride and an amide.

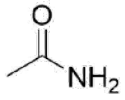
(a)



(b)

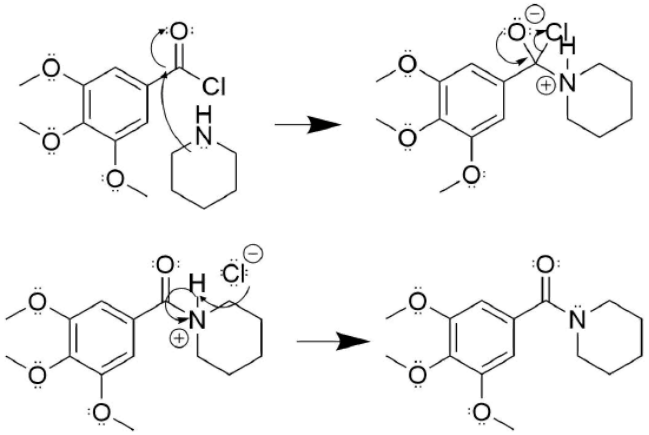


(c)



SOLUTIONS

S21.4.1



S21.4.2

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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21.5 CHEMISTRY OF ACID ANHYDRIDES

Objectives

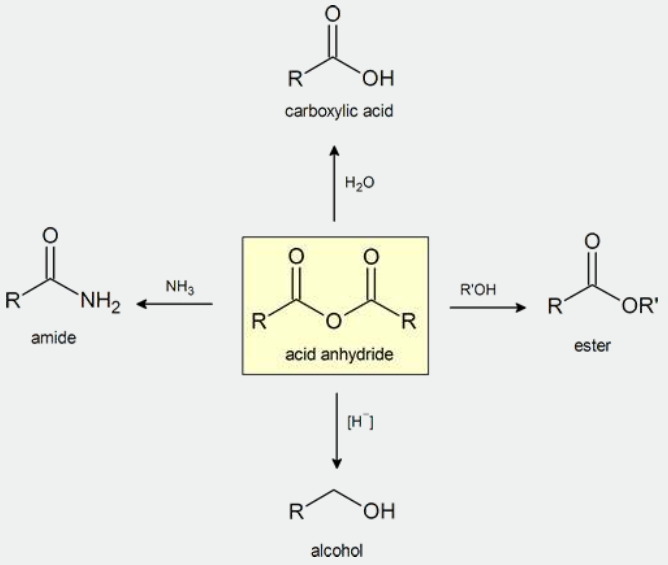
After completing this section, you should be able to

1. write an equation to illustrate the preparation of an acid anhydride from an acid halide and the sodium salt of a carboxylic acid.
2. identify the product formed from the reaction of a given acid halide with the sodium salt of a given carboxylic acid.
3. identify the acid halide, carboxylate salt, or both, required to prepare a given acid anhydride.
4. write an equation to describe the reaction of an acid anhydride with each of the following: water, alcohol, ammonia, a primary or secondary amine, lithium aluminum hydride.
5. identify the product formed when a given acid anhydride is reacted with any of the reagents listed in Objective 4, above.
6. write a detailed mechanism for the reaction of an acid anhydride with any of the reagents listed in Objective 4, above.
7. identify the acid anhydride, the nucleophilic reagent, or both, needed to prepare a specified carboxylic acid, ester, amide, or primary alcohol.

STUDY NOTES

The reactions described in this section are, in principle, identical to those discussed in Section 21.4. Once you have understood the mechanism of nucleophilic acyl substitution, these reactions should not present you with any great difficulty, and memorization can be kept to a minimum.

This figure provides a convenient general summary of a few of the reactions described in Section 21.5. Note that from a synthetic perspective the ester- and amide-forming reactions are the most common, so they are the focus of this section.



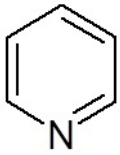
PREPARATION OF ACID ANHYDRIDES

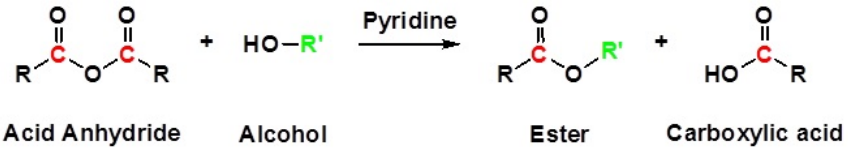
Acid Chlorides react with carboxylic acids to form anhydrides



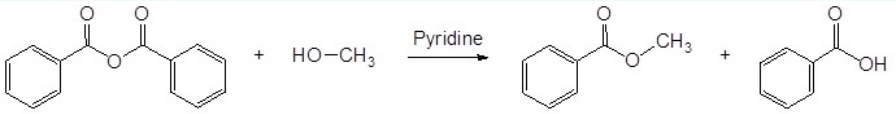
ACID ANHYDRIDES REACT WITH ALCOHOLS TO FORM ESTERS

Reactions of anhydrides use Pyridine as a solvent



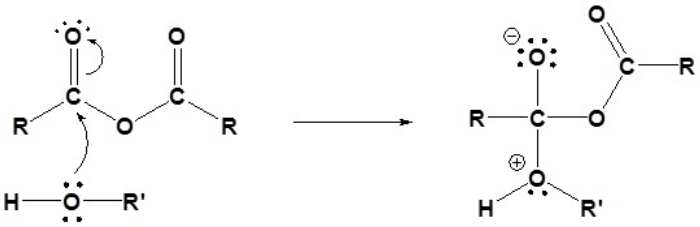


EXAMPLE 21.5.1

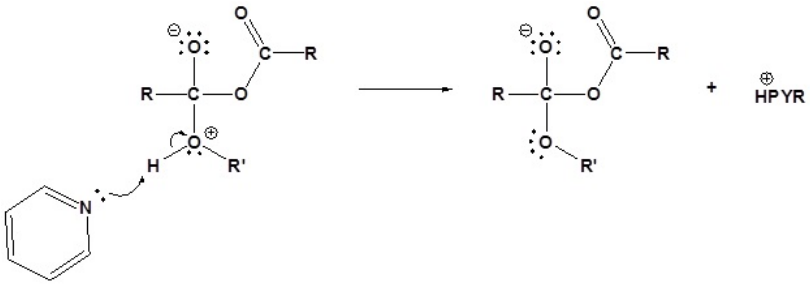


MECHANISM

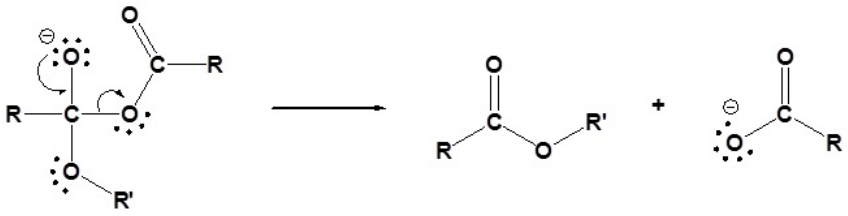
1) Nucleophilic Attack by the Alcohol



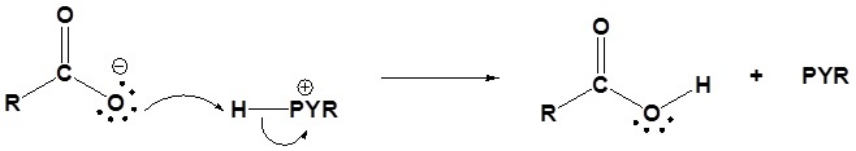
2) Deprotonation by pyridine



3) Leaving group removal

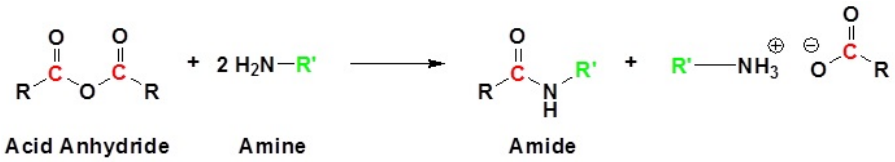


4) Protonation of the carboxylate

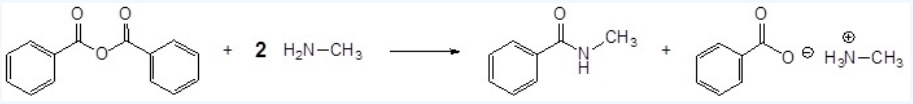


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ACID ANHYDRIDES REACT WITH AMINES TO FORM AMIDES

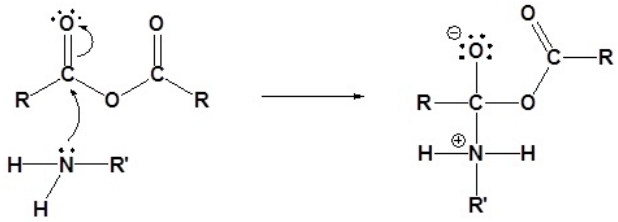


EXAMPLE 21.5.2

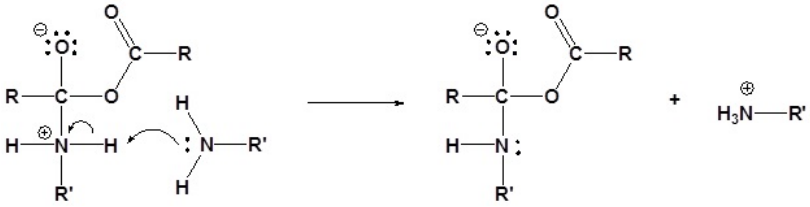


MECHANISM

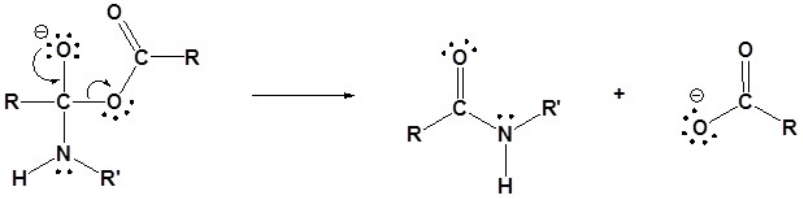
1) Nucleophilic Attack by the Amine



2) Deprotonation by the amine



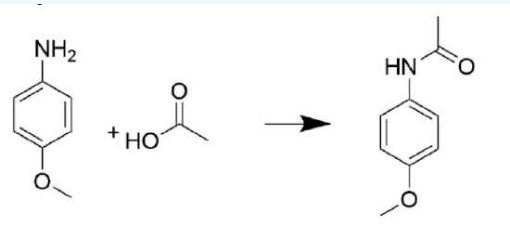
3) Leaving group removal



EXERCISES

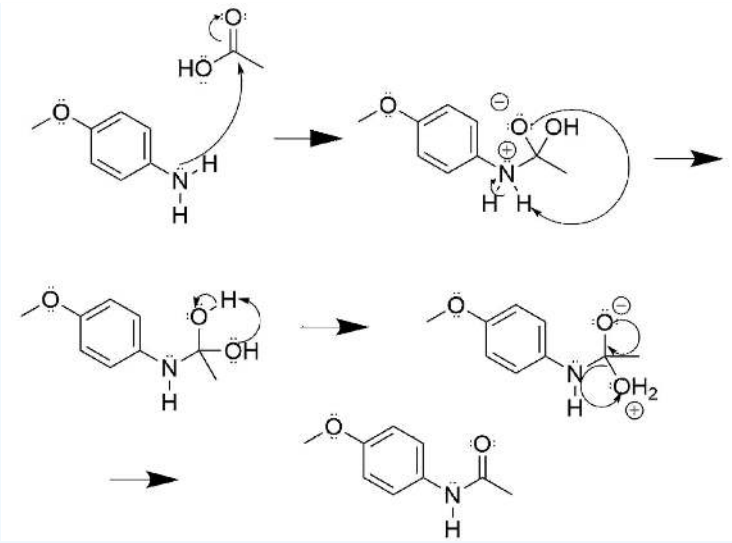
EXERCISE 21.5.1

Draw out the mechanism for the following reaction.



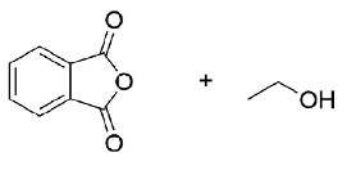
Answer

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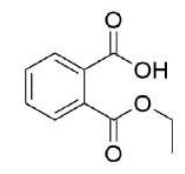


EXERCISE 21.5.2

Draw the product of the reaction between these two molecules.



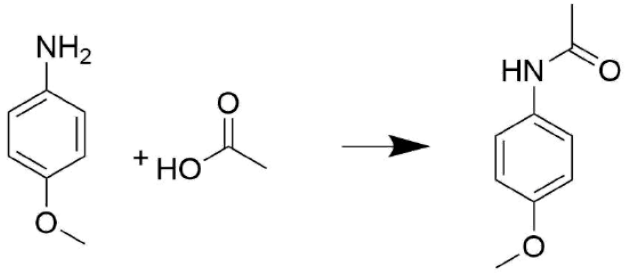
Answer



QUESTIONS

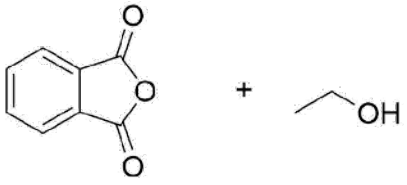
Q21.5.1

Draw out the mechanism for the following reaction.



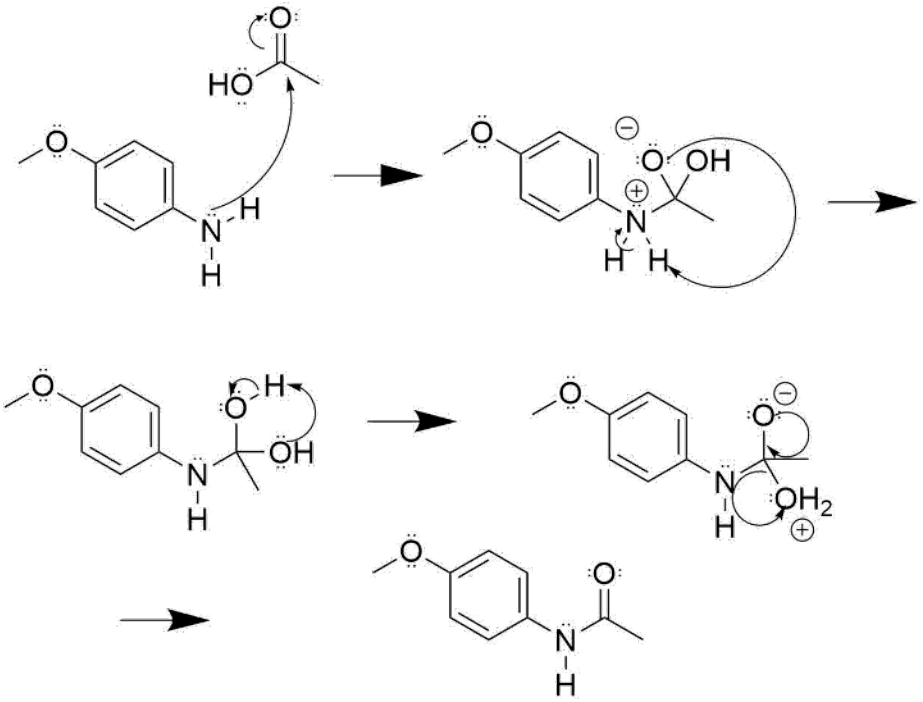
Q21.5.2

Draw the product of the reaction between these two molecules.

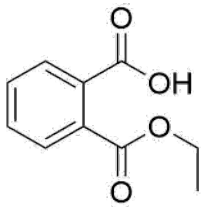


SOLUTIONS

S21.5.1



S21.5.1



CONTRIBUTORS AND ATTRIBUTIONS

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

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21.6 CHEMISTRY OF ESTERS

Objectives

After completing this section, you should be able to

1. discuss the wide occurrence of esters in nature, and their important commercial uses, giving one example of an ester linkage in nature, and one example of a commercially important ester.
2. write an equation to describe the hydrolysis of an ester under acidic or basic conditions.
3. identify the products formed from the hydrolysis of an given ester.
4. identify the reagents that can be used to bring about ester hydrolysis.
5. identify the structure of an unknown ester, given the products of its hydrolysis.
6. write the mechanism of alkaline ester hydrolysis.
7. write the mechanism of acidic ester hydrolysis.
8. write an equation to describe the reduction of an ester with lithium aluminum hydride.
9. identify the product formed from the reduction of a given ester (or lactone) with lithium aluminum hydride.
10. identify the ester, the reagents, or both, that should be used to prepare a given primary alcohol.
11. write a detailed mechanism for the reduction of an ester by lithium aluminum hydride.
12. identify diisobutylaluminum hydride as a reagent for reducing an ester to an aldehyde, and write an equation for such a reaction.
13. write an equation to describe the reaction of an ester with a Grignard reagent.
14. identify the product formed from the reaction of a given ester with a given Grignard reagent.
15. identify the ester, the Grignard reagent, or both, needed to prepare a given tertiary alcohol.
16. write a detailed mechanism for the reaction of an ester with a Grignard reagent.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- lactone
- saponification

STUDY NOTES

Many esters have characteristic aromas and flavours. Some examples are listed below.

Basic structure:

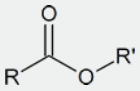
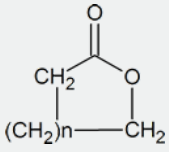


Table 21.1 Structures and characteristic odours of selected esters

IUPAC name	R	R′	Aroma
octyl ethanoate	CH_3	$CH_3(CH_2)_6CH_2$	orange
propyl ethanoate	CH_3	$CH_3CH_2\ CH_2$	pear
2-methylpropyl propanoate	CH_3CH_2	$(CH_3)_2CHCH_2$	rum
methyl butanoate	$CH_3CH_2CH_2$	CH_3	apple
ethyl butanoate	$CH_3CH_2CH_2$	CH_3CH_2	pineapple

A “lactone” is a cyclic ester and has the general structure

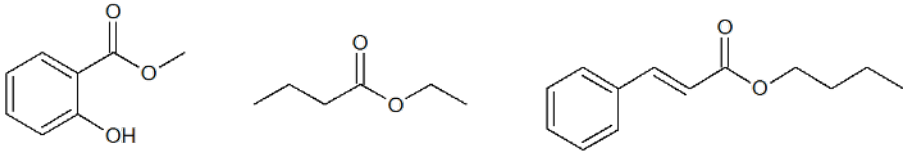


By recognizing that the steps in the acidic hydrolysis of an ester are exactly the same as those in a Fischer esterification (but in the reverse order!), you can again minimize the amount of memorization that you must undertake. The details of both mechanisms can be

deduced from the knowledge that both reactions are acid-catalyzed nucleophilic acyl substitutions.

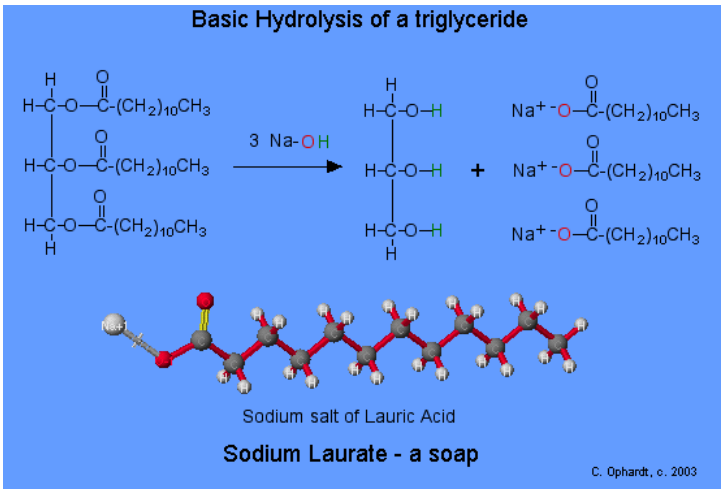
INTRODUCTION

Esters are readily synthesized and naturally abundant contributing to the flavors and aromas in many fruits and flowers.



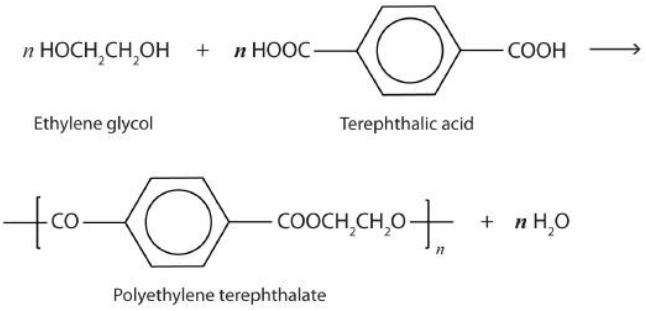
oil of wintergreen | pineapple | chocolate

They 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.



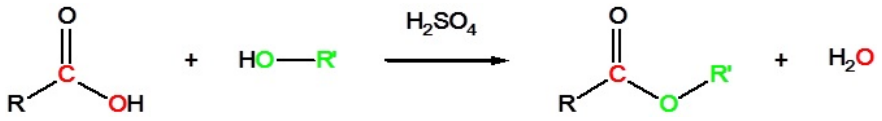
Esters are also present in a number of important biological molecules and have several commercial and synthetic application. For example, polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or 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:

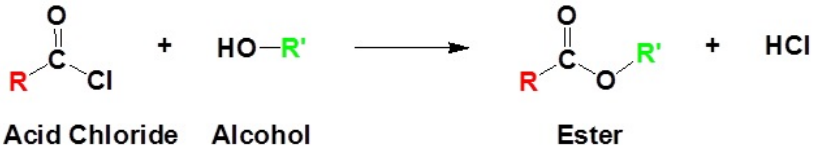


PREPARATION OF ESTERS

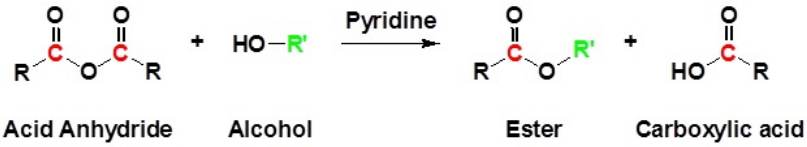
Carboxylic acids can react with alcohols to form esters



Acid chlorides react with alcohols to form esters

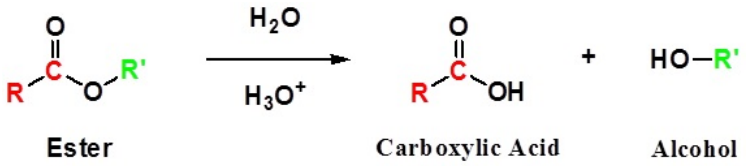


Acid Anhydrides react with alcohols to form esters

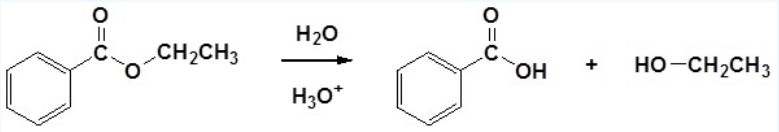


CONVERSION OF ESTER INTO CARBOXYLIC ACIDS: HYDROLYSIS

Esters can be cleaved back into a carboxylic acid and an alcohol by reaction with water and a catalytic amount of acid.

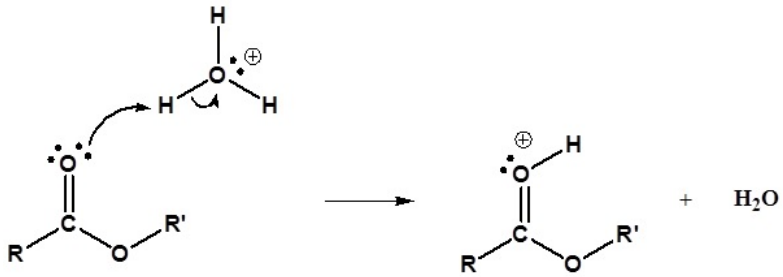


EXAMPLE 21.6.1

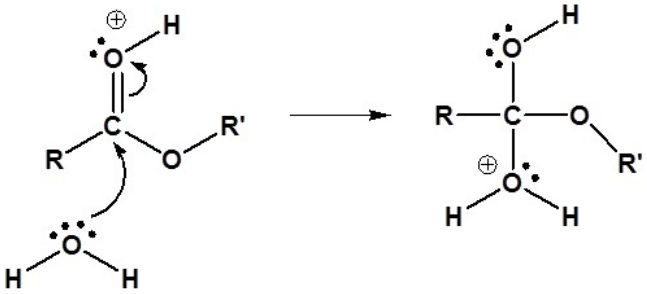


MECHANISM

1) Protonation of the Carbonyl

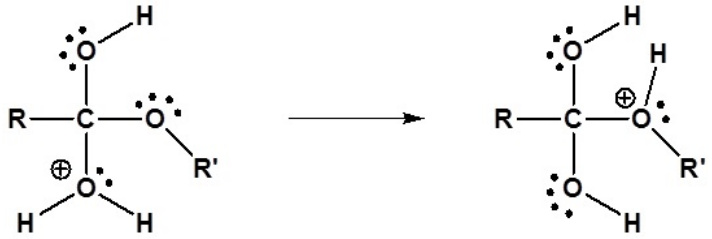


2) Nucleophilic attack by water

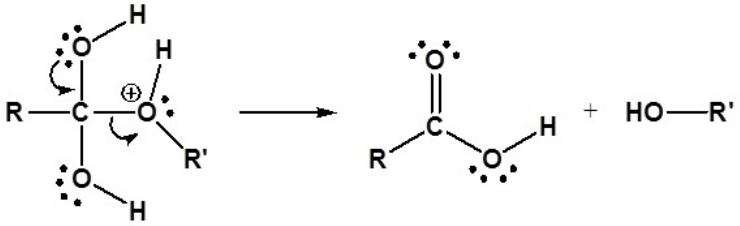


3) Proton transfer

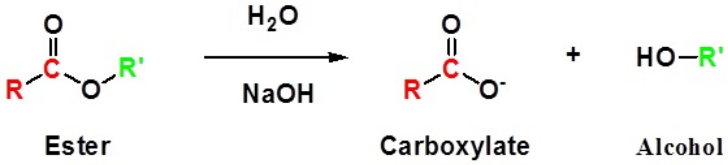
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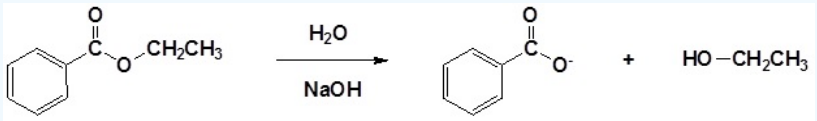
4) Leaving group removal



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.

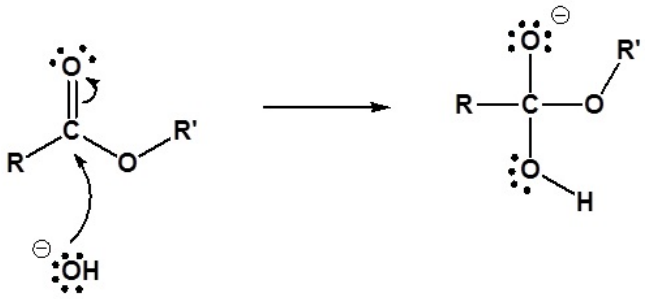


EXAMPLE 21.6.2

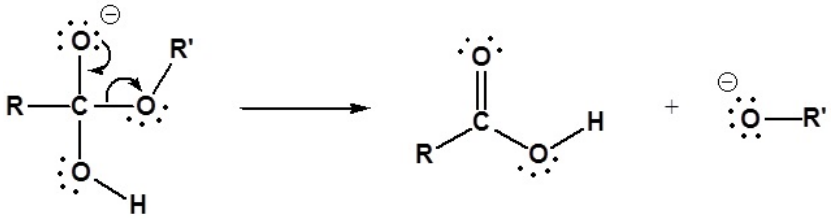


MECHANISM

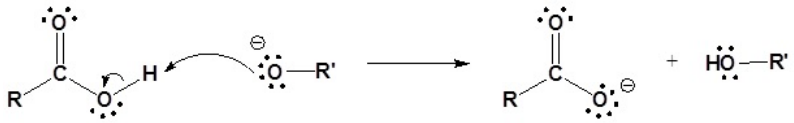
1) Nucleophilic attack by hydroxide



2) Leaving group removal

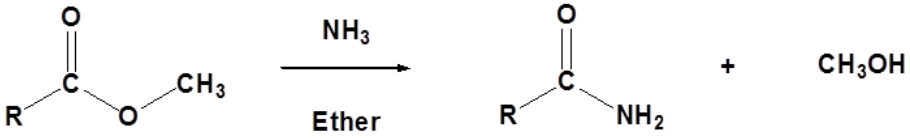


3) Deprotonation



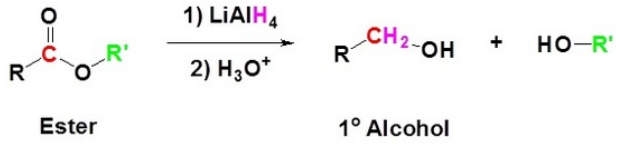
CONVERSION OF ESTERS INTO AMIDES: AMINOLYSIS

Esters reaction with ammonia and alkyl amines to yield amides.

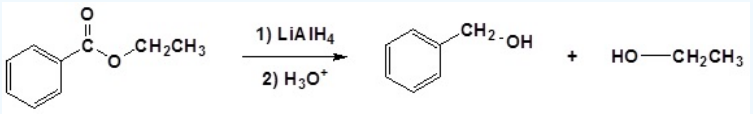


CONVERSION OF ESTER INTO ALCOHOLS: REDUCTION

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

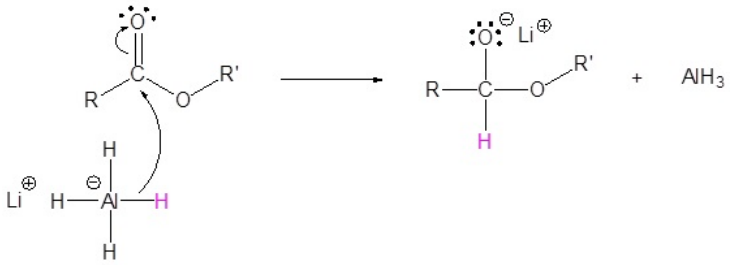


EXAMPLE 21.6.3

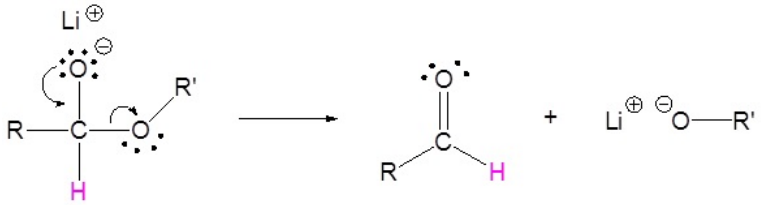


MECHANISM

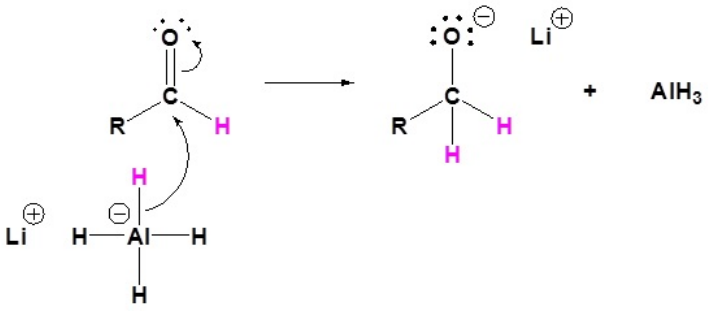
1) Nucleophilic attack by the hydride



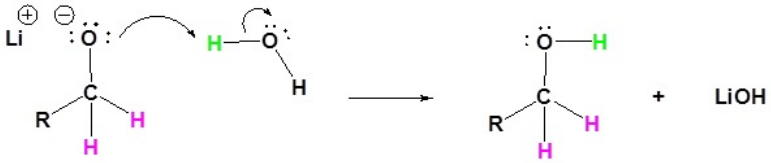
2) Leaving group removal



3) Nucleopilic attack by the hydride anion

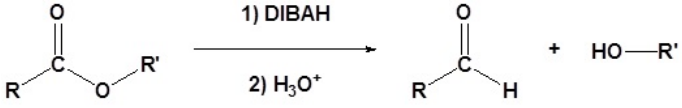


4) The alkoxide is protonated

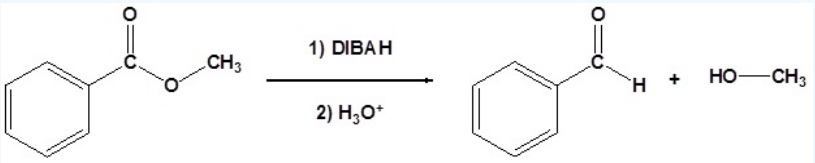


ESTERS CAN BE CONVERTED TO ALDEHYDES USING DIISOBUTYLALUMINUM HYDRIDE (DIBAH)

The reaction is usually carried out at -78 ^{o}C to prevent reaction with the aldehyde product.

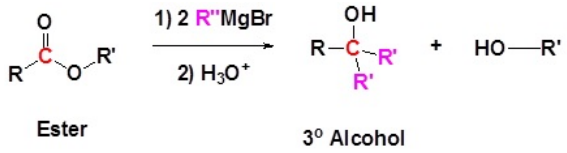


EXAMPLE 21.6.4

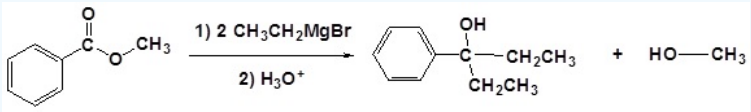


ADDITION OF GRIGNARD REAGENTS CONVERT ESTERS TO 3° ALCOHOLS.

In effect the Grignard reagent adds twice.



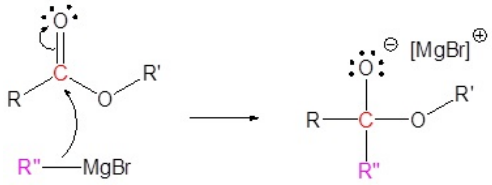
EXAMPLE 21.6.5



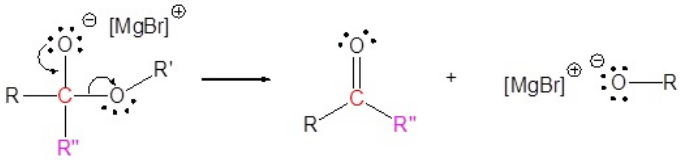
MECHANISM

1) Nucleophilic attack

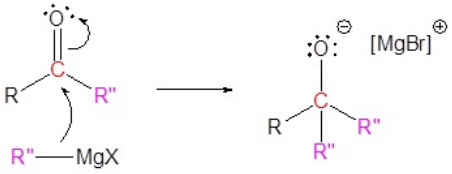
https://chem.libretexts.org/@go/page/90997



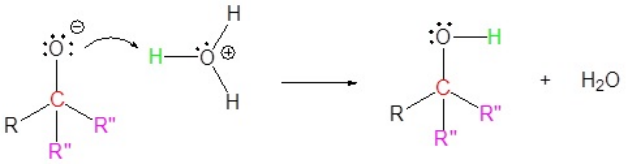
2) Leaving group removal



3) Nucleophilic attack



4) Protonation



EXERCISES

? EXERCISE 21.6.1

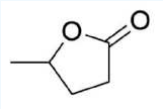
Why is the alkaline hydrolysis of an ester not a reversible process? Why doesn't the reaction with a hydroxide ion and a carboxylic acid produce an ester?

Answer

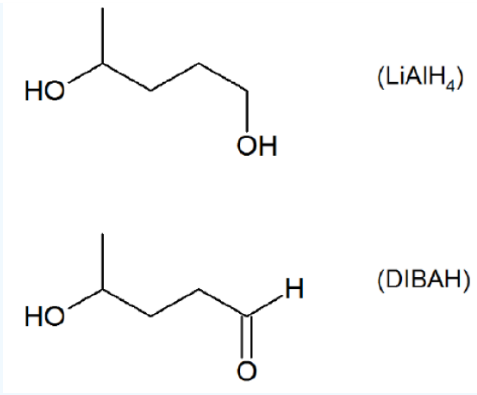
The reaction between a carboxylic acid and a hydroxide ion is an acid base reaction, which produces water and a carboxylate anion.

? EXERCISE 21.6.2

Draw the product of the reaction between the following molecule and LiAlH, and the product of the reaction between the following molecule and DIBAL.

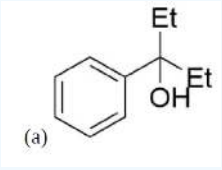


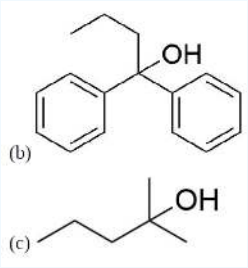
Answer



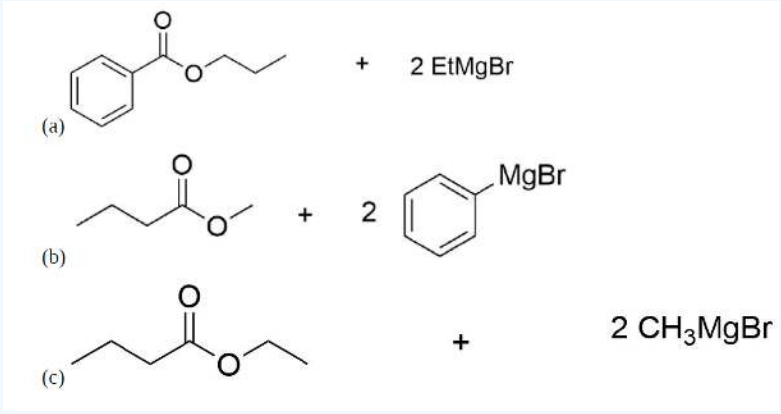
EXERCISE 21.6.3

How might you Prepare the following molecules from esters and Grignards?





Answer



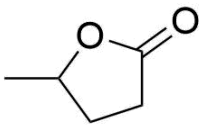
QUESTIONS

Q21.6.1

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?

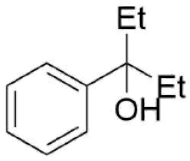
Q21.6.2

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.

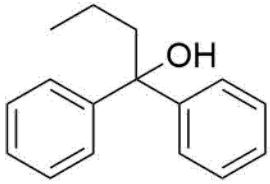


Q21.6.3

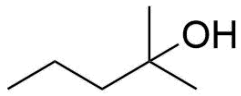
How might you Prepare the following molecules from esters and Grignards?



(a)



(b)



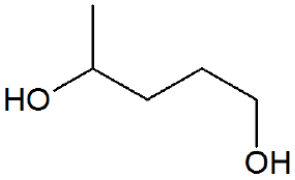
(c)

SOLUTIONS

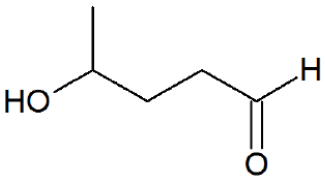
S21.6.1

The reaction between a carboxylic acid and a hydroxide ion is an acid base reaction, which produces water and a carboxylate anion.

S21.6.2

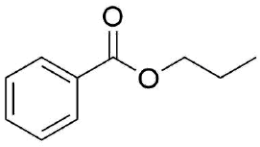


$(LiAlH_4)$



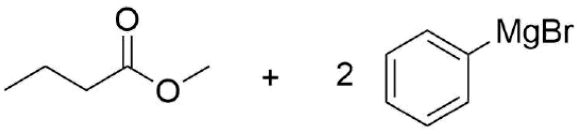
(DIBAH)

S21.6.3

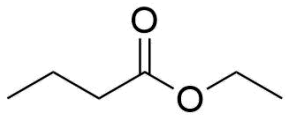


+ 2 EtMgBr

(a)



(b)

(c)  + 2 CH_3MgBr

.

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

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21.7 CHEMISTRY OF AMIDES

Objectives

After completing this section, you should be able to

1. write an equation to describe the preparation of an amide from an acid chloride.
2. identify the amide linkage as the basic unit from which all proteins are made, and hence recognize the importance of the amide linkage to biologists and biochemists.
3. write detailed mechanisms for the acidic and basic hydrolysis of amides.
4. write an equation to describe the reduction of an amide to an amine.
5. write a detailed mechanism for the reduction of an amide to an amine.
6. identify the product formed when a given amide is reduced with lithium aluminum hydride.
7. identify the amide, the reagents, or both, necessary to prepare a given amine by direct reduction.
8. identify lactams as being cyclic amides which undergo hydrolysis and reduction in a manner analogous to that of their acyclic counterparts.

KEY TERMS

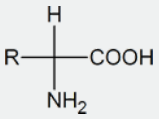
Make certain that you can define, and use in context, the key term below.

- lactam

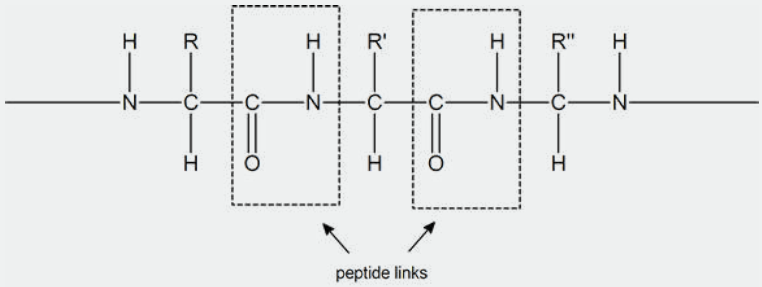
STUDY NOTES

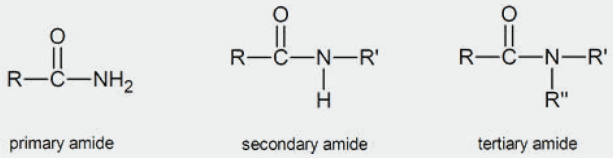
As the chapter which deals with amino acids and proteins is optional, it is possible for you to complete this course without studying these compounds in detail. However, because of their importance in biological systems, it is essential for all students completing this course to have some knowledge of their structure and properties.

When we talk about amino acids, we are generally referring to α-amino acids; that is, compounds in which an amino (NH_2) group and a carboxyl group are attached to the same carbon atom:

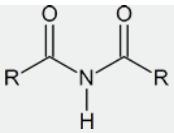


Notice that such compounds contain a chiral carbon atom (unless R = H). Proteins can be considered to consist of amino acid residues joined by amide (or peptide) links. These peptide links consist of exactly the same structural units that we find in secondary amides

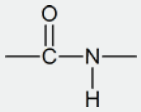




Note: Although the terms secondary amide and tertiary amide have been used here, this usage is not in agreement with IUPAC recommendations. According to IUPAC, the secondary amide shown above should be referred to as an *N*-substituted primary amide, and the tertiary amide should be referred to as a *N*, *N*-disubstituted primary amide. IUPAC reserves the term secondary amide for compounds of the type

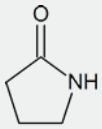


Because of the presence of the amide link in proteins,

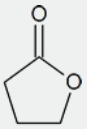


we can expect the properties of these compounds to resemble those of secondary amides.

A lactam is a cyclic amide, in the same way that a lactone is a cyclic ester:

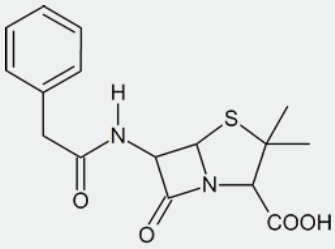


a lactam



a lactone

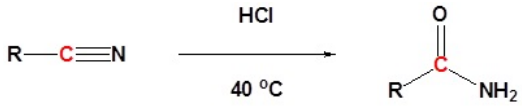
Among the most important molecules that contain lactam rings are the penicillins:



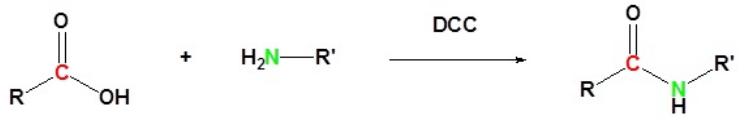
penicillin G (benzylpenicillin)

PREPARATION OF AMIDES

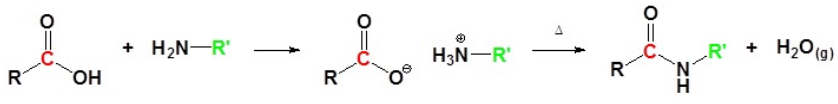
Nitriles can be converted to amides. This reaction can be acid or base catalyzed



Carboxylic acid can be converted to amides by using DCC as an activating agent

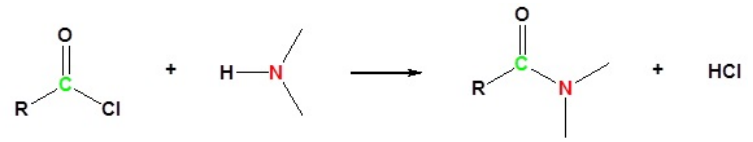


Direct conversion of a carboxylic acid to an amide by reaction with an amine.

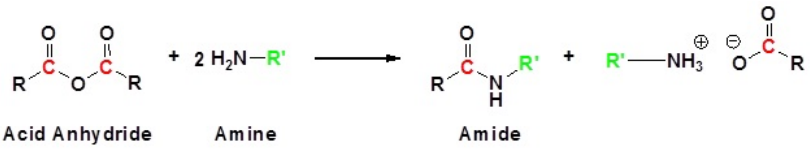


Acid chlorides react with ammonia, 1° amines and 2° amines to form amides

https://chem.libretexts.org/@go/page/90998



Acid Anhydrides react with ammonia, 1° amines and 2° amines to form amides



CONVERSION OF AMIDES INTO CARBOXYLIC ACIDS: HYDROLYSIS

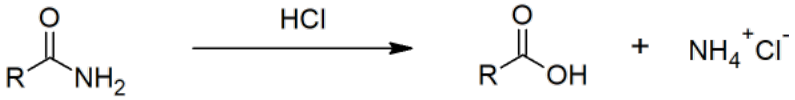
This page describes the hydrolysis of amides under both acidic and alkaline conditions. It also describes the use of alkaline hydrolysis in testing for amides.

WHAT IS HYDROLYSIS?

Technically, hydrolysis is a reaction with water. That is exactly what happens when amides are hydrolyzed in the presence of dilute acids such as dilute hydrochloric acid. The acid acts as a catalyst for the reaction between the amide and water. The alkaline hydrolysis of amides actually involves reaction with hydroxide ions, but the result is similar enough that it is still classed as hydrolysis.

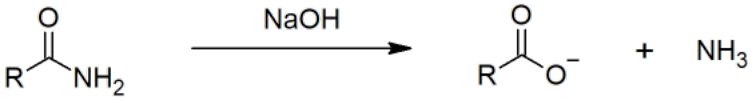
HYDROLYSIS UNDER ACIDIC CONDITIONS

Taking ethanamide as a typical amide. If ethanamide is heated with a dilute acid (such as dilute hydrochloric acid), ethanoic acid is formed together with ammonium ions. So, if you were using hydrochloric acid, the final solution would contain ammonium chloride and ethanoic acid.



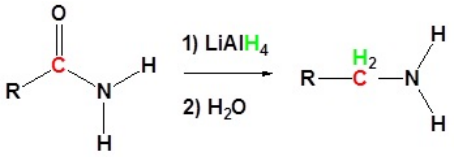
HYDROLYSIS UNDER ALKALINE CONDITIONS

Also, if ethanamide is heated with sodium hydroxide solution, ammonia gas is given off and you are left with a solution containing sodium ethanoate.

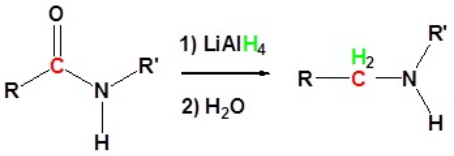


CONVERSION OF AMIDES INTO AMINES: REDUCTION

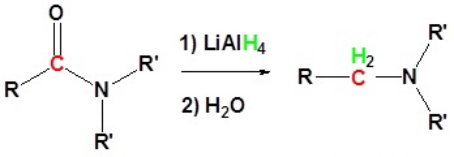
Amides can be converted to 1°, 2° or 3° amines using $LiAlH_4$.



Amide 1° Amine

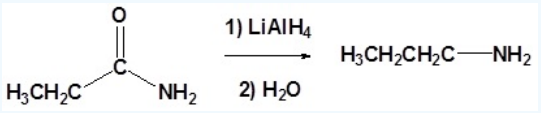


Amide 2° Amine

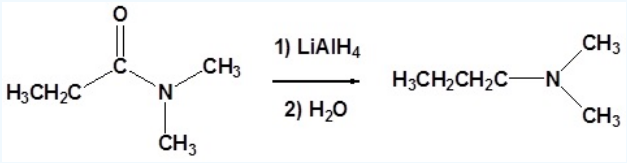


Amide 3° Amine

EXAMPLE 21.7.1: AMIDE REDUCTIONS

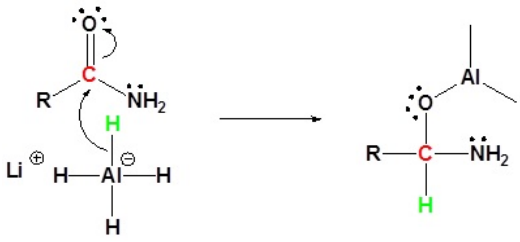


Alkyl groups attached to the nitrogen do not affect the reaction.

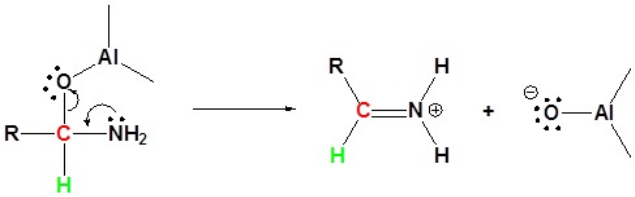


MECHANISM

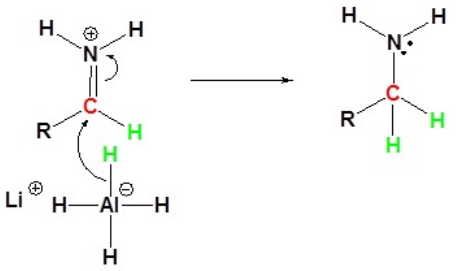
1) Nucleophilic attach by the hydride



2) Leaving group removal

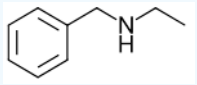


3) Nucleophilic attach by the hydride



EXAMPLE 21.7.1

How could the following molecule be synthesized using an aminolysis of an acid chloride?



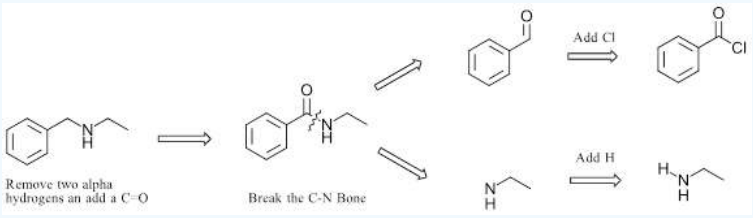
Answer

One of the preferred methods for making amines is through a nucleophilic acyl substitution using an acid chloride and amine to form an amide. The amide is then reduced to the amine during a hydride reduction with $LiAlH_4$.

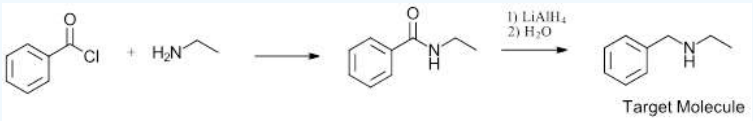
In the first step of retrosynthetic analysis, one of the carbons alpha to the amine nitrogen is converted to a carbonyl thus creating an amide intermediate. The key bond formed during this pathway is the C-N sigma bond between the carbonyl carbon and the nitrogen created during amide formation. Breaking this bond separated the target molecule into the two starting materials for the pathway. The carbonyl carbon gains a –Cl to become an acid chloride and the nitrogen fragment gains an H to become a 1° amine. In the forward reaction pathway, the acid chloride and the 1° amine are linked to from an amide in the first step of the reaction. Subsequent hydride reduction of the amide using $LiAlH_4$ produces the amine target molecule.

The target molecule has two alpha carbons which could possibly be converted to a carbonyl. This allows there to be two possible synthetic pathways.

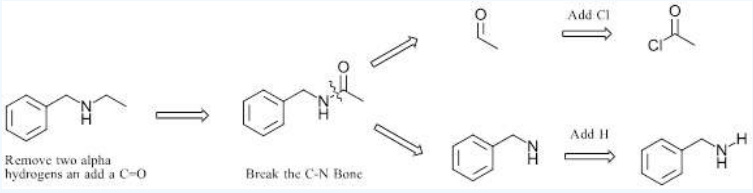
Pathway 1



Solution 1

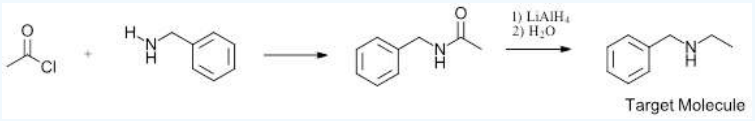


Pathway 2



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Solution 2

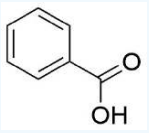


EXERCISES

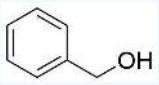
? EXERCISE 21.7.1

How would you prepare the following compounds from N-Propypl benzamide?

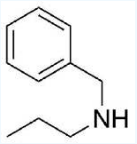
(a)



(b)



(c)



Answer

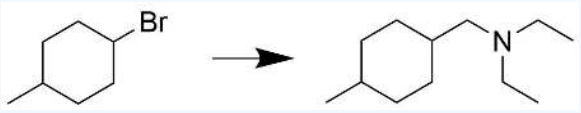
(a) NaOH, H_2O

(b) NaOH, H_2O, then $LiAlH_4$

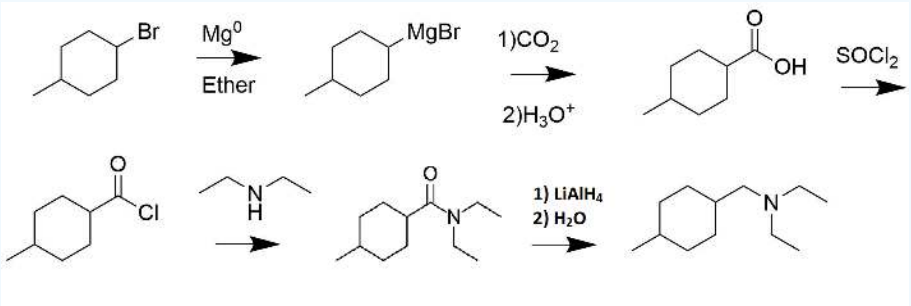
(c) $LiAlH_4$

? EXERCISE 21.7.2

Propose a synthesis pathway for the following conversion:



Answer

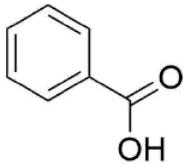


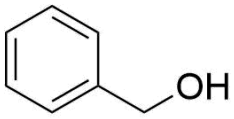
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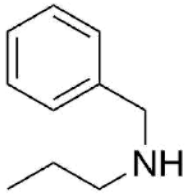
QUESTIONS

Q21.7.1

How would you prepare the following compounds from N-Propypl benzamide?

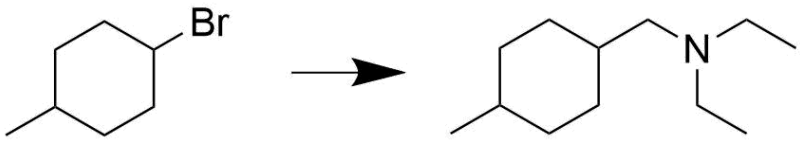
(a) 

(b) 

(c) 

Q21.7.2

Propose a synthesis for the following.

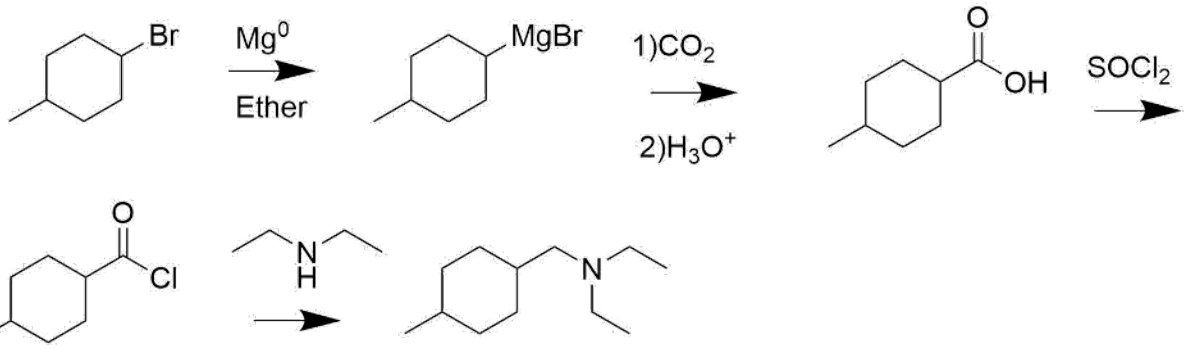


SOLUTIONS

S21.7.1

a. NaOH, H_2O
b. NaOH, H_2O, then LAH
c. LAH

S21.7.2



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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21.8 CHEMISTRY OF THIOESTERS AND ACYL PHOSPHATES: BIOLOGICAL CARBOXYLIC ACID DERIVATIVES

Objectives

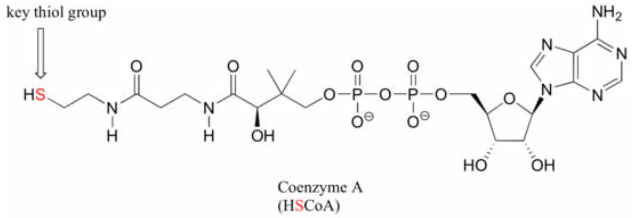
After completing this section, you should be able to

1. discuss, briefly, the role played in nature by acetylating agents, such as acetyl coenzyme A, and explain what is happening in reactions such as the acetylation in biological systems, without necessarily being able to write a detailed equation.
2. rank the reactivity of thioesters and acyl phosphates towards nucleophiles compared with other carboxylic acid derivatives.

INTRODUCTION TO THIOESTERS AND COENZYME A

Acyl phosphates and acyl adenosine phosphates are not the only activated forms of carboxylate groups in biochemical reactions. Slightly lower on the reactivity scale are thioesters. 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
(HSCoA)

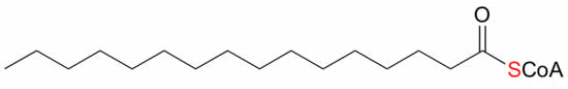
Coenzyme A is often abbreviated HSCoA, in order to emphasize that it is the thiol sulfur that provides the critical thioester linkage to acyl groups. When fuel (carbohydrate and fat) is broken down in your body, it is eventually converted to a simple two-carbon unit called acetyl CoA, which is essentially a thioester derivative of acetic acid:



acetic acid acetyl-SCoA

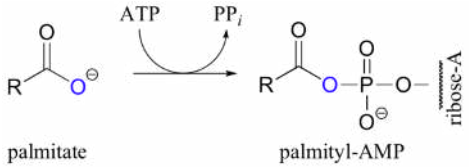
ACTIVATION OF FATTY ACIDS BY COENZYME A: A THIOESTERIFICATION REACTION

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:



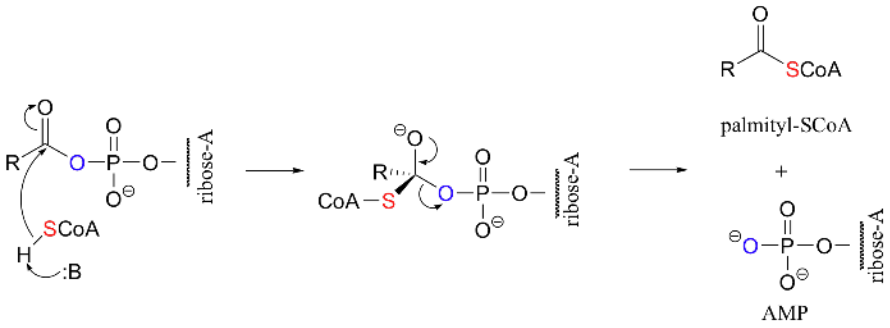
palmityl-SCoA

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 (section 12.2B).



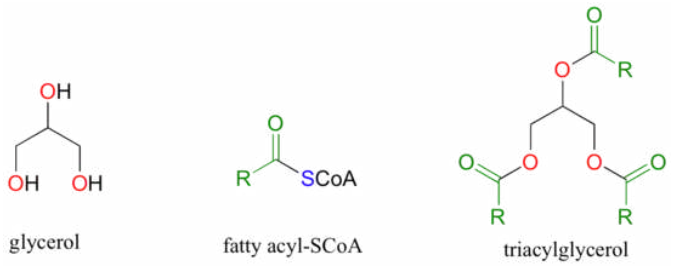
palmitate palmityl-AMP

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.

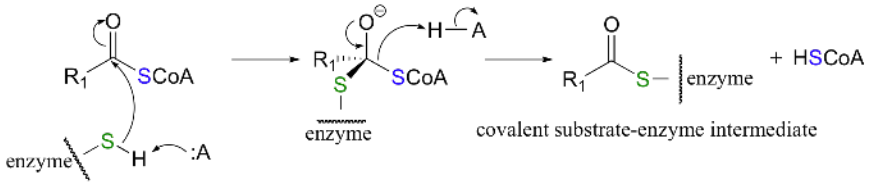


TRANSFER OF FATTY ACYL GROUPS TO GLYCEROL: A THIOESTER TO ESTER SUBSTITUTION

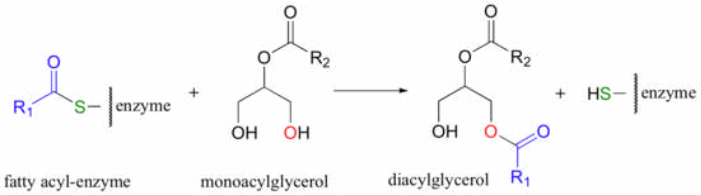
The -SCoA thioester form of the fatty acid is a good substrate for a number of metabolic transformations. This is the form of fatty acid, for example, that is oxidized and broken down for energy in the mitochondria of your cells. Fatty acyl CoA also serves as substrate for the construction of triacylglycerol, which is the fat molecule that your body uses to store energy in fat cells. Recall (section 12.1B) 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.



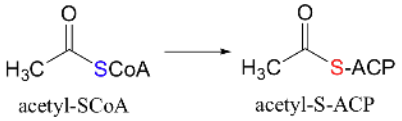
The fatty acyl group is now ready to be transferred to glycerol, trading its thioester linkage to the cysteine for a new ester linkage to one of the alcohol groups on glycerol. The attacking nucelophile in this reaction is of course the alcohol oxygen of monoacylglycerol.

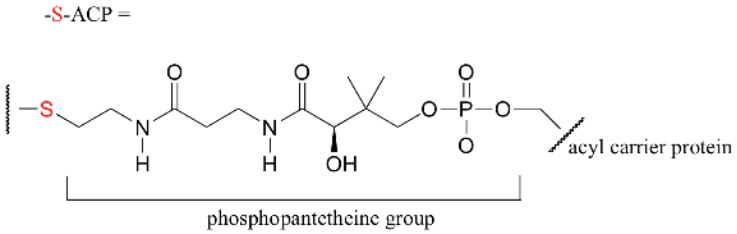


Because esters are more stable than thioesters, this is an energetically downhill reaction.

TRANSTHIOESTERIFICATION REACTIONS

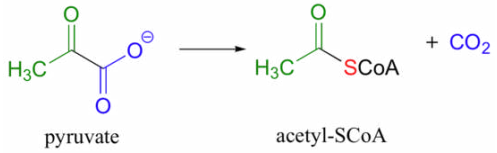
In the previous section we saw one example of a transthioesterification. Another important transthioesterification reaction involves acetyl CoA, the activated form of acetic acid and the basic two-carbon building block for fats and oils. Before it can be incorporated into a growing fatty acid molecule, 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.



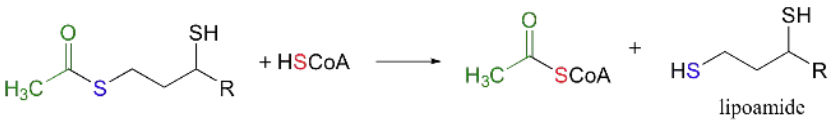


Notice that the structure of this carrier group (called phosphopantetheine) is identical to the region of coenzyme A (structure shown earlier in this section) near the thiol group. Once attached to the ACP, the two-carbon acetyl group condenses with another acyl group (which is also attached to its own ACP), and the fatty acid chain begins to grow. We will study these important carbon-carbon bond forming reactions in section 13.4.

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.



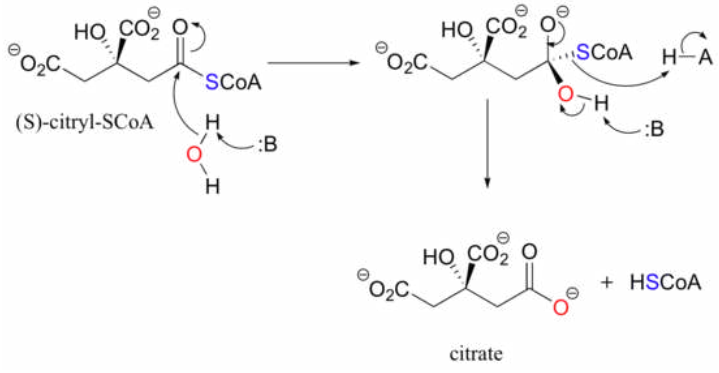
The overall reaction looks simple, but is actually quite complex and involves several intermediate species. The final step in the process is a transthioesterification, involving a dithiol molecule called lipoamide:



We will look more closely at the complete biochemical transformation catalyzed by the pyruvate dehydrogenase complex in section 16.12B.

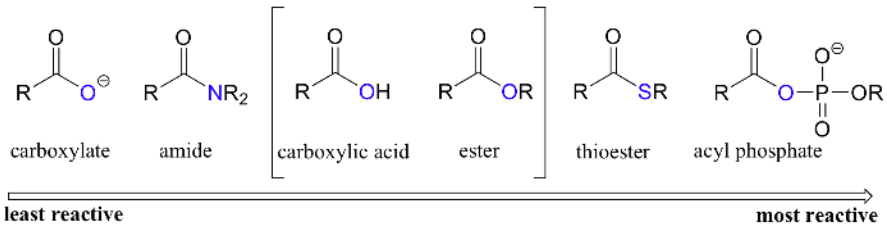
HYDROLYSIS OF THIOESTERS

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

Recall from Section 21.2 that thioesters and acyl phosphates are the most reactive among the biologically relevant acyl groups. However, neither is as reactive as an acid chloride or acid anhydride.



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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21.9 POLYAMIDES AND POLYESTERS: STEP-GROWTH POLYMERS

Objectives

After completing this section, you should be able to

1. write an equation to represent the formation of nylon 66 from adipic acid and hexamethylenediamine.
2. write an equation to represent the formation of nylon 6 from caprolactam.
3. predict the structure of the step-growth polymer formed from the reaction of two given monomers.
4. identify the monomers needed to prepare a step-growth polymer of a given structure.
5. write an equation to describe the formation of a polyester, such as poly(ethylene terephthalate), from a given diol and diester.
6. write an equation to describe the formation of a polycarbonate from a carbonate and a bisphenol.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- chain-growth polymer
- polyamide
- polyester
- step-growth polymer

STUDY NOTES

You may wish to review chain-growth polymerization in Section 8.10 and Section 14.6. In this section we discuss another important class of polymerization know as step-growth polymerization.

As you can see from the equation given in the discussion on forming condensation polymers, Dacron is formed from two monomers, one of which possesses two carboxylate groups and the other two hydroxyl groups.

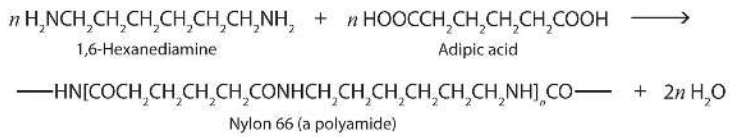
It is also possible to form a polyester using two monomers that each possess one carboxyl group and one hydroxyl group. An example is the polymer formed between lactic acid and glycolic acid. This polymer has been used to produce absorbable staples that provide surgeons with a convenient method of closing incisions made during operations on the bladder or intestines, or during hysterectomies. Two advantages of this polyester in such applications are, first, that it begins to hydrolyze in the body after six to eight weeks, and then, that the products of the hydrolysis are both compounds normally present in the body.



lactic acid (2-hydroxypropanoic acid) glycolic acid (2-hydroxyethanoic acid)

POLYAMIDES EDIT SECTION

Just as the reaction of a diol and a diacid forms a polyester (Section 15.8), 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.



1,6-Hexanediamine Adipic acid

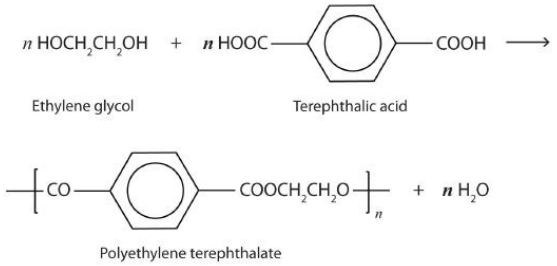
Nylon 66 (a polyamide)

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 EDIT SECTION

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:

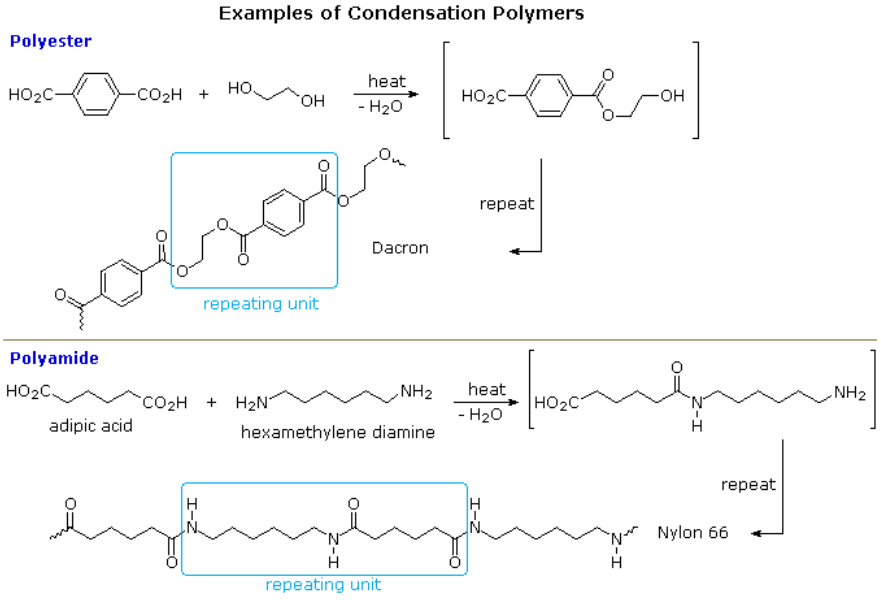


Polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or replace diseased sections of blood vessels. PET is used to make bottles for soda pop and other beverages. It is also formed into films called 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

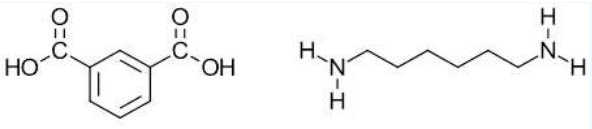
A large number of important and useful polymeric materials are not formed by chain-growth processes involving reactive species such as radicals, but proceed instead by conventional functional group transformations of polyfunctional reactants. These polymerizations often (but not always) occur with loss 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.



EXAMPLE 21.9.1

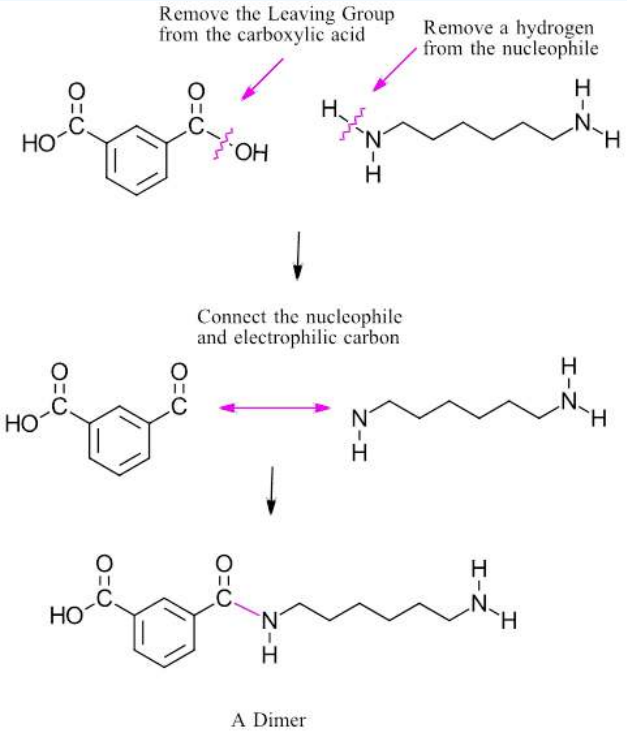
Provide the structure of the polyamide made from the monomers as indicated. Please use bracketed notation.



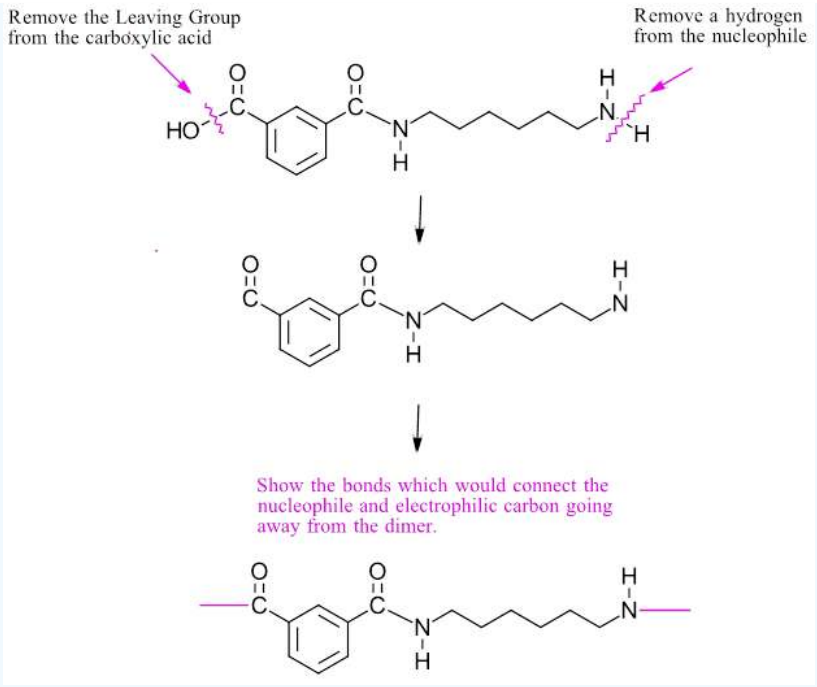
Solution

When drawing the polymer product of a step-growth polymerization, it is important to first identify the reaction which forms the repetitive linkage between monomers. In this case, the reaction is anucleophilic acyl substitution btween a carboxylic acid and an amine to form an amide. In total, the bracket structure of a polymer shows two versions of the linkage formation. The first is clearly shows connecting the monomers to form the dimer making up the repeating unit in the polymer. The second version involves bonds going out of the bracket and represents how the linkage repeats throughout the polymer.

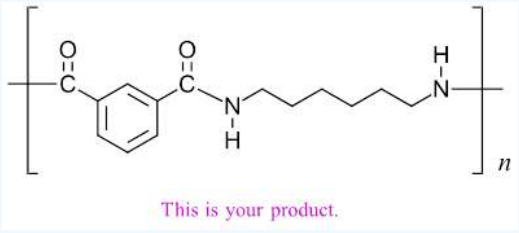
1) The connect two monomers to make a dimer using the indicated reaction.



2) Beak the same bonds as before ecepptt the bonds for the final connection will be shown going away from the dimer.



3) Place brackets around the dimer and put an italicized lower case "n" in the lower right.

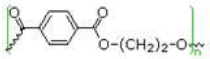
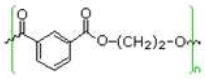
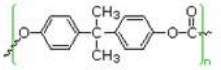
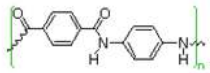
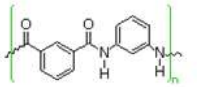


CHARACTERISTICS OF CONDENSATION POLYMERS

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.

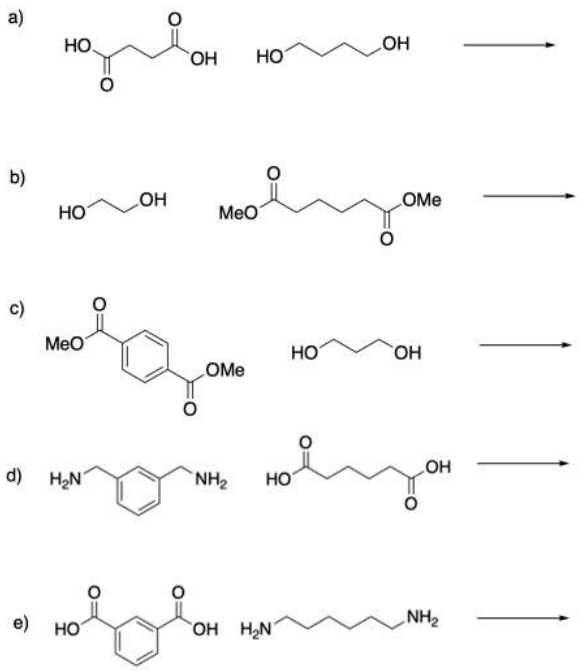
SOME CONDENSATION POLYMERS

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

EXERCISES

? EXERCISE 21.9.1

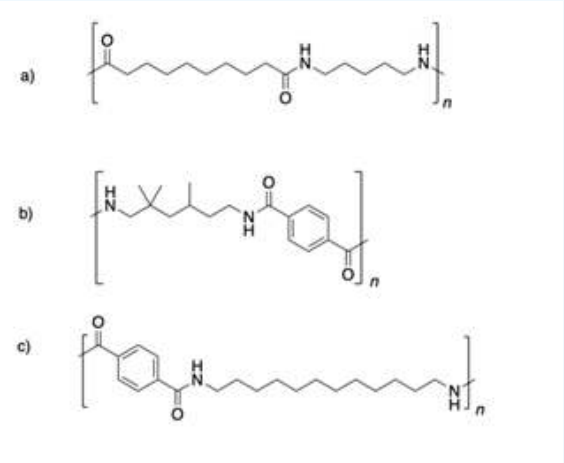
Provide structures of the polyesters made from the monomers as indicated.



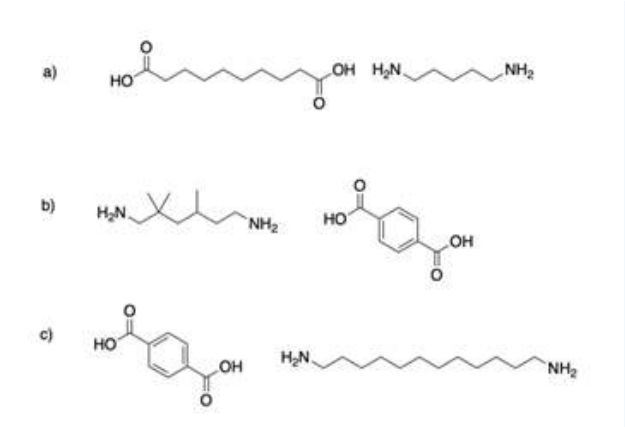
Answer

? EXERCISE 21.9.2

Identify the monomers that would be used to produce these polymers.



Answer



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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21.10 SPECTROSCOPY OF CARBOXYLIC ACID DERIVATIVES

Objectives

After completing this section, you should be able to

1. identify the region of the infrared spectrum in which absorptions resulting from the carbonyl group of carboxylic acid derivatives occur.
2. identify the characteristic features of the infrared spectra of acid anhydrides and nitriles that allow us to use infrared spectroscopy to distinguish between these compounds and the others discussed in this unit.
3. use a table of characteristic infrared absorptions to interpret the infrared spectra of carbonyl-containing compounds.
4. use infrared spectroscopy and ^{1}H NMR spectroscopy in the deduction of the structure of an unknown compound.

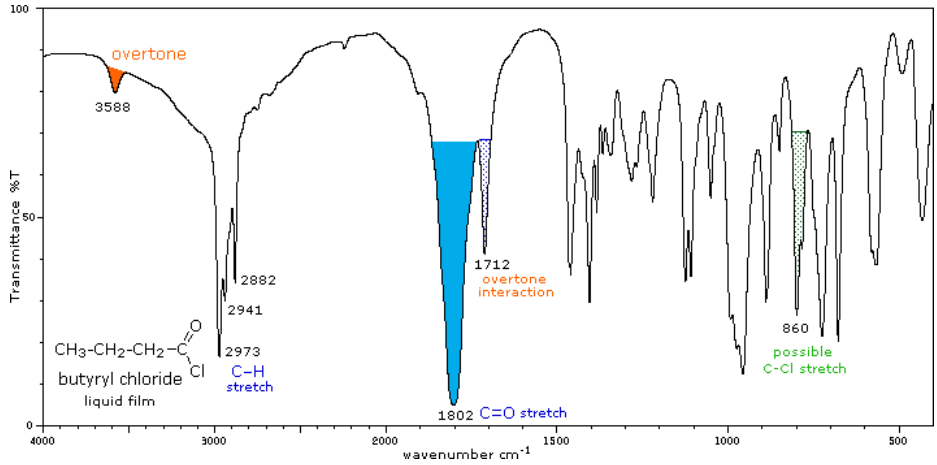
STUDY NOTES

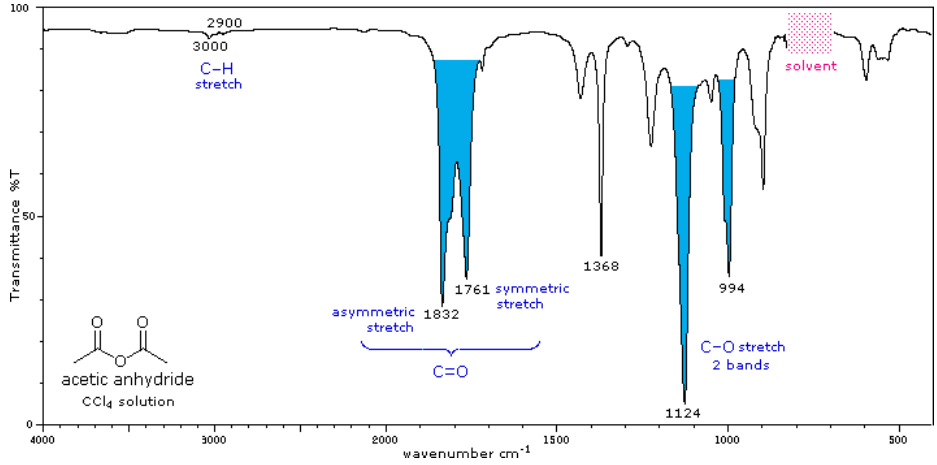
Note: You should recognize that protons on carbon atoms next to carbonyl groups are slightly deshielded, and absorb near 2 δ in the ^{1}H NMR spectrum.

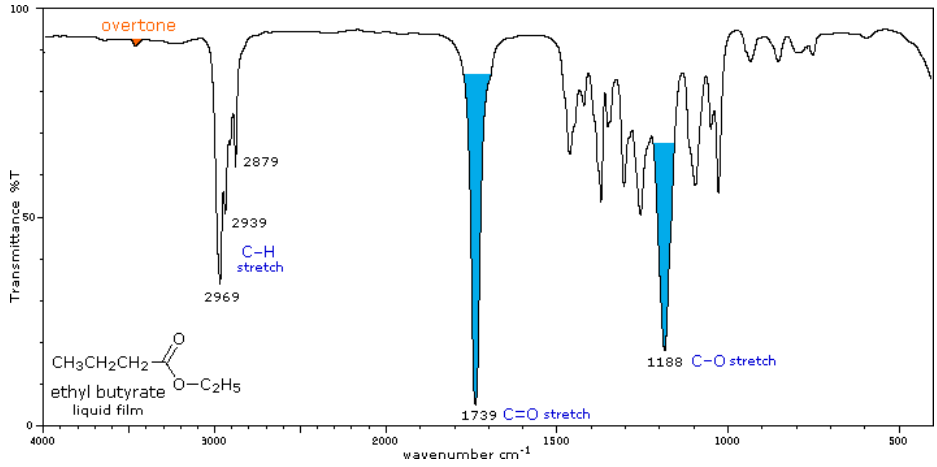
The influence of heteroatom substituents on the reactivity of carbonyl functions toward nucleophiles was discussed earlier with respect to carboxylic acid derivatives. A useful relationship exists between the reactivity of these derivatives and their carbonyl stretching frequencies. Thus, the very reactive acyl halides and anhydrides absorb at frequencies significantly higher than ketones, whereas the relatively unreactive amides absorb at lower frequencies. These characteristics are listed below.

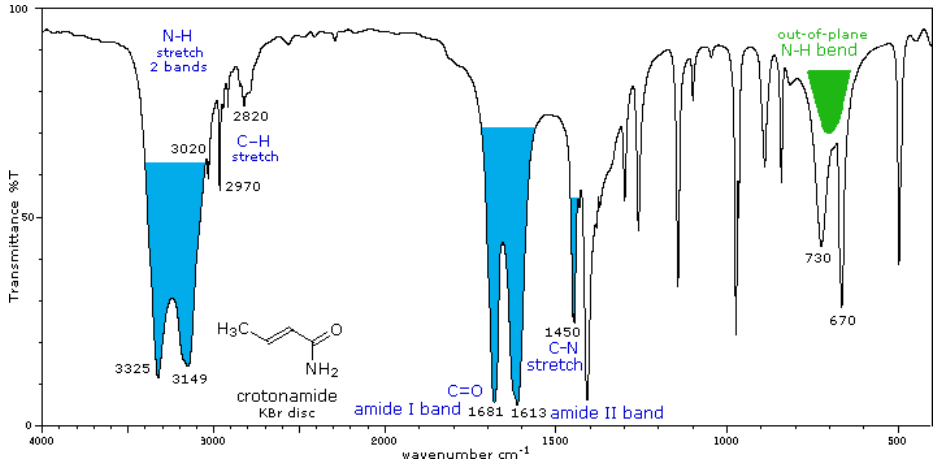
Infrared spectra of many carboxylic acid derivatives will be displayed in the figure below the table by clicking the appropriate buttons presented there.

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}	
X = Cl	1800 ± 15	
X = Br	1800 ± 15	In acyl chlorides a lower intensity shoulder or peak near 1740 cm^{-1} is due to an overtone interaction.
Acid Anhydride, $(RCO)_2O$	**C=O stretch** (2 bands)	Conjugation lowers the C=O frequencies reported here, as with aldehydes & ketones. 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. Cyclic anhydrides also display two carbonyl stretching absorptions, but the lower frequency band is the strongest. One or two -CO-O-CO- stretching bands are observed in the 1000 to 1300 cm^{-1} region.
acyclic	1750 & 1820 cm^{-1}	
6-membered ring	1750 &1820	
5-membered ring	1785 & 1865	
Esters & Lactones (RCOOR')	**C=O stretch**	Conjugation lowers the C=O frequencies reported here, as with aldehydes & ketones Strong CO-O stretching absorptions (one ot two) are found from 1150 to 1250 cm^{-1}
esters	1740 cm ± 10 cm^{-1}	
6-membered lactone	1740 cm ± 10	
5-membered lactone	1765 cm± 5	
4-membered lactone	1840 cm ± 5	
Amides & Lactams $(RCONR_2)$	**C=O bands**	The effect of conjugation is much less than for aldehydes & ketones. 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. **N-H stretch**: 3170 to 3500 cm^{-1}. Two bands for 1°-amides, one for 2°-amides.
1° & 2°-amides	1510 to 1700 cm^{-1} (2 bands)	
3°-amides	1650± 15 (one band)	
6-membered lactams	1670 ± 10 (one band)	
5-membered lactams	1700 ± 15	
4-membered lactams	1745 ± 15	


overtone
3588
2882
2941
2973
C–H
stretch
1712
overtone
interaction
860
possible
C-Cl stretch
1802 C=O stretch
butyryl chloride
liquid film
Transmittance %T
wavenumber cm-1


2900
3000
C–H
stretch
solvent
1761 symmetric
stretch
1368
994
asymmetric
stretch
1832
C=O
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
ethyl butyrate
liquid film
Transmittance %T
wavenumber cm-1

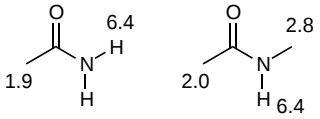


^{1}H NMR SPECTRA

Protons on carbons adjacent to carbonyls absorb at ~2.0-2.5 ppm.

The N-H protons attached to primary and secondary amines absorb at ~7.5-8.5 ppm.

Resonances from protons directly attached to the carbon bonded to nitrogen in an amide tend to resonate in the 2.0-3.0 ppm region of an NMR spectra. The NH protons of primary and secondary amides resonate in the 5.5-8.5 ppm regions. Like other hydrogen bonding protons, these NH proton peaks appear broad (^{14}N quadrapole broadening) and can be washed out by the hydrogen-deuterium exchange created by D_2O addition.



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
- Jim Clark (Chemguide.co.uk)

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21.S: CARBOXYLIC ACID DERIVATIVES (SUMMARY)

CONCEPTS & VOCABULARY

21.0 Chapter Objectives and Introduction to Carboxylic Acid Derivatives

- Carboxylic acid derivatives formed when the hydroxyl group of the carboxylic acid is replaced by a different group.
- Carboxylic acid derivatives are also known as acyl derivatives.
- Many types of carboxylic acid derivatives, the chapter focused on acid halides (acyl halides), anhydrides, esters, amides, thioesters, and acylphosphates.
- Cyclic esters are referred to as lactones and cyclic amides are referred to as lactams.
- Nucleophilic acyl substitution reactions convert the carboxylic acid to one of the derivatives.

21.1 Naming Carboxylic Acid Derivatives

- Acid halide are named following the IUPAC rules with the carboxylic acid ending with -oyl or -yl and the halide ending in an -ide.
- Anhydrides are named following the IUPAC rules with the carboxylic acid ending -acid being replaced by -anhydride.
- Esters are named following the IUPAC rules with the carboxylic acid ending with -oic acid being replaced by -ate and the alkoxy alkyl chain as a substituent.
- Thioesters are named following the IUPAC rules with the carboxylic acid ending with -oic acid being replaced by -thioate and the sulfide alkyl chain as a substituent.
- Primary amides are named following the IUPAC rules with the carboxylic acid ending with -oic acid being replaced by -amide.
- Secondary or tertiary amides are named as primary amides are, but in additon an upper case N is used to designate the alkyl groups attached to the nitrogen atom, which are names as substituents.
- Cyclic amides (lactams) use a Greek letter to identify the location of the nitrogen in relation the carbonyl group.
- Acyl phosphates are named following the IUPAC rules with the carboxylic acid ending with -oyl or -yl and -phosphate.

21.2 Nucleophilic Acyl Substitution Reactions

- Carboxylic acid derivatives contain an electronegative heteroatom (typically oxygen, nitrogen, sulfur, or phosphorus) bonded directly to the carbonyl carbon represented by the symbol Y.
- The acyl group is the remainder of the molecule, which includes the carbonyl and the attached alkyl group.
- The Y group acts as a leaving group during the nucleophilic acyl substitution reaction.
- Stability of the negative charge on the Y group can be guaged by the pK_a of its corresponding acid (HY).
- Carboxylic acid derivatives undergo a reaction called nucleophilic acyl substitution.
- The electrophile is the carbon of the carbonyl, which undergoes an attack by a nucelophile followed by the elimination of the Y group in the carboxylic acid derivative.
- The Y group is substituted for the nucleophile.
- The reactivity of the carboxylic acid derivatives depends on the stability of the carbonyl and the effectiveness of the leaving group.
- Stabilization of the carbonyl reduces the electrophilic character of the carbonyl group.
- The ability of the leaving group to stabilize negative charge creates a more effective leaving group.
- More reactive carboxylic acid derivatives can be used to make less reactive carboxylic acid derivatives.

21.3 Nucleophilic Acyl Substitution Reactions of Carboxylic Acids

- The hydroxyl of a carboxylic acid is a poor leaving group, but activating the carbonyl and converting the hydroxyl to a better leaving group allow for reactions to occur.
- Carboxylic acids can be converted to acid chlorides using thionyl chloride ($SOCl_2$).
- Carboxylic acids can be converted into anhydrides by condensing two carboxylic acids together and the loss of water.
- Carboxylic acids can be converted into esters in two ways.
  - Using the carboxylate in an SN_2 mechanism.
  - The Fischer Esterification
    - Acid catalyzed
    - Pushing equilibrium in the forward direction using Le Chatelier's principle
- Carboxylic acids can be converted into amides in two ways.
  - Direct conversion by heating ammonium carboxylate salts
  - Using a coupling agent like dicyclohexylcarbodiimide (DCC)

- Carboxylic acids can be reduced to primary alcohols using lithium aluminum hydride or borane tetrahydrofurane (THF).
- In biological chemistry, carboxylate anions are converted to an acyl phosphate, which requires phosphrylation using TAP as the phosphate donor or thioesters using coenzyme A.

21.4 Chemistry of Acid Halides

- Carboxylic acids react with thionyl chloride to form acid chlorides.
- Carboxylic acids react with phosphorus tribromide to form acid bromides.
- Acid chlorides are the most reactive carboxylic acid derivative, which allows them to easily convert to other acyl compounds.
- Acid chlorides undergo hydrolysis to form carboxylic acids.
- Acid chlorides react with carboxylic acid to from anhydrides through a nucleophilic acyl substitution.
- Acid chlorides react with alcohol nucleophiles to produce esters with pyridine being used to neutralize the HCl produced.
- Acid chlorides can be reduced to aldehydes using hindered reducing agents that have only one equivalent of hydride.
- Acid chlorides react with amines to form amides, usually an excess of amine is used to neutralize the HCl produced.
- Acid chlorides react with Grignard reagents to from tertiary alcohols.
- Acid chlorides react with Gillman reagents to produce ketones.

21.5 Chemistry of Acid Anhydrides

- Anhydrides generally made by nucleophlic acyl substitution reactions using an acid chloride and a carboxylic acid or carboxylate anion.
- Anhydrides are not as reactive as acid chlorides, but still undergo many of the same reactions.
- Asymmetrical anhydrides not used to make amides or esters since multiple products can be formed.
- Anhydrides undergo hydrolysis to form carboxylic acids.
- Anhydrides react with alcohol nucleophiles to produce esters.
- Anhydrides can react with amines to form the corresponding amides.

21.6 Chemistry of Esters

- Esters are present in many biologically important molecules.
- Esters are often the sources of pleasant aromas of many fruits and perfumes.
- Esters are also present in commercial and synthetic applications.
- Esters are prepared
  - most often using nucleophilic acyl substitution using an acid chloride and an alcohol
  - using nucleophilic acyl substitution using an anhydride and an alcohol
  - using nucleophilic acyl substitution using a carboxylic acid and an alcohol
  - deprotonating a carboxlylic acid for an SN_2 reaction
- Esters can be converted to a carboxylic acid through a reaction witt water and a catalytic amount of strong acid.
- Saponification is the reaction between an ester and water under basic conditions to produce a carboxylate anion.
- Esters can be inter-converted using a transesterfication reaction.
- Esters can be converted into amides using an ester and a large excess of amine.
- Esters can be reduced to primary alcohols using lithium aluminum hydride.
- Like acid chlorides, esters can be reduced to aldehydes using weak, bulky reducing agents.
- Esters can react with Grignard reagents to form tertiary alcohols.

21.7 Chemistry of Amides

- Amides make up the backbone of proteins when the amino group of one amino acid reacts with the carboxylate carbon of another amino acid and from an amide linkage (peptide bond).
- Amides are most commonly prepared through the reaction of an acid chloride and amine.
- Amides are relatively unreactive towards nucleophilic acyl substitutions due to the poor leaving group ability of its nitrogen containing Y group.
- Amides can be hydrolzyed to a carboxylic acid and ammonia or amine by heating the reaction under acidic or basic aqueous solutions.
- Hydrolysis of amines is the first step in metabolism of dietary proteins.
- Primary amines can be converted into a nitrile through a reaction with thionyl chloride.
- Amides are reduced to amines by treatment with lithium aluminum hydride.

21.8 Chemistry of Thioesters and Acyl Phosphates - Biological Carboxylic Acid Derivatives

- Acyl phosphates, acyl adenosine phosphophates, and thioesters are all activated forms of carboxylate groups in biochemical reactions.
- Carboxylate groups of fatty acids are converted to thioesters using coenzyme A

- Thioesters are a good substrate for a number of metabolic transformations.
- Thioesters can be hydrolyzed, resulting back to a carboxylate anion.
- Thioesters and acyl phosphates are the most reactive biologically relevant acyl groups, but not as reactive as an acid chloride or anhydride.

21.9 Polyamides and Polyesters - Step-Growth Polymers

- Step-growth is one of two broad classes of polymerization methods.
- Step-growth polymerizations are linked by a carbon-heteroatom bond formed in non-sequential steps.
- A step-growth polymerization starts with two complementary functional groups on different monomers reacting to form a dimer.
- Using a difunctional monomer, allows step-growth polymers to grow in two directions at once.
- Fibers are made from some form of polymer.
- Nylon
  - First successful fully synthetic polymer was nylon-6,6 in 1938 by the company DuPont, which is a polyamide.
  - Nylons are widely used synthetic fibers, which are found in commercial products such as rope, sails, clothing, and more.
- Esterfication
  - Can also be used to form primary linkages in step-growth polymers.
  - Polyester is typically produced when a dicarboxylic acid and a diol react together.
  - The most important polyester is polyethylene terephthalate (PET), which is used to make bottles for soda.
  - Polyesters are fibers often used in many fabrics.
- Polycarbonates
  - Monomer is a carbonate, which acts like a double ester and can undergo a type of double transesterification reaction with two alcohols.
  - A carbonate is difunctional and can react with a diol to form polymers called polycarbonates.
  - Used in engineering because they are strong materials, but easily molded.
  - Polycarbonates are found in DVDs, compact discs, and Blu-ray discs.

21.10 Spectroscopy of Carboxylic Acid Derivatives

- IR of acid chlorides shows a strong carbonyl stretch around 1800 cm^{-1}.
- IR of anhydrides show two strong carbonyl stretch around 1750 and 1820 cm^{-1}.
- IR of esters shows a strong carbonyl stretch around 1740 cm^{-1} and a strong CO-O stretch around 1150 to 1250 cm^{-1}.
- IR of amides shows a strong carbonyl stretch around 1700 cm^{-1}, primary and secondary amides have two bands and tertiary amides have one band and a strong N-H stretch around 3170 to 3500 cm^{-1} in primary and secondary amides.
- ^{1}H NMR of acid halides do not have any distinctive peaks.
- ^{1}H NMR of anhydrides do not have any distinctive peaks, but symmetrical anhydrides will produce equivalent protons on either side.
- ^{1}H NMR of esters and thioesters have an alkyl group attached to the heteroatom. For esters, the alkoxide protons will show up in the 3.5-4.5 ppm region, while those attached to the sulfur in thioesters will show up in the 2.0-3.0 ppm region.
- ^{1}H NMR of amides have the possibility of alkyl groups or hydrogens attached. Resonances for protons attached to the carbon bonded to the nitrogen of the amide resonate between 2.0-3.0 ppm region. The NH protons of primary and secondary amides resonate in the 7.5-8.5 ppm regions, which will be broad.
- ^{13}C NMR of carboxylic acid derivatives show the carbonyl carbon at 160-180 ppm.
- ^{13}C NMR of esters also have the carbon attached to the alkoxide of the ester, which appears at 50-90 ppm.
- ^{13}C NMR of amides also have the carbon attached to the nitrogen of the amide, which appears at 20-65 ppm.
- ^{13}C NMR of thioesters also have the carbon attached to the sulfur, which appears at 20-45 ppm.
- Mass spectra of carboxylic acid derivatives show a base peak due to the acylium ion.

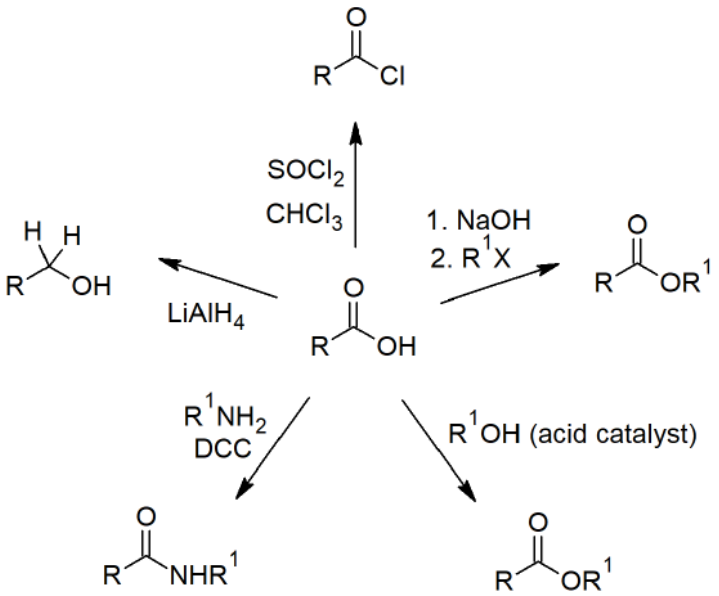
Skills to Master

- Skill 21.1 Name carboxyilic acid derivatives using IUPAC rules.
- Skill 21.2 Draw the structure of carboxylic acid derivatives from the IUPAC name.
- Skill 21.3 Compare the stability of different carboxylic acid derivatives to determine reactivity.
- Skill 21.4 Determine the products for nucleophilic acyl substitution reactions.
- Skill 21.5 Provide step-by-step mechanism for the Fischer esterification.
- Skill 21.6 Show how to synthesize an ester from a carboxylic acid and alcohol.

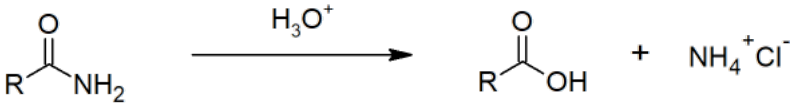
- Skill 21.7 Show mechanisms for the different carboxylic acid derivatives starting from an acid chloride.
- Skill 21.8 Show how to synthesize the different carboxylic acid derivatives starting from an acid chloride.
- Skill 21.9 Provide step-by-step mechanisms for the different carboxylic acid derivatives starting from an anhydride.
- Skill 21.10 Show how to synthesize the different carboxylic acid derivatives starting from an anhydride.
- Skill 21.11 Understand why the hydrolysis of an ester is not reversible under basic conditions and why the reverse does not produce an ester.
- Skill 21.12 Be able to synthesize tertiary alcohols from esters.
- Skill 21.13 Provide a step-by-step mechanism for the hydrolysis of an amide under acidic and basic conditions.
- Skill 21.14 Provide the structure of different polymers using the bracketed notation and the monomers from the polymer.
- Skill 21.15 Use IR, NMR, and MS to identify different carboxylic acid derivatives.

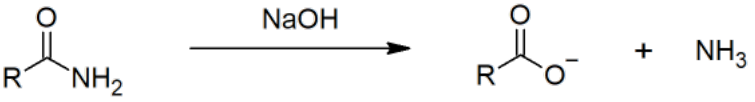
SUMMARY OF REACTIONS

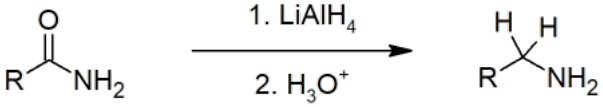
Carboxylic Acid Reactions



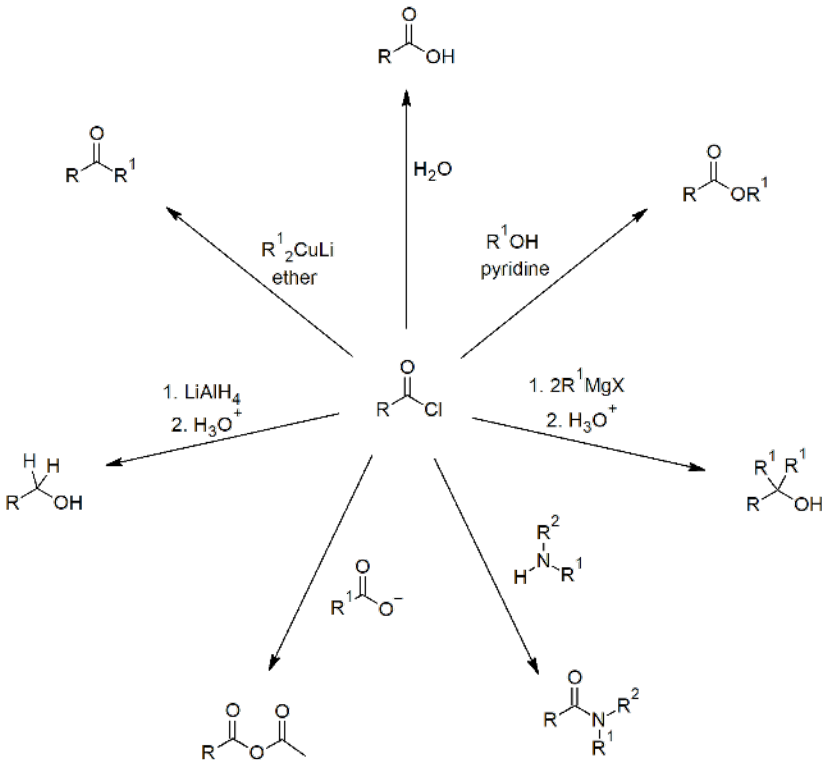
Amide Reactions



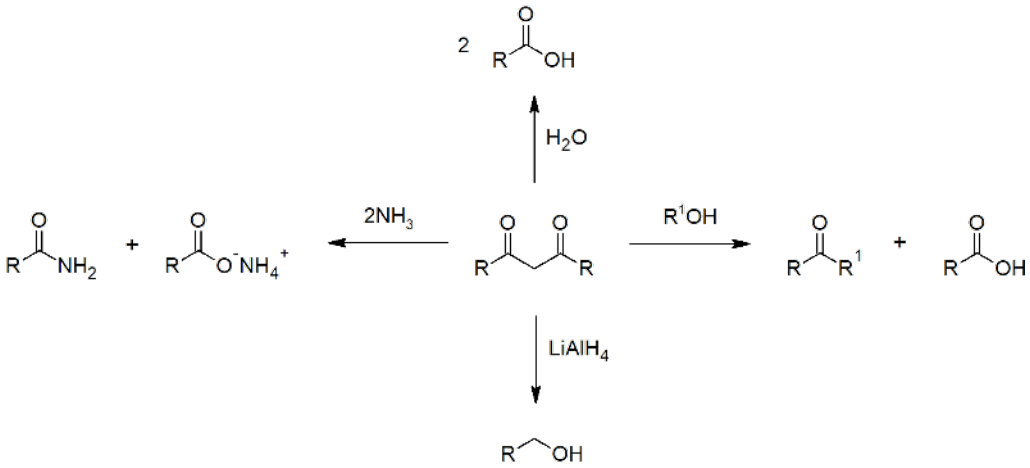




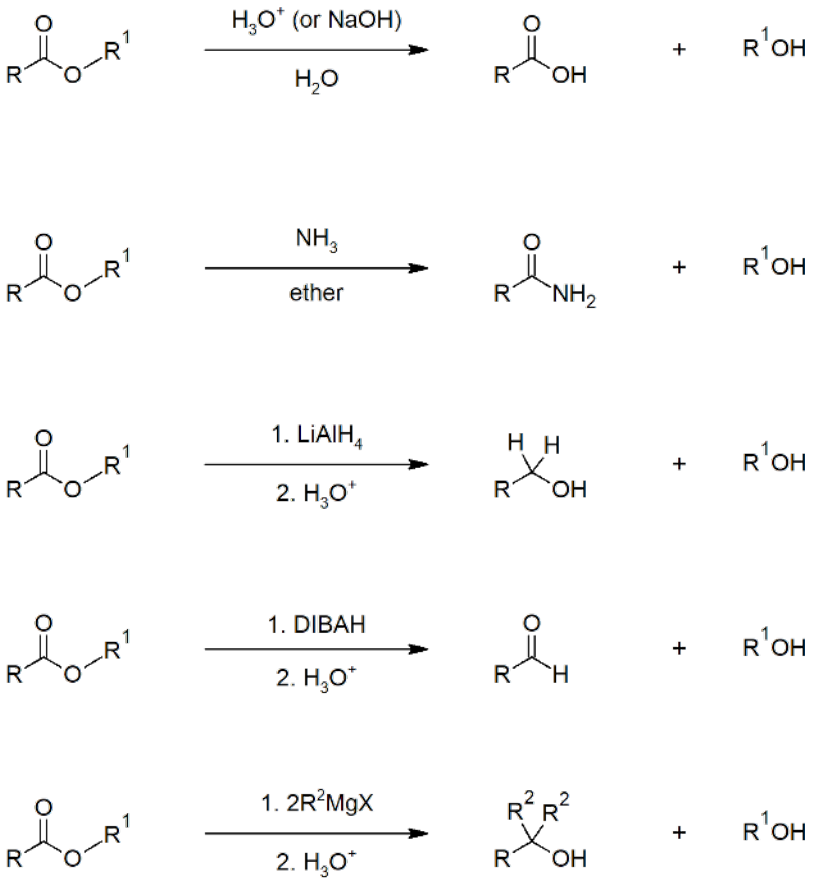
Acid Chloride Reactions



Acid Anhydride Reactions



Ester Reactions



21.S: Carboxylic Acid Derivatives (Summary) is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

CHAPTER OVERVIEW

CHAPTER 22: CARBONYL ALPHA-SUBSTITUTION REACTIONS

Alpha-substitution reactions are the third major type of reaction that you will study in your investigation of the chemistry of carbonyl compounds. As you will see, these reactions proceed through the formation of the enol form of the carbonyl compound.

After a brief review of keto-enol tautomerism, we begin our discussion of alpha-substitution reactions by looking at the methods used to introduce a halogen atom into a carbonyl-containing compound—reactions in which the enol form of the carbonyl compound is directly involved. After discussing the factors that influence the formation and stability of enolate anions, we examine some halogenation reactions in which an enolate ion is formed as an intermediate.

The chapter concludes with a study of the alkylation of enolate anions. These reactions are of tremendous use in organic syntheses, as they provide a method of forming new carbon-carbon bonds, and hence facilitate the laboratory preparation of increasingly complex compounds.

Chapter Objectives
22.0 Introduction
22.1 Keto-Enol Tautomerism
22.2 Reactivity of Enols: The Mechanism of Alpha-Substitution Reactions
22.3 Alpha Halogenation of Aldehydes and Ketones
22.4 Alpha Bromination of Carboxylic Acids
22.5 Acidity of Alpha Hydrogen Atoms: Enolate Ion Formation
22.6 Reactivity of Enolate Ions
22.7 Alkylation of Enolate Ions
22.S: Carbonyl Alpha-Substitution Reactions (Summary)

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CHAPTER OBJECTIVES

When you have completed Chapter 22, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design multi-step syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
3. solve road-map problems that require a knowledge of carbonyl alpha-substitution reactions.
4. define, and use in context, the key terms introduced.

CONTRIBUTORS AND ATTRIBUTIONS

Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

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22.0 INTRODUCTION

Objectives

After completing this section, you should be able to write a general mechanism for an alpha-substitution reaction of a carbonyl compound.

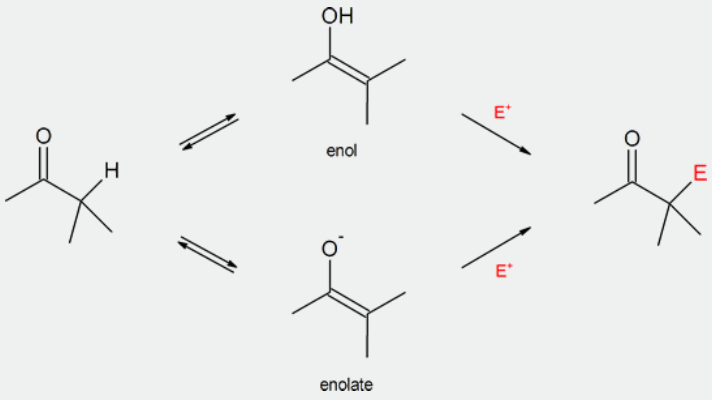
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- alpha (α) position
- alpha-substitution reaction

STUDY NOTES

An "alpha-substitution reaction" of a carbonyl compound is a reaction in which one of the hydrogen atoms on the carbon adjacent to the carbonyl group is substituted by some other atom or group. Attack by the electrophile (E^+) can occur on the enol or enolate intermediate.



CONTRIBUTORS AND ATTRIBUTIONS

Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

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22.1 KETO-ENOL TAUTOMERISM

Objectives

After completing this section, you should be able to

1. write an equation to illustrate keto-enol tautomerism.
2. write a detailed mechanism for acid-catalyzed keto-enol tautomerism.
3. write a detailed mechanism for base-catalyzed keto-enol tautomerism.
4. draw the structure of the enol form of a given carbonyl compound.

KEY TERMS

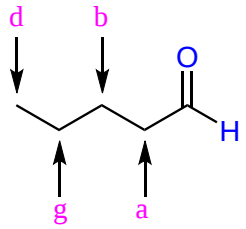
Make certain that you can define, and use in context, the key terms below.

- enol
- keto
- tautomerism
- tautomers
- enolate ion

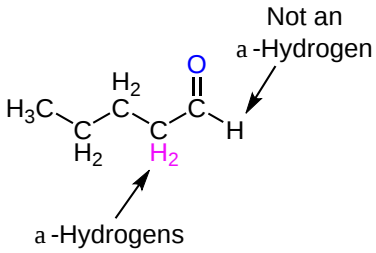
STUDY NOTES

Keto-enol tautomerism was first introduced in Section 9.4, in the discussion of the hydration of alkynes. The subject was raised again in the chapter entitled A Preview of Carbonyl Compounds, during the brief overview of the alpha-substitution reactions of carbonyl compounds. You may wish to review these sections before proceeding.

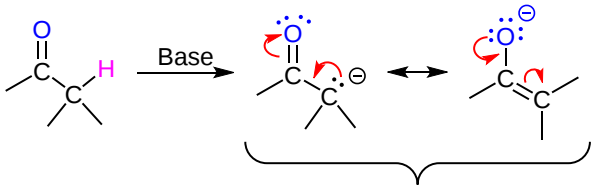
Often, the position of a carbon atom near a carbonyl group is designated using Greek letters. The atom adjacent to the carbonyl is alpha, the next removed is beta and so on. The carbon in the carbonyl group is used as reference point and is not assigned a Greek letter. Likewise, hydrogens bare the same Greek letter as the carbon atoms to which they are attached. α-Hydrogens are bonded to α-carbons and β-hydrogens are bonded to β-carbons etc.



The presence of α-hydrogens in a molecule provides the possibility of certain chemical reactions, which will be discussed in this chapter and in **Chapter 23**. Because of this, the ability to identify α-hydrogens is an important skill. As shown below, pentanal has two α-hydrogens. Note that aldehyde hydrogens are not given a Greek letter, they are simply referred to as an aldehyde hydrogen.

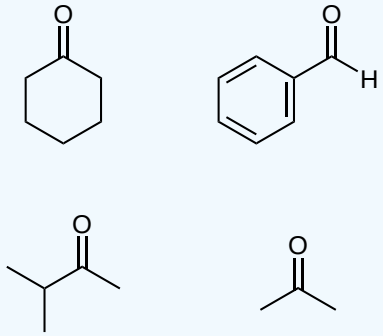


α-hydrogens, which are attached to a carbon directly adjacent to a carbonyl group, display unusual acidity. This is almost exclusively due to the resonance stabilization of the carbanion conjugate base, called an enolate, as illustrated in the diagram below. The effect of the the stabilizing C=O is seen when comparing the pK_a for the α-hydrogens of aldehydes (~16-18), ketones (~19-21), and esters (~23-25) to that of a typical alkyl C-H bond (~40-50).

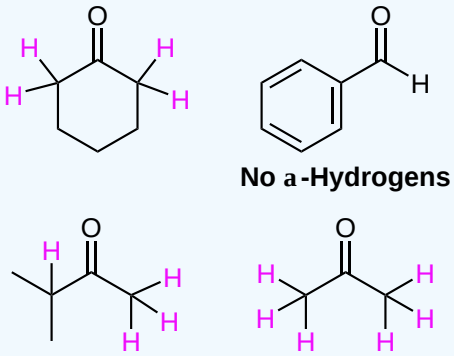


EXAMPLE 1

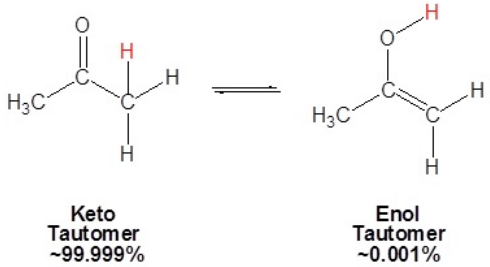
Indicate any α-hydrogens contained in the following molecules:



Solution



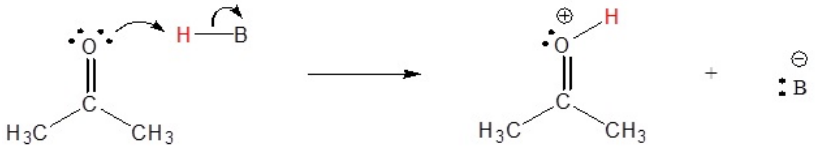
Because of the acidity of α hydrogens carbonyls undergo keto-enol tautomerism. Tautomers are rapidly interconverted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom and a differently located double bond. The equilibrium between tautomers is not 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.



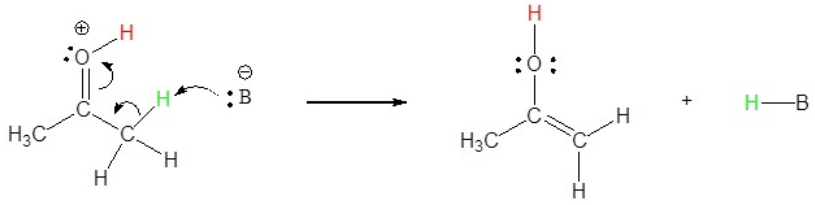
MECHANISM FOR ENOL FORMATION

Acid conditions

1) Protonation of the Carbonyl

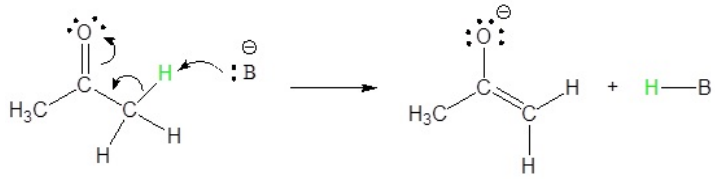


2) Enol formation

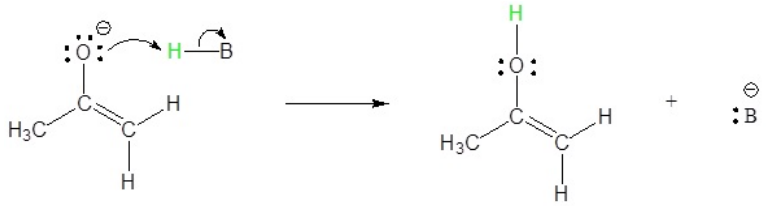


Basic conditions

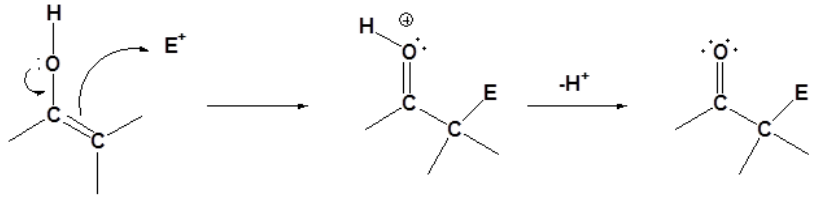
1) Enolate formation



2) Protonation



HOW ENOLS REACT



EXERCISES

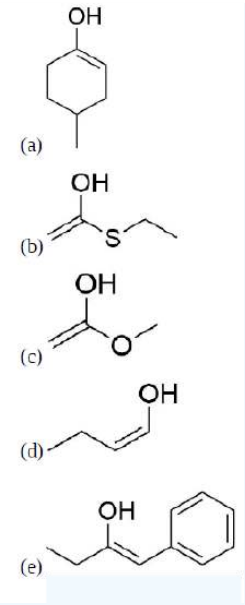
? EXERCISE 22.1.1

Draw the enol forms of the following molecules

a. 4-methylcyclohexanone
b. Ethyl thioactetate
c. Methyl acetate
d. Butanal
e. 1-phenyl-2-butanone

Answer

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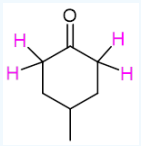


EXERCISE 22.1.2

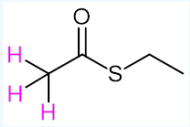
How many α-hydrogens do each of the molecules from the previous question have? Label them.

Answer

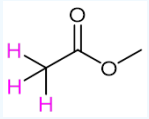
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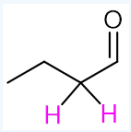
(b)



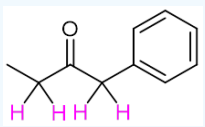
(c)



(d)



(e)

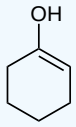


? EXERCISE 22.1.3

Under normal conditions cyclohexanone exists in the enol tautomer in a much higher percentage than acetone. Explain.

Answer

The enol tautomer of cyclohexanone has more alky substituents than the enol tautomer of acetone. This makes the double bond of the enol double bond of cyclohexanone more stable and easier to form.



Enol of Cyclohexane



Enol of Acetone

QUESTIONS

Q22.1.1

Draw the enol forms of the following molecules

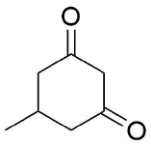
a. 4-methylcyclohexanone
b. Ethyl thioactetate
c. Methyl acetate
d. Butanal
e. Propionic Acid
f. 1-phenyl-2-butanone

Q22.1.2

How many acid protons do each of the molecules from the previous question have? Label them.

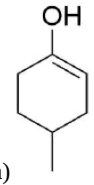
Q22.1.3

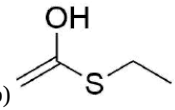
Draw all of the monoenol forms for the following molecule. Which ones are most stable? Why?

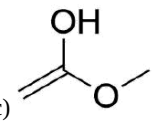


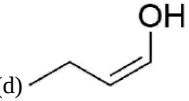
SOLUTIONS

S22.1.1

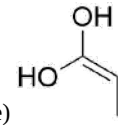
(a)


(b)


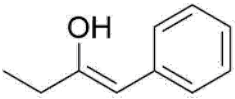
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(d)


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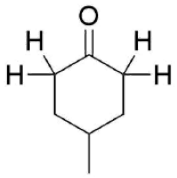


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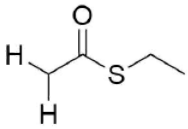


S22.1.2

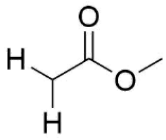
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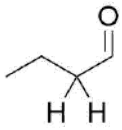
(b)



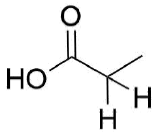
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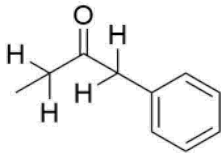
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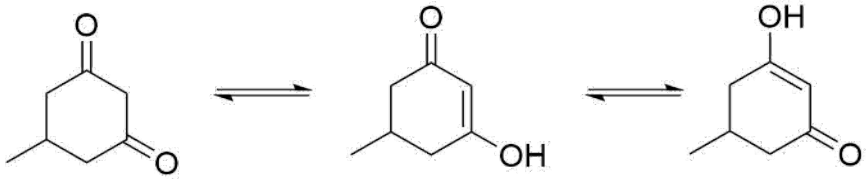
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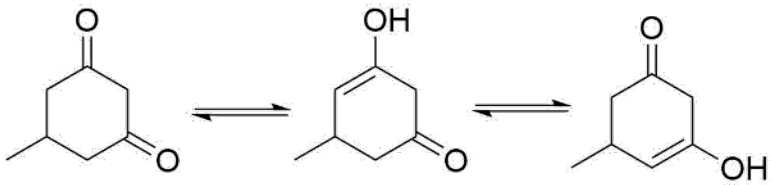
(f)



S22.1.3



The ability to resonate stabilizes this enol form.



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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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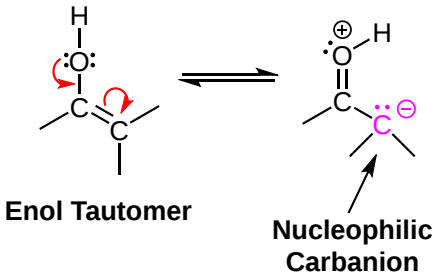
22.2 REACTIVITY OF ENOLS: THE MECHANISM OF ALPHA-SUBSTITUTION REACTIONS

Objectives

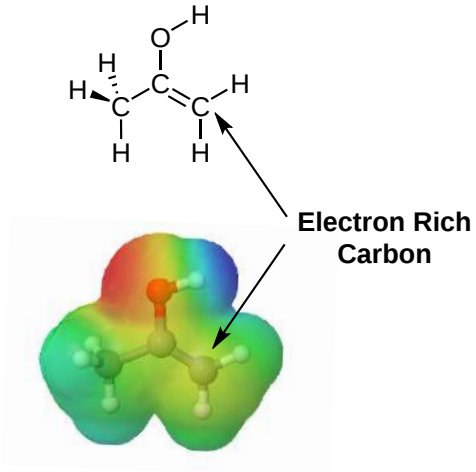
After completing this section, you should be able to write a detailed mechanism for an acid-catalyzed, alpha-substitution reaction of a carbonyl compound.

HOW ENOLS REACT

The oxygen of an enol can donate electron density into its double bond making it electron-rich and more reactive than typical alkenes.



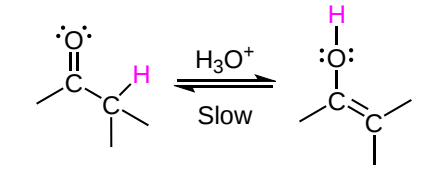
As seen in the electrostatic potential map for propen-2-ol ($CH_3COH=CH_2$), the enol tautomer of acetone, shows an increased electron density on the α-carbon (yellow) especially when compared to the -CH_3 carbon (blue/green). One of the resonance forms of an enol places a lone pair of electrons and a negative charge on the α-carbon forming a carbanion nucleophile. Enols react with electrophiles in a similar fashion as other carbanion nucleophiles, such as Grignard reagents.



MECHANISM OF ALPHA SUBSTITUTION REACTIONS USING AN ENOL

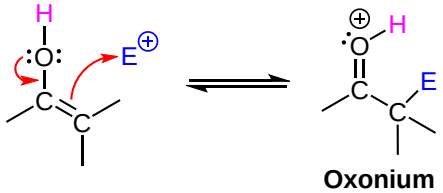
The mechanism begins with the acid-catalyzed tautomerization to form an enol via the mechanism discussed in **Section 22.1**. Lone pair electrons on the enol oxygen move to become a C=O pi bond thus creating a positively charged oxonium ion. This also causes electrons from the C=C enol pi bond to attack an electrophile forming a C-E sigma bond. These two electron movements in concert represent the enol acting as a nucleophile. In the last step, an H^+ is removed from the carbonyl oxygen, regenerating the acid catalyst, and forming an *α*-substituted carbonyl .

1) Acid catalyzed tautomerization to form an enol



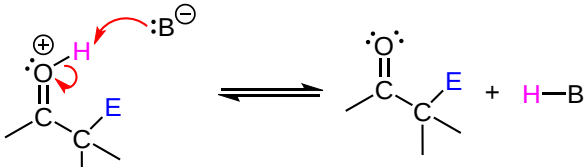
Keto Tautomer **Enol Tautomer**

2) The nucleophilic enol attacks the electrophile



Oxonium Ion

3) Deprotonation of the carbonyl to produce an α-substituted product

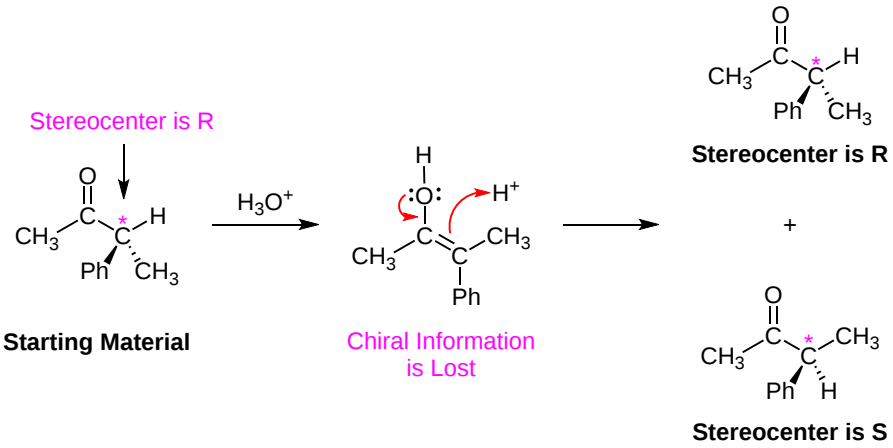


a-Substitution

STEREOCHEMICAL IMPLICATION OF ENOL FORMATION

During an acid-catalyzed enol formation, an α-hydrogen is removed to form a sp^2-hybridized, trigonal planar C=C bond which removes any chiral information from the original alpha carbon. Because the enol alkene is planar the incoming electrophile can attack from either the top or the bottom of the molecule. If the α-carbon of the starting material has a defined stereochemistry or if a new stereocenter if formed during the reaction, the product will typically be a racemic mixture of enantiomers at the site of substitution.

One of the easiest ways of displaying this process is through acid-catalyzed racemization. If a carbonyl compound has an α-carbon with a defined stereochemisty and an α-hydrogen, a racemic mixture can be formed simply through tautomerization. The addition of acid promotes the formation of the enol tautomer which removes the chiral information of the α-carbon. The enol then attacks an H^+ electrophile to reform the keto tautomer which then contains a racemic mixture of enantiomers.

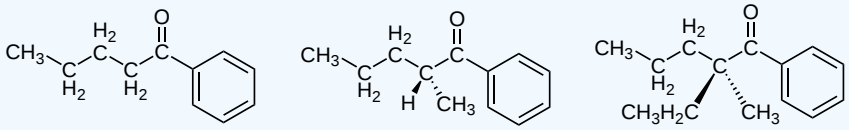


Example of Acid-Catalyzed Racemization

EXERCISES

EXERCISE 22.2.1

Which of the following optically active ketones would undergo acid-catalyzed racemization? Explain.



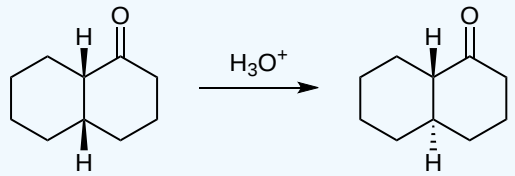
A **B** **C**

Answer

Molecule A would not because the alpha carbon is not a stereocenter. Molecule B would because the alpha carbon is a stereocenter and contains a hydrogen. Molecule C would not because it does not contain an alpha hydrogen.

EXERCISE 22.2.2

When *cis*-Decalone is treated with an acid it becomes *trans*-Decalone almost exclusively becomes *trans*-Decalone. Explain.



***Cis*-Decalone** ***Trans*-Decalone**

Answer

This change involves a process call epimerization. Epimers as diastereomers which differ at only one chiral carbon. Epimerization is a process where only one of multiple chiral carbons is changed. In this example, the stereocenter in questions is a chiral carbon. The addition of an acid promotes this carbon becoming part of an enol thereby losing its chiral information. When the enol tautomer converts back the ketone tautomer the a mixture of both *cis* and *trans* epimers should form. However, as discussed in a previous section, we know that the *trans* isomer of the decalin ring system is more stable than the *cis*. Because there is a defined difference in stability, the trans isomer of decalone is preferred.

CONTRIBUTORS AND ATTRIBUTIONS

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

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22.3 ALPHA HALOGENATION OF ALDEHYDES AND KETONES

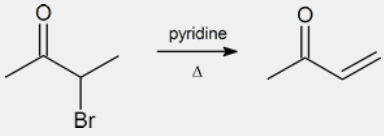
Objectives

After completing this section, you should be able to

1. write an equation to illustrate the alpha halogenation of aldehydes and ketones.
2. identify the product formed from the alpha halogenation of a given aldehyde or ketone.
3. identify the carbonyl compound, the reagents, or both, needed to prepare a given α-halogenated aldehyde or ketone.
4. illustrate the importance of the alpha halogenation of carbonyl compounds as an intermediate step in the synthesis of α,β-unsaturated aldehydes and ketones.
5. write a detailed mechanism for the acid-catalyzed halogenation of a ketone.
6. describe the evidence provided by kinetic experiments supporting the suggestion that the acid-catalyzed, alpha halogenation of ketones proceeds via the rate-determining formation of an enol.

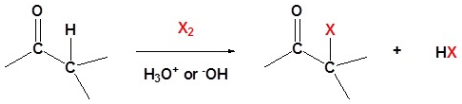
STUDY NOTES

Note: α-bromo ketones are a good starting material to generate α,β-unsaturated ketones by dehydrobromination.

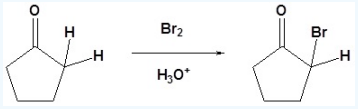


A carbonyl containing compound with α hydrogens can undergo a substitution reaction with halogens. This reaction comes about because of the tendency of carbonyl compounds to form enolates in basic condition and enols in acidic condition. In these cases even weak bases, such as the hydroxide anion, is 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



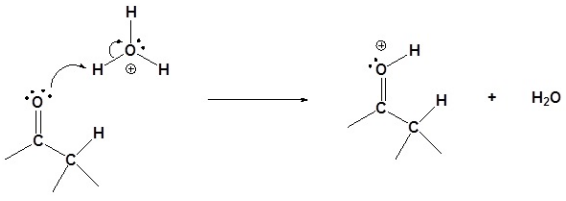
EXAMPLE 22.3.1



ACID CATALYZED MECHANISM

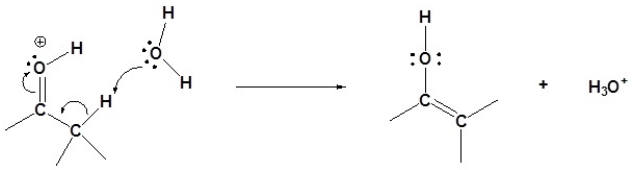
Under acidic conditions the reaction occurs thought the formation of an enol which then reacts with the halogen.

1) Protonation of the carbonyl

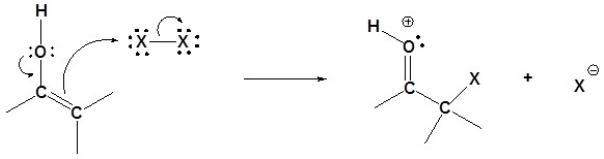


2) Enol formation

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3) S_N2 attack



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:

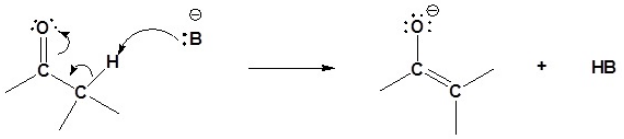
$$\text{rate} = [\text{ketone}][H^+]$$

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.

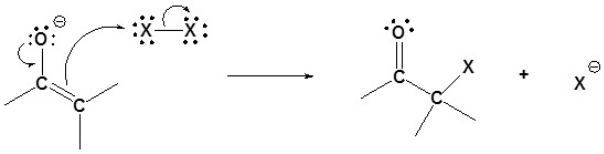
BASE CATALYZED MECHANISM

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.

1) Enolate formation

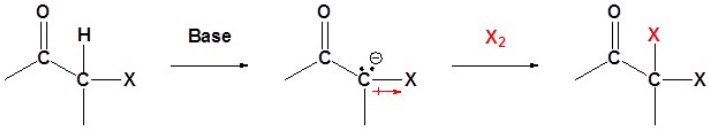


2) S_N2 attack



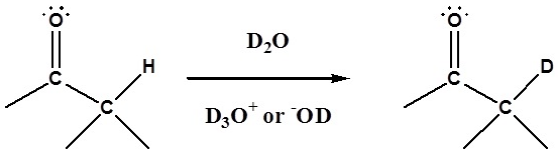
OVERREACTION DURING BASE PROMOTED A HALOGENATION

The fact that an electronegative halogen is placed on an α carbon means that the product of a base promoted α halogenation is actually more reactive than the starting material. The electron withdrawing effect of the halogen makes the α carbon even more acidic and therefor promotes further reaction. Because of this multiple halogenations can occur. This effect is exploited in the haloform reaction discussed later. If a monohalo product is required then acidic conditions are usually used.

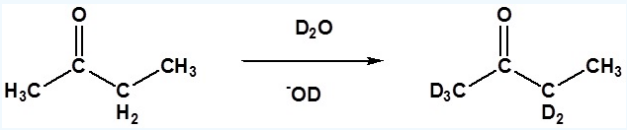


DEUTERIUM EXCHANGE

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.

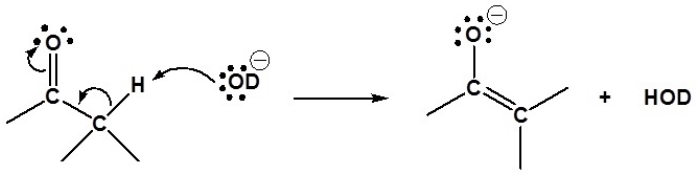


EXAMPLE 22.3.2

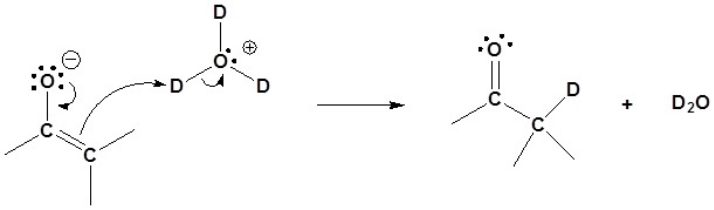


MECHANISM IN BASIC CONDITIONS

1) Enolate Formation



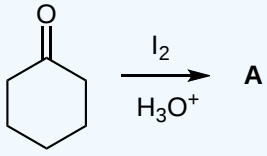
2) Deuteration



EXERCISES

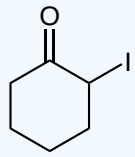
EXERCISE 22.3.1

Please draw the products of the following reaction.



Answer

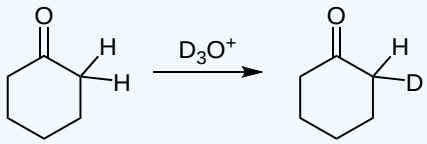
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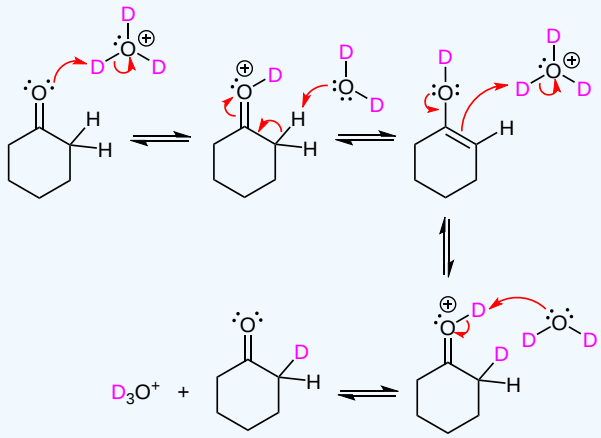
A

EXERCISE 22.3.2

Draw out the mechanism for the following reaction.



Answer



EXERCISE 22.3.3

How might you form 2-hepten-4-one from 4-heptanone?

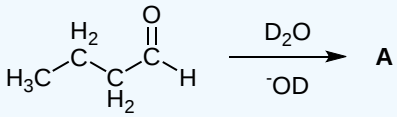
Answer

1) Br_2, H_3O^+

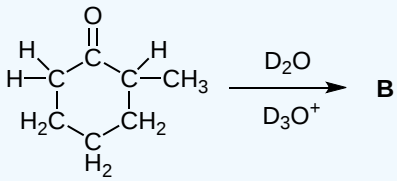
2) Pyridine, Heat

EXERCISE 22.3.4

Show the products of the following reactions:



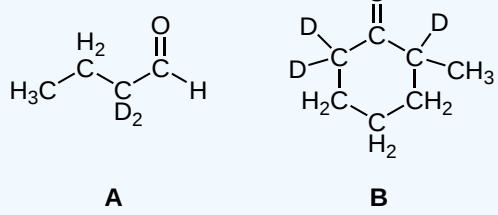
A



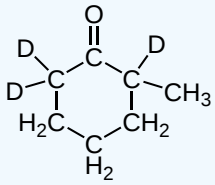
B

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Answer



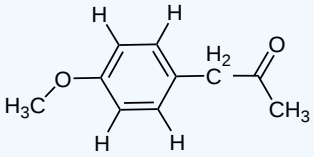
A



B

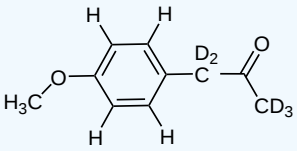
? EXERCISE 22.3.5

The following compound was reacted with D_3O^+. The only signals that could be found in the 1H NMR spectrum of the product were at 3.9 ppm (3H) and 6.6-6.9 ppm (4H). Please explain the results of the NMR.



Answer

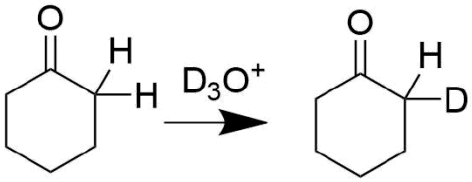
A deuterium exchange reaction occurred. All of the alpha-hydrogens in the molecule have been exchanged with deuterium. Because detueriums do not appear in a typical ^1H NMR, only the remaining hydrogens appear.



QUESTIONS

Q22.3.1

Draw out the mechanism for the following reaction.



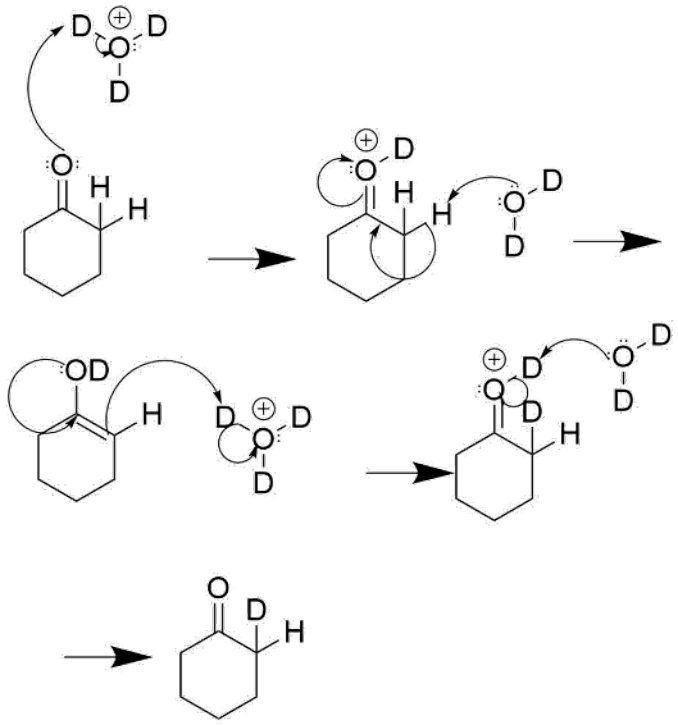
Q22.3.2

How might you form 2-hepten-4-one from 4-heptanone?

SOLUTIONS

S22.3.1

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S22.3.2

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)

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22.4 ALPHA BROMINATION OF CARBOXYLIC ACIDS

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the Hell-Volhard-Zelinskii reaction.
2. identify the product formed from the reaction of a given carboxylic acid with bromine and phosphorus tribromide.
3. identify the carboxylic acid, the reagents, or both, needed to synthesize a given α-bromo carboxylic acid.
4. outline the stereochemical implications of the fact that the Hell-Volhard-Zelinskii reaction proceeds through the formation of an acid bromide enol.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- Hell-Volhard-Zelinskii reaction

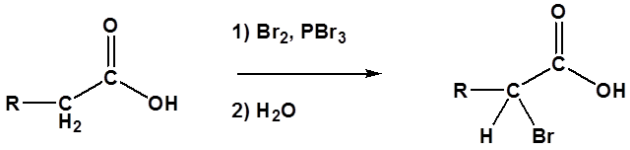
STUDY NOTES

The reagents for the Hell-Volhard-Zelinskii reaction are given as bromine and phosphorus tribromide. In some questions, you may observe that only bromine and phosphorus are listed as reagents. Really there is no difference, as phosphorus tribromide would be formed *in situ* by the combination of bromine and red phosphorus:

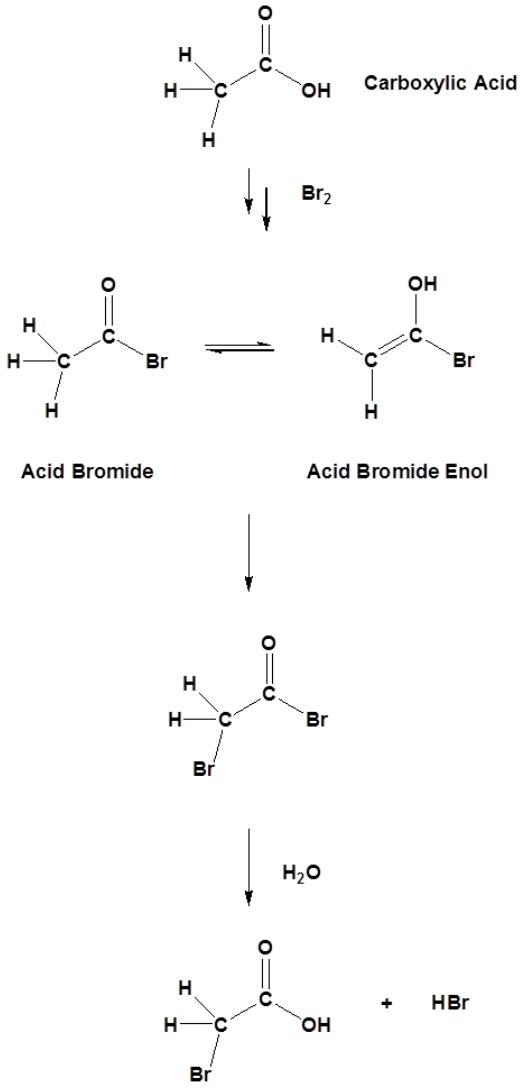
$3BR_2 + 2P \rightarrow 2PBr_3$

Excess bromine is required to ensure that enough reagent is available for the reaction with the enol.

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 reaction.



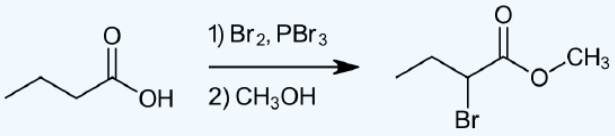
The mechanism of this reaction involves an acid bromide enol instead of the expected carboxylic acid enol. The reaction stats with the reaction of the carboxylic acid with PBr_3 to form the acid bromide and HBr. The HBr then catalyzes the formation of the acid bromide enol which subsequently reacts with Br_2 to give alpha bromination. Lastly, the acid bromide reacts with water to reform the carboxylic acid.



EXERCISES

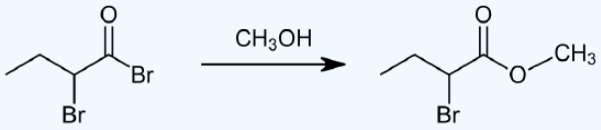
? EXERCISE 22.4.1

Explain why the following reaction occurs.



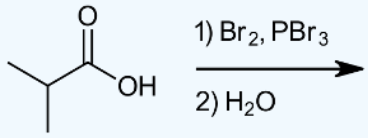
Answer

The first step represents the beginning of the Hell-Volhard-Zelinskii reaction which provides a-bromination and creates and acid bromide intermediate. The second step adds methanol which reacts with the acid bromide to produce an ester.

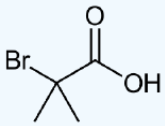


EXERCISE 22.4.2

Draw the products of the following reaction:



Answer



CONTRIBUTORS AND ATTRIBUTIONS

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

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22.5 ACIDITY OF ALPHA HYDROGEN ATOMS: ENOLATE ION FORMATION

Objectives

After completing this section, you should be able to

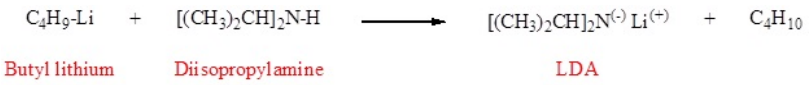
1. explain why the alpha hydrogens of carbonyl compounds are more acidic than the hydrogens in a typical hydrocarbon.
2. list the properties that make lithium diisopropylamide a suitable reagent for converting a wide range of carbonyl compounds into their enolate anions.
3. arrange a given list of carbonyl compounds in order of increasing or decreasing acidity.
4. determine whether a given carbonyl-containing compound is more or less acidic than selected other compounds, such as water, ammonia, alcohols, alkanes, alkenes, alkynes and amines.
5. explain why dicarbonyl compounds, such as *β*-diketones, are more acidic than compounds that contain only a single carbonyl group.

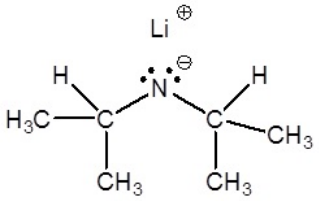
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

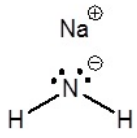
- *β*-diketone
- *β*-keto ester

For alkylation 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.





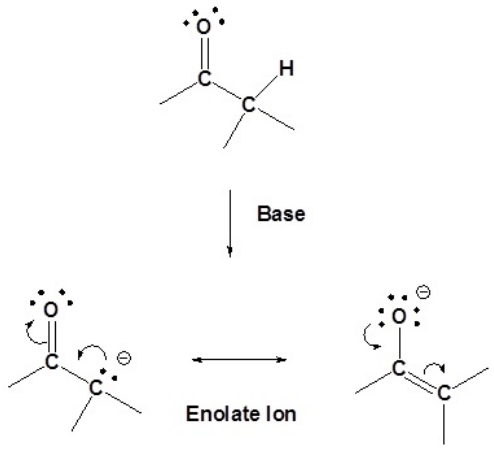
LDA



Sodium Amide

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).

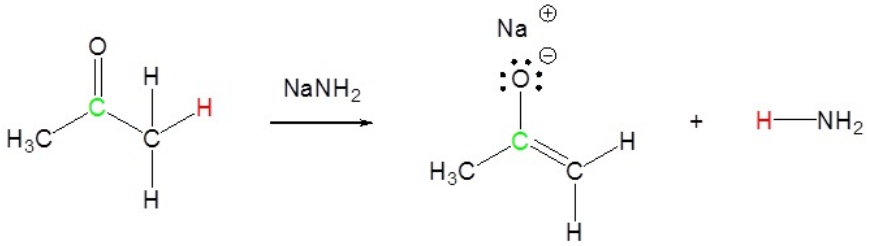


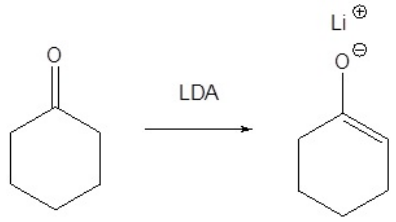
Of the two resonance structures of the enolate ion the one which places the negative charge on the oxygen is the most stable. This is because the negative change will be better stabilized by the greater electronegativity of the oxygen.

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	$RCH_2–C\equiv N$	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.

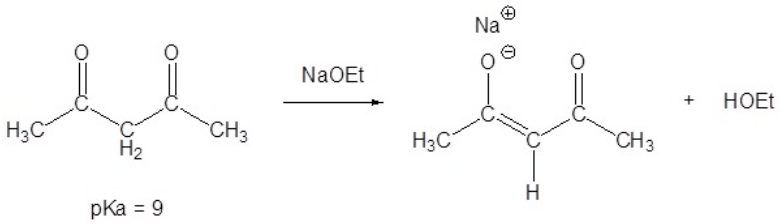
EXAMPLES





If the formed enolate is stabilized by more than one carbonyl it is possible to use a weaker base such as sodium ethoxide.

$NaOCH_2CH_3 = Na^+ {}^-OCH_2CH_3 = NaOEt$



pKa = 9

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.

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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22.6 REACTIVITY OF ENOLATE IONS

Objectives

After completing this section, you should be able to

1. identify the two possible ways in which a given enolate anion could conceivably react with an electrophile.
2. write an equation to illustrate the haloform reaction.
3. identify the products formed from the reaction of a given methyl ketone with a halogen and excess base.
4. identify the methyl ketone, the reagents, or both, needed to obtain a specified carboxylic acid through a haloform reaction.

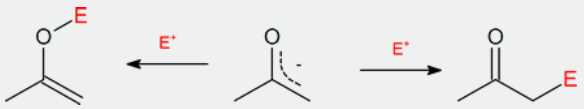
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- haloform
- haloform reaction

STUDY NOTES

Because the negative charge on an enolate ion is delocalized, there are two reactive sites and therefore two potential products. The α-substituted product is much more common.



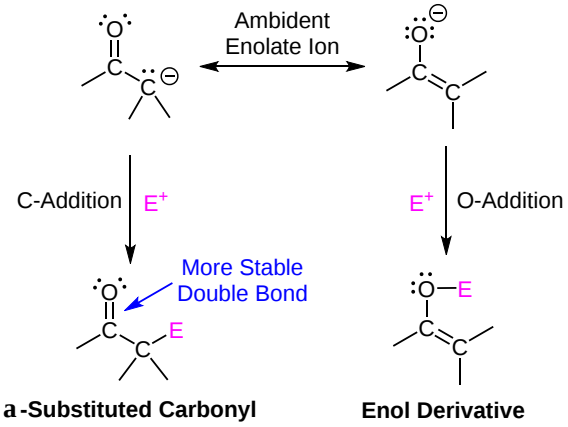
A "haloform" is any compound of the type CHX_3, where X = Cl, Br or I. Of these three compounds, chloroform is the most common.

The haloform reaction describedin the reading is usually carried out with iodine. This reaction is called the "iodoform test," and is one of the reactions carried out in the laboratory as a simple qualitative test for methyl ketones.

HOW ENOLATES REACT

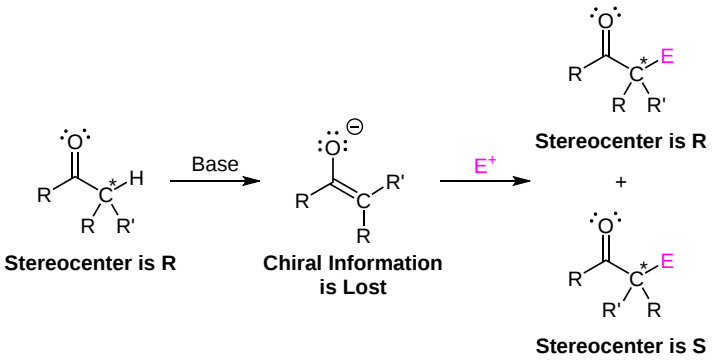
Due to their negative charges, enolates are better and more versatile nucleophiles than enols. The increased reactivity of enolates makes them capable of a wider range of reactions than enols. Also, α-hydrogen containing compounds can be completely converted to an enolate by reaction with a strong base. Whereas enols can only be created in small amounts through manipulating their equilibrium.

Since the negative charge of an enolate anion is delocalized between the α-carbon and an oxygen, electrophiles may bond to either atom. Reactants having two or more reactive sites are called ambident, so this term applies to enolate anions. Either the C of the O reactive site in an enolate may act as a nucleophile depending on the reaction conditions. Reactions with the oxygen would create a new O-E bond and produce an enol derivative. Reactions with the α-carbon creates a new C-E bond and creates an α-substituted carbonyl compound. Although reactions with the nucleophilic oxygen are possible, reactions involving the nucleophilic α-carbon are much more common, partially due to the thermodynamic stability of the C=O bonds in the final products. Also, the enolate counter ion, such as Li^+ or Na^+, is more tightly associated with the negatively charged enolate oxygen which can then block incoming electrophiles, reducing their chance of reaction at the oxygen.



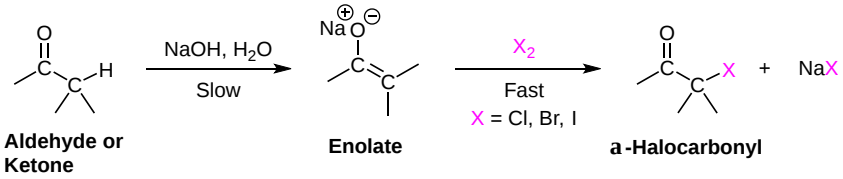
STEREOCHEMICAL IMPLICATION OF ENOLATE FORMATION

During enolate formation, an α-hydrogen is removed to form a sp^2-hybridized, trigonal planar C=C bond which removes any chiral information from the original α-carbon. Because the enol alkene is planar, the incoming electrophile can attack from either the top or the bottom. If the α-carbon of the starting material has a defined stereochemistry or if a new stereocenter is formed during the reaction, the product will be a racemic mixture of enantiomers.



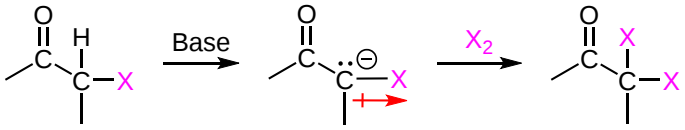
BASE PROMOTED A-HALOGENATION

An enolate reacts rapidly with a halogen to produce α-halogenated carbonyl products. This reaction has the tendency to overreact and create polyhalogenated products. If a monohalogenated product is sought, the acid catalyzed halogenation reaction discussed in section 22.3 is preferred. Because complete formation to the enolate is not necessary, weak bases, such as the hydroxide anion, are sufficient to produce this reaction. Once a small amount of enolate is formed, it quickly reacts with the halogen. This removes the enolate and shifts the equilibrium toward forming more enolate by Le Chatelier's principle.



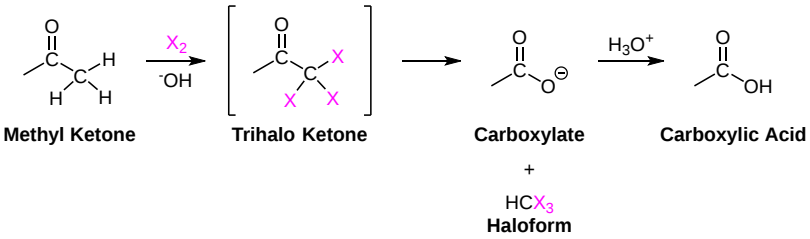
OVERREACTION DURING BASE PROMOTED A-HALOGENATION

The α-hydrogens of halogenated carbonyl products are usually more acidic than the corresponding non-halogenated compounds. The inductive electron withdrawing effect of the electronegative halogen stabilizes the negative charge of the enolate ion. This promotes further enolate formation and also further halogenation of the α-carbon. Monohalogenated carbonyls form an enolate over 100 times faster than their non-halogenated counterparts making multiple halogenations of the α-carbon frequent. This effect is exploited to cause the haloform reaction.

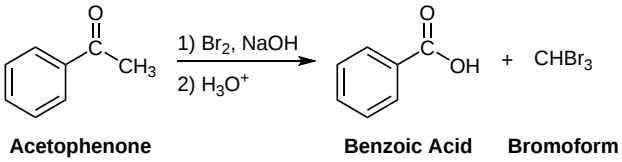


THE HALOFORM REACTION

Overall, the haloform reaction represents a method for the conversion of methyl ketones to carboxylic acids. Due to the increased reactivity of α-halogenated products, methyl ketones typically undergo base promoted halogenation three times to give a trihalo-ketone. A halomethyl ion leaving group is then substituted with a hydroxide ion during nucleophilic acyl substitution. The resulting carboxylate can then be protonated to form a carboxylic acid.



EXAMPLE

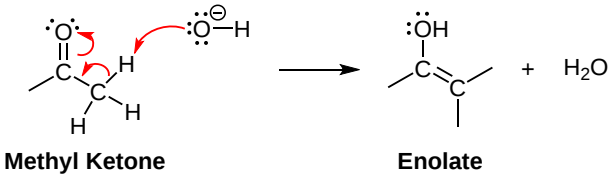


MECHANISM

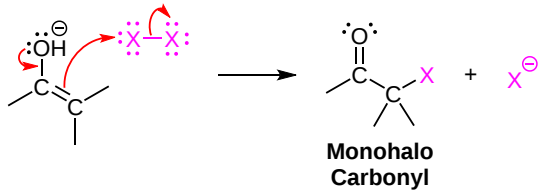
Note! This reaction is considered to be base promoted and not base catalyzed because an entire equivalent of base is required for each α-halogenation. Deprotonation of an α-hydrogen with hydroxide produces the nucleophilic enolate ion which subsequently reacts with the halogen. The increasing acidity of α-halogenated ketone causes this reaction to occur two more times. Once formed, the $-CX_3$ group attached to the carbonyl can act as a leaving group. Nucleophilic acyl substitution with a hydroxide anion causes C-C bond cleavage and eventually produces a haloform ($CHCl_3$, $CHBr_3$, CHI_3) and a carboxylate anion. The carboxylate ion is easily protonated with acid to form a carboxylic acid functional group. Often, this reaction is performed using iodine (I_2) because the subsequent iodoform (CHI_3) side-product is a bright yellow solid which is easily filtered off.

This reaction represents one of the few examples of a carbanion leaving group. The trihalomethyl ion ($^{-}:CX_3$) is particularly stabilized due to the inductive electron-withdrawing effects of the three halogens. The stability of the carbanion can be seen when considering the pK_a corresponding conjugate acid. In particular, bromoform ($CHBr_3$) has a pK_a of 13.7 which is more than 10^{20} times more acidic than a typical alkane C-H bond.

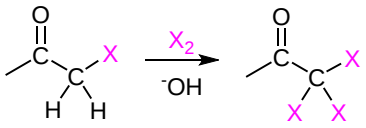
1) Enolate formation



2) Nucleophilic attack on the halogen

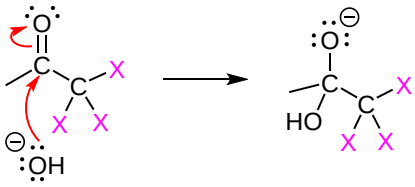


3) Repeat the halogenation two more times

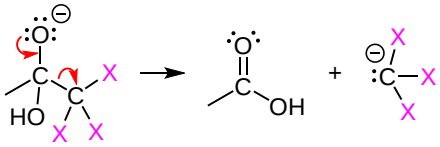


Trihalo Ketone

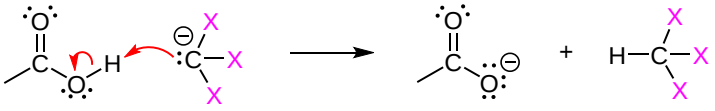
4) Nucleophilic attack on the electrophilic carbonyl carbon



5) Nucleophilic acyl substitution

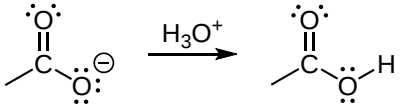


6) Deprotonation



Carboxylate **Haloform**

7) Protonation of the carboxylate

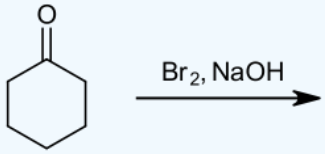


Carboxylic Acid

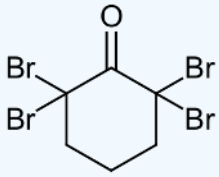
EXERCISES

? EXERCISE 22.6.1

Please predict the expected products of the following reaction.

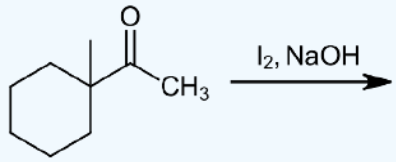


Answer

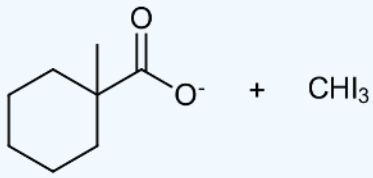


EXERCISE 22.6.2

Please predict the expected products of the following reaction.



Answer



CONTRIBUTORS AND ATTRIBUTIONS

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Prof. Steven Farmer (Sonoma State University)

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22.7 ALKYLATION OF ENOLATE IONS

Objectives

After completing this section, you should be able to

1. write a general mechanism for the attack of an enolate anion on an alkyl halide.
2. write a reaction sequence to illustrate the preparation of carboxylic acids via the malonic ester synthesis.
3. identify the product formed, and all the intermediates, in a given malonic ester synthesis.
4. identify all of the compounds needed to prepare a given carboxylic acid by a malonic ester synthesis.
5. write a detailed mechanism for each of the steps involved in a malonic ester synthesis.
6. write a reaction sequence to illustrate the preparation of ketones through the acetoacetic ester synthesis.
7. identify the product formed, and all the intermediates, in a given acetoacetic ester synthesis.
8. identify all of the compounds needed to prepare a given ketone by an acetoacetic ester synthesis.
9. write a detailed mechanism for each of the steps involved in an acetoacetic ester synthesis.
10. identify the product or products formed when a given lactone, ester, nitrile or ketone is treated with lithium diisopropylamide followed by an alkyl halide.
11. identify the compounds needed to prepare a given *α*-substituted ketone, ester, lactone or nitrile by a method involving the alkylation of an enolate anion.

KEY TERMS

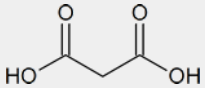
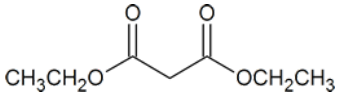
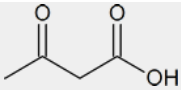
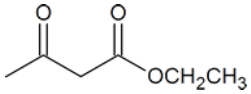
Make certain that you can define, and use in context, the key terms below.

- alkylation
- malonic ester synthesis

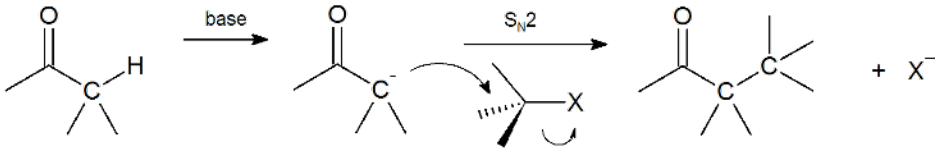
STUDY NOTES

The two syntheses discussed in this section provide routes to a wide variety of carboxylic acids and methyl ketones. You may wish to review the factors influencing S_N2 reactions (Section 11.3) in conjunction with this section.

You should try to memorize the structures of malonic ester and ethyl acetoacetate. The IUPAC names of these compounds are shown in the table below.

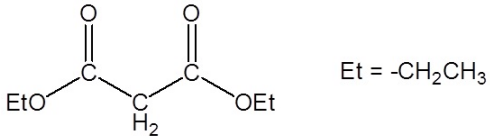
Structure	Common name	IUPAC name
	malonic acid	propanedioic acid
	malonic ester or diethyl malonate	diethyl propanedioate
	acetoacetic acid	3-oxobutanoic acid
	ethyl acetoacetate or acetoacetic ester	ethyl 3-oxobutanoate

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.



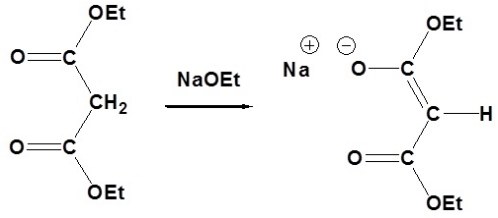
MALONIC ESTER SYNTHESIS

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.



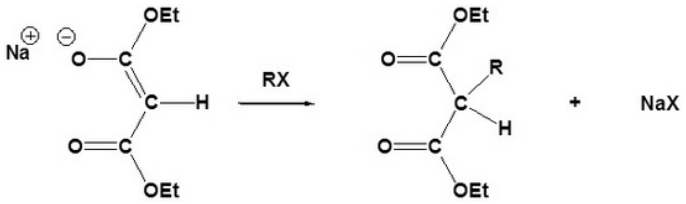
Malonic Ester

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.

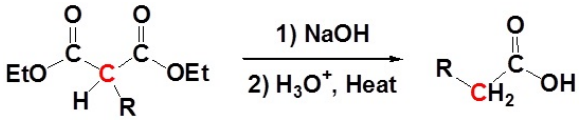


Malonic Ester **Sodio Malonic Ester**

Because Sodio Malonic Ester is an enolate, it can then be alkylated with alkyl halides.

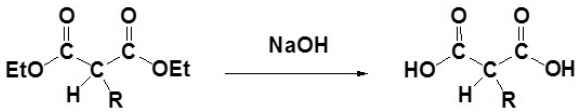


After alkylation the product can be converted to a dicarboxylic acid through saponification and subsequently one of the carboxylic acids can be removed through a decarboxylation step.

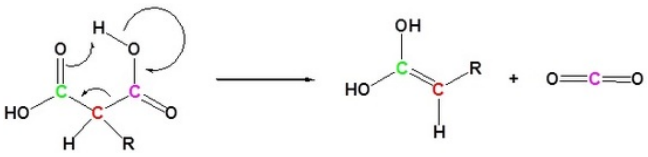


MECHANISM

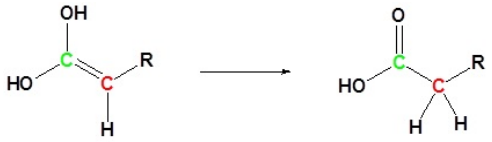
1) Saponification



2) Decarboxylation



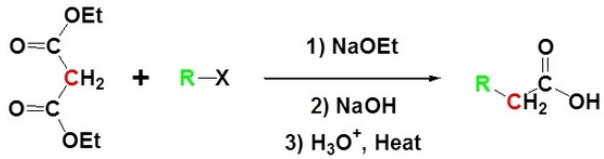
3) Tautomerization



All of the steps together form the Malonic ester synthesis.

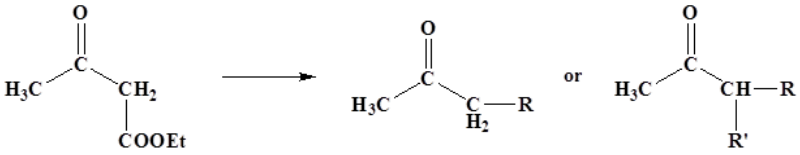
$$RX \rightarrow RCH\text{-}_2CO_2H \quad (1)$$

Example



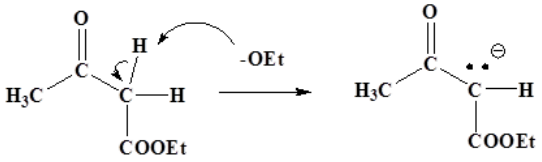
THE ACETOACETIC ESTER SYNTHESIS

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.

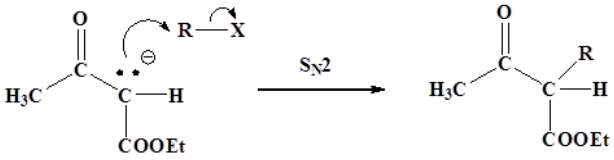


STEPS

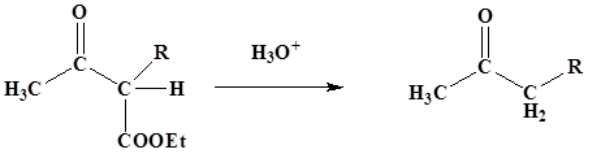
1) Deprotonation with ethoxide



2) Alkylation via and SN2 Reaction

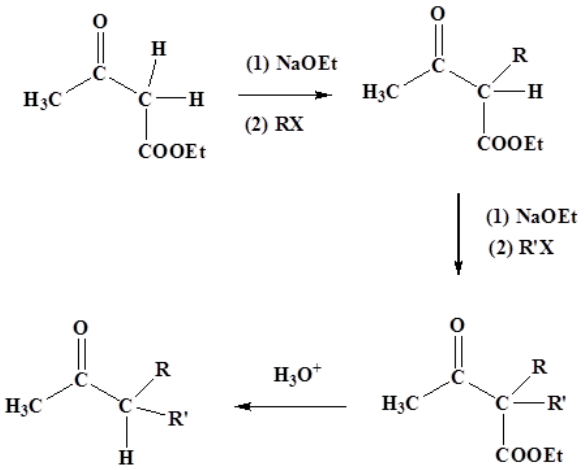


3) Hydrolysis and decarboxylation



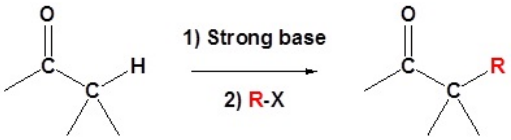
ADDITION OF A SECOND ALKY GROUP

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.

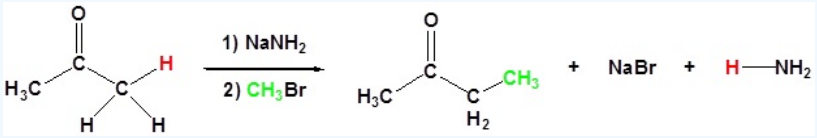


DIRECT ALKYLATION

Both the malonic ester synthesis and acetoacetic ester synthesis can be preformed with relatively mild bases, such as sodium ethoxide, because of the unusually acidic nature of the dicarbonyl compounds. However, if a stronger base is used, such as LDA, monocarbonyl compounds can also be alkylated in the alpha position.

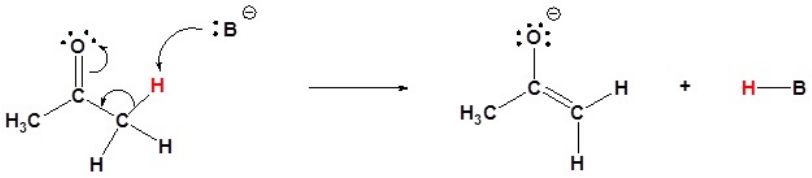


EXAMPLE 22.7.1: ALPHA ALKYLATION

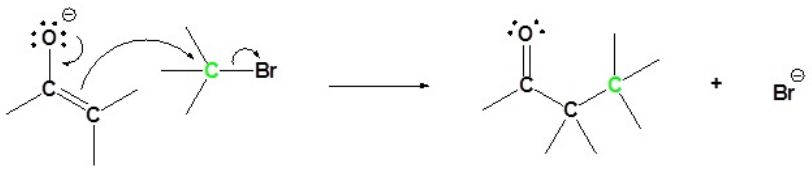


MECHANISM

1) Enolate formation



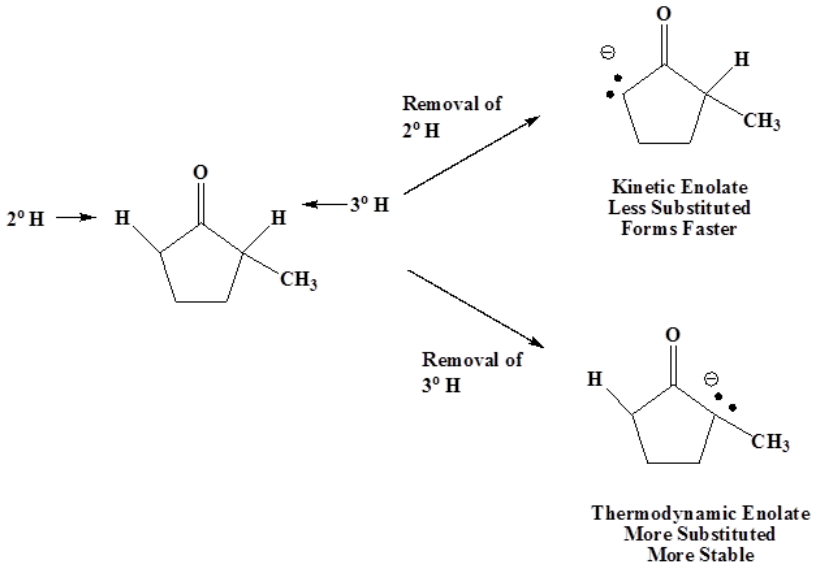
2) S_N2 attack



https://chem.libretexts.org/@go/page/91011

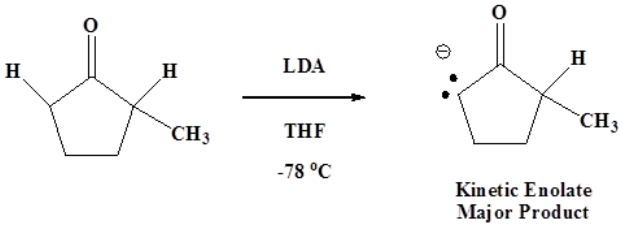
ENOLATE OF UNSYMMETRICAL CARBONYL COMPOUNDS

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.



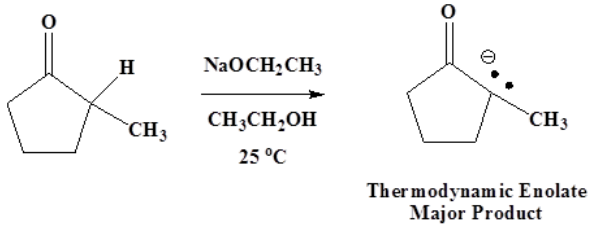
KINETIC ENOLATES

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

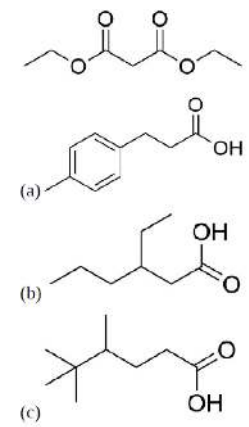
The thermodynamic enolate is favored by conditions which allow for equilibration. The thermodynamic enolate is usually formed by using a strong base at room temperature. At equilibrium the lower energy of the thermodynamic enolate is preferred, so that the more stable, more stubstituted enolate is formed.



EXERCISES

EXERCISE 22.7.1

Propose a synthesis for each of the following molecules from this malonic ester.



Answer

(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

EXERCISE 22.7.2

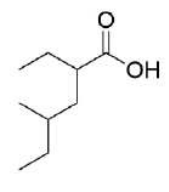
Why can't you prepare tri substituted acetic acids from a malonic ester?

Answer

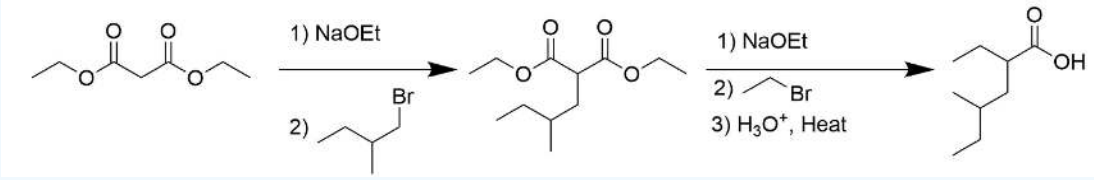
Malonic esters only contain two acid protons.

EXERCISE 22.7.3

Propose a synthesis for the following molecule via a malonic ester.

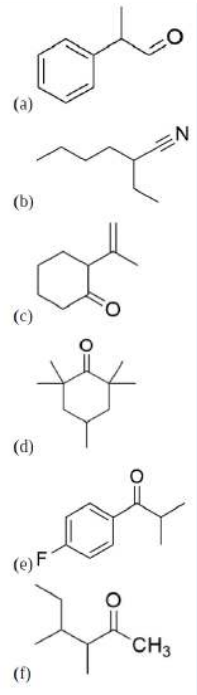


Answer

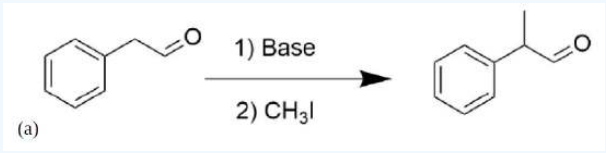


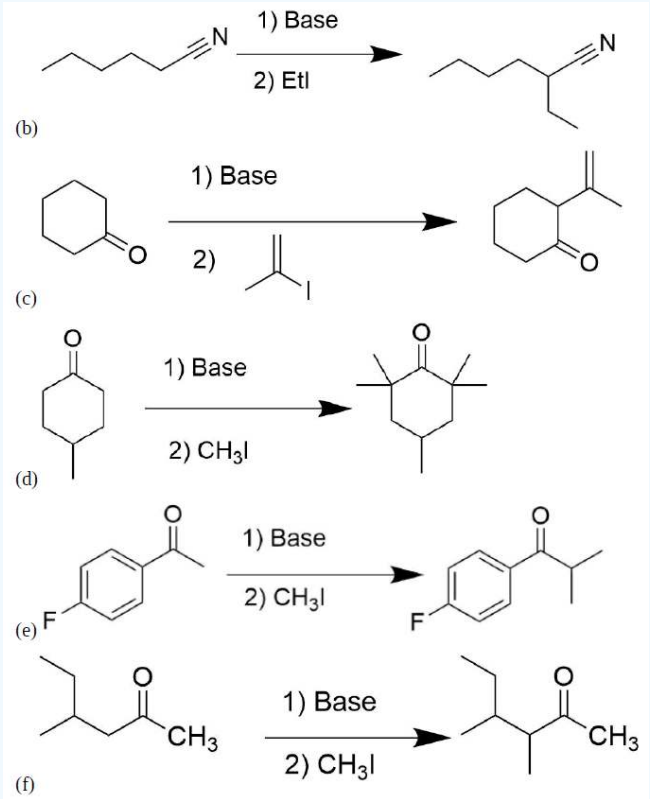
EXERCISE 22.7.4

How might you prepare the following compounds from an alkylation reaction?


(a)
O
(b)
N
(c)
O
(d)
O
(e)
F
O
(f)
O
CH3

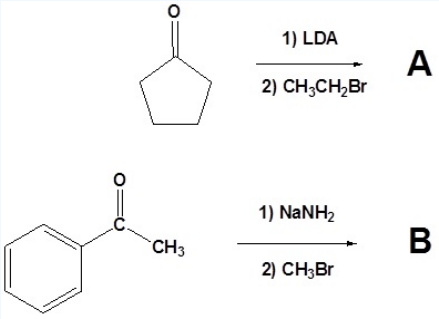
Answer


(a)
O
1) Base
2) CH3I
O

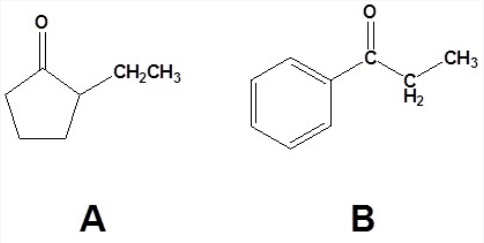

(b)
N
1) Base
2) EtI
N
(c)
O
1) Base
2)
I
O
(d)
O
1) Base
2) CH3I
O
(e)
F
O
1) Base
2) CH3I
F
O
(f)
O
CH3
1) Base
2) CH3I
O
CH3

EXERCISE 22.7.5

Please write the structure of the product for the following reactions.



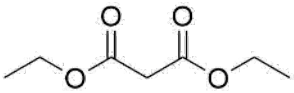
Answer

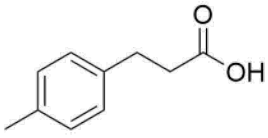


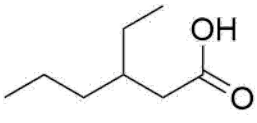
QUESTIONS

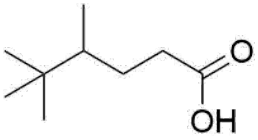
Q22.7.1

Propose a synthesis for each of the following molecules from this malonic ester.



(a) 

(b) 

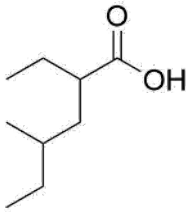
(c) 

Q22.7.2

Why can't you prepare tri substituted acetic acids from a malonic ester?

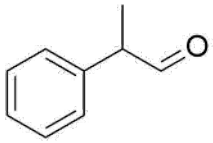
Q22.7.3

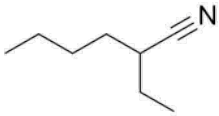
Propose a synthesis for the following molecule via a malonic ester.

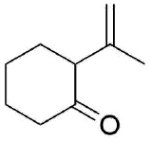


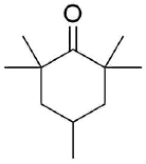
Q22.7.4

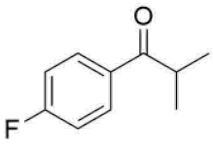
How might you prepare the following compounds from an alkylation reaction?

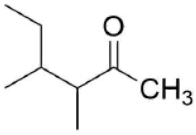
(a)


(b)


(c)


(d)


(e)


(f)


SOLUTIONS

S22.7.1

(a) 1) Malonic Ester, NaOEt, 2) 4-Methylbenzyl Bromide, 3) Base, 4) Acid, Heat

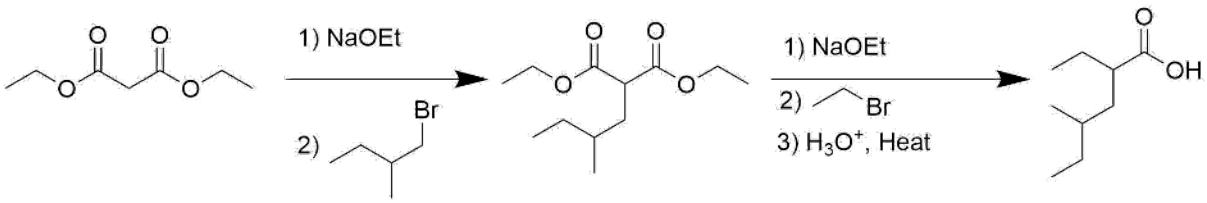
(b) 1) Malonic Ester, NaOEt, 2) 3-bromohexane, 3) Base, 4) Acid, Eat

(c) 1) Malonic Ester, NaOEt, 2) 1-Bromo-2,3,3-trimethylbutane, 3) Base, 4) Acid, Heat

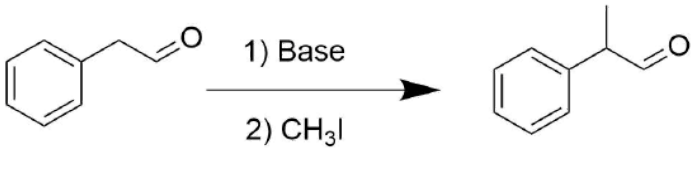
S22.7.2

Malonic esters only contain two acid protons.

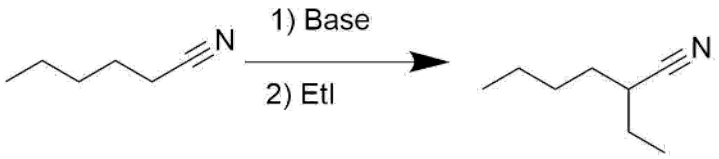
S22.7.3



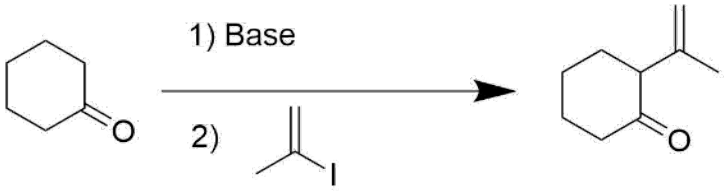
S22.7.4



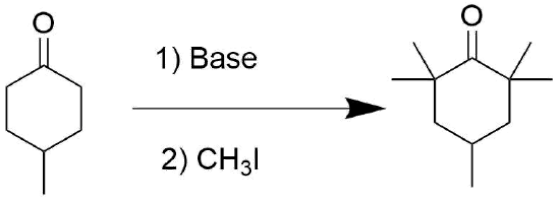
(a)



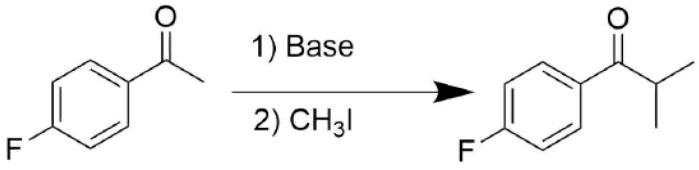
(b)



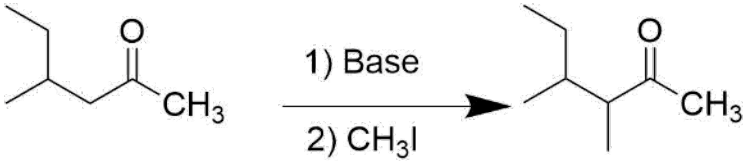
(c)



(d)



(e)



(f)

CONTRIBUTORS AND ATTRIBUTIONS

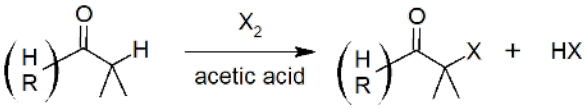
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

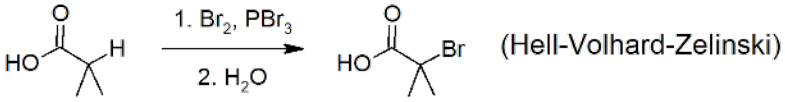
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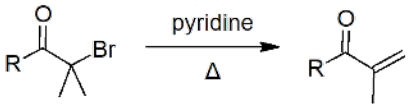
- **22.7: Alkylation of Enolate Ions** by Dietmar Kennepohl, Layne Morsch, Steven Farmer, William Reusch is licensed CC BY-SA 4.0.

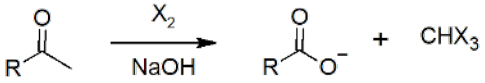
22.S: CARBONYL ALPHA-SUBSTITUTION REACTIONS (SUMMARY)

SUMMARY OF REACTIONS

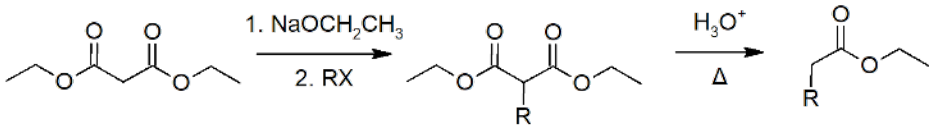


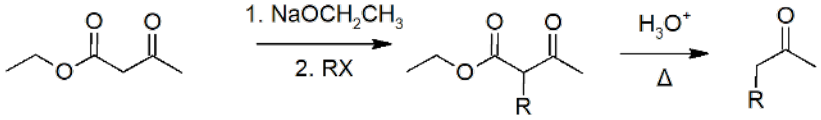


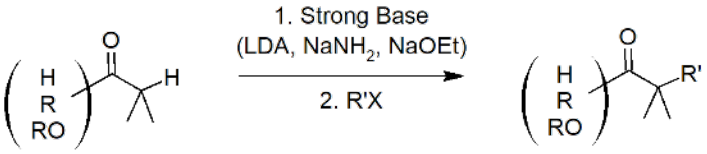




Alkylation







22.S: Carbonyl Alpha-Substitution Reactions (Summary) is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

CHAPTER OVERVIEW

CHAPTER 23: CARBONYL CONDENSATION REACTIONS

In this chapter, we consider the fourth and final general type of reaction that carbonyl compounds undergo—the carbonyl condensation reaction. Carbonyl condensation reactions take place between two carbonyl-containing reactants, one of which must possess an alpha-hydrogen atom. The first step of the reaction involves the removal of an alpha-hydrogen atom by a base. In the second step, the enolate anion that results from this removal attacks the carbonyl-carbon of the second reacting molecule. In the final step of the reaction, a proton is transferred to the tetrahedral intermediate formed in the second step, although in some cases the product that results may subsequently be dehydrated.

The importance of carbonyl condensation reactions to synthetic organic chemistry arises from the large number of combinations of carbonyl compounds that can be used in such reactions. Aldehydes or ketones can be used in a simple aldol condensation to produce β-hydroxy aldehydes, β-hydroxy ketones, or their dehydration products. Mixtures of aldehydes, ketones, or both, can be used in a mixed aldol condensation. Internal aldol condensations can occur in compounds containing two suitable carbonyl groups. Aldol-like condensations can be brought about between aldehydes and a variety of compounds containing acidic alpha-hydrogen atoms, including diethyl malonate, acetic anhydride, nitriles and nitro compounds. Esters can be used in Claisen condensations and 1,6- and 1,7-diesters can give rise to internal condensations, called Dieckmann cyclizations. Related reactions include the Michael reaction, in which an α,β-unsaturated carbonyl compound is reacted with an enolate anion; and the Stork enamine reaction, where an enamine adds to an α,β-unsaturated ketone.

The chapter concludes with a look at how condensation reactions can be used in the synthesis of complex ring-containing organic compounds, and at the role played by carbonyl condensation reactions in biological systems.

Chapter Objectives
23.1 Carbonyl Condensations - The Aldol Reaction
23.2 Carbonyl Condensations versus Alpha Substitutions
23.3 Dehydration of Aldol Products - Synthesis of Enones
23.4 Using Aldol Reactions in Synthesis
23.5 Mixed Aldol Reactions
23.6 Intramolecular Aldol Reactions
23.7 The Claisen Condensation Reaction
23.8 Mixed Claisen Condensations
23.9 Intramolecular Claisen Condensations - The Dieckmann Cyclization
23.10 Conjugate Carbonyl Additions - The Michael Reaction
23.11 Carbonyl Condensations with Enamines - The Stork Reaction
23.12 The Robinson Annulation Reaction
23.13 Some Biological Carbonyl Condensation Reactions
23.S: Carbonyl Condensation Reactions (Summary)

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CHAPTER OBJECTIVES

When you have completed Chapter 23, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design multi-step syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
3. solve road-map problems that require a knowledge of carbonyl condensation reactions.
4. define, and use in context, any of the key terms introduced.

CONTRIBUTORS AND ATTRIBUTIONS

Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

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23.1 CARBONYL CONDENSATIONS - THE ALDOL REACTION

Objectives

After completing this section, you should be able to

1. write a general mechanism for carbonyl condensation reactions.
2. write an equation to illustrate the aldol condensation reaction.
3. identify the product formed when an aldehyde or ketone having an alpha-hydrogen atom is treated with base in a protic medium.
4. identify the aldehyde or ketone, and other reagents required to produce a given β-hydroxy carbonyl compound by an aldol reaction.
5. determine whether a given aldehyde or ketone will undergo an aldol reaction.
6. write the detailed mechanism of the aldol reaction.

KEY TERMS

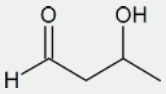
- aldol
- aldol reaction
- carbonyl condensation reaction (see Chapter 18 Affix)

STUDY NOTES

It is important that you understand the general mechanism of carbonyl condensation described in this section: once you grasp this mechanism, you will see that all the reactions that follow are very similar.

The aldol reaction is sometimes referred to as the aldol condensation. However, a condensation reaction is often regarded as a reaction in which two molecules join together with the elimination of a molecule of water (or some other compound of low molar mass). Thus, the aldol reaction described here is not a true condensation; the true aldol condensation is described later, in Section 23.3. It is perhaps unfortunate that the reactions discussed in this unit are all described as condensation reactions whether or not water is eliminated.

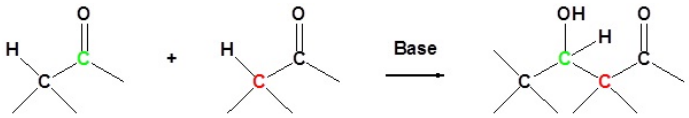
The term “aldol” (from "aldehyde alcohol") is used both to describe the specific compound 3-hydroxybutanal:



and to describe β-hydroxy aldehydes in general.

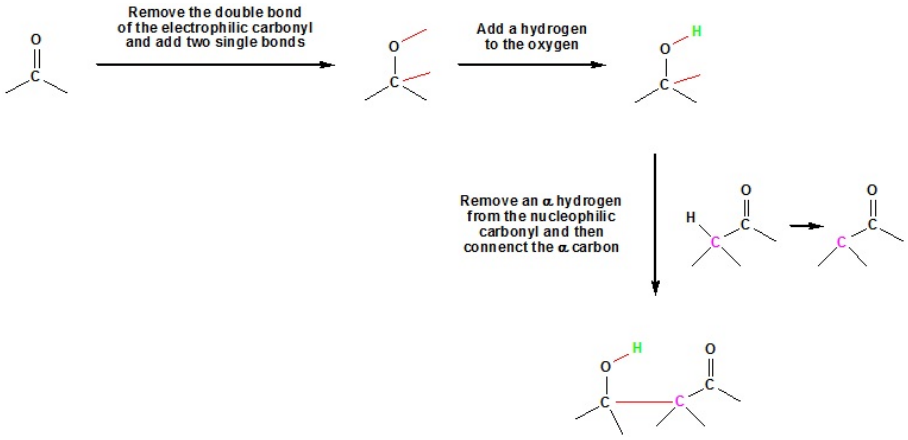
A useful carbon-carbon bond-forming reaction known as the **Aldol Reaction** is yet another example of electrophilic substitution at the alpha carbon in enolate anions. The fundamental transformation in this reaction is a dimerization of an aldehyde (or ketone) to a beta-hydroxy aldehyde (or ketone) 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 α hydrogens.

GENERAL ALDOL REACTION

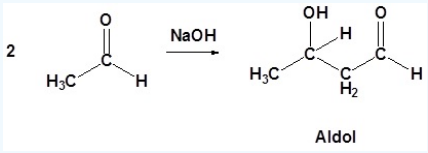


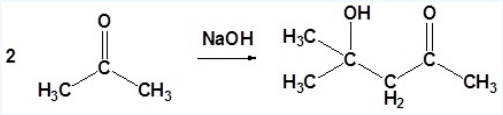
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GOING FROM REACTANTS TO PRODUCTS SIMPLY



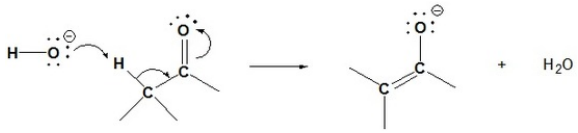
EXAMPLE 23.1.1: ALDOL REACTIONS



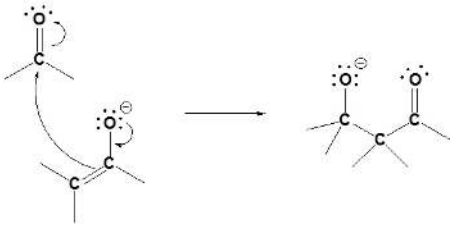


ALDOL REACTION MECHANISM

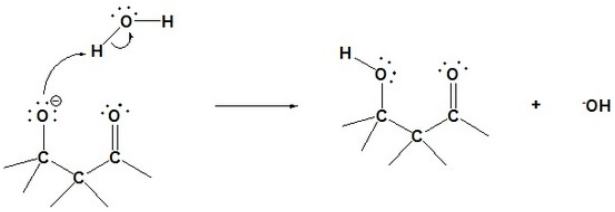
Step 1: Enolate formation



Step 2: Nucleophilic attack by the enolate

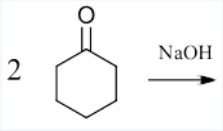


Step 3: Protonation



WORKED EXAMPLE

What would be the expect product of the following aldol reaction?

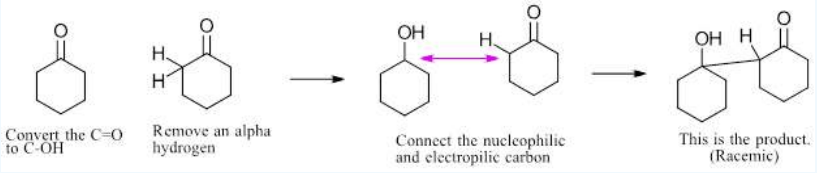


Answer

Analysis:

When considering the product of an aldol reaction it is vital to consider each reactant molecule separately. Also,

Identify electrophilic carbonyl carbon and any alpha hydrogens present.

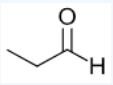


EXERCISES

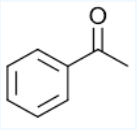
EXERCISE 23.1.1

Predict the product of an aldol reaction with the following molecules:

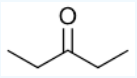
a)



b)

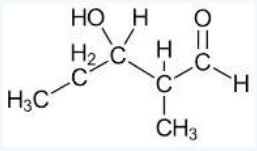


c)

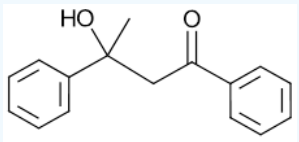


Answer

a)

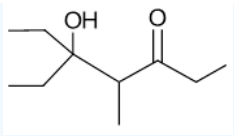


b)



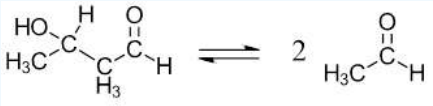
c)

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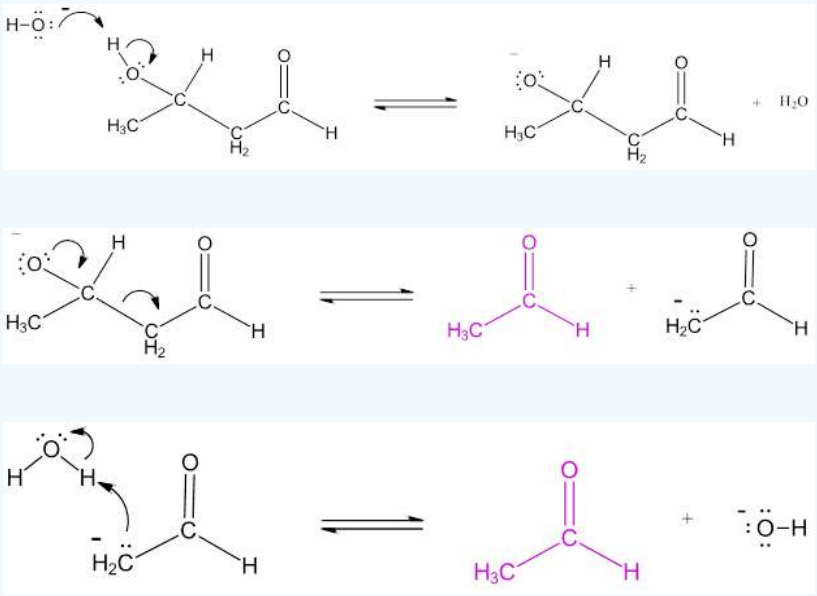


EXERCISE 23.1.2

Because the aldol reaction is reversible it is possible for a beta-hydroxy carbonyl compound to undergo a retro-aldol reaction. Please draw the mechanism or the based catalyzed retro-aldol reaction shown below.



Answer



CONTRIBUTORS AND ATTRIBUTIONS

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

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23.2 CARBONYL CONDENSATIONS VERSUS ALPHA SUBSTITUTIONS

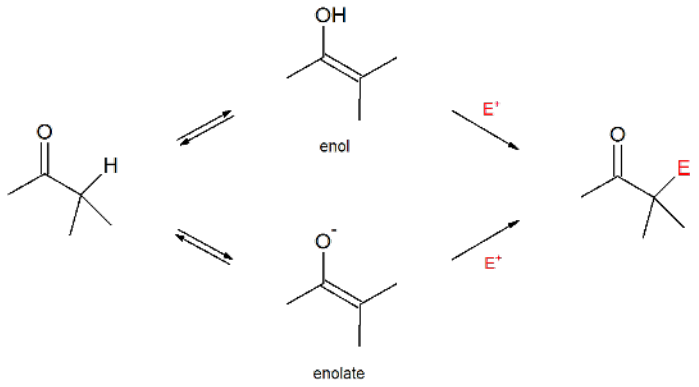
Objectives

After completing this section, you should be able to describe the difference between a carbonyl condensation reaction and an alpha-substitution reaction, and determine which of these two types of reaction is most likely to occur, given the appropriate experimental data.

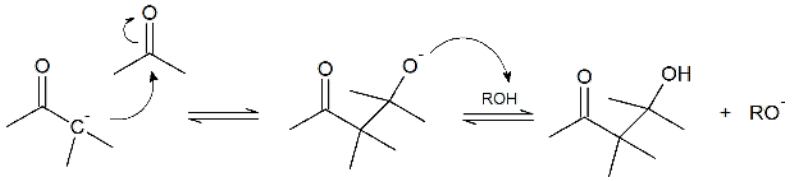
STUDY NOTES

So far we have discussed three of the four general reactions of carbonyl compounds: nucleophile additions of aldehydes and ketones (Chapter 19), nucleophilic acyl substitution reactions of carboxylic acid derivatives (Chapter 21) and alpha-substitution reactions (Chapter 22). The fourth general reaction, carbonyl condensation, is similar to the alpha-substitution reaction, so you need to appreciate how it differs from the other three and the conditions under which it occurs.

Carbonyl condensation reactions are a type of alpha-substitution reaction. Both occur through an enolate ion intermediate under basic conditions and involve substitution at the carbon alpha to the carbonyl group. However, in a carbonyl condensation reaction the electrophile (E^+) being attacked is another carbonyl compound.

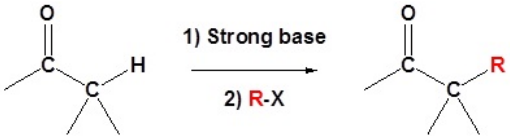


In a carbonyl condensation a catalytic amount of base is used to generate the enolate ion which attacks any unreacted carbonyl compound to form the carbon-carbon bond at the alpha site. The resulting alkoxide is then protonated, which regenerates the base that will produce more enolate ion in the next cycle.

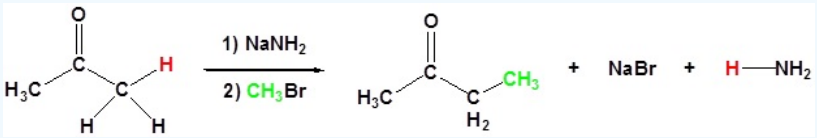


These steps are all reversible and it should be noted that reactants and products that are close in energy level can potentially undergo the reverse reaction if conditions change enough. While from a synthetic point of view in the laboratory this may mean increasing yields by driving the reaction to completion (e.g. adding heat, removing product), in biological systems it can have more drastic consequences. Indeed, depending on metabolic conditions, retro-aldol reactions (the reverse of aldol condensations, in which carbon-carbon bonds are broken) can occur.

In contrast, the alpha-substitution reaction is often more directional by design. To reduce unwanted competition from carbonyl condensation, the enolate ion intermediate is generated all at once with a full equivalent of strong base at low temperature. The reactive enolate intermediate generated is then quenched with rapid addition of the electrophile to complete the substitution. In Section 22.7, under direct alkylation, the use of strong bases like $NaNH_2$ and LDA to generate the enolate intermediate followed by addition of an alkylhalide was discussed.



EXAMPLE 22.7.1: ALPHA ALKYLATION



CONTRIBUTORS AND ATTRIBUTIONS

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

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23.3 DEHYDRATION OF ALDOL PRODUCTS - SYNTHESIS OF ENONES

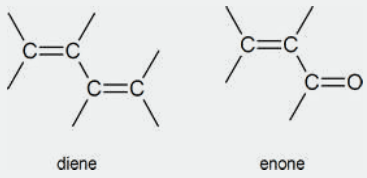
Objectives

After completing this section, you should be able to

1. write an equation to illustrate the formation of a conjugated enone from a β-hydroxy aldehyde or ketone.
2. write a detailed mechanism for the basic or acidic elimination of water from a β-hydroxy aldehyde or ketone.
3. explain why β-hydroxy aldehydes and ketones undergo elimination reactions much more readily than most other alcohols.
4. identify the enone products from the aldol condensation of a given aldehyde or ketone.

STUDY NOTES

Conjugated enones, like conjugated dienes, have more inherent stability compared with their non-conjugated counterparts. You may wish to review Section 14.1 on dienes, which gives a molecular orbital description showing π electron distribution over four atomic centres.



Note that both of the elimination mechanisms described here (acidic and basic) involve either the enol form or the enolate anion of the β-hydroxy carbonyl compound.

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:

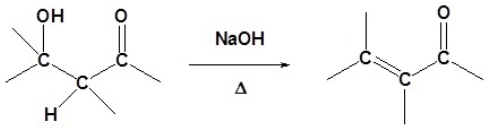


***Figure**: General reaction for an aldol condensation*

Going from reactants to products simply

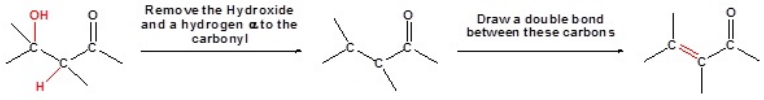
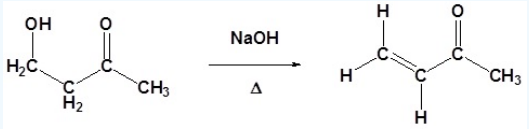


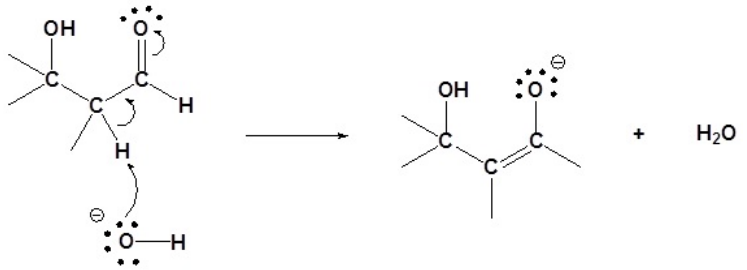
***Figure**: The aldol condensation* example

EXAMPLE 23.3.2: ALDOL CONDENSATION

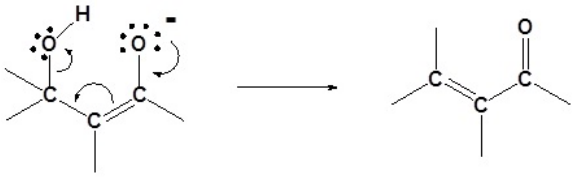


ALDOL CONDENSATION BASE CATALYZED MECHANISM

1) Form enolate

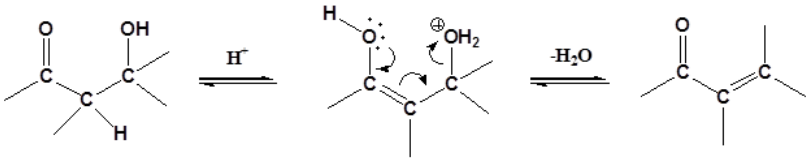


2) Form enone



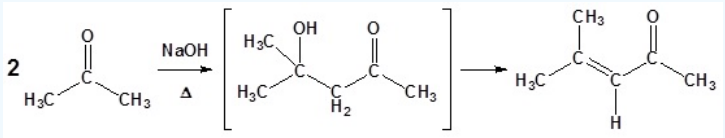
ALDOL CONDENSATION ACID CATALYZED MECHANISM

Under Acidic conditions an enol is formed and the hydroxy group is protonated. Water is expelled by either and E1 or E2 reaction.



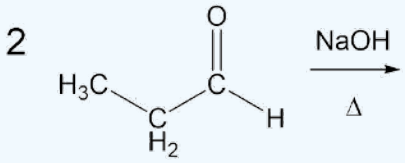
When performing both reactions together always consider the aldol product first then convert to the enone. Note! The double bond always forms in conjugation with the carbonyl.

EXAMPLE 23.3.3



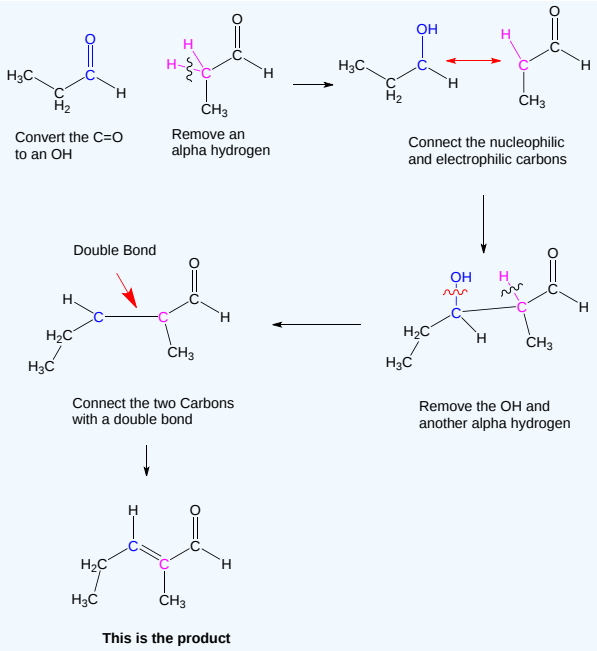
WORKED EXAMPLE

Draw the product of an aldol condensation with the following molecule:



Answer

The overall reaction is a combination of two major steps, an aldol reaction followed by a dehydration to form the enone. In this situation it is best to consider the aldol product first (as discussed in Section 23.3, then convert it to the enone. Note! The double bond always forms in conjugation with the carbonyl.



CONTRIBUTORS AND ATTRIBUTIONS

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

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23.4 USING ALDOL REACTIONS IN SYNTHESIS

Objectives

After completing this section, you should be able to identify the aldehyde or ketone and other necessary reagents that should be used to prepare a given enone by an aldol condensation.

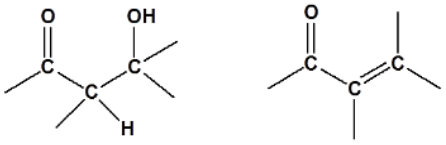
STUDY NOTES

This section stresses the importance of being able to think logically.

The experience that you have already gained through designing multi-step syntheses and solving road-map problems should help you to recognize when an aldol reaction may have been one of the steps in the synthesis of a given compound.

It is important that you recognize that the aldol condensation is an important part of a synthetic chemist's repertoire, both because it involves the formation of a new carbon-carbon bond, and also because it yields a product containing two functional groups.

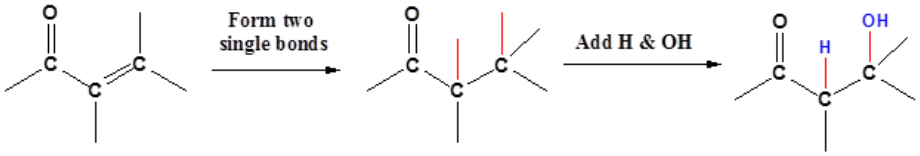
Aldol reactions are excellent methods for the synthesis of many enones or beta hydroxy carbonyls. Because of this, being able to predict when an aldol reaction might be used in a synthesis in an important skill. This accomplished by mentally breaking apart the target molecule and then considering what the starting materials might be.



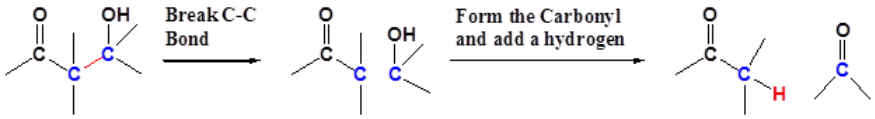
Fragments which are easily made by an aldol reaction

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.

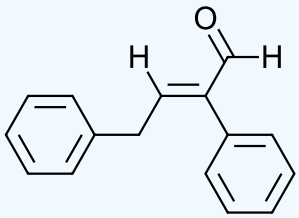


2) From the aldol product break the C-C bond between the alpha carbon and the carbon attached to the OH. Then turn the OH into a carbonyl and add an hydrogen to the other carbon.



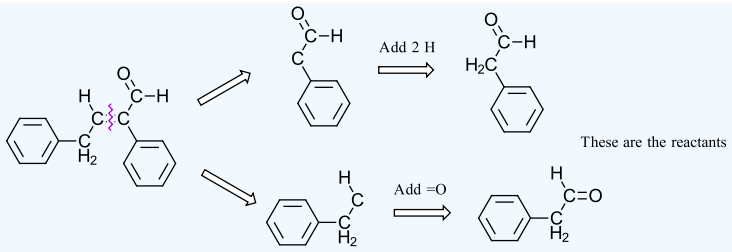
Worked Example 23.4.1

Show how the following molecule could be made using an aldol condensation?

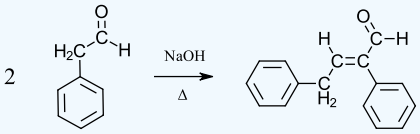


Answer

Analysis: The C=C bond in the target molecule is cleaved to form two fragments. The fragment with the carbonyl gains two alpha hydrogens. The other fragment gains a =O to form a carbonyl. Both fragments end up producing the same reactant which is typical for an aldol condensation.



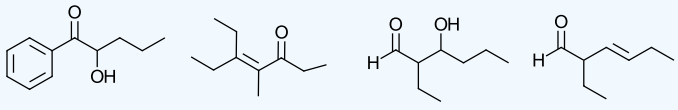
Solution



EXERCISES

EXERCISE 23.4.1

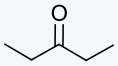
Which of the following molecules could be made using an aldol reaction or condensation. Please show the starting material for the reactions that are possible.



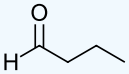
Answer

Molecules B and C are possible.

Solution for molecule B



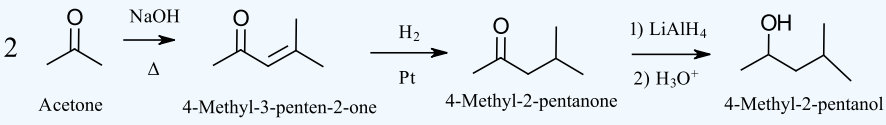
Solution for molecule C



EXERCISE 23.4.2

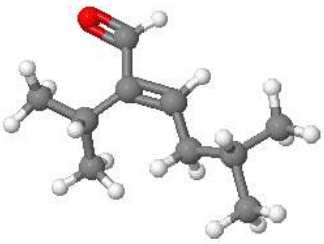
Please show the reaction steps required to make 4-methyl-2-pentanol from an aldol condensation.

Answer

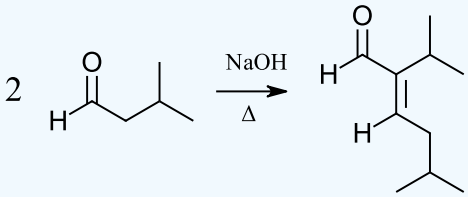


EXERCISE 23.4.3

Please design a synthesis for the following molecule: Red = Oxygen, Grey = Carbon, White = Hydrogen



Answer



CONTRIBUTORS AND ATTRIBUTIONS

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

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23.5 MIXED ALDOL REACTIONS

Objectives

After completing this section, you should be able to

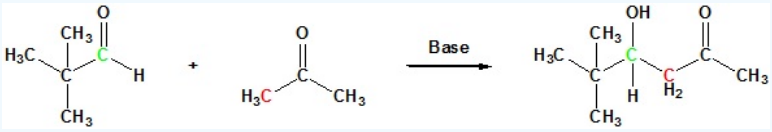
1. write an equation to illustrate a mixed aldol reaction.
2. identify the structural features necessary to ensure that two carbonyl compounds will react together in a mixed aldol reaction to give a single product rather than a mixture of products.
3. determine whether a given mixed aldol reaction is likely to produce a single product or a mixture of products.
4. identify the product or products formed in a given mixed aldol reaction.
5. identify the carbonyl compounds needed to produce a given enone or β-hydroxy aldehyde or ketone by a mixed aldol reaction.

STUDY NOTES

You should satisfy yourself that you understand how the four products shown in Example 23.5.2 arise from the condensation of 2-propanone and 2-phenylacetaldehyde.

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 23.5.1: MIXED ALDOL REACTION (ONE PRODUCT)

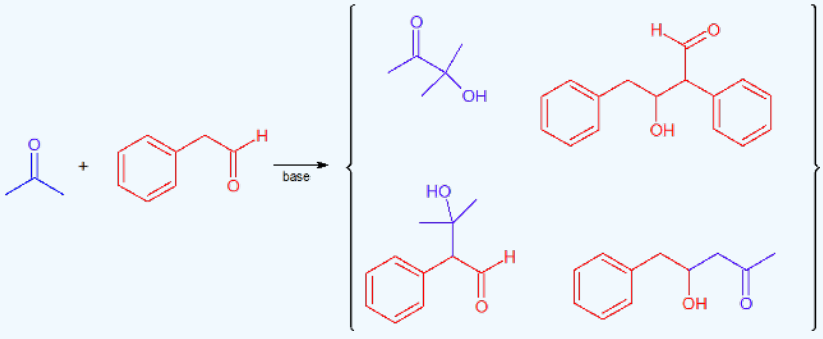


The success of these mixed aldol reactions is due to two factors. First, aldehydes are more reactive acceptor electrophiles than ketones, and formaldehyde is more reactive than other aldehydes. Second, aldehydes lacking alpha-hydrogens can only function as acceptor reactants, and this reduces the number 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 23.5.2: PRODUCTS OF A MIXED ALDOL REACTION



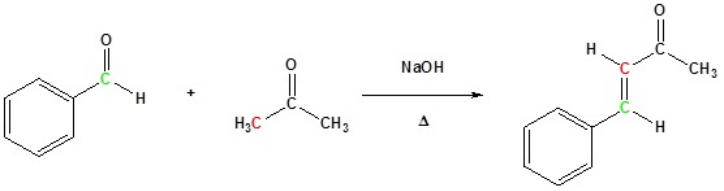
To avoid complex reaction mixtures the reactants should be chosen to favor one particular donor/acceptor reaction. Successful mixed aldol reactions usually use one of two combination of factors.

1) A reaction of an aldehyde with no alpha-hydrogens with a ketone that has alpha hydrogens: Aldehydes lacking alpha-hydrogens cannot form an enolate so they can only function as electrophilic acceptor reactants. This reduces the number of possible products by half. Although it would be possible for the ketone to react with itself it is unlikely. Aldehydes are more reactive acceptor electrophiles than ketones. This makes the preferred reaction one with the ketone as an enoloate donor and the aldehyde as an electrophilic acceptor.

The aldol condensation between an aromatic aldehyde with no α-hydrogens and an aliphatic aldehyde or ketone with α-hydrogen is called a **Claisen–Schmidt condensation**. The reaction product is a highly conjugated α,β-unsaturated aldehyde or ketone which forms in the more stable (E)-alkene isomer.

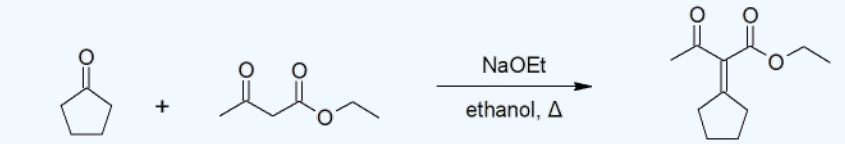
The aldol condensation of ketones with aryl aldehydes to form α,β-unsaturated derivatives is called the **Claisen-Schmidt** reaction.

EXAMPLE 23.5.3: CLAISEN-SCHMIDT REACTION



2) One of the reactants has alpha-hydrogens which are highly acidic: The acidic compound will be preferably converted into an enolate donor which removes the possibility of its carbonyl acting as an electrophilic acceptor. An example is the aldol condensation of ethylacetoacetate and cyclopentanone. Ethylacetoacetate has α-hydrogens which are particularly acidic due to their conjugate base being stabilized by two carbonyl bonds (**Section 22.5**). Upon reaction with base, ethylacetoacetate is converted to the enolate donor leaving cyclopentanone to be the electrophilic acceptor. This provides one predominant aldol condensation product. In this reaction sodium ethoxide is used as a base to prevent hydrolysis side-reactions with the ester of ethylacetoacetate.

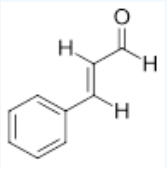
EXAMPLE 23.5.4



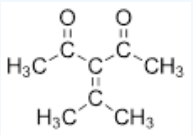
EXERCISE 23.5.1

Show the reactants required to make the following using a mixed aldol condensation. Indicate those which would be likely to produce a mixture of products.

a)

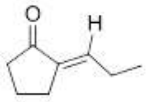


b)



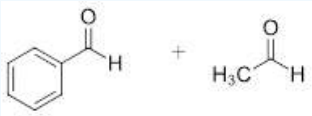
c)

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Answers

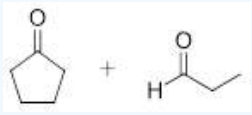
a)



b)



c) Because both reactants have α-hydrogens and neither are particularly acidic, the reaction probably will produce a mixture of condensation products.



CONTRIBUTORS AND ATTRIBUTIONS

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

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23.6 INTRAMOLECULAR ALDOL REACTIONS

Objectives

After completing this section, you should be able to

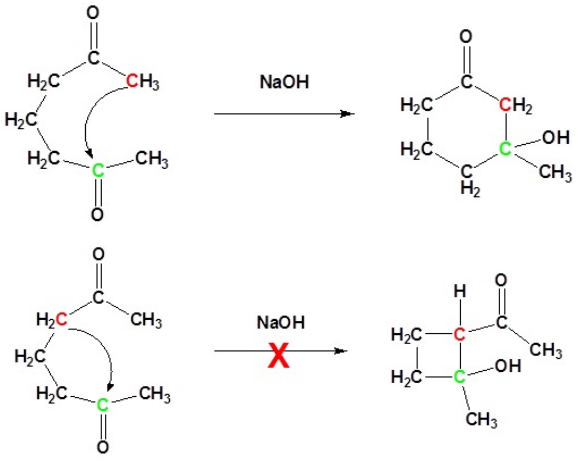
1. write an equation to illustrate an intramolecular aldol reaction.
2. identify the product formed when a given dicarbonyl compound undergoes an intramolecular aldol condensation.
3. identify the dicarbonyl compound which, when treated with a suitable base, could be used to prepare a given cyclic enone by an intramolecular aldol condensation.

STUDY NOTES

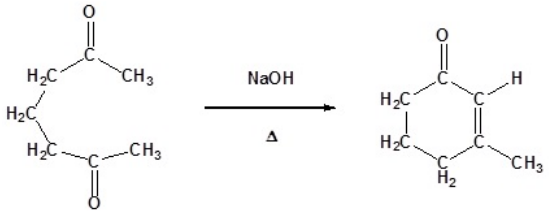
"Intramolecular " means "within the same molecule." You have already seen some examples of intramolecular reactions in previous chapters. Another term for intramolecular aldol reaction is "internal aldol reaction."

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).

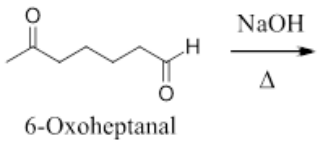


As with other aldol reaction the addition of heat causes an aldol condensation to occur.



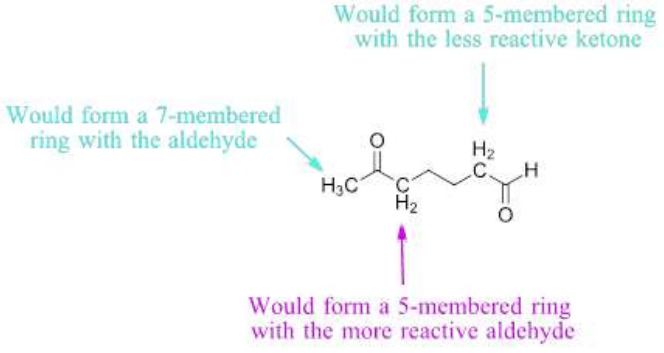
WORKED EXAMPLE 23.6.1

Please draw the expected product of an intramolecular aldol condensation with the following molecule:

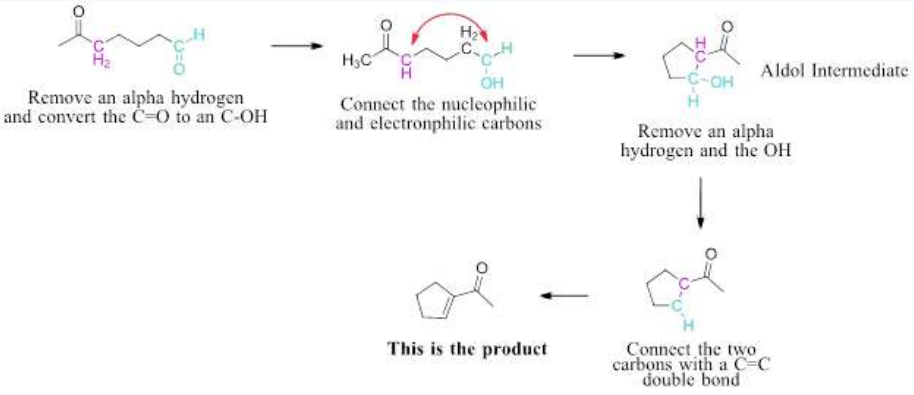


Answer

Analysis: 6-Oxoheptanal has three unique sets of alpha-hydrogens which could be deprotonated to form an enolate. Selecting the correct set involves analyzing the carbonyl reactivity's along with the possible ring sizes of the products.



Solution: Once the preferred alpha-hydrogens are determined go through the steps discussed in the previous sections to determine the aldol condensation product. Remember to form the aldol intermediate first.



EXERCISES

? EXERCISE 23.6.1

Briefly explain why the molecule, 2,4-pentanedione, when reacted with a base would mostly likely not produce an intramolecular aldol condensation product.

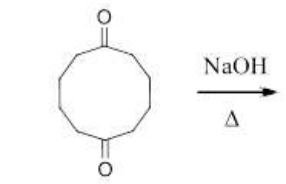
Answer

2,4-Pentanedione like other 1,3-Diketones have particularly acidic alpha-hydrogens between the two carbonyl. When base is applied these will be the first to deprotonate and form an enolate. For an intramolecular aldol condensation to occur an alpha-hydrogen one of the methyl groups would have to be removed which would be difficult.



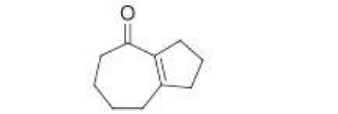
? EXERCISE 23.6.2

Draw the product of the following aldol condensation:



1,6-Cyclodecanedione

Answer


Bicyclo[5.3.0]dec-1(7)-en-2-one

CONTRIBUTORS AND ATTRIBUTIONS

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

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23.7 THE CLAISEN CONDENSATION REACTION

Objectives

After completing this section, you should be able to

1. write an equation to illustrate a Claisen condensation reaction.
2. write a detailed mechanism for a Claisen condensation reaction or its reverse.
3. identify the product formed in a given Claisen condensation reaction.
4. identify the ester and other reagents needed to form a given β-keto ester by a Claisen condensation reaction.

KEY TERMS

- Claisen condensation reaction

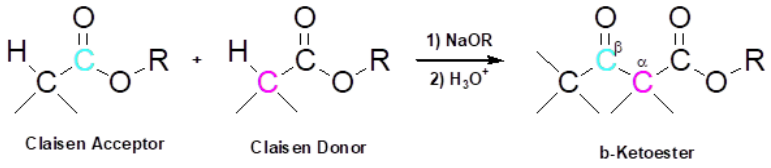
STUDY NOTES

You have already seen that ethyl acetoacetate-type compounds are very useful in organic syntheses. Any reaction which results in the formation of these compounds will also be of importance. In the next section, you will see how the range of β-keto esters that can be prepared by this method is extended through the use of two different esters as starting materials.

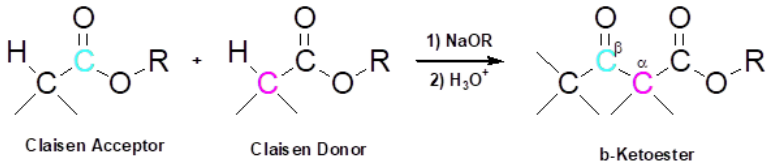
CLAISEN CONDENSATION

Because esters commonly contain both α-hydrogens and a carbonyl bond, they can undergo a reversible condensation similar to the aldol reaction called a Claisen Condensation. In a fashion similar to the aldol reaction, one ester acts as a Claisen enolate donor (nucleophile) while a second ester acts as the Claisen acceptor (electrophile). During the reaction a new carbon-carbon is formed to produce a β-keto ester product. This reaction is considered a condensation because it eliminates a small alcohol as an unwanted side-product.

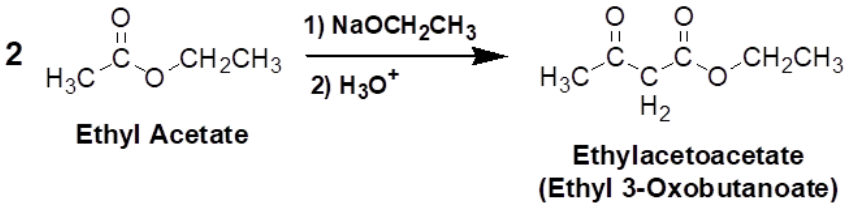
GENERAL REACTION



PREDICTING THE PRODUCT OF A CLAISEN CONDENSATION



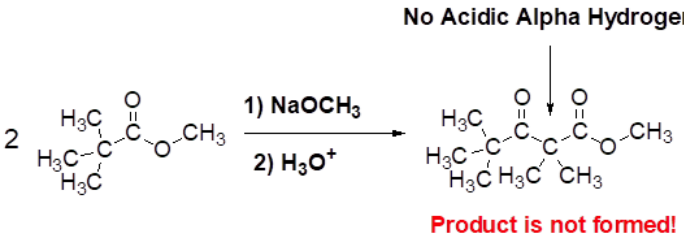
EXAMPLE



Although they may appear similar, there are a number of fundamental differences between an aldol and Claisen condensation. During the mechanism of the reaction, the formed tetrahedral alkoxide intermediate is not protonated to from an “aldol” type product. Rather, the alkoxide intermediate will reform the C=O carbonyl bond and eliminate a (-OR) leaving group to produce a nucleophilic acyl substitution product.

Claisen condensations cannot use a hydroxide for the reaction base due to the possibility of ester hydrolysis. Also, to prevent transesterification side products, the alkoxide base typically has the same alkyl group as alkoxy group present in the ester starting material.

Lastly, the β-keto ester products of Claisen condensation can be acidic enough to be deprotonated by the reaction's base during the final steps of the mechanism. This means the base is not catalytically regenerated during the reaction and a full equivalent of base is required. The β-keto ester condensation products are removed from the equilibrium by this deprotonation, which causes the reaction to be driven forward by Le Chatelier's principle. This concept is so important that a Claisen product will not form unless it contains an alpha hydrogen acidic enough to react completely with the reaction base. This requires that the ester starting materials have at least two alpha-hydrogens for a Claisen condensation product to form. One is removed to form an ester enolate and the second is removed to drive the reaction forward.

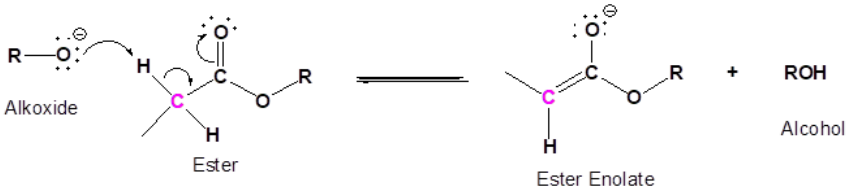


MECHANISM

The Claisen condensation mechanism is analogous to the ester saponification reaction seen in *Section 21.6*.

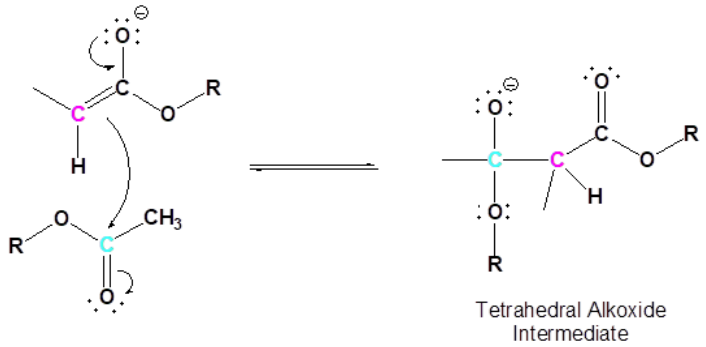
1) ENOLATE FORMATION

The mechanism starts with the alkoxide base removing an alpha-hydrogen from the ester to form a nucleophilic ester enolate ion.



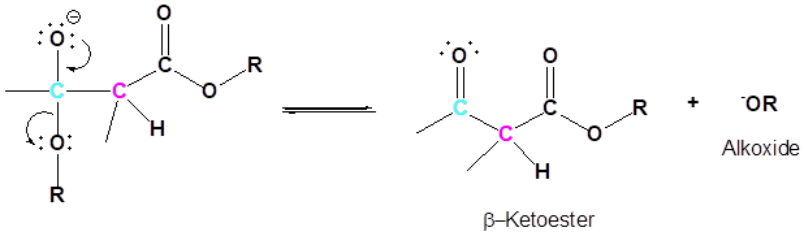
2) NUCLEOPHILIC ATTACK

The enolate nucleophile adds to carbonyl carbon of a different ester, forming a tetrahedral alkoxide intermediate.



3) REMOVAL OF LEAVING GROUP

The alkoxide then reforms the carbonyl, eliminating the –OR leaving group to form a beta-ketoester.

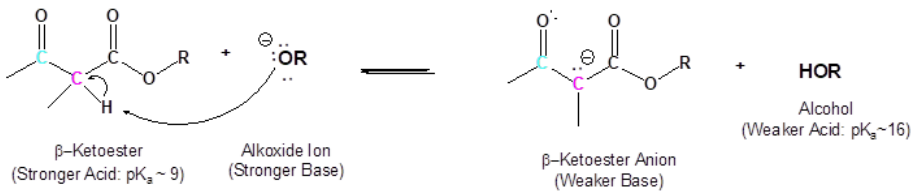


4) DEPROTONATION

The acidity of beta-ketoesters (pK_a ~9) is high enough to allow them to be completely deprotonated by alkoxide bases (pK_a of an alcohol ~16) to form a second enolate. This make the equilibrium of this step very favorable, which is enough to drive the whole reaction towards

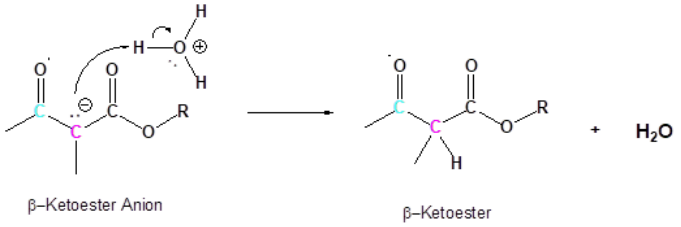
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the product.



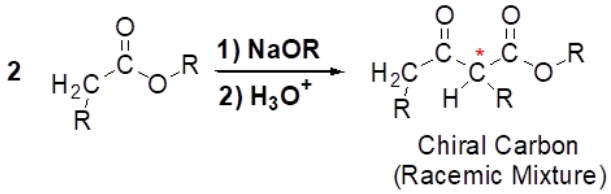
5) PROTONATION

The enolate is protonated in an acid work-up to form the neutral beta-ketoester product.



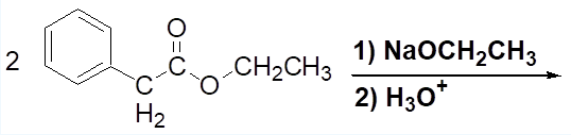
Stereochemical Considerations

The alpha-carbon gains a substituent during the reaction which means it will most likely form a chiral carbon. The fact that the alpha-carbon is temporarily converted to an enolate in the last step of the mechanism means that a racemic mixture of enantiomers will form.



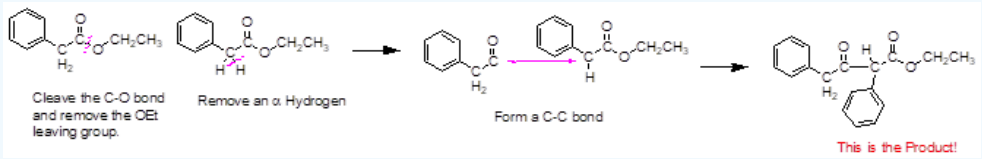
? WORKED EXAMPLE 23.7.1

Draw the products of the following reaction:



Answer

Analysis: Remember to consider each start ester separately.

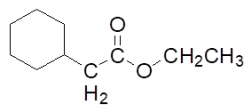


EXERCISES

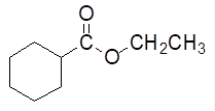
? EXERCISE 23.7.1

Please draw the products if the following molecules were to undergo a Claisen condensation.

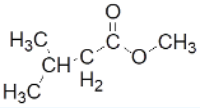
a)



b)

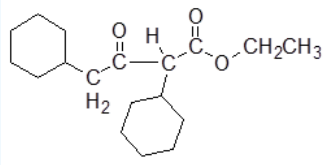


c)

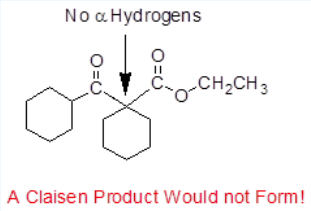


Answer

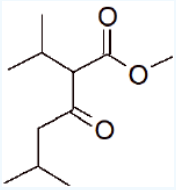
a)



b)

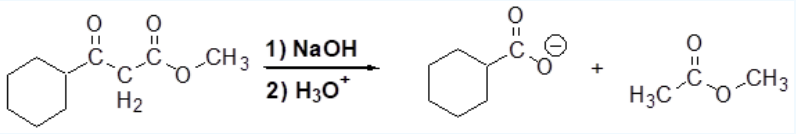


c)



EXERCISE 23.7.2

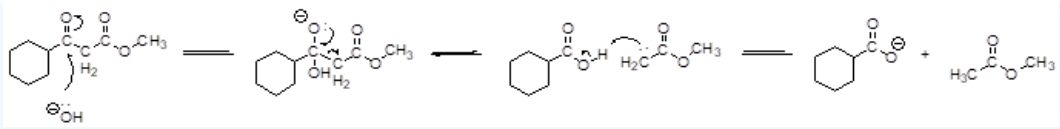
The beta-keto ester product of a claisen condensation can under hydrolysis with Sodium Hydroxide as shown in the reaction below. Please draw a curved arrow mechanism to explain how the products are formed. Also, explain why the ketone functional group preferably reacts with hydroxide instead of the ester.



Answer

The carbonyl of the ketone is more likely to be attacked by the hydroxide nucleophile because is more reactive than the ester's.

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CONTRIBUTORS AND ATTRIBUTIONS

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

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23.8 MIXED CLAISEN CONDENSATIONS

Objectives

After completing this section, you should be able to

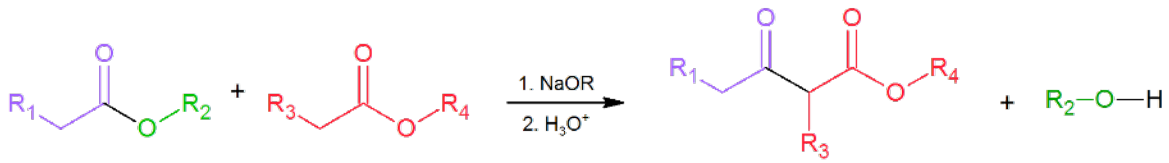
1. write an equation to illustrate a mixed Claisen condensation.
2. identify the structural features that should be present in the two esters if a mixed Claisen condensation is to be successful.
3. determine whether a given pair of esters is likely to produce a good yield of a single product when subjected to a mixed Claisen condensation.
4. identify the product formed when a given pair of esters is used in a mixed Claisen condensation.
5. identify the esters that should be used to produce a given β-keto ester by a mixed Claisen condensation.
6. write an equation to illustrate the formation of a β-diketone through a mixed Claisen-type condensation between an ester and a ketone.
7. identify the β-diketone formed as the result of a mixed Claisen-type condensation between a given ester and a given ketone.
8. identify the reagents necessary to synthesize a given β-diketone by a mixed Claisen-type condensation between an ester and a ketone.
9. write detailed mechanisms for mixed Claisen reactions and reactions that are related to the mixed Claisen reaction, including those in which both reacting moieties are present in the same compound.

STUDY NOTES

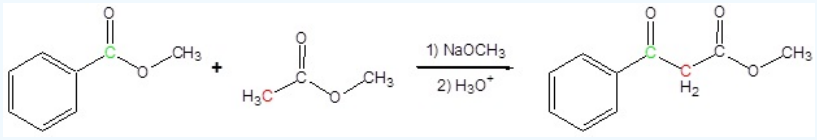
Just as we can react together two different aldehydes or ketones in a mixed aldol condensation, so can we react together two different esters in a mixed (or "crossed") Claisen condensation. Again, by carefully selecting our substrates we can obtain a good yield of the desired product and minimize the number of possible by-products. Note that even if we replace one of the esters with a ketone, the reaction is still referred to as Claisen condensation. The important thing to realize as you study these reactions is that they all take place by essentially the same mechanism—attack by an enolate anion on a carbonyl 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.

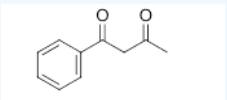


EXAMPLE 23.8.1: CROSSED CLAISEN CONDENSATION



WORKED EXAMPLE 23.8.1

Show how the following molecule can be made using a Claisen-like condensation.

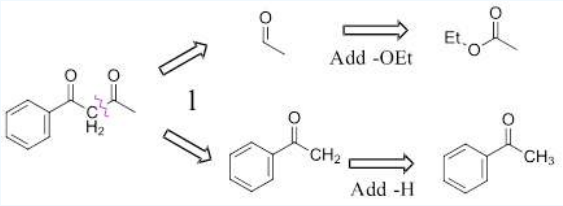


1-Phenyl-1,3-butanedione

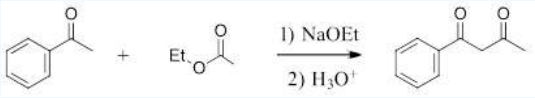
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Answer

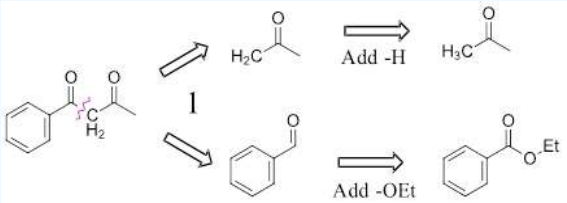
Pathway 1



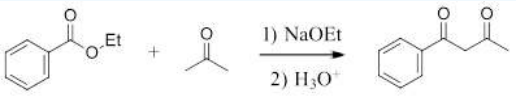
Solution 1



Pathway 2



Solution 2

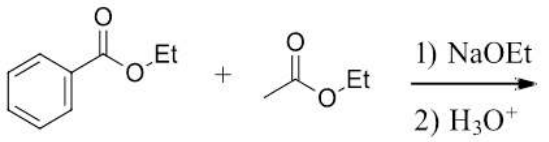


EXERCISE

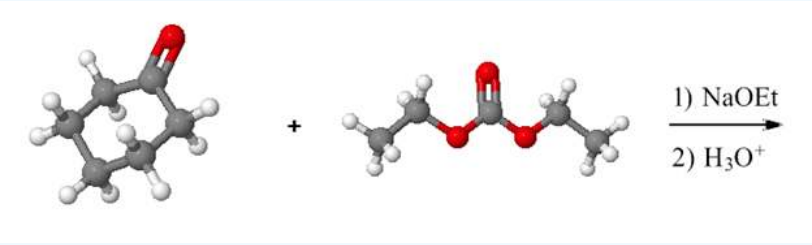
? EXERCISE 23.8.1

Draw the product of the following reactions:

a)

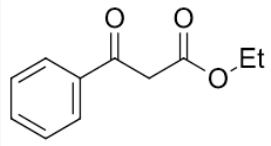


b)

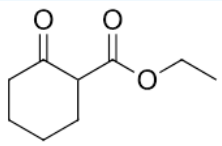


Answers

a)



b)



CONTRIBUTORS AND ATTRIBUTIONS

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

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23.9 INTRAMOLECULAR CLAISEN CONDENSATIONS - THE DIECKMANN CYCLIZATION

Objectives

After completing this section, you should be able to

1. write an equation to illustrate an internal Claisen condensation, that is, a Dieckmann cyclization.
2. identify the product formed when a 1,6- or 1,7-diester undergoes an internal Claisen condensation.
3. identify the diester needed to prepare a given cyclic β-keto ester by an internal Claisen condensation.
4. identify the structural features present in a diester that lead to the formation of more than one product in an internal Claisen condensation.

KEY TERMS

- Dieckmann cyclization

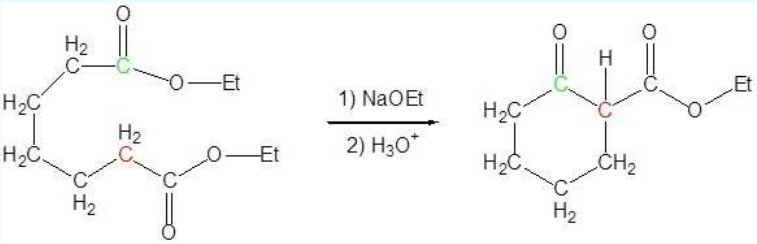
STUDY NOTES

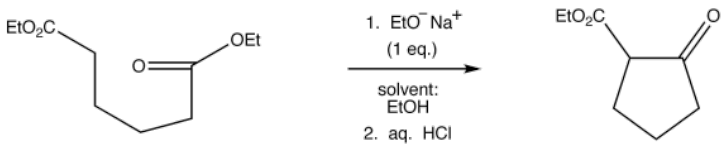
Essentially no new material is introduced in this section; Dieckmann cyclizations are intramolecular Claisen condensations. These reactions occur for 1,6- and 1,7-diesters, as these substances result in the formation of compounds containing five- and six-membered rings, respectively. You may recall that the formation of such ring systems is favoured because they are relatively free of strain.

DIECKMANN CONDENSATION

A diester can undergo an intramolecular reaction called a Dieckmann condensation.

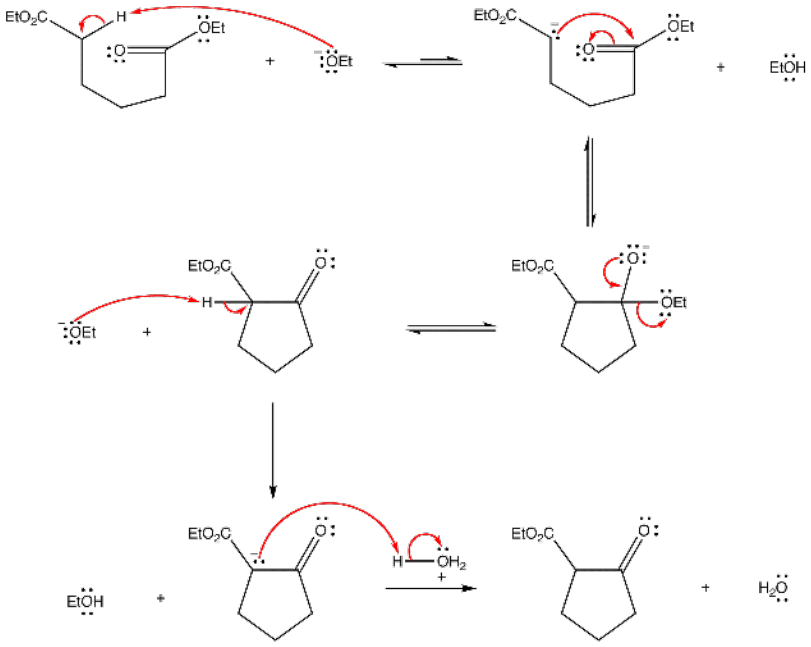
EXAMPLE 23.9.1: DIECKMAN CONDENSATION





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MECHANISM

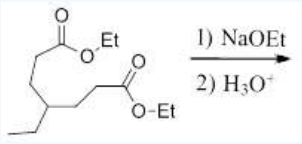


1. Dieckmann, W. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 102–103.

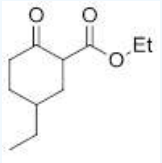
EXERCISES

EXERCISE 23.9.1

Draw the expected product for the following reaction:

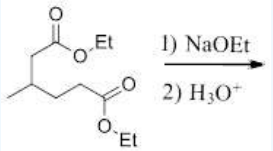


Answer

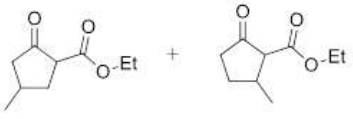


EXERCISE 23.9.2

The Dieckmann cyclization of the following molecule is expected to give a mixture of two cyclized products. Draw the structure of the two products and briefly explain why a mixture is formed.



Answer



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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23.10 CONJUGATE CARBONYL ADDITIONS - THE MICHAEL REACTION

Objectives

After completing thissection, you should be able to

1. write an equation to illustrate the Michael reaction.
2. write a detailed mechanism for a given typical Michael reaction.
3. identify the product formed in a given Michael reaction.
4. identify the reagents necessary to synthesize a given compound by a Michael reaction.

KEY TERMS

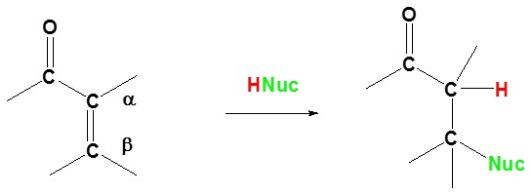
- Michael reaction

STUDY NOTES

Before studying this section in detail, you should review conjugate addition to *α,β*-unsaturated carbonyl compounds (Section 19.13).

Notice the wide variety of compounds that can take part in a Michael reaction. As usual, you should not feel overwhelmed by the number of different compounds that can be used, just keep in mind that in all cases the mechanism is essentially the same.

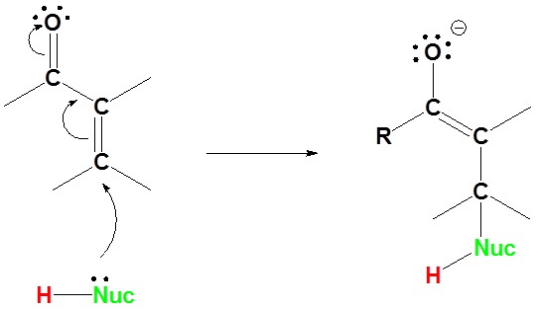
BASIC REACTION OF 1,4 ADDITION



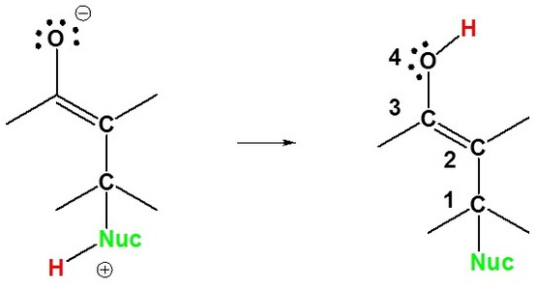
In 1,4 addition the Nucleophile is added to the carbon β to the carbonyl while the hydrogen is added to the carbon α to the carbonyl.

MECHANISM FOR 1,4 ADDITION EDIT SECTION

1) Nucleophilic attack on the carbon β to the carbonyl

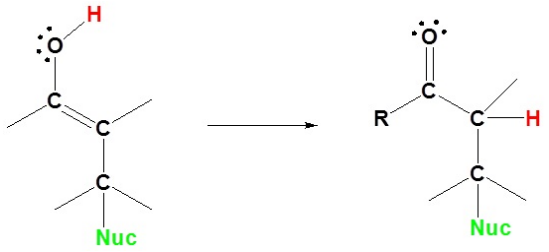


2) Proton Transfer



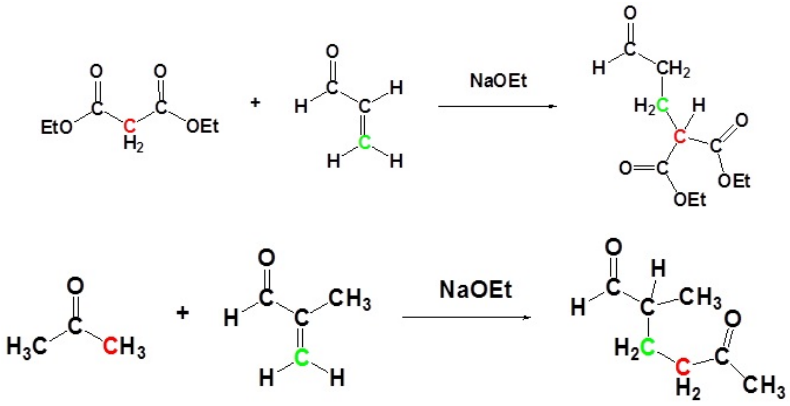
Here we can see why this addition is called 1,4. The nucleophile bonds to the carbon in the one position and the hydrogen adds to the oxygen in the four position.

3) Tautomerization

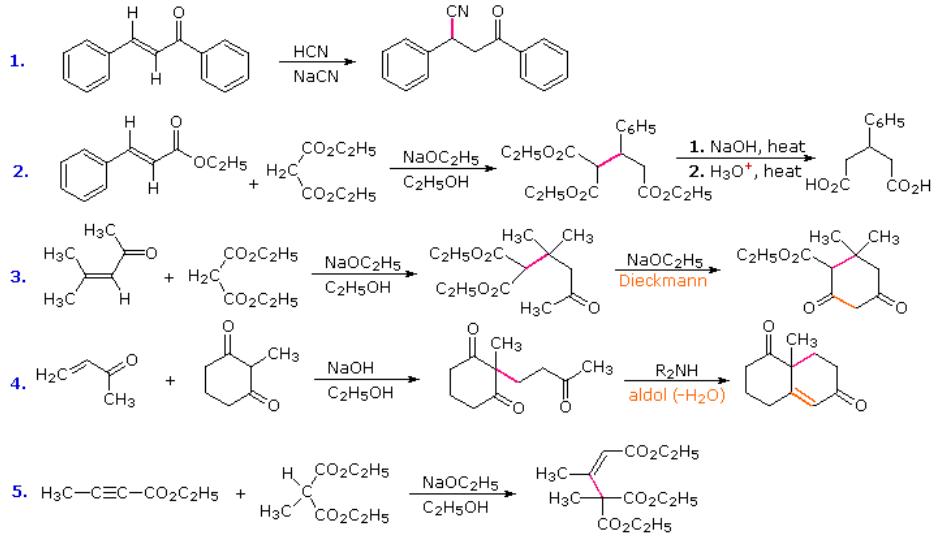


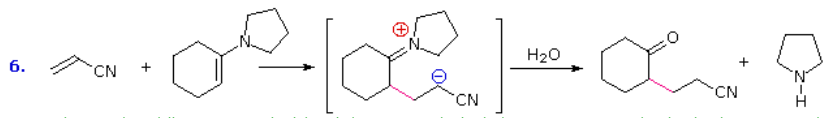
Enolates undergo 1,4 addition to α, β-unsaturated carbonyl compounds is a process called a Michael addition. The reaction is named after American chemist Arthur Michael (1853-1942).

EXAMPLES OF MICHAEL ADDITIONS

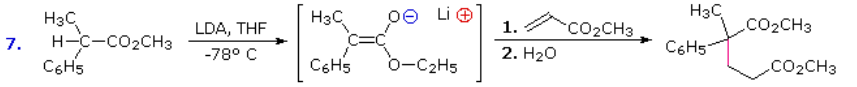


In combination with alkylations and condensations, the Michael reaction may be used to construct a wide variety of complex molecules from relatively simple starting materials. The carbon nucleophiles used in the following examples include cyanide ion, sodium diethylmalonate and the conjugate base of cyclohexane-1,3-dione. 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.

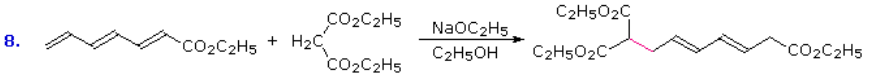




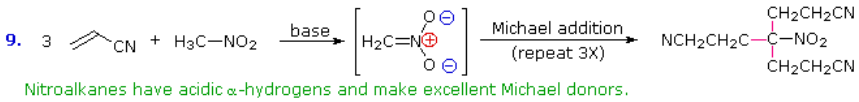
Enamine nucleophiles are good Michael donors. Hydrolysis is necessary to obtain the ketone product.



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).

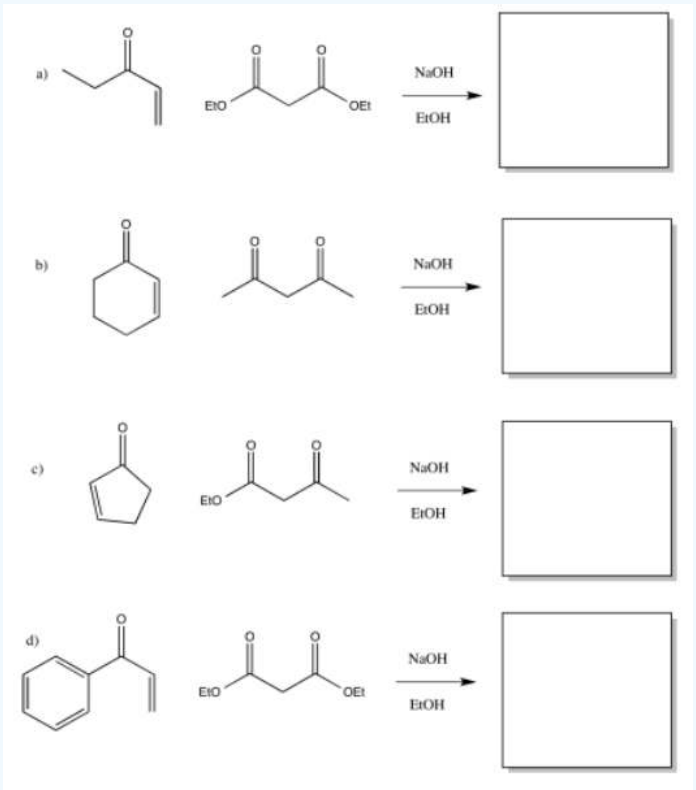


Nitroalkanes have acidic α-hydrogens and make excellent Michael donors.

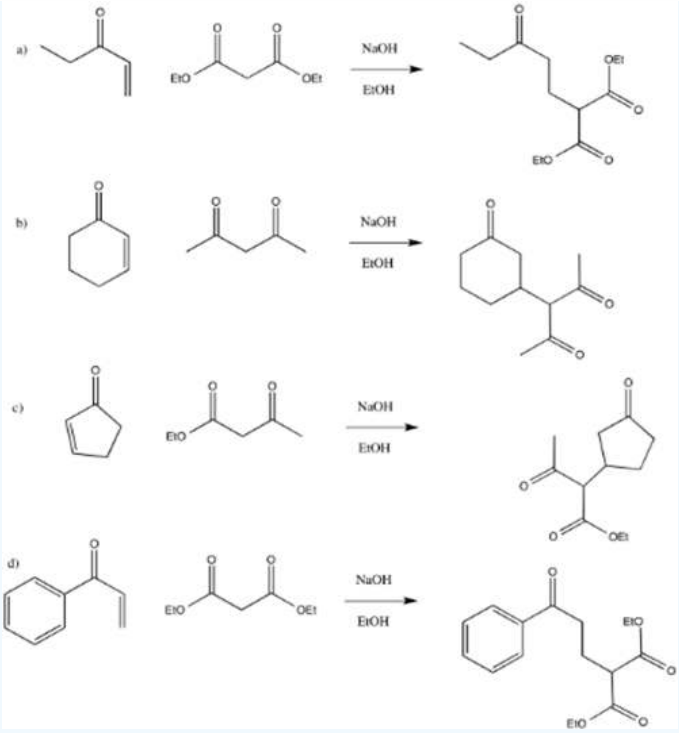
EXERCISES

? EXERCISE 23.10.1

Provide the products of the following Michael additions:

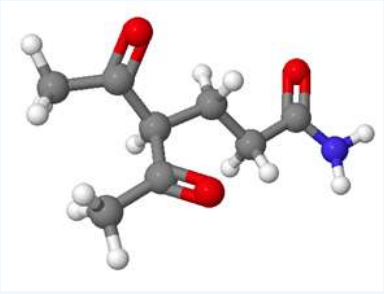


Answer

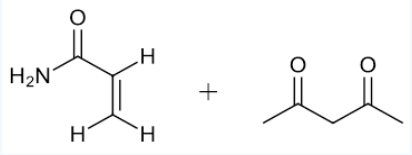


? EXERCISE 23.10.2

What would be the starting materials required to make the following molecule using a Michael reaction? Red = Oxygen, Grey = Carbon, White = Hydrogen, Blue = Nitrogen.



Answer



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 CARBONYL CONDENSATIONS WITH ENAMINES - THE STORK REACTION

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the three-step Stork enamine reaction.
2. write a detailed mechanism for each of the three steps of the Stork enamine reaction.
3. identify the product formed, and the various intermediates (i.e., the enamine, the Michael-type adduct), in a given Stork enamine reaction.
4. identify the reagents needed to synthesize a given compound by a Stork enamine reaction.

KEY TERMS

- Stork enamine reaction

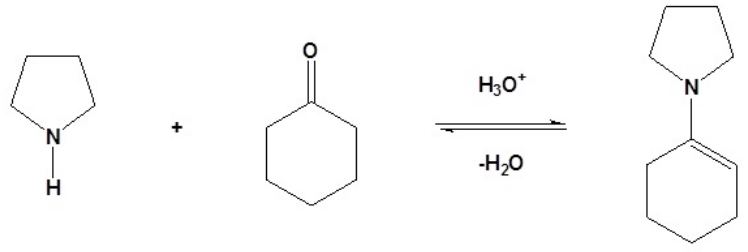
STUDY NOTES

If we try to use a monoketone as a donor molecule in a Michael reaction, we will obtain a poor yield. An alternative route to the product that would be expected from such a synthesis is via the Stork enamine reaction. You may wish to review the formation of enamines (from ketones and secondary amines) before you proceed with this section; if so, review Section 19.8.

OVERVIEW

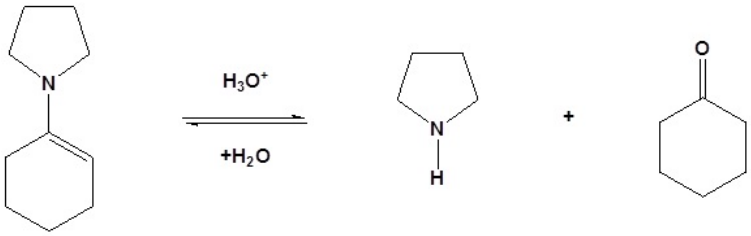
As previously seen, aldehydes and ketones react with 2° amines to reversibly form enamines.

Example



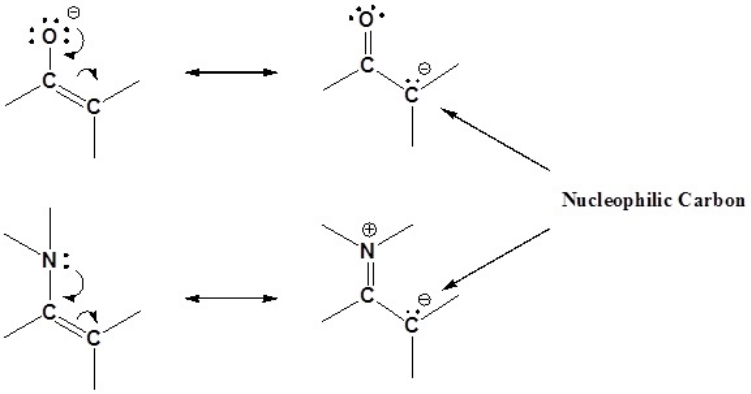
2° Amine Enamine

Reversible

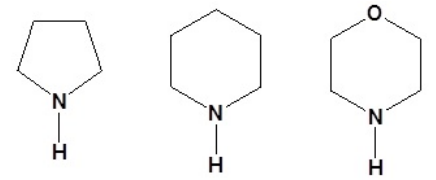


Enamines act as nucleophiles in a fashion similar to enolates. Because of this enamines can be used as synthetic equivalents as enolates in many reactions. This process requires a three steps: 1) Formation of the enamine, 2) Reaction with an eletrophile to form an iminium salt, 3) Hydrolysis of the iminium salt to reform the aldehyde or ketone. Some of the advantages of using an enamine over and enolate are enamines are neutral, easier to prepare, and usually prevent the overreaction problems plagued by

enolates. These reactions are generally known as the Stork enamine reaction after Gilbert Stork of Columbia University who originated the work.



Typically we use the following 2° amines for enamine reactions

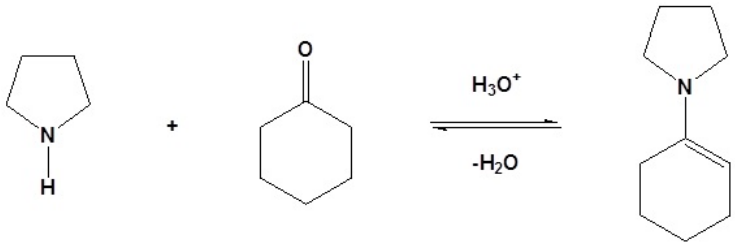


ALKYLATION OF AN ENAMINE

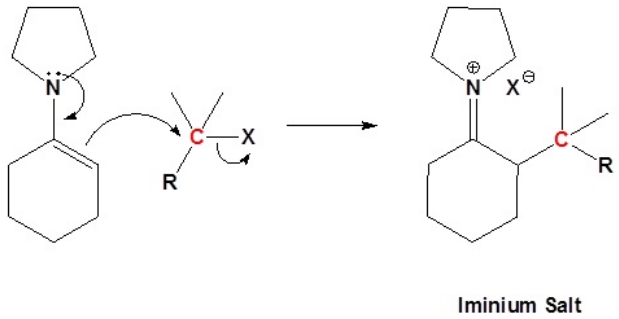
Enamined undergo an S_N2 reaction with reactive alkyl halides to give the iminium salt. The iminium salt can be hydrolyzed back into the carbonyl.

Individual steps

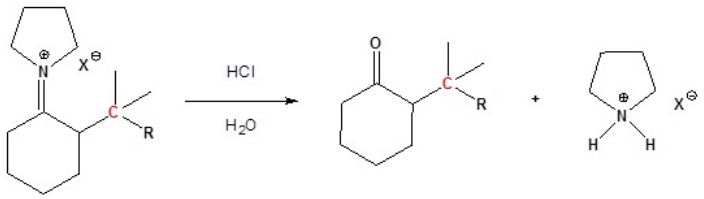
1) Formation of an enamine



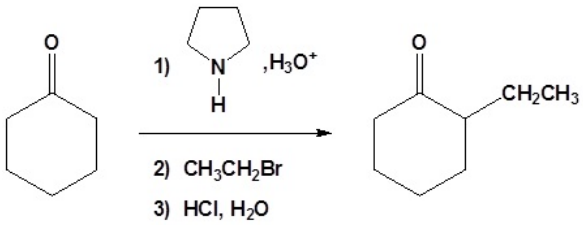
2) S_N2 Alkylation



3) Reform the carbonyl by hydrolysis



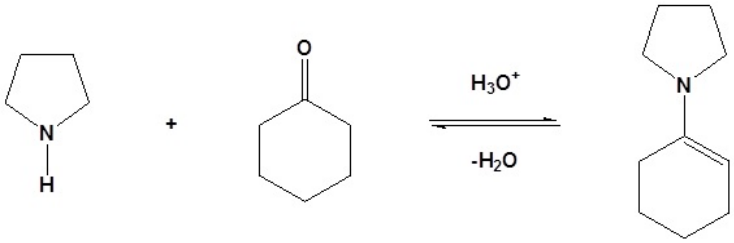
All three steps together:



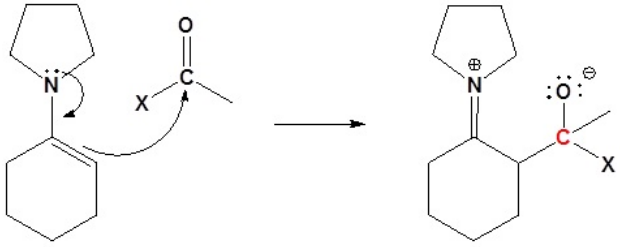
ACYLATION OF ENAMINES

Enamine can react with acid halides to form β-dicarbonyls

1) Formation of the enamine

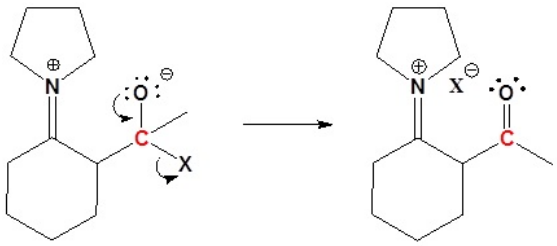


2) Nucleophilic attack

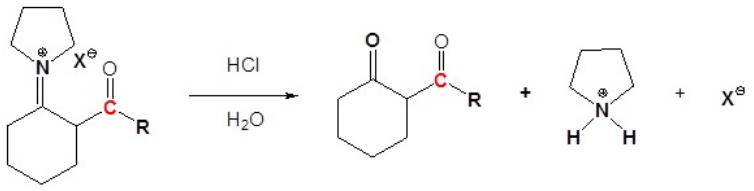


Iminium Salt

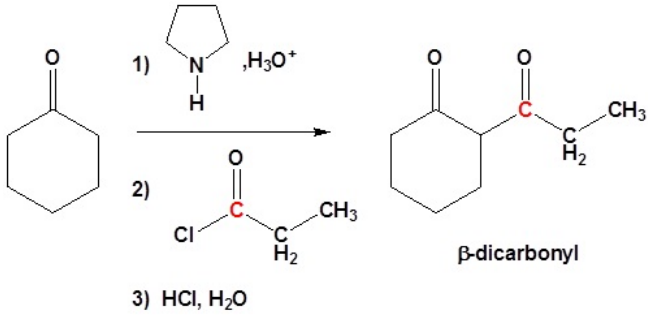
3) Leaving group removal



4) Reform the carbonyl by hydrolysis

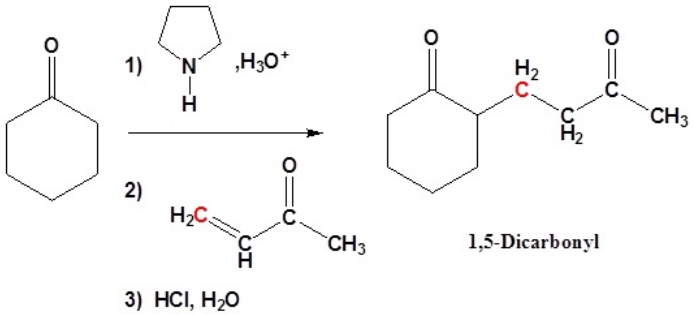


All three steps together:



MICHAEL ADDITION USING ENAMINES

Enamines, like other weak bases, add 1,4 to enones. The end product is a 1,5 dicarbonyl compound.

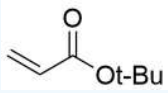


EXERCISES

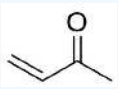
? EXERCISE 23.11.1

Draw the product of the reaction with the enamine prepared from cyclopentanone and pyrrolidine, and the following molecules.

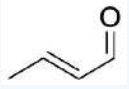
a)



b)

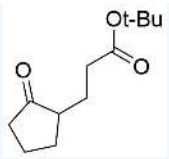


c)

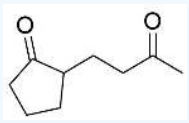


Answer

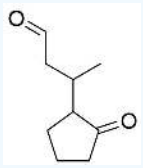
a)



b)



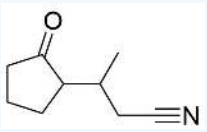
c)



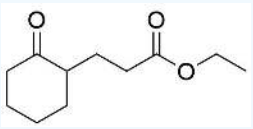
EXERCISE 23.11.2

What would be the starting materials necessary to make the following molecules during a Stork enamine reaction?

a)

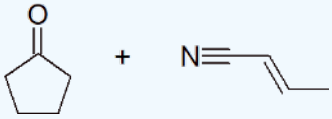


b)

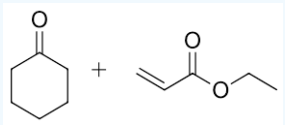


Answer

a)



b)

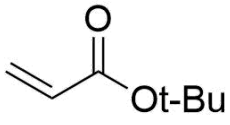


QUESTIONS

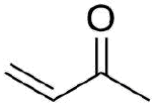
Q23.11.1

Draw the product of the reaction with the enamine prepared from cyclopentanone and pyrrolidine, and the following molecules.

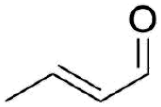
(a)



(b)



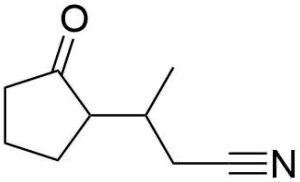
(c)



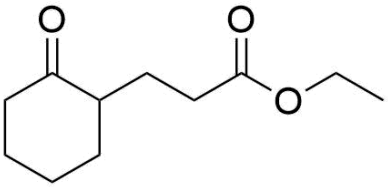
Q23.11.2

Propose a synthesis for the following compounds via an enamine.

(a)



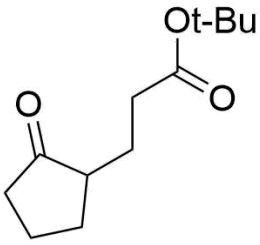
(b)



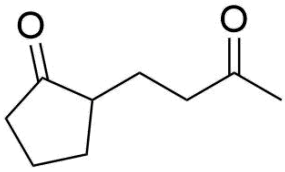
SOLUTIONS

S23.11.1

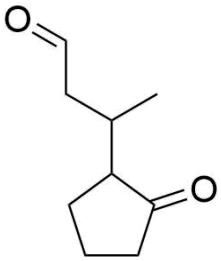
(a)



(b)



(c)



S23.11.2

(a) cyclopentanone enamine + 2-cyanopropene

(b) cyclohexanone enamine + ethyl acrylate

CONTRIBUTORS AND ATTRIBUTIONS

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

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23.12 THE ROBINSON ANNULATION REACTION

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the Robinson annulation reaction.
2. identify the cyclic product formed when a 1,5-diketone is treated with base.
3. identify the carbonyl compounds and any other reagents needed to synthesize a given cyclic compound by a series of reactions, one of which is a Robinson annulation.

KEY TERMS

- Robinson annulation reaction

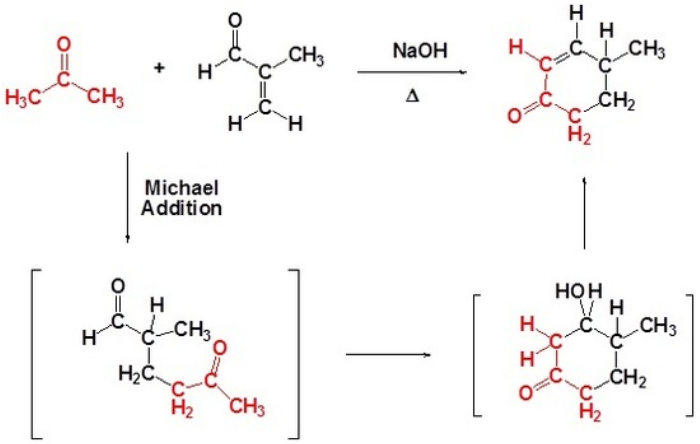
STUDY NOTES

The building of an alicyclic compound from acyclic starting materials can present an interesting challenge to the synthetic organic chemist. One route by which such a synthesis can be achieved is through the use of the Robinson annulation reaction. This reaction, which may at first look very complex, can be readily understood once you realize that it simply involves a Michael reaction followed by an intramolecular aldol condensation. Both of these steps involve attack by enolate anions.

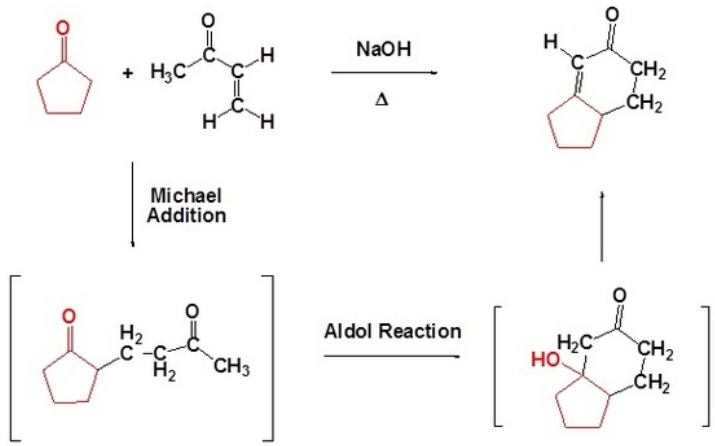
As in some of the other syntheses that you have studied, when you are simply given the structure of a compound and asked how it could have been prepared, it can be difficult to recognize which reactions might have been used. In this instance, keep in mind that you have studied relatively few reactions which have resulted in the formation of an alicyclic compound. Thus, when asked how such a compound might be prepared, you should keep the possibility of using a Robinson annulation reaction in mind.

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.

EXAMPLES OF ROBINSON ANNULATIONS

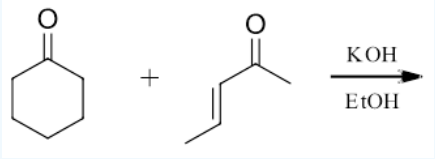


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WORKED EXAMPLE 23.12.1

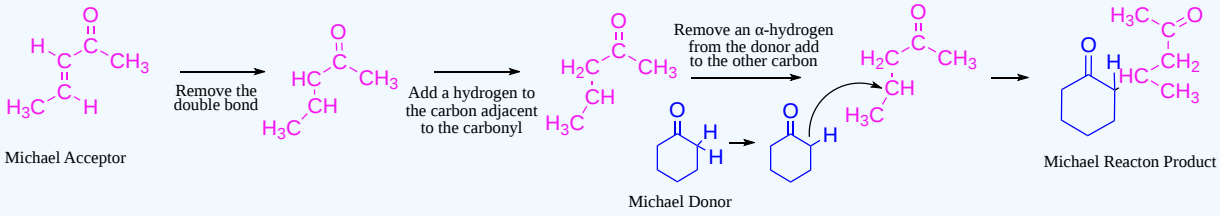
Draw the product of the following Robinson Annulation.



Answer

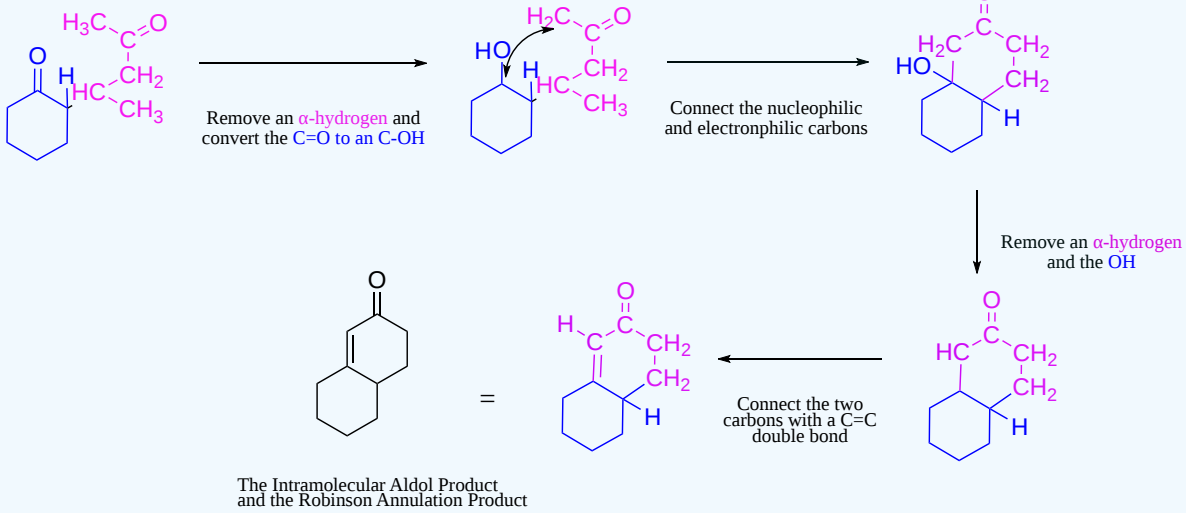
Analysis: When considering the product of a Robinson annulation it is usually best to consider each reaction individually. Use the steps discussed in Section 23.10 to convert the starting materials into the product of a Michael reaction, then into the product of an intramolecular aldol condensation. If the starting materials are drawn in a skeletal structure it may be helpful to convert to a condensed formula to better keep track of carbons and hydrogens.

Formation of the Michael reaction product



Formation of the intramolecular Aldol condensation product

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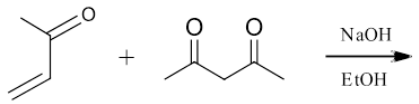
The Intramolecular Aldol Product and the Robinson Annulation Product

EXERCISES

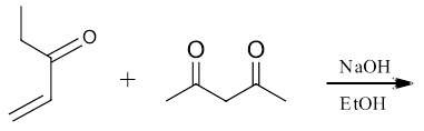
? EXERCISE 23.12.1

Provide products of the following Robinson annulations.

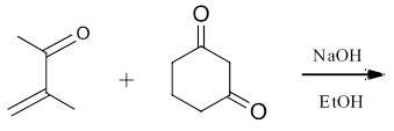
a)



b)

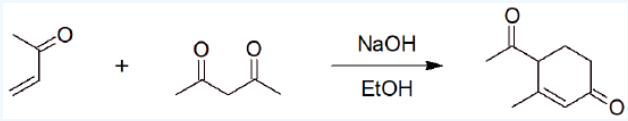


c)

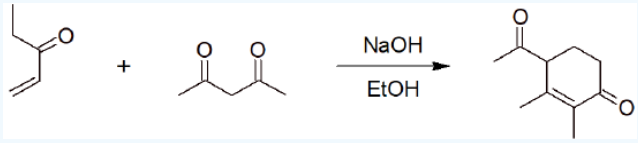


Answer

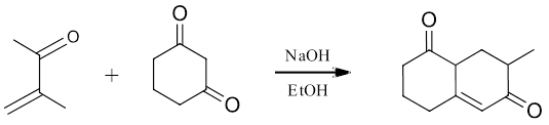
a)



b)

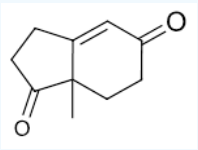


c)

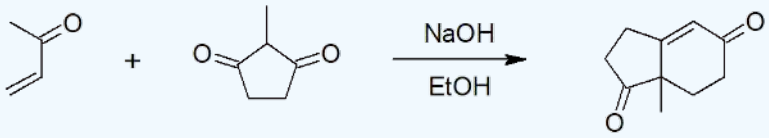


EXERCISE 23.12.2

What would be the starting materials required to make the following molecule using a Robinson annulation?



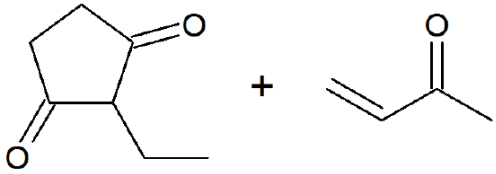
Answer



QUESTIONS

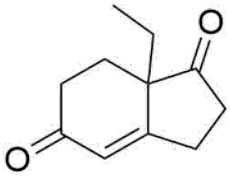
Q23.12.1

Draw the product of the following reaction.



SOLUTIONS

S23.12.1



CONTRIBUTORS AND ATTRIBUTIONS

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

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23.13 SOME BIOLOGICAL CARBONYL CONDENSATION REACTIONS

Objectives

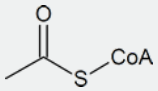
After completing this section, you should be able to

1. identify acetyl coenzyme A as an important biomolecule which undergoes carbonyl condensation reactions.
2. identify aldoases as enzymes that catalyze aldol reactions in biological systems.
3. identify the steps in which a carbonyl condensation reaction has occurred, given a general outline of a specific biosynthesis.

STUDY NOTES

Carbonyl condensation reactions occur in biological systems; for example, in the biosynthesis of citric acid.

You first met acetyl coenzyme A in Section 21.8. Again, we stress that it is not essential that you know the detailed structure of this compound (or other large biochemical stuctures discussed), but you should know that it may be represented as



and that it has the ability to behave just as any other acetyl-containing compound.

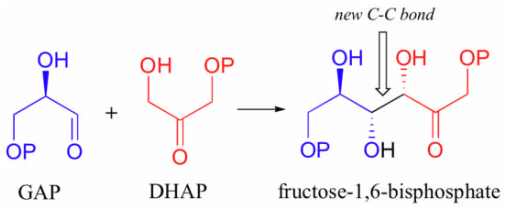
ALDOL REACTIONS IN NATURE

So far, we have examined the non-enzymatic reaction of an aldehyde or ketone with itself (a so-called 'self-condensation' reaction, where 'condensation' means the formation of one larger molecule from two smaller ones). However, aldol reactions occur in several biological pathways, most commonly in the metabolism of carbohydrates (sugars). The enzymes that catalyze aldol reactions are called, not surprisingly, '**aldolases**'. They occur in all organisms, but note that **Class I aldoases** are usually found in animals and higher plants, while **Class II aldoases** normally appear in bacteria and fungi.

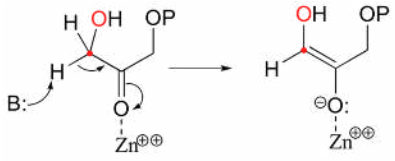
TYPICAL ALDOLASE REACTIONS - THREE VARIATIONS ON A THEME

The first step in an aldolase reaction is the deprotonation of an alpha-carbon to generate a nucleophilic carbanion. Nature has evolved several distinct strategies to stabilize the intermediate that results. Some aldolases use a metal ion to stabilize the negative charge on an enolate intermediate, while others catalyze reactions that proceed through neutral Schiff base or enol intermediates.

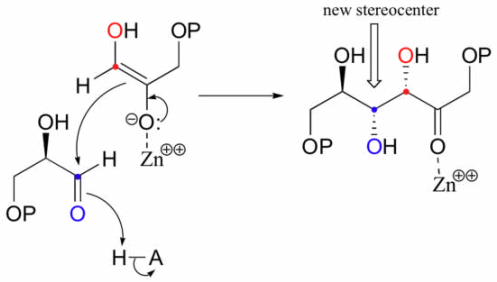
Let's examine first a reaction catalyzed by a so-called **'Class II' aldolase**, in which a metal cation - generally Zn^{2+} - bound in the active site serves to stabilize the negative charge on an enolate intermediate. Fructose 1,6-bisphosphate aldolase is an enzyme that participates in both the glycolytic (sugar burning) and gluconeogenesis (sugar building) biochemical pathways. For now, we will concentrate on its role in the gluconeogenesis pathway, but we will see it again later in its glycolytic role. The reaction catalyzed by fructose 1,6-bisphosphate aldolase is a condensation between two 3-carbon sugars, glyceraldehyde-3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP), forming a six-carbon product (which leads, after three more enzymatic steps, to glucose).



In the first step of the condensation, an alpha-carbon on DHAP is deprotonated, leading to an enolate intermediate. The strategy used to stabilize this key intermediate is to coordinate the negatively-charged enolate oxygen to an enzyme-bound zinc cation.

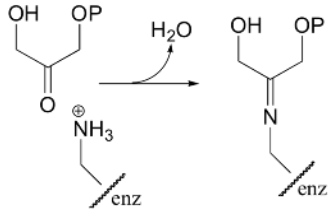


Next, the deprotonated a-carbon attacks the carbonyl carbon of GAP in a nucleophilic addition reaction, and protonation of the resulting alcohol leads directly to the fructose 1,6-bisphosphate product.

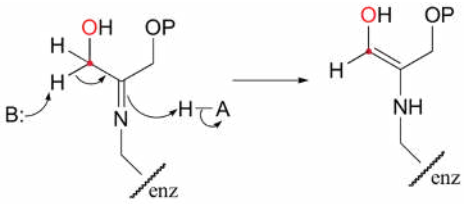


As with many other nucleophilic carbonyl addition reactions, a new stereocenter is created in this reaction, as a planar, achiral carbonyl group is converted to a tetrahedral, chiral alcohol. The enzyme-catalyzed reaction, not surprisingly, is completely stereospecific: the DHAP substrate is positioned in the active site so as to attack the *re* (front)face of the GAP carbonyl group, leading to the *R* configuration at the new stereocenter.

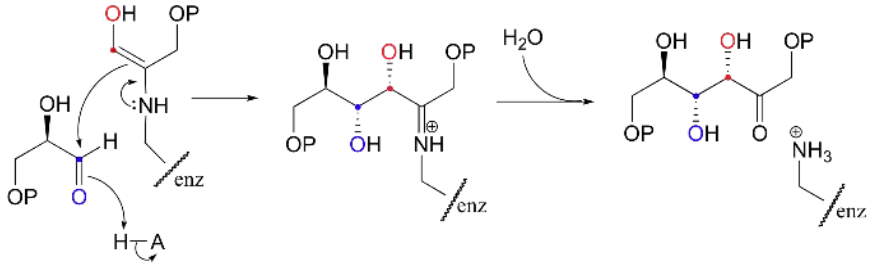
Interestingly, it appears that in bacteria, the fructose bisphosphate aldolase enzyme evolved separately from the corresponding enzyme in plants and animals. In plants and animals, the same aldol condensation reaction is carried out by a significantly different mechanism, in which the key intermediate is not a zinc-stabilized enolate but an enamine. The nucleophilic substrate (DHAP) is first linked to the enzyme through the formation of an imine (also known as a Schiff base) with a lysine residue in the active site.



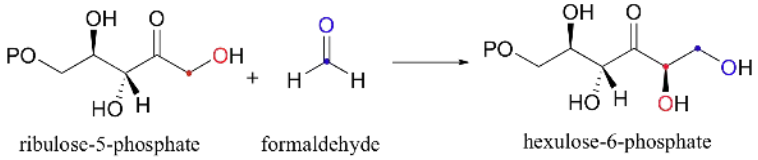
The alpha-proton is then abstracted by an active site base to form an enamine.



In the next step, the alpha-carbon attacks the carbonyl carbon of GAP, and the new carbon-carbon bond is formed. In order to release the product from the enzyme active site and free the enzyme to catalyze another reaction, the imine is hydrolyzed back to a ketone group.



There are many more examples of **'Class I' aldolase** reactions in which the key intermediate is a lysine-linked imine. Many bacteria are able to incorporate formaldehyde, a toxic compound, into carbohydrate metabolism by condensing it with ribulose monophosphate. The reaction proceeds through imine and enamine intermediates.



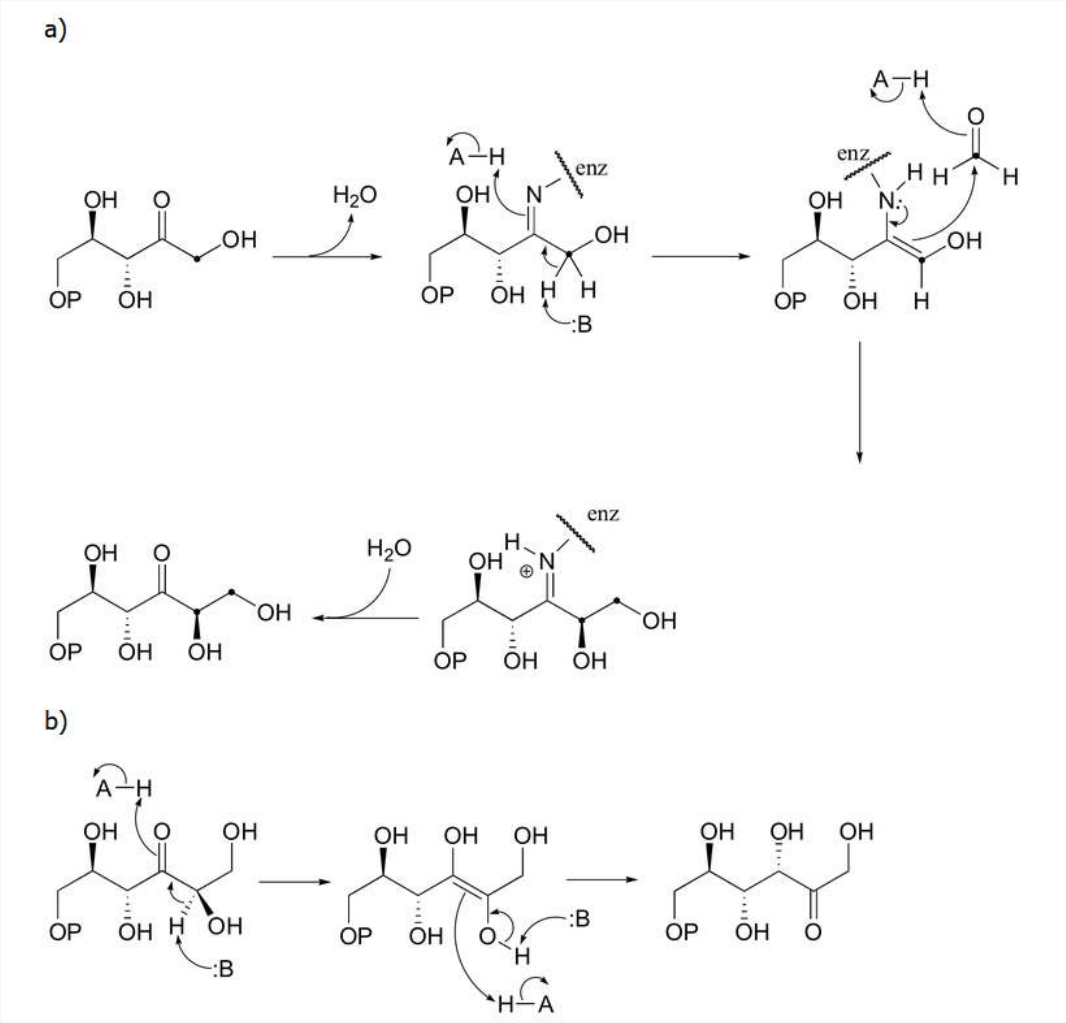
ribulose-5-phosphate formaldehyde hexulose-6-phosphate

EXAMPLE 23.13.1

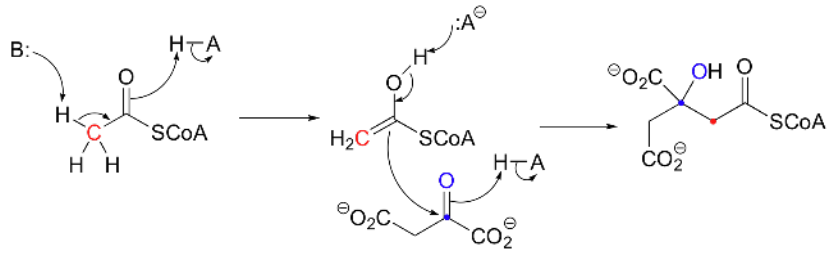
a) Propose a complete mechanism for the condensation reaction shown above.

b) Propose a complete mechanism for the conversion of hexulose-6-phosphate (formed from the condensation of ribulose-5-phosphate and formaldehyde) into fructose-6-phosphate.

Answer



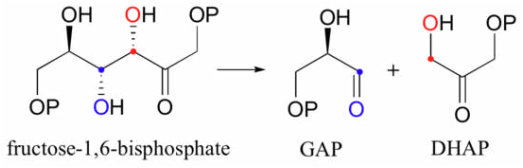
Along with aldehydes and ketones, esters and thioesters can act as the nucleophilic partner in aldol condensations. In the first step of the citric acid (Krebs) cycle, acetyl CoA condenses with oxaloacetate to form (S)-citryl CoA.



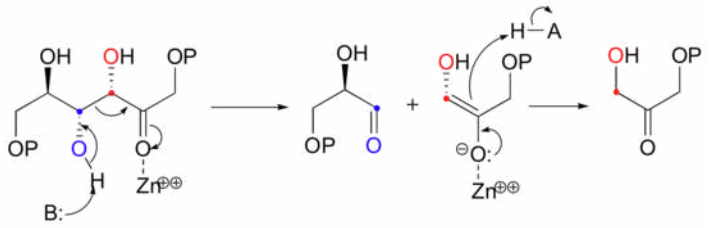
Notice that in this aldol reaction, the nucleophilic intermediate is stabilized by protonation, rather than by formation of an imine (as in the Class I aldolases) or by a metal ion (as in the Class II aldolases).

GOING BACKWARDS: THE RETROALDOL REACTION

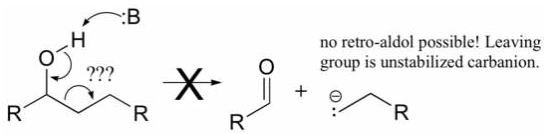
Although aldol reactions play a very important role in the formation of new carbon-carbon bonds in metabolic pathways, it is important to emphasize that they are also highly reversible: in most cases, the energy level of starting compounds and products are very close. This means that, depending on metabolic conditions, aldolases can also catalyze **retro-aldol** reactions (the reverse of aldol condensations, in which carbon-carbon bonds are *broken*). Recall that fructose 1,6-bisphosphate aldolase (section 13.3B) is active in the direction of sugar breakdown (glycolysis) as well as sugar synthesis (gluconeogenesis). In the glycolytic direction, the enzyme catalyzes - either by zinc cation or by imine/enamine mechanisms, depending on the organism - the retro-aldol cleavage of fructose bisphosphate into DHAP and GAP.



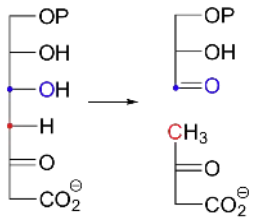
The mechanism is the exact reverse of the condensation reaction. Shown below is the mechanism for a Zn^{2+} - dependent (Type II) retroaldol cleavage. Notice that in the retroaldol reaction, the enolate intermediate is the *leaving group*, rather than the nucleophile.



The key thing to keep in mind when looking for a possible retro-aldol mechanism is that, when the carbon-carbon bond breaks, the electrons must have some place to go, where they will be stabilized by resonance. Generally, this means that there *must* be a carbonyl or imine group on the next carbon. If there is no adjacent carbonyl or imine group, the carbon-carbon bond is not free to break.



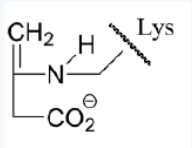
Here are two more examples of retro-aldol reactions. Bacterial carbohydrate metabolism involves this reversible, class I retro-aldol cleavage: (*Proc. Natl. Acad. Sci* **2001**, *98*, 3679).



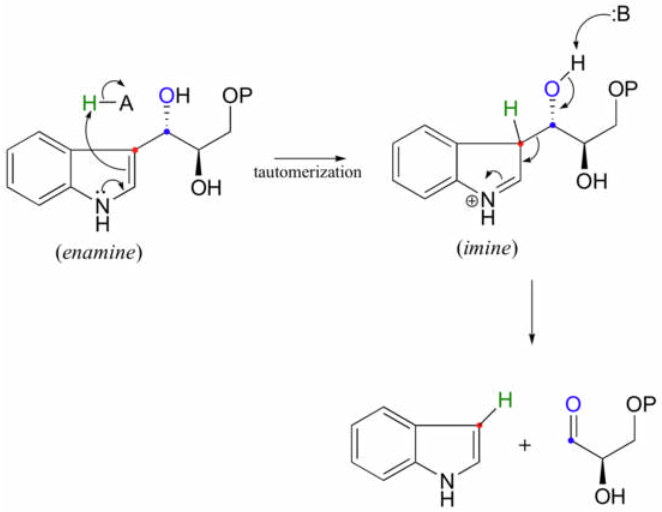
? EXAMPLE 23.13.2

Draw the structure of the enamine intermediate in the retroaldol reaction shown above.

Answer



Solution Another interesting example is the retro-aldol cleavage of indole-3-glycerol phosphate, a step in the biosynthesis of tryptophan.

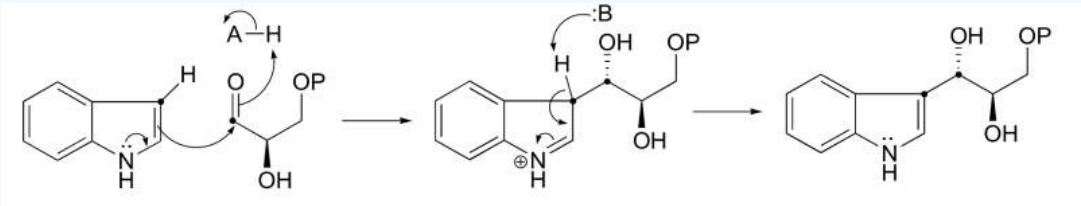


Look carefully at this reaction - how is the leaving group stabilized? There is an imine group involved, but no participation by an enzymatic lysine. The imine is 'built into' the starting compound, available from the initial tautomerization of the cyclic enamine group in indole-3-glycerol phosphate.

? EXAMPLE 23.13.3

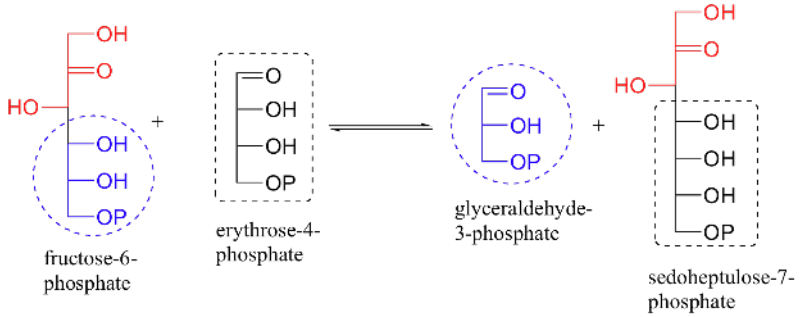
Draw the reverse (aldol condensation) direction of the reaction above.

Answer



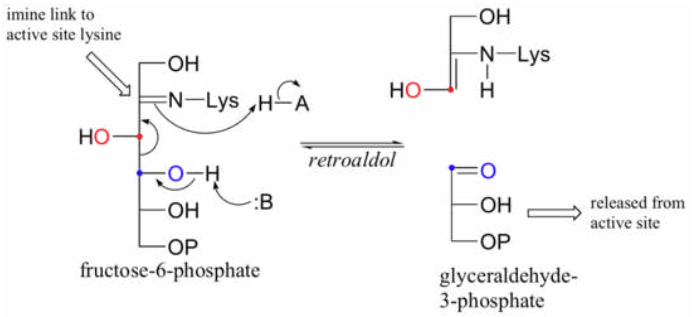
GOING BOTH WAYS: TRANSALDOLASE

An enzyme called transaldolase, which is part of the 'pentose phosphate pathway' of carbohydrate metabolism, catalyzes an interesting combination of class I aldol and retro-aldol reactions. The overall reaction, which can proceed in either direction depending on metabolic requirements, converts 3- and 7-carbon sugars into 6- and 4-carbon sugars. Essentially, a 3-carbon unit breaks off from a ketone sugar (ketose) and then is condensed directly with an aldehyde sugar (aldose).

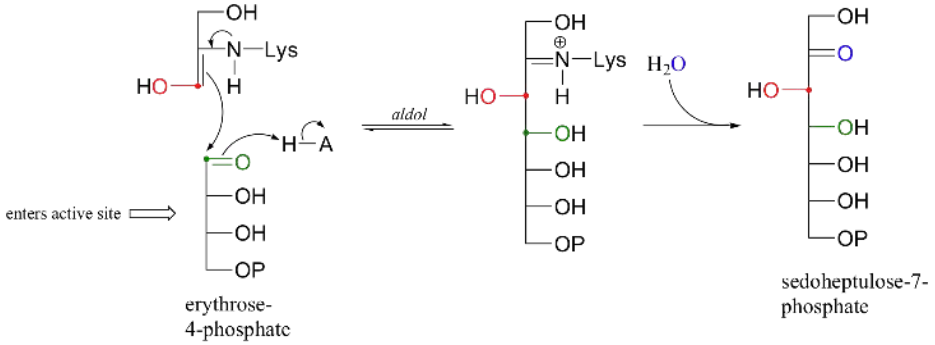


Let's follow the progress of the reaction in the left-to-right direction as depicted above. Because this is a class I aldolase, the first step is the formation of an imine linkage between the ketone carbon of fructose-6-phosphate (F6P) and a lysine group from the enzyme. The enzyme-substrate adduct then undergoes a retro-aldol step to free glyceralde-3-phosphate (GAP), which leaves the active site.

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The second substrate, erythrose 4-phosphate (E4P), enters the active site, and an aldol condensation occurs between E4P and the 3-carbon fragment remaining from the cleavage of fructose-6-phosphate.



The final step is hydrolysis of the imine and subsequent dissociation of sedoheptulose 7-phosphate from the active site.

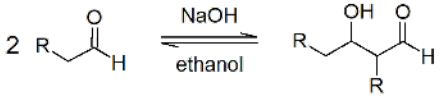
CONTRIBUTORS AND ATTRIBUTIONS

- 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)

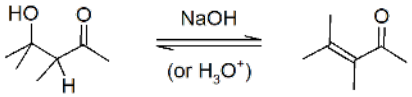
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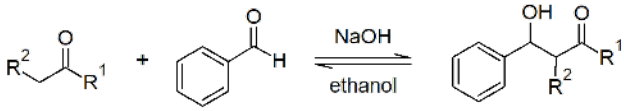
23.S: CARBONYL CONDENSATION REACTIONS (SUMMARY)

SUMMARY OF REACTIONS

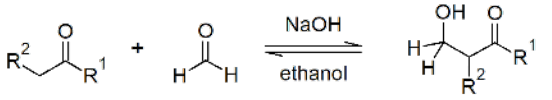


(Aldol)

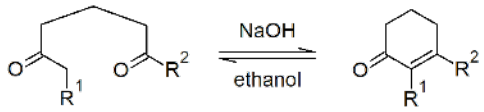




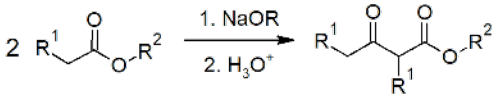
(mixedAldol)



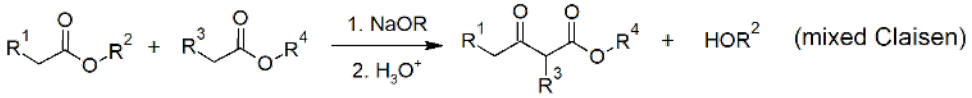
(mixedAldol)



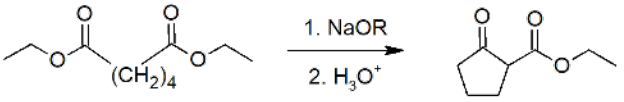
(intramolecular Aldol)



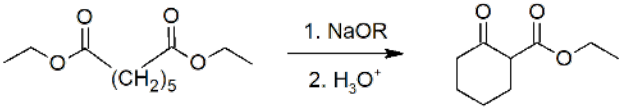
(Claisen)



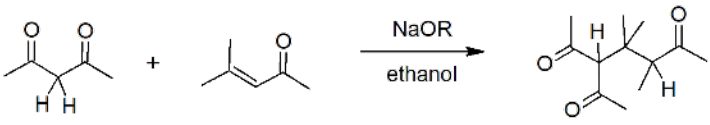
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(Dieckmann)

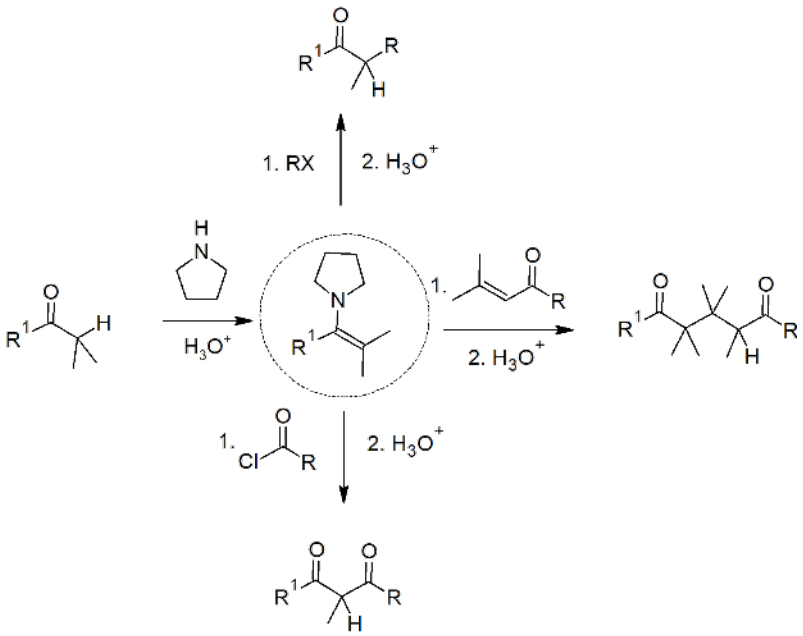


(Dieckmann)



(Michael)

Stork Enamine Reactions



23.S: Carbonyl Condensation Reactions (Summary) is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

CHAPTER OVERVIEW

CHAPTER 24: AMINES AND HETEROCYCLES

Amines are the first nitrogen-containing compounds that we study in detail in this course. We begin the chapter with an explanation of the differences in structure among primary, secondary and tertiary amines. We explain the nomenclature of aliphatic and arylamines, and examine the structure and bonding of these compounds, relating these features to their physical properties and basicity. We describe the use of amines to resolve racemic mixtures of chiral carboxylic acids.

Amines may be prepared by a number of different synthetic methods. We describe each of these methods and assess the relative merits of each. After a description of the reactions of aliphatic amines, we devote sections to a discussion of the use of tetraalkylammonium salts as phase-transfer agents. The chapter concludes with a summary of the spectroscopic properties of amines.

Chapter Objectives

24.1 Naming Amines

24.2 Structure and Properties of Amines

24.3 Basicity of Amines

24.4 Basicity of Arylamines

24.5 Biological Amines and the Henderson-Hasselbalch Equation

24.6 Synthesis of Amines

24.7 Reactions of Amines

24.8 Reactions of Arylamines

24.9 Heterocyclic Amines

24.10 Spectroscopy of Amines

24.S: Amines and Heterocycles (Summary)

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CHAPTER OBJECTIVES

When you have completed Chapter 24, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design a multi-step synthesis that involves the use of any of the reactions described in this unit, and any of the reactions described in any previous unit.
3. solve road-map problems that require a knowledge of amine chemistry in addition to any of the chemistry discussed in previous units.
4. define, and use in context, the key terms introduced.

CONTRIBUTORS AND ATTRIBUTIONS

Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

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24.1 NAMING AMINES

Objectives

After completing this section, you should be able to

1. classify a given amine as being primary, secondary or tertiary.
2. explain, briefly, the difference in meaning of the terms primary, secondary and tertiary when they are applied to the structures of amines and alcohols.
3. determine whether a given structure represents a quaternary ammonium cation.
4. provide an acceptable IUPAC name for an amine, given its Kekulé, condensed or shorthand structure.
5. draw the structure of an amine, given its IUPAC name.
6. give the name and structure of one typical heterocyclic amine (e.g., pyridine).

KEY TERMS

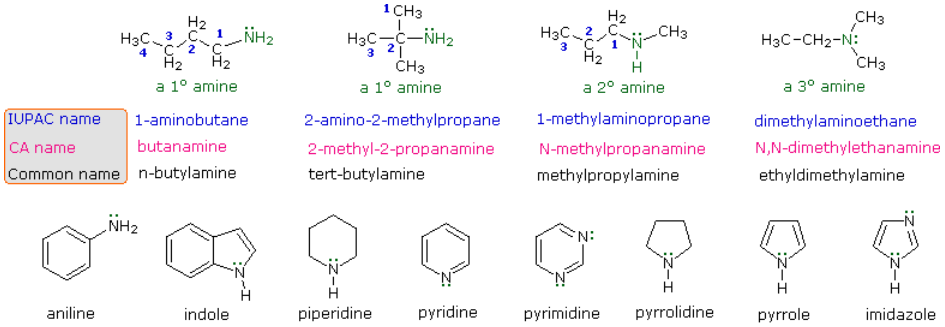
Make certain that you can define, and use in context, the key terms below.

- amine
- primary amine
- secondary amine
- quaternary ammonium cation
- tertiary amine

STUDY NOTES

You should recognize that heterocyclic amines—compounds in which the nitrogen atom occurs as part of a ring—are very common in organic chemistry. Be prepared to meet such compounds throughout this, and subsequent chapters, but do not try to memorize all of the names and structures givenin the reading. You should, however, commit the structures of pyridine and pyrrole to memory.

Amines are derivatives of ammonia in which one or more of the hydrogens has been replaced by an alkyl or aryl group. The nomenclature of amines is complicated by the fact that several different nomenclature systems exist, and there is no clear preference for one over the others. Furthermore, the terms primary (1º), secondary (2º) & tertiary (3º) are used to classify amines in a completely different manner than they were used for alcohols or alkyl halides. **When applied to amines these terms refer to the number of alkyl (or aryl) substituents bonded to the nitrogen atom**, whereas in other cases they refer to the nature of an alkyl group. The four compounds shown in the top row of the following diagram are all $C_4H_{11}N$ isomers. The first two are classified as 1º-amines, since only one alkyl group is bonded to the nitrogen; however, the alkyl group is primary in the first example and tertiary in the second. The third and fourth compounds in the row are 2º and 3º-amines respectively. A nitrogen bonded to four alkyl groups will necessarily be positively charged, and is called a quaternary (4º)-ammonium cation. For example, $(CH_3)_4N^{(+)}$ $Br^{(-)}$ is tetramethylammonium bromide.



- The IUPAC names are listed first and colored blue. This system names amine functions as substituents on the largest alkyl group. The simple -NH substituent found in 1º-amines is called an **amino group**. For 2º and 3º-amines a compound prefix (e.g. dimethylamino in the fourth example) includes the names of all but the root alkyl group.
- The Chemical Abstract Service has adopted a nomenclature system in which the suffix **-amine** is attached to the root alkyl name. For 1º-amines such as butanamine (first example) this is analogous to IUPAC alcohol nomenclature (-ol suffix). The additional nitrogen

substituents in 2º and 3º-amines are designated by the prefix **N-** before the group name. These CA names are colored magenta in the diagram.

- Finally, a common system for simple amines names each alkyl substituent on nitrogen in alphabetical order, followed by the suffix -**amine**. These are the names given in the last row (colored black).

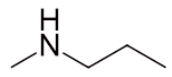
Many aromatic and heterocyclic amines are known by unique common names, the origins of which are often unknown to the chemists that use them frequently. Since these names are not based on a rational system, it is necessary to memorize them. There is a systematic nomenclature of heterocyclic compounds, but it will not be discussed here.

EXERCISES

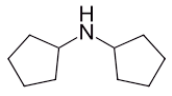
? EXERCISE 24.1.1

Name the following compounds:

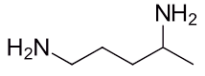
a)



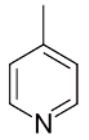
b)



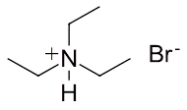
c)



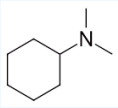
d)



e)



f)



Answer

a) N-Methylpropylamine

b) Dicyclopentylamine

c) 1,4-Pentanediamine

d) 4-Methylpyridine

e) Triethylammonium Bromide

f) N,N-Dimethylcyclohexylamine

EXERCISE 24.1.2

Draw the structures corresponding to the following names:

a) 3-Bromo-pentan-2-amine

b) Cyclopentanamine

c) *Trans*-3-ethylcyclohexanamine

d) *Sec*-butyl-*tert*-butyl amine

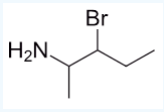
e) N,N-Dimethyl-3-pentanamine

f) 4-Methyl-2-hexanamine

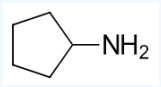
g) 6-Bromo-4-amino-2-heptanol

Answer

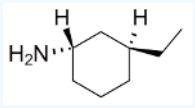
a)



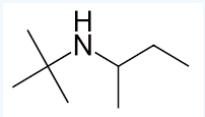
b)



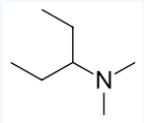
c)



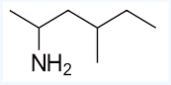
d)



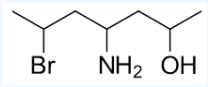
e)



f)



g)



EXERCISE 24.1.3

Draw the structures of the following heterocyclic compounds:

a) 4-Methoxyindole

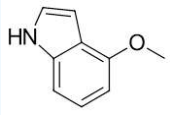
b) 1,4-Dimethylpyrrole

c) 3-(N,N-Dimethylamino)pyridine

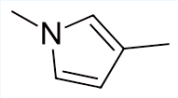
d) 2-Aminopyrimidine

Answer

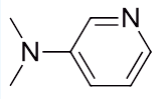
a)



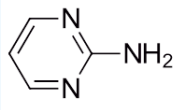
b)



c)



d)



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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24.2 STRUCTURE AND PROPERTIES OF AMINES

Objectives

After completing this section, you should be able to

1. describe the geometry and bonding of simple amines.
2. explain why most chiral amines cannot be resolved into their two enantiomers.

KEY TERMS

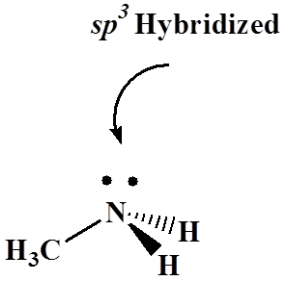
Make certain that you can define, and use in context, the key term below.

- pyramidal inversion

STUDY NOTES

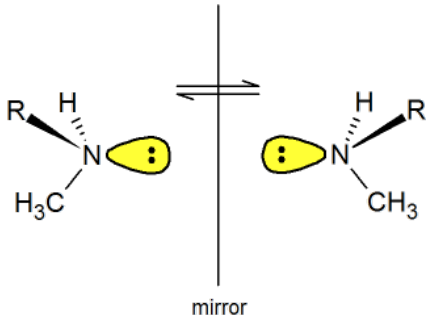
Molecular models may help you to understand pyramidal inversion.

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.



STEREOGENIC NITROGEN

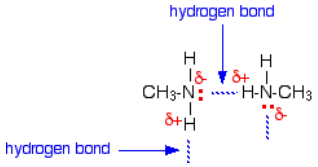
Single-bonded nitrogen is pyramidal in shape, with the non-bonding electron pair pointing to the unoccupied corner of a tetrahedral region. Since the nitrogen in these compounds is bonded to three different groups, its configuration is chiral. The non-identical mirror-image configurations are illustrated 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.



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.

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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24.3 BASICITY OF AMINES

Objectives

After completing this section, you should be able to

1. account for the basicity and nucleophilicity of amines.
2. explain why amines are more basic than amides, and better nucleophiles.
3. describe how an amine can be extracted from a mixture that also contains neutral compounds illustrating the reactions which take place with appropriate equations.
4. explain why primary and secondary (but not tertiary) amines may be regarded as very weak acids, and illustrate the synthetic usefulness of the strong bases that can be formed from these weak acids.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- amide

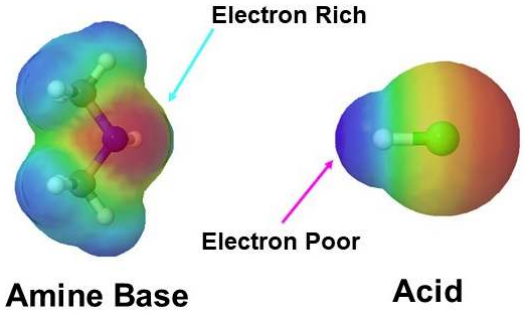
STUDY NOTES

The lone pair of electrons on the nitrogen atom of amines makes these compounds not only basic, but also good nucleophiles. Indeed, we have seen in past chapters that amines react with electrophiles in several polar reactions (see for example the nucleophilic addition of amines in the formation of imines and enamines in Section 19.8).

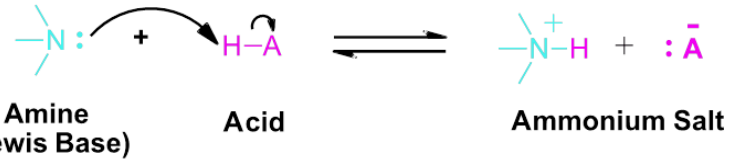
The ammonium ions of most simple aliphatic amines have a pK_a of about 10 or 11. However, these simple amines are all more basic (i.e., have a higher pK_a) than ammonia. Why? Remember that, relative to hydrogen, alkyl groups are electron releasing, and that the presence of an electron-releasing group stabilizes ions carrying a positive charge. Thus, the free energy difference between an alkylamine and an alkylammonium ion is less than the free energy difference between ammonia and an ammonium ion; consequently, an alkylamine is more easily protonated than ammonia, and therefore the former has a higher pK_a than the latter.

BASICITY OF NITROGEN GROUPS

In this section we consider the relative basicity of amines. When evaluating the basicity of a nitrogen-containing organic functional group, the central question we need to ask ourselves is: how reactive (and thus how basic and nucleophilic) 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. The lone pair electrons makes the nitrogen in amines electron dense, which is represents by a red color in the electrostatic potential map present below left. Amine are basic and easily react with the hydrogen of acids which are electron poor as seen below.



Amines are one of the only neutral functional groups which are considered bases which is a consequence of the presence of the lone pair electrons on the nitrogen. During an acid/base reaction the lone pair electrons attack an acidic hydrogen to form a N-H bond. This gives the nitrogen in the resulting ammonium salt four single bonds and a positive charge.



Amines react with water to establish an equilibrium where a proton is transferred to the amine to produce an ammonium salt and the hydroxide ion, as shown in the following general equation:

$$RNH2_{(aq)} + H_2O_{(l)} \rightleftharpoons RNH3^+_{(aq)} + OH^-_{(aq)} \quad (1)$$

The equilibrium constant for this reaction is the base ionization constant (K_b), also called the base dissociation constant:

$$K_b = \frac{[RNH3^+][OH^-]}{[NH2]} \quad (2)$$

$$pK_b = -\log K_b$$

Just as the acid strength of a carboxylic acid can be measured by defining an acidity constant K_a (Section 2-8), the base strength of an amine can be measured by defining an analogous basicity constant K_b. The larger the value of K_b and the smaller the value of pK_b, the more favorable the proton-transfer equilibrium and the stronger the base.

However, Kb values are often not used to discuss relative basicity of amines. It is common to compare basicity's of amines by using the K_a's of their conjugate acids, which is the corresponding ammonium ion. Fortunately, the K_a and K_b values for amines are directly related.

Consider the reactions for a conjugate acid-base pair, $RNH_3^+ - RNH_2$:

$$RNH_3^+(aq) + H_2O(l) \rightleftharpoons RNH_2(aq) + H_3O^+(aq) \quad K_a = \frac{[RNH2][H3O]}{[RNH3+]} \quad (3)$$

$$RNH_2(aq) + H_2O(l) \rightleftharpoons RNH_3^+(aq) + OH^-(aq) \quad K_b = \frac{[RNH3+][OH-]}{[RNH2]} \quad (4)$$

Adding these two chemical equations together yields the equation for the autoionization for water:

$$\cancel{RNH_3^+(aq)} + H_2O(l) + \cancel{RNH_2(aq)} + H_2O(l) \rightleftharpoons H_3O^+(aq) + \cancel{RNH_2(aq)} + OH^-(aq) + \cancel{RNH_3^+(aq)} \quad (5)$$

$$2\,H_2O(l) \rightleftharpoons H_3O^+(aq) + OH^-(aq) \quad (6)$$

Given that the *K* expression for a chemical equation formed from adding two or more other equations is the mathematical product of the input equations' *K* constants.

$$K_a \text{ X } K_b = \{2\ H_2O\} / (H_3O^+)\{OH^-\} = Kw$$

$$K_a = \frac{K_w}{K_b} \quad (7)$$

$$pK_a + pK_b = 14$$

Thus if the K_a for an ammonium ion is know the K_b for the corresponding amine can be calculated using the equation $K_b = K_w / K_a$. This relationship shows that as an ammonium ion becomes more acidic (K_a increases / pK_a decreases) the correspond base becomes weaker (K_b decreases / pK_b increases)

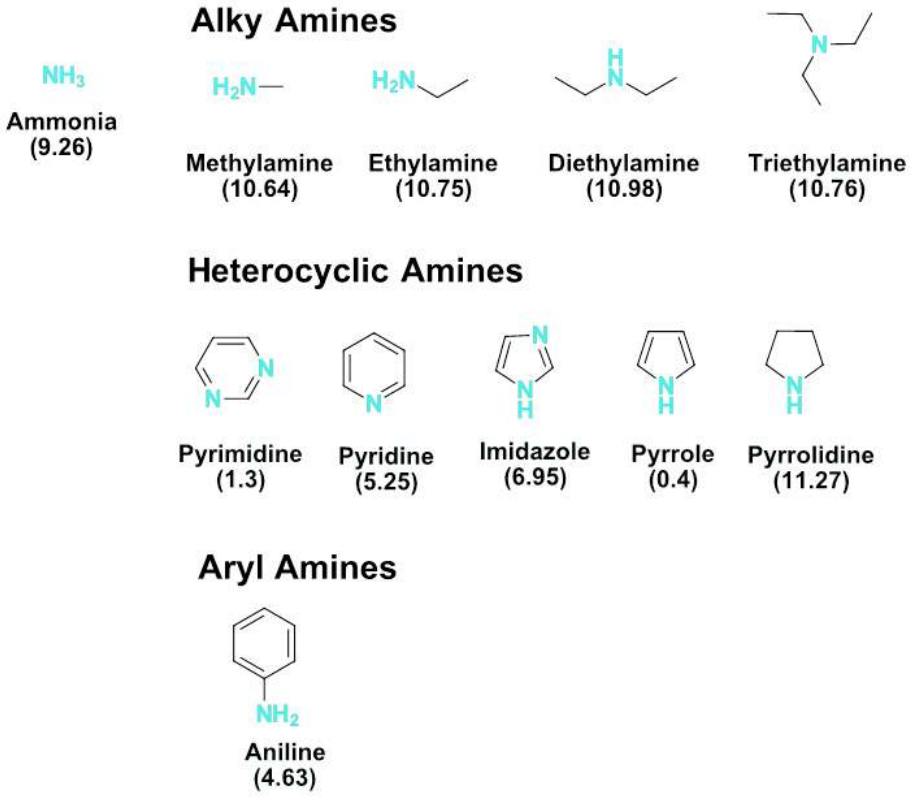
Weaker Base = Larger K_a and Smaller pK_a of the Ammonium ion

Stronger Base = Smaller K_a and Larger pK_a of the Ammonium ion

Like ammonia, most amines are Brønsted-Lowry and Lewis bases, but their base strength can be changed enormously by substituents. Most simple alkyl amines have pK_a's in the range 9.5 to 11.0, and their aqueous solutions are basic (have a pH of 11 to 12, depending on concentration).

Aromatic herterocyclic amines (such as pyrimidine, pyridine, imidazole, pyrrole) are significantly weaker bases as a consequence of three factors. The first of these is the hybridization of the nitrogen. In each case the heterocyclic nitrogen is sp^2 hybridized. The increasing s-character brings it closer to the nitrogen nucleus, reducing its tendency to bond to a proton compared to sp^3 hybridized nitrogens. The very low basicity of pyrrole reflects the exceptional delocalization of the nitrogen electron pair associated with its incorporation in an aromatic

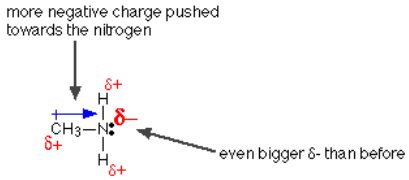
ring. Imidazole (pK_a = 6.95) is over a million times more basic than pyrrole because the sp^2 nitrogen that is part of one double bond is structurally similar to pyridine, and has a comparable basicity.



Basicity of common amines (pK_a of the conjugate ammonium ions)

INDUCTIVE EFFECTS IN NITROGEN BASICITY

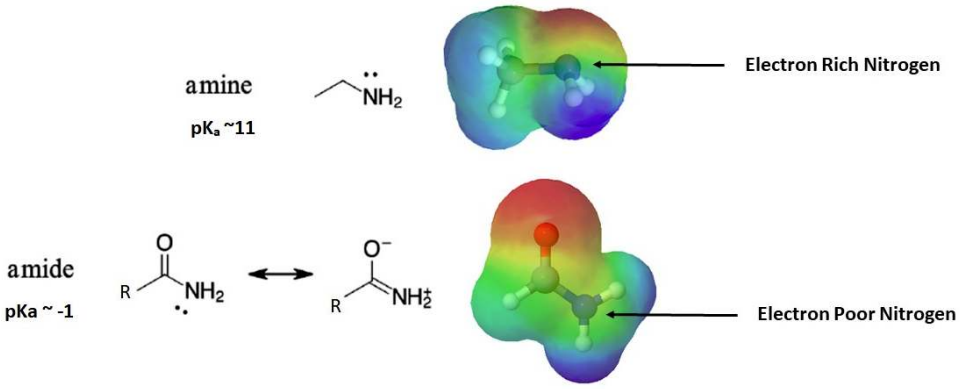
Alkyl groups donate electrons to the more electronegative nitrogen. The inductive effect makes the electron density on the alkylamine's nitrogen greater than the nitrogen of ammonia. The small amount of extra negative charge built up on the nitrogen atom makes the lone pair even more attractive towards hydrogen ions. Correspondingly, primary, secondary, and tertiary alkyl amines are more basic than ammonia.



Compound	pK_a of the conjugate acid
NH_3	9.3
CH_3NH_2	10.66
$(CH_3)_2NH$	10.74
$(CH_3)_3N$	9.81

COMPARING THE BASICITY OF ALKYLAMINES TO AMIDES

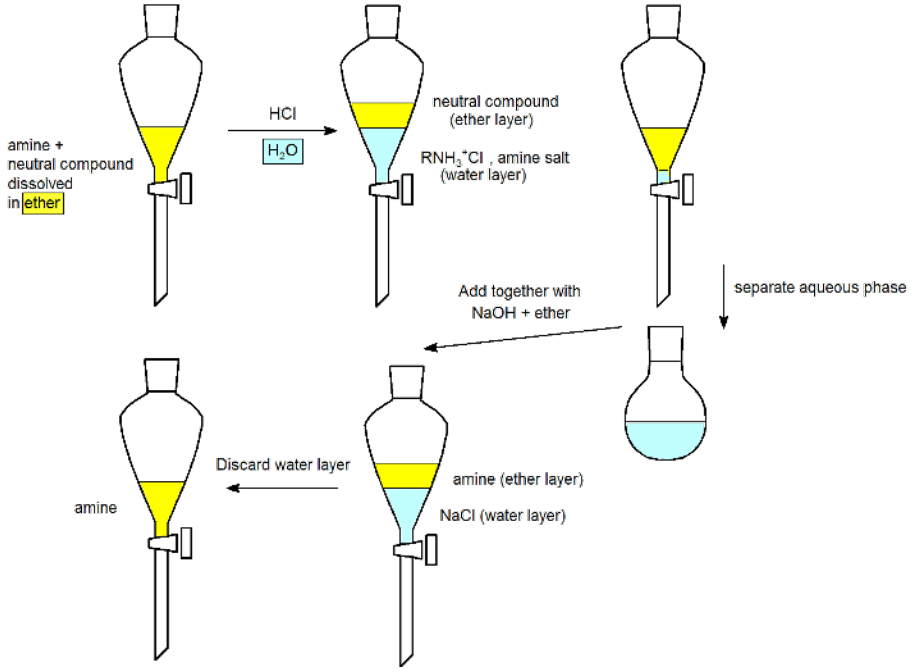
The nitrogen atom is strongly basic when it is in an amine, but *not* significantly basic when it is part of an amide group. While the electron lone pair of an amine nitrogen is localized in one place, the lone pair on an amide nitrogen is delocalized by resonance. The electron density – in the form of a lone pair – is stabilized by resonance delocalization, even though there is not a negative charge involved. Here's another way to think about it: the lone pair on an amide nitrogen is not as available for bonding with a proton – these two electrons are too stable being part of the delocalized pi-bonding system. The electrostatic potential map shows the effect of resonance on the basicity of an amide. The map shows that the electron density, shown in red, is almost completely shifted towards the oxygen. This greatly decreases the basicity of the lone pair electrons on the nitrogen in an amide.



Comparison of amines and amides to rationalize the the pK_a values of their conjugate acids

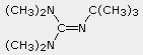
AMINE EXTRACTION IN THE LABORATORY

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

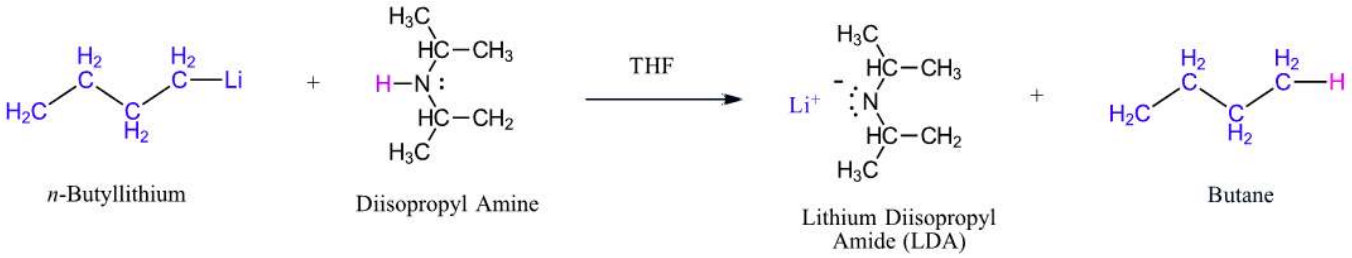
The significance of all these acid-base relationships to practical organic chemistry lies in the need for organic bases of varying strength, as reagents tailored to the requirements of specific reactions. The common base sodium hydroxide is not soluble in many organic solvents, and is therefore not widely 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 amine bases, and fill the gap in base strength between amines and amide salts.

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 of conjugate acid	5.3	10.7	11.4	14	19	26	35.7

Basicity of common amines (pK_a of the conjugate ammonium ions)

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 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 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.

In addition to acting as a base, 1° and 2° amines can act as very weak acids. Their N-H proton can be removed if they are reacted with a strong enough base. An example is the formation of lithium diisopropylamide (LDA, $LiN[CH(CH_3)_2]_2$) by reacting *n*-butyllithium with diisopropylamine (pK_a 36) **(**Section 22-5**)**. LDA is a very strong base and is commonly used to create enolate ions by deprotonating an alpha-hydrogen from carbonyl compounds **(**Section 22-7**)**.

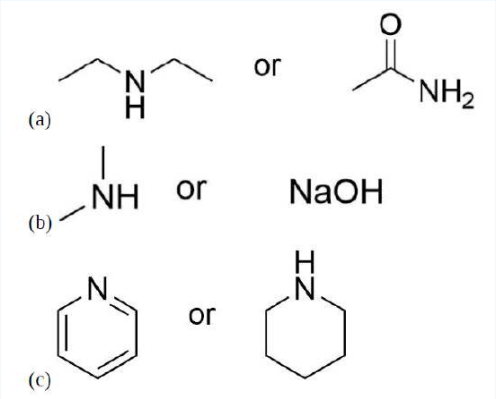


n-Butyllithium + Diisopropyl Amine → Lithium Diisopropyl Amide (LDA) + Butane

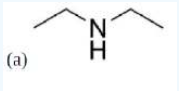
EXERCISES

? EXERCISE 24.3.1

Select the more basic compound from each of the following pairs of compounds.

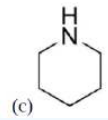


Answer



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(b) NaOH

(c) 

? EXERCISE \24.3.2

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?

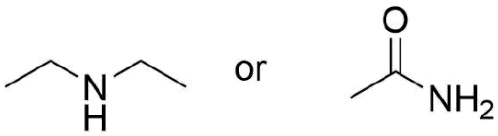
Answer

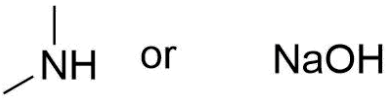
The butylammonium is more basic. The pKb for butylammonium is 3.41, the pKb for 4-methylbenzylammonium is 4.49

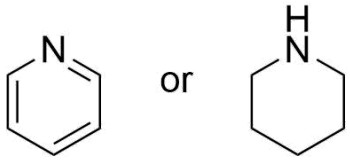
QUESTIONS

Q24.3.1

Select the more basic amine from each of the following pairs of compounds.

(a) 

(b) 

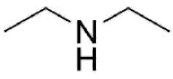
(c) 

Q24.3.2

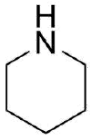
The 4-methylbenzylammonium ion has a pKa of 9.51, and the butylammonium ion has a pKa of 10.59. Which is more basic? What's the pKb for each compound?

SOLUTIONS

S24.3.1

(a) 

(b) NaOH

(c) 

S24.3.2

The butylammonium is more basic. The pKb for butylammonium is 3.41, the pKb for 4-methylbenzylammonium is 4.49.

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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24.4 BASICITY OF ARYLAMINES

Objectives

After completing this section, you should be able to

1. use the concept of resonance to explain why arylamines are less basic than their aliphatic counterparts.
2. arrange a given series of arylamines in order of increasing or decreasing basicity.
3. discuss, in terms of inductive and resonance effects, why a given arylamine is more or less basic than aniline.

STUDY NOTES

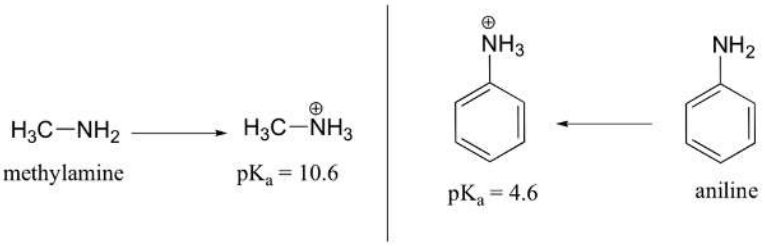
With reference to the discussion of base strength, the traditional explanation for the base-strengthening effect of electron-releasing (I) substituents is that such substituents help to stabilize the positive charge on an arylammonium ion more than they stabilize the unprotonated compound, thereby lowering ΔG°.

The electron-withdrawing (i.e., deactivating) substituents decrease the stability of a positively charged arylammonium ion.

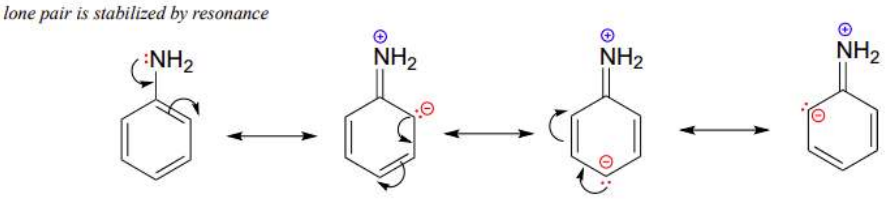
Note that the arylammonium ion derived from aniline, $PhNH_3^+$, is commonly referred to as the anilinium ion.

BASICITY OF ANILINE

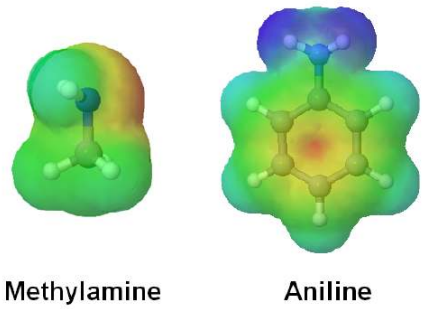
Aniline is substantially less basic than methylamine, as is evident by looking at the pK_a values for their respective ammonium conjugate acids (remember that the lower the pKa of the conjugate acid, the weaker the base).



This difference is basicity can be explained by the observation that, in aniline, the lone pair of electrons on the nitrogen are delocalized by the aromatic p system, making it less available for bonding to H^+ and thus less basic. The lone pair electrons of aniline are involved in four resonance forms making them more stable and therefore less reactive relative to alkylamines.

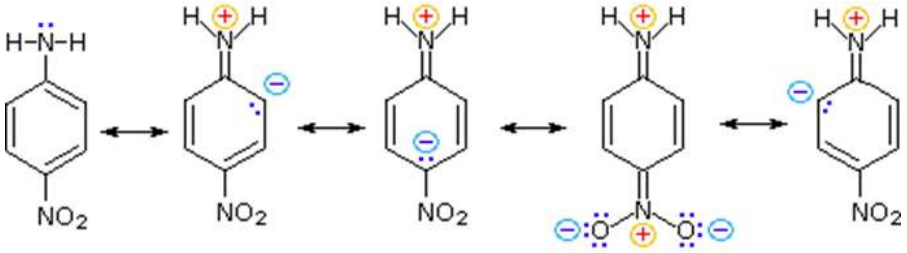


The effect of delocalization can be seen when viewing the electrostatic potential maps of aniline an methyl amine. The nitrogen of methyl amine has a significant amount of electron density on its nitrogen, shown as a red color, which accounts for it basicity compared to aniline. While the electron density of aniline's nitrogen is delocalized in the aromatic ring making it less basic.



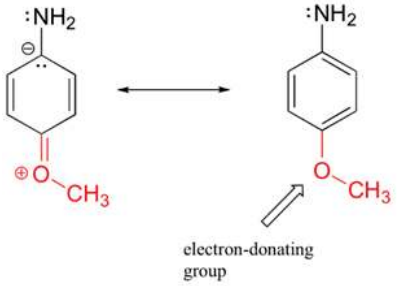
BASICITY OF SUBSTITUTED ARYLAMINES

The addition of substituents onto the aromatic ring can can make arylamines more or less basic. Substituents which are electron-withdrawing (-Cl, -CF_3, -CN, -NO_2) decrease the electron density in the aromatic ring and on the amine making the arylamine less basic. In particular, the nitro group of *para*-nitroaniline allows for an additional resonance form to be drawn, which further stabilizes the lone pair electrons from the nitrogen, making the substituted arylamine less basic than aniline. This effect is analogous to the one discussed for the acidity of substituted phenols in **Section 17.2**.



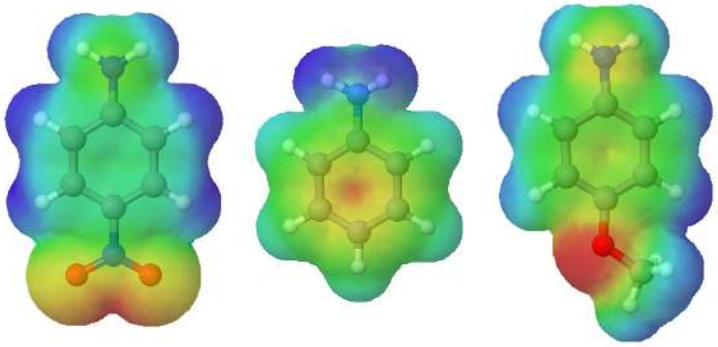
Reduced Basicity of *para*-Nitroaniline due to Electron Pair Delocalization

Substituents which are electron-donating (-CH_3, -OCH_3, -NH_2) increase the electron density in the aromatic ring and on the amine making the arylamine more basic. In the case of *para*-methoxyaniline, the lone pair on the methoxy group donates electron density to the aromatic system, and a resonance contributor can be drawn in which a negative charge is placed on the carbon adjacent to the nitrogen, which makes the substituted arylamine more basic than aniline.



Increased Basicity of para-Methoxyaniline due to Electron-Donation

The shifting electron density of aniline, *p*-nitroaniline, and *p*-methoxyaniline are seen in their relative electrostatic potential maps. For *p*-Nitroaniline virtually all of the electron density, shown as a red/yellow color. is pulled toward the electron-withdrawing nitro group. In *p*-methoxyaninline the electron donating methoxy group donates electron density into the ring. The amine in p-methoxyaniline is shown to have more electron density, shown as a yellow color, when compared to the amine in aniline.



p-Nitroaniline Aniline *p*-Methoxyaniline

EXERCISE

Exercise 24.4.1

Using the knowledge of the electron donating or withdrawing effects of subsituents gained in Section 16.6, rank the following compound in order of decreasing basicity.

a) *p*-Nitroaniline, methyl p-aminobenzoate, *p*-chloroaniline
b) *p*-Bromoaniline, *p*-Aminobenzonitrile, *p*-ethylaniline
c) p-(Trifluoromethyl)aniline, *p*-methoxyaniline, *p*-methylaniline

Answers

a) *p*-Chloroaniline, methyl p-aminobenzoate, *p*-nitroaniline
b) *p*-Ethylaniline, *p*-Bromoaniline, *p*-aminobenzonitrile
c) *p*-Methoxyaniline, *p*-methylaniline, *p*-(trifluoromethyl)aniline

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24.5 BIOLOGICAL AMINES AND THE HENDERSON-HASSELBALCH EQUATION

Objectives

1. identify the form that amine bases take within living cells.
2. use the Henderson-Hasselbalch equation to calculate the percentage of a base that is protonated in a solution, given the pK_a value of the associated ion and the pH of the solution.
3. explain why organic chemists write cellular amines in their protonated form and amino acids in their ammonium carboxylate form.

The Henderson-Hasselbalch equation is a very useful equation relating the pKa of a buffered solution to the relative amounts of an acid and its conjugate base.

The Henderson-Hasselbalch equation:

$$pH = pKa + log\frac{[A^-]}{[HA]}$$

If an acid is exactly 50% dissociated in aqueous solution, then the concentration of A^- is equal to the concentration of HA, and the fraction term in the Henderson-Hasselbalch equation is equal to 1. Because log(1) = 0, it follows that pH = pK_a at these conditions. This is very useful: it means that *the pK_a of an acid is equal to the pH at which it is 50% disassociated* (deprotonated). For example, if a 0.1 M aqueous solution of acetic acid is brought to pH 4.8 by the addition of sodium hydroxide, we know by the Henderson-Hasselbalch equation that the solution is now 0.05 M in acetic acid and 0.05 M in acetate ion.

The above situation – an aqueous solution that contains equal or nearly equal concentrations of a weak acid and its conjugate base – should sound very familiar to you. This is a buffer! As we discuss the organic reactions that occur in living things, it will be very important to always keep in mind that most of these reactions are occurring in an aqueous solution that is buffered to approximately pH 7.3 (the exceptions are reactions occuring in lysosomes and endosomes, specialized organelles in eukaryotic cells that maintain a slightly acidic interior). The buffer in a living cell is not composed of acetic acid/acetate mixture, or course – that would make the pH far too acidic. Rather, the chemistry of life occurs in a buffer that consists of a mixture of various phosphate and ammonium compounds.

So, what does the side chain of an aspartate amino acid residue look like if it is on the surface of a protein in an aqueous solution buffered to pH 7.0? Is it protonated or deprotonated? With an approximate pK_a of 3.9, the Henderson-Hasselbalch equation tells us that the side chain should be greater than 99% deprotonated:

$$7.0 = 3.9 + \log([A^-] / [HA])$$

$$([A^-] / [HA]) = 1.3 \times 10^3$$

$$\ldots \text{so, } [A^-] >> [HA]$$

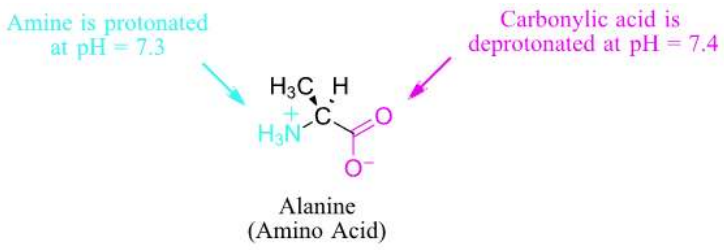
What about the amino group on a lysine side chain? With an approximate pK_a of 10.8, it should be >99% protonated, in the positively-charged, ammonium form:

$$7.0 = 10.8 + \log([A] / [HA^+])$$

$$([A] / [HA^+]) = 1.6 \times 10^{-4}$$

$$\ldots \text{so, } [HA^+] >> [A]$$

So, in an aqueous solution buffered at pH 7, carboxylic acid groups can be expected to be essentially 100% deprotonated and negatively charged (ie. in the carboxylate form), and amine groups essentially 100% protonated and positively charged (i.e., in the ammonium form). Alcohols are fully protonated and neutral at pH 7, as are thiols. The imidizole group on the histidine side chain has a pK_a near 7, and thus exists in physiological solutions as mixture of both protonated and deprotonated forms.



Alanine
(Amino Acid)

https://chem.libretexts.org/@go/page/91033

EXERCISE

EXERCISE 24.5.1

Would you expect an aromatic hetererocycle, pyrrole, to be protonated at pH = 7.3? Use the Henderson-Hasselbalch equation to determine your answer. pKa of protonated pyrrole is 0.4.

Answer

$7.3 = 0.4 + \log ([RNH_2] / [RNH_3^+])$

$([RNH_2] / [RNH_3^+]) = 7.9 \times 10^6$

. . . so, $[RNH_2] >> [RNH_3^+]$ so pyrrole would be almost completely unprotonated at pH = 7.

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24.6 SYNTHESIS OF AMINES

Objectives

After completing this section, you should be able to

1. write equations to illustrate the synthesis of amines by
   a. reduction of nitriles or amides and nitro compounds.
   b. reactions involving alkyl groups:
      i. S_N2 reactions of alkyl halides, ammonia and other amines.
      ii. nucleophilic attack by an azide ion on an alkyl halide, followed by reduction of the azide so formed.
      iii. alkylation of potassium phthalimide, followed by hydrolysis of the *N*-alkyl phthalimide so formed (i.e., the Gabriel synthesis).
   c. reductive amination of aldehydes or ketones.
   d. Hofmann or Curtius rearrangements.
2. write detailed mechanisms for each of the steps involved in the synthetic routes outlined in Objective 1.
3. identify the product or products formed when
   a. a given nitrile or amide is reduced using lithium aluminum hydride.
   b. a given alkyl halide is reacted with ammonia or an alkylamine.
   c. a given alkyl halide is reacted with azide ion and the resulting product is reduced.
   d. a given alkyl halide is reacted with potassium phthalimide and the resulting product is hydrolyzed.
   e. a given aldehyde or ketone is reacted with ammonia or an amine in the presence of nickel catalyst.
   f. a given amide is treated with halogen and base.
   g. a given acyl azide is heated and then hydrolyzed.
4. identify the starting material, the other reagents, or both, needed to synthesize a given amine by any of the routes listed in Objective 1.
5. write a general equation to illustrate the preparation of an arylamine by the reduction of a nitro compound, and balance such an equation.
6. identify the product formed from the reduction of a given aromatic nitro compound.
7. identify the organic compound, the inorganic reagents, or both, needed to prepare a given arylamine.

KEY TERMS

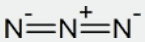
Make certain that you can define, and use in context, the key terms below.

- azide synthesis
- Curtius rearrangement
- Hofmann rearrangement
- Gabriel synthesis
- imide
- reductive amination

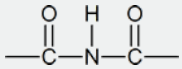
STUDY NOTES

You may wish to review the mechanism of S_N2 reactions which is discussed in some detail in Sections 11.2 and 11.3.

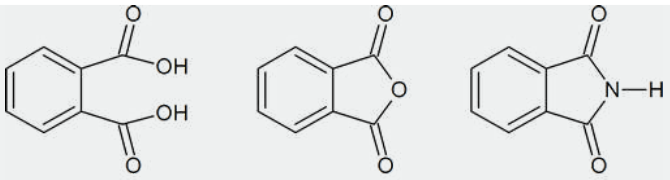
Azide synthesis is the first method on the table of synthesis of primary amines. The Lewis structure of the azide ion, N_3^-, is as shown below.



An “imide” is a compound in which an N—H group is attached to two carbonyl groups; that is,



You should note the commonly used trivial names of the following compounds.



phthalic acid phthalic anhydride phthalimide

The phthalimide alkylation mentioned in the reading is also known as the Gabriel synthesis.

If necessary, review the reduction of nitriles (Section 20.7) and the reduction of amides (Section 21.7).

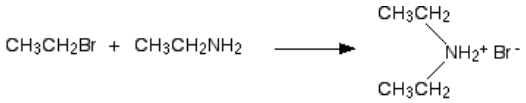
Before you read the section on reductive amination you may wish to remind yourself of the structure of an imine (see Section 19.8).

The Hofmann rearrangement is usually called the Hofmann degradation. In a true rearrangement reaction, no atoms are lost or gained; however, in this particular reaction one atom of carbon and one atom of oxygen are lost from the amide starting material, thus the term "rearrangement" is not really appropriate. There is a rearrangement step in the overall degradation process, however: this is the step in which the alkyl group of the acyl nitrene migrates from carbon to nitrogen to produce an isocyanate.

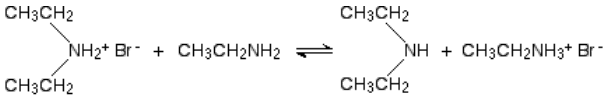
You get a complicated series of reactions on heating primary amines with halogenoalkanes to give a mixture of products - probably one of the most confusing sets of reactions you will meet at this level. The products of the reactions include secondary and tertiary amines and their salts, and quaternary 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



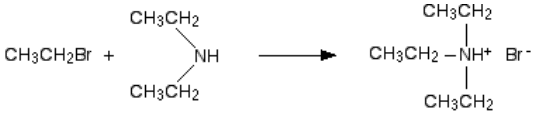
In the presence of excess ethylamine in the mixture, there is the possibility of a reversible reaction. The ethylamine removes a hydrogen from the diethylammonium ion to give free diethylamine - a secondary amine.



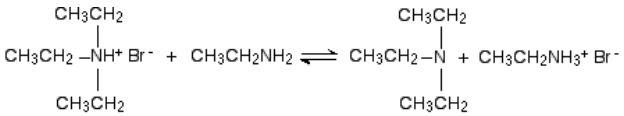
MAKING TERTIARY AMINES AND THEIR SALTS

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.



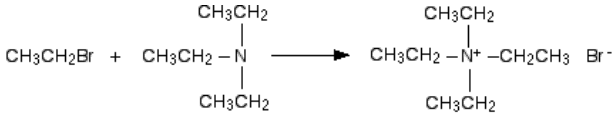
There is again the possibility of a reversible reaction between this salt and excess ethylamine in the mixture.



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).



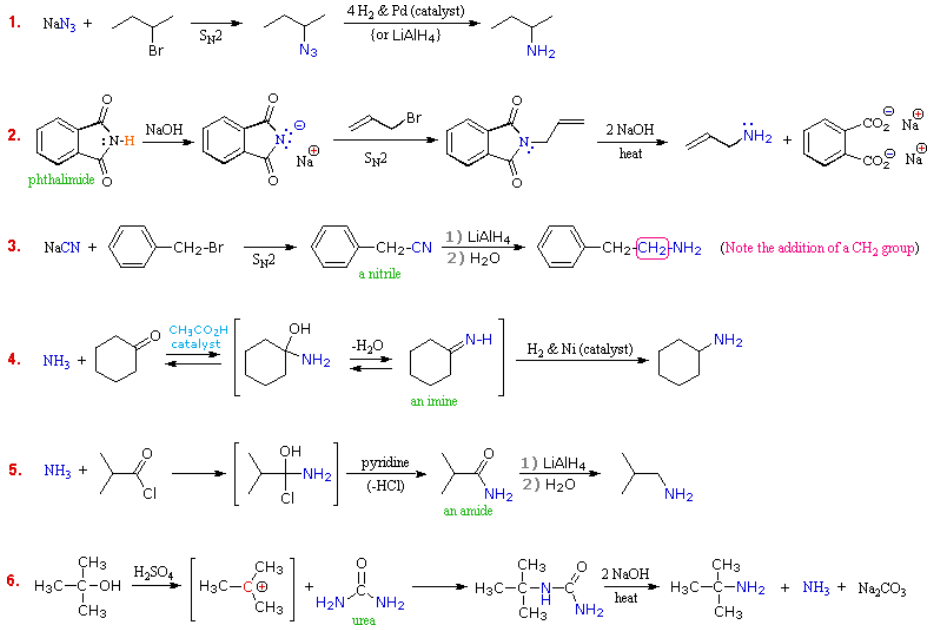
This time there isn't any hydrogen left on the nitrogen to be removed. The reaction stops here.

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
$C_6H_5SO_2NH^{(-)}$	RCH_2-X or R_2CH-X	S_N2	RCH_2-$NHSO_2C_6H_5$ or R_2CH-$NHSO_2C_6H_5$	Na in NH_3 (liq)	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 an acidic phthalimide derivative of ammonia has been substituted for the sulfonamide analog listed in the table. The principle is the same for the two cases, as will be noted later. Example #3 is similar in nature, but extends the carbon system 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 attack of ammonia, or equivalent nitrogen nucleophiles, at the electrophilic carbon of a carbonyl group. A full discussion of carbonyl chemistry is presented later, but for present purposes it is sufficient to recognize that the C=O double bond is polarized so that the carbon atom is electrophilic. Nucleophile 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 $LiAlH_4$.

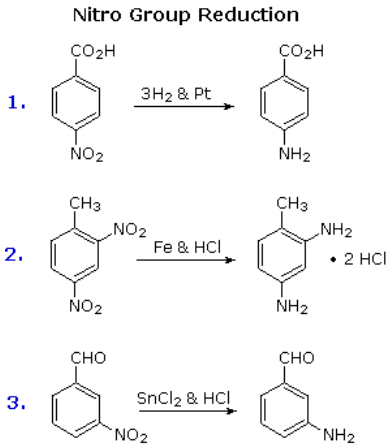
The 6th example is a specialized procedure for bonding an amino group to a 3º-alkyl group (none of the previous methods accomplishes this). Since a carbocation is the electrophilic species, rather poorly nucleophilic nitrogen reactants can be used. Urea, the diamide of carbonic acid, fits this requirement 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.

The Hofmann rearrangement of 1º-amides provides an additional synthesis of 1º-amines.

REDUCTION OF OTHER FUNCTIONAL GROUPS THAT CONTAIN NITROGEN

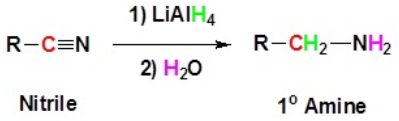
REDUCTION OF NITRO GROUPS

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

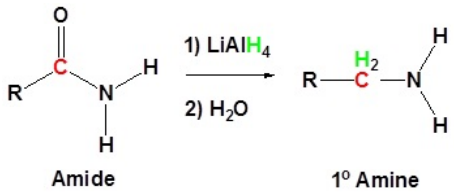


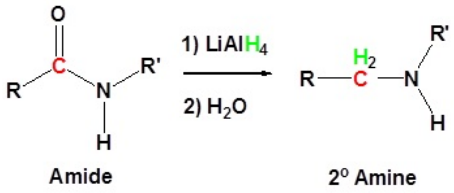
NITRILES CAN BE CONVERTED TO 1° AMINES BY REACTION WITH $LiALH_4$

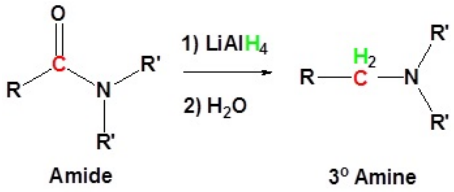
During this reaction the hydride nucleophile attacks the electrophilic carbon in the nitrile to form an imine anion. Once stabilized by a Lewis acid-base complexation the imine salt can accept a second hydride to form a dianion. The dianion can then be converted to an amine by addition of water.



AMIDES CAN BE CONVERTED TO 1°, 2° OR 3° AMINES USING $LiALH_4$

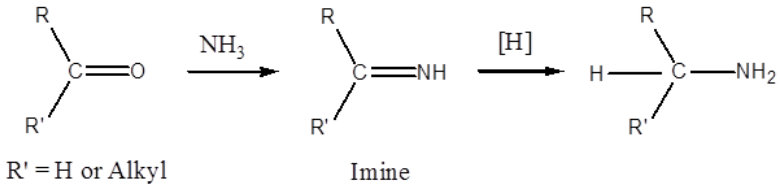


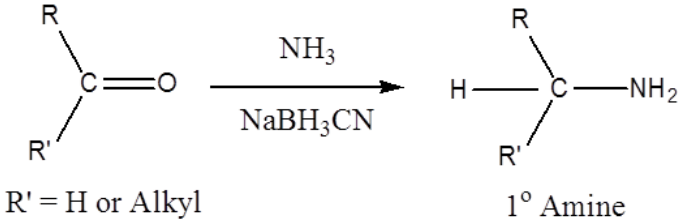


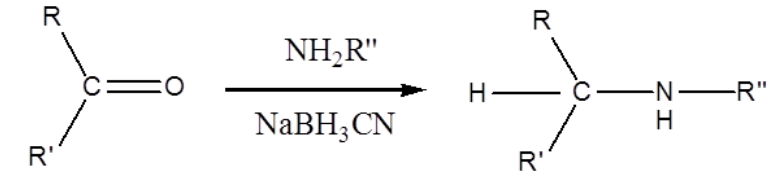


REDUCTIVE AMINATION

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 ($NaBH_3CN$).

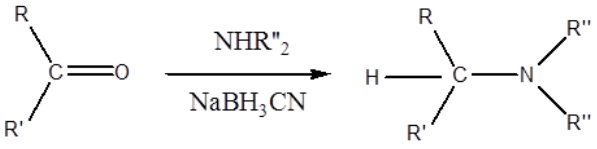






R' = H or Alkyl

2° Amine

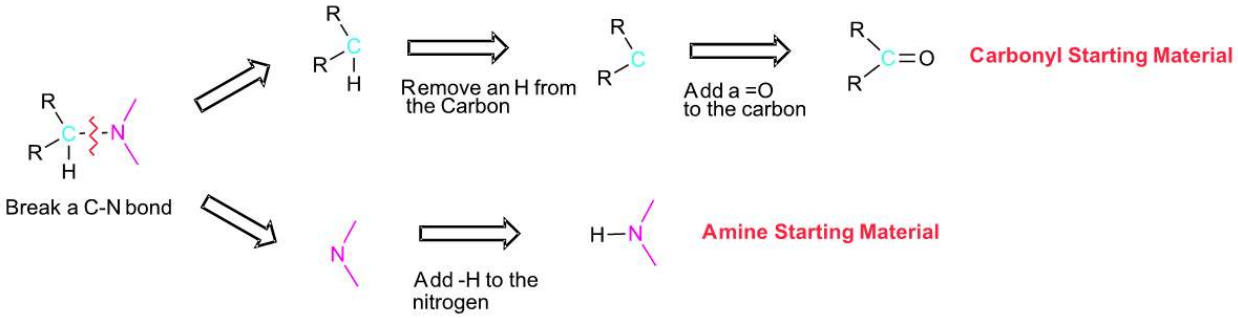


R' = H or Alkyl

3° Amine

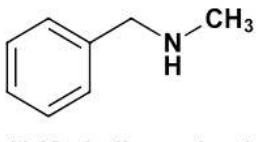
Planning a Synthesis using a Reductive Amination

If you are trying to develop a synthesis of an amine molecule, the key bond break is a C-N bond in the target molecule. There may be multiple C-N bonds present, so each should be broken separately to produce a possible set of starting materials. Because the amine is commonly used in excess during a reductive animation, the pathway which provides the simplest amine starting material is preferred. The carbon from the broken C-N bond goes on to become a carbonyl starting material. The nitrogen gains a hydrogen to become the amine starting material.



? WORKED EXERCISE 24.6.1

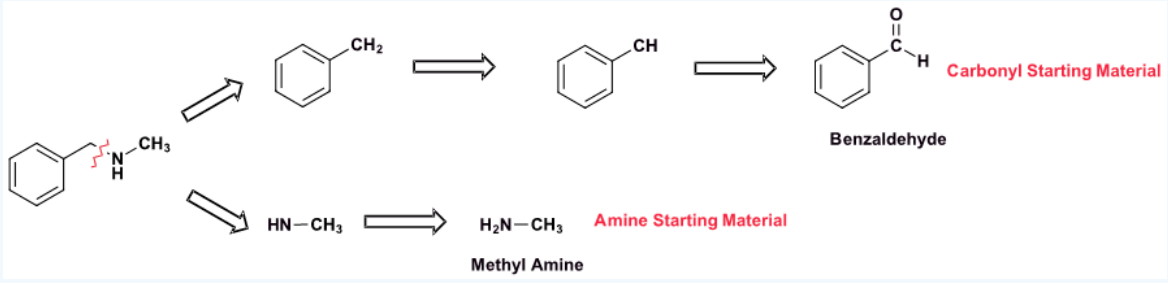
Show how N-methylbenzylamine can be synthesized using a reductive amination. If more than one pathway is possible, draw them both and determine which one would be preferred.



N-Methylbenzylamine

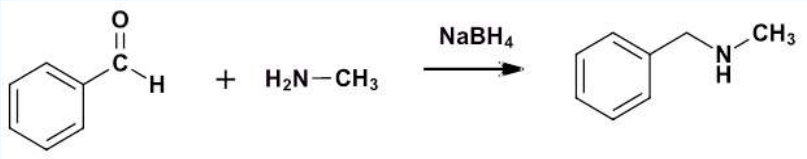
Answer

Pathway 1

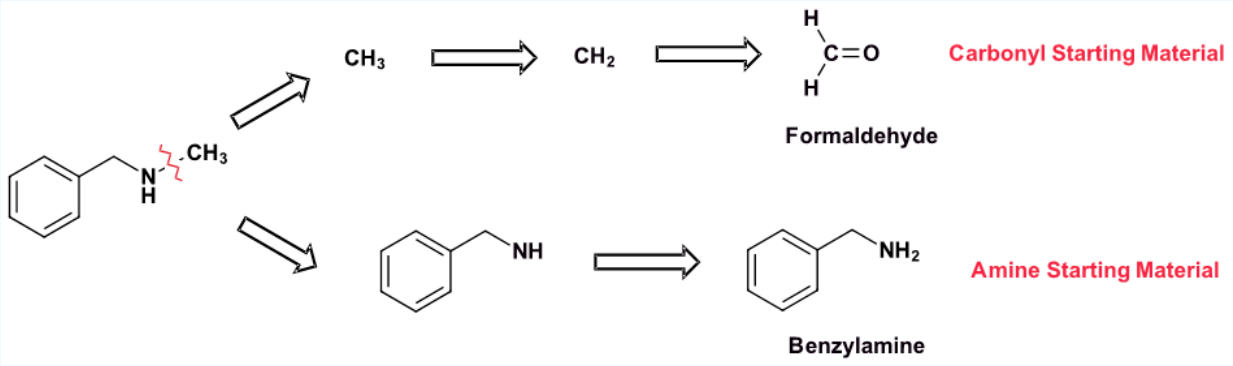


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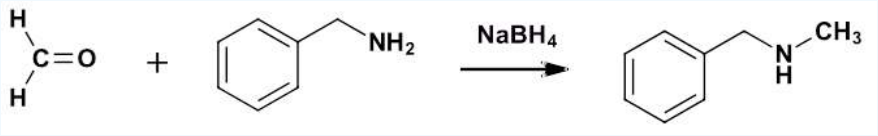
Solution 1



Pathway 2



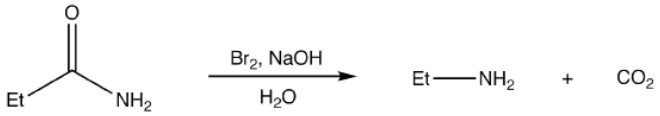
Solution 2



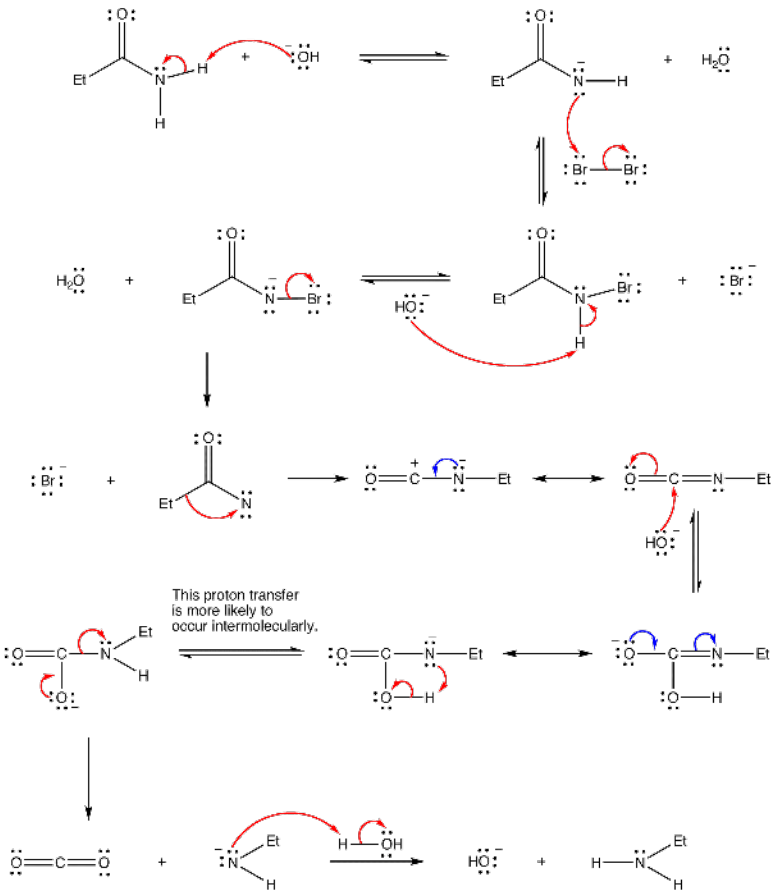
Because N-methylbenzylamine has two C-N bonds there are two possible synthesis pathways. Pathway 1 is most likely preferred because it uses the simplest amine starting material, methyl amine.

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:

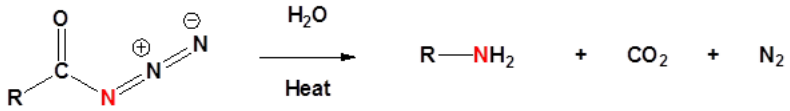


Mechanism:

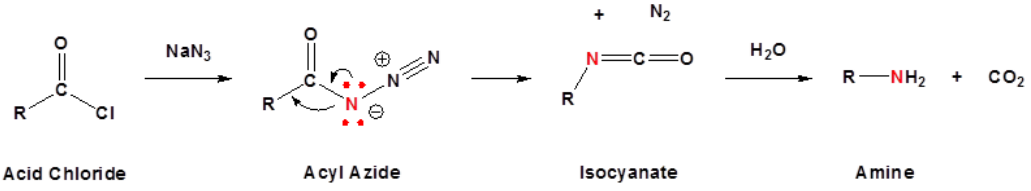


CURTIUS REARRANGEMENT

The Curtius rearrangement involves an acyl azide.

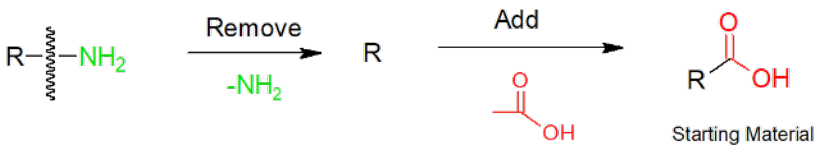


The mechanism of the Curtius rearrangement involves the migration of an -R group form the carbonyl carbon to the the neighboring nitrogen.



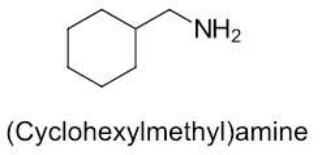
Planning a Synthesis using a Hofman or Curtius Rearrangement

Because the amide and the acyl azide required for these rearrangements both are best made from an acid chloride, synthesis of amines using these reaction are best started from the corresponding carboxylic acid. For retrosynthetic analysis starting from the desired amine product - the key break is the C-NH_2 bond. The amine is removed and replaced with a -CO_2H fragment to provide the required carboxylic acid starting material.



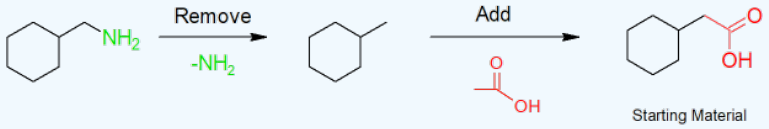
WORKED EXAMPLE 24.6.2

Show how the following molecule could be prepared from a carboxylic acid starting material using both the Hoffman and Curtius rearrangements.



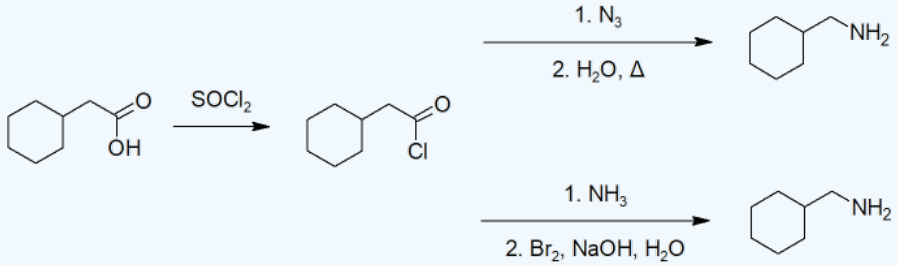
Answer

First determine the structure of the carboxylic acid starting material. This will be the starting material for both rearrangements. In the first step, convert the carboxylic acid into an acid halide using thionyl chloride ($SOCl_2$). Then use the required conditions for each rearrangement.



Solution

The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



EXERCISES

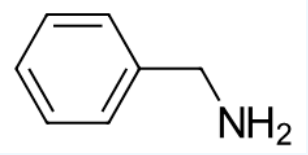
EXERCISE 24.6.1

Propose structures of the starting materials needed to make the the following amines using the reduction of a nitrile or an amide:

a) $CH_3CH_2CH_2CH_2NH_2$

b) $(CH_3CH_2)_2NH$

c)



e) N-Propylaniline

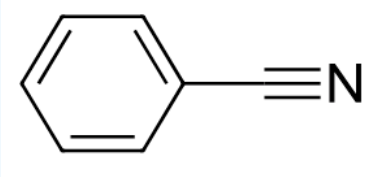
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Answer

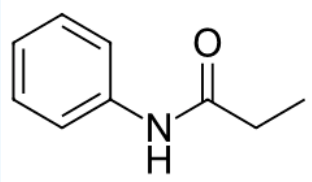
a) $CH_3CH_2CH_2CONH_2$

b) $CH_3CONHCH_2CH_3$

c)



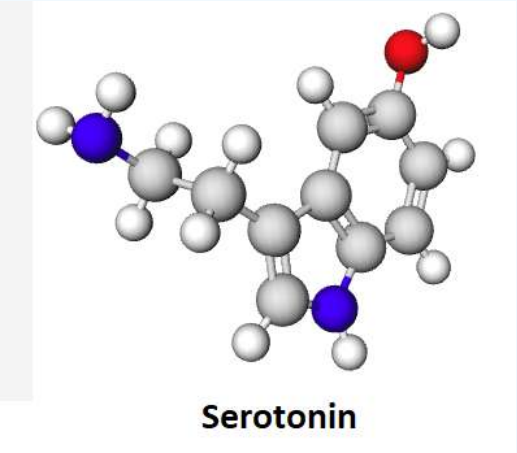
e)



? EXERCISE 24.6.2

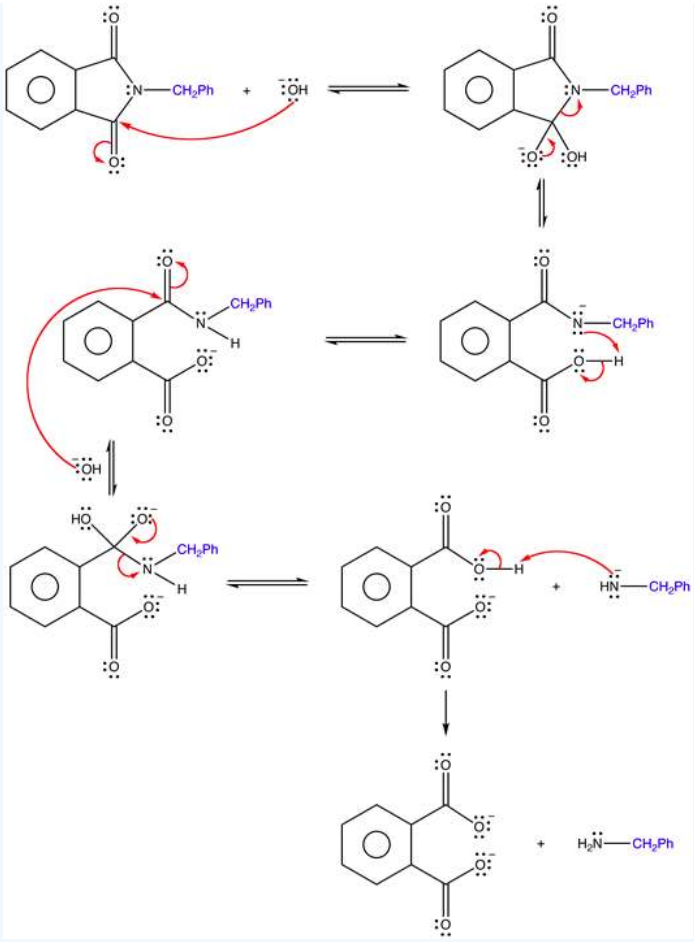
1) Write the mechanism for the base promoted hydrolysis of an N-alkyl phthalimide to create a 1° amine and the phthalate ion.

2) Starting with any alkyl halide, show two methods to synthesize the neurotransmitter serotonin.

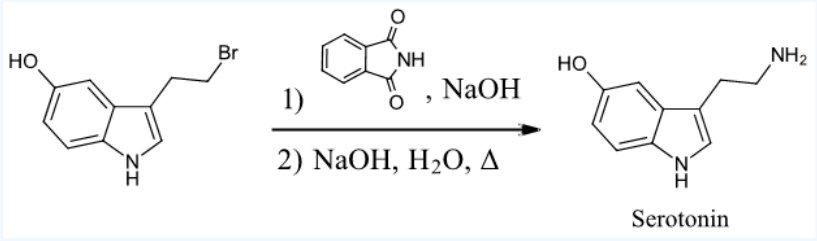


Answers

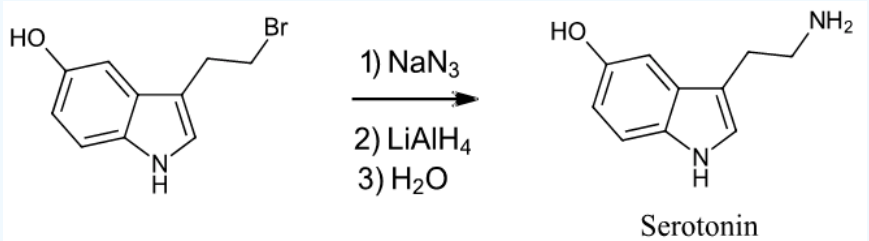
1)



2)



Serotonin



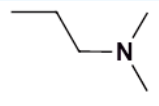
Serotonin

? EXERCISE 24.6.3

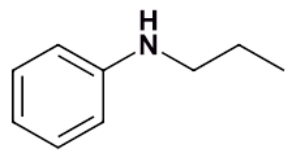
Provide starting materials which could be used to prepare the following compounds using a reductive amination. Show all possible pathways.

1)

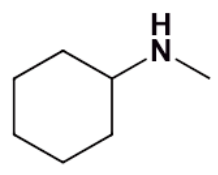
a)



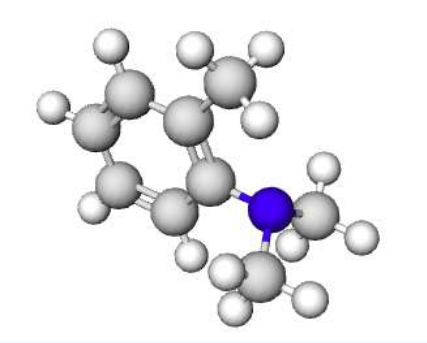
b)



c)



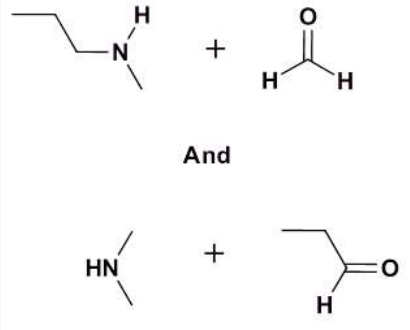
2) Please give the starting materials which could provide the following molecule using a reductive amination.



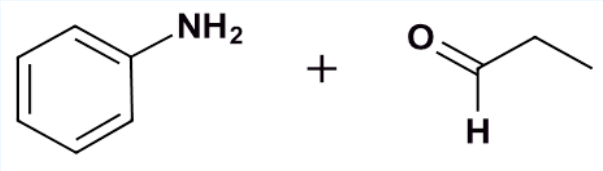
Answer

1)

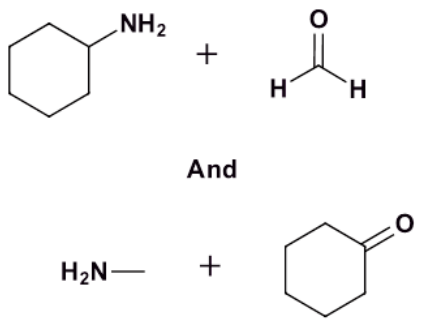
a)



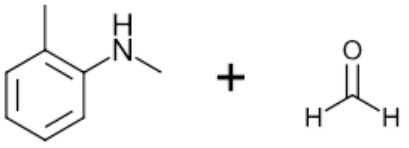
b)



c)



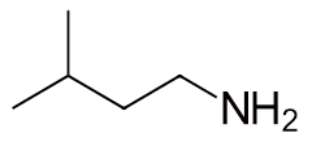
2)



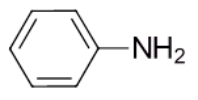
EXERCISES 24.6.4

1) Using a carboxylic acid starting material explain how to prepare the following molecules using both the Hoffman and Curtius rearrangements.

a)



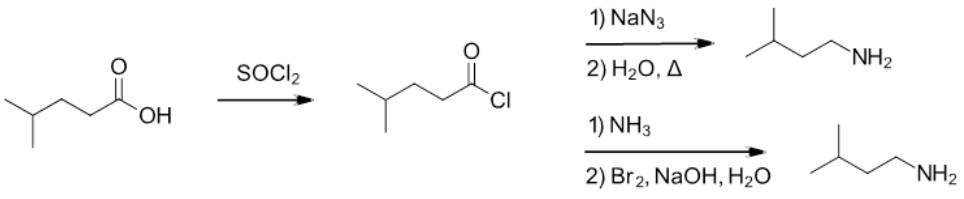
b)



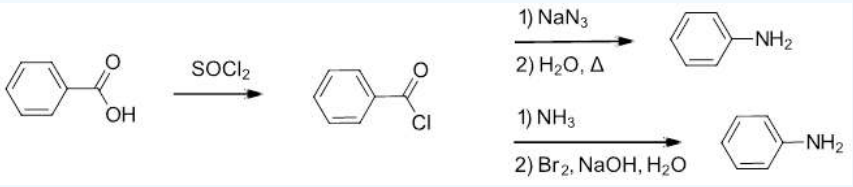
Answers

1)

a) The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



b) The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



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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24.7 REACTIONS OF AMINES

Objectives

After completing this section, you should be able to

1. write an equation to represent the reaction that takes place between ammonia, a primary or secondary amine, and an acid chloride.
2. identify the product formed when a given amine reacts with a given acid chloride.
3. identify the amine, the acid chloride, or both, needed to synthesize a given amide.
4. write a reaction sequence to illustrate the overall conversion of an amine to an alkene via a Hofmann elimination.
5. identify the alkene most likely to be formed when a given quaternary ammonium salt is heated with moist silver oxide (or silver hydroxide).
6. deduce the structure of an unknown quaternary ammonium salt, given the identity of the alkene or alkenes produced when the salt is heated with moist silver oxide.

KEY TERMS

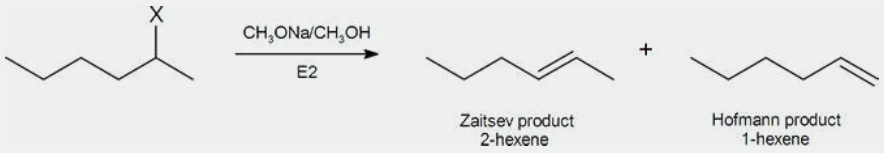
Make certain that you can define, and use in context, the key term below.

- Hofmann elimination

STUDY NOTES

The alkylation and acylation of amines have been dealt with in previous sections: alkylation in Section 24.6 and acylation in Sections 21.4 and 21.5. Review these sections if necessary.

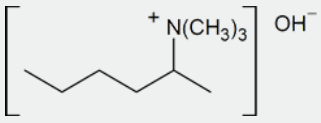
One explanation is given for Hofmann elimination further on in this reading. Another argument, based on the consideration of the structures of the possible transition states, has been suggested by Joseph Bunnett (Professor Emeritus, University of California, Santa Cruz) and is widely accepted. We can begin to understand Bunnett's reasoning by considering the elimination products formed from by the dehydrohalogenation of a number of substituted hexanes in the reaction



The table below describes the proportion of each product you would expect when X in the above reaction represents a given halogen.

X	% 2-hexene	% hexene
I	81	19
Br	72	28
Cl	67	33
F	30	70

As we descend this table, the electron-withdrawing ability of X increases, and the percentage of Hofmann product also increases. Given that the $(CH_3)_3N^+$ group is strongly electron-withdrawing, it is quite consistent for a compound of the type



to give 96% Hofmann product and 4% Zaitsev product in an E2 elimination reaction. But why does the proportion of Hofmann product increase as the electron-withdrawing ability of X increases? Bunnett suggests that the transition state in an E2 process can vary from being "carbocation-like" on one hand to "carbanion-like" on the other.

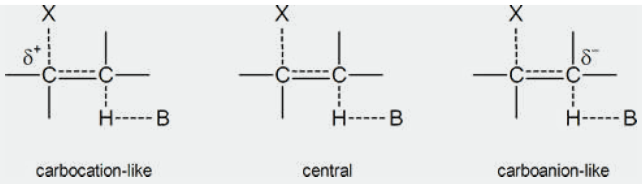
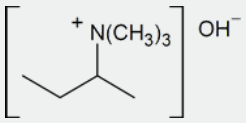


Figure24.1 Various transition states for an E2 elimination reaction

In a carbocation-like transition state, the C—X bond is broken to a greater extent than the C—H bond; in the central transition state both, the C—X bond and the C—H bond are broken to an equal extent; and in the carbanion-like transition state, the C—H bond is broken to a greater extent than the C—X bond. In the latter case, a partial negative charge will develop on the carbon atom to which the hydrogen is attached, hence the term "carbanion-like." As we already know, any species or transition state bearing a full or partial negative charge is stabilized by the presence of electron-withdrawing groups and destabilized by the presence of electron-releasing groups.

Let us now consider the two possible transition states for an E2 elimination of $(CH_3)_3NH^+$ from a quaternary ammonium hydroxide,



One transition state leads to Zaitsev elimination, the other to Hofmann elimination.

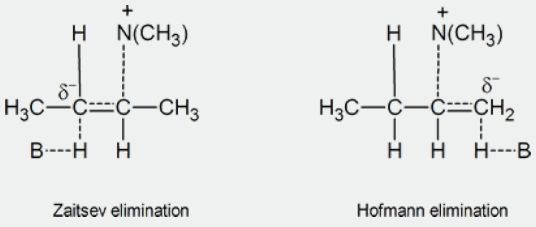
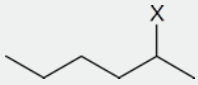


Figure24.2 Possible carbanion-like transition states

In the transition state leading to the Zaitsev product, the carbon atom carrying the partial negative charge is bonded to an electron-releasing methyl group. This is clearly a less favourable situation than the one that exists in the transition state leading to Hofmann elimination, where there are no electron-releasing groups attached to the carbon atom bearing the partial negative charge. Bunnett's argument is that carbanion-like transition states are much more likely when the atom or group X in a compound such as



is strongly electron withdrawing, because the C—X bond becomes stronger as the electron-withdrawing ability of X increases.

Thus, as we go along the series X = I, Br, Cl, F, $(CH_3)_3N^+$, the electron-withdrawing ability of X increases, the C—X bond becomes more difficult to break, the transition state becomes more carbanion-like in character, and Hofmann elimination becomes more pronounced.

ALKYLATION

It is instructive to examine these nitrogen substitution reactions, using the common alkyl halide class of electrophiles. Thus, reaction of a primary alkyl bromide with a large excess of ammonia yields the corresponding 1°-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 1°-alkyl halides to give alcohols, so the enhanced nucleophilicity of nitrogen relative to oxygen is clearly demonstrated.

$$2\ RCH_2Br + NH_3\ (\text{large excess}) \longrightarrow RCH_2NH_2 + NH_4^{(+)}\ Br^{(-)}$$

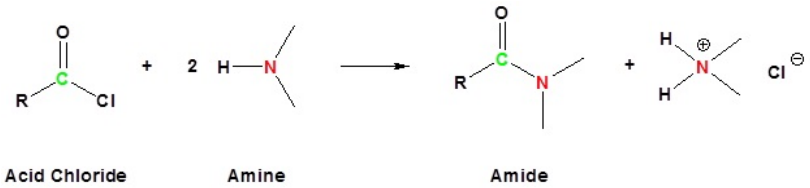
It follows that simple amines should also be more nucleophilic than their alcohol or ether equivalents. If, for example, we wish to carry out an S_N2 reaction of an alcohol with an alkyl halide to produce an ether (the Williamson synthesis), it is necessary to convert the weakly nucleophilic alcohol 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.

$$2\ RNH_2 + C_2H_5Br \longrightarrow RNHC_2H_5 + RNH_3^{(+)}\ Br^{(-)} \rightleftharpoons RNH_2C_2H_5^{(+)}\ Br^{(-)} + RNH_2$$

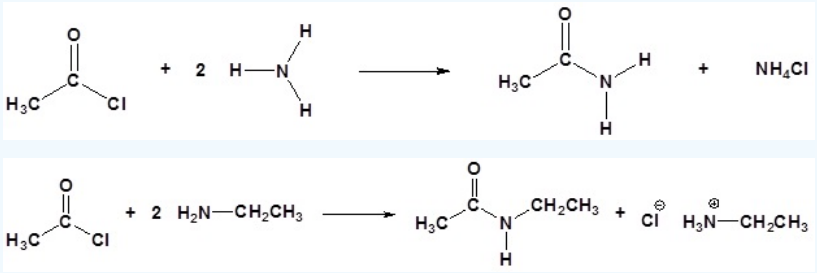
Unfortunately, the direct alkylation of 1º or 2º-amines to give a more substituted product does not proceed cleanly. If a 1:1 ratio of amine to alkyl halide is used, only 50% of the amine will react because the remaining amine will be tied up as an ammonium halide salt (remember that one equivalent of 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.

$$C_6H_5NH_2 + 3\ CH_3I + \text{Hünig's base} \longrightarrow C_6H_5N(CH_3)_3^{(+)}\ I^{(-)} + \text{HI salt of Hünig's base}$$

ACYLATION



EXAMPLE 24.7.1



Amine functions 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. In the case of alcohols and ethers, a useful technique for enhancing the reactivity of the oxygen function was to modify the leaving group ($OH^{(-)}$ or $OR^{(-)}$) to improve its stability as an anion (or equivalent). This stability is conveniently estimated from the strength of the corresponding conjugate acids.

As noted earlier, 1º and 2º-amines are much weaker acids than alcohols, so it is not surprising that it is difficult to force the nitrogen function to assume the role of a nucleophilic leaving group. For example, heating an amine with HBr or HI does not normally convert it to the corresponding alkyl halide, as in the case of alcohols and ethers. In this context we note that the acidity of the putative ammonium leaving group is at least ten powers of ten less than that of an analogous oxonium species. The loss of nitrogen from diazonium intermediates is a notable exception in this comparison, due to the extreme stability of this leaving group (the conjugate acid of N_2 would be an extraordinarily strong acid).

One group of amine derivatives that have proven useful in S_N2 and E2 reactions is that composed of the tetraalkyl (4º-) ammonium salts. Most applications involving this class of compounds are eliminations, but a few examples of S_N2 substitution have been reported.

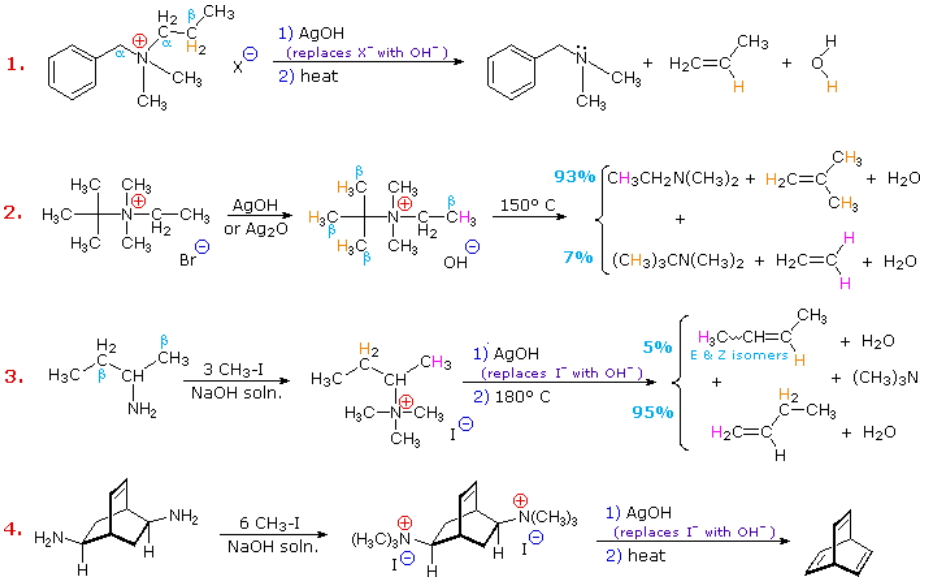
$$C_6H_5\text{–}N(CH_3)_3^{(+)}\ Br^{(-)} + R\text{-}S^{(-)}\ Na^{(+)} \xrightarrow{\text{acetone \& heat}} R\text{-}S\text{-}CH_3 + C_6H_5\text{–}N(CH_3)_2 + NaBr$$

$$(CH_3)_4N^{(+)}\ OH^{(-)} \xrightarrow{\text{heat}} CH_3\text{–}OH + (CH_3)_3N$$

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.



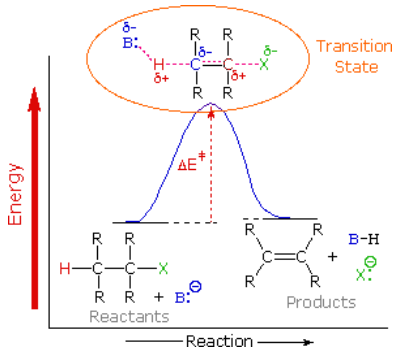
In example #2 above, two of the alkyl substituents on nitrogen have beta-hydrogens, all of which are on methyl groups (colored orange & magenta). The chief product from the elimination is the alkene having the more highly substituted double bond, reflecting not only the 3:1 numerical advantage of those 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 4°-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 4°-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.

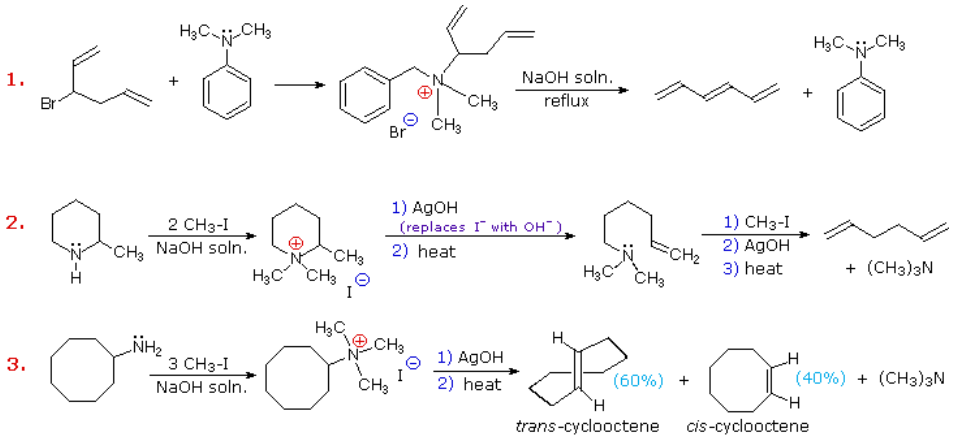


The E2 transition state is less well defined than is that of S_N2 reactions. More bonds are being broken and formed, with the possibility of a continuum of states in which the extent of C–H and C–X bond-breaking and C=C bond-making varies. For example, if the bond to the leaving group (X) is substantially 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**.

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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.

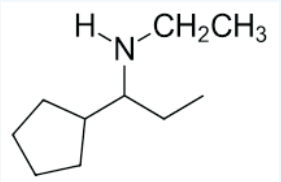


Example #2 illustrates an important aspect of the Hofmann elimination. If the nitrogen atom is part of a ring, then a single application of this elimination procedure does not remove the nitrogen as a separate 3º-amine product. In order to sever the nitrogen function from the molecule, a second Hofmann 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.

? WORKED EXERCISE 24.7.1

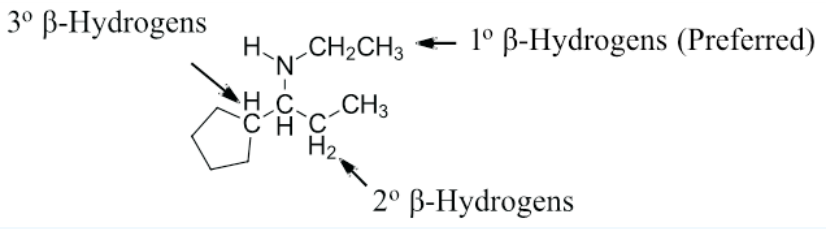
Predict the preferred product of a Hofmann elimination with the following molecule.



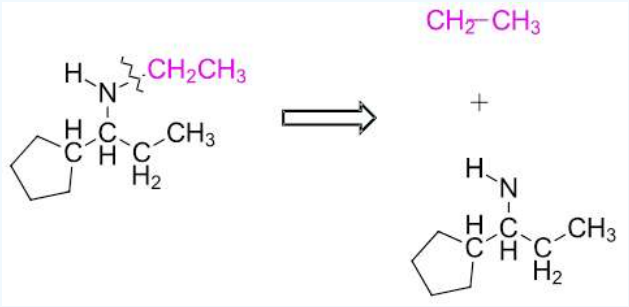
Answer

Predicting the product of a Hofmann elimination can be difficult so it is best done stepwise.

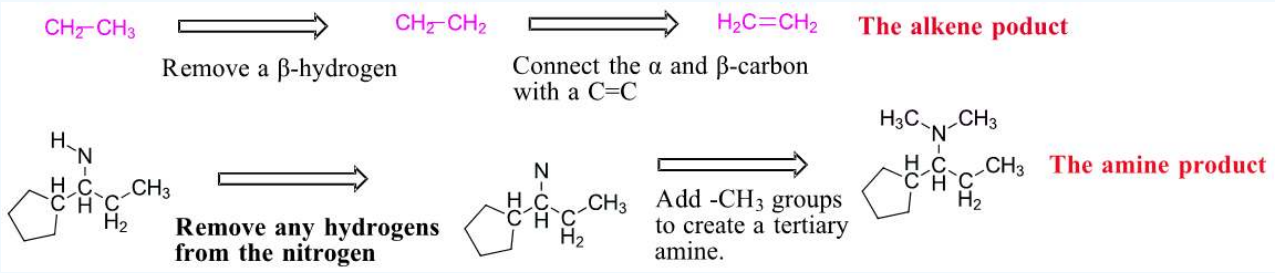
1) Find the least sterically hindered beta hydrogens. Beta hydrogens are on the second carbon away from the nitrogen. The order of preferred hydrogens are 1º > 2º > 3º. If the molecule is presented as a line structure it is usually beneficial to convert to a condensed structure first.



2) Break the C-N bond of the alkyl group which contains the preferred hydrogens. This will form two fragments.



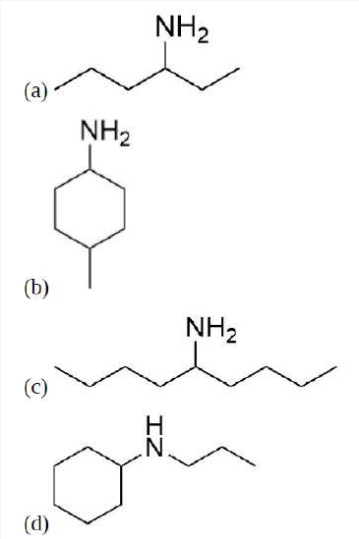
3) Remove one of the original beta hydrogens in the alkyl fragment then draw a C=C between the alpha and beta carbon. This produces the alkene product of the Hofmann elimination. Sometimes the amine fragment of a Hofmann elimination is of interest. Remember that prior to elimination the amine is exhaustively alkylated with CH_3I. This means any hydrogens attached to amine will starting material will be removed and the amine product will have enough methyl ($-CH_3$) groups added to become a tertiary amine. In this case two methyl groups are added to the nitrogen. The end result are the two products of a Hofmann elimination.



EXERCISES

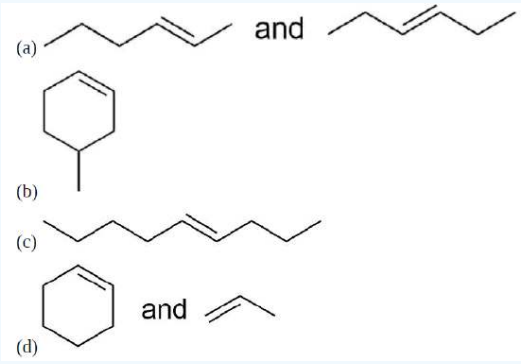
? EXERCISE 24.7.1

Draw the product for a Hofmann elimination for each of the following molecules.



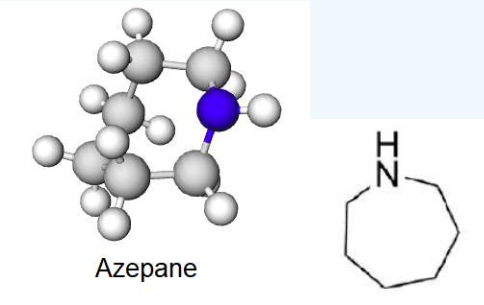
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Answer

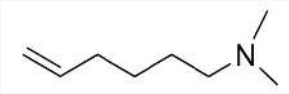


? EXERCISE 24.7.2

Draw the product of a Hofmann elimination for the following molecule.



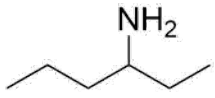
Answer

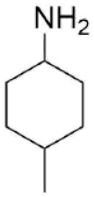


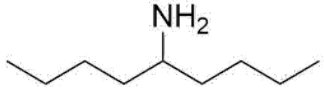
QUESTIONS

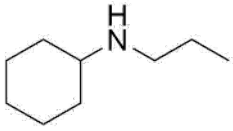
Q24.7.1

Draw the product for a Hoffman elimination for each of the following molecules.

(a) 

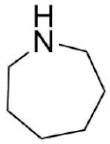
(b) 

(c) 

(d) 

Q24.7.2

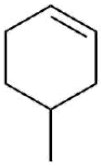
Draw the product of a Hoffman elimination for the following molecule.

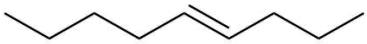


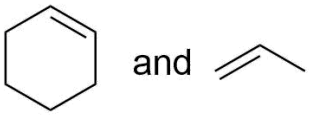
SOLUTIONS

S24.7.1

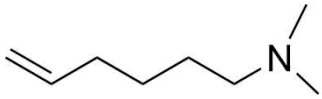
(a) 

(b) 

(c) 

(d) 

S24.7.2



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

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24.8 REACTIONS OF ARYLAMINES

Objectives

After completing this section, you should be able to

1. a. identify the product formed when a given arylamine is reacted with aqueous bromine.
   b. give an appropriate example to illustrate the high reactivity of arylamines in electrophilic aromatic substitution reactions.
   c. explain why arylamines cannot be used in Friedel-Crafts reactions.
2. a. show how the problems associated with carrying out electrophilic aromatic substitution reactions on arylamines can be circumvented by first converting the amine to an amide, and illustrate this process with an appropriate example.
   b. outline a possible synthetic route for the preparation of a given sulfa drug.
   c. identify the starting material, the necessary organic reagents, inorganic reagents, or both, and the intermediate compounds formed during the synthesis of a given sulfa drug.
   d. design a multi-step synthesis for a given compound in which it is necessary to protect the amino group by acetylation.
3. a. write a general equation to describe the formation of an arenediazonium salt.
   b. identify the product formed when a given arenediazonium salt is reacted with any of the following compounds: copper(I) chloride, copper(I) bromide, sodium iodide, copper(I) cyanide, hot aqueous acid, hypophosphorous acid.
   c. identify the arenediazonium salt, the inorganic reagents, or both, needed to produce a given compound by a diazonium replacement reaction.
4. a. illustrate, with appropriate examples, the importance to the synthetic chemist of the overall reaction sequence A nitration, B reduction, C diazotization, and D replacement.
   b. show how the removal of an amino (or nitro) group from an aromatic ring through the reaction of an arenediazonium salt with hypophosphorous acid (H_3PO_2) can sometimes be of use in organic synthesis.
5. a. write a general equation to represent a diazonium coupling reaction.
   b. write the detailed mechanism for the coupling reaction which takes place between arenediazonium salts and the electon-rich aromatic rings of phenols and arylamines.
   c. identify the product formed from the reaction of a given arenediazonium salt with a given arylamine or phenol.
   d. identify the arenediazonium salt and the arylamine or phenol needed to prepare a given azo compound.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

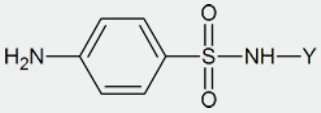
- arenediazonium salt
- azo compound
- Sandmeyer reaction
- sulfa drug

STUDY NOTES

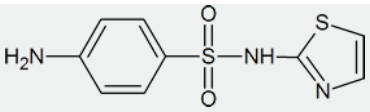
This section contains a considerable amount of new information. To absorb all of it, you should use the three subsections indicated in the reading: electrophilic aromatic substitution and overreaction of aniline (Objectives 1 and 2), the preparation of diazonium salts and the Sandmeyer reaction (Objectives 3 and 4), and diazonium coupling reactions (Objective 5).

The general process in which an aromatic amine is reacted with acetic anhydride, substituted, and then hydrolyzed is known as “protecting the amino group.”

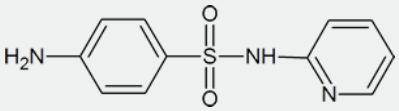
Sulfa drugs have the general formula



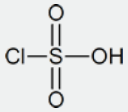
Typical examples are sulfathiazole



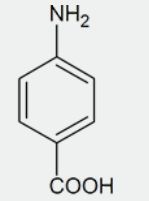
and sulfapyridine



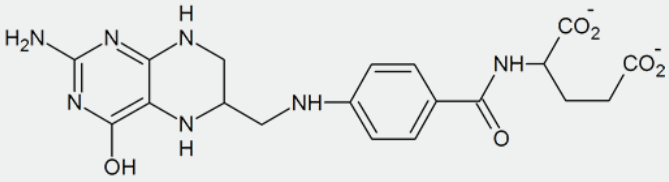
The reagent used to bring about the chlorosulfonation of acetanilide is chlorosulfuric acid



Sulfanilamide itself is toxic to humans, but derivatives of this compound, such as sulfathiazole, are less harmful to humans and are effective in killing many types of bacteria. The drugs work by "deceiving" the bacteria in the following way. To survive, many micro-organisms use *p*-aminobenzoic acid to synthesize folic acid, a coenzyme in a number of biochemical processes. These micro-organisms cannot distinguish between sulfa drugs and *p*-aminobenzoic acid; so, when the drug is administered, the bacteria use it to produce a compound which has a structure similar to that of folic acid, but which is unable to act as a coenzyme in essential biochemical processes. The result is that many of the bacteria's amino acids and nucleotides cannot be made, and the bacteria die. Amino acids are discussed in Chapter 26; nucleotides are discussed in Section 28.1.

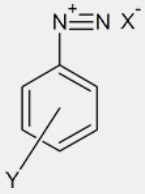


p-aminobenzoic acid



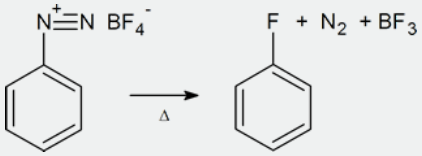
folic acid

An "arenediazonium salt" is formed by the reaction of an aromatic amine with nitrous acid at 0–5°C, and has the structure shown below.



Alkanediazonium salts are very unstable; therefore, arenediazonium salts are often simply referred to as diazonium salts.

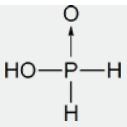
As is mentioned in the textbook, arenediazonium salts are very useful intermediates from which a wide variety of aromatic compounds can be prepared. You should be thoroughly familiar with the use of diazonium salts to prepare each of the classes of compounds. In addition, you should be aware that fluoroarenes can also be prepared from diazonium salts, as follows:



In this case the diazonium salt is prepared using fluoroboric acid, HBF_4, and sodium nitrite. The thermal decomposition of the salt, called the Schiemann reaction, can be quite hazardous.

Note that the IUPAC-preferred name for cuprous chloride is copper(I) chloride; similarly, cuprous cyanide is called copper(I) cyanide.

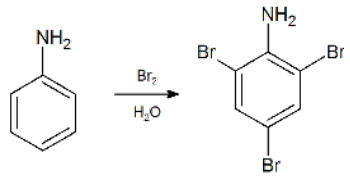
Hypophosphorous acid has the structure shown below:



The presence of the letters “azo” in a compound’s name usually implies that a nitrogen-nitrogen double bond is present in its structure. Azo compounds t in which two aryl groups are joined by an —N=N— linkage are usually very colourful.

OVERREACTION OF ANILINE

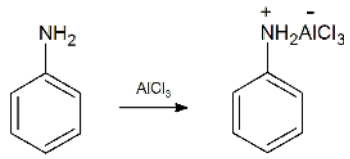
Arylamines are very reactive towards electrophilic aromomatic substitution. The strongest activating and ortho/para-directing substituents are the amino (-NH_2) and hydroxyl (-OH) groups. Direct nitration of phenol (hydroxybenzene) by dilute nitric acid gives modest yields of nitrated phenols and considerable 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.



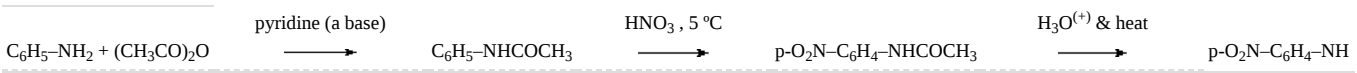
In addition to overreactivity, we have previously seen (Section 16.3) that Friedel-Crafts reactions employing $AlCl_3$ catalyst does not work with aniline. A salt complex forms and prevents electrophilic aromatic substitution.



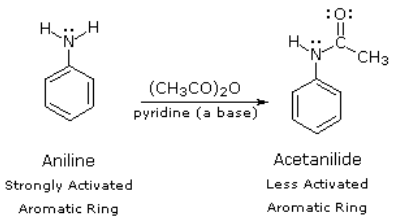
Both this problem and the aniline overreactivity can be circumvented by first going through the corresponding amide.

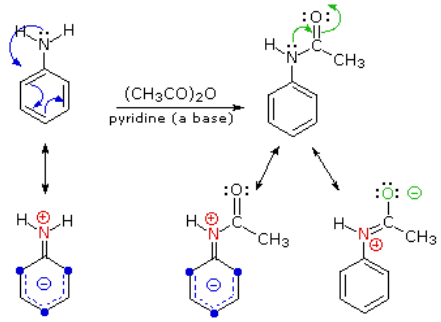
MODIFYING THE INFLUENCE OF STRONG ACTIVATING GROUPS

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.



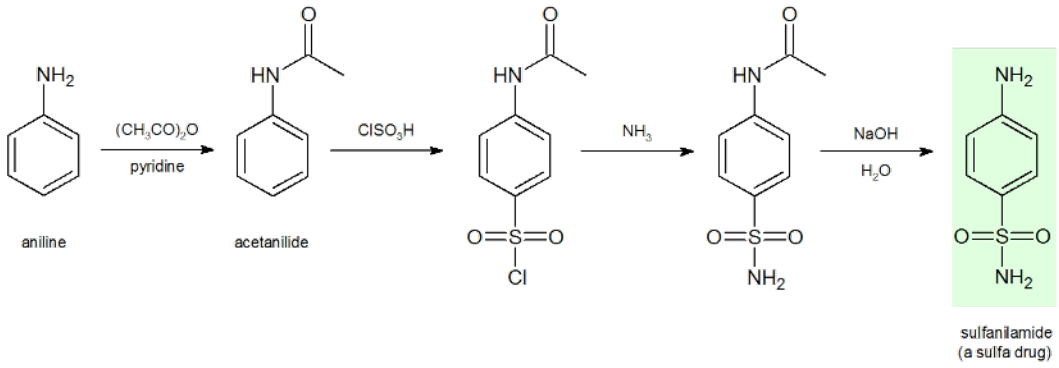
The following diagram illustrates how the acetyl group acts to attenuate the overall electron donating character of oxygen and nitrogen. The non-bonding valence electron pairs that are responsible for the high reactivity of these compounds (blue arrows) are diverted to the adjacent carbonyl group (green arrows). However, the overall influence of the modified substituent is still activating and ortho/para-directing.





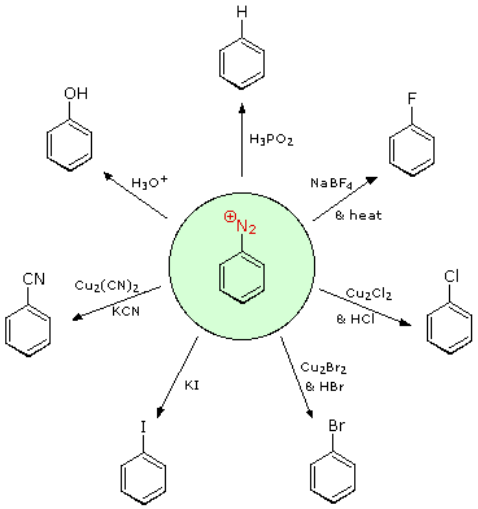
SULFA DRUG SYNTHESIS

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.



DIAZONIUM SALTS: THE SANDMEYER REACTION

Aryl diazonium salts are important intermediates. They are prepared in cold (0 ° 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:

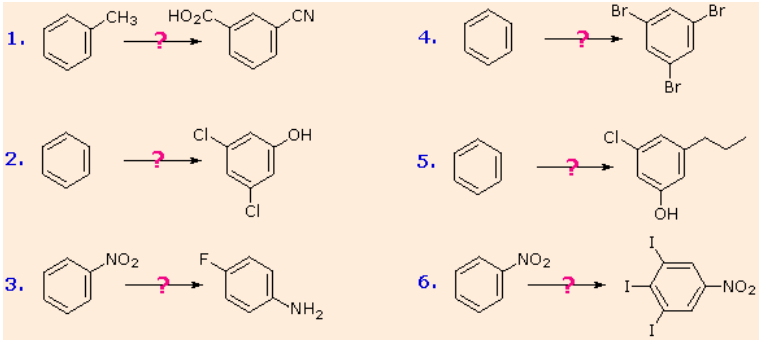
I. The usual precursor to an aryl amine is the corresponding nitro compound. A nitro substituent deactivates an aromatic ring and directs electrophilic substitution to meta locations.

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.

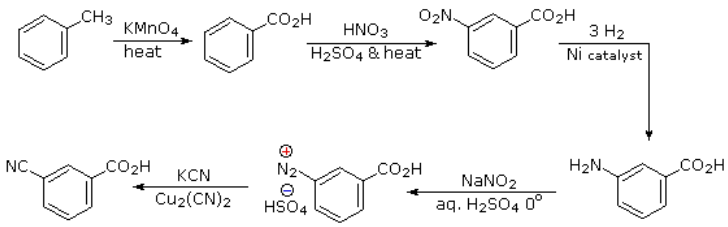
The following examples illustrate some combined applications of these options to specific cases. You should try to conceive a plausible reaction sequence for each. Once you have done so, you may check suggested answers below.



Answer 1:

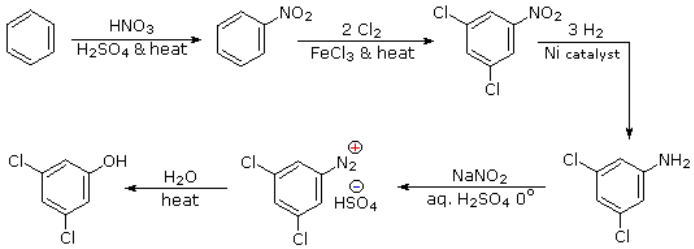
It should be clear that the methyl substituent will eventually be oxidized to a carboxylic acid function. The timing is important, since a methyl substituent is ortho/para-directing and the carboxyl substituent is meta-directing. The cyano group will be introduced by a diazonium intermediate, so a nitration followed by reduction to an amine must precede this step.

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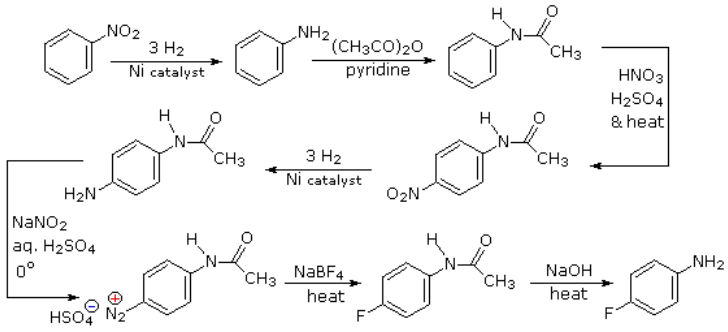
Answer 2:

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.



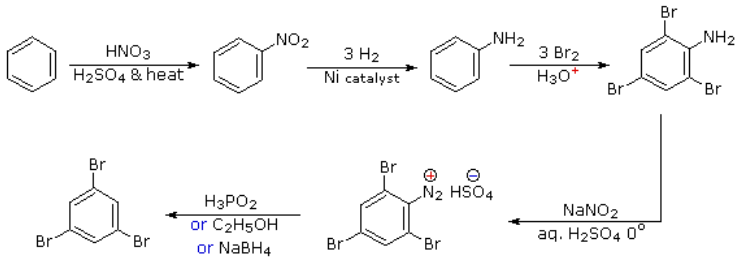
Answer 3:

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.



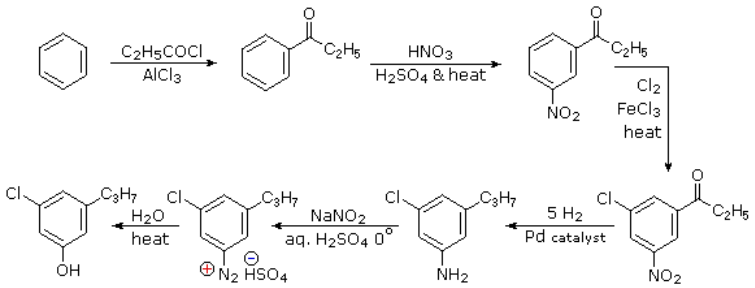
Answer 4:

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).



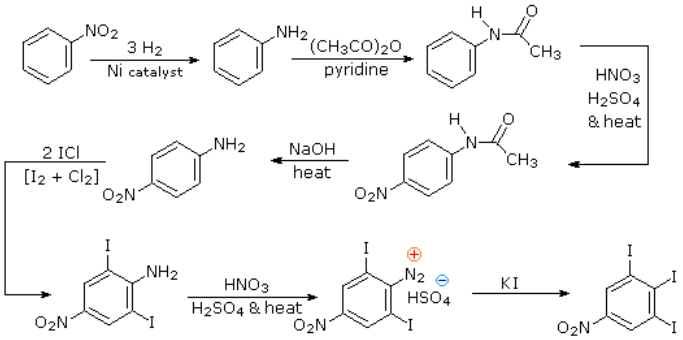
Answer 5:

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.



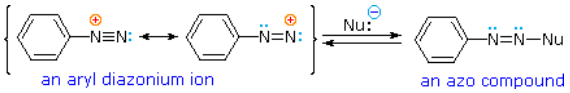
Answer 6:

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.



DIAZONIUM COUPLING REACTIONS

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.



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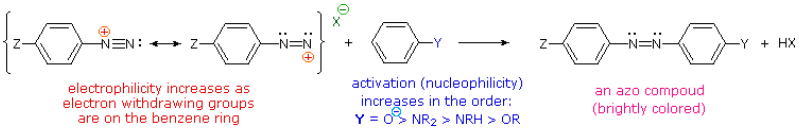
Unless these azo products are trapped or stabilized in some manner, reversal to the diazonium ion and slow nucleophilic substitution at carbon (with irreversible nitrogen loss) will be the ultimate course of reaction, as described in the previous section. For example, if phenyldiazonium bisufate is added 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.

$$Ar\text{-}N_2^{(+)}\ X^{(-)} \xrightarrow{NaHSO_3} Ar\text{-}N{=}N\text{-}SO_3H \xrightarrow{NaHSO_3} Ar\text{-}NH\text{-}NH\text{-}SO_3H \xrightarrow{H_2O} Ar\text{-}NH\text{-}NH_2 + H_2SO_4$$

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.



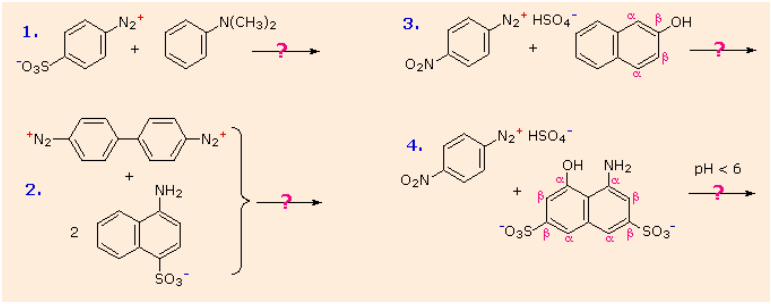
Some examples of azo coupling reactions are shown below. A few simple rules are helpful in predicting the course of such reactions:

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.

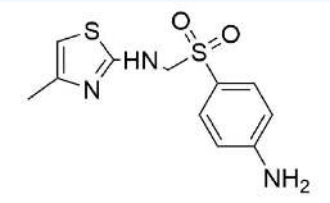
You should try to conceive a plausible product structure for each of the following couplings.



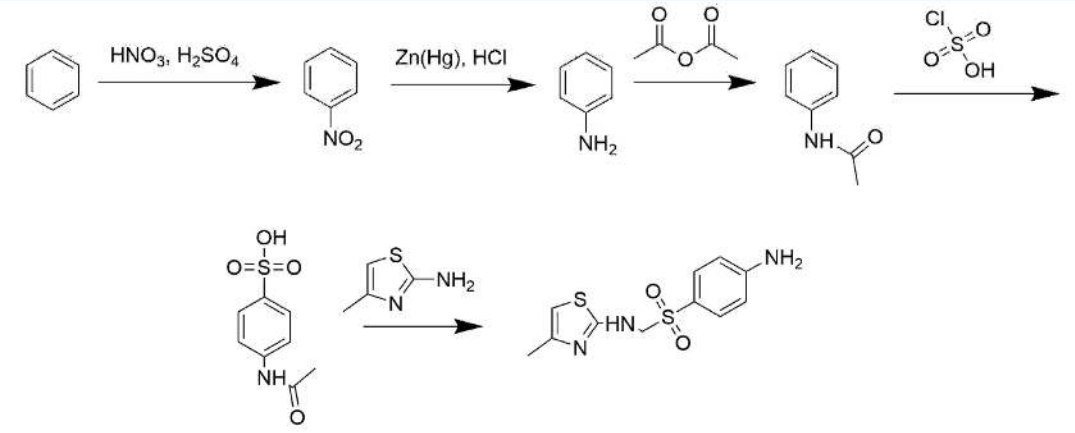
EXERCISES

? EXERCISE 24.8.1

Propose a synthesis for the following compound via benzene and any amine you may require.



Answer



EXERCISE 24.8.2

Propose a synthesis for each of the following compounds via benzene.

(a) N,N-Diethylaniline

(b) p-Bromoaniline

(c) m-Bromoaniline

(d) 2,4-Diethylaniline

Answer

(a) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. EtBr

(b) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. (CH CO)O ; 4. Br , FeBr ; 5. H O, NaOH

(c) 1. HNO , H SO ; 2. Br , FeBr ; 3. Zn(Hg), HCl

(d) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. (CH CO)O ; 4. EtCl, AlCl ; 5. H O, NaOH

EXERCISE 24.8.3

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

Answer

(a) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. EtBr

(b) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. (CH CO)O ; 4. Br , FeBr ; 5. H O, NaOH

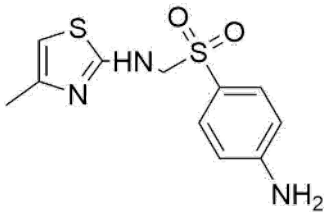
(c) 1. HNO , H SO ; 2. Br , FeBr ; 3. Zn(Hg), HCl

(d) 1. HNO , H SO ; 2. Zn(Hg), HCl; 3. (CH CO)O ; 4. EtCl, AlCl ; 5. H O, NaOH

QUESTIONS

Q24.8.1

Propose a synthesis for the following compound via benzene and any amine you may require.



Q24.8.2

Proposes synthesis for each of the following compounds via benzene.

(a) *N*,*N*-Diethylaniline

(b) *p*-Bromoaniline

(c) *m*-Bromoaniline

(d) 2,4-Diethylaniline

Q24.8.3

Propose a synthesis for each of the following molecules from benzene via the diazonium ion.

(a) *p*-Chlorobenzoic acid

(b) *m*-Chlorobenzoic acid

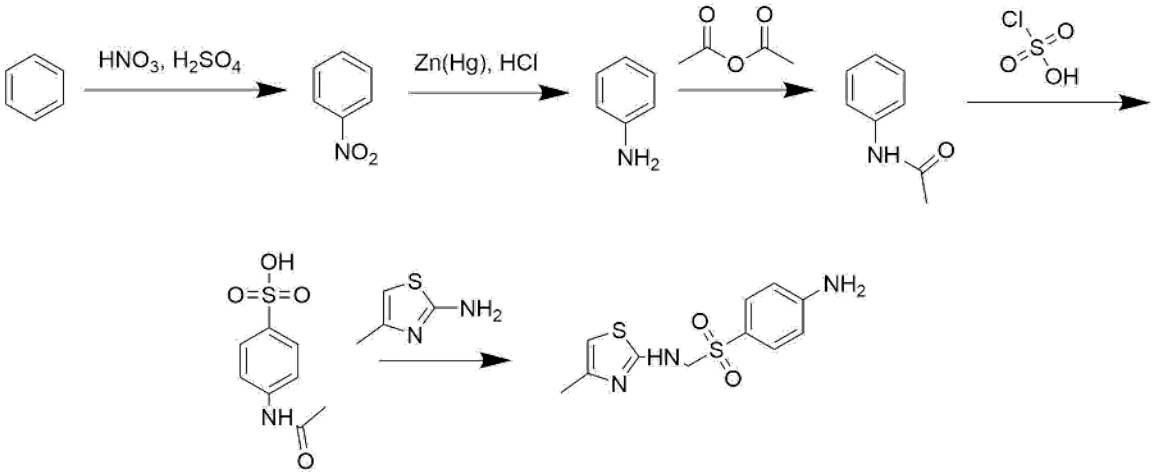
(c) *m*-Dichlorobenzene

(d) *p*-Ethylbenzoic acid

(e) 1,2,4-Trichlorobenzene

SOLUTIONS

S24.8.1



S24.8.2

(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

S24.8.3

(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

24.8 Reactions of Arylamines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

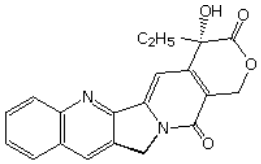
24.9 HETEROCYCLIC AMINES

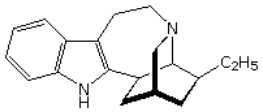
OBJECTIVES

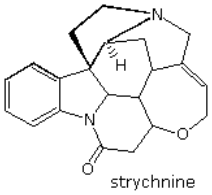
After completing this section, you should be able to

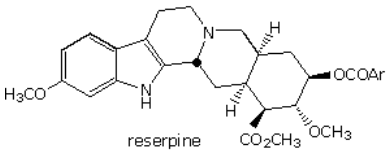
1. draw the structure of furan, pyrrole and imidazole.
2. use the Hückel $2n + 4$ rule to explain the aromaticity of pyrrole.
3. predict the product formed when pyrrole is subjected to an aromatic electrophilic substitution, such as nitration, etc.
4. write the detailed mechanism for the electrophilic aromatic substitution of pyrrole to account for the fact that substitution takes place at C2 rather than C3.
5. describe the geometry of the pyridine molecule.
6. account for the difference in basicity between pyridine, pyrrole and other amines.
7. explain why pyridine undergoes electrophilic substitution much less readily than does benzene.
8. identify the presence of a fused-ring heterocycle in a given structure.
9. make predictions about the chemical behaviour of the fused-ring heterocycle based on what you have learned about pyrrole, imidazole, pyridine and pyrimidine.

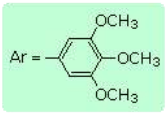
Heterocyclic structures are found in many natural products. Examples of some nitrogen compounds, known as alkaloids because of their basic properties, were given in the amine chapter. Some other examples are displayed in the following diagram. Camptothecin is a quinoline alkaloid which inhibits the DNA enzyme topoisomerase I. Reserpine is an indole alkaloid, which has been used for the control of high blood pressure and the treatment of psychotic behavior. Ajmaline and strychnine are also indole alkaloids, the former being an antiarrhythmic agent and latter an extremely toxic pesticide. The neurotoxins saxitoxin and tetrodotoxin both have marine origins and are characterized by guanidiniun moieties. Aflatoxin B_1 is a non-nitrogenous carcinogenic compound produced by the Aspergillus fungus. Porphyrin is an important cyclic tertrapyrrole that is the core structure of heme and chlorophyll.

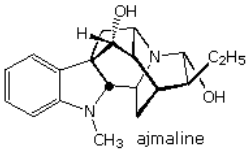

camptothecin


ibogamine

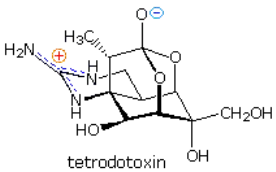

strychnine

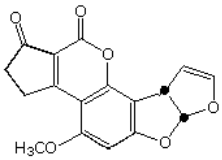

reserpine



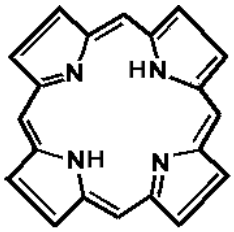

ajmaline


saxitoxin

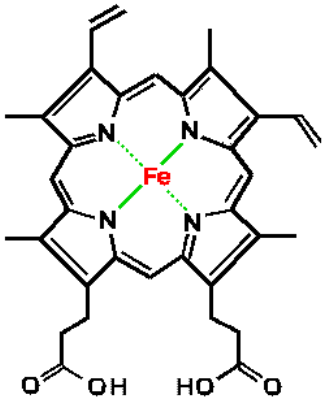

tetrodotoxin


aflatoxin B_1

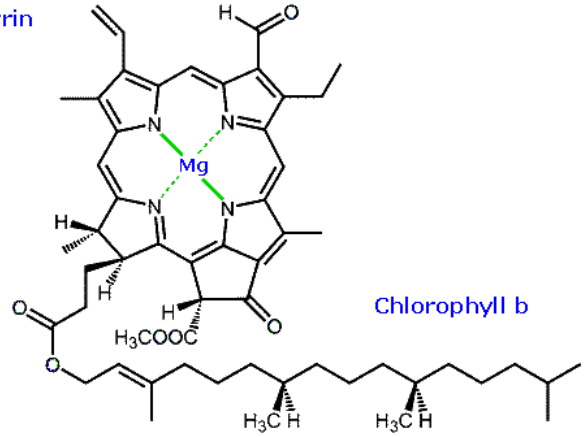
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Porphyrin



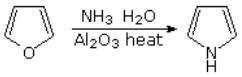
Heme



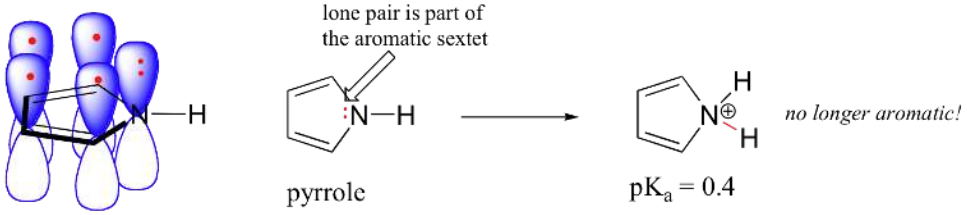
Chlorophyll b

PYRROLE AND IMIDAZOLE

Pyrrole is obtained commercially by the reaction of furan with ammomia .

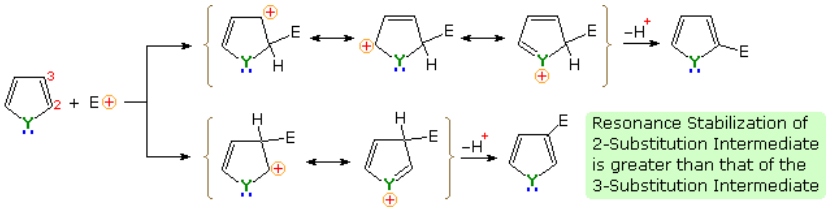


In a pyrrole ring, in contrast, the nitrogen lone pair *is* part of the aromatic sextet. This means that these electrons are very stable right where they are (in the aromatic system), and are much less available for bonding to a proton (and if they *do* pick up a proton, the aromic system is destroyed). For these reasons, pyrrole nitrogens are not strongly basic.



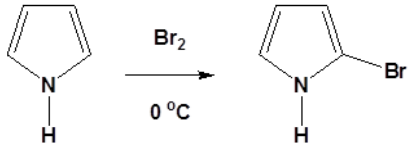
There is a clear preference for substitution at the 2-position (α) of the ring. Reactions of pyrrole require careful evaluation, since N-protonation destroys its aromatic character. Indeed, N-substitution of this 2º-amine is often carried out prior to subsequent reactions. For example, pyrrole reacts with acetic anhydride or acetyl chloride and triethyl amine to give N-acetylpyrrole

An explanation for the general α-selectivity of these substitution reactions is apparent from the mechanism outlined below. The intermediate formed by electrophile attack at C-2 is stabilized by charge delocalization to a greater degree than the intermediate from C-3 attack. From the Hammond postulate we may then infer that the activation energy for substitution at the former position is less than the latter substitution.

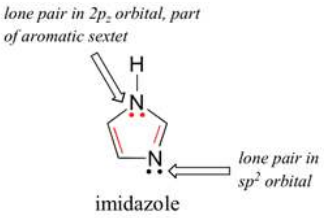


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EXAMPLE

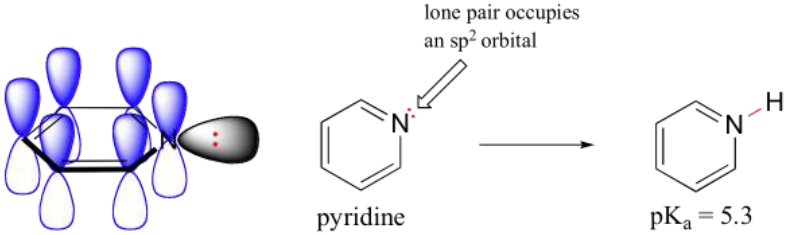


Another five-membered heterocyclic amine is imidazole which is part of the amino acid histidine.

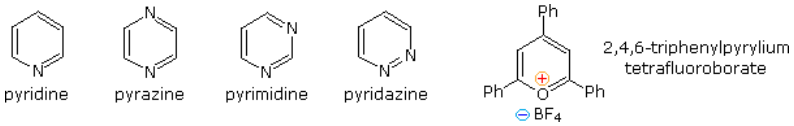


PYRIDINE AND PYRIMIDINE

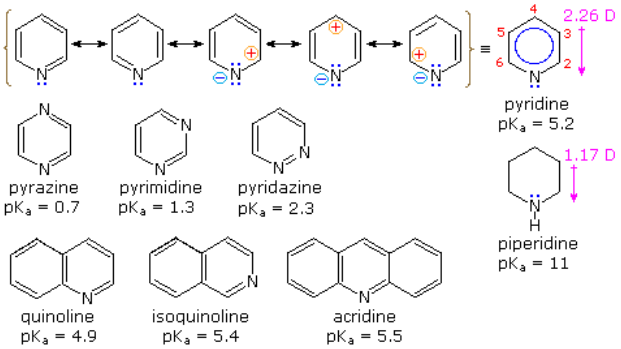
When a nitrogen atom is incorporated directly into an aromatic ring, its basicity depends on the bonding context. In a pyridine ring, for example, the nitrogen lone pair occupies an sp^2-hybrid orbital, and is *not* part of the aromatic sextet - it is essentially an imine nitrogen. Its electron pair is available for forming a bond to a proton, and thus the pyridine nitrogen atom is somewhat basic.



Fully unsaturated six-membered nitrogen heterocycles, such as pyridine, pyrazine, pyrimidine and pyridazine, have stable aromatic rings. Oxygen and sulfur analogs are necessarily positively charged, as in the case of 2,4,6-triphenylpyrylium tetrafluoroborate.



From heat of combustion measurements, the aromatic stabilization energy of pyridine is 21 kcal/mole. The resonance description drawn at the top of the following diagram includes charge separated structures not normally considered for benzene. The greater electronegativity of nitrogen (relative to carbon) suggests that such canonical forms may contribute to a significant degree. Indeed, the larger dipole moment of pyridine compared with piperidine supports this view. Pyridine and its derivatives are weak bases, reflecting the sp^2 hybridization of the nitrogen. From the polar canonical forms shown here, it should be apparent that electron donating substituents will increase the basicity of a pyridine, and that substituents on the 2 and 4-positions will influence this basicity more than an equivalent 3-substituent. The pK_a values given in the table illustrate a few of these substituent effects. Methyl substituted derivatives have the common names picoline (methyl pyridines), lutidine (dimethyl pyridines) and collidine (trimethyl pyridines). The influence of 2-substituents is complex, consisting of steric hindrance and electrostatic components. 4-Dimethylaminopyridine is a useful catalyst for acylation reactions carried out in pyridine as a solvent. At first glance, the sp^3 hybridized nitrogen might appear to be the stronger base, but it should be remembered that N,N-dimethylaniline has a pK_a slightly lower than that of pyridine itself. Consequently, the sp^2 ring nitrogen is the site at which protonation occurs.

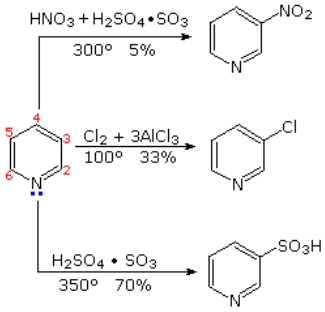


Pyridine Basicities

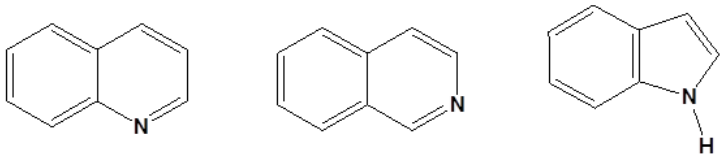
Substituent(s)	pK$_a$
4-methyl	6.0
3-methyl	5.7
2,6-dimethyl	6.7
2,4,6-trimethyl	7.5
2,6-di-*t*-butyl	3.6
3-methoxy	4.9
4-methoxy	6.5
4-dimethylamino	9.7
2-chloro	0.7
4-chloro	3.8
2,6-dichloro	−2.9

The diazines pyrazine, pyrimidine and pyridazine are all weaker bases than pyridine due to the inductive effect of the second nitrogen. However, the order of base strength is unexpected. A consideration of the polar contributors helps to explain the difference between pyrazine and pyrimidine, but the basicity of pyridazine seems anomalous. It has been suggested that electron pair repulsion involving the vicinal nitrogens destabilizes the neutral base relative to its conjugate acid

From the previous resonance description of pyridine, we expect this aromatic amine to undergo electrophilic substitution reactions far less easily than does benzene. Furthermore, the electrophilic reagents and catalysts employed in these reactions coordinate with the nitrogen electron pair, exacerbating the positive charge at positions 2,4 & 6 of the pyridine ring. Three examples of the extreme conditions required for electrophilic substitution are shown below.

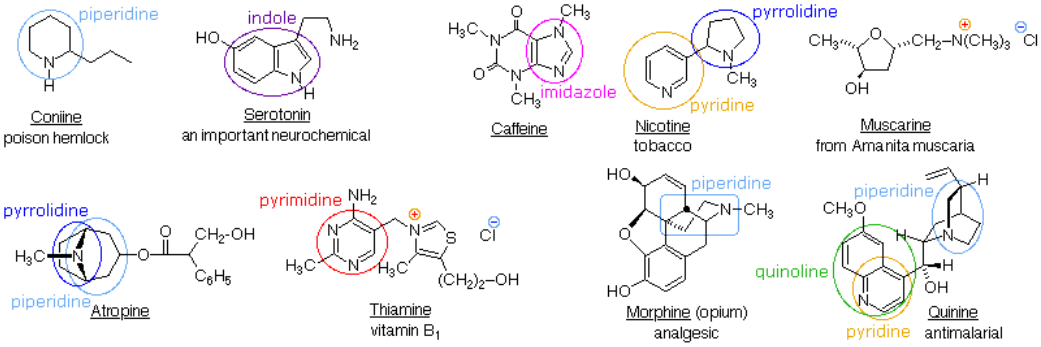


POLYCYCLIC HETEROCYCLES



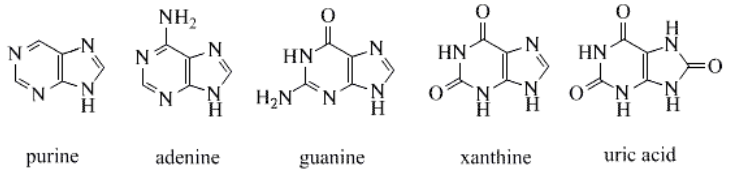
Quinoline **Isoquinoline** **Indole**

Polycyclic Heterocyclic structures are found in many natural products.

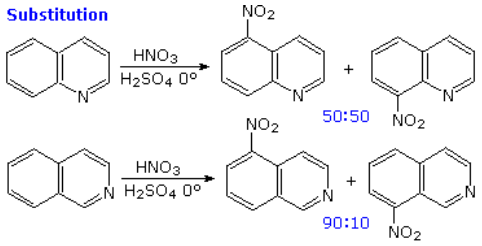


Derivatives of the simple fused ring heterocycle purine constitute an especially important and abundant family of natural products. The amino compounds adenine and guanine are two of the complementary bases that are essential components of DNA. Structures for these

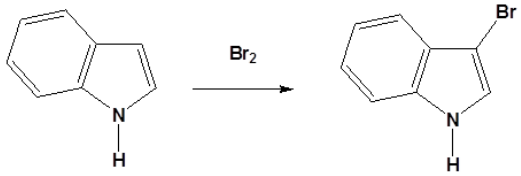
compounds are shown in the following diagram. Xanthine and uric acid are products of the metabolic oxidation of purines. Uric acid is normally excreted in the urine; an excess serum accumulation of uric acid may lead to an arthritic condition known as gout.



The fused ring heterocycles quinoline and isoquinoline provide additional evidence for the stability of the pyridine ring. Vigorous permanganate oxidation of quinoline results in predominant attack on the benzene ring; isoquinoline yields products from cleavage of both rings.



Indole has a nonbasic nitrogen similar to to pyrrole. It undergo electrophilic substitution more easily than benzene and substitution typically occurs at the C3 position on the pyrole ring.

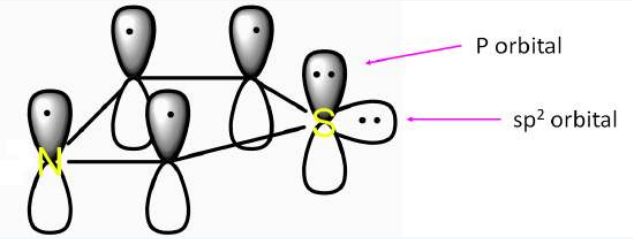


EXERCISES

? EXERCISE 24.9.1

Describe how thiazole is aromatic. Use an orbital picture and include the lone pair electrons on sulfur. Assume the sulfur is sp^2 hybridized.

Answer



? EXERCISE 24.9.2

Would you expect a thiazole ring to be protonated at the physiological pH of 7.3 **(Section 24-5)**?

Answer

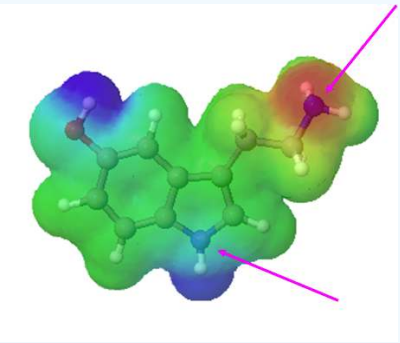
$7.3 = 2.44 + \log([RNH_2] / [RNH_3^+])$

$([RNH_2] / [RNH_3^+]) = 7.2 \times 10^4$

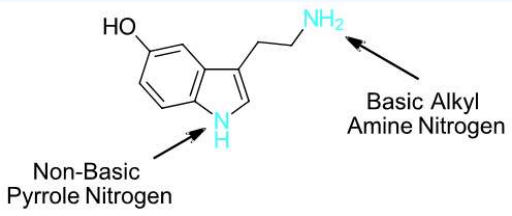
. . . so, $[RNH_2] >> [RNH_3^+]$ so thiazole would be almost completely unprotonated at pH = 7.3.

EXERCISE 24.9.3

Which nitrogen atom in the neurotransmitter serotonin is expected to be the most basic? Please explain your answer.



Answer

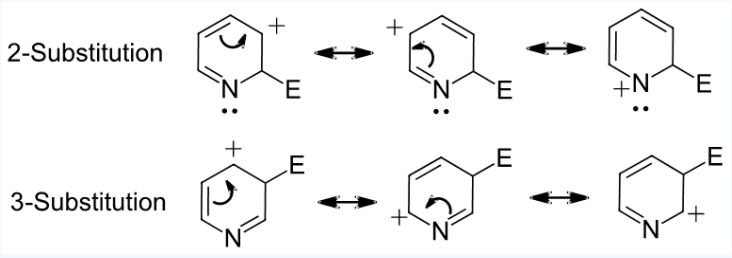


EXERCISE 24.9.4

Pyridine reacts with electrophiles to product a 3-substituted product rather than a 2-substituted product. Write a series of resonance forms for the cation intermediate formed during the reaction. Use these structures to explain the experimental result.

Answer

The resonance forms of 2-substitution places a positive charge on the ring nitrogen. The resonance forms of 3-substitution do not place a positive charge on the ring nitrogen. Having a positive charge on a nitrogen is less stable than on a carbon. Nitrogen is more electronegative than carbon making it less able to stabilize the positive charge. The 3-substituted product is preferred because it causes resonance forms which are more 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

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24.10 SPECTROSCOPY OF AMINES

Objectives

After completing this section, you should be able to

1. identify the region of the infrared spectrum that shows absorptions resulting from the N—H bonds of primary and secondary amines.
2. describe a characteristic change that occurs in the infrared spectrum of an amine when a small amount of mineral acid is added to the sample.
3. use ^{1}H NMR spectra in determining the structure of an unknown amine.
4. use the "nitrogen rule" of mass spectrometry to determine whether a compound has an odd or even number of nitrogen atoms in its structure.
5. predict the prominent peaks in the mass spectrum of a given amine.
6. use the mass spectrum of an unknown amine in determining its structure.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- nitrogen rule

STUDY NOTES

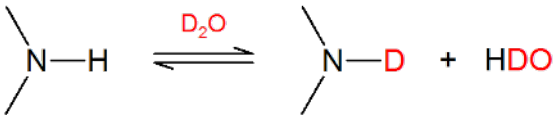
You should note the spectroscopic similarities between amines and alcohols: both have infrared absorptions in the 3300–3360 cm^{-1} region, and in both cases, the proton that is attached to the heteroatom gives rise to an often indistinct signal in the ^{1}H NMR spectrum.

^{1}H NMR OF AMINES

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.



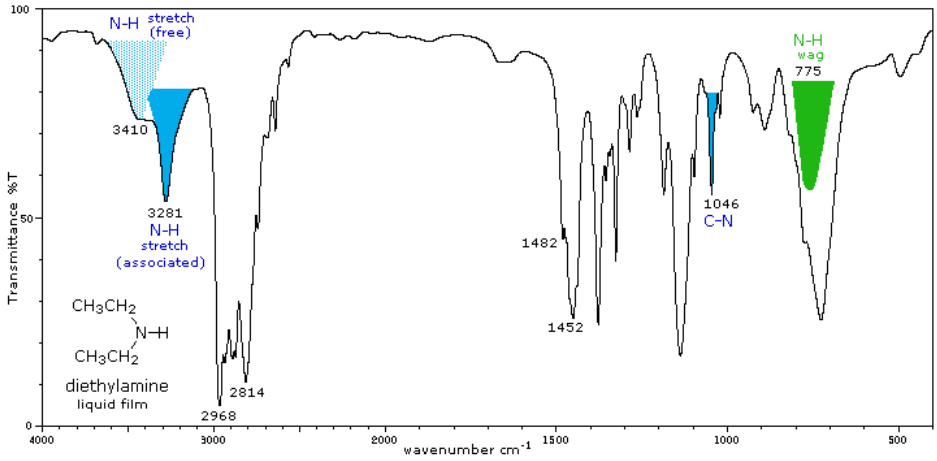
IR

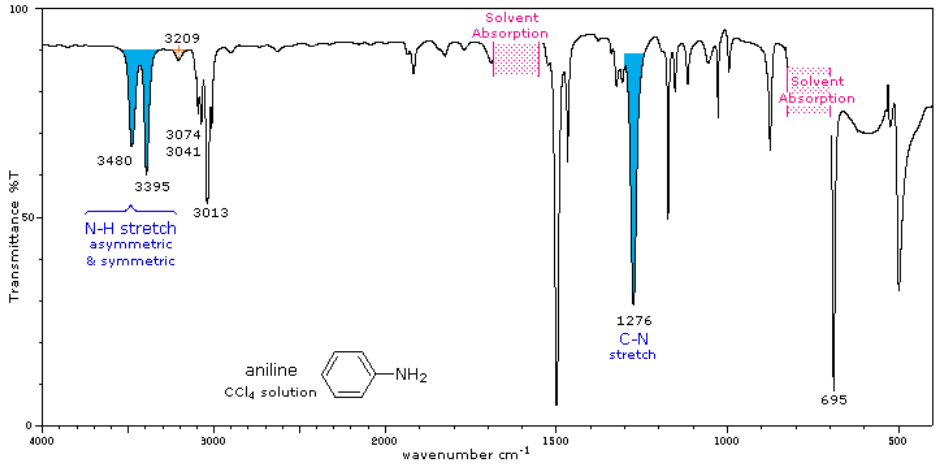
The infrared spectrum of aniline is shown beneath the following table. Some of the characteristic absorptions for C-H stretching and aromatic ring substitution are also marked, but not colored.

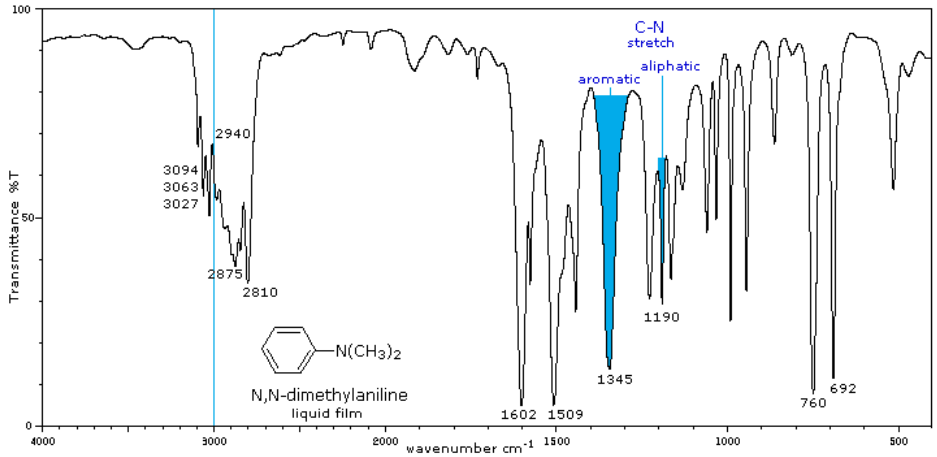
Amine Class	Stretching Vibrations	Bending Vibrations
Primary (1°)	The N-H stretching absorption is less sensitive to hydrogen bonding than are O-H absorptions. In the gas phase and in dilute CCl_4 solution free N-H absorption is observed in the 3400 to 3500 cm^{-1} region. Primary aliphatic amines display 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.





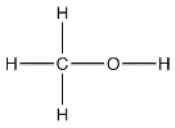


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NITROGEN RULE

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

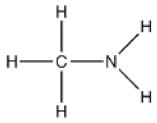
nominal mass = (1x12) + (4x1) + (1x16)

= 32

N atoms = 0

nominal mass = 32 (even #)

eg. 2:



molecular formula = CH_5N

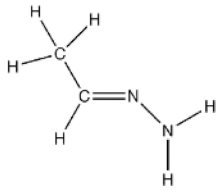
nominal mass = (1x12) + (5x1) + (1x14)

= 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 #)

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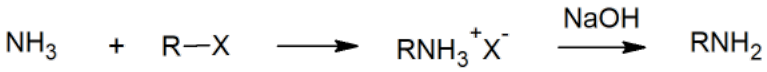
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

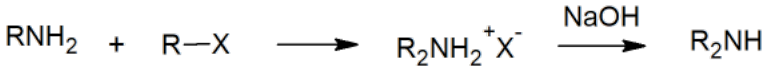
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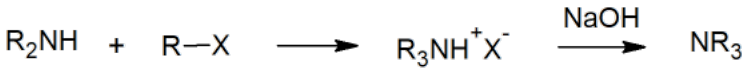
24.S: AMINES AND HETEROCYCLES (SUMMARY)

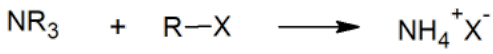
SUMMARY OF REACTIONS

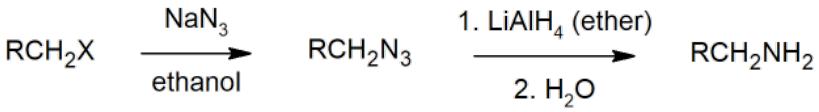
Amine Preparation

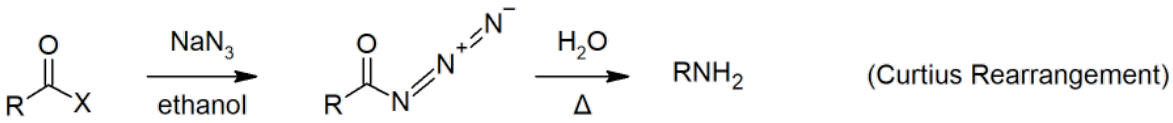


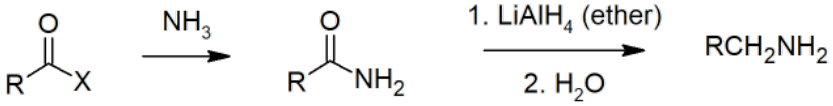


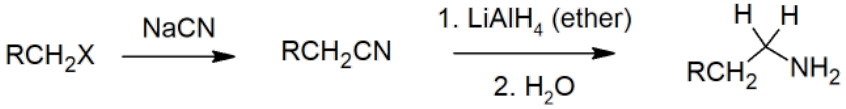


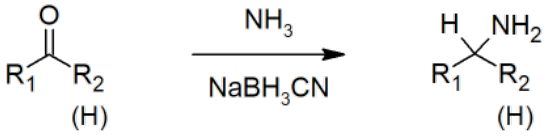


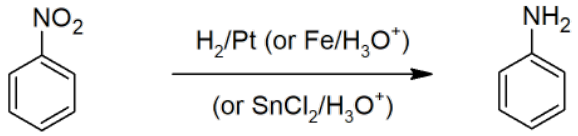


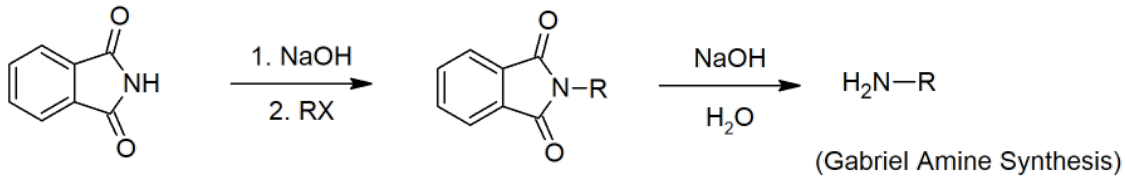






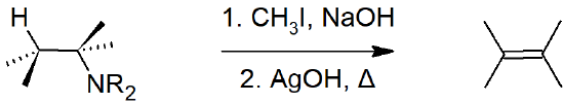


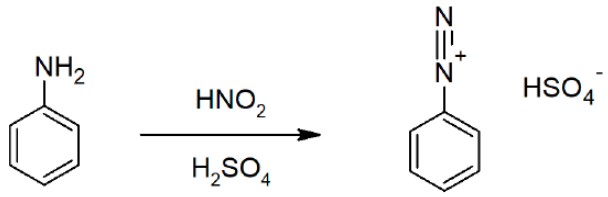


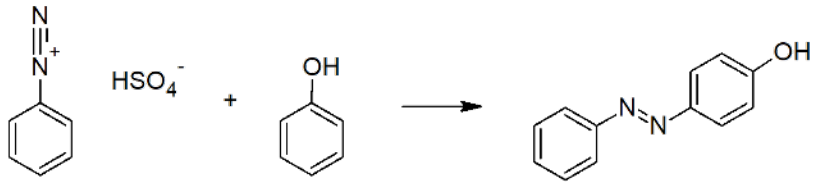


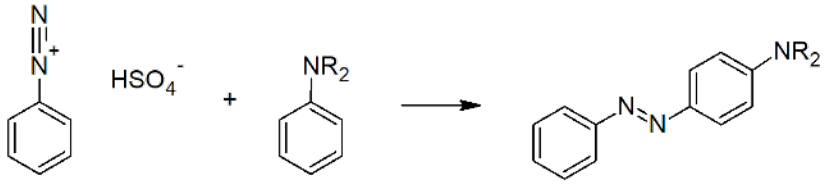


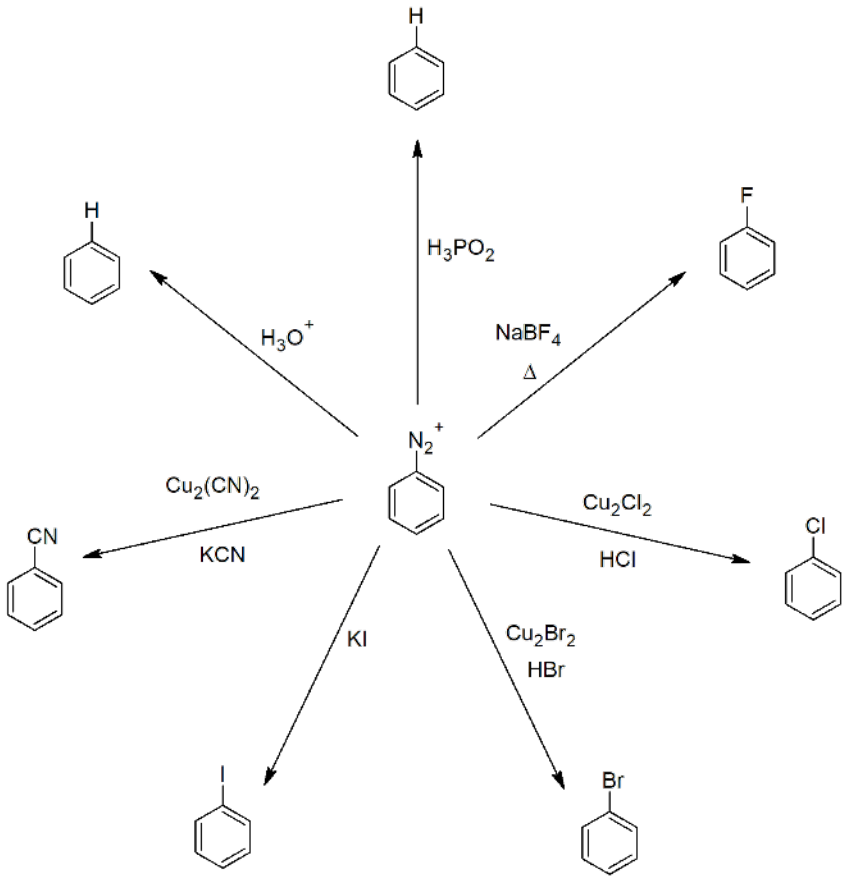
Amine Reactions











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CHAPTER OVERVIEW

CHAPTER 25: BIOMOLECULES: CARBOHYDRATES

This chapter is designed to provide you with an overview of the biologically important group of compounds known as carbohydrates. Many of the compounds you will encounter while studying this chapter may appear to have very complex structures, but much of their chemistry can be readily understood in terms of the concepts and reactions discussed in earlier chapters of the course.

The chapter begins with an explanation of the classification schemes used to simplify the study of carbohydrates. We make extensive use of Fischer projection formulas throughout the chapter. We place considerable emphasis on gaining an appreciation of the configurations of carbohydrates, particularly of the aldoses. We describe the disadvantages of representing monosaccharides by open-chain structures, and at this point, introduce you to cyclic representations—called Haworth projections—of these substances. We describe the mutarotation of glucose, explaining it in terms of the existence of anomers. We then examine some reactions of monosaccharides, including the formation of ethers and esters, the formation of glycosides, and reduction and oxidation. We discuss the structures of some common disaccharides and polysaccharides, and conclude the chapter with a brief explanation of the role played by carbohydrates in cell recognition.

Chapter Objectives
25.0 Introduction
25.1 Classification of Carbohydrates
25.2 Depicting Carbohydrate Stereochemistry: Fischer Projections
25.3 D, L Sugars
25.4 Configurations of Aldoses
25.5 Cyclic Structures of Monosaccharides: Anomers
25.6 Reactions of Monosaccharides
25.7 The Eight Essential Monosaccharides
25.8 Disaccharides
25.9 Polysaccharides and Their Synthesis
25.10 Other Important Carbohydrates
25.11 Cell-Surface Carbohydrates and Influenza Viruses
25.S: Biomolecules- Carbohydrates (Summary)

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CHAPTER OBJECTIVES

When you have completed Chapter 25, you should be able to:

1. fulfill all of the detailed objectives listed under each individual section.
2. define, and use in context, any of the key terms introduced in this chapter.

CONTRIBUTORS AND ATTRIBUTIONS

Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

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25.0 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.

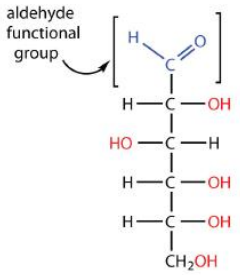
KEY TERMS

Make certain that you can define, and use in context, the key term below.

- carbohydrate

INTRODUCTION

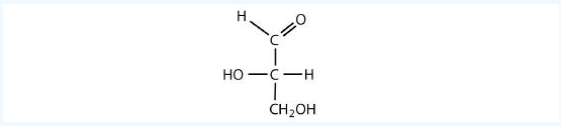
All carbohydrates consist of carbon, hydrogen, and oxygen atoms and are polyhydroxy aldehydes or ketones or are compounds that can be broken down to form such compounds. Examples of carbohydrates include starch, fiber, the sweet-tasting compounds called sugars, and structural materials such as cellulose. 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 $C_6 \cdot 6H_2O$.

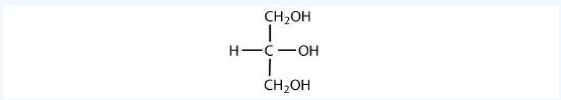


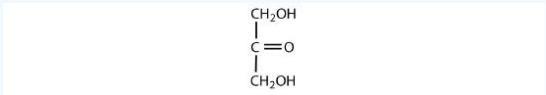
Because glucose has an aldehyde functional group and several –OH (hydroxyl) groups, it is described as a polyhydroxy aldehyde.

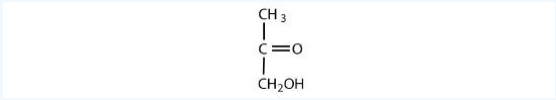
EXAMPLE 1

Which compounds would be classified as carbohydrates?

a. 

b. 

c. 

d. 

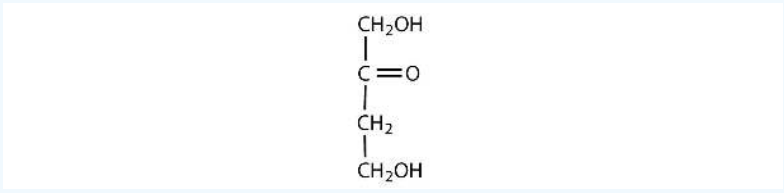
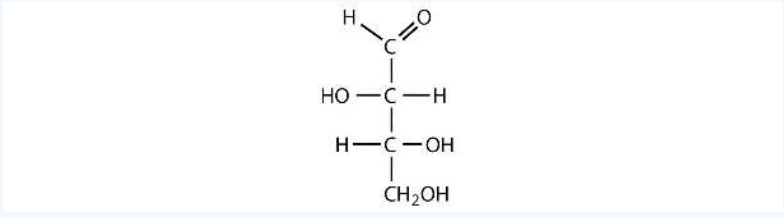
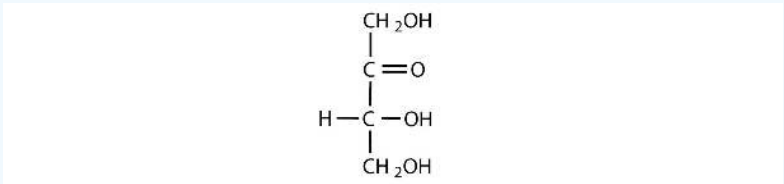
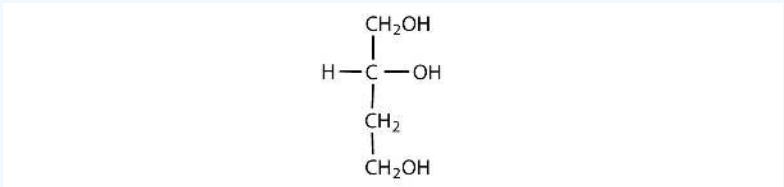
Solution

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. 

Answer

Only 2 and 3.

1 has a ketone, but on of the other carbons has no -OH group.

4 has no aldehyde or ketone.

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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25.1 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.

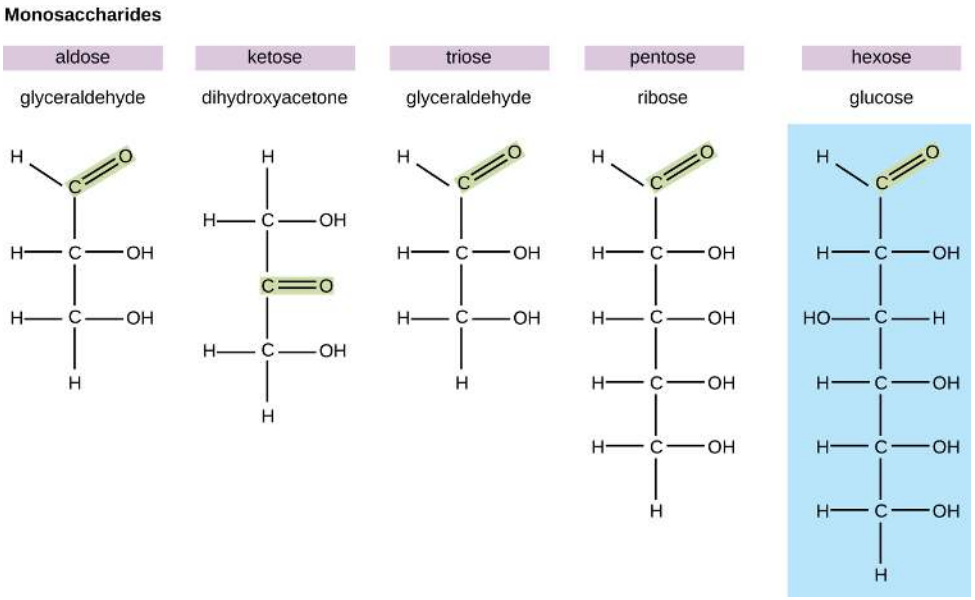
- aldose
- disaccharide
- ketose
- monosaccharide (simple sugar)
- polysaccharide

WHAT ARE CARBOHYDRATES?

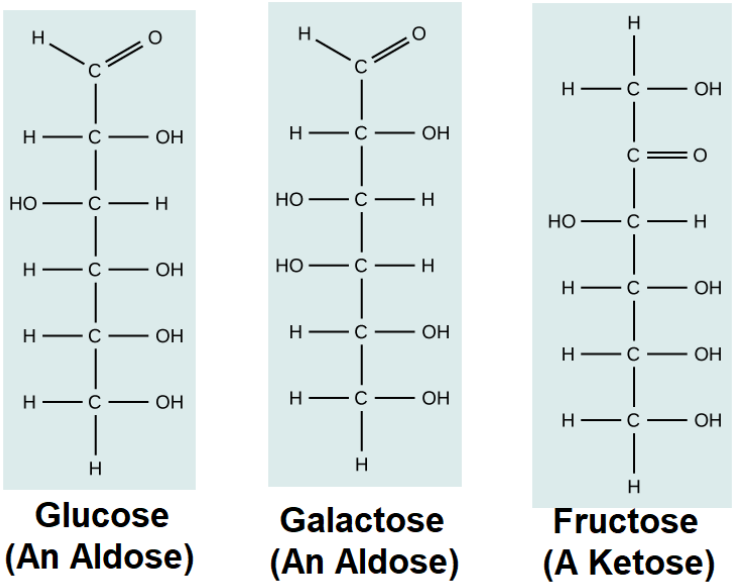
The most abundant biomolecules on earth are carbohydrates. From a chemical viewpoint, carbohydrates are primarily a combination of carbon and water, and many of them have the empirical formula $(CH_2O)_n$, where *n* is the number of repeated units. This view represents these molecules simply as "hydrated" carbon atom chains in which water molecules attach to each carbon atom, leading to the term "carbohydrates." Although all carbohydrates contain carbon, hydrogen, and oxygen, there are some that also contain nitrogen, phosphorus, and/or sulfur. Carbohydrates have myriad different functions. They are abundant in terrestrial ecosystems, many forms of which we use as food sources. These molecules are also vital parts of macromolecular structures that store and transmit genetic information (i.e., DNA and RNA). They are the basis of biological polymers that impart strength to various structural components of organisms (e.g., cellulose and chitin), and they are the primary source of energy storage in the form of starch and glycogen.

MONOSACCHARIDES

In biochemistry, carbohydrates are often called saccharides, from the Greek *sakcharon*, meaning sugar, although not all the saccharides are sweet. The simplest carbohydrates are called monosaccharides, or simple sugars. They are the building blocks (monomers) for the synthesis of polymers or complex carbohydrates, as will be discussed further in this section. Monosaccharides are classified based on the number of carbons in the molecule. General categories are identified using a prefix that indicates the number of carbons and the suffix *–ose*, which indicates a saccharide; for example, triose (three carbons), tetrose (four carbons), pentose (five carbons), and hexose (six carbons). The hexose D-glucose is the most abundant monosaccharide in nature. Other very common and abundant hexose monosaccharides are galactose, used to make the disaccharide milk sugar lactose, and the fruit sugar fructose.



A second comparison can be made when looking at glucose, galactose, and **fructose**. All three are hexoses; however, there is a major structural difference between glucose and galactose versus fructose: the carbon that contains the **carbonyl** (C=O). In glucose and galactose, the carbonyl group is on the C_1 carbon, forming an **aldehyde** group. In fructose, the carbonyl group is on the C_2 carbon, forming a **ketone** group. The former sugars are called **aldoses** based on the aldehyde group that is formed; the latter is designated as a **ketose** based on the ketone group. Again, this difference gives fructose different chemical and structural properties from those of the related aldoses, glucose, and galactose, even though fructose, glucose, and galactose all have the same chemical composition: $C_6H_{12}O_6$.



COMPLEX CARBOHYDRATES

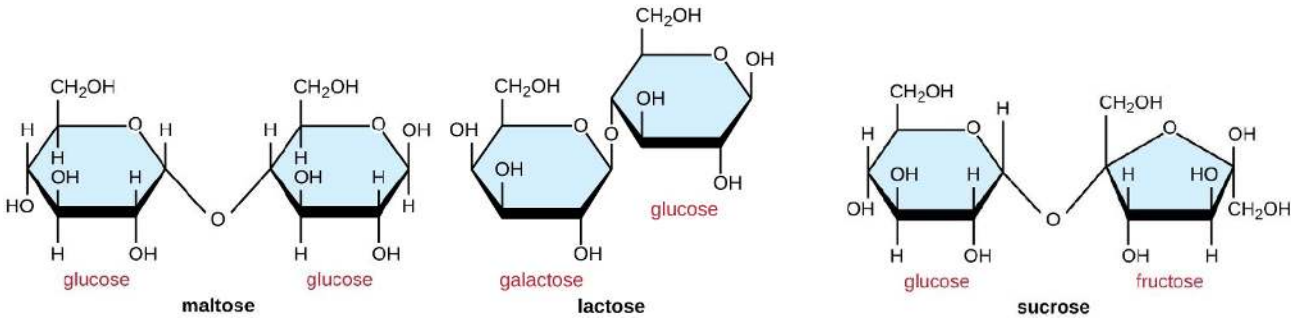
The simple sugars form the foundation of more complex carbohydrates. The cyclic forms of two sugars can be linked together by means of a condensation reaction to form a disaccharide. Multiple sugars can be linked to form polysaccharides.

DISACCHARIDES

Two monosaccharide molecules may chemically bond to form a disaccharide. The name given to the covalent bond between the two monosaccharides is a glycosidic bond. **Glycosidic bonds** form between hydroxyl groups of the two saccharide molecules, an example of the dehydration synthesis described later in this chapter.

$$\text{monosaccharide—OH} + \text{HO—monosaccharide} \longrightarrow \underbrace{\text{monosaccharide—O—monosaccharide}}_{\text{disaccharide}}$$

Common disaccharides are the grain sugar maltose, made of two glucose molecules; the milk sugar lactose, made of one galactose and one glucose molecule; and the table sugar sucrose, made of one glucose and one fructose molecule.

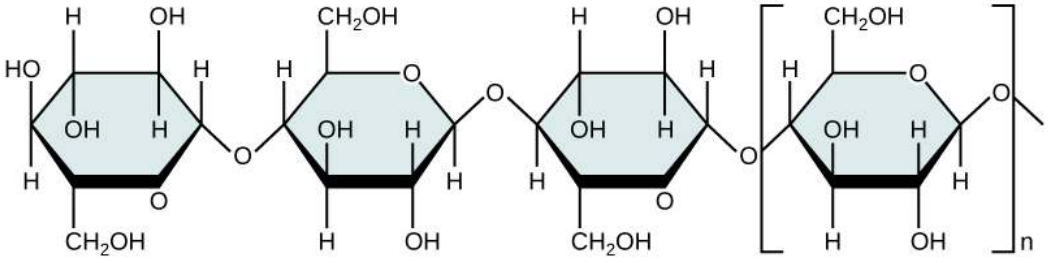


POLYSACCHARIDES

Polysaccharides, also called glycans, are large polymers composed of hundreds of monosaccharide monomers. Unlike mono- and disaccharides, polysaccharides are not sweet and, in general, they are not soluble in water. Like disaccharides, the monomeric units of polysaccharides are linked together by glycosidic bonds.

Polysaccharides are very diverse in their structure. Three of the most biologically important polysaccharides—starch, glycogen, and cellulose—are all composed of repetitive glucose units, although they differ in their structure. **Cellulose** consists of a linear chain of glucose molecules and is a common structural component of cell walls in plants and other organisms. **Glycogen** and **starch** are branched polymers; glycogen is the primary energy-storage molecule in animals and bacteria, whereas plants primarily store energy in starch. The orientation of the glycosidic linkages in these three polymers is different as well and, as a consequence, linear and branched macromolecules have different properties.

Cellulose structure



SUMMARY

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.

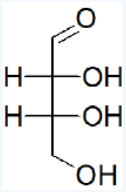
C=O Function	**Aldose** sugars having an aldehyde function or an acetal equivalent. **Ketose** sugars having a ketone function or an acetal equivalent.

EXERCISE

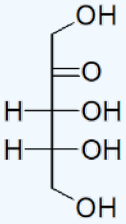
? EXERCISE 25.1.1

Classify each of the following sugars.

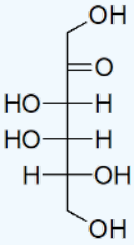
a)



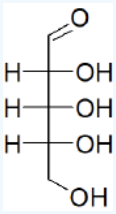
b)



c)



d)



Answer

a) Aldoterose

b) Ketopentose

c) Ketohexose

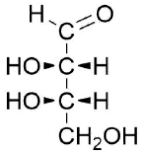
d) Aldopentose

QUESTIONS

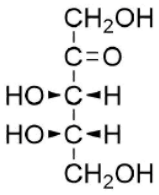
Q25.1.1

Classify each of the following sugars.

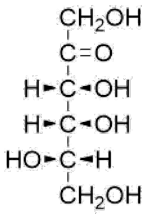
(a)



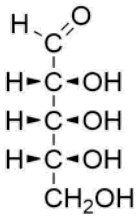
(b)



(c)



(d)



SOLUTIONS

S25.1.1

(a) Aldoterose

(b) Ketopentose

(c) Ketohexose

(d) Aldopentose

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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25.2 DEPICTING CARBOHYDRATE STEREOCHEMISTRY: 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

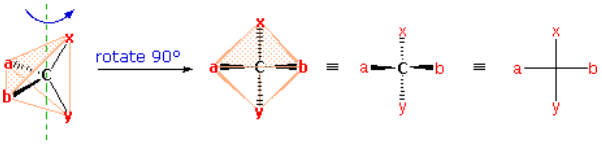
Make certain that you can define, and use in context, the key term below.

- Fischer projection

STUDY NOTES

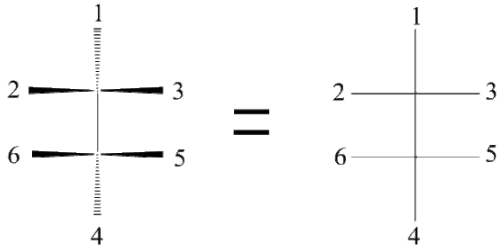
When studying this section, use your molecular model set to assist you in visualizing the structures of the compounds that are discussed. It is important that you be able to determine whether two apparently different Fischer projections represent two different structures or one single structure. Often 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**.

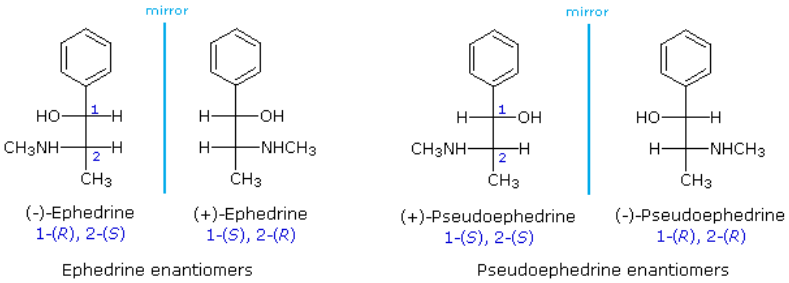


In the above diagram, if x = CO_2H, y = CH_3, a = H & b = OH, the resulting formula describes (*R*)-(–)-lactic acid. The mirror-image formula, where x = CO_2H, y = CH_3, a = OH & b = H, would, of course, represent (*S*)-(+)-lactic acid.

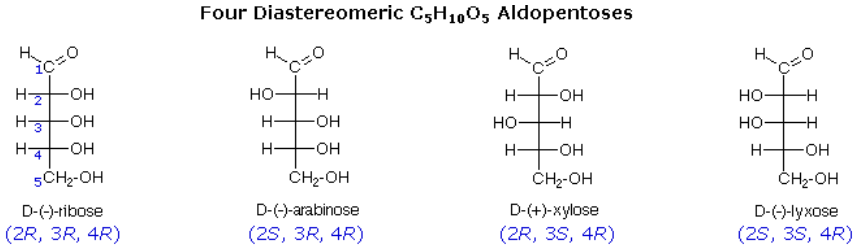
The Fischer Projection consists of both horizontal and vertical lines, where the horizontal lines represent the atoms that are pointed toward the viewer while the vertical line represents atoms that are pointed away from the viewer. The point of intersection between the horizontal and vertical lines 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.



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.

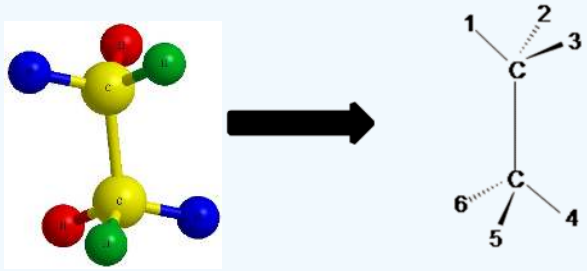


Figure A Figure B

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.

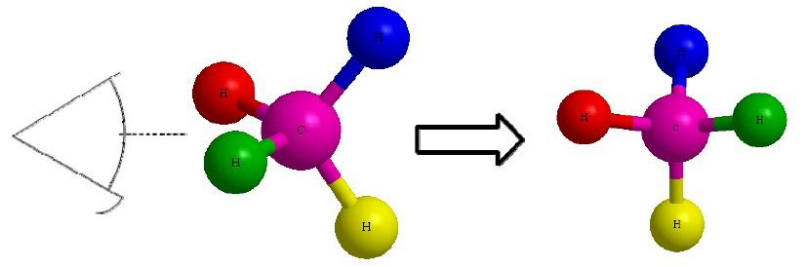
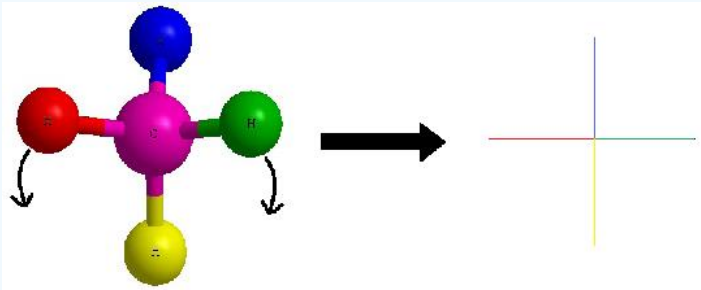


Figure C Figure D

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.

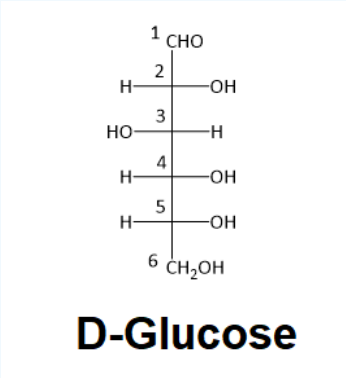


As a reminder, the horizontal line represents atoms that are coming out of the paper and the vertical line represents atoms that are going into the paper. The cross image to the right of the arrow is a Fischer projection.

EXERCISES

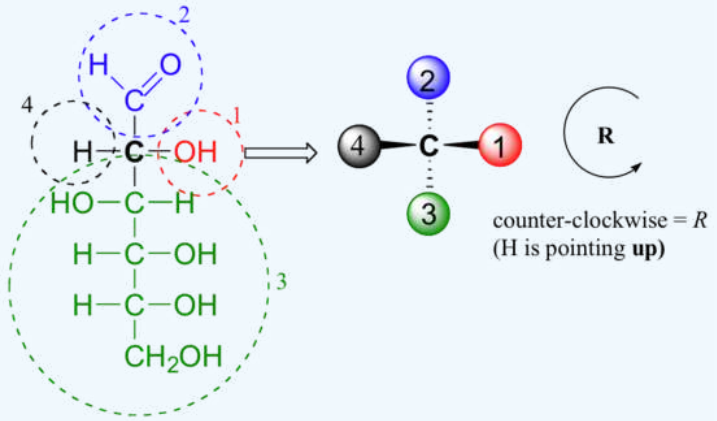
Exercise 25.2.1

Determine if carbon #2 in D-glucose is R or S.



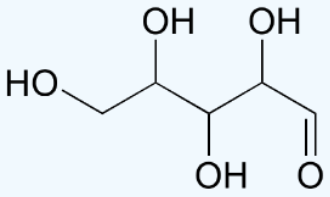
Answer

When deciding whether a stereocenter in a Fischer projection is *R* or *S*, realize that the hydrogen, in a horizontal bond. Therefore, the orientation of the three remaining substituents is reversed to create the correct answer or a counterclockwise circle means *R*, and a clockwise circle means *S*. For carbon #2 in D-Glucose substituent 1, 2, and 3 form a counterclockwise circle so the carbon is R.

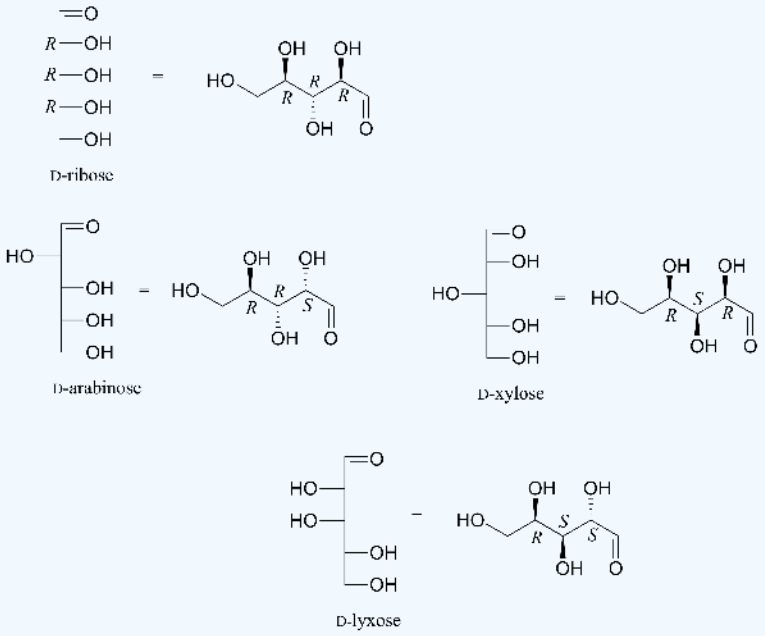


EXERCISE 25.2.2

Draw 'zigzag' structures (using the solid/dash wedge convention to show stereochemistry) for the four sugars in the figure below. Label all stereocenters *R* or *S*.



Answer



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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25.3 D, 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.

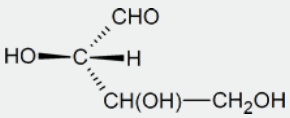
- D sugar
- L sugar

STUDY NOTES

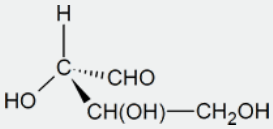
If you find that you have forgotten the meanings of terms such as dextrorotatory and polarimeter, refer back to Section 5.3 in which the fundamentals of optical activity were introduced.

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?

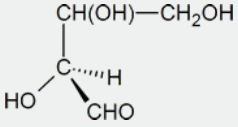
One approach is to focus on the carbon atom of interest and sketch a three-dimensional representation of the configuration around that atom, remembering the convention used in Fischer projections: vertical lines represent bonds going into the page, and horizontal lines represent bonds coming out of the 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.



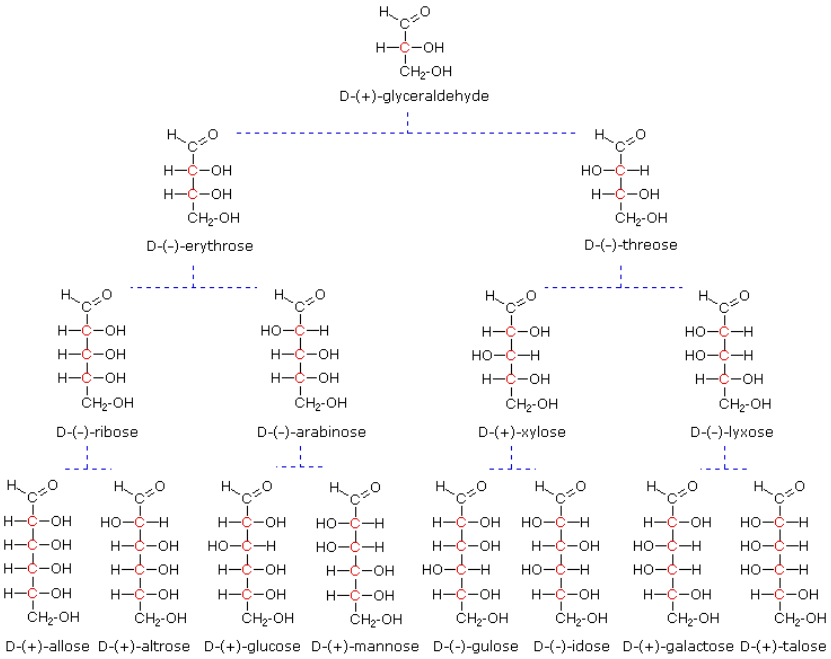
The Cahn-Ingold-Prelog order of priority for the three remaining groups is OH > CHO > $CH(OH)CH_2OH$; thus, we see that we could trace out a counterclockwise path going from the highest-priority group to the second- and third-highest, and we conclude that the central carbon atom has an *S* configuration.

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.

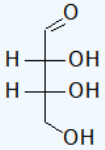


EXERCISE

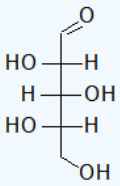
? EXERCISE 1

In the following Fischer projections, assign R and S for each chiral center and determine whether each sugar is a D or L sugar.

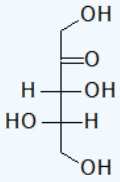
a)



b)



c)



Answer

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.

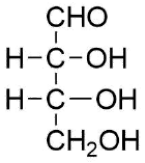
c) From to to bottom, 3R, 4S, and it is an L sugar.

QUESTIONS

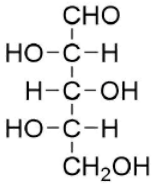
Q25.3.1

Assign R and S for each chiral center and determine whether each sugar is a D or L sugar.

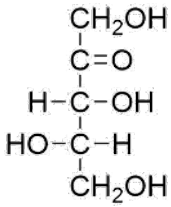
(a)



(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.

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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25.4 CONFIGURATIONS OF ALDOSES

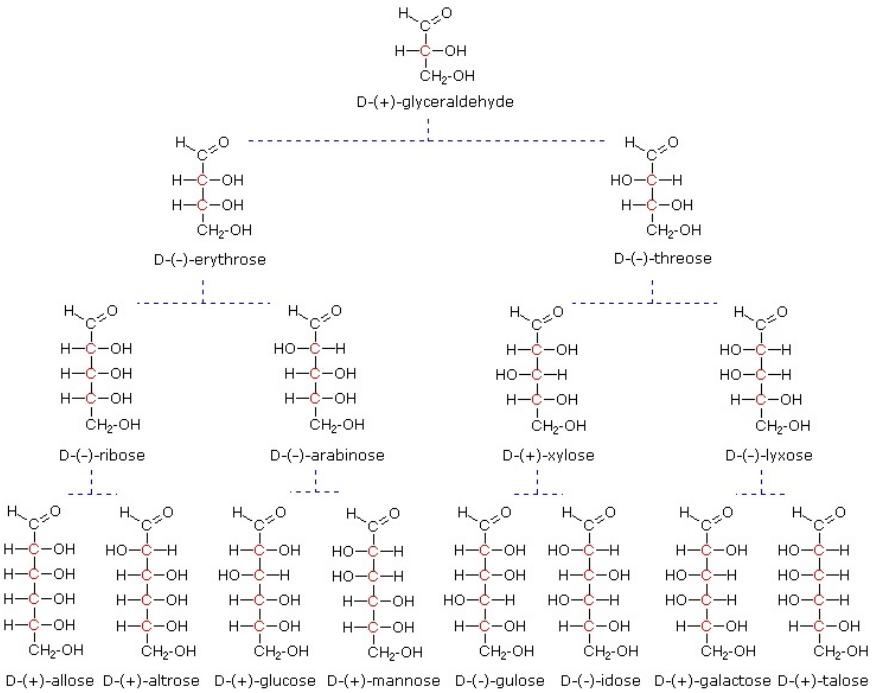
Objectives

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.

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 (pronounced "buy foot"), proved that Fischer's choice was correct.

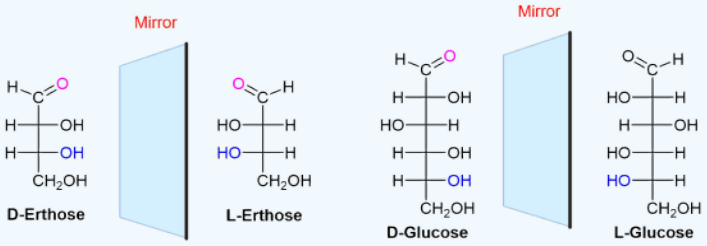
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WORKED EXAMPLE 25.4.1

Draw the Fisher projection of L-erythrose and L-Glucose

Solution

Use the Fischer projection provided above and reverse all of the chiral centers to provide the L-sugar. Note that in both cases the D sugars have the OH going to the right on the chiral center furthest away from the carbonyl. The L-sugars have the OH going to the left.

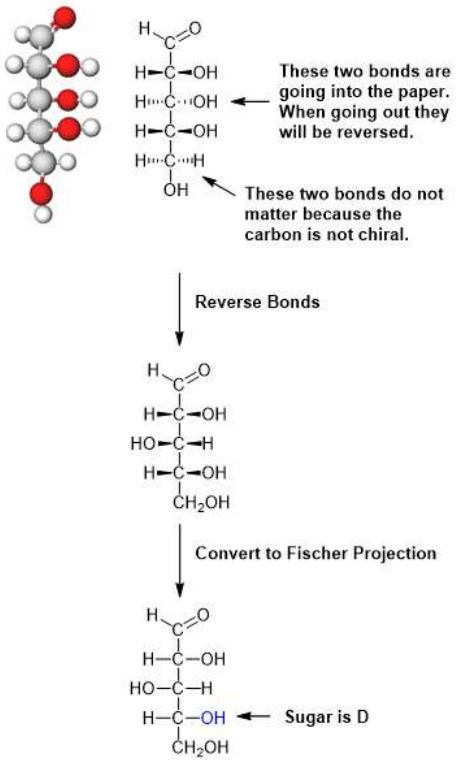


WORKED EXAMPLE 25.4.2

Please draw the Fischer projection fo the following aldopentose and determine if the sugars is D or L.

Solution

First, rotate the model so that the carbonyl is at the top. This is requirement of a Fischer projection. Next rotate the model so that the H and OH of the chiral carbon just below the carbonyl are facing towards you. In this orientation, a dash/wedge model will have every other set of bonds going into the plane of the page. This is not the correct orientation of a Fischer project so they must be modified. The H and OH bonds need to be coming out of the plane of the page in a Fisher projects. When converting bonds from going into the page to going out of the page the orientation of the H and OH are reversed. Remember that the last -CH_2OH of a sugar is achiral so the orientation does not need to be shown. Once the bonds are oriented correctly the wedge bonds can be converted to those of a Fischer projection.



EXERCISES

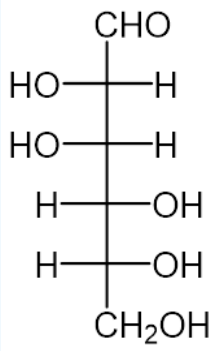
EXERCISE 25.4.1

For the following model of a sugar, please draw its Fischer projection and name it.

https://chem.libretexts.org/@go/page/91045

Answer

D-Mannose



EXERCISE 25.4.2

How many heptose stereoisomers would there expected to be? How many would be D-Sugars?

Answer

There would be $2^5 = 32$ heptose stereoisomers. Half of these would be D-sugars or 16.

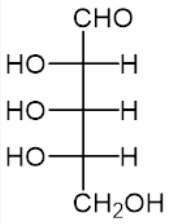
EXERCISE 25.4.3

Draw the Fischer projection of the following sugars.

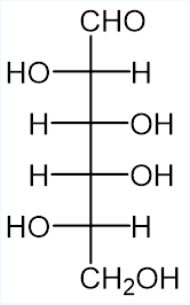
a. L-Ribose
b. L-Galactose
c. L-Talose

Answer

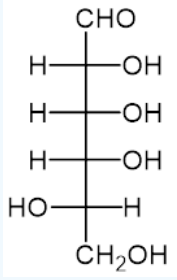
a)



b)



c)



QUESTIONS

Q25.4.1

Draw the following sugars.

(a) D-Xylose

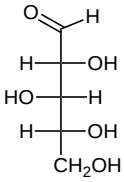
(b) D-Galactose

(c) D-Allose

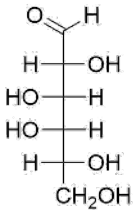
SOLUTIONS

S25.4.1

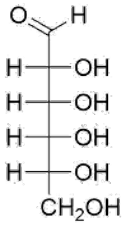
(a)



(b)



(c)



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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25.5 CYCLIC STRUCTURES OF MONOSACCHARIDES: ANOMERS

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

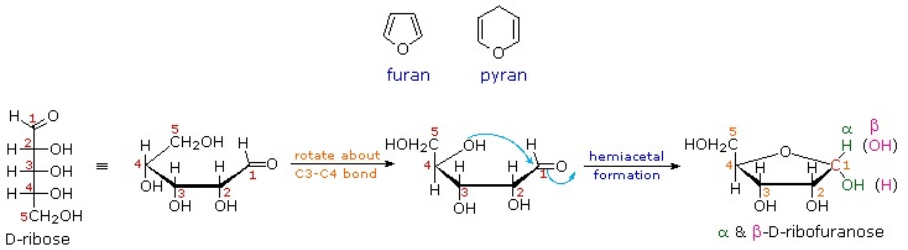
Make certain that you can define, and use in context, the key terms below.

- alpha anomer
- anomer
- anomeric centre
- beta anomer
- furanose
- mutarotation
- pyranose

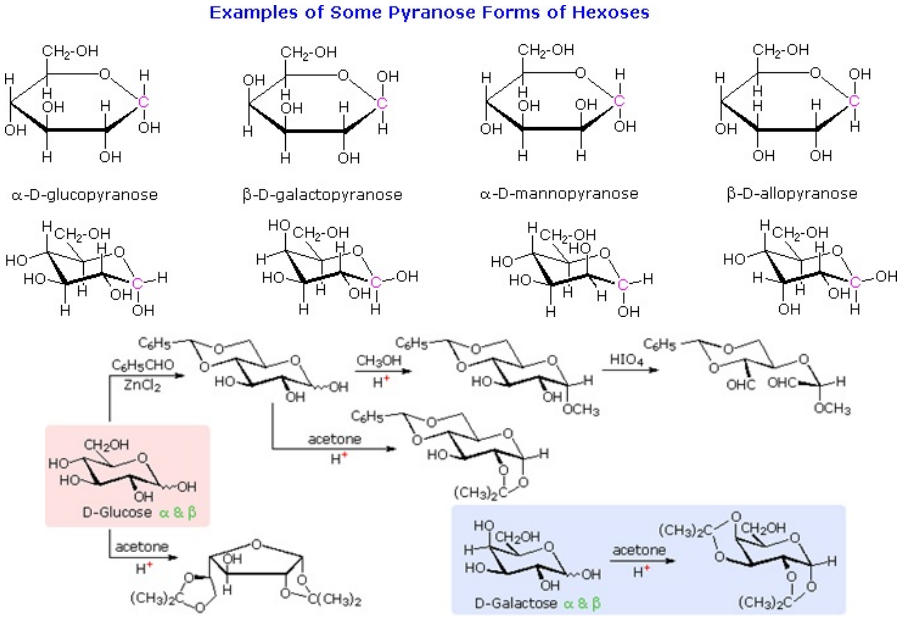
STUDY NOTES

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

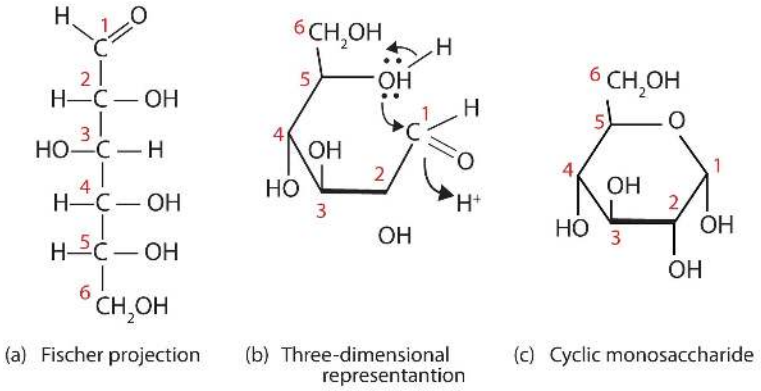


Figure 1: *Cyclization of D-Glucose. D-Glucose can be represented with a Fischer projection (a) or three dimensionally (b). By reacting the OH group on the fifth carbon atom with the aldehyde group, the cyclic monosaccharide (c) is produced.*

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.

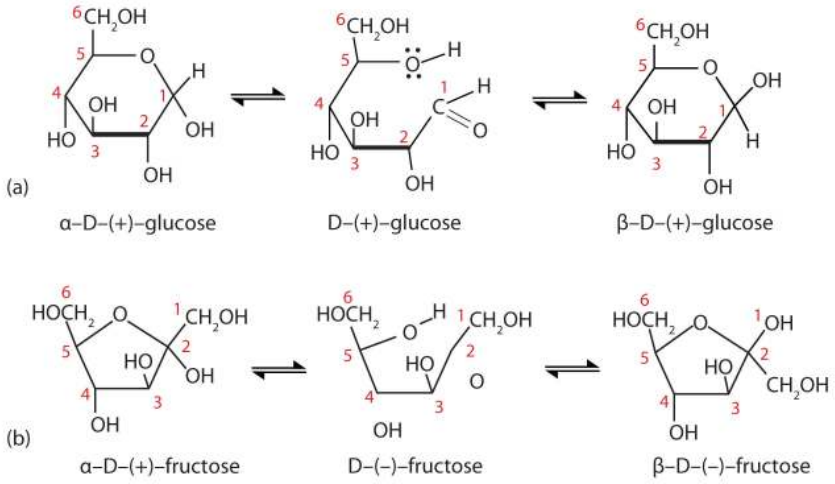


Figure 2: *Monosaccharides. In an aqueous solution, monosaccharides exist as an equilibrium mixture of three forms. The interconversion between the forms is known as mutarotation, which is shown for D-glucose (a) and D-fructose (b).*

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.

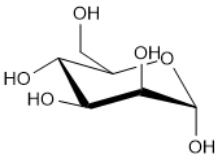
EXERCISES

EXERCISE 25.5.1

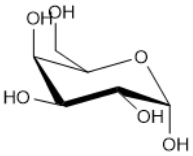
Draw the following in their most stable chair conformation: α-D-galactopyranose and α-D-mannopyranose. Which is expected to be the more stable?

Answer

Because the both have two axial OH's their chair conformations should be roughly the same stability.



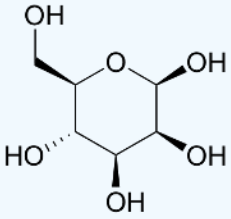
a-D-Mannose



a-D-Galactose

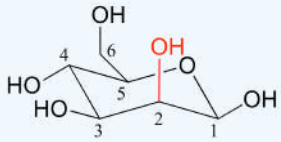
EXERCISE 25.5.2

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

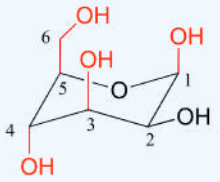


mannose

Answer



major chair form of mannose
(only one substituent axial)

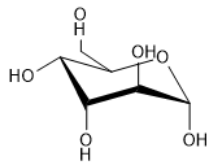


minor chair form of mannose
(four substituents axial)

EXERCISE 25.5.3

Draw the cyclic structure of α-D-altrose.

Answer

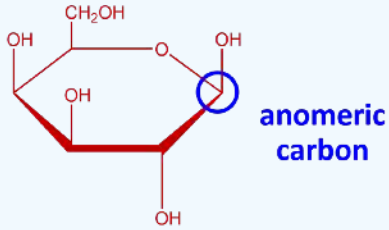


a-D-Altrose

EXERCISE 25.5.4

Draw the cyclic structure for β-D-galactose. Identify the anomeric carbon.

Answer

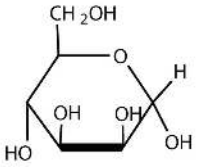


To identify the structure, we should first start with the Fischer projection of D-galactose. Since it is an aldohexose, we will start with the pyranose ring. The beta anomer was requested, so the OH on the anomeric carbon (C1) is cis to C6. Since C6 is top face (pointing up), the OH will be top face. Carbons 2, 3, and 4 are then arranged based on the Fischer projection arrangement at those carbons (C2 right, C3 left, and C4 left).

EXERCISE 25.5.5

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.

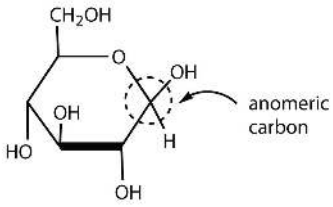
Answer



EXERCISE 25.5.6

Draw the cyclic structure for β-D-glucose. Identify the anomeric carbon.

Answer



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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25.6 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

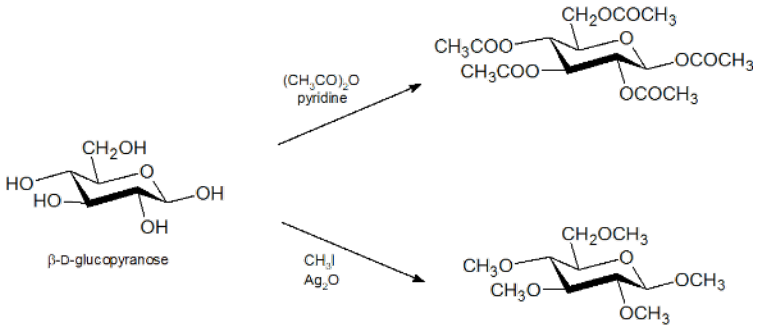
While several reactions are covered in this section, keep in mind that you have encountered them in previous sections. The active functional groups on monosaccharides are essentially carbonyls and hydroxyls. Although they now are a part of much larger molecules, their chemistry should be familiar.

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

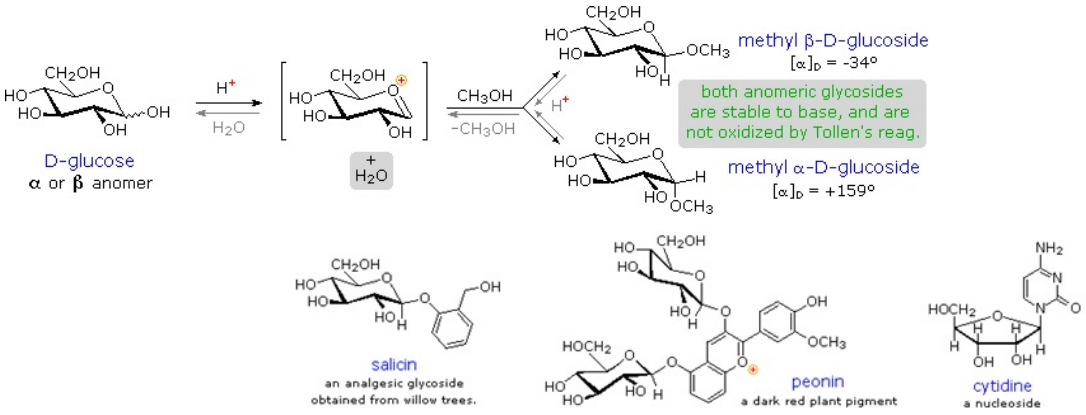
The -OH groups on a monosaccharide can be readily converted to esters and ethers. Esterfication can be done with an acid chloride (Section 21.4) or acid anhydride (Section 21.5), while treatment with an alkyl halide by a Williamson ether synthesis (Section 18.2) leads to the ether.



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.

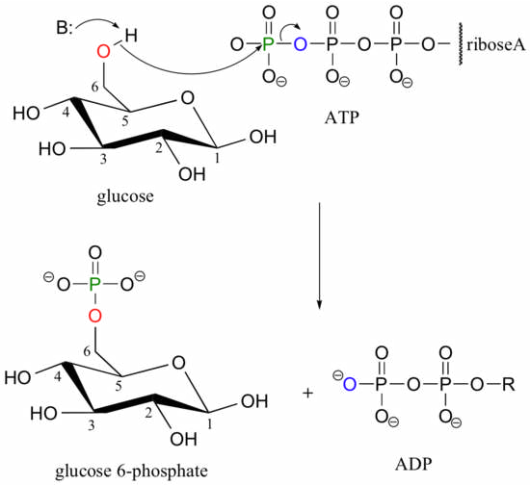


Glycosides abound in biological systems. By attaching a sugar moiety to a lipid or benzenoid structure, the solubility and other properties of the compound may be changed substantially. Because of the important modifying influence of such derivatization, numerous enzyme systems, known as glycosidases, 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).

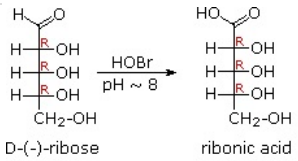


OXIDATION EDIT SECTION

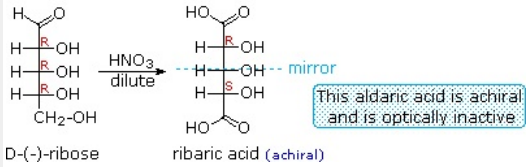
As noted above, sugars may be classified as **reducing** or **non-reducing** based on their reactivity with **Tollens'**, **Benedict's** or **Fehling's** reagents. If a sugar is oxidized by these reagents it is called reducing, since the oxidant ($Ag^{(+)}$ or $Cu^{(+2)}$) is reduced in the reaction, 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.

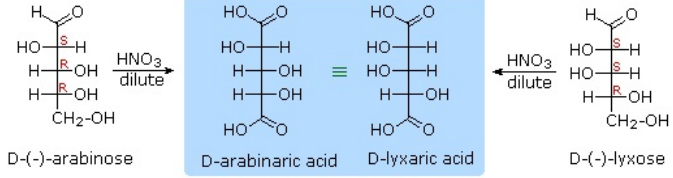
1.



2.



3.



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

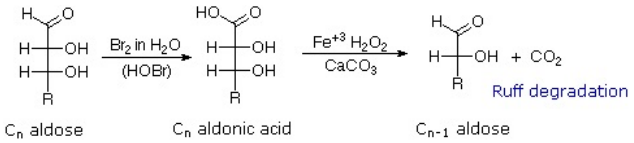
Sodium borohydride reduction of an aldose makes the ends of the resulting **alditol** chain identical, $HOCH_2(CHOH)_nCH_2OH$, thereby accomplishing the same configurational change produced by oxidation to an aldaric acid. Thus, allitol and galactitol from reduction of allose and galactose are achiral, 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 $HOCH_2(CHOH)_nCHO$

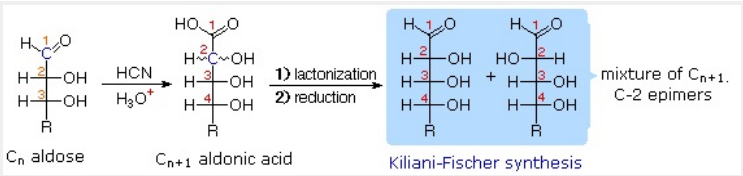
$HOBr$ Oxidation	→	$HOCH_2(CHOH)_nCO_2H$ an Aldonic Acid
HNO_3 Oxidation	→	$H_2OC(CHOH)_nCO_2H$ an Aldaric Acid
$NaBH_4$ Reduction	→	$HOCH_2(CHOH)_nCH_2OH$ an Alditol

CHAIN SHORTENING AND LENGTHENING

1. Ruff Degradation

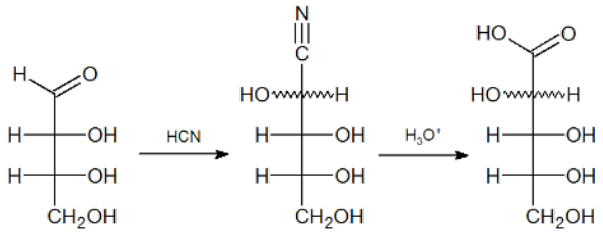


2. Kiliani-Fischer Synthesis



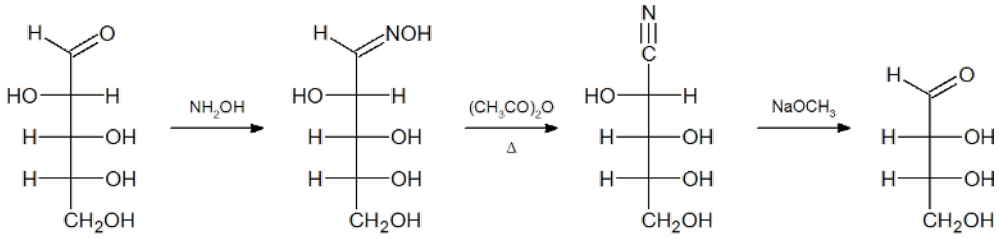
These two procedures permit an aldose of a given size to be related to homologous smaller and larger aldoses. The importance of these relationships may be seen in the array of aldose structures presented earlier, where the structural connections are given by the dashed blue lines. Thus Ruff degradation 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.



EXERCISES

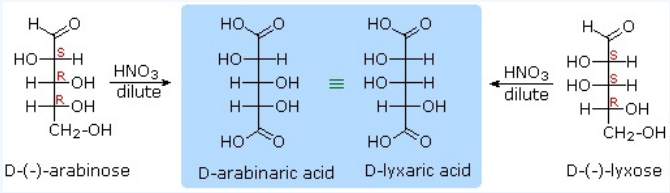
? EXERCISE 25.6.1

1) D-arabinose and D-lyxose produce the same chiral aldaric acid product when oxidized with dilute HNO_3. Please explain.

2) Which two D-aldohexoses are oxidized to produce an optically inactive (meso) aldaric acid?

Answer

1) Remember, a Fischer projection formula may be rotated by 180° in the plane of projection without changing its configuration.



2) D-Allose and D-galactose.

? EXERCISE 25.6.2

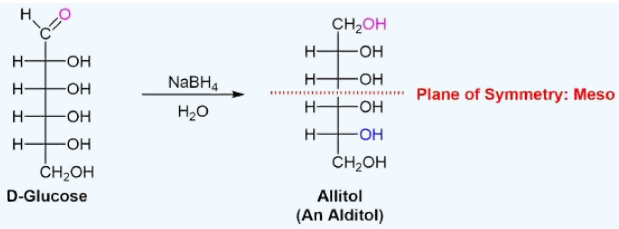
1) Allitol and galactitol from the reduction of allose and galactose are achiral. Explain why this occurs.

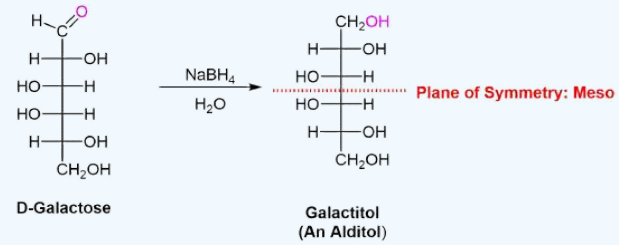
2) Altrose and talose are reduced to the same chiral alditol. Explain why this occurs.

Answer

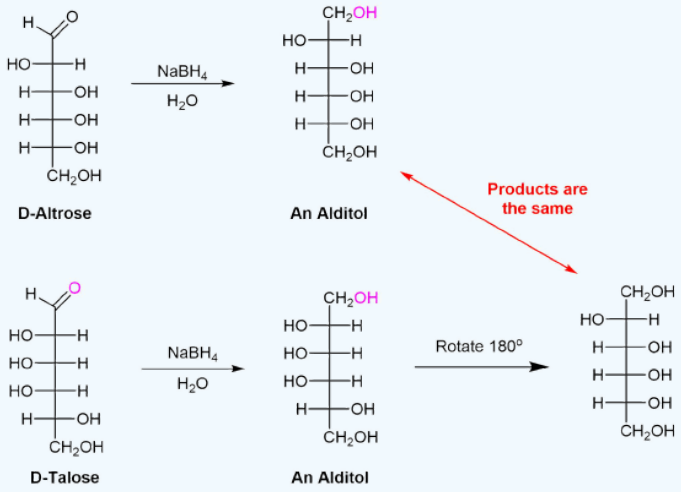
1)

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2)



? EXERCISE 25.6.3

1) What products would you expect from Kiliani–Fischer reaction of D-xylose?

2) What aldopentose would be expected to produce a mixture of D-xylose and D-lyxose from an Kiliani–Fischer synthesis?

Answer

1) D-Gluose and D-idose

2) D-Threose

? EXERCISE 25.6.4

Two of the four D- aldopentoses yield D-erythrose on Wohl degradation. What are their structures?

Answer

D-Ribose and D-arabinose

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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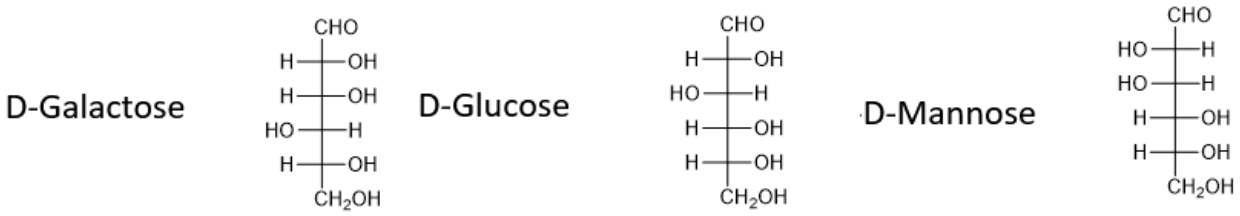
25.7 THE EIGHT ESSENTIAL MONOSACCHARIDES

OBJECTIVES

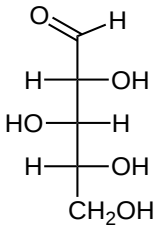
You may omit Section 25.7.

Eight monosaccharides are required for the proper functioning of human beings. Although they are typically supplied through a healthy diet, they can be biosynthesized if required. The eight monosaccharides are L-fucose, D-galactose, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine, D-glucose, D-mannose, N-acetyl-D-neuraminic acid, and D-xylose.

D-Galactose, D-Glucose, and D-Mannose are commonly found aldohexoses:

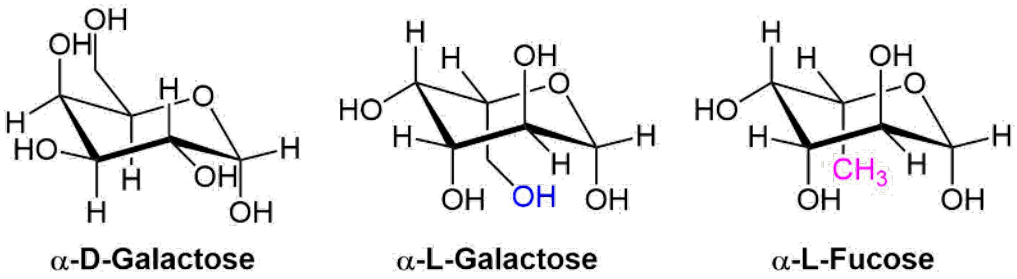


D-Xylose is a common aldopentose.

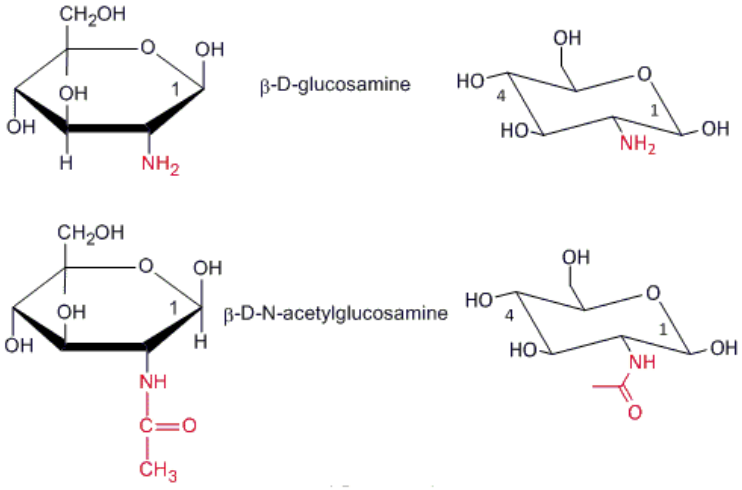


D-Xylose

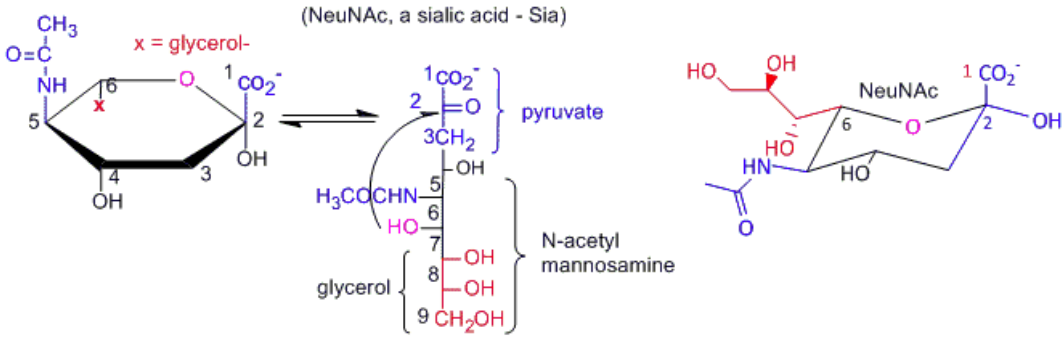
L-Fucose is a deoxy sugar. Fucose is is the monosaccaride L-galactose with the -OH group on C6 replaced with an -H.



N-acetylgalactosamine and N-acetylglucosamine are derivatives where the corresponding amino sugars have been converted to amides by N-acylation. Amino sugars have had their -OH groups at C2 replaced by an $-NH_2$.

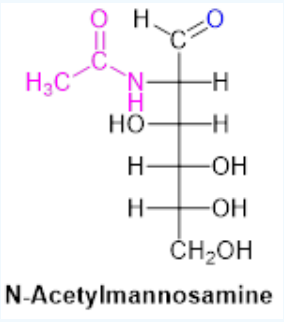


N-Acetylneuraminic acid is nine carbon sugar created by an aldol reaction between N-acetymannosamine and pyruvate. N-acetylneuaminic acid forms a pyranose ring by a intramolecular hemiacetal formation between the -OH on C6 and the ketone functional group in the pyruvate moiety.



EXERCISE 25.7.1

1) Please show the mechanism of the aldol reaction between *N*-acetylmannosamine and pyruvate to form neuraminic acid.



Answer

1)

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25.8 DISACCHARIDES

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

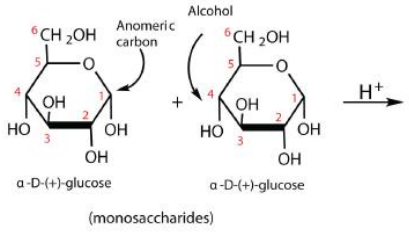
Make certain that you can define, and use in context, the key terms below.

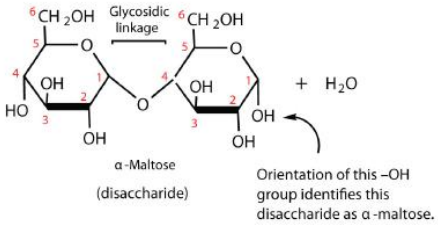
- 1,4′ link
- disaccharide (see Section 25.1)
- invert sugar

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.

$$\text{maltose} \xrightarrow{H^+ \text{ or maltase}} 2\ \text{D-glucose} \qquad (1)$$

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.

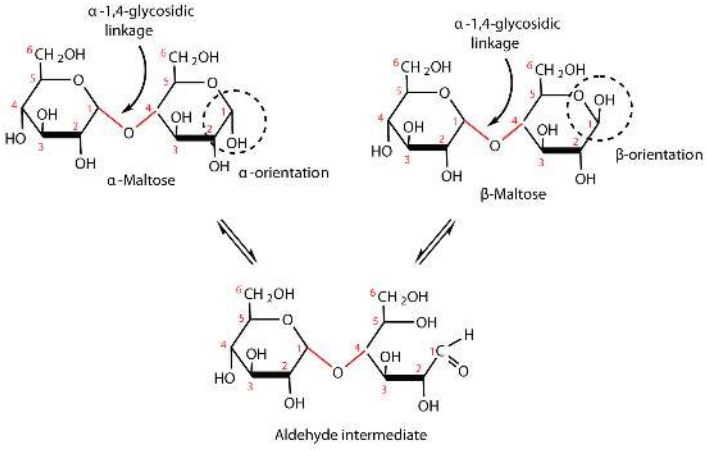
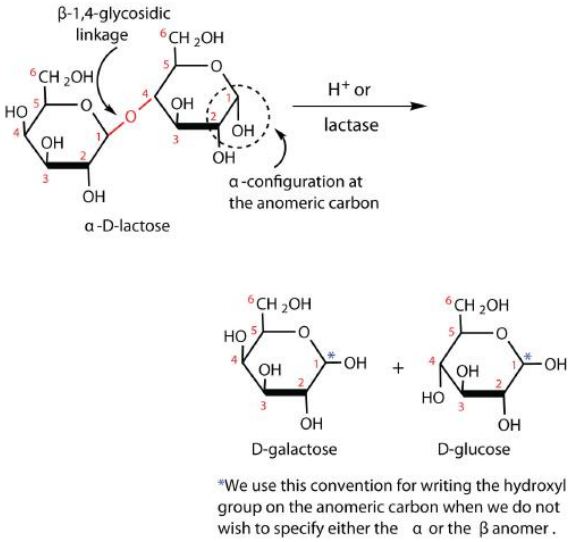


Figure 1 *An Equilibrium Mixture of Maltose Isomers*

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.

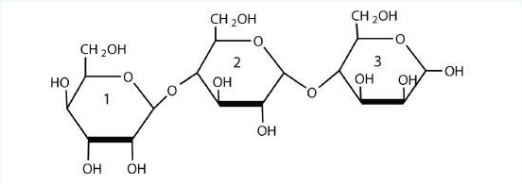
Lactose is a reducing sugar composed of one molecule of D-galactose and one molecule of D-glucose joined by a β-1,4-glycosidic bond (the bond from the anomeric carbon of the first monosaccharide unit being directed upward). The two monosaccharides are obtained from lactose by acid hydrolysis or the catalytic 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 25.8.1

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.

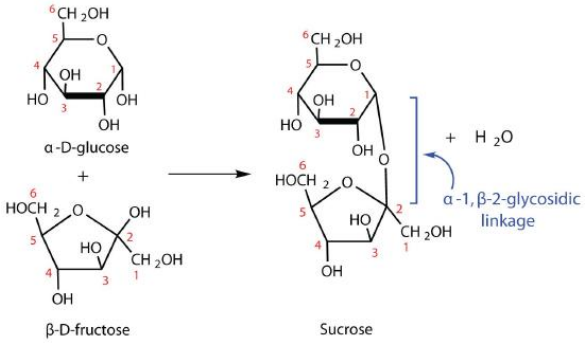
The symptoms disappear if milk or other sources of lactose are excluded from the diet or consumed only sparingly. Alternatively, many food stores now carry special brands of milk that have been pretreated with lactase to hydrolyze the lactose. Cooking or fermenting milk causes at least partial hydrolysis 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.

EXERCISES

? EXERCISE 25.8.1

What monosaccharides are obtained by the hydrolysis of each disaccharide?

a. sucrose
b. maltose

c. lactose

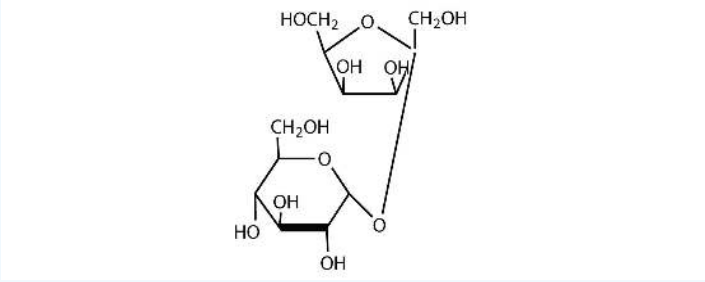
Answer

a. D-glucose and D-fructose
b. two molecules of D-glucose
c. D-glucose and D-galactose

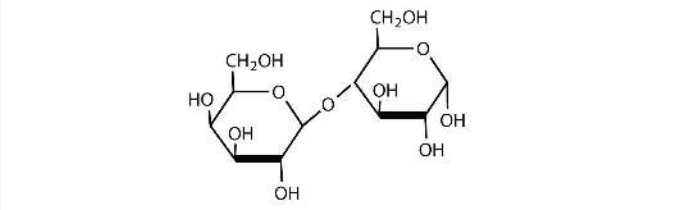
? EXERCISE 25.8.2

For each disaccharide, indicate whether the glycosidic linkage is α or β.

a)

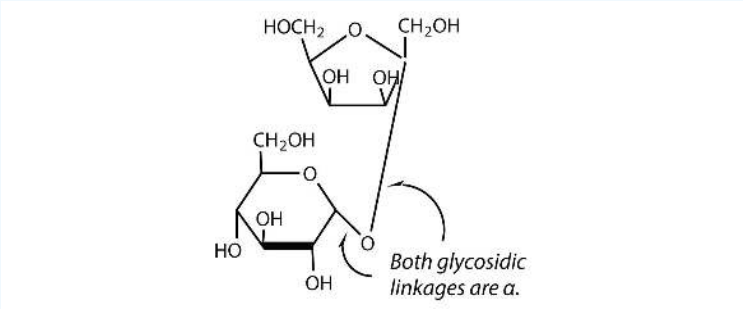


b)

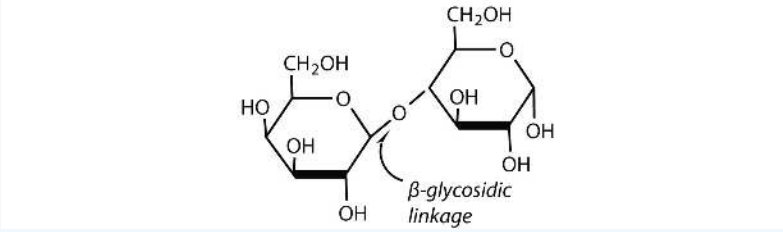


Answer

a)



b)



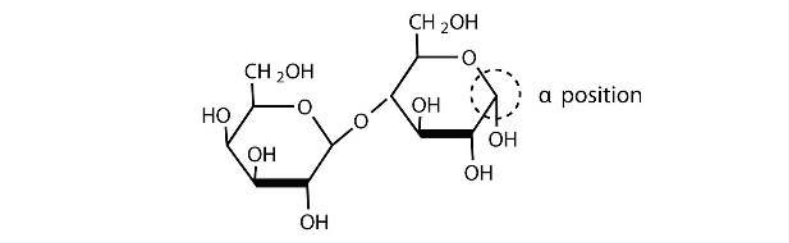
EXERCISE 25.8.3

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.

Answer

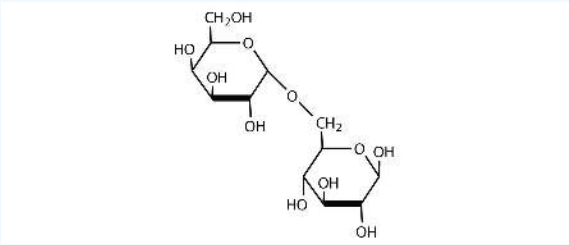
a) nonreducing

b) reducing



EXERCISE 25.8.4

Melibiose is a disaccharide that occurs in some plant juices. Its structure is as follows:



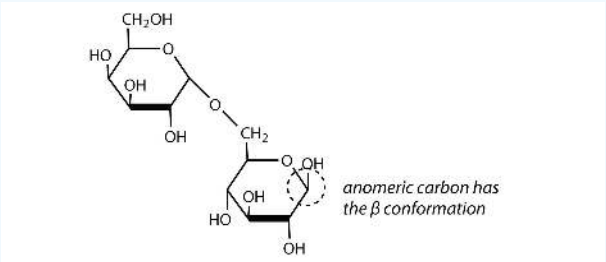
a. What monosaccharide units are incorporated into melibiose?

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

Answer

a) galactose and glucose



.

b) α-glycosidic linkage

c) β.

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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25.9 POLYSACCHARIDES AND THEIR SYNTHESIS

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 **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 **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.

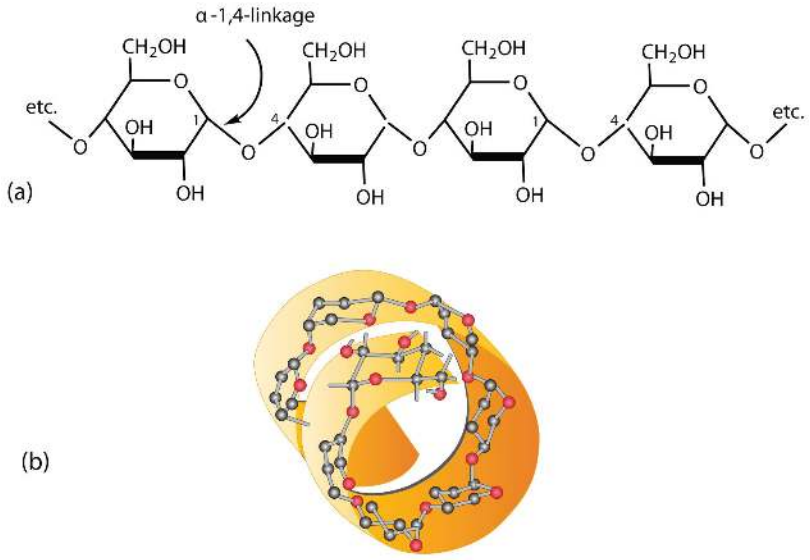


Figure 1: Amylose. (a) Amylose is a linear chain of α-D-glucose units joined together by α-1,4-glycosidic bonds. (b) Because of hydrogen bonding, amylose acquires a spiral structure that contains six glucose units per turn.

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 **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.

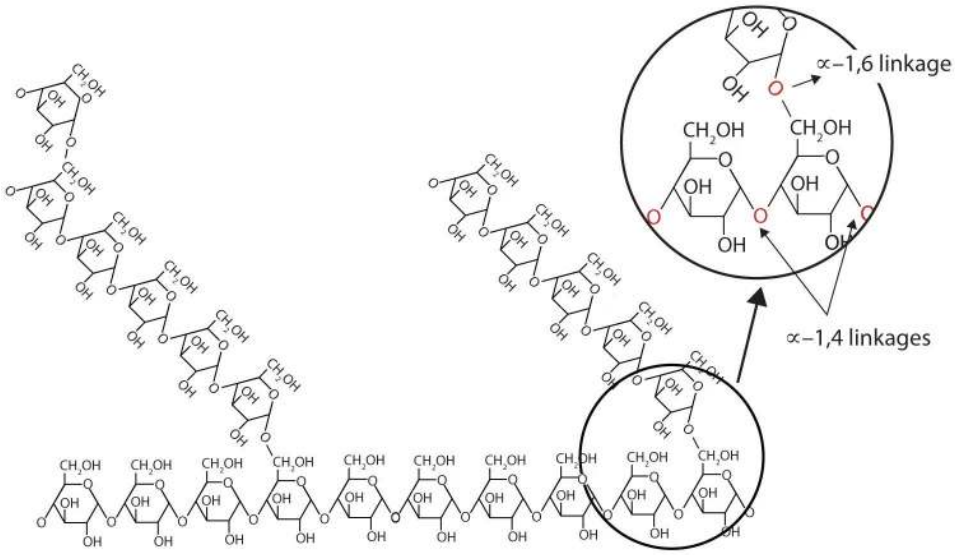


Figure **2**: Representation of the Branching in Amylopectin and Glycogen. Both amylopectin and glycogen contain branch points that are linked through α-1,6-linkages. These branch points occur more often in glycogen.

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 **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 **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.

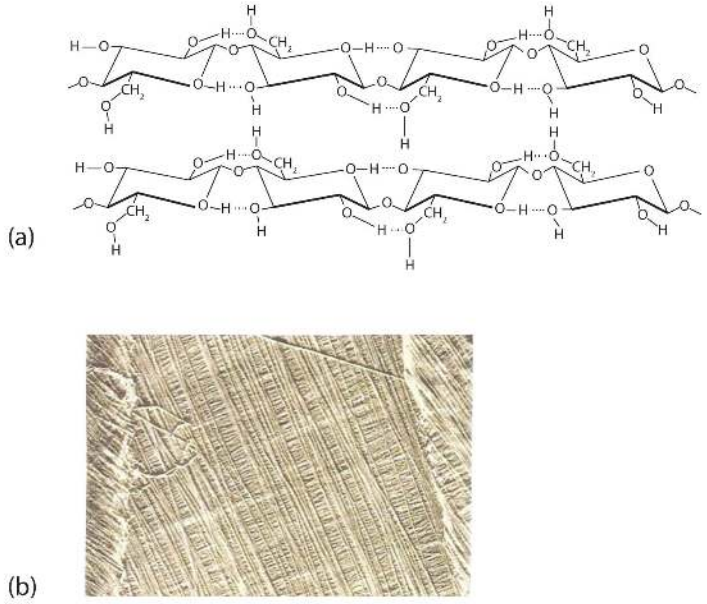


Figure **3**: Cellulose. (a) There is extensive hydrogen bonding in the structure of cellulose. (b) In this electron micrograph of the cell wall of an alga, the wall consists of successive layers of cellulose fibers in parallel arrangement.

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.

CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Anonymous by request
- *The Basics of General, Organic, and Biological Chemistry* by David W. Ball, John W. Hill, and Rhonda J. Scott.

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25.10 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.

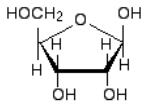
- amino sugar
- deoxy sugar

THE SUGARS IN THE BACKBONE OF DNA

EDIT SECTION

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.

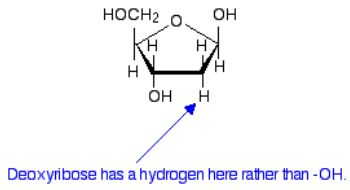
RIBOSE



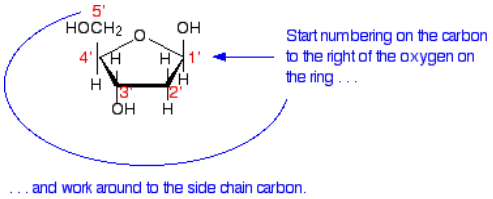
This diagram misses out the carbon atoms in the ring for clarity. Each of the four corners where there isn't an atom shown has a carbon atom. The heavier lines are coming out of the screen or paper towards you. In other words, you are looking at the molecule from a bit above the plane of the ring.

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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25.11 CELL-SURFACE CARBOHYDRATES AND INFLUENZA VIRUSES

OBJECTIVES

You may omit Section 25.11.

OLIGOSACCHARIDES

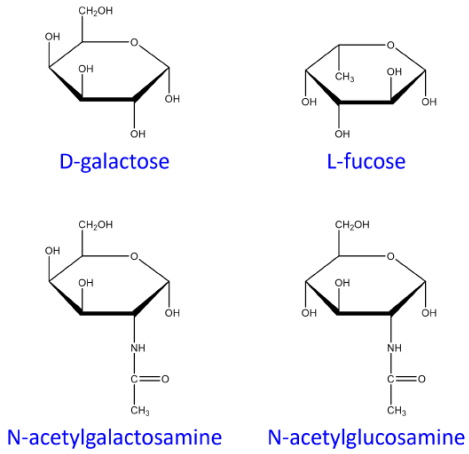
An **oligosaccharide** is a saccharide polymer containing a small number (typically two to ten) of monosaccharides. Oligosaccharides can have many functions; for example, they are commonly found on the plasma membrane of animal cells where they can play a role in cell-cell recognition. In general, they are found attached to compatible amino acid side-chains in proteins or to lipids. Oligosaccharides are often found as a component of **glycoproteins** or **glycolipids**. They can be used as chemical markers on the outside of cells, often for cell recognition. Oligosaccharides are also responsible for determining blood type.

GLYCOPROTEINS

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. 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, their 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 as well, allowing for their import into the cell.

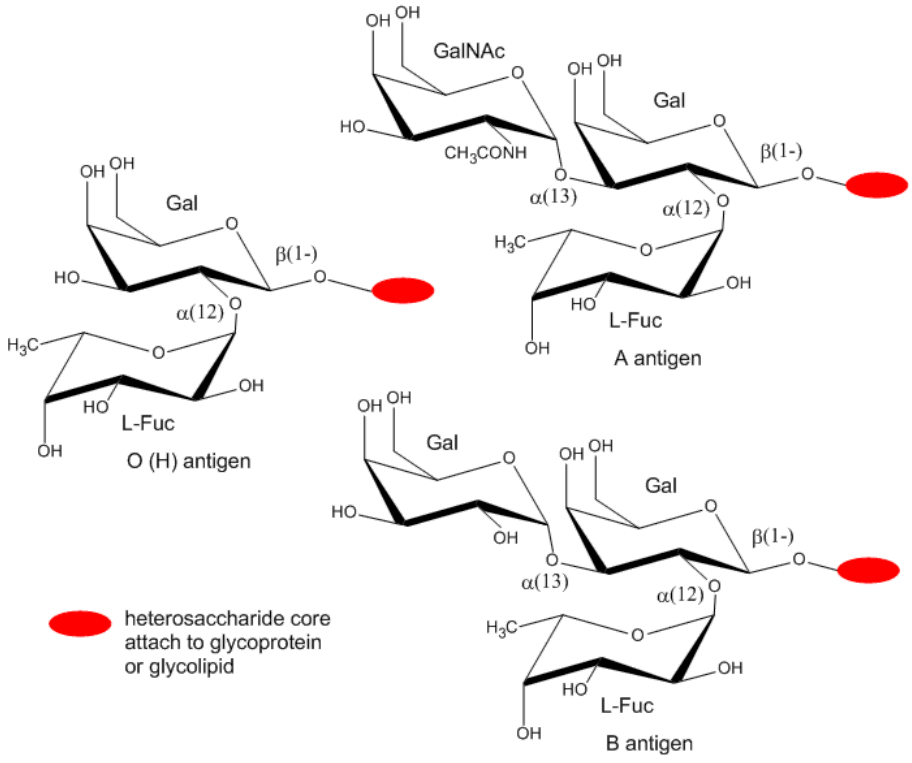
BLOOD TYPE

Cell markers are carbohydrate chains on the surface of cells where they act as “road signs” allowing molecules to distinguish one cell from another. Blood markers are exclusively made from four monosaccharides: D-galactose, L-fucose, N-acetylgalactosamine, and N-acetylglucosamine.



Structures of monosaccharide units present in ABO blood markers

ABO blood markers found on red blood cells are made up of oligosaccharides that contain either three or four sugar units as shown below. Oligosaccharides attached to red blood cells determine the ABO blood type



ABO blood types. 6.7.2

Of the four blood types, type O has the fewest types of saccharides attached to it while type AB has the most. As a result, type O blood is considered the universal donor because it doesn't have any saccharides present that will appear as foreign when transfused into blood of another type. The reverse is not true. For example:

- If type A blood is given to a patient with type O blood, it will be rejected by the body because there is an unknown species being introduced to the body. Type A blood cells contain N-acetylgalactosamine which is not present in type O blood.
- Since type AB blood has all possible saccharides, type AB blood is considered the **universal acceptor**.

The Rhesus factor (Rh) in blood also affects donor and acceptor properties but it does not depend on carbohydrates. The Rh factor is determined by the presence (Rh+) or absence (Rh-) of a specific protein on the surface of red blood cells.

INFLUENZA AND THE AVIAN FLU

Three pandemics of influenza have swept the world since the "Spanish" flu of 1918.

- The "Asian" flu pandemic of 1957;
- the "Hong Kong" flu pandemic of 1968;
- the "Swine" flu pandemic that began in April of 2009.

The influenza virus is a simple yet deadly virus. It interacts with human cells through a surface protein, hemagglutinin (HA). The virus binds to host cells through interaction of HA with cell surface carbohydrates. Once bound the virus internalizes, ultimately leading to release of the RNA genome of the virus into the host cell. The HA protein is the most abundant protein on the viral surface (as surmised by antibody formation).

The influenza virus is typically classified by two kinds of glycoproteins on the surface of the virus: in addition to HA is the enzyme neuraminidase. Two viral strains which have been often discussed are H5N1 and H1N1 which stands for hemagglutinin (H: type 5 or type 1) and neuraminidase (N: type 1). 15 avian and mammalian variants have been identified (based on antibody studies). Only 3 adapted to humans in the last 100 yr, giving pandemic strains H1 (1918), H2 (957) and H3 (1968). Three recent avian variants (H5, H7, and H9) have jumped directly to humans recently but have low human to human transmissibility.

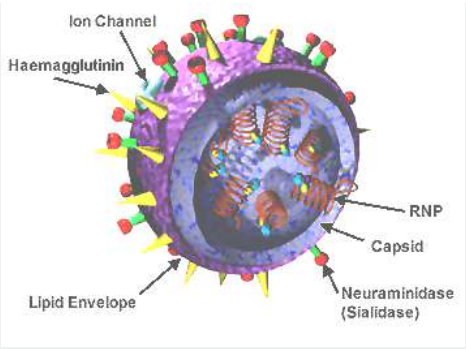
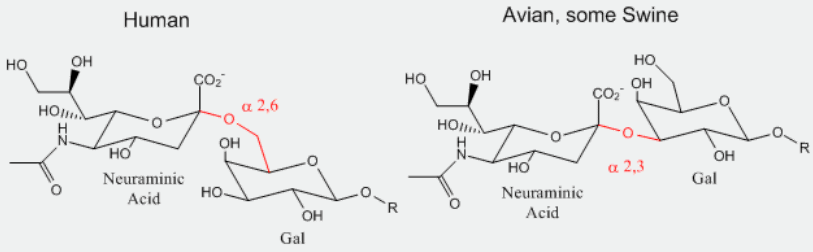


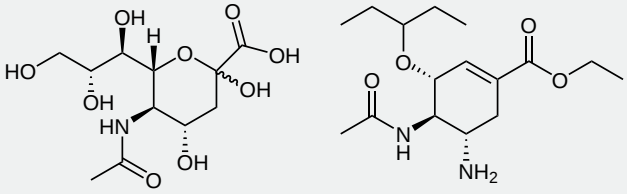
Figure 1: Structure (3D) of the Influenza Virus: The image depicts the major components of the virus structure, including the neuraminidase. (Public Domain; National Institutes of Healt via Wikipedia)

Influenza Virus binds to Cell Surface Glycoproteins with Neu5Ac - A protein on the surface of influenza virus. Hemagluttinin binds to sialic acid (Sia), which is covalently attached to many cell membrane glycoproteins. 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, as the major form in the human respiratory tract. The swine influenza HA bind to Sia (alpha 2,6) Gal and some Sia (alpha 2,3) both of which are commonly found in swine.

Binding Site for Influenza Hemagluttinin Protein



The virus, before it leaves the cell, forms a bud on the intracellular side of the cell with the HA and NA in the cell membrane of the host cell. The virus in this state would not leave the cell since its HA molecules would interact with sialic acid residues in the host cell membrane, holding the virus in the membrane. Neuraminidase hydrolyzes sialic acid from cell surface glycoproteins, allowing the virus to complete the budding process and be released from the cell as new viruses. By mimicking the structure of sialic acid, the drugs Oseltamivir (Tamiflu) and zanamivir (Relenza) bind to and inhibit neuraminidase whose activity is necessary for viral release from infected cells. Tamiflu appears to work against N1 of the present H5N1 avian influenza viruses. Governments across the world are stockpiling this drug in case of a pandemic caused by the avian virus jumping directly to humans and becoming transmissible from human to human.



Sialic Acid **Tamiflu**

CONTRIBUTORS AND ATTRIBUTIONS

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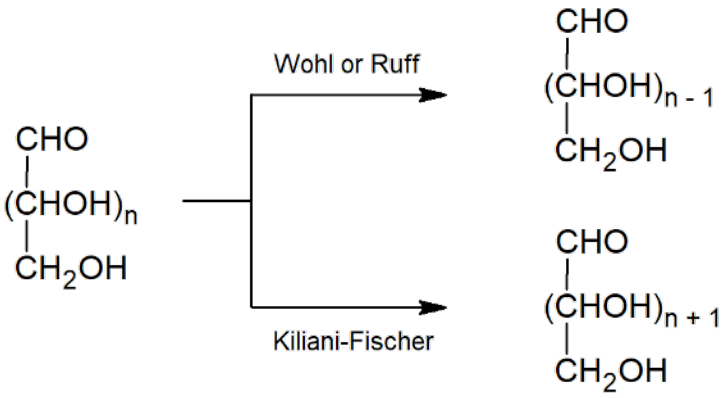
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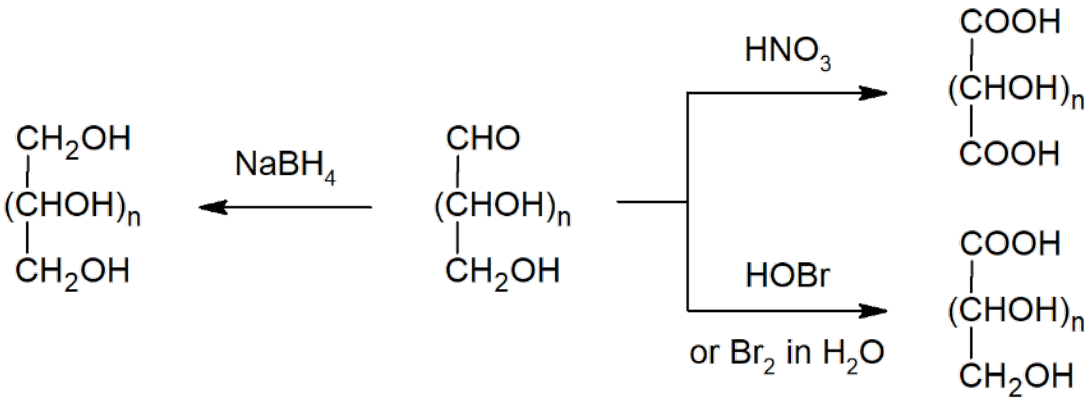
25.S: BIOMOLECULES- CARBOHYDRATES (SUMMARY)

SUMMARY OF REACTIONS

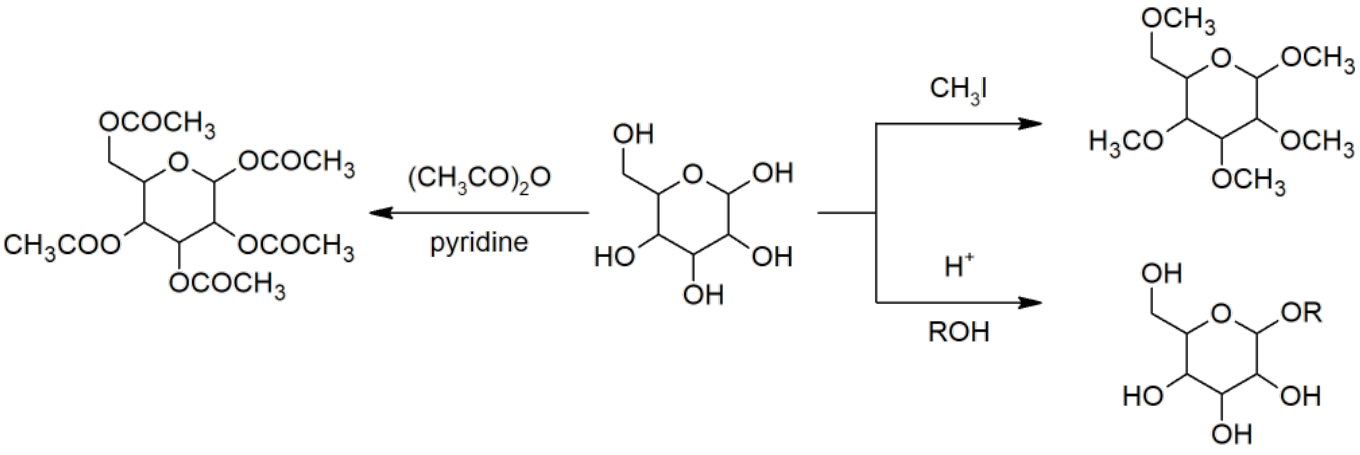
Chain Length



Oxidation - Reduction



Ester and Ether Formation



CONTRIBUTORS

- Dietmar Kennepohl (Athabasca University)

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CHAPTER OVERVIEW

CHAPTER 26: BIOMOLECULES: AMINO ACIDS, PEPTIDES, AND PROTEINS

Amino acids are important biochemicals, as they are the building blocks from which proteins and polypeptides are assembled. We begin this chapter with an examination of some of the fundamental chemistry of amino acids: their structures, stereochemistry and synthesis. We then discuss the nature of peptides and of the peptide bond, and present the complex issue of determining the order in which the various amino-acid residues occur in a given peptide. Once a chemist knows the exact order the of the residues in a given peptide, the next challenge is to determine a method by which the same peptide can be prepared in the laboratory. Thus, two sections are devoted to the problem of protein synthesis. The final sections in the chapter deal with the classification, overall structure and denaturation of proteins.

Chapter Objectives
26.0 Introduction
26.1 Structures of Amino Acids
26.2 Amino Acids, the Henderson-Hasselbalch Equation, and Isoelectric Points
26.3 Synthesis of Amino Acids
26.4 Peptides and Proteins
26.5 Amino Acid Analysis of Peptides
26.6 Peptide Sequencing: The Edman Degradation
26.7 Peptide Synthesis
26.8 Automated Peptide Synthesis: The Merrifield Solid-Phase Technique
26.9 Protein Structure
26.10 Enzymes and Coenzymes
26.11 How do Enzymes Work? Citrate Synthase

Chapter 26: Biomolecules: Amino Acids, Peptides, and Proteins is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

CHAPTER OBJECTIVES

When you have completed Chapter 26, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. use the information provided by an amino acid analysis, an Edman degradation and a carboxypeptidase hydrolysis to determine the structure of an unknown polypeptide.
3. outline the approach that you would use to synthesize a given peptide, providing appropriate mechanistic details if requested to do so.
4. define, and use in context, the key terms introduced in this chapter.

CONTRIBUTORS AND ATTRIBUTIONS

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26.0 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

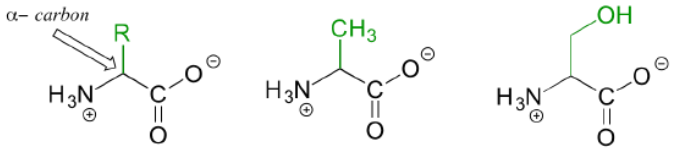
Make certain that you can define, and use in context, the key terms below.

- 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.

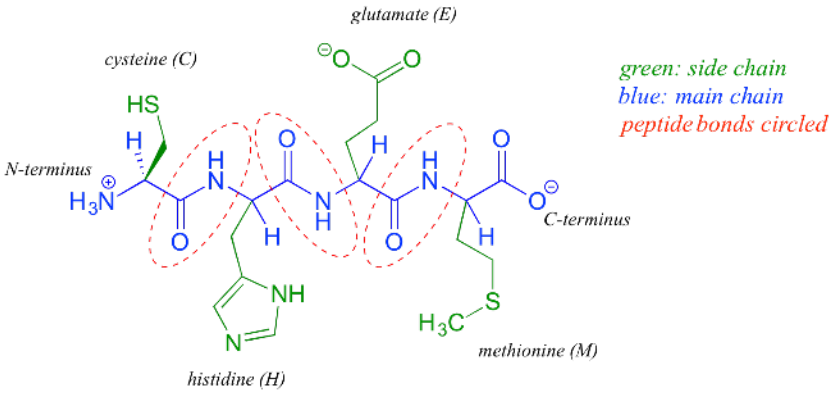
Proteins are polymers of **amino acids**, linked by amide groups known as **peptide bond**s. An amino acid can be thought of as having two components: a 'backbone', or 'main chain', composed of an ammonium group, an 'alpha-carbon', and a carboxylate, and a variable 'side chain' (in green below) bonded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



amino acid alanine serine

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

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



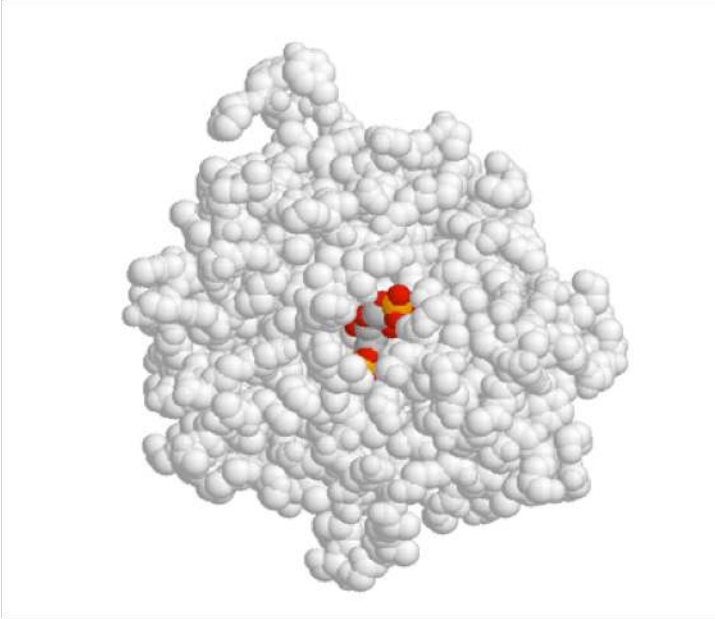
CHEM peptide

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

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

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

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



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

Intro to nucleic acids ⇒

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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26.1 STRUCTURES OF 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 nucleophilic attack by the amino group of an amino acid at the electrophilic carbonyl carbon of 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)

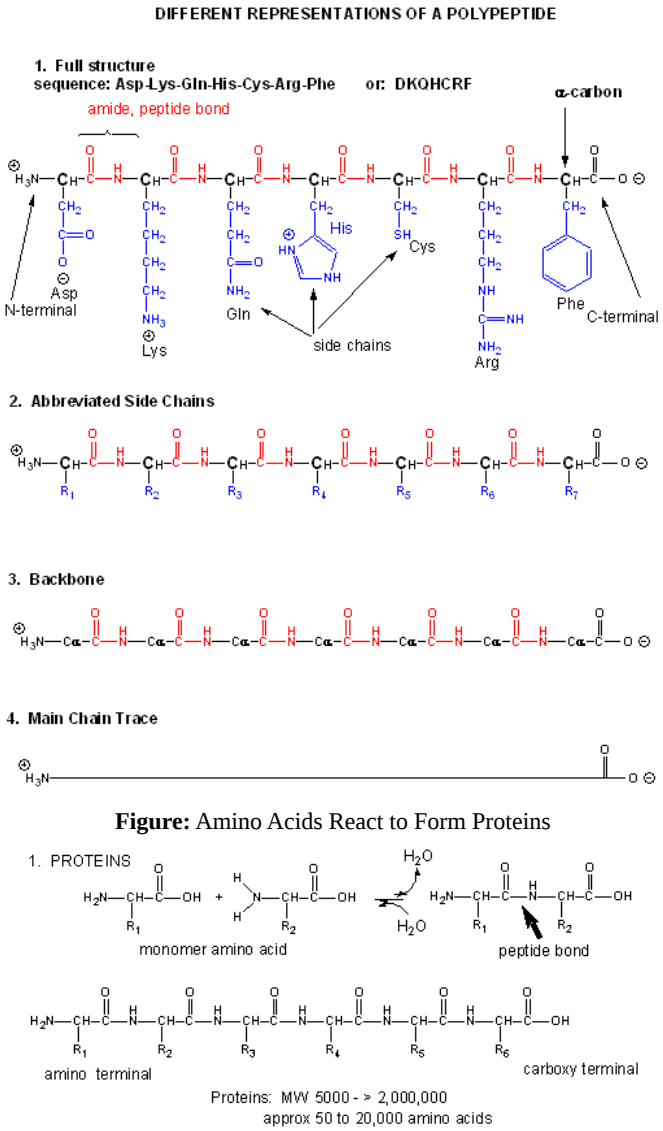


Figure: Amino Acids React to Form Proteins

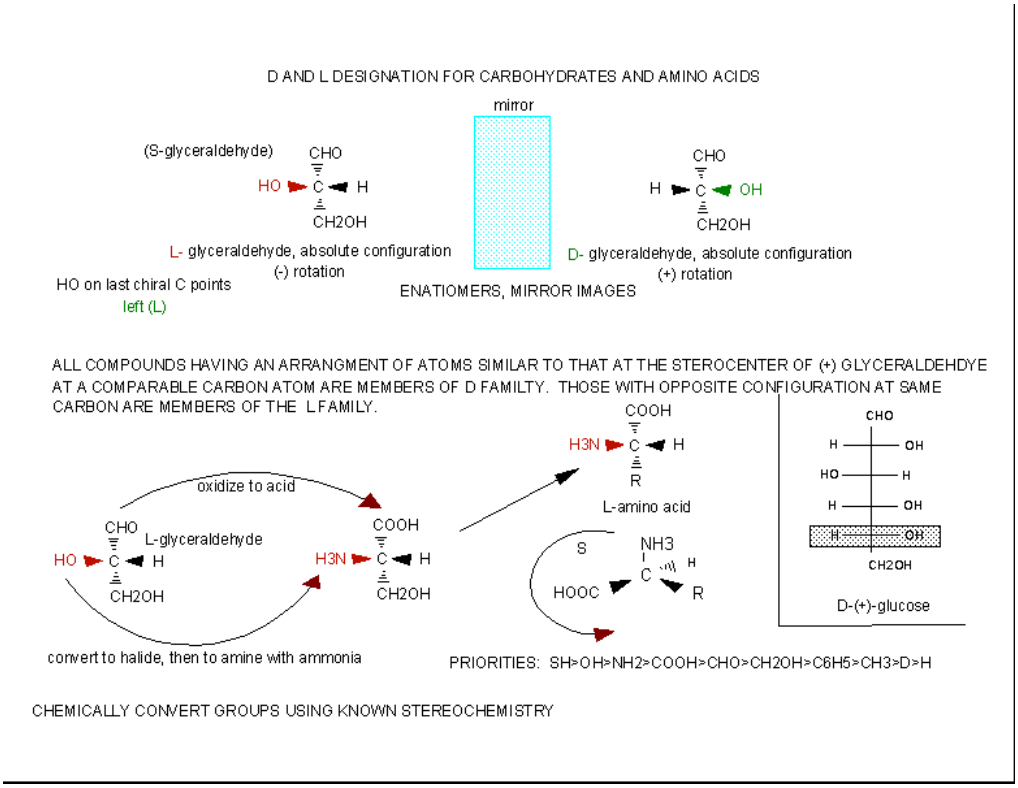
(Note: above picture represents the amino acid in an unlikely protonation state with the weak acid protonated and the weak base deprotonated for simplicity in showing removal of water on peptide bond formation and the hydrolysis reaction.) Proteins are polymers of twenty naturally occurring amino acids. 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.*

https://chem.libretexts.org/@go/page/91056



Why do biochemists still use D and L for sugars and amino acids? This explanation (taken from the link below) seems reasonable.

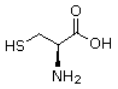
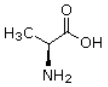
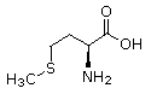
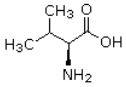
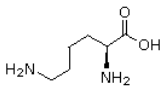
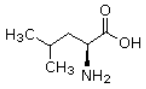
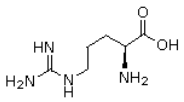
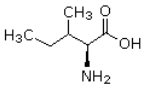
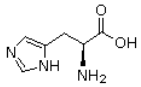
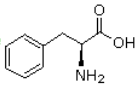
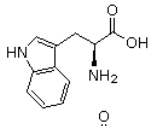
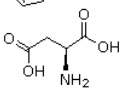
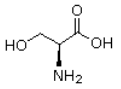
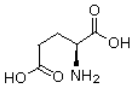
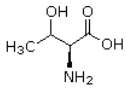
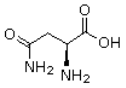
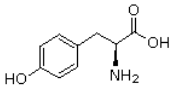
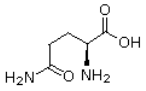
"In addition, however, chemists often need to define a configuration unambiguously in the absence of any reference compound, and for this purpose the alternative (R,S) system is ideal, as it uses priority rules to specify configurations. These rules sometimes lead to absurd results when they are applied 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 1º-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

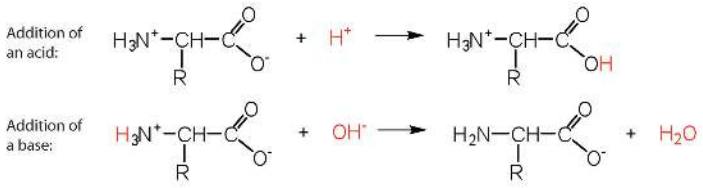
ZWITTERION

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.

$$CH_3CH(NH_2)CO_2H \rightleftharpoons CH_3CH(NH_3)^{(+)}CO_2^{(-)}$$

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.

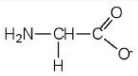


EXAMPLE 26.1.1

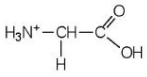
a. Draw the structure for the anion formed when glycine (at neutral pH) reacts with a base.
b. Draw the structure for the cation formed when glycine (at neutral pH) reacts with an acid.

Solution

a. The base removes H^+ from the protonated amine group.



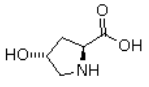
b. The acid adds H^+ to the carboxylate group.

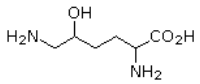


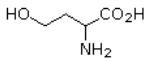
OTHER NATURAL AMINO ACIDS

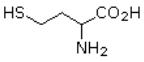
The twenty alpha-amino acids listed above are the primary components of proteins, their incorporation being governed by the genetic code. Many other naturally occurring amino acids exist, and the structures of a few of these are displayed below. Some, such as hydroxylysine and hydroxyproline, are simply 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

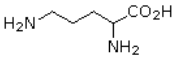
pyrophosphorylated derivative of a pantothenic acid amide. The gamma-amino homolog GABA is a neurotransmitter inhibitor and antihypertensive agent.

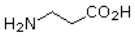

4-hydroxyproline

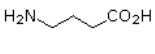

5-hydroxylysine

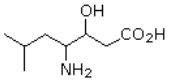

homoserine


homocysteine


ornithine


β-alanine


γ-aminobutyric acid (GABA)


statine

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

? EXERCISE 26.1.1

Why is cysteine the only L amino acid with an R configuration at the alpha carbon?

Answer

The sulfur atom in the side chain causes the side chain to have higher priority than the other substituents.

? EXERCISE 26.1.2

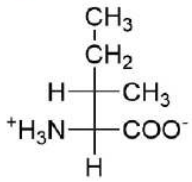
Isoleucine has two stereogenic centers.

(a) Draw a Fischer projection of isoleucine.

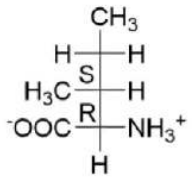
(b) Draw a Fischer projection of an isoleucine diastereomer, and label each stereocenter as R or S.

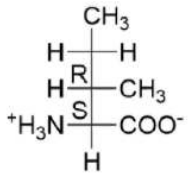
Answer

(a)



(b)





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.

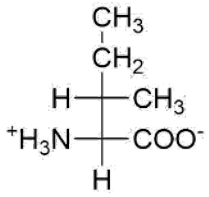
SOLUTIONS

S26.1.1

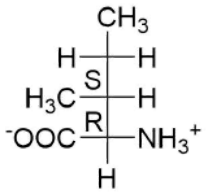
The sulfur atom in the side chain causes the side chain to have higher priority than the other substituents.

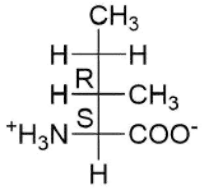
S26.1.2

(a)



(b)





CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Henry Jakubowski (College of St. Benedict/St. John's University)

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26.2 AMINO ACIDS, THE HENDERSON-HASSELBALCH EQUATION, AND ISOELECTRIC POINTS

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).

$$pK_a = pH + \log_{10} \frac{[HA]}{A^-]} \quad (1)$$

The titration curve for alanine in Figure **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.

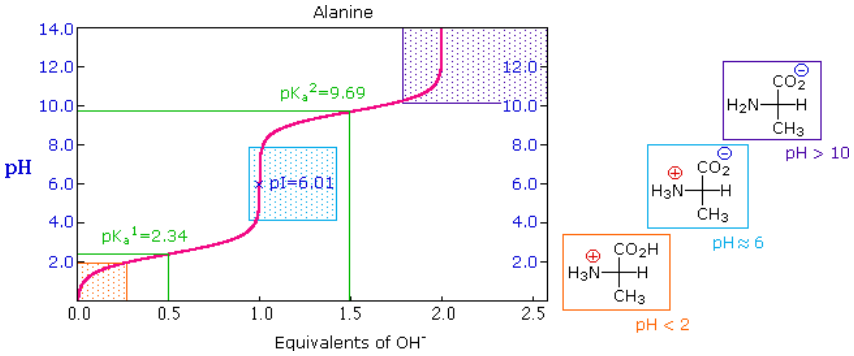


***Figure* 1:** *Titration curves for many other amino acids may be examined at a useful site provided by The University of Virginia in Charlottesville.*

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 **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.

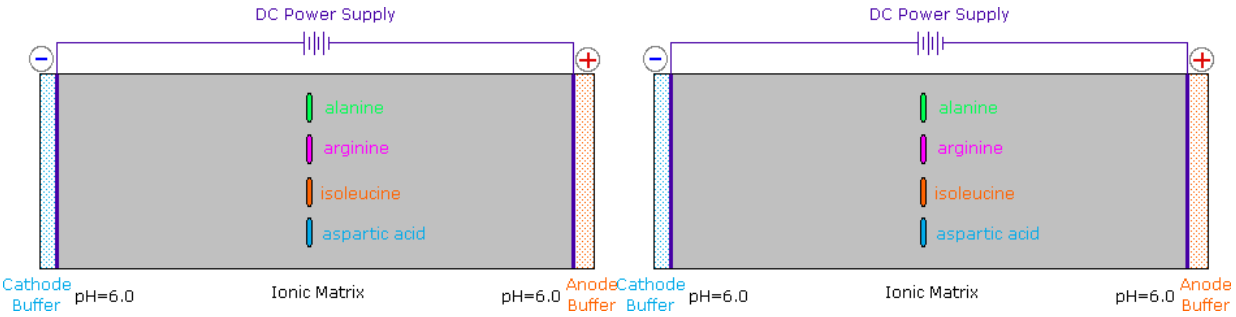
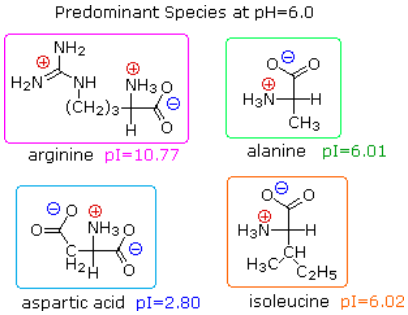


Figure 2: *In the example shown here, four different amino acids are examined simultaneously in a pH 6.00 buffered medium. To see the result of this experiment, click on the illustration. Note that the colors in the display are only a convenient reference, since these amino acids are colorless.*

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 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 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.

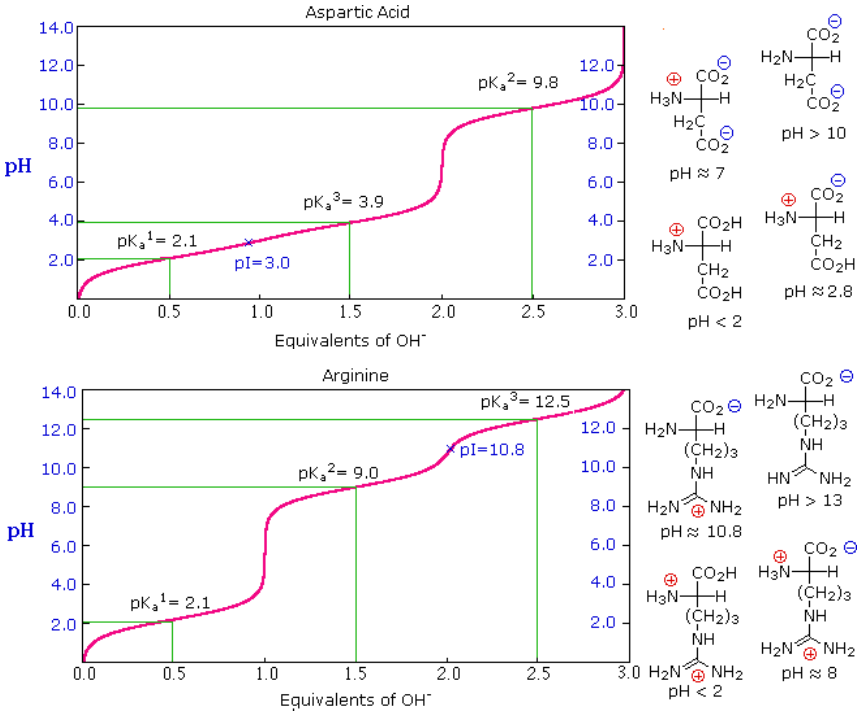


***Figure* 3**

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

26.2 Amino Acids, the Henderson-Hasselbalch Equation, and Isoelectric Points is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

26.3 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.

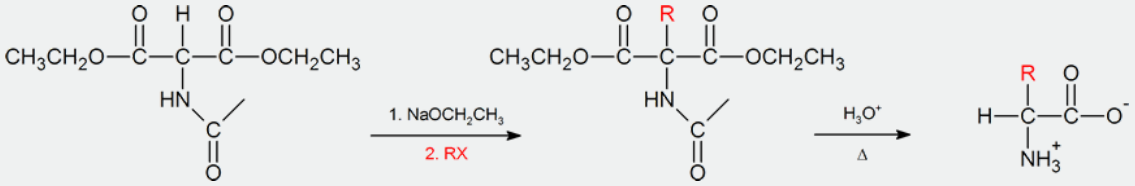
- amidomalonate synthesis
- enantioselective synthesis
- racemic mixture

STUDY NOTES

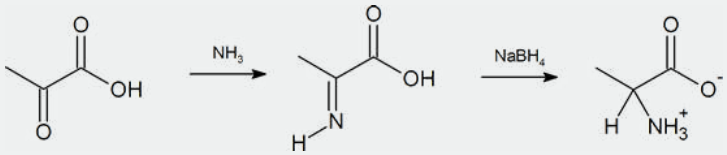
Do not be alarmed by the number of methods to synthesize amino acids described in this section.You have seen many of these reactions in previous sections and should already be familiar with the approaches discussed here.

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.

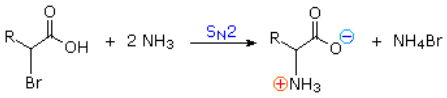


Another method of getting to the α-amino acid is by **reductive amination** of the α-keto acid which you have also previously encountered (Section 24.6).

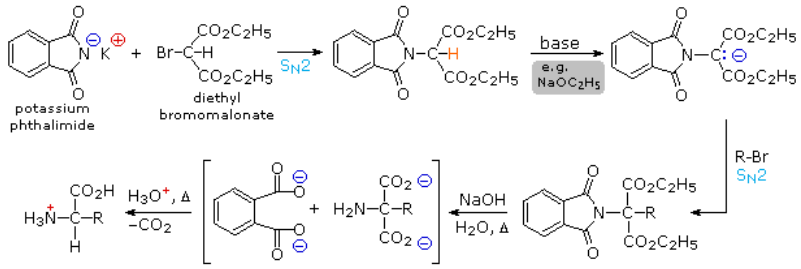


SYNTHESIS OF A-AMINO ACIDS EDIT SECTION

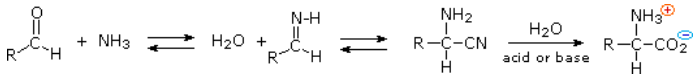
1) Amination of alpha-bromocarboxylic acids, illustrated by the following equation, provides a straightforward method for preparing alpha-aminocarboxylic acids. The bromoacids, in turn, are conveniently prepared from carboxylic acids by reaction with Br_2 + PCl_3. Although this direct approach gave mediocre 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).

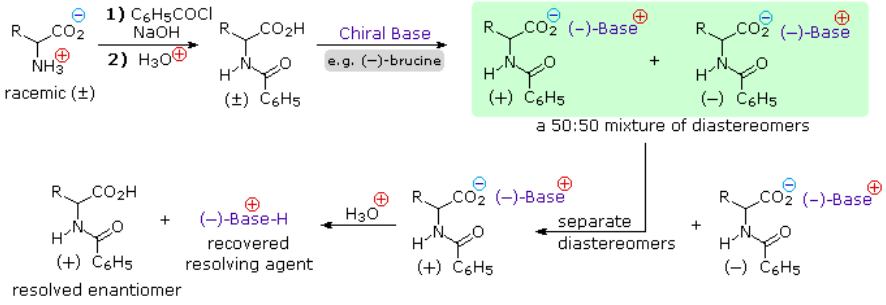


3) An elegant procedure, known as the **Strecker synthesis**, assembles an alpha-amino acid from ammonia (the amine precursor), cyanide (the carboxyl precursor), and an aldehyde. This reaction (shown below) is essentially an imino analog of cyanohydrin formation. The alpha-amino nitrile formed in this way can then be hydrolyzed to an amino acid by either acid or base catalysis.

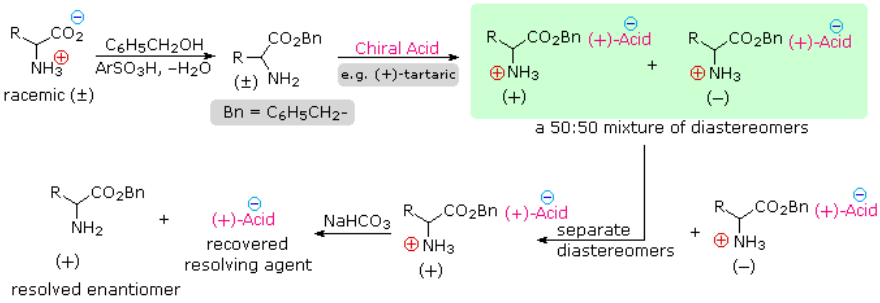


4) Resolution The three synthetic procedures described above, and many others that can be conceived, give racemic amino acid products. If pure **L** or **D** enantiomers are desired, it is necessary to resolve these racemic mixtures. A common method of resolving racemates is by diastereomeric salt formation 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.



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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

- 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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26.4 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.

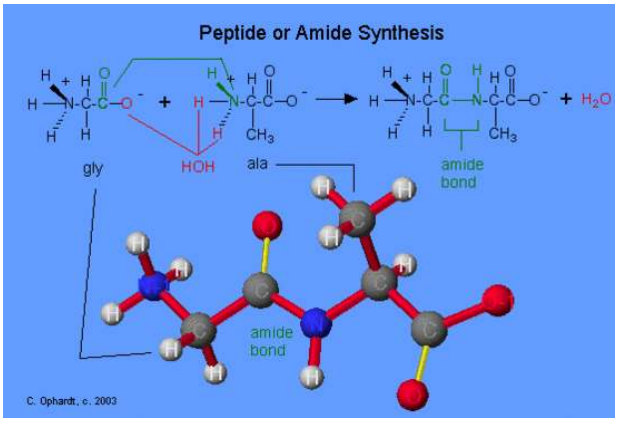
- C-terminal amino acid
- N-terminal amino acid
- peptides
- residues

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

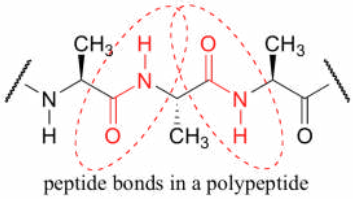
The formation of peptides is nothing more than the application of the **amide synthesis reaction**. By convention, the amide bond in the peptides should be made in the order that the amino acids are written. The amine end (N terminal) of an amino acid is always on the left, while the acid end (C terminal) 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.



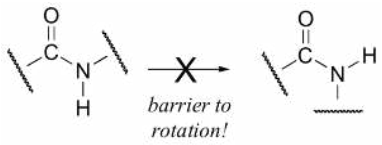
If the order of listing the amino acids is reversed, a different dipeptide is formed such as alaninylglycine.

RESONANCE CONTRIBUTORS FOR THE PEPTIDE BONDS

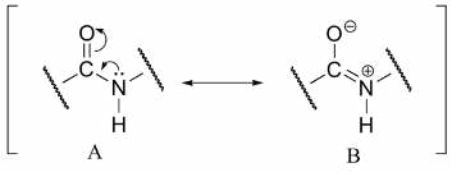
A consideration of resonance contributors is crucial to any discussion of the amide functional group. One of the most important examples of amide groups in nature is the 'peptide bond' that links amino acids to form polypeptides and proteins.



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.



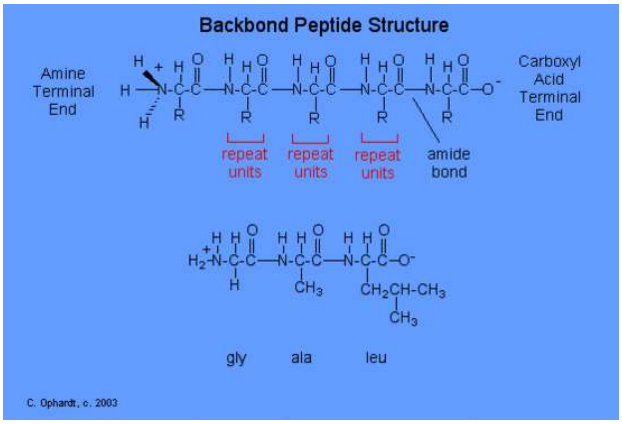
Although B is a minor contributor due to the separation of charges, it is still very relevant in terms of peptide and protein structure – our proteins would simply not fold up properly if there was free rotation about the peptide C-N bond.

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).

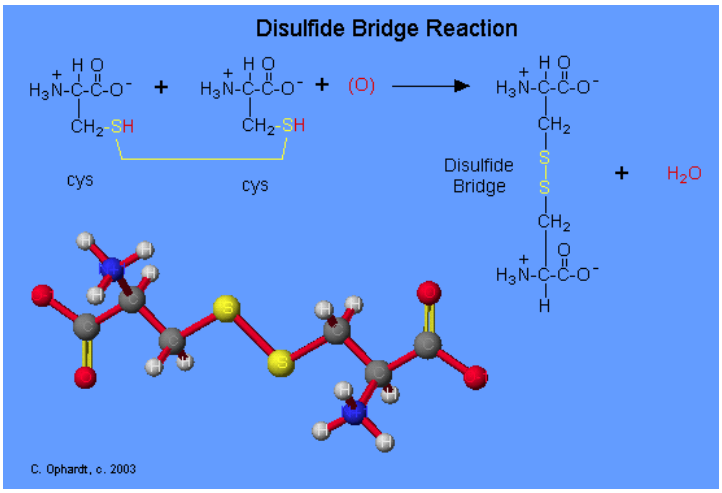


DISULFIDE BRIDGES AND OXIDATION-REDUCTION

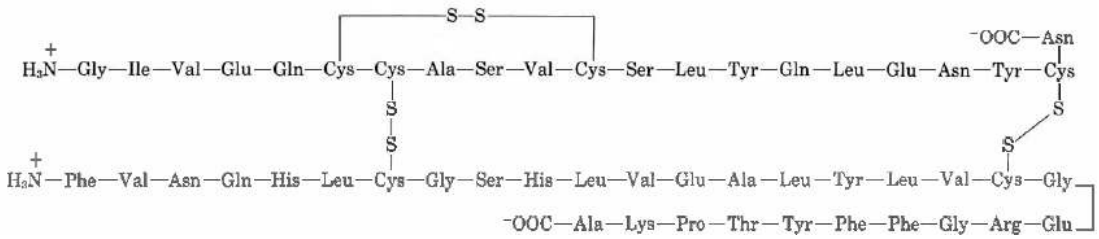
The amino acid cysteine undergoes oxidation and reduction reactions involving the -SH (sulfhydryl group). The oxidation of two sulfhydryl groups results in the formation of a **disulfide bond** by the removal of two hydrogens. The **oxidation** of two cysteine amino acids is shown in the graphic. An 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

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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.



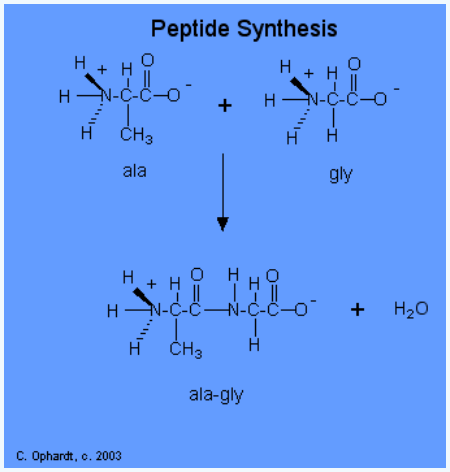
Insulin

EXERCISES

? EXERCISE 26.4.1

Write the reaction for: ala + gly --->

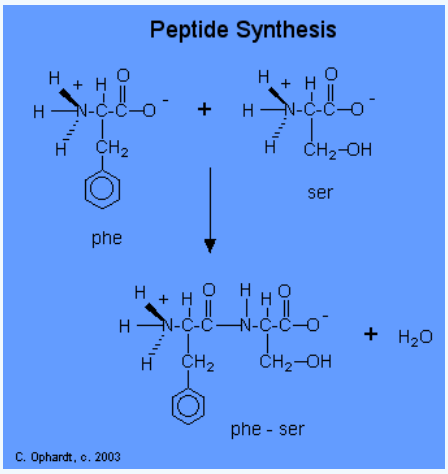
Answer



EXERCISE 26.4.2

Write the reaction for: phe + ser --->

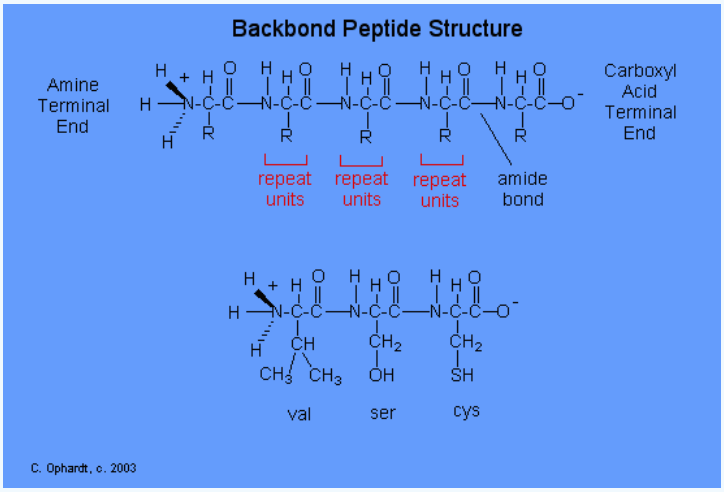
Answer



EXERCISE 26.4.3

Write the tripeptide structure for val-ser-cys. First write the "backbone" and then add the specific side chains.

Answer

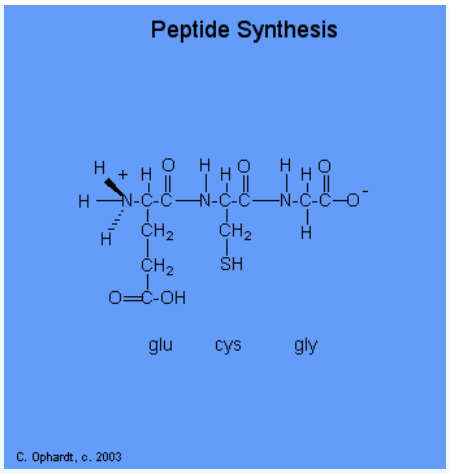


EXERCISE 26.4.4

Write the tripeptide structure for glu-cyc-gly. First write the "backbone" and then add the specific side chains.

Answer

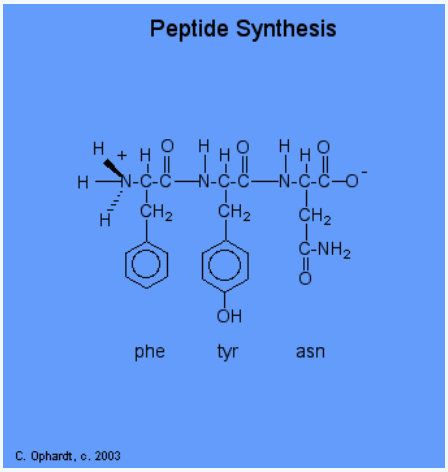
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EXERCISE 26.4.5

Write the tripeptide structure for phe-tyr-asn. First write the "backbone" and then add the specific side chains.

Answer



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

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

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26.5 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 analysed, 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.

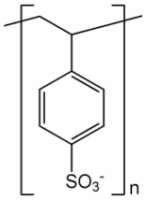


Fig 26.5.1: A Cation Rasin like Dowex 50 is a polymeric bead bearing aryl sulfonic acid groups

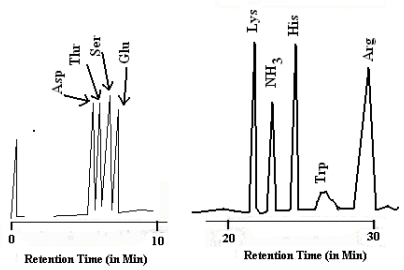
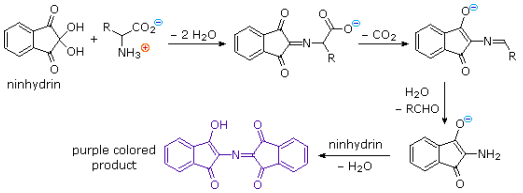


Fig 26.5.2: Some typical chromatograms from an amino acid analyzer

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.



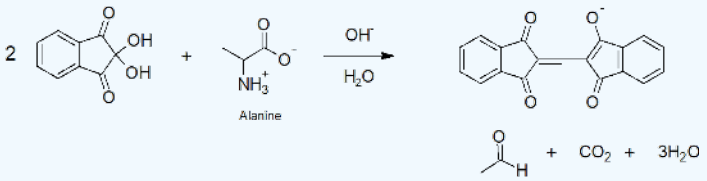
EXERCISE

EXERCISE 26.5.1

Show the structure of the products obtained of reaction of alanine with ninhydrin.

Answer

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CONTRIBUTORS AND ATTRIBUTIONS

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26.6 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

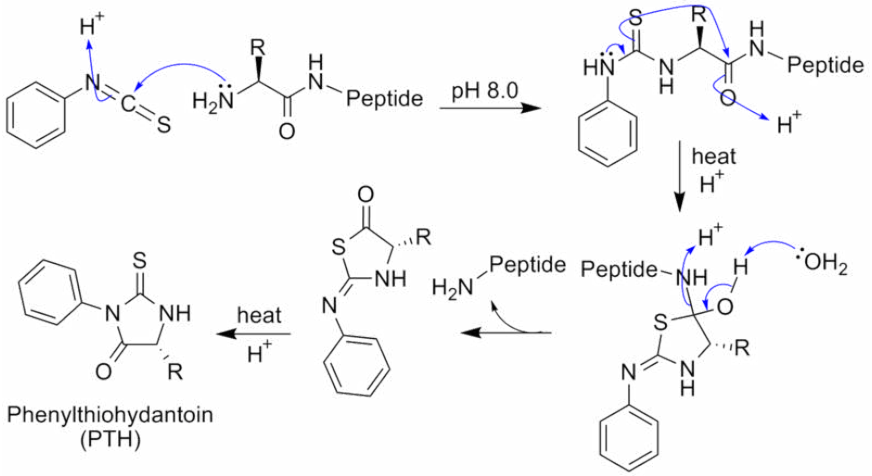
STUDY NOTES

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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26.7 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).

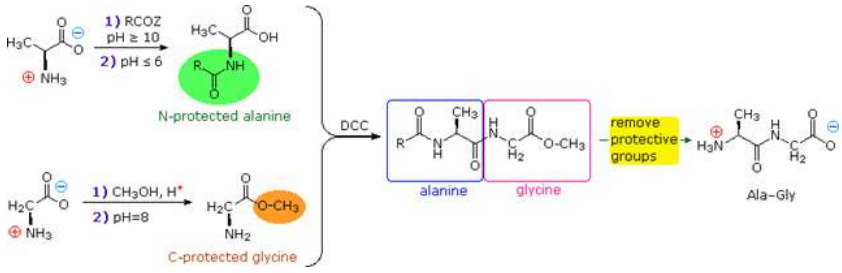
From the perspective of an organic chemist, peptide synthesis requires selective acylation of a free amine. To accomplish the desired amide bond formation, we must first deactivate all extraneous amine functions so they do not compete for the acylation reagent. Then we must selectively activate the designated 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.

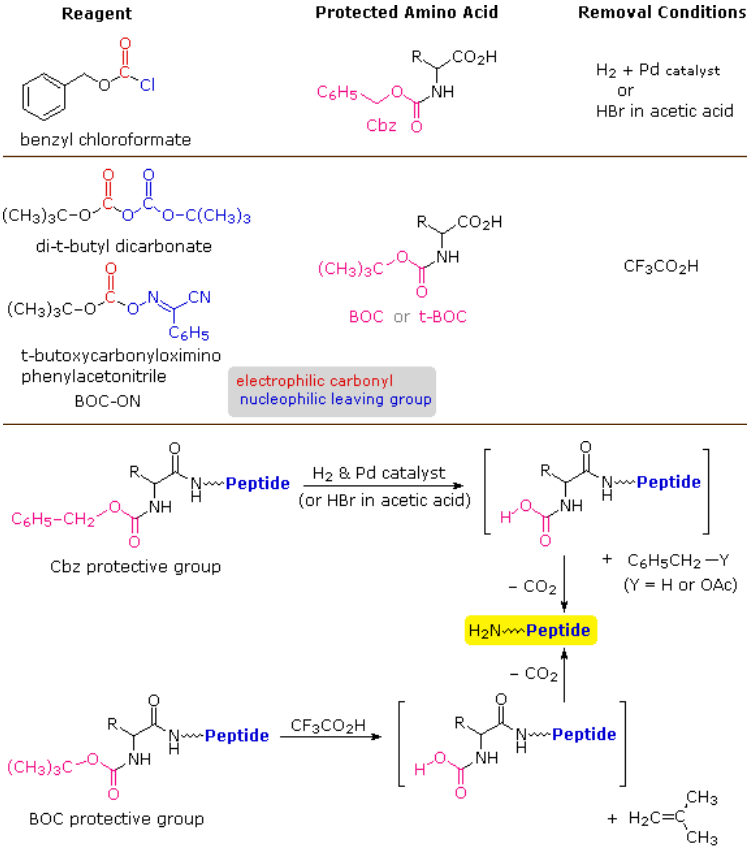
The strategy for peptide synthesis, as outlined here, should now be apparent. The following example shows a selective synthesis of the dipeptide Ala-Gly.



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.

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26.8 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)

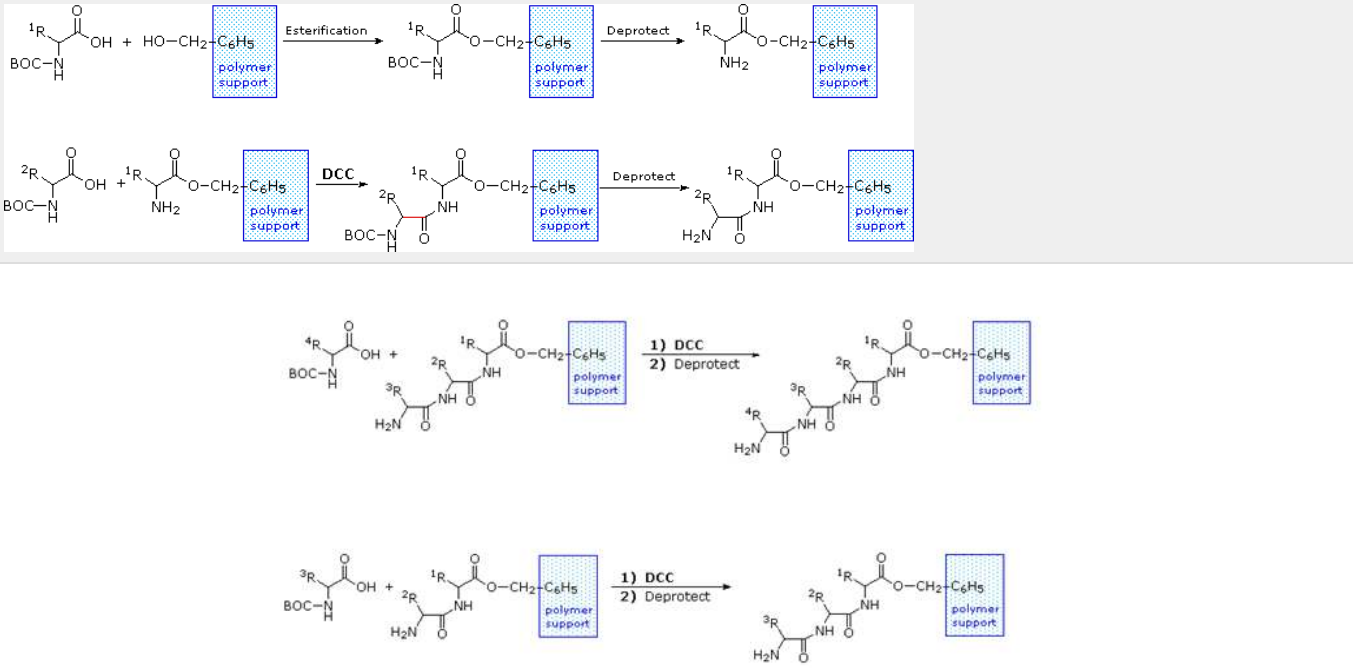
STUDY NOTES

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.

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26.9 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

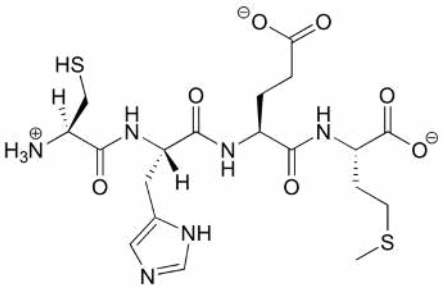
STUDY NOTES

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.

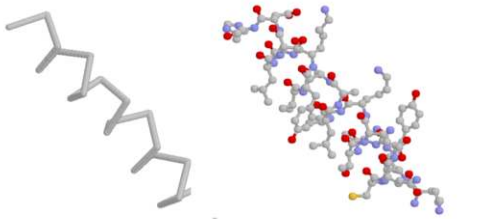
THE FOUR LEVELS OF PROTEIN STRUCTURE

EDIT SECTION

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)

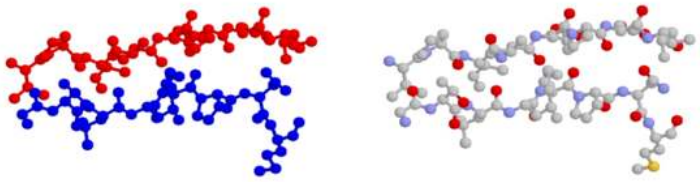


Secondary structure is three-dimensional, but is a local phenomenon, confined to a relatively short stretch of amino acids. For the most part, there are three important elements of secondary structure: helices, beta-sheets, and loops. In a helix, the main chain of the protein adopts the shape of a clockwise spiral staircase, and the side chains point out laterally.



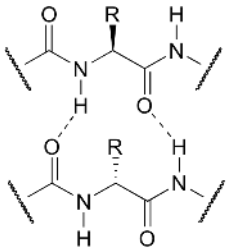
main chain view main chain + side chain

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

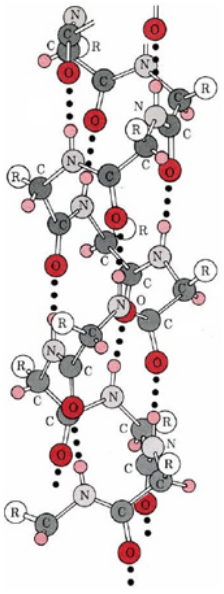


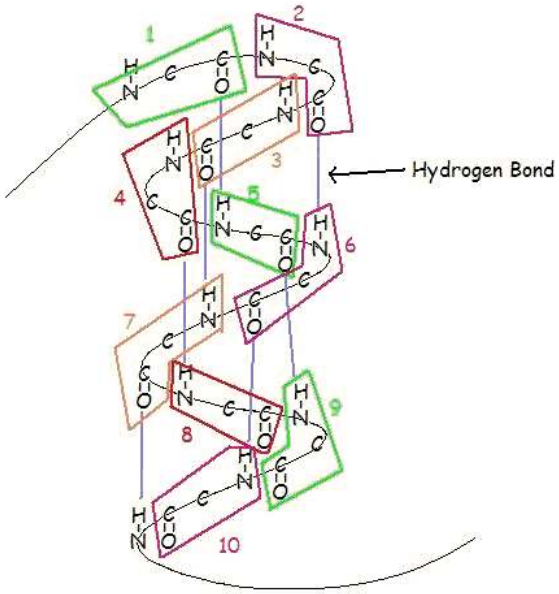
Figure 26.9.1 *Ball-and-stick model of the α helix. Hydrogen bonds are shown as dotted bonds. Note that R groups extend almost perpendicular from the axis.*

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.

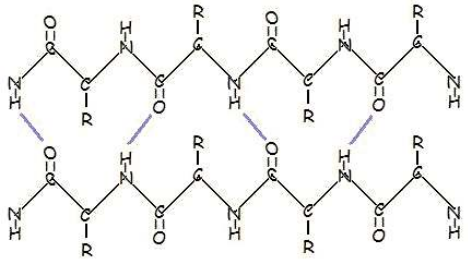
The structural integrity of an α-helix is in part dependent on correct steric configuration. Amino acids whose R-groups are too large (tryptophan, tyrosine) or too small (glycine) destabilize α-helices. Proline also destabilizes α-helices because of its irregular geometry; its R-group bonds back to the 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.



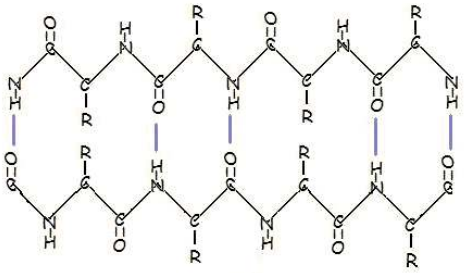
BETA-PLEATED SHEETS EDIT SECTION

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:



Parallel

Or in anti-parallel arrangement:



Anti-Parallel

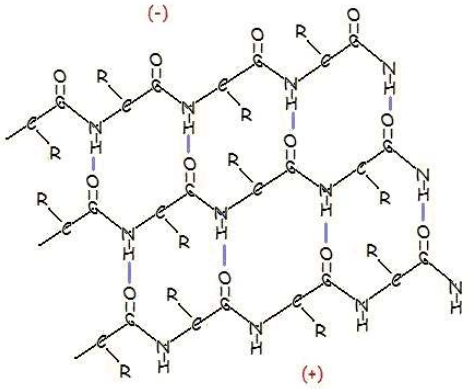
Parallel and anti-parallel arrangement is the direct consequence of the directionality of the polypeptide chain. In anti-parallel arrangement, the C-terminus end of one segment is on the same side as the N-terminus end of the other segment. In parallel arrangement, the C-terminus end and the N-terminus 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.

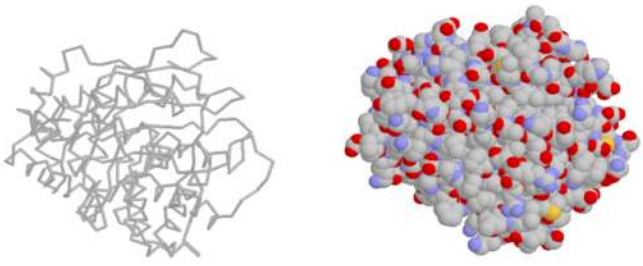
A-PLEATED SHEETS EDIT SECTION

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

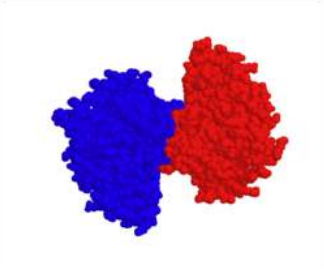
A protein's **tertiary structure** is the shape in which the entire protein chain folds together in three-dimensional space, and it is this level of structure that provides protein scientists with the most information about a protein's specific function.



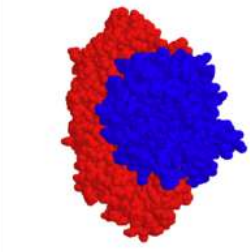
folded protein chain (main chain view)

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).

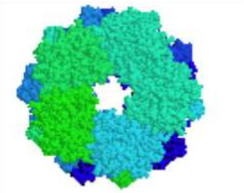


a homodimer

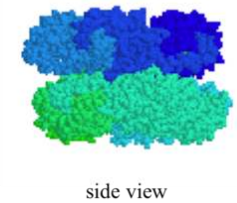


a heterodimer

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):



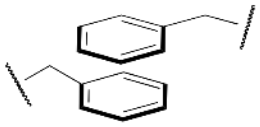
top view



side view

THE MOLECULAR FORCES THAT HOLD PROTEINS TOGETHER EDIT SECTION

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

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- 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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26.10 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 **1**.

Table 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.
ligase	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.

Class	Type of Reaction Catalyzed	Examples
ses		

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 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 2):

$$S + E \rightleftharpoons E\text{–}S \tag{1}$$

$$E\text{–}S \rightarrow P + E \tag{2}$$

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 1).

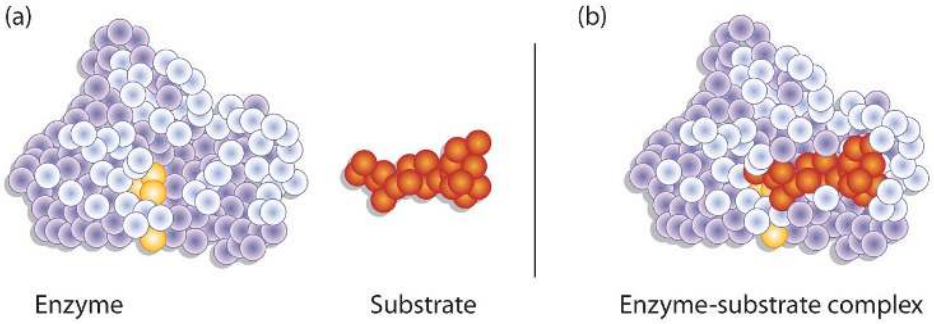


Figure 1: *Substrate Binding to the Active Site of an Enzyme. The enzyme dihydrofolate reductase is shown with one of its substrates: $NADP^+$ (a) unbound and (b) bound. The $NADP^+$ (shown in red) binds to a pocket that is complementary to it in shape and ionic properties.*

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 2). This model portrayed the enzyme as conformationally rigid and able to bond only to substrates that exactly fit the active site.

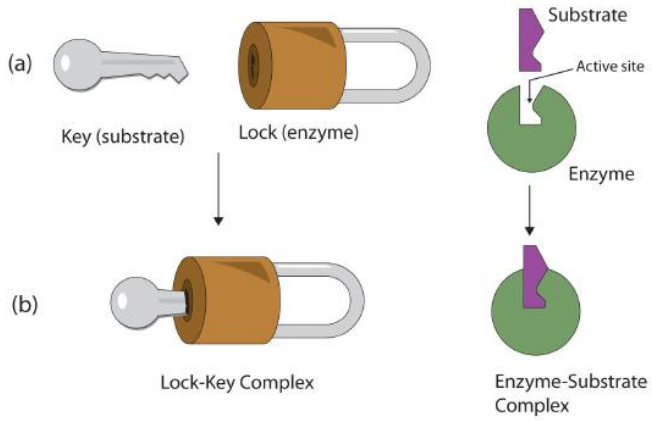


Figure 2: *The Lock-and-Key Model of Enzyme Action. (a) Because the substrate and the active site of the enzyme have complementary structures and bonding groups, they fit together as a key fits a lock. (b) The catalytic reaction occurs while the two are bonded together in the enzyme-substrate complex.*

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 **3**. After catalysis, the enzyme resumes its original structure.

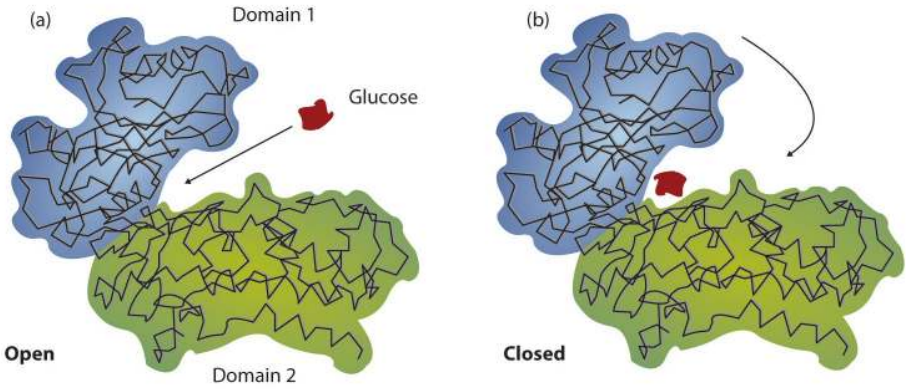


Figure 3: The Induced-Fit Model of Enzyme Action. (a) The enzyme hexokinase without its substrate (glucose, shown in red) is bound to the active site. (b) The enzyme conformation changes dramatically when the substrate binds to it, resulting in additional interactions between hexokinase and glucose.

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 26.10.1

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.

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 **2**: Fat-Soluble Vitamins and Physiological Functions

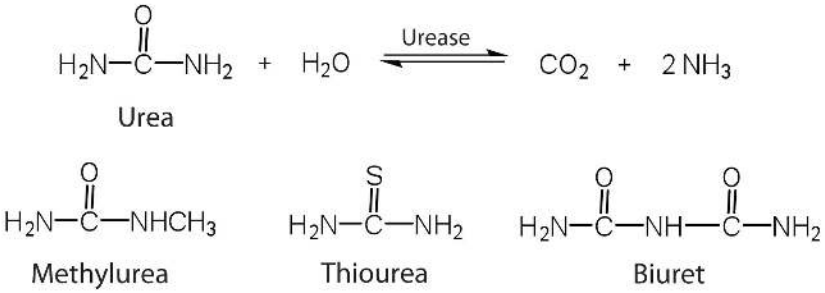
Vitamin	Physiological Function	Effect of Deficiency
vitamin A (retinol)	formation of vision pigments; differentiation of epithelial cells	night blindness; continued deficiency leads to total blindness
vitamin D (cholecalciferol)	increases the body's ability to absorb calcium and phosphorus	osteomalacia (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 **2**), which include vitamins A, D, E, and K, and the *water-soluble vitamins*, which are the B complex vitamins and vitamin C (Table **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 **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

? EXERCISE 26.10.1

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. COOH
b. NH_3^+
c. OH
d. $CH(CH_3)_2$

Answer

a. hydrogen bonding

b. ionic bonding

c. hydrogen bonding

d. dispersion forces

? EXERCISE 26.10.2

For each functional group in the previous exercise, suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you identified.

Answer

a. The amino acid has a polar side chain capable of engaging in hydrogen bonding; serine (answers will vary).

b. The amino acid has a negatively charged side chain; aspartic acid (answers will vary).

c. The amino acid has a polar side chain capable of engaging in hydrogen bonding; asparagine (answers will vary).

d. The amino acid has a nonpolar side chain; isoleucine (answers will vary).

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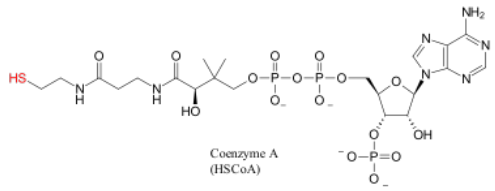
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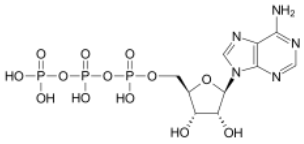
26.11 HOW DO ENZYMES WORK? CITRATE SYNTHASE

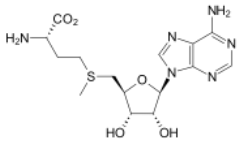
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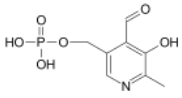
After completing this section, you should be able to

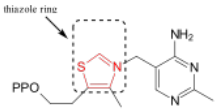
1. describe and explain the general function of an enzyme like citrate synthase in a reaction.
2. identify the structures of ten common coenzymes.

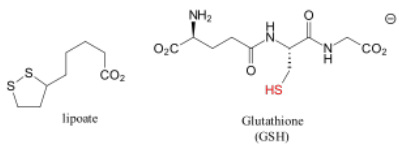






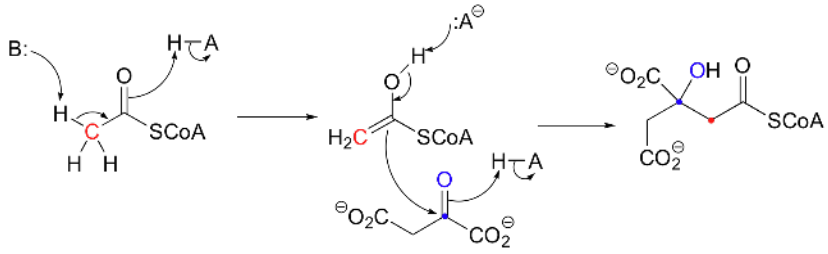






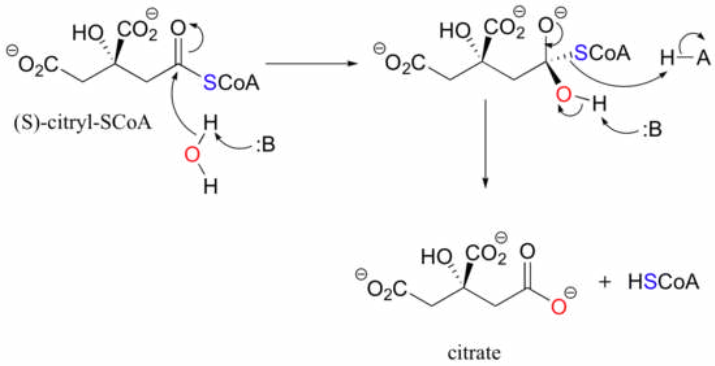
OXALOACETATE TO CITRATE CATALYZED BY CITRATE SYNTHASE

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.



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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)
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26.11 How do Enzymes Work? Citrate Synthase is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

CHAPTER OVERVIEW

CHAPTER 27: BIOMOLECULES - LIPIDS

Lipids are naturally occurring organic compounds that can be extracted from cells and tissues using nonpolar solvents. Although many lipids have complex structures, their chemistry can often be understood quite readily by applying the basic concepts you have studied in previous chapters. We begin the chapter with a study of fats and oils, and explain the different origins of these structurally similar substances. A discussion of soaps follows, as soap is obtained by the reaction of a fat with sodium hydroxide. Phospholipids are substances whose structures are somewhat similar to those of fats, except that the former contain a phosphate group. Prostaglandins are lipids that play important roles in biological systems and are of great interest to those involved in the medical and pharmaceutical professions. Terpenoids form a series of compounds whose structural similarity can be seen through the application of the isoprene rule. The chapter concludes with a discussion of steroids, with particular attention being paid to the stereochemistry of these substances.

Chapter Objectives

27.0 Introduction to Lipids

27.1 Waxes, Fats, and Oils

27.2 Soap

27.3 Phospholipids

27.4 Prostaglandins and Other Eicosanoids

27.5 Terpenoids

27.6 Steroids

27.7 Biosynthesis of Steroids

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CHAPTER OBJECTIVES

When you have completed Chapter 27, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. distinguish among fats and oils, phospholipids, prostaglandins, terpenes and steroids, and be familiar with the sources and biological roles of these substances.
3. define, and use in context, the key terms introduced in this chapter.

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27.0 INTRODUCTION TO LIPIDS

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. Figure 27.0.1 presents one scheme for classifying the various kinds of lipids.

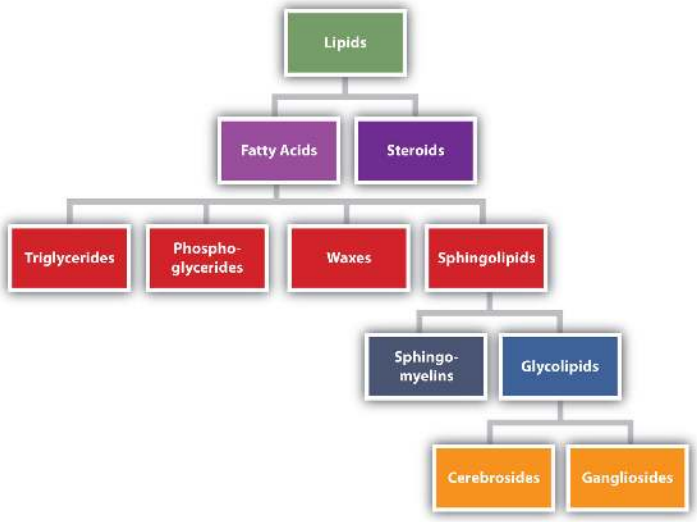


Figure 27.0.1: *Lipid Organization Based on Structural Relationships*

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- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

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27.1 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

Trivial Name	Systematic Name
lauric acid	dodecanoic acid
myristic acid	tetradecanoic acid
palmitic acid	hexadecanoic acid
stearic acid	octadecanoic acid
arachidic acid	eicosanoic acid

Table 27.1 Systematic names of some common saturated fatty acids

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

Table 27.2 Systematic names of some common unsaturated fatty acids

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.

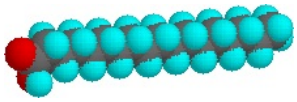
The common fats and oils including fatty acid content are listed below.

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	-

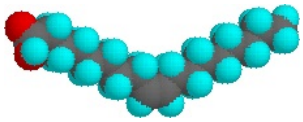
Saturated Fatty Acids		
Formula	**Common Name**	**Melting Point**
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 °C
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 °C
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 °C
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 °C
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 °C

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.

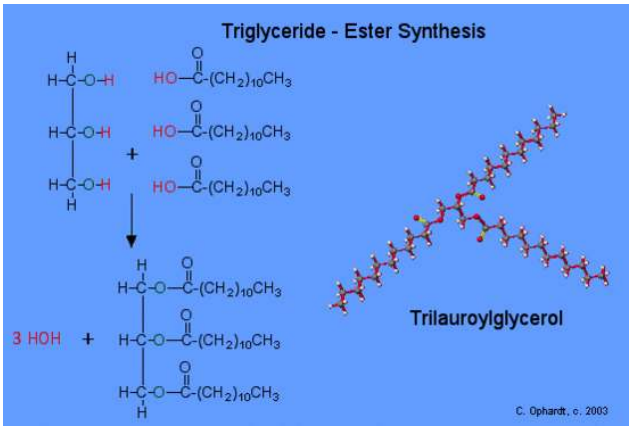


Stearic acid



Oleic acid

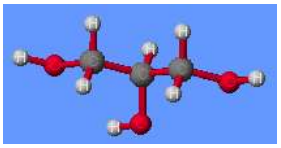
Two polyunsaturated fatty acids, linoleic and linolenic, are designated "essential" because their absence in the human diet has been associated with health problems, such as scaley skin, stunted growth and increased dehydration. These acids are also precursors to the prostaglandins, a family of physiologically potent lipids present in minute amounts in most body tissues.



SYNTHESIS OF A TRIGLYCERIDE

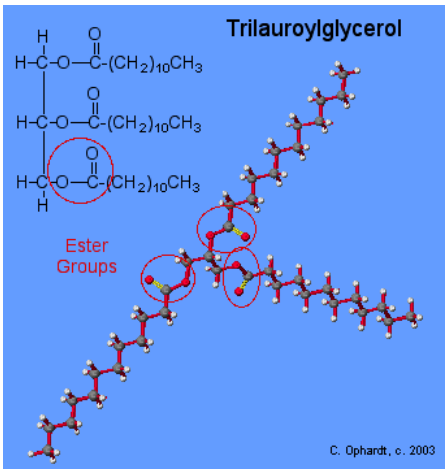
Since glycerol, (IUPAC name is 1,2,3-propantriol), has three alcohol functional groups, three fatty acids must react to make three ester functional groups. The three fatty acids may or may not be identical. In fact, three different fatty acids may be present. nThe synthesis of a triglyceride is another 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

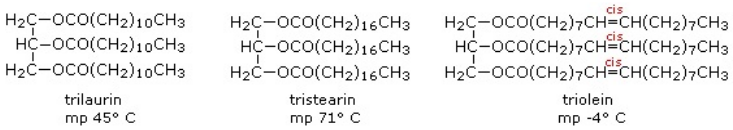


The simplified reaction reveals the process of breaking some bonds and forming the ester and the by product, water. Refer to the graphic on the left for the synthesis of **trilauroylglycerol**. First, the -OH (red) bond on the acid is broken and the -H (red) bond on the alcohol is also broken. Both join 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 ° C, whereas olive oil melts near -6 ° C. Since fats are valued over oils by some Northern European and North American populations, vegetable oils are extensively converted to solid triglycerides (e.g. Crisco) by partial hydrogenation of their unsaturated components. Some of the remaining double bonds are isomerized (to trans) in this operation. These saturated and trans-fatty acid glycerides in the diet have been linked to long-term health issues such as atherosclerosis.



Triglycerides having three identical acyl chains, such as tristearin and triolein (above), are called "simple", while those composed of different acyl chains are called "mixed". If the acyl chains at the end hydroxyl groups (1 & 3) of glycerol are different, the center carbon becomes a chiral center and enantiomeric configurations must be recognized.

The hydrogenation of vegetable oils to produce semisolid products has had unintended consequences. Although the hydrogenation imparts desirable features such as spreadability, texture, "mouth feel," and increased shelf life to naturally liquid vegetable oils, it introduces some serious health problems. These occur when the cis-double bonds in the fatty acid chains are not completely saturated in the hydrogenation process. The catalysts used to effect the addition of hydrogen isomerize the remaining double bonds to their trans configuration. These unnatural trans-fats appear to to be associated with increased heart disease, cancer, diabetes and obesity, as well as immune response and reproductive problems.

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
- Charles Ophardt, Professor Emeritus, Elmhurst College; Virtual Chembook

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27.2 SOAP

Objectives

After completing this section, you should be able to

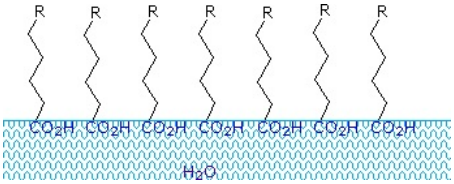
1. a. write an equation to represent the formation of a soap.
   b. identify the structure of the fat required to produce a given soap.
   c. identify the structure of a soap, given the structure of the fat from which it is produced.
2. describe the mechanism by which soaps exert their cleansing action.
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

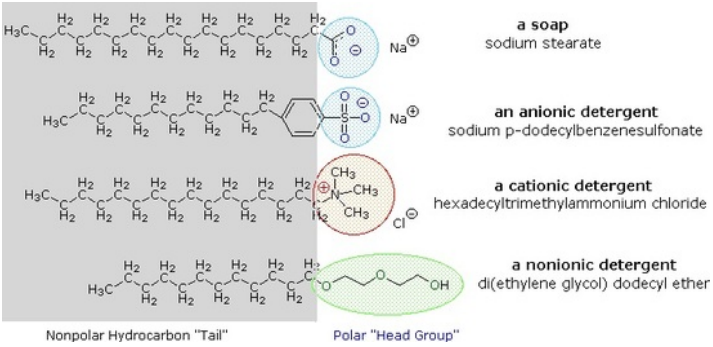
Make certain that you can define, and use in context, the key terms below.

- 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**.

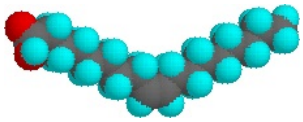


Alkali metal salts of fatty acids are more soluble in water than the acids themselves, and the amphiphilic character of these substances also make them strong surfactants. The most common examples of such compounds are soaps and detergents, four of which are shown below. Note that each of these molecules 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.

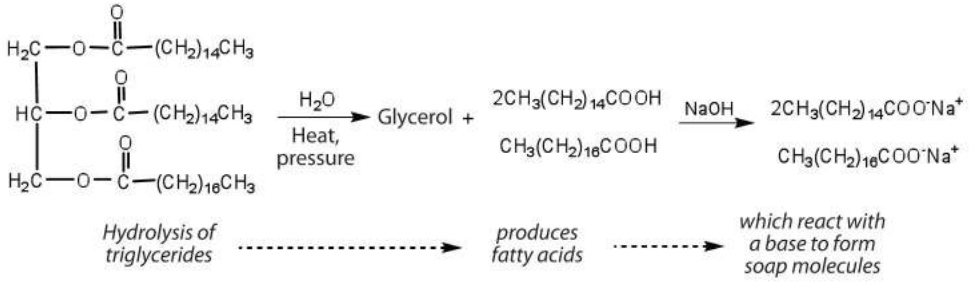


The oldest amphiphilic cleaning agent known to humans is soap. Soap is manufactured by the base-catalyzed hydrolysis (saponification) of animal fat (see below). Before sodium hydroxide was commercially available, a boiling solution of potassium carbonate leached from wood ashes was used. Soft potassium 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.

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27.3 PHOSPHOLIPIDS

Objectives

After completing this section, you should be able to

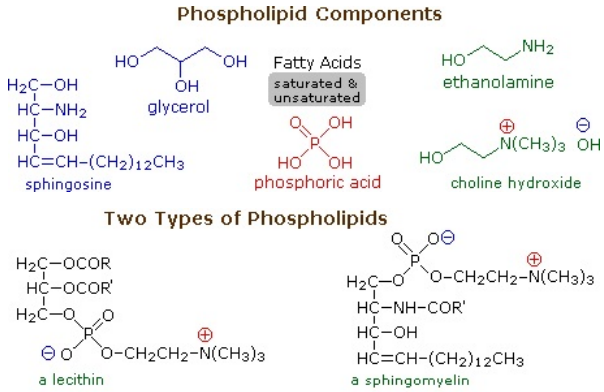
1. draw the general structure of a phosphoglyceride.
2. describe the occurrence and importance of phosphoglycerides in plant and animal tissues.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

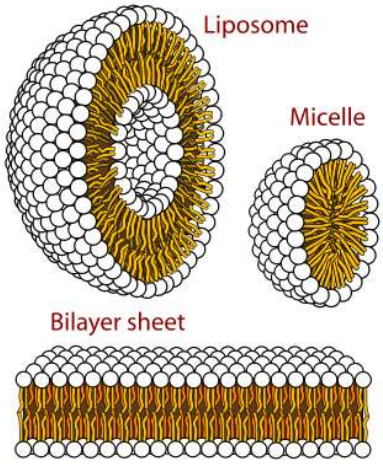
- phosphoglyceride
- phospholipid

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

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27.4 PROSTAGLANDINS AND OTHER EICOSANOIDS

Objectives

After completing this section, you should be able to

1. describe the general structure of the prostaglandins, and identify a prostaglandin from a given list of organic structures.
2. identify at least two important biological functions of prostaglandins.

KEY TERMS

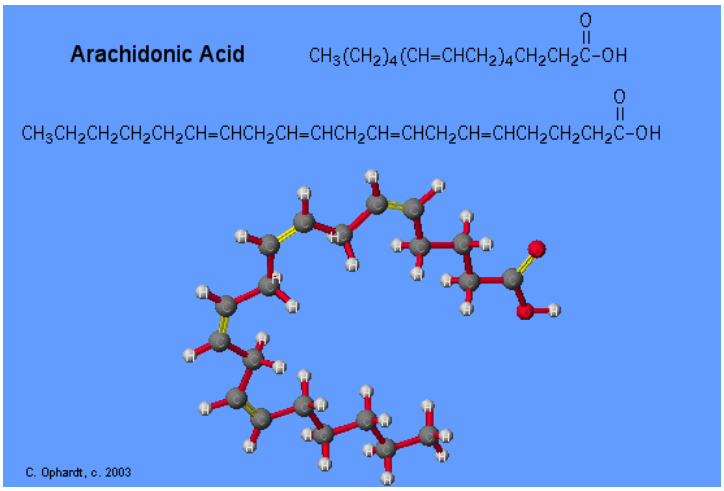
Make certain that you can define, and use in context, the key term below.

- prostaglandin

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.

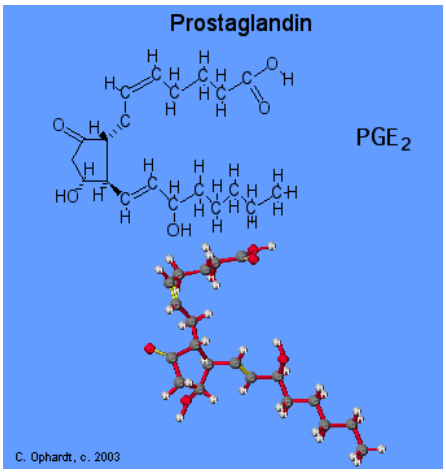
INTRODUCTION

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 below. 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.



PROSTAGLANDIN STRUCTURE

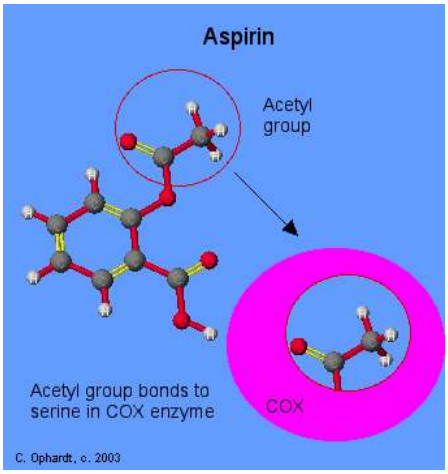
Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring and are based upon the fatty acid, arachidonic acid. There are a variety of structures one, two, or three double bonds. On the five member ring there may also be double bonds, a ketone, or alcohol groups. A typical structure is shown below.



FUNCTIONS OF PROSTAGLANDINS

There are a variety of physiological effects 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.

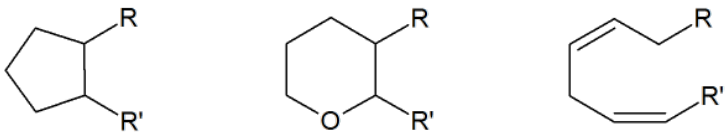


EFFECTS OF ASPIRIN AND OTHER PAIN KILLERS

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.

EICOSANOIDS

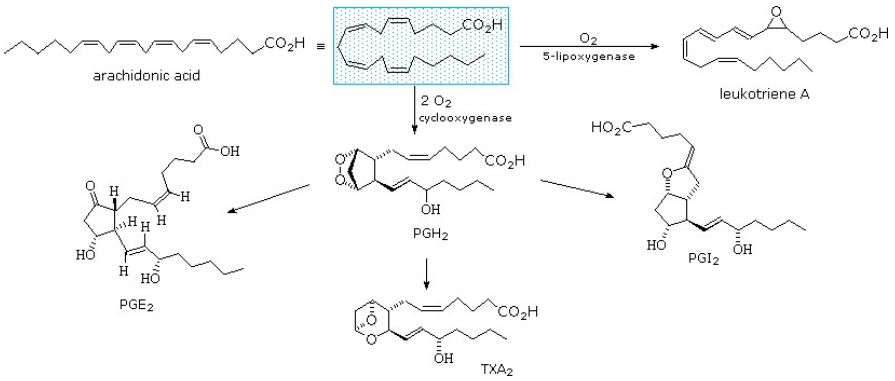
Prostaglandins are one example of biologically important class of fatty acids called eicosanoids. Derived primarily from arachidonic acid (5,8,11,14-eicosatetraenoic acid), eicosanoids include prostaglandins, leukotrienes, and thromboxanes.



prostaglandin (PG) thromboxane (TX) leukotriene (LT)

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.

The metabolic pathways by which arachidonic acid is converted to the various eicosanoids are complex and will not be discussed here. A rough outline of some of the transformations that take place is provided below. It is helpful to view arachadonic acid in the coiled conformation shown in the shaded box.



CONTRIBUTORS AND ATTRIBUTIONS

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27.5 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

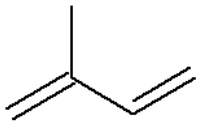
Make certain that you can define, and use in context, the key terms below.

- 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.

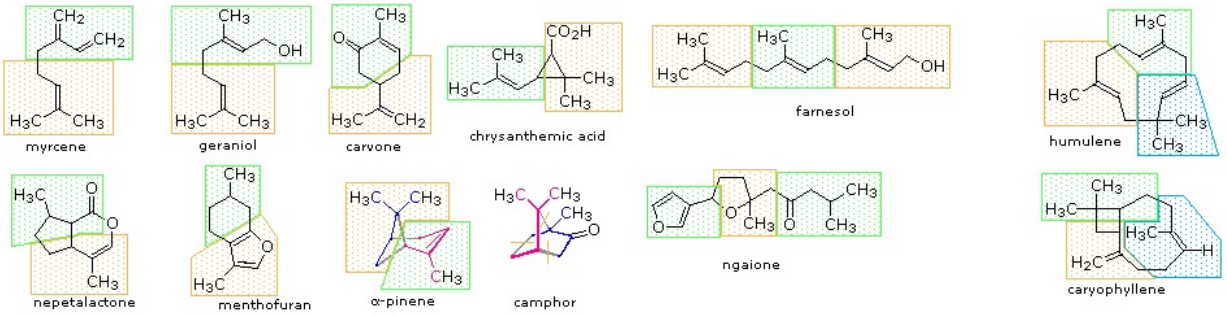


Figure 27.5.1: Monoterpenes and sesquiterpenes

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.

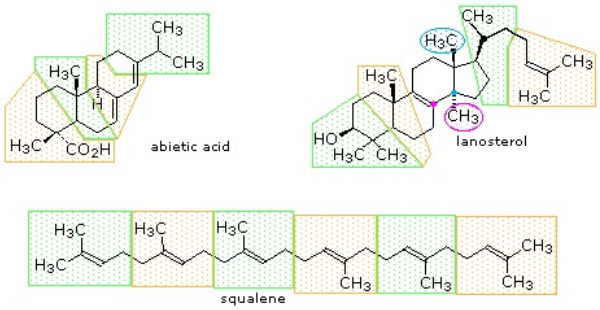
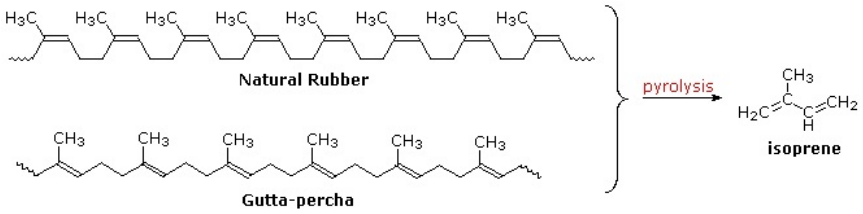


Figure 27.5.2: Triterpenes

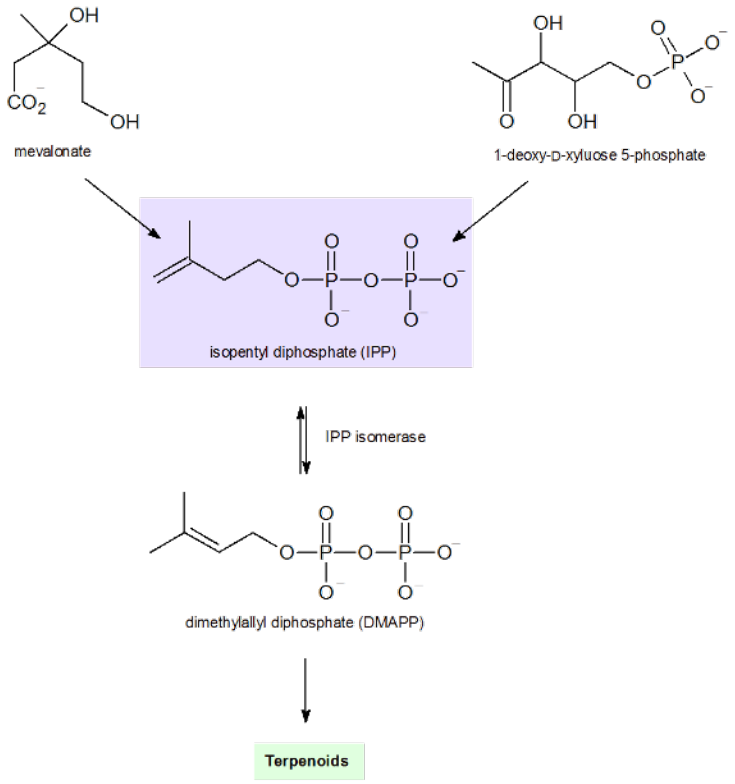
Polymeric isoprenoid hydrocarbons have also been identified. Rubber is undoubtedly the best known and most widely used compound of this kind. It occurs as a colloidal suspension called latex in a number of plants, ranging from the dandelion to the rubber tree (*Hevea brasiliensis*). Rubber is a polyene, 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

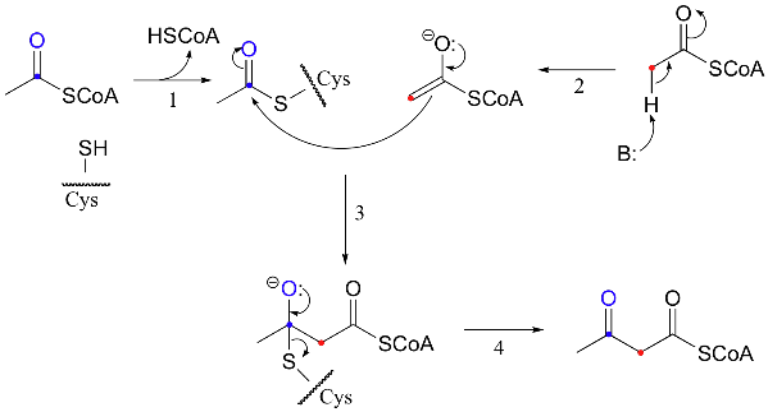
While we can identify isoprene units within a terpenoid structure and use that in its classification, the building block for terpenoid synthesis in nature is isopentenyl diphosphate (formerly called isopentenyl pyrophosphate and abbreviated IPP). There are two major routes to the synthesis of IPP; namely (1) the mevalonate pathway and (2) the 1-deoxyxylulose pathway.



MEVALONATE PATHWAY

Step 1 - Claisen Condensation

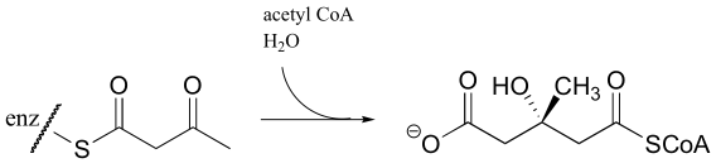
An early step in the biosynthesis of cholesterol and other 'isoprenoid' compounds is a Claisen condensation between two acetyl CoA molecules. An initial trans-thioesterase process transfers the acetyl group of the first acetyl CoA to an enzymatic cysteine (Reaction 1). In the Claisen condensation phase 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

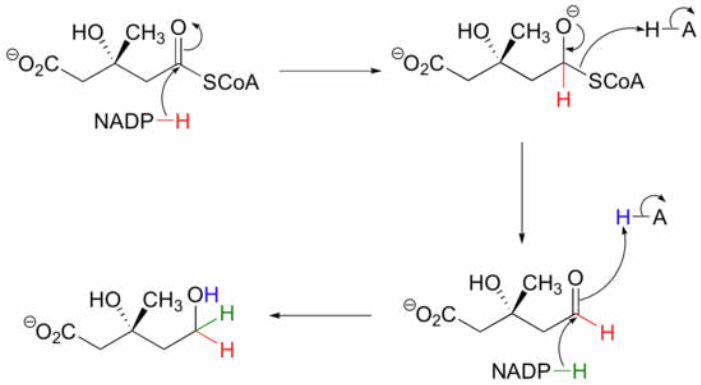
Acetyl CoA then reacts with the acetoacetyl CoA in an aldol-like addition. Subsequent hydrolysis produces (3*S*)-3-hydroxy-3-methylglutaryl CoA (HMG-CoA).



Generating HMG-CoA

Step 3 - Reduction of the Thioester

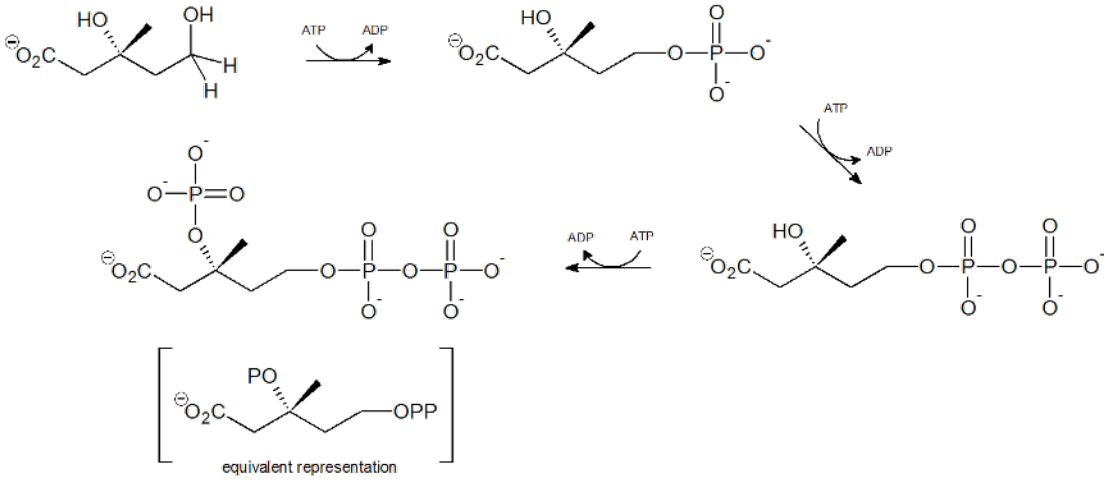
The thioester is reduced first to an aldehyde, then to a primary alcohol by two equivalents of NADPH producing (*R*)-mevalonate. The enzyme catalyzing this reaction is the target of the statin family of cholesterol-lowering drugs.



Generating (*R*)-Mevalonate

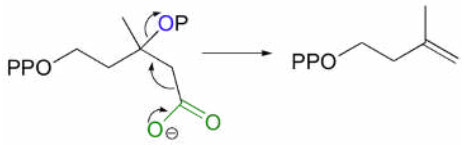
Step 4 - Mevalonate Phosphorylation

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.



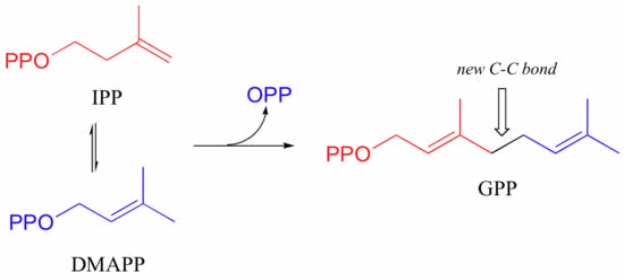
Step 5 - Decarboxylation

Finally isopentenyl diphosphate (IPP), the 'building block' for all isoprenoid compounds, is formed from a decarboxylation-elimination reaction.

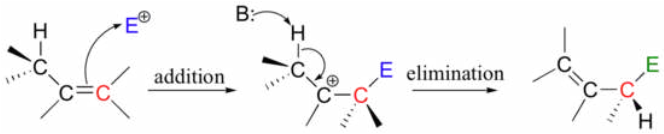


CONVERSION OF IPP TO TERPENOIDS

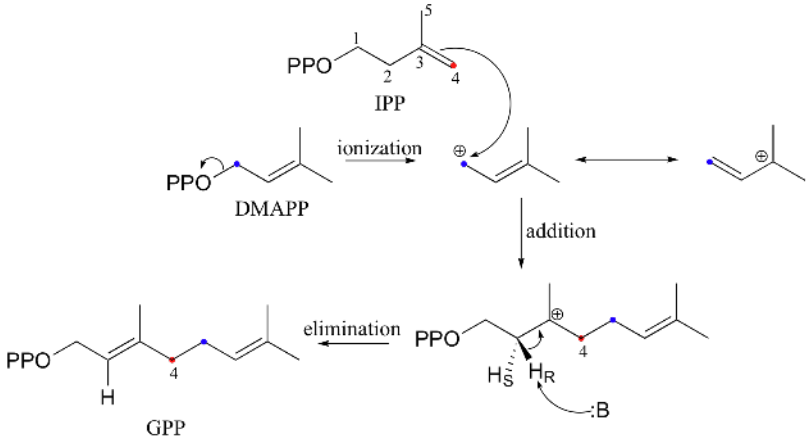
The electrophilic double bond isomerization catalyzed by IPP isomerase is a highly reversible reaction, with an equilibrium IPP:DMAPP ratio of about 6:1. In the next step of isoprenoid biosynthesis, the two five-carbon isomers condense to form a 10-carbon isoprenoid product called geranyl diphosphate (GPP).



This is a nice example of an electrophilic addition/elimination mechanism:

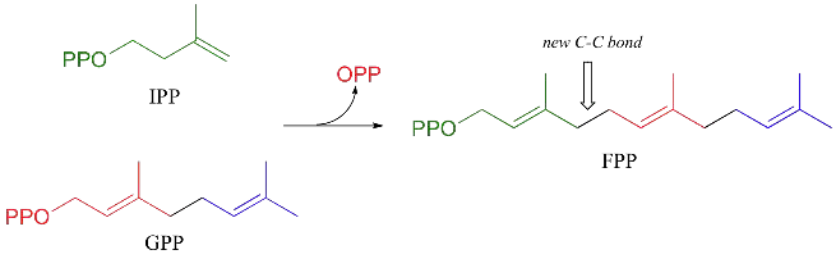


The first step is ionization of the electrophile - in other words, the leaving group departs and a carbocation intermediate is formed. In this case, the pyrophosphate group on DMAPP is the leaving group, and the electrophilic species is the resulting allylic carbocation.



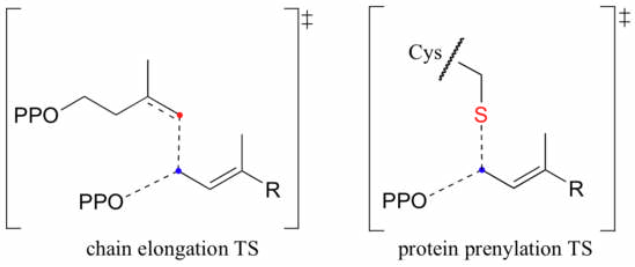
In the condensation (addition) step, the C_3-C_4 double bond in IPP attacks the positively-charged C_1 of DMAPP, resulting in a new carbon-carbon bond and a second carbocation intermediate, this time at a tertiary carbon. In the elimination phase, proton abstraction leads to re-establishment of a double 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).



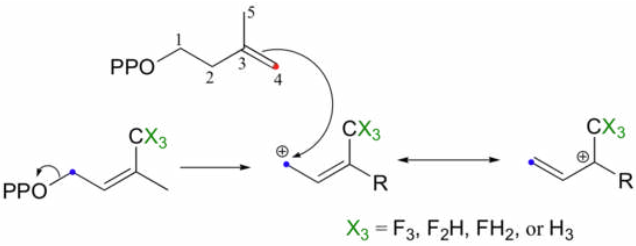
How do we know that these are indeed S_N1-like mechanisms with carbocation intermediates, rather than concerted S_N2-like mechanisms? First of all, recall that the question of whether a substitution is dissociative (S_N1-like) or associative (S_N2-like) is not always clear-cut - it could be somewhere 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.

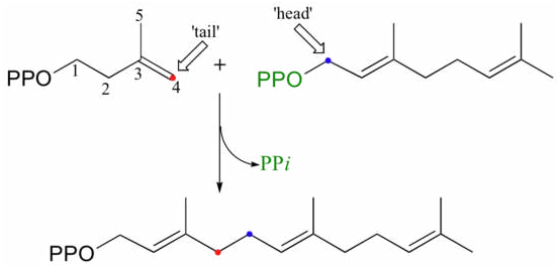
So it makes perfect sense that the chain elongation reaction should more S_N1-like than S_N2-like. Is this in fact the case? We know how to answer this question experimentally - just run the reaction with fluorinated DMAPP or GPP substrates and observe how much the fluorines slow things down.



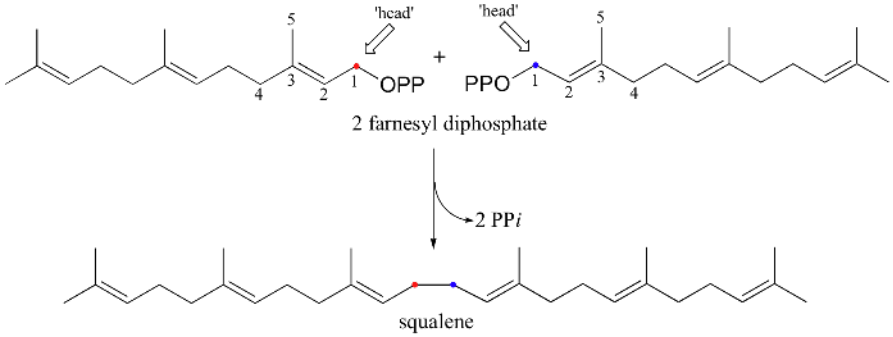
If the reaction is S_N1-like, the electron-withdrawing fluorines should destabilize the allylic carbocation intermediate and thus slow the reaction down considerably. If the mechanism is S_N2-like, the fluorine substitutions should not have a noticeable effect, because a carbocation intermediate would 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.

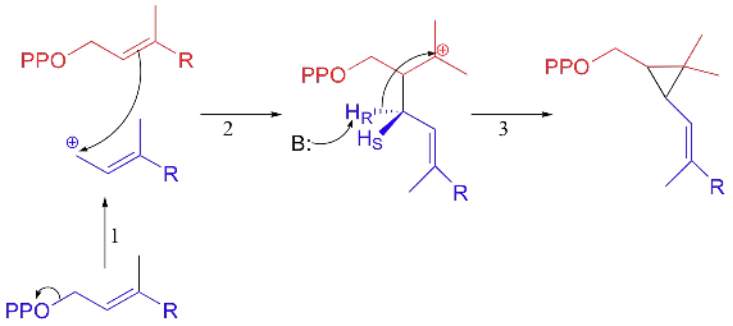
Cholesterol, as we discussed earlier in this chapter, is derived from a 30-carbon isoprenoid molecule called squalene. Squalene, in turn, is derived from the condensation of two molecules of farnesyl diphosphate (FPP), a 15-carbon isoprenoid. You may recall that FPP is the product of the C_4 to C_1, 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.

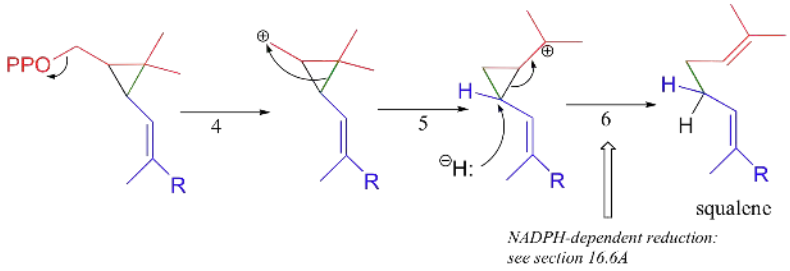


The first two steps are familiar: first, the pyrophosphate on one FPP molecule leaves (step 1), resulting in an allylic carbocation that is attacked by the C_2-C_3 π bond of the second molecule (step 2).

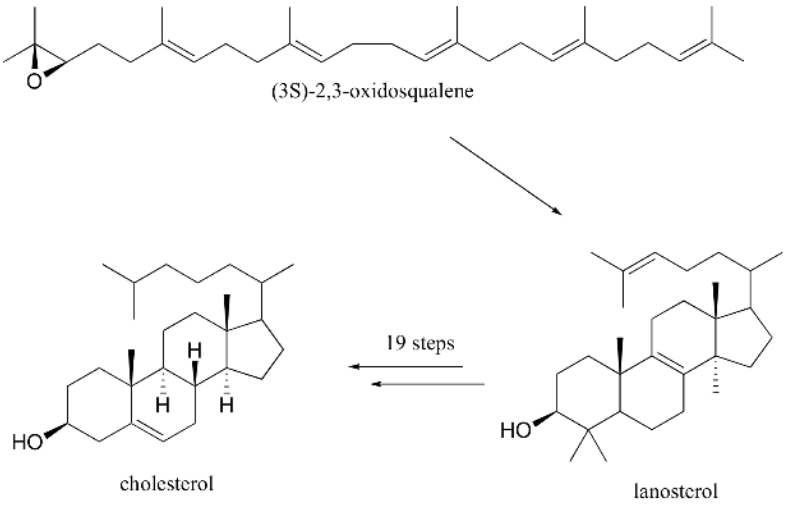


This results in a new carbon-carbon bond between the two FPP molecules, but with incorrect C_1 to C_2 connectivity (remember, the overall reaction is a C_1 to C_1 condensation). In step 3, a proton is abstracted and the electrons from the broken C-H bond bridge across a 2-carbon gap to form a cyclopropyl 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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27.6 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.

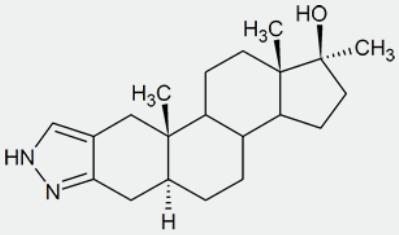
KEY TERMS

Make certain that you can define, and use in context, the key term below.

- steroid

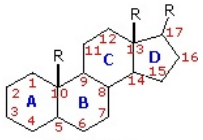
STUDY NOTES

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

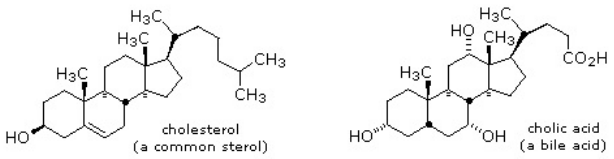
The important class of lipids called **steroids** are actually metabolic derivatives of terpenes, but they are customarily treated as a separate group. Steroids may be recognized by their tetracyclic skeleton, consisting of three fused six-membered and one five-membered ring, as shown in the diagram 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.



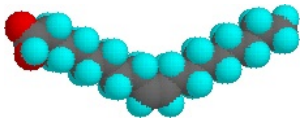
The Steroid
Carbon Skeleton

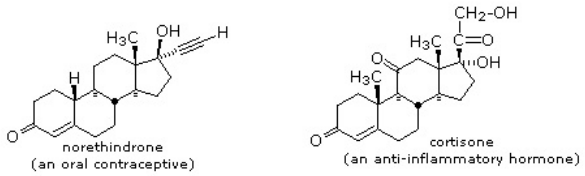
Steroids are widely distributed in animals, where they are associated with a number of physiological processes. Examples of some important steroids are shown in the following diagram. Norethindrone is a synthetic steroid, all the other examples occur naturally. A common strategy in pharmaceutical chemistry 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.

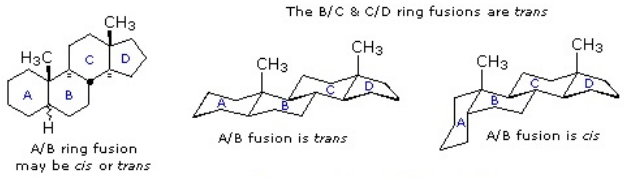


Typical Animal Steroids





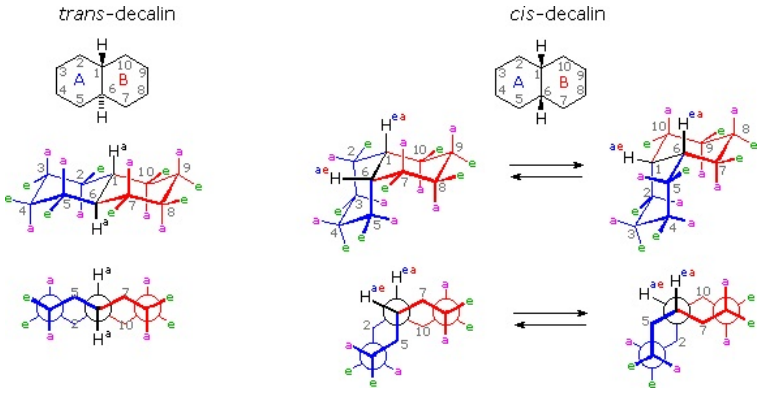
Medicinally Useful Steroids

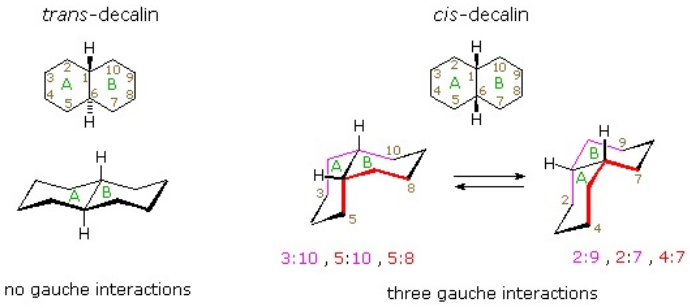


Common Steroid Conformations

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.



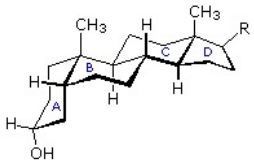


The trans-isomer is the easiest to describe because the fusion of the A & B rings creates a rigid, roughly planar, structure made up of two chair conformations. Each chair is fused to the other by equatorial bonds, leaving the angular hydrogens (Ha) axial to both rings. Note that the bonds directed above 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.



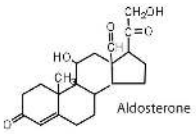
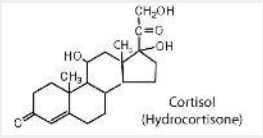
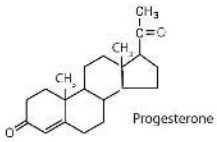
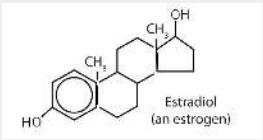
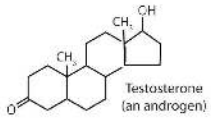
STEROID HORMONES

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.Edit section

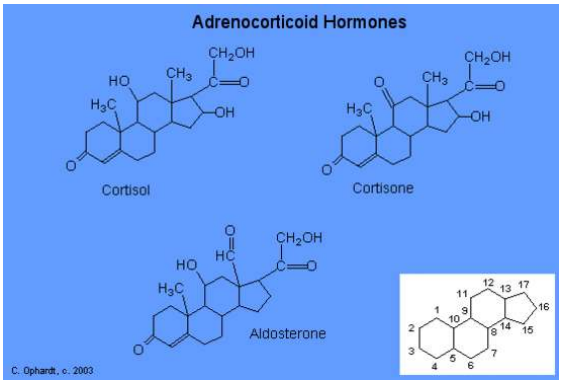
Sex hormones, both natural and synthetic, are sometimes used therapeutically. For example, a woman who has had her ovaries removed may be given female hormones to compensate. Some of the earliest chemical compounds employed in cancer chemotherapy were sex hormones. For example, estrogens are one treatment 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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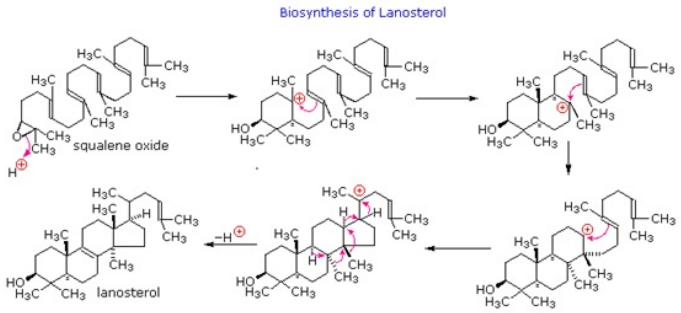
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27.7 BIOSYNTHESIS OF STEROIDS

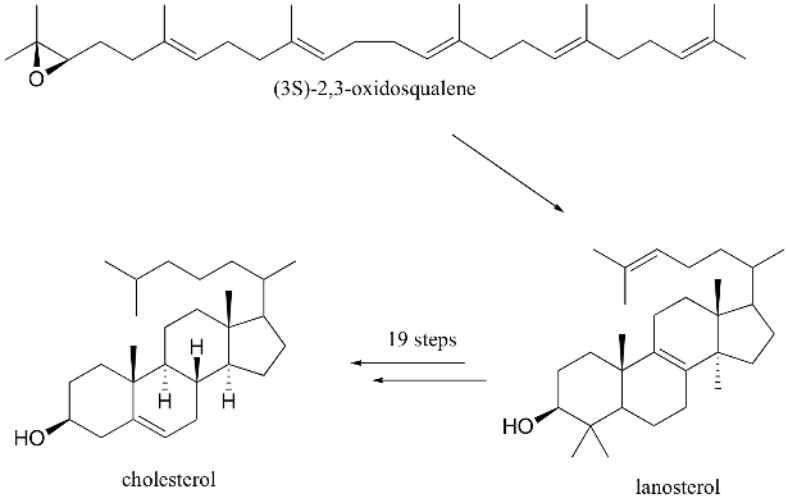
OBJECTIVES

You may omit Section 27.7. You will not be examined on this material.

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.

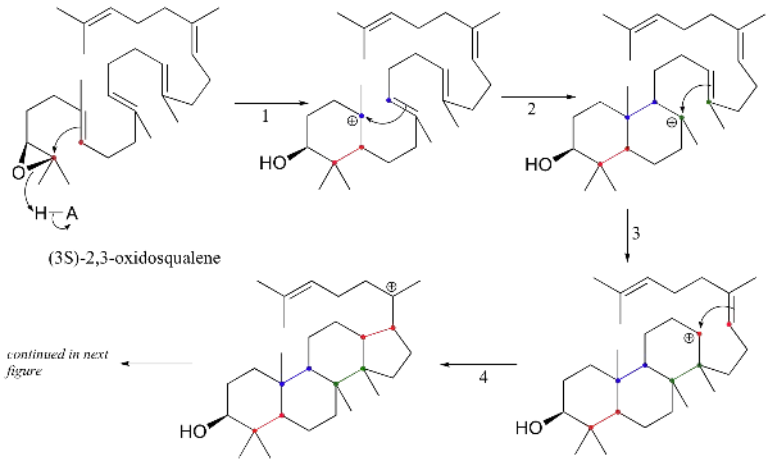


Rearrangements are particularly important in carbocation-intermediate reactions in which isoprenoid molecules cyclize to form complex multi-ring structures. One of the key steps in the biosynthesis of cholesterol is the electrophilic cyclization of oxidosqualene to form a steroid called lanosterol.

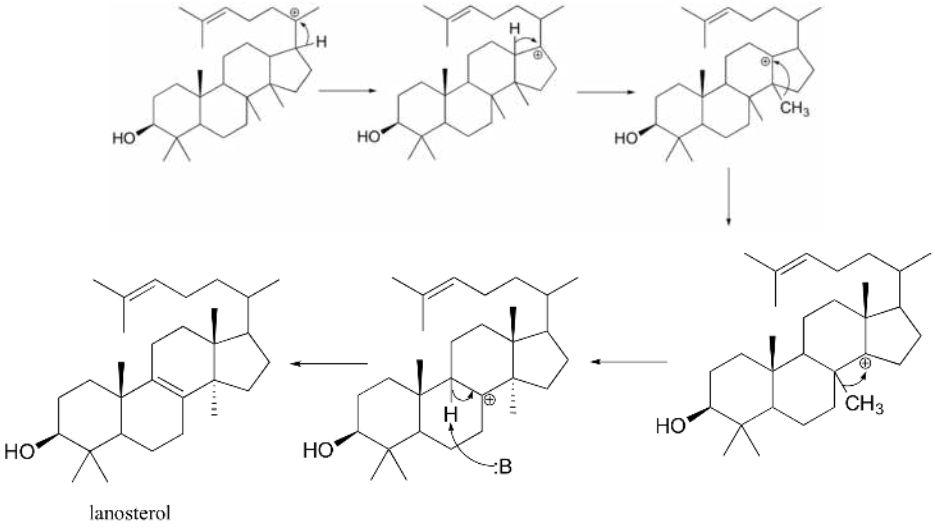


This fascinating reaction has two phases. The first phase, in which the actual cyclization takes place, is a series of electrophilic addition steps. The second phase is a series of hydride and methyl shifts. There is some argument about whether these processes occur in a stepwise fashion (with discreet 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

- 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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CHAPTER OVERVIEW

CHAPTER 28: BIOMOLECULES - NUCLEIC ACIDS

Two types of nucleic acids are found in cells—deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). These highly complex substances are built up from a number of simpler units, called nucleotides. Each nucleotide consists of three parts: a phosphoric acid residue, a sugar and a nitrogen-containing heterocyclic base. Thus, in order to understand the biochemistry of the nucleic acids, you must first study the chemistry of the sugars (see Chapter 25) and simple heterocyclic systems. We have already discussed certain aspects of the structure of heterocyclic ring systems during our study of aromaticity (Sections 15.5–15.6). You may find it helpful to review this chapter.

Chapter 28 examines the structure and replication of DNA and then describes the structure and synthesis of RNA. The chapter closes with a brief study of the role played by RNA in the biosynthesis of proteins.

- Chapter Objectives
- 28.1 Nucleotides and Nucleic Acids
- 28.2 Base Pairing in DNA: The Watson-Crick Model
- 28.3 Replication of DNA
- 28.4 Transcription of DNA
- 28.5 Translation of RNA: Protein Biosynthesis
- 28.6 DNA Sequencing
- 28.7 DNA Synthesis
- 28.8 The Polymerase Chain Reaction

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CHAPTER OBJECTIVES

When you have completed Chapter 28, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. draw the structure of a given nucleotide.
3. discuss the structure of DNA and RNA.
4. describe the processes involved in DNA replication, transcription, translation, and protein synthesis.
5. define, and use in context, the key terms introduced in this chapter.

CONTRIBUTORS AND ATTRIBUTIONS

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28.1 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

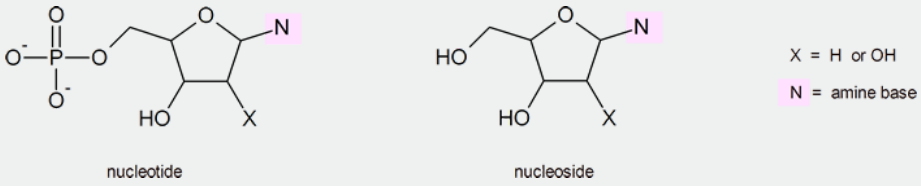
Make certain that you can define, and use in context, the key terms below.

- 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.



nucleotide nucleoside

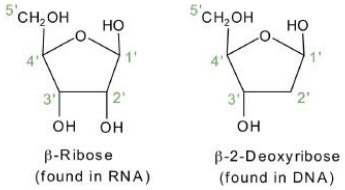
To fulfill Objective 7, you should study (but not necessarily memorize) Figure 28.1.2 The Pyrimidine and Purine Nucleotides below.

The Learning Objective of this Module is to identify the different molecules that combine to form nucleotides.

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).

$$\text{nucleic acids} \xrightarrow[\text{down into}]{\text{can be broken}} \text{nucleotides} \xrightarrow[\text{down into}]{\text{can be broken}} \underset{+\ \text{nitrogen base} + \text{pentose sugar}}{H_3PO_4} \tag{28.1.1}$$

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 28.1.1).

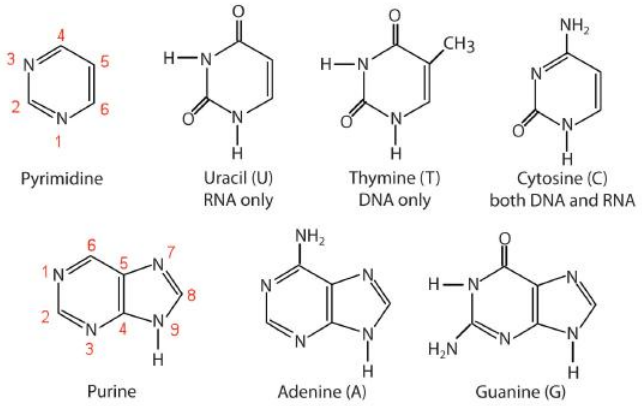


Figure 28.1.1: *The Nitrogenous Bases Found in DNA and RNA*

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

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 28.1.1: 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 28.1.2.

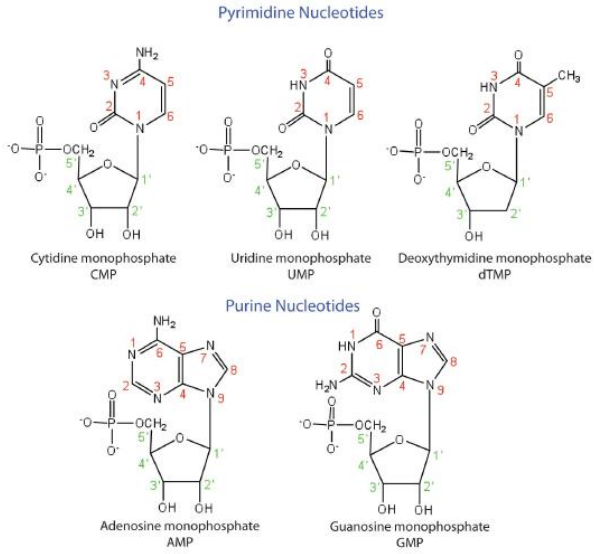


Figure 28.1.2 *The Pyrimidine and Purine Nucleotides*

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 28.1.3, 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.

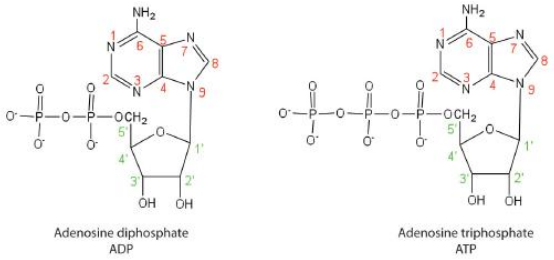


Figure 28.1.3*: Structures of Two Important Adenine-Containing Nucleotides*

PRIMARY STRUCTURE OF NUCLEIC ACIDS EDIT SECTION

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*.Edit sectionEdit section

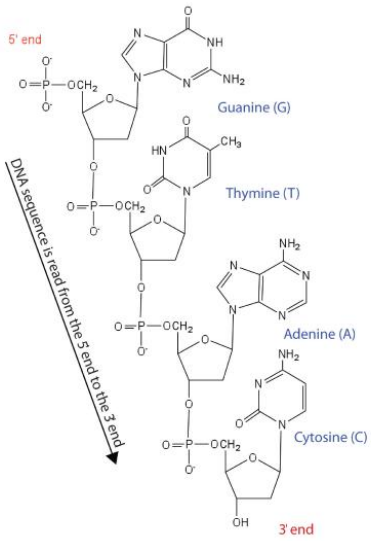


Figure 28.1.4 *Structure of a Segment of DNA. A similar segment of RNA would have OH groups on each C2', and uracil would replace thymine.*Edit section

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.Edit section

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

? EXERCISE 28.1.1

Classify each compound as a pentose sugar, a purine, or a pyrimidine.

a. adenine
b. guanine
c. deoxyribose
d. thymine
e. ribose
f. cytosine

Answer

a) purine
b) purine
c) pentose sugar
d) pyrimidine
e) pentose sugar
f) pyrimidine

EXERCISE 28.1.2

Identify the three molecules needed to form the nucleotides in each nucleic acid.

a. DNA
b. RNA

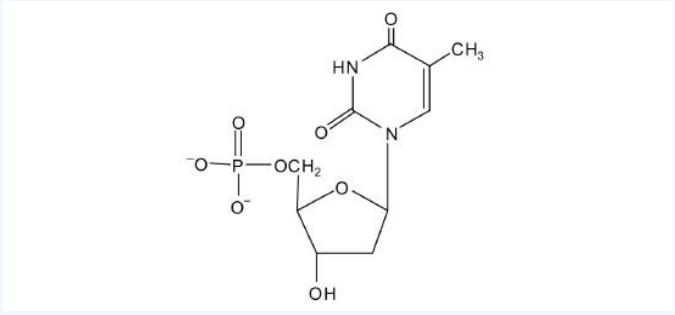
Answer

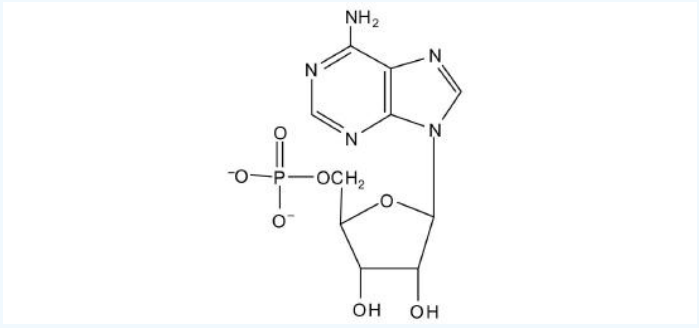
a)nitrogenous base (adenine, guanine, cytosine, and thymine), 2-deoxyribose, and H_3PO_4

b) nitrogenous base (adenine, guanine, cytosine, and uracil), ribose, and H_3PO_4

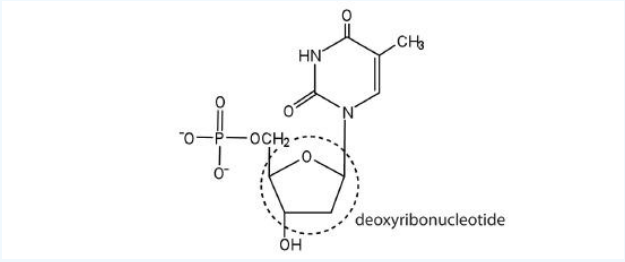
EXERCISE 28.1.3

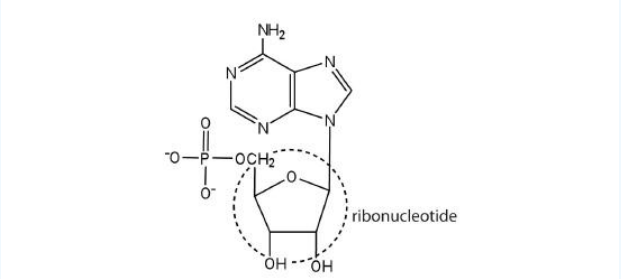
For each structure, circle the sugar unit and identify the nucleotide as a ribonucleotide or a deoxyribonucleotide.

a. 

- 

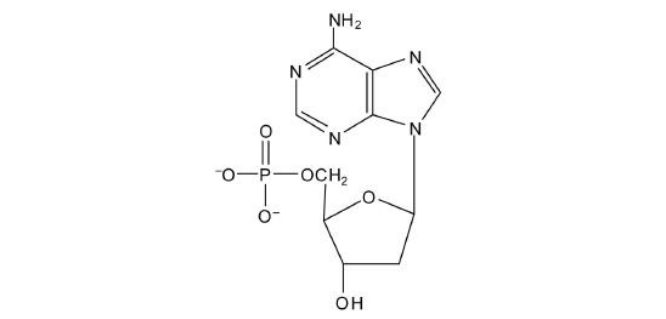
Answer

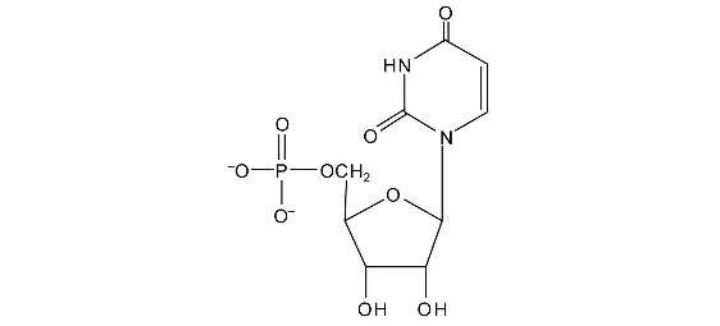
a. 

b. 

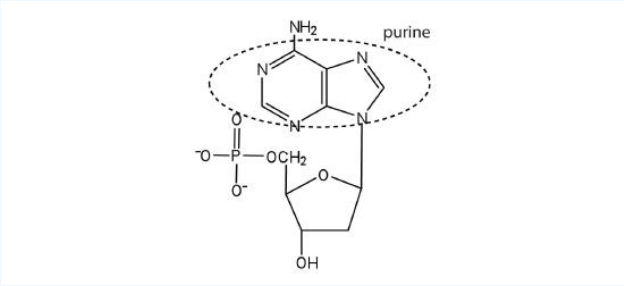
? EXERCISE 28.1.4

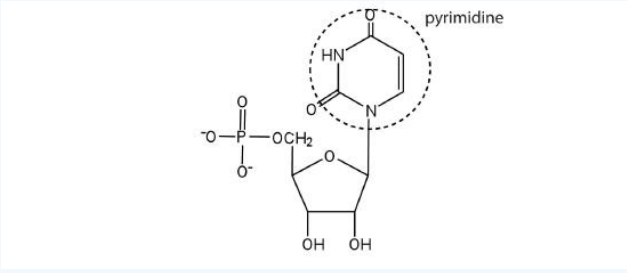
For each structure, circle the nitrogenous base and identify it as a purine or pyrimidine.

a. 

- 

Answer

a. 

b. 

CONTRIBUTORS AND ATTRIBUTIONS

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

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28.2 BASE PAIRING IN DNA: THE WATSON-CRICK MODEL

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.

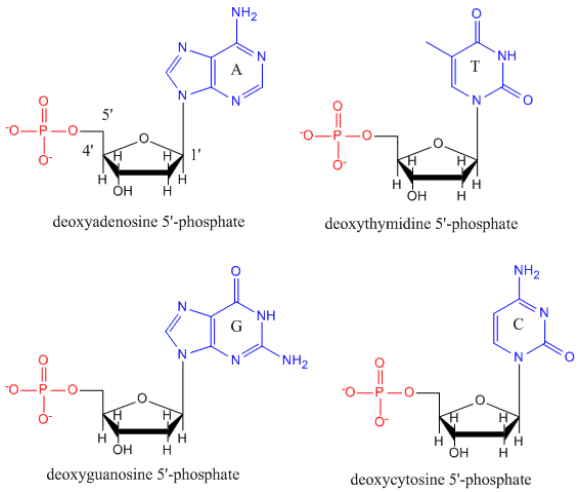
Maddox, B. Rosalind Franklin: The Dark Lady of DNA. New York: HarperCollins, 2002.

INTERMOLECULAR FORCES IN NUCLEIC ACIDS

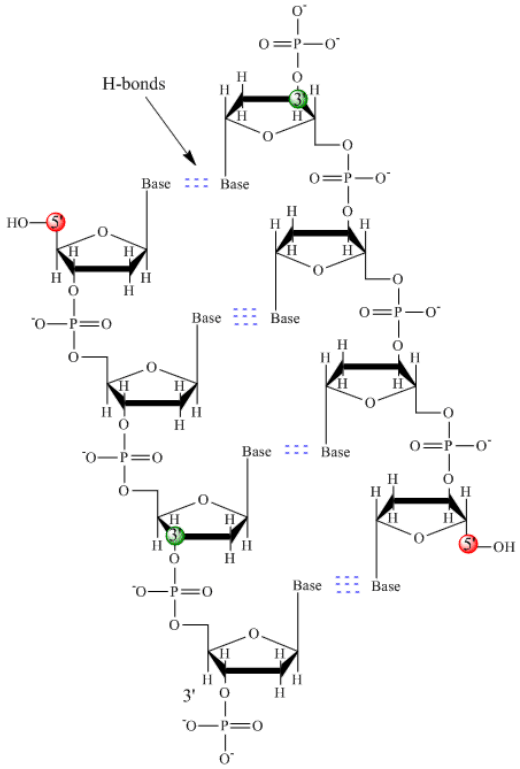
The nucleic acids RNA and DNA are involved in the storage and expression of genetic information in a cell. Both are polymers of monomeric nucleotides. DNA exists in the cell as double-stranded helices while RNA typically is a single-stranded molecule which can fold in 3D space to form complex secondary (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.

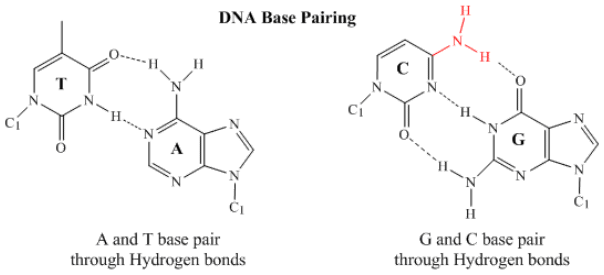


Only four bases are used in DNA (in contrast to the 20 different side chains in proteins) which we will abbreviate, for simplicity, as A, G, C and T. They are bases since they contain amine groups that can accept protons. The polymer consists of a sugar - phosphate - sugar - phosphate backbone, with 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.



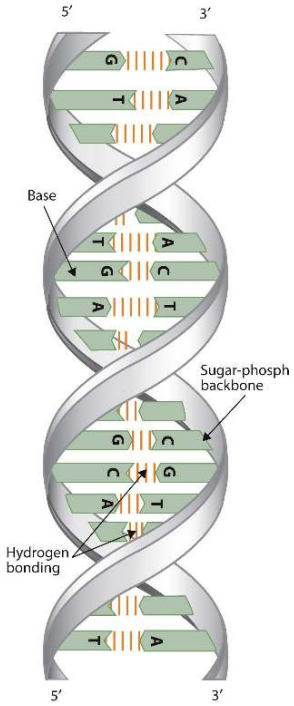
In 1950, Erwin Chargaff of Columbia University showed that the molar amount of adenine (A) in DNA was always equal to that of thymine (T). Similarly, he showed that the molar amount of guanine (G) was the same as that of cytosine (C). Chargaff's findings clearly indicate that some type of heterocyclic amine base pairing exists in the DNA structure. 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.

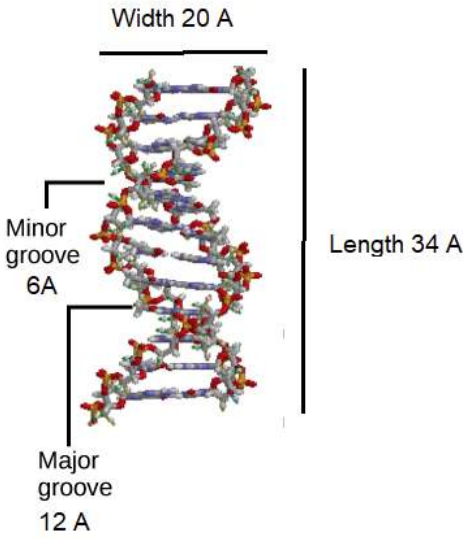


SECONDARY STRUCTURE OF DNA

The three-dimensional structure of DNA was the subject of an intensive research effort in the late 1940s to early 1950s. DNA exists as a double-stranded molecule that twists around its axis to form a helical structure,stabilized through Watson-Crick hydrogen bonding between purines and pyrimidines, and through pi-pi stacking interactions among the bases arranged in structure. helical column. Each strand is a complement to the other; the nucleotides on one strand hydrogen-bond with complementary nucleotides on the opposite strand—that is, side-by-side with the 5′ end of one chain next to the 3′ end of the other. The purine and pyrimidine bases face the inside of the helix, with guanine always opposite cytosine and adenine always opposite thymine. The double helical "twist" occurs because of the angular geometry of each bonded nucleotide.



Initial work revealed the DNA polymer had a regular repeating pattern X-ray diffraction data shows that a repeating helical pattern is 20 Angstrom units wide and occurs every 34 Angstrom units with 10 nucleotide subunits per turn. Each subunit occupies 3.4 Angstrom units which is the same amount of space occupied by a single nucleotide unit. The helix is Under most conditions, the two strands are slightly offset, which creates a 12 Angstrom major groove on one face of the double helix, and a 6 Angstrom minor groove on the other. The overall DNA polymer 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).



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.

Deoxyribonucleic acid (DNA) stores genetic information, while ribonucleic acid (RNA) is responsible for transmitting or expressing genetic information by directing the synthesis of thousands of proteins found in living organisms. But how do the nucleic acids perform these functions?

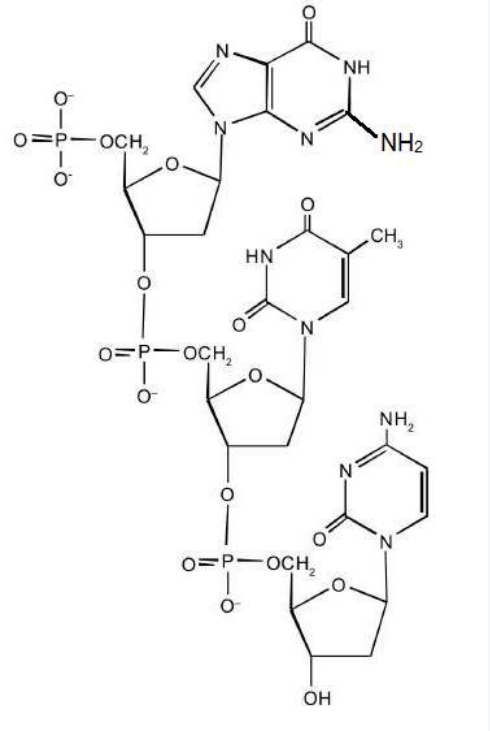
Three processes are required:

1. ***Replication***, in which new copies of DNA are made.
2. ***Transcription***, in which a segment of DNA is used to produce RNA.
3. ***Translation***, in which the information in RNA is translated into a protein sequence.

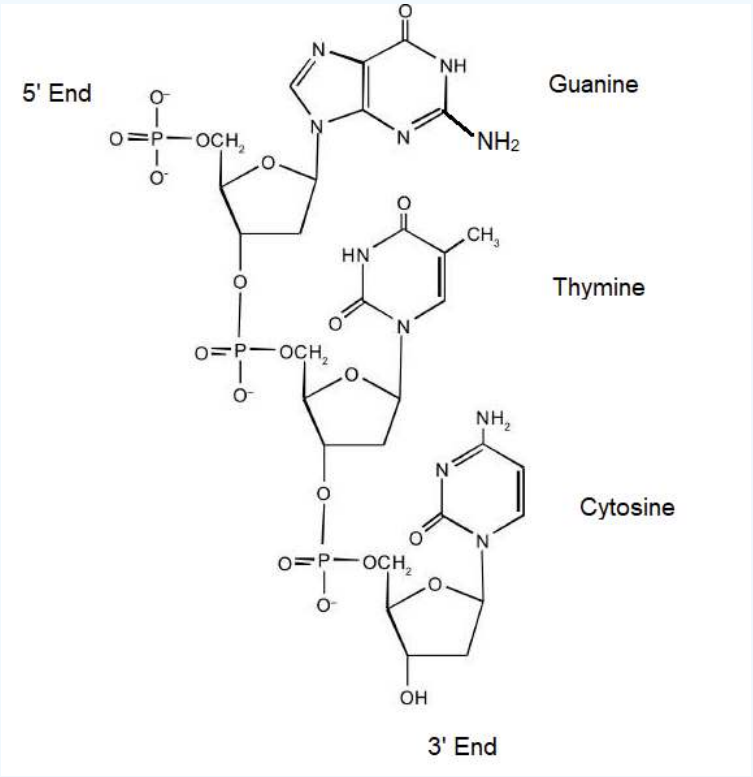
? EXERCISE 28.2.1

For this short DNA segment,

a. Identify the 5′ end and the 3′ end of the molecule.
b. Circle the atoms that comprise the backbone of the nucleic acid chain.
c. Write the nucleotide sequence of this DNA segment.



Answer



EXERCISE 28.2.2

Which nitrogenous base in DNA pairs with each listed nitrogenous base?

a. Cytosine
b. Adenine
c. Guanine
d. Thymine

Answer

a. Guanine
b. Thymine
c. Cytosine
d. Adenine

EXERCISE 28.2.3

How many hydrogen bonds can form between the two strands in the short DNA segment shown below?

5′ ATGCGACTA 3′ 3′ TACGCTGAT 5′

Answer

22 (2 between each AT base pair and 3 between each GC base pair).

EXERCISE 28.2.4

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?

Answer

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).

CONTRIBUTORS AND ATTRIBUTIONS

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

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28.3 REPLICATION OF DNA

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.

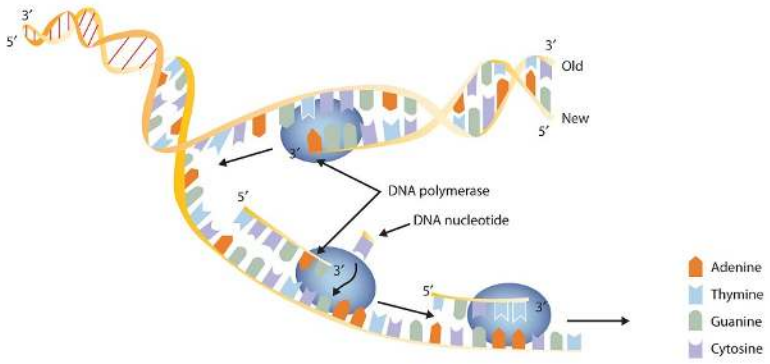


Figure 28.3.1 *A Schematic Diagram of DNA Replication. DNA replication occurs by the sequential unzipping of segments of the double helix. Each new nucleotide is brought into position by DNA polymerase and is added to the growing strand by the formation of a phosphate ester bond. Thus, two double helixes 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 28.3.1

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).

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.

EXERCISE

? EXERCISE 28.3.1

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?

Answer

3′-GGTCACTTAACGGATA-5′

CONTRIBUTORS AND ATTRIBUTIONS

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

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28.4 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 RNA.
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.

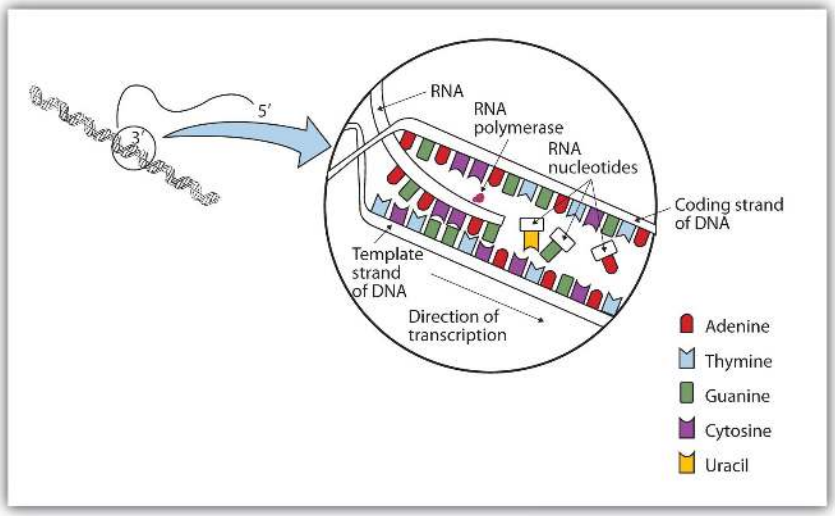


Figure 28.4.1 A Schematic Diagram of RNA Transcription from a DNA Template. The representation of RNA polymerase is proportionately much smaller than the actual molecule, which encompasses about 50 nucleotides at a time.

EXAMPLE 28.4.1

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′).

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 28.4.1: 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.

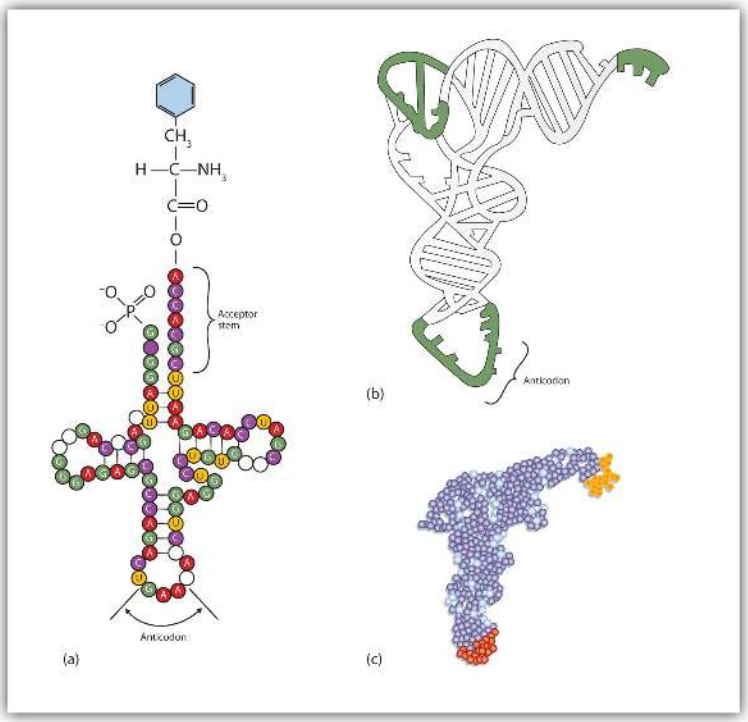


***Figure 28.4.2**" Transfer RNA. (a) In the two-dimensional structure of a yeast tRNA molecule for phenylalanine, the amino acid binds to the acceptor stem located at the 3′ end of the tRNA primary sequence. (The nucleotides that are not specifically identified here are slightly altered analogs of the 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.*

EXERCISE

? EXERCISE 28.4.1

What would be the DNA base sequence of the coding strand required to transcribe the following RNA sequence?

5′-AUGAGCGACUUUGCGGGAUUA-3′

Answer

5′-ATGAGCGACTTTGCGGGATTA-3′.

CONTRIBUTORS AND ATTRIBUTIONS

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

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28.5 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*.

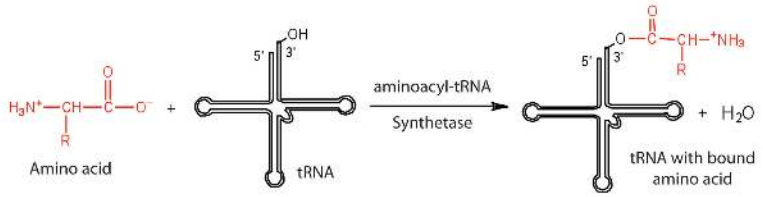
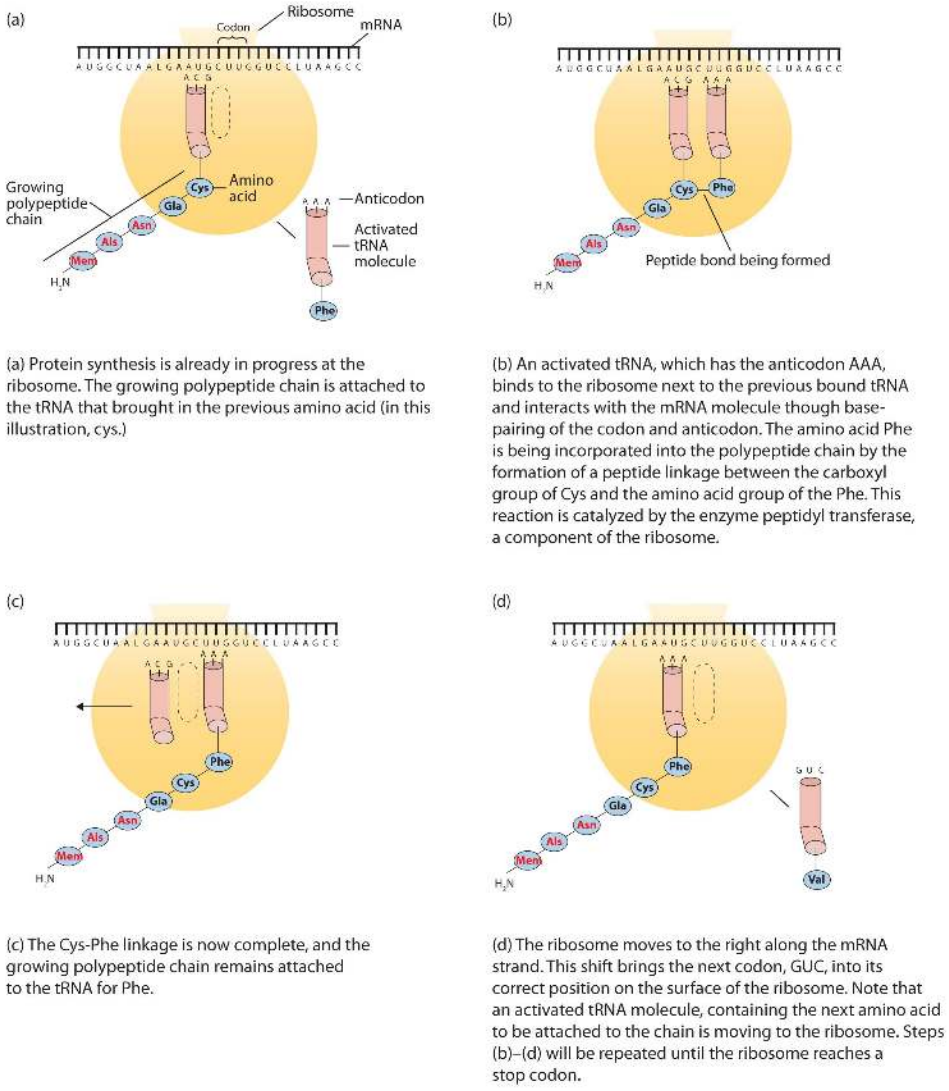


Figure 28.5.1 *Binding of an Amino Acid to Its tRNA*

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 28.5.2: *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.

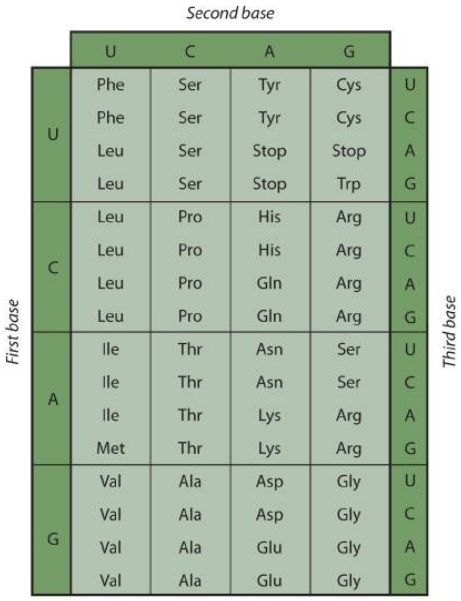


***Figure 28.5.3**: The Genetic Code*

EXAMPLE 28.5.1

A portion of an mRNA molecule has the sequence 5′-AUGCCACGAGUUGAC-3′. What amino acid sequence does this code for?

Solution

Use Figure 28.5.3to 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.

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.

EXERCISES

EXERCISE 28.5.1

What are the roles of mRNA and tRNA in protein synthesis?

Answer

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.

EXERCISE 28.5.2

A portion of an mRNA molecule has the sequence 5′-AUGCCACGAGUUGAC-3′. What amino acid sequence does this code for?

Answer

Use Figure 28.5.1 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 28.5.3

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′

Answer

a) 3′-AAA-5′

b) 3′-GUA-5′

c) 3′-UCG-5′

d) 3′-GGC-5′

EXERCISE 28.5.4

The peptide hormone oxytocin contains 9 amino acid units. What is the minimum number of nucleotides needed to code for this peptide?

Answer

27 nucleotides (3 nucleotides/codon)

EXERCISE 28.5.5

Determine the amino acid sequence produced from this mRNA sequence: 5′-AUGAGCGACUUUGCGGGAUUA-3′.

Answer

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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28.6 DNA SEQUENCING

OBJECTIVES

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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

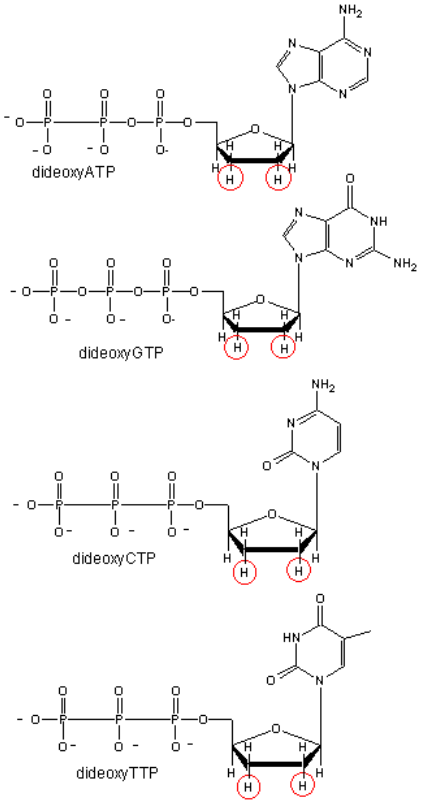


Figure: Didexoynucleotides

$$t = \frac{0.9\lambda}{\sqrt{B_M^2 - B_S^2}\cos\theta}$$

EXAMPLE 28.6.1

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)

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.

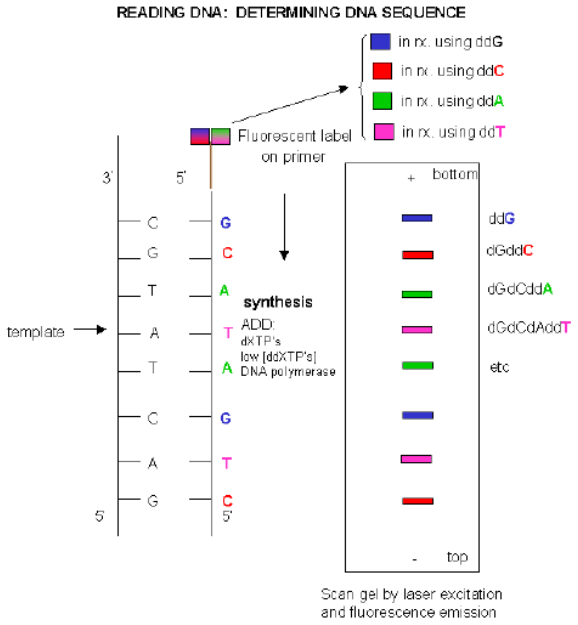
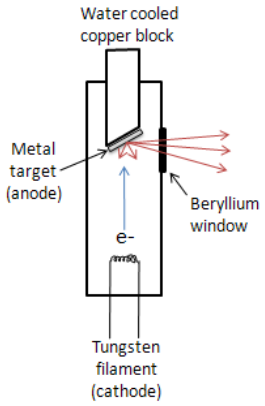


***Figure**: DNA sequencing using different fluorescent primers for each ddXTP reaction*

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.



- SMART - Single Molecule Real Time Sequencing
- Pacific Biosystems

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28.7 DNA SYNTHESIS

OBJECTIVES

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28.8 THE POLYMERASE CHAIN REACTION

OBJECTIVES

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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)*

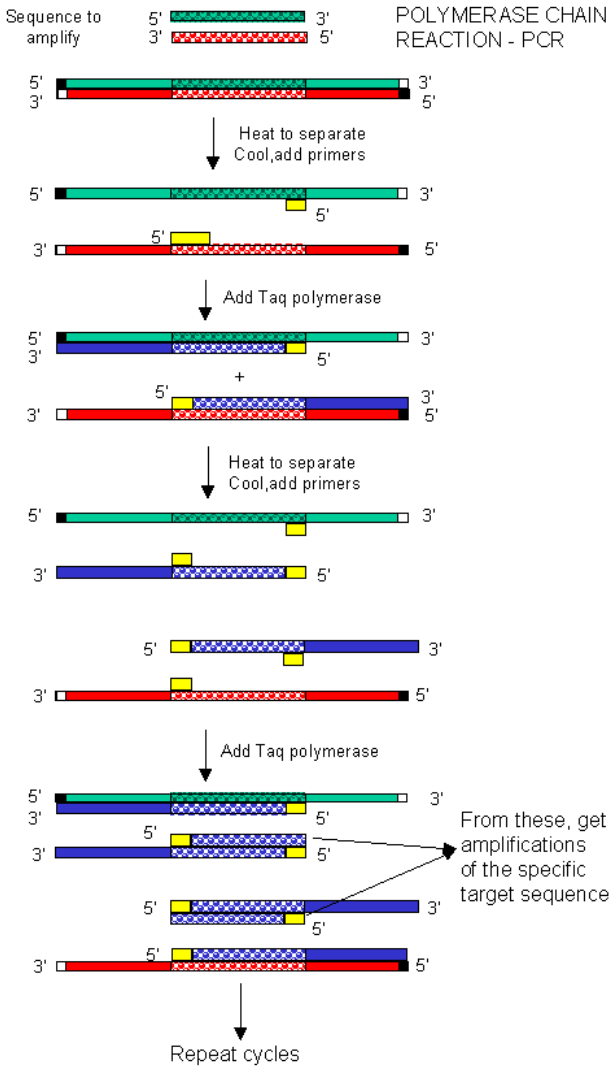
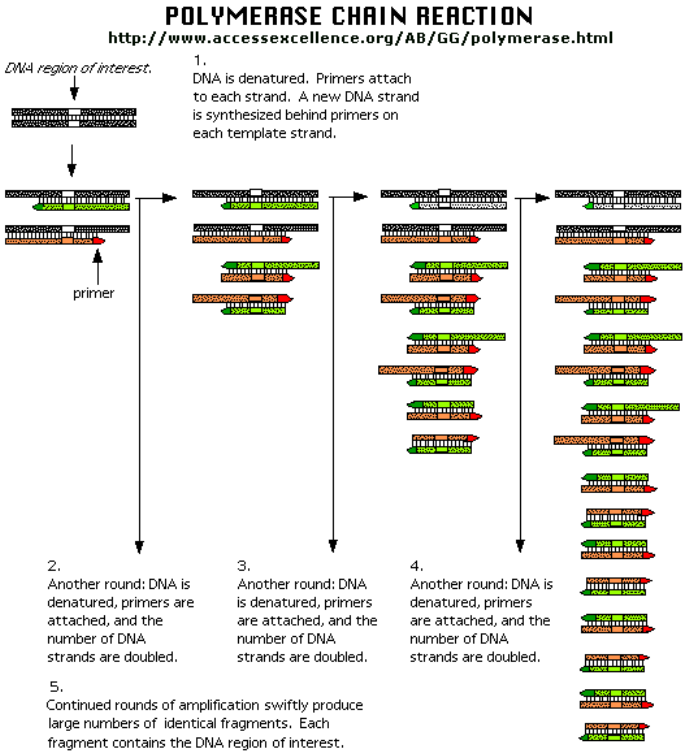


Figure: Another View of PCR



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