CHAPTER 7
ALCOHOLS, THIOLS, PHENOLS, ETHERS

Several new functional groups are presented in this chapter. All of the functions are based on oxygen and sulfur in the sp^2 hybridized state. The functional groups contain two pairs of non-bonding electrons and are the cornerstone of many organic processes. The structures for alcohols, phenols, thiols, ethers and thioethers are shown below.

Alkyl-OH	Ph-OH	Alkyl-SH	R-O-R	R-S-R
alcohol	phenol	thiol	ether	thioether

7.1 Alcohols

7.1a Nomenclature

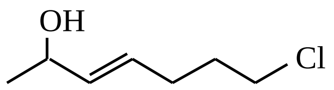
Priorities in nomenclature

Several functional groups have been encountered as we have advanced through the chapters. When a new functional group is presented, its nomenclature is always based on the parent name with an ending that designates the functional group. When several functional groups are present in a molecule, priority rules must be used to determine which function is the parent system that determines the numbering of the system and the suffix used in the final name.

The priority list is as follows:
carboxylic acids > aldehydes> ketones> alcohols > amines > alkene > alkyne
> alkyl, halogen, nitro

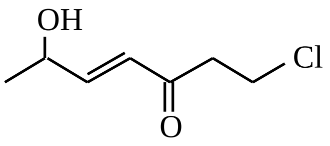
Thus a compound that contained hydroxy, alkene and ketone functions would be named as a ketone with the ketone getting the lowest number possible, and substituents are numbered accordingly and named in alphabetical order.

Below the compound on the left is named as an alcohol, but the one on the right is named as a ketone even though both compounds have the seven carbon backbone.



7-chloro-3-hepten-2-ol

OH has priority



1-chloro-6-hydroxy-4-hepten-3-one

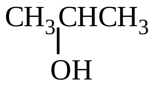
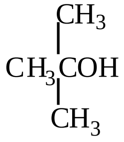
ketone has priority

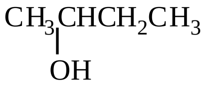
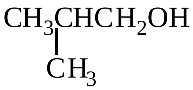
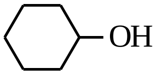
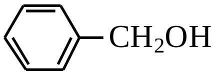
Alcohol Nomenclature

Hydroxy compounds are encountered frequently in organic chemistry and the OH function is of high priority with only acids, aldehydes and ketones having higher priority. Thus many compounds have the alcohol parent system.

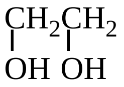
The IUPAC system names the longest chain hydrocarbon as the parent, drops the ending -e and adds a new ending of -ol. The alcohol has a higher priority in nomenclature than alkenes, alkynes, alkyl groups and halogen and is given a number lower than any of those groups. Once the parent compound is identified and the location of the alcohol function is specified, other functions are named in alphabetical order.

The IUPAC and common names for several alcohols are given below.

Structure	**Common**	**IUPAC**
CH_3OH	methyl alcohol	methanol
CH_3CH_2OH	ethyl alcohol	ethanol
$CH_3CH_2CH_2OH$	n-propyl alcohol	1-propanol
 $CH_3\underset{\underset{OH}{\vert}}{C}HCH_3$	isopropyl alcohol	2-propanol
 $CH_3\overset{\overset{CH_3}{\vert}}{\underset{\underset{CH_3}{\vert}}{C}}OH$	tert-butyl alcohol	2-methyl-2-propanol

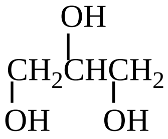
$CH_3CH_2CH_2CH_2OH$	n-butyl alcohol	1-butanol
 $CH_3\underset{OH}{C}HCH_2CH_3$	sec-butyl alcohol	2-butanol
 $CH_3\underset{CH_3}{C}HCH_2OH$	isobutyl alcohol	3-methyl-1-propanol
	cyclohexyl alcohol	cyclohexanol
	benzyl alcohol	phenylmethanol

When more than one hydroxyl group is present, the IUPAC system uses numbers to designate the location of the hydroxyls along with a prefix di, tri, to denote the number of hydroxyls. Some systems with more than one hydroxyl have common names as shown.


$\underset{OH}{CH_2}\underset{OH}{CH_2}$

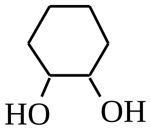
1,2-ethandiol

ethylene glycol


$\underset{OH}{CH_2}\overset{OH}{CH}\underset{OH}{CH_2}$

1,2,3-propantriol

glycerol



1,2-cyclohexandiol

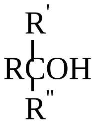
Aliphatic alcohols are classified as primary, secondary or tertiary, according to the type of carbon atom attached to the alcohol function. If the carbon attached carries one alkyl group, the alcohol is primary. With two alkyl groups attached to the carbon the alcohol is secondary, and three alkyl groups attached the alcohol is tertiary.

RCH_2OH

primary


$R\overset{R'}{C}HOH$

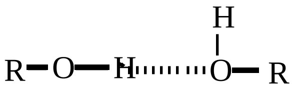
secondary


$R\overset{R'}{\underset{R''}{C}}OH$

tertiary

7.1b Physical Properties of Alcohols

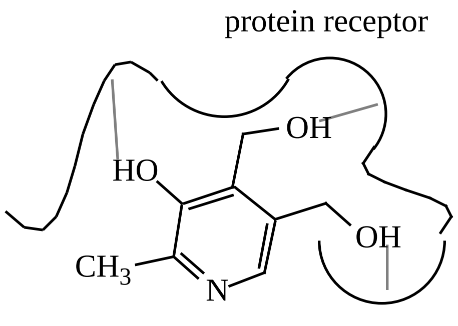
Many of the physical properties of alcohols are directly related to the hydrogen bonding exhibited by the hydroxyl group. In pure alcohol systems, extra energy must be added in order to cause the sample to boil, thus high boiling points are observed. Also, alcohols form hydrogen bonds with water and as a result are very soluble in water unless more than six carbon atoms are present.



High boiling points of alcohols as a result of hydrogen bonding are demonstrated in the examples given below. The hydrocarbon of closest mass is shown below each alcohol. The difference in boiling points is as much as 153 ^{o} because of the hydrogen bonding.

CH_3OH	CH_3CH_2OH	$CH_3CH_2CH_2OH$	$CH_3CH_2CH_2CH_2OH$
65^o	78^o	97^o	118^o
CH_3CH_3	$CH_3CH_2CH_3$	$CH_3CH_2CH_2CH_3$	$CH_3CH_2CH_2CH_2CH_3$
-88^0	-42^0	-0.5^0	35^0

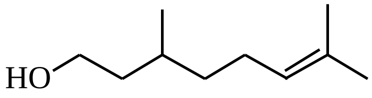
Hydrogen bonding is exceptionally important in biological function. Many molecules that are active in biological processes have the OH function present. When the molecule is in a living system it must interact with a protein. The interaction must have a specific fit as to the shape and stereochemistry of the protein and the molecule, and much of the intermolecular attraction comes from hydrogen bonding from the hydroxyls of the molecule to oxygen and nitrogen sites present in the protein as shown below for pyridoxine, vitamin B_6 interacting with a protein receptor.



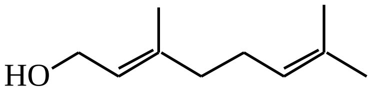
Pyridoxine
Vitamin B_6
(grains, milk, eggs)

7.1c Naturally Occurring Alcohols

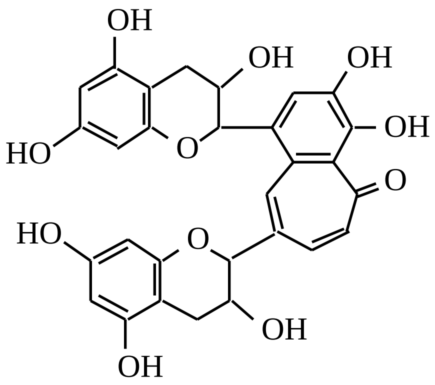
The R-OH function is truly abundant in nature. All carbohydrates, also called sugars, are compounds that contain the alcohol function. A few common compounds are listed below. Both citronellol and geraniol are found in plants and trees and belong to a family of compounds called terpenes. They are used as blends in perfumes and spices. Citronellol is used in candles to help repel mosquitoes. Meso-inisotol, a carbohydrate, is a compound found in food sources and is important in healthy metabolism. Theaflavine found in black tea, contains both aliphatic and aromatic hydroxyl functions and ether functions.



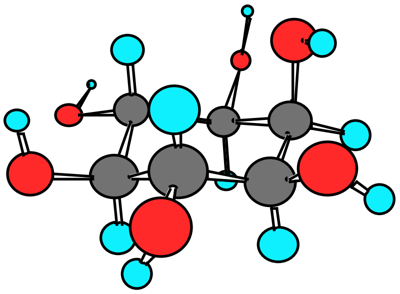
Citronellol

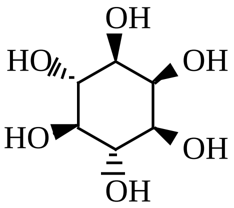


Geraniol



theaflavine
from black tea





Meso-inositol
possible cell growth factor
(fruits, vegetables, meats)

7.1d Preparation of Alcohols

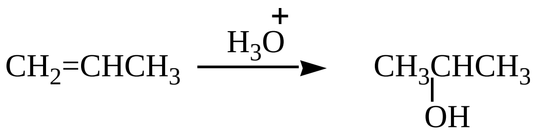
Several of the low molecular mass alcohols are prepared on an industrial scale that produces millions of tons. The alcohols are used throughout the chemical and academic world, commercially as solvents, as medicinal preparations, and in alcoholic drinks (ethanol)

Methanol is produced in a special process that involves catalytic hydrogenation of carbon monoxide. Methanol is extremely toxic and causes blindness when ingested.

$$CO + H_2 \xrightarrow[\text{high temp and press}]{ZnO/Cr_2O_4} CH_3OH$$

Both ethyl alcohol and isopropyl alcohol are synthesized by acid-catalyzed addition of water to ethylene and propylene respectively.

$$CH_2{=}CH_2 \xrightarrow{H_3O^+} CH_3CH_2OH$$



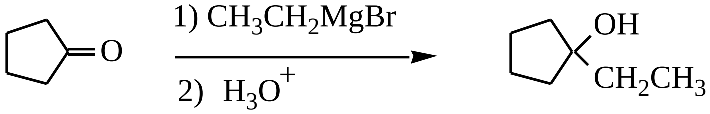
$$CH_2{=}CHCH_3 \xrightarrow{H_3O^+} CH_3\underset{\underset{OH}{|}}{C}HCH_3$$

Ethanol is also produced as a supplement for auto fuels by fermentation of the carbohydrates found in grain. The process gives ethanol that contains 5% water after distillation. The water is removed by reaction with lime, calcium oxide.

Grignard Reactions with Carbonyl Compounds

Grignard reagents were introduced in the halogen chapter. Their use is so valuable and general in organic chemistry that their reactions will be shown throughout many chapters. The example shown below could be expanded into many variations just by changing the halide and the carbonyl compound. Variations with other types of organometallic compounds are also available.

$$CH_3CH_2Br + Mg \xrightarrow{\text{diethyl ether}} \underset{\text{ether complex}}{CH_3CH_2MgBr}$$



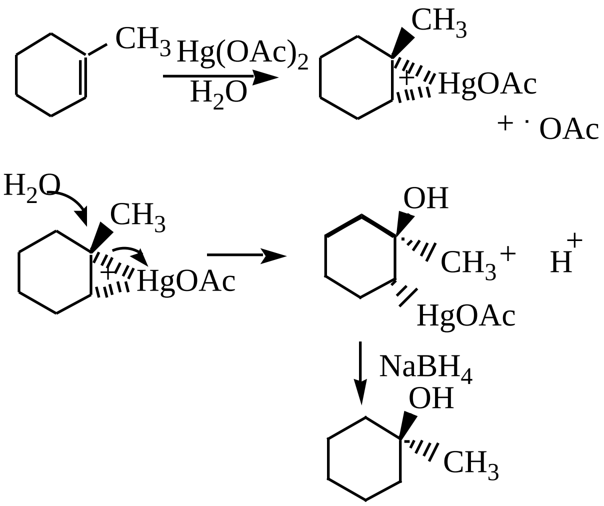
There are many examples of the use of Grignard reactions. The example above could be expanded into many variations just by changing the halide and the carbonyl compound. Variations with other types of organometallic compound are also available. The reaction is given in more detail in chapter 8 on aldehydes and ketones.

Hydration of Alkenes

The reactions shown to prepare ethanol and isopropyl alcohol industrially are examples of electrophilic addition of water to an alkene. The preparation of higher molecular weight alcohols by hydration is not as important because rearrangements occur and product yields are reduced.

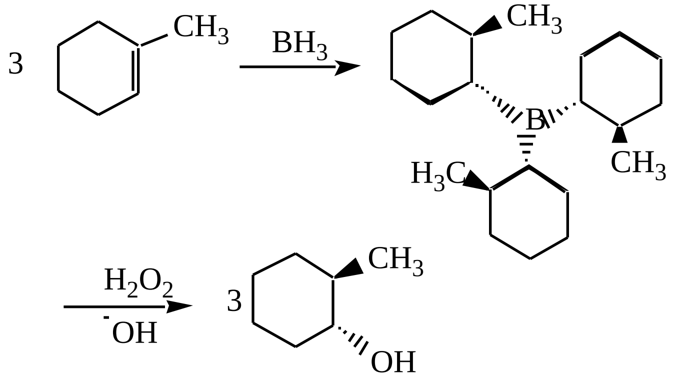
Oxymercuration-demercuration provides alcohols from alkenes under mild conditions without rearrangement. Mercuric acetate reacts with the alkene to form a cyclic mercurinium ion with a positive charge. Water attacks the intermediate from the carbon with the highest positive charge, the tertiary carbon here, and from the backside of the mercury atom. Water and mercury will be anti in an intermediate product which is not isolated, but it is reacted with sodium borohydride to convert the carbon-mercury bond into a carbon-hydrogen bond. The final result is the production of the alcohol at the most substituted carbon of the alkene, the Markovnikov product.

Oxymercuration-demercuration



Alkenes react with borane, BH_3 ether, by syn-addition of hydrogen and boron to the alkene. The boron atom adds to the least substituted carbon atom. After three alkene units have added the intermediate is treated with basic hydrogen peroxide to form the alcohol. The process is called hydroboration-oxidation. The process provides the alcohol with anti-Markovnikov selectivity.

Hydroboration-oxidation



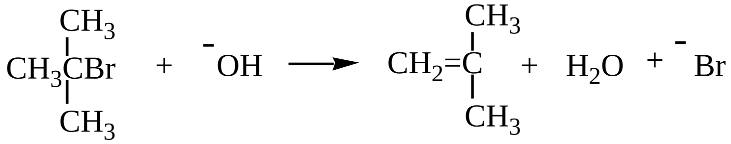
Reactions of Haloalkanes

Halogenated alkanes can be converted to alcohols by reactions described in chapter 5 on *Nucleophilic Substitution and Elimination.* The main points of reactions of alkyl halides are that the primary halides react by S_N2 and E2 reactions, while secondary and tertiary substrates react primarily by S_N1, E1 and E2 reactions. Results are shown for reactions of primary and tertiary halides with hydroxide, which is both a good nucleophile and strong base.

S_N2

$$CH_3CH_2Br + {}^{-}OH \longrightarrow CH_3CH_2OH + {}^{-}Br$$

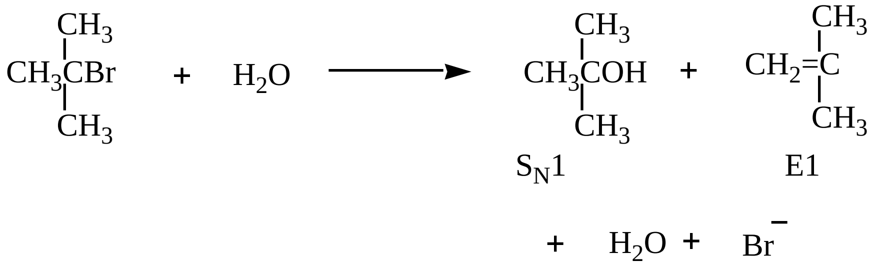
E2



$$CH_3\underset{CH_3}{\overset{CH_3}{C}}Br + {}^{-}OH \longrightarrow CH_2{=}\underset{CH_3}{\overset{CH_3}{C}} + H_2O + {}^{-}Br$$

Reactions of the same substrates with water (or water in a solvent), which is very non-nucleophilic and non-basic, show only S_N1 and E1 processes with the tertiary halide.

$$CH_3CH_2Br + H_2O \longrightarrow \text{No Reaction}$$

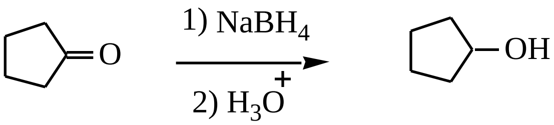


$$CH_3\overset{CH_3}{\underset{CH_3}{C}}Br + H_2O \longrightarrow \underset{S_N1}{CH_3\overset{CH_3}{\underset{CH_3}{C}}OH} + \underset{E1}{CH_2{=}\overset{CH_3}{\underset{CH_3}{C}}} + H_2O + Br^-$$

Reduction of Acids, Esters, Aldehydes and Ketones

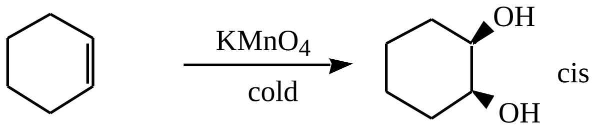
The carbonyl group of several functional groups may be converted to the alcohol by reducing agents. The reduction of a carboxylic acid with lithium aluminum hydride and the reduction of a ketone with sodium borohydride are shown below. Both reactions exemplify very common and reliable procedures. These reactions are given in detail in the aldehyde and ketone chapter 8.

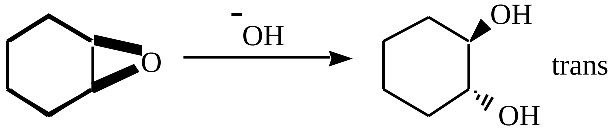
$$CH_3CH_2CH_2COOH \xrightarrow[2)\ H_3O^+]{1)\ LiAlH_4} CH_3CH_2CH_2CH_2OH$$



Oxidation of Alkenes to Vicinal Diols

Compounds with hydroxyl groups on adjacent carbons are called vicinal diols. Oxidation of alkenes with cold KMnO4 or OsO4 provides occurs with syn addition and provides cis vicinal diols. Trans vicinal diols can be prepared by ring opening of an oxirane, a three-membered ring containing oxygen.





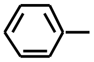
7.1e Reactions of Alcohols

Acidic properties of alcohols

The high electronegativity of the oxygen atom in alcohols causes the oxygen to take electrons away from the hydrogen atom. The OH bond is polarized and is able to give up a proton, H^+. Thus alcohols are weak acids, but can become stronger acids depending on the types of organic substituents present.

$$R\text{-}\overset{\delta^-}{O}\text{-}\overset{\delta^+}{H} \rightleftharpoons R\text{-}O^- + H^+$$

The ionization constant for the above equilibrium is given by Ka = $[RO^-][H^+] / [ROH]$. Acidity is often expressed as pKa which is the negative logarithm of the Ka. Thus, $pK_a = -\log K_a$. The pK_a is shown below for several alcohols. Electron donating groups weaken the acidity (higher pK_a) while electron attracting groups strengthen the acidity (lower pK_a). Phenol, the last entry, represents a very acidic class of organic compounds and is presented later in this chapter.

	H_2O	CH_3OH	CH_3CH_2OH	CF_3CH_2OH	 OH
pK_a	15.7	16	17	12.4	10

The acidic property of alcohols is important as it permits the formation of alcoholate salts, called alkoxides. Alkoxides are useful both as strong bases and as good nucleophiles for S_N2 reactions. Alkali metals and other very strong bases can be used to generate the alkoxides.

$$2\ CH_3OH + 2\ Na \longrightarrow 2\ CH_3O^-\ Na^+ + H_2$$

$$CH_3OH + NaH \longrightarrow CH_3O^-\ Na^+ + H_2$$

Conversion of Alcohols to Alkyl Halides

Reaction with Hydrogen Halides

Aliphatic alcohols react with hydrogen halides to produce alkyl halides.

$$ROH + HX \longrightarrow RX + H_2O$$

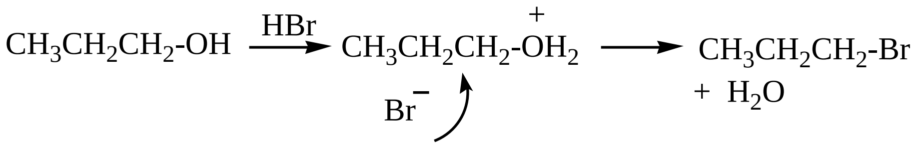
$$X = Cl, Br, I$$

The mechanism of the reaction depends on the structure of the alcohol, but the first step always involves protonation of the alcohol to form an oxonium ion.

$$ROH + HX \longrightarrow \underset{\text{oxonium ion}}{R\overset{+}{O}H_2} + X^-$$

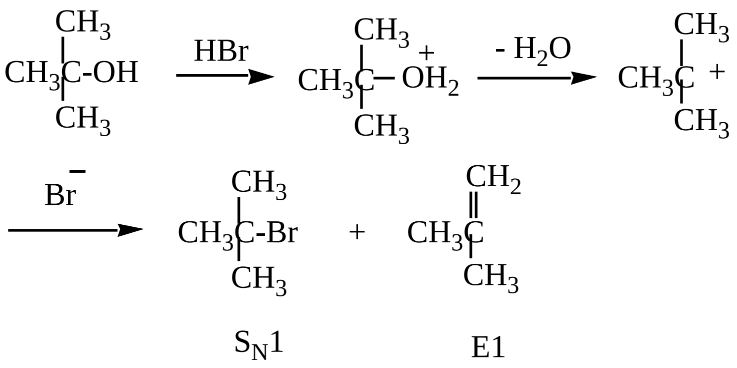
The $^+OH_2$ group is an excellent leaving group as it forms a neutral molecule of water. The rules for substitution and elimination reactions apply here just as with alkyl halides. Primary alcohols react by the S_N2 - E2 mechanism while secondary and tertiary alcohols follow S_N1 - E1 carbocation paths.

The reaction of n-butyl alcohol with HBr gives first the oxonium ion which then is attacked from the backside in a S_N2 manner to give 1-bromobutane.



$$CH_3CH_2CH_2\text{-}OH \xrightarrow{HBr} CH_3CH_2CH_2\text{-}\overset{+}{O}H_2 \longrightarrow CH_3CH_2CH_2\text{-}Br + H_2O$$

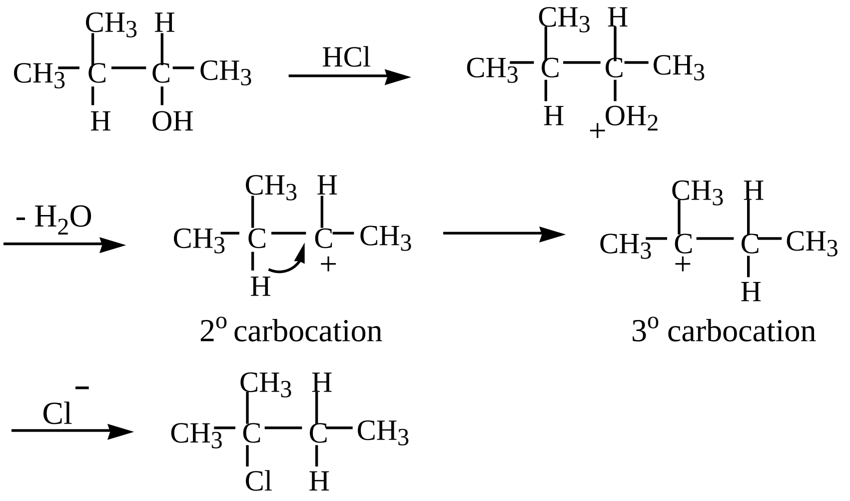
The reaction of tert-butyl alcohol, a tertiary alcohol, with HBr gives the oxonium ion first also. But in this case, water is lost to give the tert-butyl cation. The cation reacts with Br ⁻ to give mostly the substitution product accompanied by some alkene elimination product.



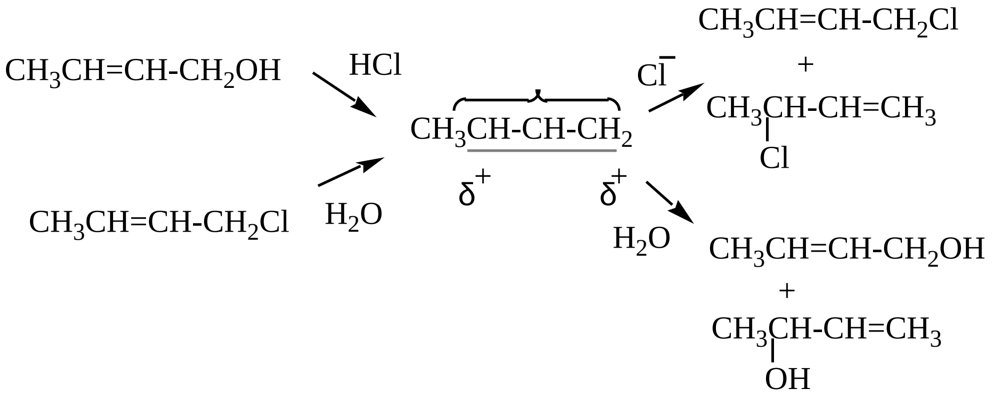
$$(CH_3)_3C\text{-}OH \xrightarrow{HBr} (CH_3)_3C\text{-}\overset{+}{O}H_2 \xrightarrow{-\ H_2O} (CH_3)_3C^+ \xrightarrow{Br^-} \underset{S_N1}{(CH_3)_3C\text{-}Br} + \underset{E1}{CH_3C(=CH_2)CH_3}$$

The reactions that involve carbocations are the more complicated because once the cation is formed many possibilities exist for their reaction: substitution, elimination, and rearrangement.

The reaction of 3-methyl-2-butanol with HCl goes through the oxonium ion to the carbocation. But the secondary cation rearranges to the more stable tertiary cation. The product arises from attack of chloride on the tertiary cation.

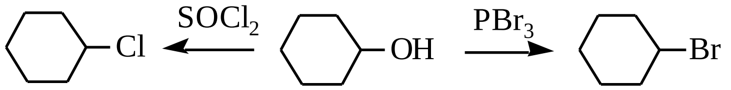


Both alcohols and halides can be used for generating carbocations, with the resulting products depending on reaction conditions. The example below illustrates the formation of a stable allylic carbocation.



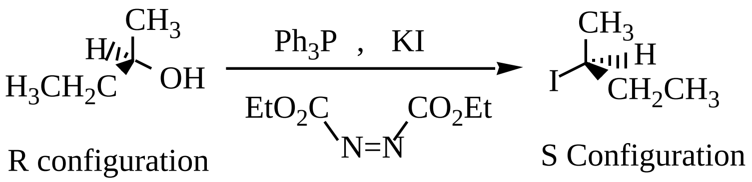
Reaction with Phosphorus and Sulfur Halides

Many reagents are known to convert alcohols to halides. Phosphorus halides and thionyl chloride are commonly used as was presented in chapter 6.



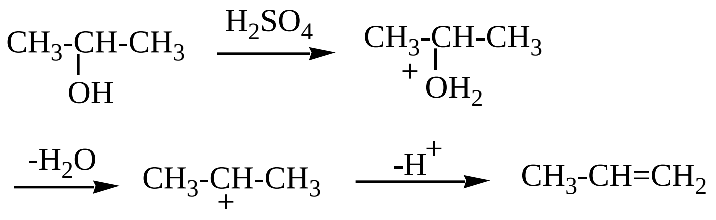
The **Mitsunobu** reaction can employ the halide as a nucleophile to displace the hydroxyl function in a S_N2 process. Thus the chirality of the halide product is inverted from that of the starting alcohol. In this reaction the hydroxyl group, which is normally a very poor leaving group as OH^-, leaves easily as a phosphine oxide. Thus alcohols may be displaced in the S_N2 reaction without being converted to another function (halide, sulfonate) first.

Mitsunobu Reaction



Dehydration

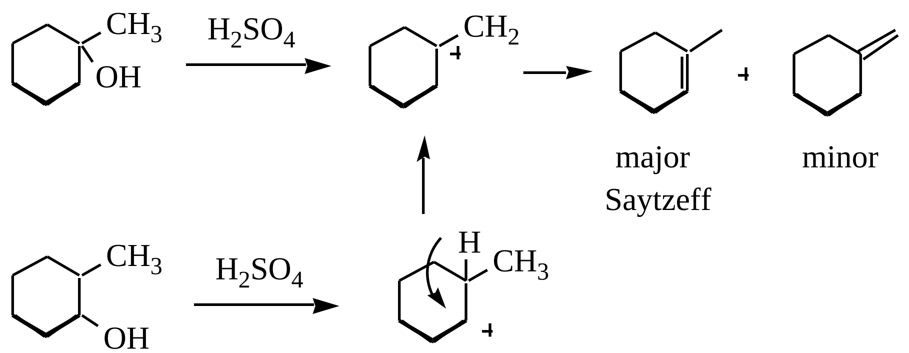
When secondary and tertiary alcohols are treated with acid, a carbocation is formed. When a nucleophile is present, such as halide in the above example, an alkyl halide is produced in the S_N1 process. But if a nucleophile is absent, then the E1 process is followed to give an alkene. Alcohols are easily dehydrated by the E1 reaction with sulfuric acid. The sulfate formed is too poor to serve as a nucleophile, thus only elimination is observed. But carbocations are the intermediates and the reactions can be complicated because of rearrangements.



$$\mathrm{CH_3\text{-}\underset{OH}{CH}\text{-}CH_3} \xrightarrow{\mathrm{H_2SO_4}} \mathrm{CH_3\text{-}\underset{{}^{+}OH_2}{CH}\text{-}CH_3}$$

$$\xrightarrow{\mathrm{-H_2O}} \mathrm{CH_3\text{-}\underset{+}{CH}\text{-}CH_3} \xrightarrow{\mathrm{-H^+}} \mathrm{CH_3\text{-}CH{=}CH_2}$$

The dehydration of the two methylcyclohexanols below shows that the major alkene formed is the most substituted (Saytzeff) product. Also rearrangement will occur to the more substituted carbocation. Thus the different alcohols give the same E1 products.



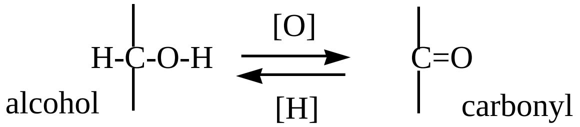
Primary alcohols are not good starting materials for dehydration because primary carbocations are not good intermediates. Reaction of ethanol with sulfuric acid gives diethyl ether, but dehydration can be achieved with an alumina catalyst at high temperature.

$$CH_3CH_2OH \xrightarrow[150^o]{H_2SO_4} CH_3CH_2OCH_2CH$$

$$CH_3CH_2OH \xrightarrow{Al_2O_3,\ 300^\circ} CH_2{=}CH_2$$

Oxidation of alcohols

Two extremely valuable functions in organic chemistry are the alcohol and carbonyl groups. The oxidation of alcohols and the reduction of carbonyl compounds represents a juncture in which each function can be prepared from the other. Any alcohol that contains and alpha hydrogen atom can be oxidized to a carbonyl compound as shown.



$$\underset{\text{alcohol}}{\text{H-}\overset{|}{\underset{|}{\text{C}}}\text{-O-H}} \underset{[H]}{\overset{[O]}{\rightleftharpoons}} \underset{\text{carbonyl}}{\overset{|}{\underset{|}{\text{C}}}{=}\text{O}}$$

$$1^o \quad RCH_2OH \xrightarrow{[O]} \underset{\text{aldehyde}}{RCH{=}O} \xrightarrow{[O]} \underset{OH}{R\underset{|}{C}{=}O} \ \text{acid}$$

$$2^0 \quad R_2CHOH \xrightarrow{[O]} R_2C{=}O \quad \text{ketone}$$

$$3^0 \quad R_3C\text{-}OH \xrightarrow{[O]} \text{no oxidation}$$

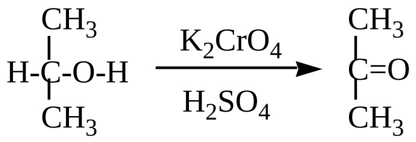
Oxidation of alcohols is so important that hundreds of reagents and procedures have bee developed to perform the oxidation. The reagents are in classes of oxidants such as chromium (VI), silver (I), aluminum (III), manganese(IV), manganese(VII), cerium (IV), iodine (V), and dimethylsulfoxide. The wide variety of reagents have been developed in order to achieve mild conditions and selectivity that avoids oxidizing other functions. Also oxidation of primary alcohols to aldehydes requires special reagents to avoid over-oxidation to the acid. Only a few common oxidation reagents will be used here.

Primary alcohols are easily oxidized to carboxylic acids with potassium dichromate in sulfuric acid (**Beckmann reagent**). The intermediate aldehyde is oxidized further to the acid. The reaction involves formation of an intermediate chromate ester which converts to chromium (IV).

$$CH_3CH_2CH_2CH_2OH \xrightarrow[H_2SO_4]{K_2CrO_4} CH_3CH_2CH_2COOH$$

Secondary alcohols are easily converted to ketones. Further oxidation of the ketone occurs only under very harsh conditions. The mechanism of the oxidation involves formation of a chromate (VI) ester of the alcohol followed by loss of chromous (IV) acid.

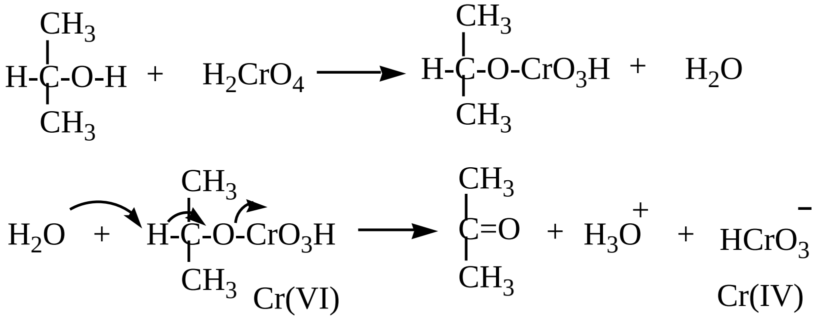
Tertiary alcohols do not possess an alpha hydrogen and cannot be oxidized, but the conditions of oxidation can sometimes cause E1 elimination reactions.



$$\text{H-}\overset{CH_3}{\underset{CH_3}{C}}\text{-O-H} \xrightarrow[H_2SO_4]{K_2CrO_4} \overset{CH_3}{\underset{CH_3}{C}}\text{=O}$$

Mechanism

$$K_2CrO_4 + H_2SO_4 \longrightarrow H_2CrO_4 + K_2SO_4$$

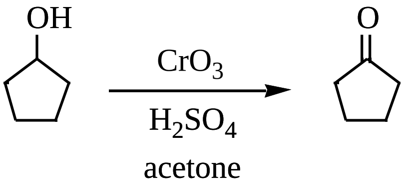


$$\text{H-}\overset{CH_3}{\underset{CH_3}{C}}\text{-O-H} + H_2CrO_4 \longrightarrow \text{H-}\overset{CH_3}{\underset{CH_3}{C}}\text{-O-}CrO_3H + H_2O$$

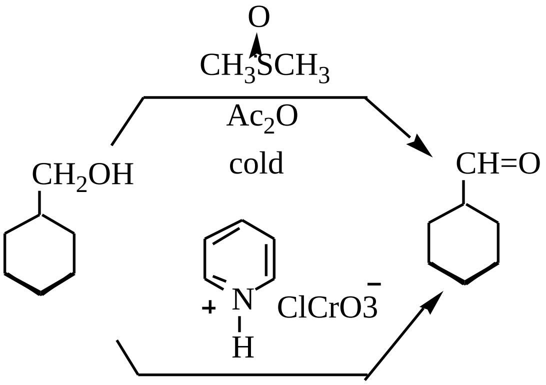
$$H_2O + \text{H-}\overset{CH_3}{\underset{CH_3}{C}}\text{-O-}CrO_3H \longrightarrow \overset{CH_3}{\underset{CH_3}{C}}\text{=O} + H_3O^+ + HCrO_3^-$$

A solution of CrO_3, H_2SO_4 and acetone, known as Jones reagent, is commonly used in many oxidation procedures.

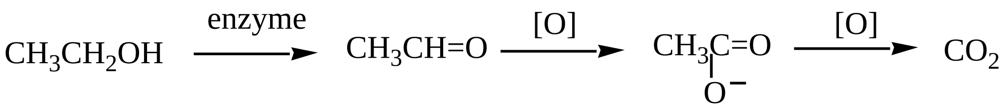
Jones Oxidation



Oxidations with dimethylsulfoxide in the presence of acetic anhydride or oxalyl chloride (**Swern oxidation**) are especially useful for conversion of primary alcohols to aldehydes without further oxidation to the acid. Pyridinium chlorochromate also serves for this selective oxidation.



Ingested alcohol is oxidized in the liver by an enzyme called *alcohol dehydrogenase*. The first product of the oxidation is acetaldehyde which is responsible for the well-known "hangover". The aldehyde is eventually further oxidized to acetate and then on to carbon dioxide.



$$CH_3CH_2OH \xrightarrow{\text{enzyme}} CH_3CH{=}O \xrightarrow{[O]} CH_3\underset{O^-}{C}{=}O \xrightarrow{[O]} CO_2$$

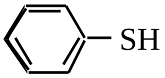
7.2 Thiols

7.2a Nomenclature

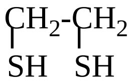
Sulfur is one row down from oxygen in the periodic table. Compounds that contain sulfur instead of oxygen might be expected to bear similar characteristics of the oxygen compound. But, the chemistry of the SH function is much different from the OH function. The SH group is called a sulfhydryl function, but organic compounds containing the SH are called thiols in the IUPAC system, or called mercaptans in older nomenclature. Thiol names in the IUPAC system are derived from the parent alkane by dropping the e followed by adding -thiol. A number is used to locate the position of the thiol. Older mercaptan names are obtained by naming the alkyl group followed by a second word, mercaptan.

CH_3SH

methanthiol
methyl mercaptan



thiophenol
phenyl mercaptan



$$\underset{SH}{CH_2}\text{-}\underset{SH}{CH_2}$$

ethandithiol

$CH_3CH{=}CHCH_2SH$

2-buten-1-thiol

7.2b Properties of Thiols

Thiols, unlike alcohols, do not form hydrogen bonds and therefore are volatile low boiling compounds. Thiols have very unpleasant odors. The 2-buten-1-thiol above is one of the components of skunk spray. Methanthiol is purposely added to bottled gas and natural gas in order to reveal leaks. Thiols (pKa = 10) are more acidic than alcohols (pKa = 16), and their proton can be removed by reaction with base.

$$CH_3SH \quad + \quad NaOH \longrightarrow CH_3\bar{S}\ Na^+ \ + \ H_2O$$

7.2c Preparation and Reactions of Thiols

Thiols are readily prepared by the S_N2 displacement of halides by sulfhydryl ion. Sulfhydryl anion is an extremely good nucleophile.

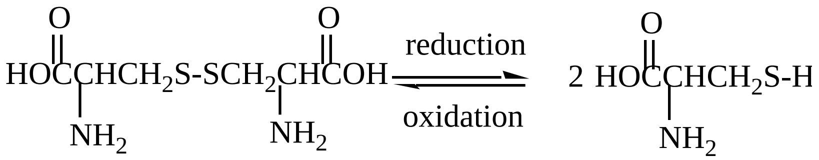
$$RX \quad + \quad NaSH \longrightarrow RSH \quad + \quad NaX$$

$$X = Cl, Br, I$$

Thiols are easily oxidized to disulfides, and the disulfides are easily reduced back to thiols.

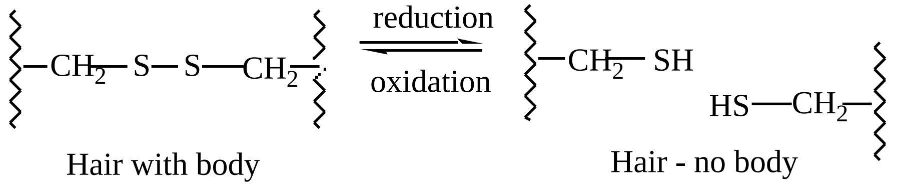
$$CH_3CH_2SH \ \underset{NaBH_4}{\overset{I_2}{\rightleftharpoons}} \ \underset{\text{disulfide}}{CH_3CH_2S\text{-}SCH_2CH}$$

The easy oxidation-reduction is important in protein structure. Keratin is a protein found in hair, and it contains the disulfide unit known as cystine. Hair treatments first reduce the disulfide bond and allow the hair to be managed. Then the disulfide bonds are reformed to keep the hair in the desired shape.



$$HOOC\text{-}CH(NH_2)CH_2S\text{-}SCH_2CH(NH_2)\text{-}COOH \underset{\text{oxidation}}{\overset{\text{reduction}}{\rightleftharpoons}} 2\ HOOC\text{-}CH(NH_2)CH_2S\text{-}H$$

cystine

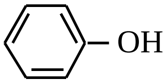


Hair with body

Hair - no body

7.3 Phenols

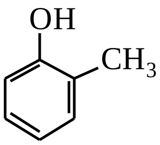
Phenols are a class of compounds that contain the hydroxyl function bonded to an aromatic ring. Although phenols and alcohols contain the OH group, their chemistry is much different. Phenols have a strongly acidic hydrogen, the C-O bond is very difficult to break, and many reactions take place in the aromatic ring.



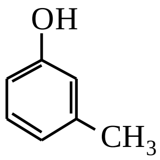
phenol

7.3a Nomenclature of phenols

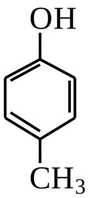
The names of phenols are derived from older common names. The names have been retained in the IUPAC system. Some common phenolic compounds are shown below.



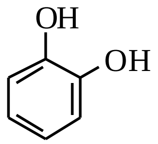
o-cresol



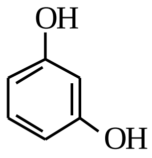
m-cresol



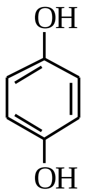
p-cresol



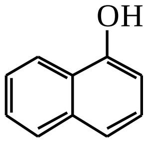
catechol



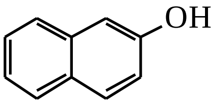
resorcinol



hydroquinone



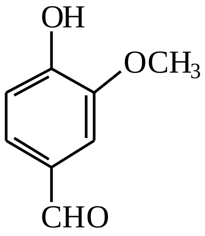
1-naphthol
α-naphthol



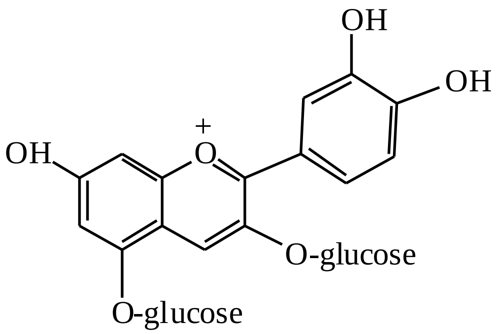
2-naphthol
β-naphthol

7.3b Naturally Occurring Phenols

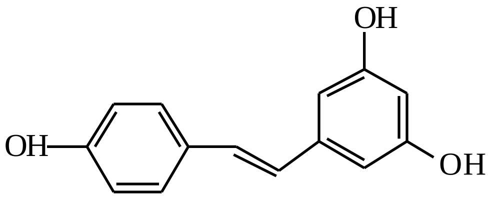
Many phenols are obtained by the distillation of coal. Vanillin, found in vanilla beans, is used as a flavoring for food. Salicylic acid is used to prepare aspirin. Resveratrol, found in grapes and peanuts, may be an anti-cancer agent. Cyanidin, a very abundant compound belong to the flavone class of compounds, is responsible for the red coloring in roses. When cyanidin is made basic with potassium ions it forms a blue color found in the blue cornflower.



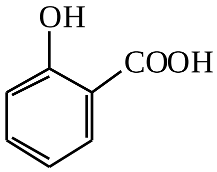
vanillin



cyanidin
red color of roses



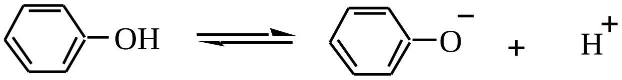
resveratrol



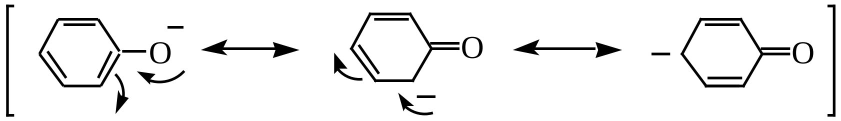
salicylic acid

7.3c Reactions of Phenols

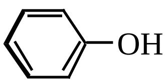
Phenols are stronger acids than alcohols. When a phenol gives up a proton, the resulting anion, the phenoxide anion, is stabilized by the aromatic ring. Thus the equilibrium for dissociation to the proton and phenoxide is greater in phenols than it is in alcohols.



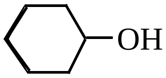
Resonance stabilization of phenoxide



The pK_a's of phenols of 8 to 10 when compared with the pK_a's of alcohols of 16 to 19 show that phenols are much stronger acids.



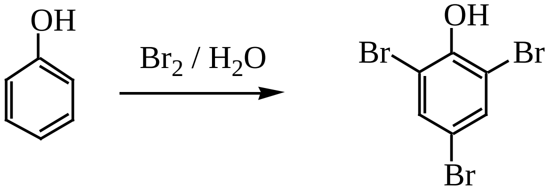
pKa 10



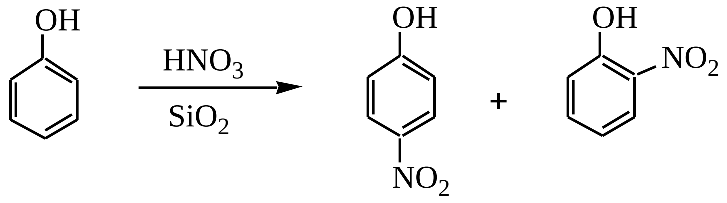
pKa 18

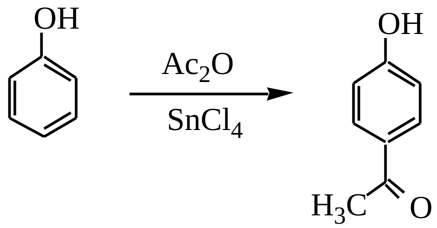
Electrophilic Aromatic Substitution

The OH group on an aromatic ring is a very strong activator and an ortho-para director. The ring is so reactive that bromination in water places three bromine atoms on the ring.



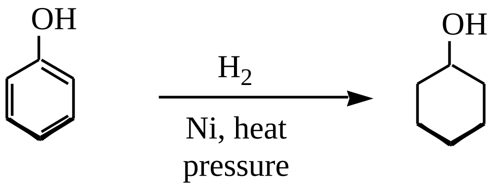
Other electrophilic substitutions occur readily under mild conditions as seen below for nitration and acylation.



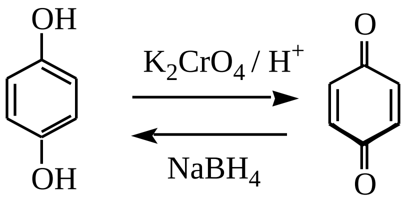


Reduction and Oxidation

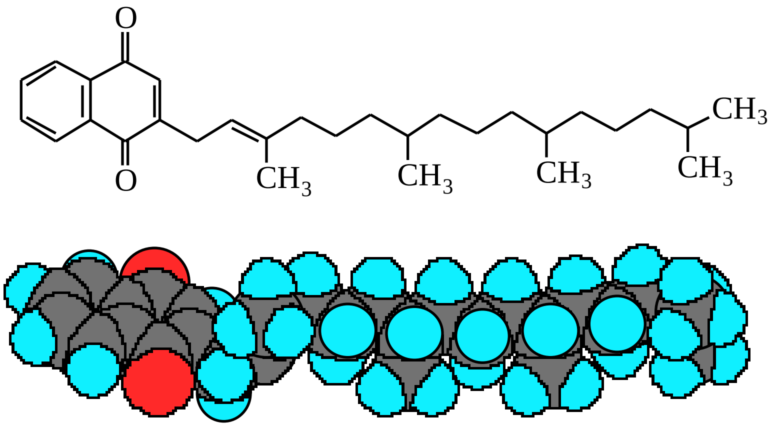
Cyclohexanol is produced from phenol by reduction with a nickel catalyst. The aromatic ring is lost in this procedure.



Hydroquinone is smoothly oxidized to the highly colored compound known as quinone. Quinone is used in photographic processes. The reaction is reversible and quinone may be reconverted to hydroquinone. Oxidation-reduction of this type is important in biological transformations.



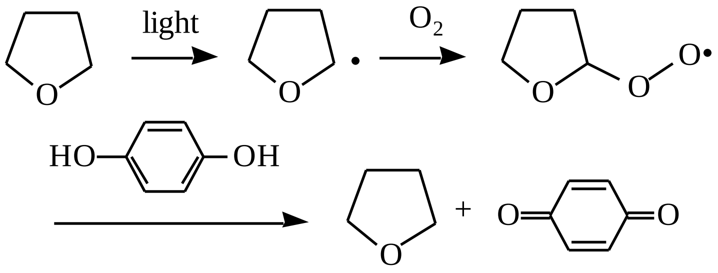
Vitamin K , a naturally occurring quinone that plays a role in blood clotting, contains the naphthoquinone structure shown.



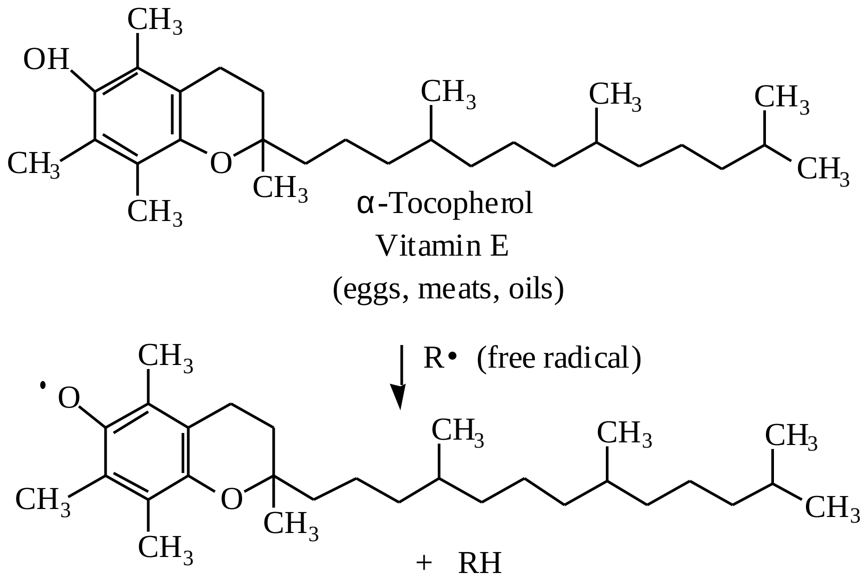
Phytonadione
Vitamin K
(green vegetables)

Reaction with free radicals

Free radicals react easily with phenols to abstract the hydrogen atom from the OH group. Hydroquinone is very efficient in reactions with radicals that it is used to terminate or inhibit radical reactions. Inhibition of radicals is important when free radicals may be present in a reaction and cause undesired reactions. Certain ethers are known to undergo free radical oxidations with oxygen to give unstable peroxides. When the bottle of ether containing the peroxide is shaken, the peroxide explodes. Addition of an inhibitor such as hydroquinone to the ether prevents formation of radicals and peroxides, and the ether remains free of explosive tendencies.



Vitamin E contains a phenolic ring in which the OH reacts with free radicals to inhibit their formation. Many people take vitamin E supplements to suppress radical formation in the body because some theories indicate that biological free radicals cause cancer.



7.4 Ethers

Ethers are compounds that have two organic groups attached to oxygen. The bonds between the organic groups and the oxygen form an angle of 110° and consequently are slightly polar. The non-bonding electrons on the oxygen atom cause ethers to act slightly basic. Ethers are well-known for their anesthetic properties but they possess other useful chemical properties as well. Structures of two anesthetic ethers are shown below, but better anesthetics are now in use.

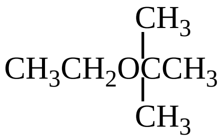
$CH_3CH_2OCH_2CH_3$	$ClCFHCF_2OCH_2F_2$
ether diethyl ether	ethrane

7.4a Nomenclature of Ethers

Ethers are named by treating each side as a substituent with an alkyl or aryl name followed by the word ether. The individual names are separate.

$CH_3CH_2OCH_2CH_3$

diethyl ether

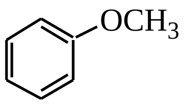


$CH_3CH_2O\underset{CH_3}{\overset{CH_3}{C}}CH_3$

methyl tert-butyl ether

$CH_3CH_2CH_2CH_2OCH(CH_3)_2$

n-butyl isopropyl ether



methyl phenyl ether

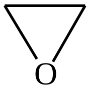
anisole

Complex ethers are named by prefixing the base name of a hydrocarbon system with an alkoxy group.

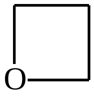
$CH_3OCH_2CH_2OCH_3$

1,2-dimethoxyethane

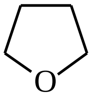
Cyclic ethers are named by the IUPAC system developed for heterocyclic compounds. Here the ox in the name denotes oxygen.



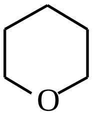
oxirane



oxetane



oxolane



oxane

7.4b Physical Properties of Ethers

Ethers have boiling points similar to the hydrocarbon obtained if the oxygen is replaced by a CH_2 group.

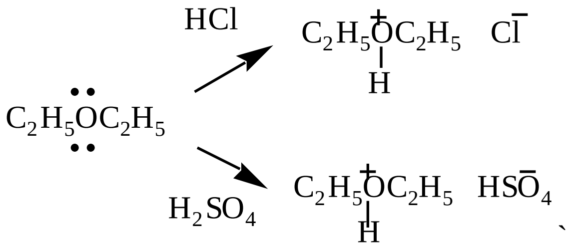
$CH_3CH_2OCH_2CH_3$ bp 35°

$CH_3CH_2CH_2CH_2OCH_2CH_2CH_2CH_3$ bp 142°

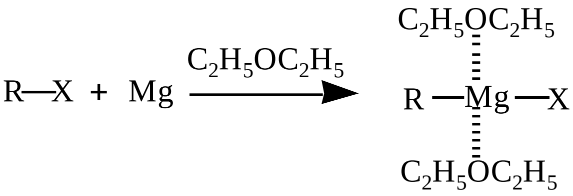
$CH_3CH_2CH_2CH_2CH_3$ bp 36°

$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$ bp 151°

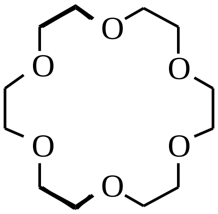
The non-bonding electrons on alkyl ethers cause a slightly basic character. Thus weak hydrogen bonds are formed with water, and ether slightly dissolves in water. The ether oxygen is protonated in the presence of strong acids.



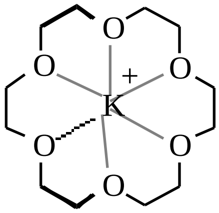
Grignard reagents require the presence of an ether, usually diethyl ether or tetrahydrofuran, because the ether oxygen forms a complex with the magnesium in the reagent.



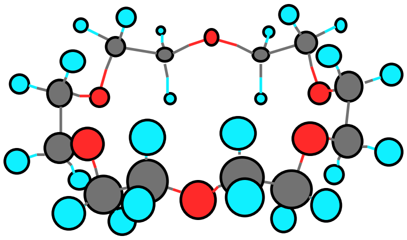
A unique class of ethers containing several oxygen atoms in a cyclic structure id called crown ethers because they adopt a crown shape. The crown ether shown below is called 18-crown-6 because it contains 18 atoms and 6 of the atoms are oxygen. The non-bonding electrons of the oxygen atoms complex with alkali metal cations. Thus salts such as KF can dissolve in organic solutions containing the crown ether.



18-crown-6



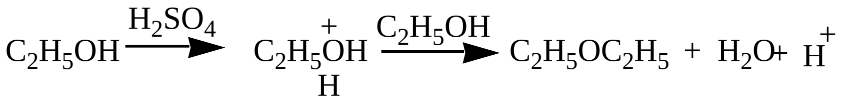
18-crown-6 Potassium Complex



18-crown-6
model

7.4c Preparation of Ethers

Diethyl ether is prepared from ethanol and sulfuric acid. The reaction involves the S_N2 displacement by ethanol on another positively charged molecule. The $^+OH_2$ is a very good leaving group.



$$C_2H_5OH \xrightarrow{H_2SO_4} C_2H_5\overset{+}{\underset{H}{O}}H \xrightarrow{C_2H_5OH} C_2H_5OC_2H_5 + H_2O + H^+$$

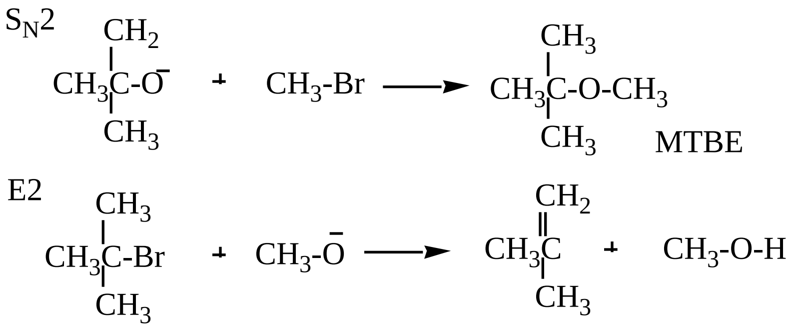
The use of an alkoxide in the S_N2 displacement of primary halides leads to ether products. The process is called the Williamson ether synthesis. The alkoxide is prepared by reacting sodium metal with the alcohol.

$$CH_3OH + Na^+ \longrightarrow CH_3ONa \longrightarrow CH_3O^- + Na^+$$

$$CH_3O^- + CH_3CH_2Br \longrightarrow CH_3OCH_2CH_3 + Br^-$$

Usually two routes are possible in the Williamson ether synthesis. The rules of S_N2 reactions must be followed in that tertiary alkyl halides cannot be used.

Thus of the two choices possible for the preparation of tert-butyl methyl ether, the route that uses methyl bromide is acceptable, but the use of tert-butyl bromide will only give E2 elimination. MTBE is an environmentally safe additive to gasoline.



S_N2

$$CH_3\overset{CH_2}{\underset{CH_3}{C}}\text{-}O^- + CH_3\text{-}Br \longrightarrow CH_3\overset{CH_3}{\underset{CH_3}{C}}\text{-}O\text{-}CH_3$$

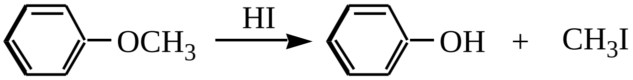
MTBE

E2

$$CH_3\overset{CH_3}{\underset{CH_3}{C}}\text{-}Br + CH_3\text{-}O^- \longrightarrow CH_3\overset{CH_2}{\overset{\|}{\underset{CH_3}{C}}} + CH_3\text{-}O\text{-}H$$

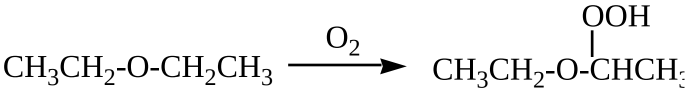
7.4d Reactions of Ethers

One of the main features of ethers is that they are relatively inert, and thus serve as excellent solvents. Hydriodic acid can be used to cleave the ether bond as shown.

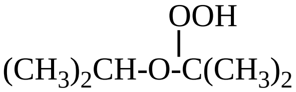


7.4e Formation of Hydroperoxides

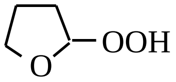
A major danger in handling ether solvents is the possibility that some hydroperoxide has formed in the solvent, and it causes the solvent to explode when handled. The reaction occurs between ethers and oxygen and is catalyzed by light. Diethyl ether, di-isopropyl ether and tetrahydrofuran are especially prone to the formation of hydroperoxides.



$$CH_3CH_2\text{-O-}CH_2CH_3 \xrightarrow{O_2} CH_3CH_2\text{-O-}\overset{OOH}{\overset{|}{C}}HCH$$



$$(CH_3)_2CH\text{-O-}\overset{OOH}{\overset{|}{C}}(CH_3)_2$$



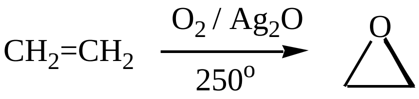
Not all hydroperoxides are undesired, and some are used as initiators in free radical reactions. Special control of their preparation is necessary..

7.4f Oxiranes (Epoxides)

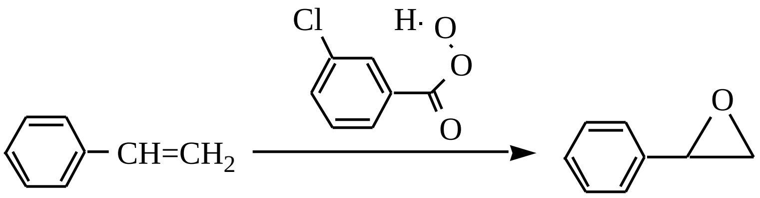
Ethers contained in a three-membered ring are called oxiranes by the IUPAC rules, but a common name for the system is epoxide. The oxirane system is highly strained and thus shows high reactivity. The reactions cause the ring to open and relieve the inherent strain.

Preparation of oxiranes

The simplest oxirane is also called ethylene oxide and is prepared by oxidation of ethylene with oxygen.



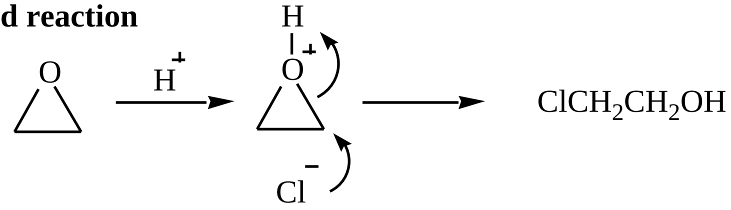
Peroxide reagents, such m-chloroperoxybenzoic acid, can be used to oxidize alkenes to oxiranes. Basic solution of ordinary hydrogen peroxide, H_2O_2, can also be used to prepare oxiranes from alkenes.



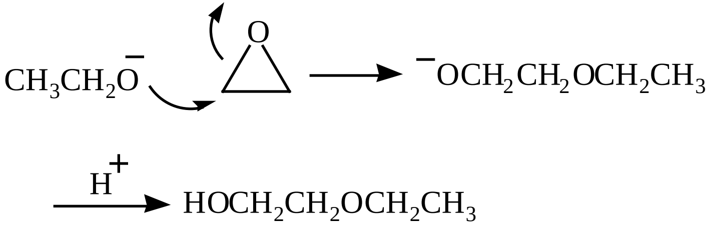
Reactions of epoxides

Both acids and bases cause the ring opening of the highly strained oxirane.

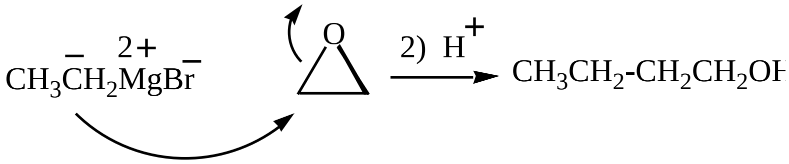
acid reaction



base reaction



Grignard reagents, and organolithium reagents, react with oxirane to give, after protonation, an alcohol that is two carbons longer than the starting Grignard reagent.



7.4g Thioethers (Sulfides)

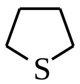
Sulfur analogs of ethers, known as thioethers or sulfides are much less known than the normal oxygen ether. But several important compounds in this family deserve mentioning. Most of the compounds have either a common name or a name derived from naming the substituents followed by the word sulfide.

$CH_3\text{-S-}CH_3$

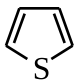
dimethyl sufide

Ph-S-Ph

diphenyl sulfide

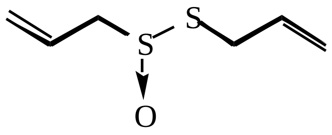


thiolane
tetrahydrothiophene

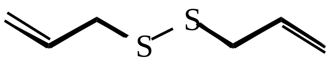


thiophene

Thioethers smell just as terrible as thiols, perhaps worse. In addition some thioethers in plants, such as garlic and onion, contribute to the taste. Garlic, which has several helpful health related properties including lowering of blood pressure, has two structures of similar structure. Allicin is a potent antibacterial agent while allylin gives the characteristic bad odor of garlic.



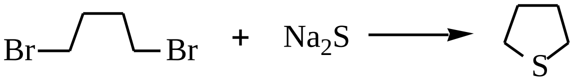
Allicin
An antibacterial found in garlic



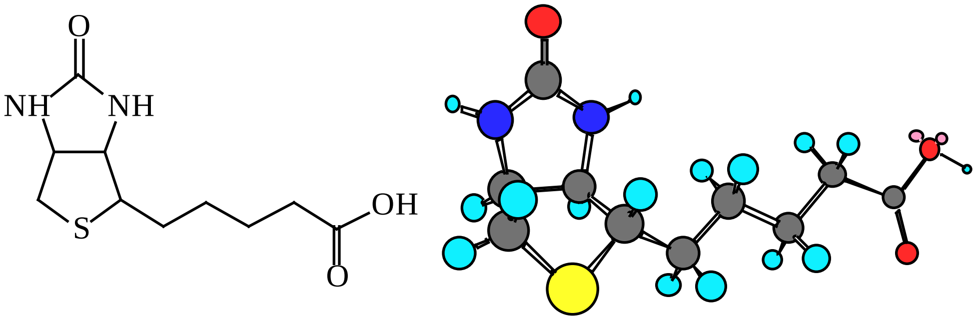
Allylin
Odor of garlic

Thioethers are prepared by a procedure related to the Williamson ether synthesis. Sulfide anions, which are excellent nucleophiles, react in S_N2 displacement of halides in alkyl halides.

$$CH_3\bar{S} + ICH_2CH_3 \longrightarrow CH_3SCH_2CH_3$$

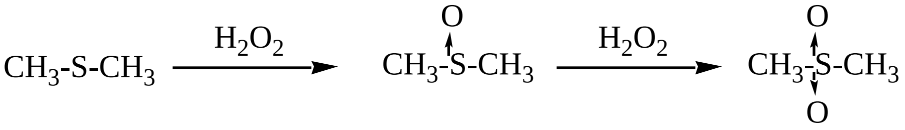


Biotin (Vitamin H) contains a cyclic sulfide ring. Biotin is a coenzyme (that means it works in conjunction with an enzyme) involved in the transfer of CO_2 in biological reactions.



Biotin
Vitamin H
(egg yolk, kidney)

A common reaction of thioethers is their oxidation to sulfoxides and sulfones. Hydrogen peroxide, and other peroxide reagents, can oxide the sulfur atom once or twice depending on the amount of peroxide used.



$$CH_3\text{-}S\text{-}CH_3 \xrightarrow{H_2O_2} CH_3\text{-}\overset{\overset{O}{\uparrow}}{S}\text{-}CH_3 \xrightarrow{H_2O_2} CH_3\text{-}\underset{\underset{O}{\downarrow}}{\overset{\overset{O}{\uparrow}}{S}}\text{-}CH_3$$

dimethyl sulfoxide dimethyl sulfone

Dimethyl sulfoxide (DMSO) is well known in organic chemistry for its ability to dissolve many substances including some salts. In medicine, dimethyl sulfoxide is used to treat arthritis as it is adsorbed through the skin. Thus rubbing affected areas with dilute DMSO solutions gives relief. Some drugs may be administered by dissolving in DMSO and absorbing through the skin. DMSO has a faint taste of oysters.

7.5 Summary

An aliphatic organic compound containing an OH function is termed an alcohol. *Alcohols* are slightly acidic and are capable of forming strong hydrogen bonds giving rise to increased boiling points. *Alcohols are classified as primary, secondary and tertiary.*

Alcohols are prepared by regio- and stereoselective hydration of alkenes by *oxymercuration-demercuration, hydroboration-oxidation,* and by direct hydroxylation. *Grignard reactions with carbonyl compounds give alcohols.* Nucleophilic substitution of primary alkyl halides with hydroxide ion produces hydroxylic compounds. *Reduction* of carboxylic acids, aldehydes, esters, aldehydes and ketones also yields alcohols. Mild *oxidation* of alkenes with permanganate or peroxide produces vicinal diols.

Alcohols, as mild acids, react with alkali metal to give alkoxide that are useful bases and nucleophiles. Alcohols react with hydrogen halides to produce alkyl halides in reactions that involve S_N2 mechanism for primary alcohols, and S_N1 and E1 mechanisms for secondary and tertiary alcohols. Alkyl halides are also prepared from thionyl chloride and phosphorus halide reagents. Alcohols are *dehydrated* with sulfuric acid in reaction processes that involve carbocations. *Alcohols are oxidized with a wide variety or reagents to give acid, aldehydes and ketones.*

Thiols are related to alcohols by having the *sulfhydryl function, SH,* in place of the hydroxyl function, OH. But thiols are very different from alcohols in their properties, most notably possessing foul odors. *Conversion of thiols to disulfides is an important biological process in protein structure.*

Aromatic alcohols, known as *phenols,* bear little resemblance to aliphatic alcohols. Phenols are solids, highly polar, highly acidic, *and do not have reactions that break the C-O bond*. The aromatic ring of phenols is very reactive to electrophilic aromatic substitution. *Oxidation-reduction processes that involve phenols and quinones are important biological transformations.*

Ethers are relatively inert , low boiling compounds useful as solvents for organic reactions. The *Williamson ether synthesis* is often used in their preparation. Cyclic, three-membered ethers, known as *oxiranes or epoxides* are reactive species useful in several ring opening reactions with nucleophiles.

7.6 Problem Set

7.1 Provide IUPAC names for the structures a-d, and provide structures for e - h.

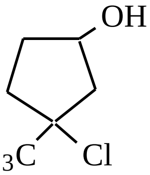
a) 4-methyl-2-pentanol

b) 4,4,4-trifluoro-2-butanol

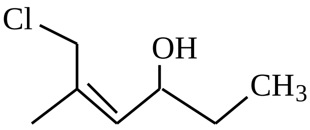
c) trans-4-tert-butylcyclohexanol

d) trans-1,2-cyclohexandiol

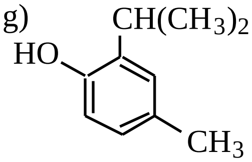
e)



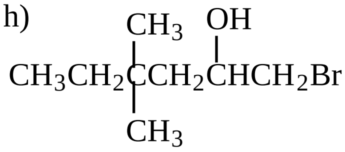
f)



g)



h)



$CH_3CH_2\overset{CH_3}{\underset{CH_3}{C}}CH_2\overset{OH}{C}HCH_2Br$

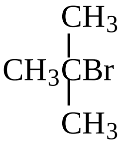
7.2 Classify the alcohols in problem 7.1 as primary, secondary, tertiary, allylic, phenolic.

7.3 Show the product for the reactions of a - f with hydroxide.

a) $CH_3CH_2CH_2OH$

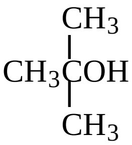
b) $CH_3CH_2CH_2Br$

c)



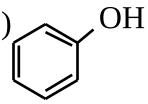
$CH_3\overset{CH_3}{\underset{CH_3}{C}}Br$

d)

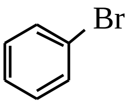


$CH_3\overset{CH_3}{\underset{CH_3}{C}}OH$

e)

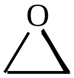


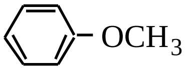
f)



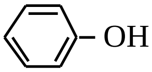
7.4 Give the products for the reactions of each substrate below with PhMgBr / H_3O^+, meta-chloroperoxybenzoic acid (MCPBA), and HI.

$CH_3CH_2CH_2OH$





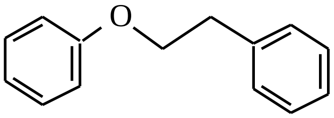
$CH_3CH{=}CHCH_3$



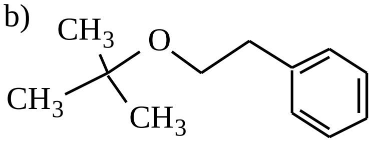
7.5 a) Reaction of methane thiol with iodine gives a new compound, $C_2H_6S_2$, that is a hamster sex attractant. What is the structure? b) Allylin, sect 7.4g, reacts with $NaBH_4$, to give a thiol. What is the thiol?

7.6 Use an alkoxide and an alkyl halide to prepare the ethers below.

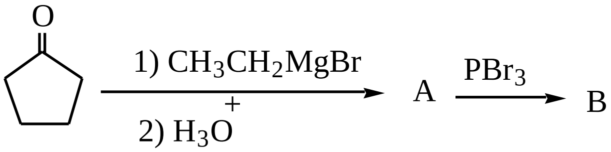
a)

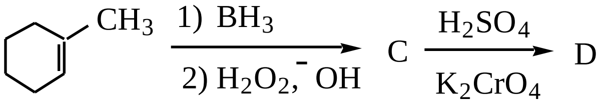


b)



7.7 Provide structures for the reaction products A - H below.





$$CH_3CH_2CH_2C{=}O \xrightarrow[\text{2)HBr}]{\text{1) NaBH}_4} E \xrightarrow{^{-}\text{O-tert-Bu}} F$$