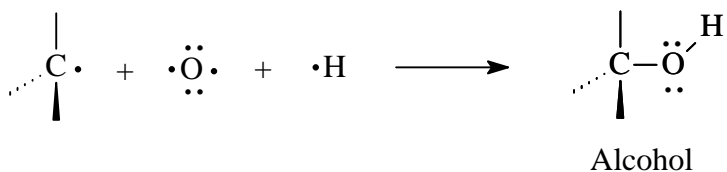
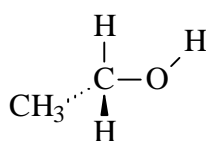


**ALCOHOL STRUCTURE AND CHEMISTRY***Jack DeRuiter***I. Introduction**

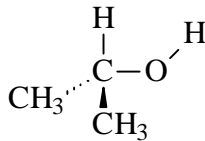
Alcohols are hydrocarbon derivatives of water. Oxygen has six valence electrons and therefore requires two electrons or bonds to complete its octet. Based on this valence and bonding order, oxygen forms two bonds in its neutral state and maintains two pairs of non-bonded electrons (NBEs):



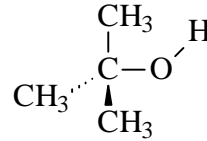
Alcohols are sub-classified as primary, secondary or tertiary based on the degree of hydrocarbon substitution on the carbon bound to oxygen as shown below:



Primary Alcohol

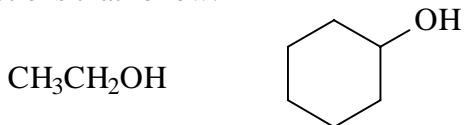
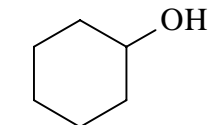


Secondary Alcohol

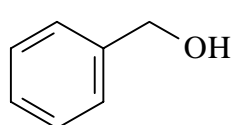
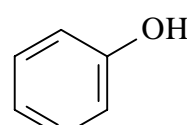


Tertiary Alcohol

Alcohols also can be sub-classified as “aliphatic” or “cycloaliphatic” (true alcohols), or as “aromatic” based on the nature of the carbon atom attached to the oxygen atom. Aromatic alcohols are more commonly referred to as phenols. “True alcohols” have alkyl, cycloalkyl or aralkyl substituents bonded to the alcohol carbon atom. In phenol the carbon atom linked to oxygen is part of an aromatic ring system. While qualitatively similar in their physico-chemical properties, phenols differ from alcohols in the nature of their O-H dipole and reactivity as is discussed in the sections that follow:

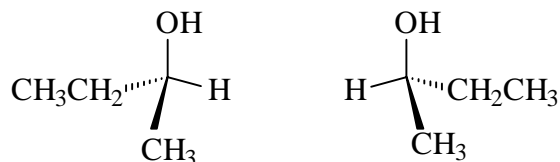
Primary Alcohol  
(Ethanol)

Cyclic Alcohol

Primary Alcohol  
(Benzyl Alcohol)

Phenol

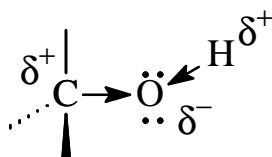
The alcohol functionality may be chiral if the carbon bound to the hydroxyl group bears four different substituents (one being the OH group) as shown in the example below:



The alcohol and phenol moieties are common functional groups found in drug compounds. The primary physicochemical property of importance in the drug chemistry of the alcohols is the O-H dipole which can impart water solubility by donating and accepting hydrogen bonds, and serves as an electronegative-electropositive center for binding to drug targets including enzymes and receptors. In addition to its dipolar character, alcohols and phenols also are capable of functioning as nucleophiles and participating in displacement reactions with electrophilic compounds. These properties are discussed in detail in the following sections.

## II. Solubility and Other Physicochemical Properties of Alcohols and Phenols

The presence of an electronegative oxygen atom between a carbon and hydrogen atom creates a permanent dipole in the alcohol and phenol structure. The negative inductive effect of the electronegative oxygen creates a partial negative charge on oxygen and partial positive charges on the carbon atom and hydrogen atom attached to oxygen. Due to the presence of this dipole, alcohols and phenols are considered to be relatively polar organic compounds:



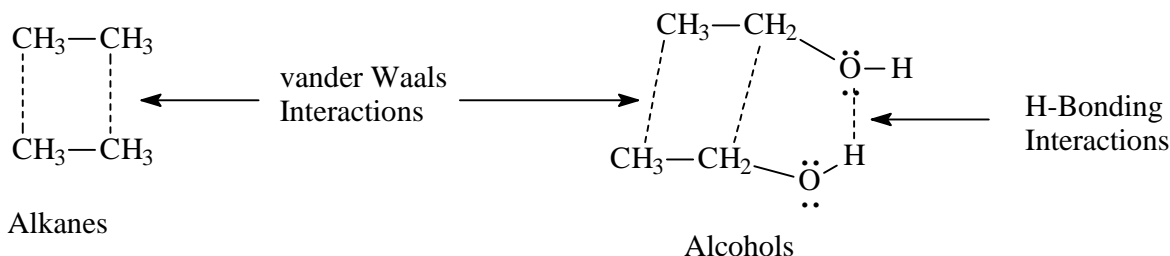
Because of the presence of a dipole, alcohols and phenols can participate in intermolecular hydrogen-bonding (H-bonding). The electronegative oxygen atoms of alcohols have two NBEs and thus can “accept” H-bonds compounds capable of donating a hydrogen. The hydrogen atom of alcohols are electropositive due to their attachment to an electronegative oxygen and thus they can “donate” a H-bond to electronegative acceptor atoms. Thus alcohols and phenols are regarded as H-bond acceptors and donors. The contribution of H-bonding toward the physicochemical properties of alcohols and phenols is illustrated by melting point, boiling point and solubility data as shown in the Table and discussed below.

**Boiling Points & Water Solubilities of Common Alcohols**

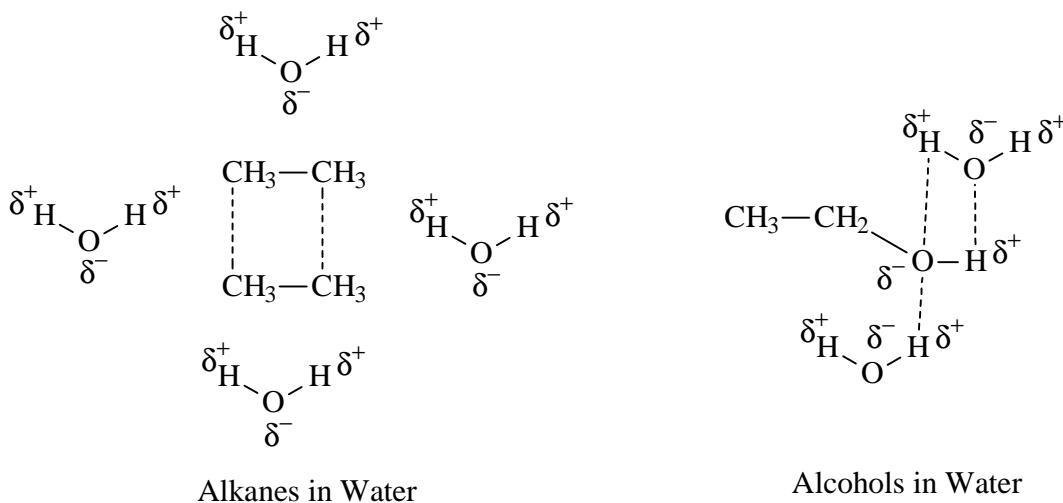
ALCOHOL	B.P.°C	SOLUBILITY (g/100g H <sub>2</sub> O)
CH <sub>3</sub> -OH (Methanol)	65.5	∞
CH <sub>3</sub> CH <sub>2</sub> -OH (Ethanol)	78.3	∞
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> -OH (n-Propanol)	97.0	∞
CH <sub>3</sub> -CHOH-CH <sub>3</sub> (i-Propanol)	82.4	∞
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -O H (1-Butanol)	117.2	7.9
CH <sub>3</sub> CH <sub>2</sub> -CHOH-CH <sub>3</sub> (2-Butanol)	99.5	12.5
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> -OH (1-Pentanol)	137.3	2.3

As a result of intermolecular H-bonding, alcohols have significantly higher boiling points than corresponding simple hydrocarbons. For example, simple hydrocarbons with fewer than five

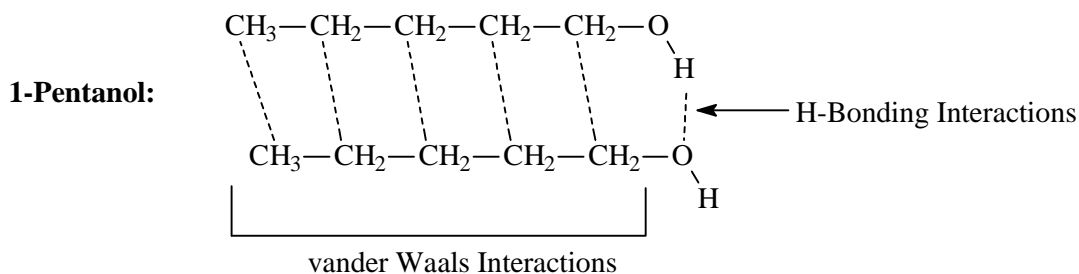
carbons are gases at normal temperatures and pressures. But even the simplest alcohol, methanol, is a liquid under normal conditions. This elevation in boiling point from simple hydrocarbons to alcohols is a result of the higher energy dipole-dipole H-bonding interactions that occur between alcohols molecules. Only relatively low energy vanderWaal interactions are possible between alkanes and like molecules, so the intermolecular forces holding these molecules together are relatively weak and easily overcome by thermal energy (low boiling point). Significantly greater energy is associated with dipolar interactions, thus the H-bonding interactions between alcohols results in a greater energy of interaction between these molecules, and therefore higher boiling points:



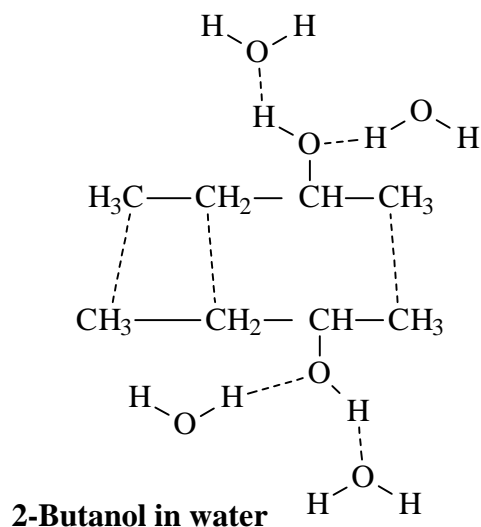
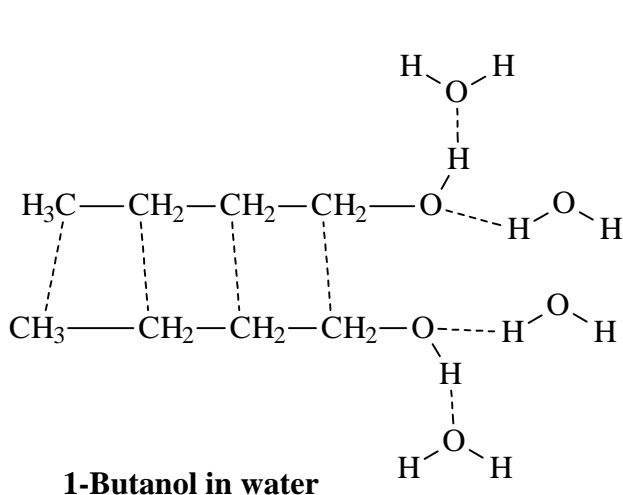
Intermolecular H-bonding also is a critical determinant of alcohol and phenol solubility. Recall that simple hydrocarbons (alkanes, alkenes, aromatics) are “water insoluble” because they contain only non-polar C-H functionality that cannot participate in efficient binding interactions with water, a dipolar substance. Alcohols exhibit higher solubility in water because they contain O-H dipoles that can interact with water dipoles as shown below:



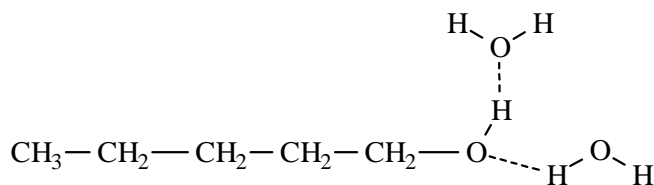
The relative solubility of alcohols is dependent on the size and structure of the hydrocarbon portion of the molecule. Alcohols of three or fewer carbons are infinitely miscible in water because the energy associated with the alcohol H-bonding with water (H-bond donation and accepting) is greater than the total energy of vander Waals interactions between the hydrocarbon portion of these alcohols. As the alcohol hydrocarbon structure increases, the energy of vanderWaal interactions between hydrocarbon portions becomes so great that it is difficult to overcome by the energy gained from H-bonding with water. Hence, alcohols such as 1-pentanol have only limited solubility in water (2 g/100 mL of water), and significantly larger alcohols are considered to be water insoluble:



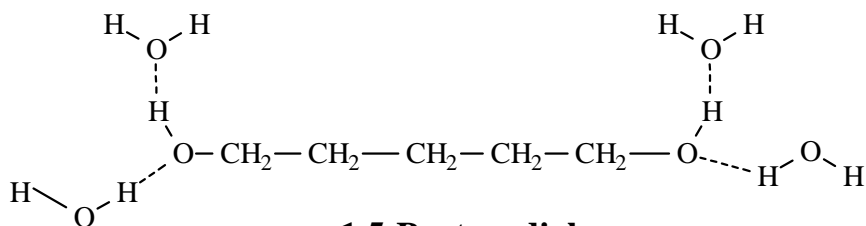
The overall structure of an alcohol's hydrocarbon functionality also effects relative solubility. For example, a hydroxyl group in the "interior" (i.e. center) of hydrocarbon structure (secondary and tertiary alcohols) has greater potential to enhance water solubility than a hydroxyl group at the end of a comparable hydrocarbon chain (primary alcohols). This is illustrated by the examples of 1-butanol and 2-butanol shown below. The water solubility of 2-butanol (7 g/100 mL) is nearly twice that of 1-butanol (12.5 g/100 mL). The presence of the OH group in the interior of the structure of 2-butanol serves to "break up" the non-polar hydrocarbon structure and reduce it's ability to bind efficiently to complimentary hydrocarbon functionality. In 1-butanol the OH group is positioned at the end of the chain, leaving the non-polar hydrocarbon functionality to interact optimally with complimentary hydrocarbon functionality in another molecule (of 1-butanol).



The degree of hydroxyl group substitution on a hydrocarbon structure effects solubility in a predictable way. For example, 1-pentanol has only limited water solubility (2 g/100 mL water). However, 1,5-dihydropentane (pentanediol) is very water soluble.



**1-Pentanol**



**1,5-Pentanediol**

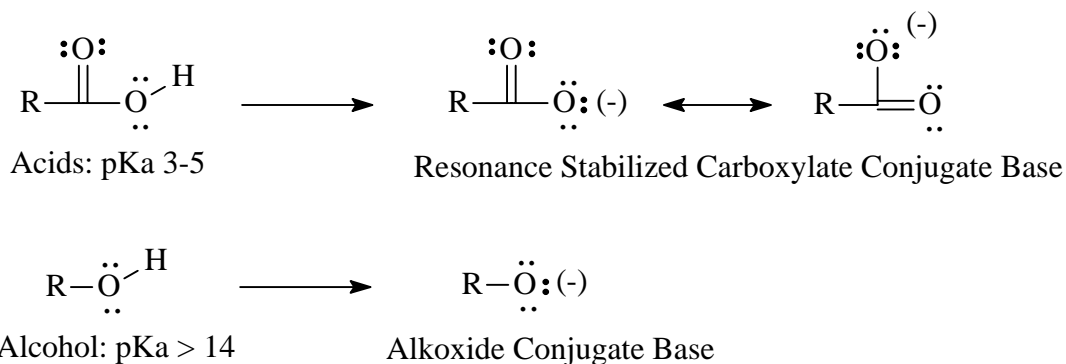
As in the case of the alcohols, the -OH function of phenols provides a dipole that significantly affects the physicochemical properties. The aromatic portion of phenols is relatively non-polar (lipophilic), thus phenols exhibit limited water solubility. Also, addition of lipophilic substituents to the aromatic ring of phenols further reduces water solubility. Yet phenols may be more water soluble than predicted or expected because they are weak acids and can ionize, particularly at higher pHs. Thus the water solubility of a phenol is pH dependent. The acidity of phenols is discussed further in the following section.

### III. Alcohol and Phenol Acid-Base Properties

Alcohols are considered to be relatively non-acidic and non-basic compounds, while most phenols are classified as very weak acids and non-bases. Structurally alcohols and phenols are similar to amines in that the heteroatom of the functionality (O for alcohols, N for amines) contains NBEs that can bond or coordinate with electropositive atoms such as proton. The nitrogen atom of amines has relatively low electronegativity, thus the NBEs of this atom can be “shared” with electropositive atoms such as protons and electrophilic carbon atoms. Thus the presence of NBEs on an atom of relatively low electronegativity (nitrogen) renders amines basic and nucleophilic (see Amine Tutorial).

Alcohols and phenols are significantly less basic and nucleophilic than amines, in spite of the presence of two pairs of NBEs. This is because oxygen is significantly less more electronegative than nitrogen and therefore less likely to share its NBEs. Thus alcohols do not protonate unless in the presence of extremely strong acids, and do not form stable, isolable salts.

Alcohols are similar to carboxylic acids in that they contain an OH group. In carboxylic acids the proton of the O-H functionality is relatively acidic. This is primarily due to the fact that the charge formed in the conjugate base (carboxylate anion) is stabilized over the carboxyl function by resonance delocalization (anion formed on an oxygen atom adjacent to an  $sp^2$  hybridized atom linked to another electronegative atom). In alcohols ionization of the OH group yields an alkoxide (anion) as the conjugate base. In the conjugate base of alcohol, oxygen alone bears the negative charge because resonance delocalization is not possible (the carbon adjacent to the alkoxide oxygen is  $sp^3$  hybridized). Since this base is not stabilized to the same degree as the conjugate base formed from carboxylic acids, it is less likely to form. Thus alcohols are less acidic than carboxylic acids. These properties are demonstrated in the following figure and summarized in the *Resonance and*



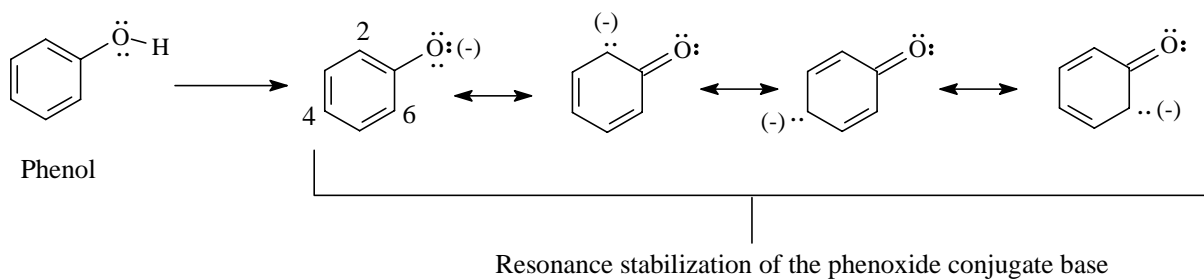
*Induction* Chapter:

It should be pointed out that, although alcohols are considered to be non-acidic and non-basic under physiologic conditions (there is no ionization between pH 0-14), they can exhibit either acidic and basic properties under extreme conditions (in the presence of very strong acids or bases) and if the hydrocarbon portion of the alcohol stabilizes the charged intermediates formed. These conditions typically chemical reactions carried out in the laboratory and are described in more detail in the following sections.

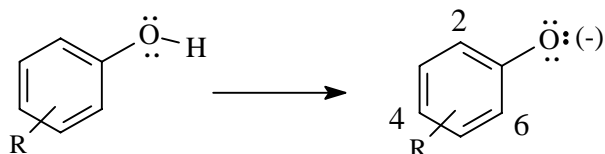
As mentioned earlier in this section, phenols are weak acids. Attachment of a phenyl ring to an alcohol functionality significantly increase the acidity of the alcohol to the point where ionization may occur in the pH range 0-14. Phenols are acidic functional groups while alcohols are “not” primarily because of two electronic effects operating in phenols:

- **Inductive effect:** the aromatic ring attached to the -OH of phenols exerts a electron withdrawing effect further polarizing this function and promoting its acidity. Conversely, alcohols contain an electron releasing nonaromatic hydrocarbon attached to the -OH function which promotes a lesser dipole in the group and a lower tendency to ionize.
- **Resonance effect:** formation of the conjugate base (phenoxide) of a phenol is promoted by aromatic ring associated resonance stabilization of the resultant anion. The stability of the conjugate based imparted by resonance enhances the likelihood of ionization relative to a simple alcohol and thereby increases acidity relative to alcohols. The resonance stabilization of the charge generated in the phenoxide conjugate base is shown below. Note that the positions of highest charge density in these resonance forms include the oxygen atom and carbon atoms 2

("ortho"), 4 ("para") and 6 ("ortho") of the aromatic ring. Further discussion of resonance effects is provided in the *Resonance and Induction* Tutorial.

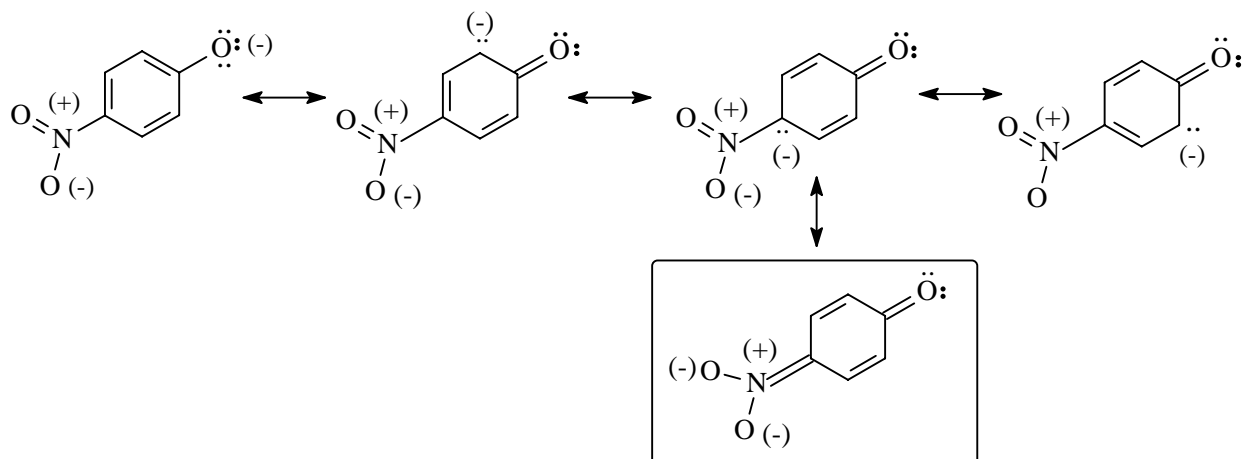


Based on this resonance stabilization phenomenon described above, it is important to consider how substituents present on the phenol ring may influence acidity. Listed below are the pKa values for a number of phenols. Note how the presence of additional substituents on the ring influences acidity (pKa). Substituents capable of withdrawing electron density by resonance (-R groups such as NO<sub>2</sub>, COOH, COOR, CONH<sub>2</sub>, CONHR, CONR<sub>2</sub>, NR<sub>3</sub>, CN, halogens, etc.) help to further stabilize the anion formed upon ionization and therefore increase the acidity (lower the pKa) of phenols. This effect is most prevalent when these groups are positioned in conjugation with the site of ionization; at the ortho (2-) and para (4-) to the phenolic hydroxyl. Conversely, electron releasing substituents (+R groups such as OR, NH<sub>2</sub>, -NHCOR, OH, R, SH) destabilize the anion base formed upon ionization and thereby decrease the acidity (raise the pKa) of the phenol. These effects are illustrated by the pKas in the following Table and with the nitrophenol example below:



R Group	pKa
H	9.96
3-CH <sub>3</sub>	10.01
4-CH <sub>3</sub>	10.17
3-NO <sub>2</sub>	8.3
4-NO <sub>2</sub>	7.16

Note that the phenol with the strongest electron withdrawing group by resonance in conjugation with the site of ionization (O<sup>-</sup>) has the lowest pKa (is most acidic). This is due to the additional stability imparted by the greater delocalization of negative charge into the nitro group functionality:



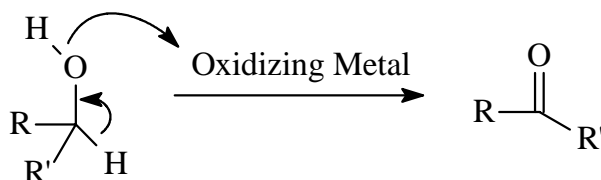
Additional resonance stabilization of phenoxide charge imparted a by 4-nitrosubstituent

To understand the role of electronic effects in the acidity of various organic compounds more broadly, it is of value to compare the pKas of “typical” alcohols, phenols and carboxylic acids. Generally carboxylic acids are more acidic (pKas 3-5) than phenols (pKas 7-10) which are more acidic than alcohols (pKas >14). Based on the resonance effects discussed above, it is not surprising that phenols are more acidic than alcohols. The difference in relative acidities of phenols and carboxylic acids is, perhaps, less obvious. In carboxylic acids the negative charge formed upon ionization (in the conjugate base) is delocalized over three atoms while in phenols the negative charge is delocalized over seven atoms. Based on the number of atoms over which charge is distributed or the degree of delocalization, one might expect phenols to be more acidic than carboxylic acids! But this is not the case. In this case the electronic nature of atoms over which the charge of the conjugate base is delocalized is more important than the extent of delocalization. In the case of the carboxylic acid the resultant charge is delocalized over two electronegative oxygen atoms and one electroneutral carbon atom. In the case of phenols, the charge of the conjugate base is delocalized over only one electronegative oxygen atom and six electroneutral carbon atoms.

#### IV. Reactions of Alcohols and Phenols

##### A. Oxidations

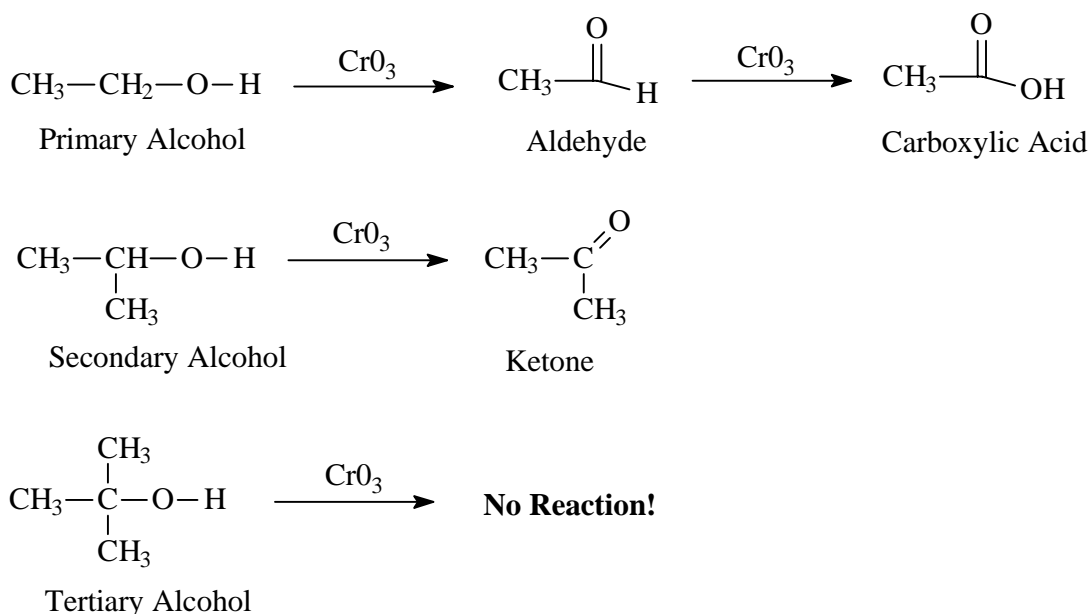
Alcohols with at least one hydrogen atom on the alcohol carbon atom (primary and secondary alcohols) may undergo oxidation under a variety of conditions including metabolism. The mechanistic details of these reactions are beyond the scope of this tutorial, but they typically involve the transfer of an electron pair from the alcohol oxygen to a metal of the oxidizing agent with loss of a proton from the alcohol carbon to form the corresponding carbonyl oxidation



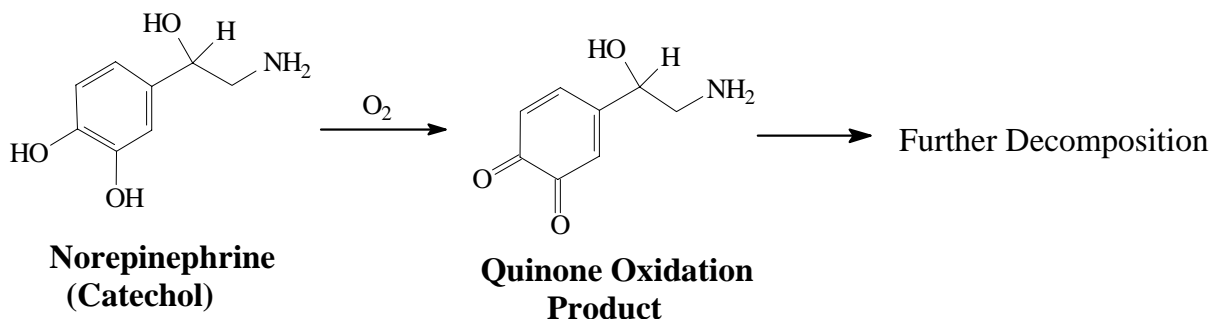


product:

Thus in the presence of simple oxidizing agents such as permanganate ( $\text{KMnO}_4$ ) or chromium trioxide ( $\text{CrO}_3$ ), primary alcohols are oxidized initially to their corresponding aldehydes (which still have one hydrogen atom attached to the carbonyl) then on to the corresponding carboxylic acids. It should be noted that more specialized chemical reagents are available to stop the oxidation of primary alcohols at the aldehyde stage. Secondary alcohols are oxidized to ketones and the oxidation typically stops at this stage since the carbonyl product no longer contains a hydrogen atom. Tertiary alcohols usually are resistant to oxidation since they do not contain a hydrogen atom attached to alcohol carbon that can be removed in the process. These reactions are illustrated in the figure below. It should also be noted that "biological" (metabolic) oxidations proceed in the same manner, so that primary alcohol drugs are metabolized ultimately to carboxylic acid metabolites by oxidative enzymes in the human tissue systems:

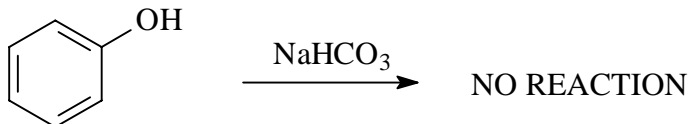
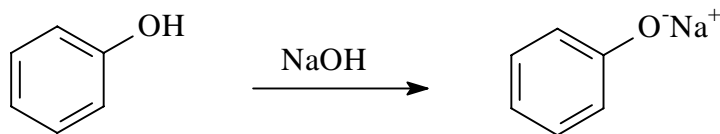
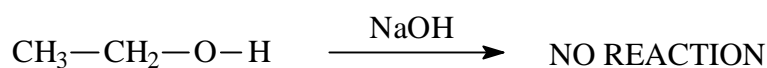


Phenol derivatives also are capable of undergoing oxidation, particularly "activated phenols" such as catechols. The catechol or 1,2-dihydroxy benzene group is present in a number of drugs, particularly in adrenergic drugs (derivatives of norepinephrine). This functionality readily oxidizes to the corresponding "quinone" as shown below for norepinephrine, and the quinone can undergo further reactions. To prevent this oxidative decomposition reaction from occurring, a number of catechol-containing drugs are formulated with antioxidants:



B. Ionization and Salt Formation

Earlier in this tutorial it was noted that alcohols are considered to be relatively non-acidic and non-basic compounds, while most phenols are classified as very weak acids and non-bases. Thus neither alcohols nor phenols are significantly ionized at physiological pHs (5-8). Also neither alcohols nor phenols yield stable salts when treated with acids. Phenols, however, because of resonance stabilization (discussed above) can be converted to phenoxide salt forms when treated with a sufficiently strong base. For example, treatment of phenol with NaOH will yield the corresponding sodium salt as shown below. Weaker bases, such as sodium bicarbonate (NaHCO<sub>3</sub>) are not sufficiently strong to ionize a typical phenol. Sodium salt forms of phenol are significantly more water soluble than the parent phenol as a result of their ability to participate in ion-dipole



bonding interactions with water.

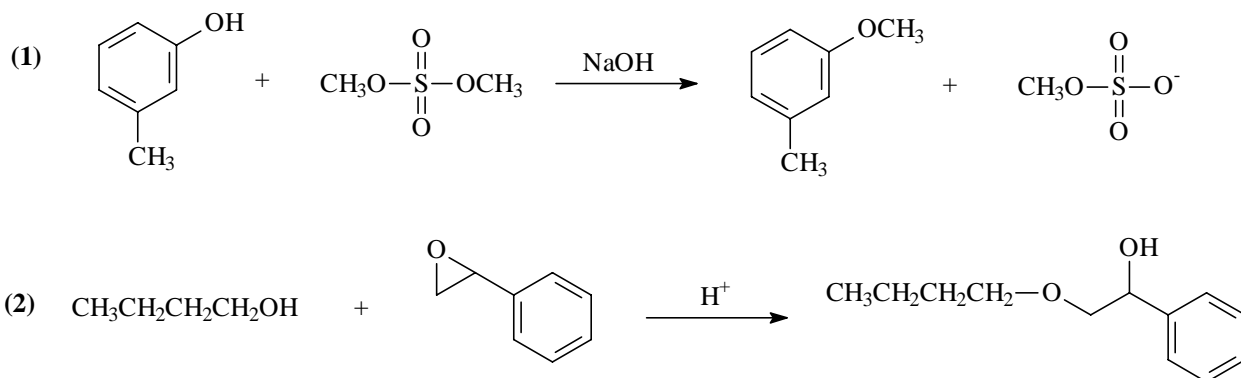
C. Nucleophilic Displacements

As was noted earlier in this tutorial, alcohols are less nucleophilic than functional groups such as amines, in spite of the presence of two pairs of NBEs. This lower nucleophilicity is a result of the electronegative nature of oxygen which reduces its ability to share its NBEs in displacement reactions relative to less electronegative (nitrogen) and more polarizable (sulfur) atoms. Furthermore, phenols typically are less nucleophilic than alcohols because their oxygen atoms are in conjugation with an aromatic ring which may withdraw electron density from the oxygen atom by resonance delocalization. However, even though their nucleophilicity is reduced relative to other functional groups, alcohols and phenols are still capable of participating in displacement reactions under the appropriate conditions.

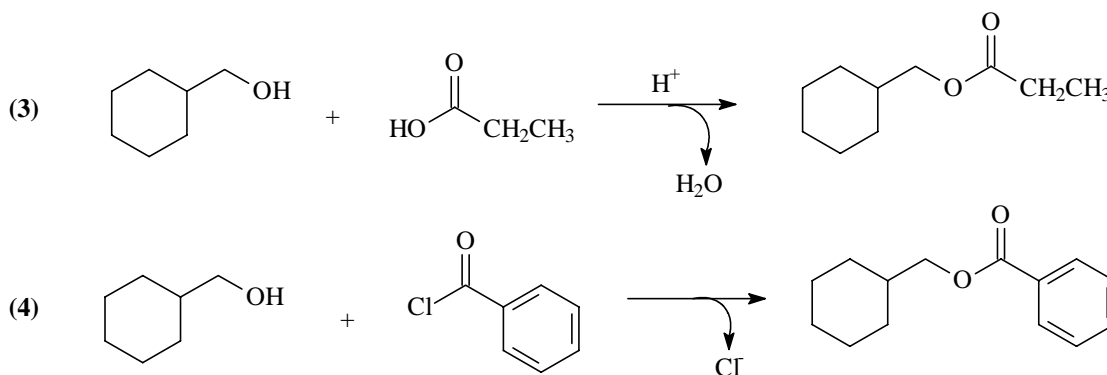
Below are several examples of typical displacement reactions involving alcohols as nucleophiles. The relative ability of an alcohol or phenol to function as a nucleophile in a displacement reaction is dependent on a number of electronic and steric factors, similar to those discussed for amines in the

Amine Tutorial. The reader should refer to that tutorial for more details on displacement reactions in general.

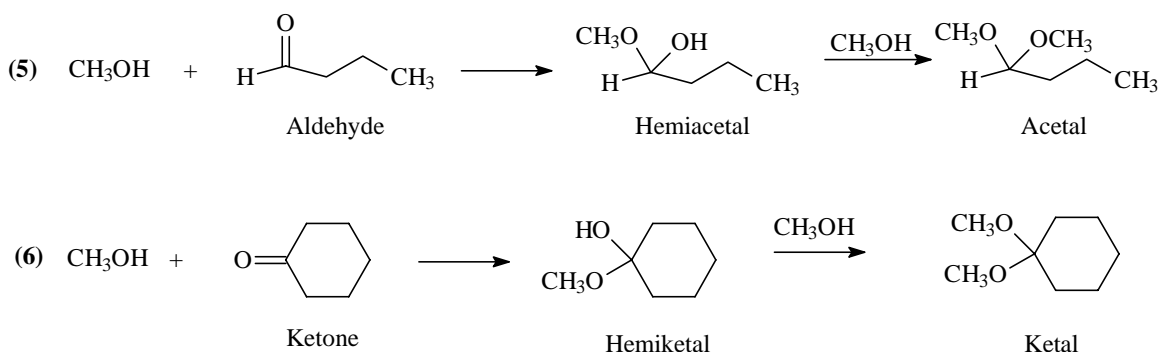
The first two examples shown below are simple displacement reactions, the first (1) involving a phenol and an electrophilic methylating agent, and the second (2) involving a primary alcohol and an epoxide. In the first case NaOH is added as a strong base to ionize the phenol and thereby enhance its nucleophilicity - the  $O^-$  base form is more electron rich than the parent phenolic OH. In the second reaction the alcohol is simply opening an oxirane (epoxide) at one of its electrophilic C-O carbons.



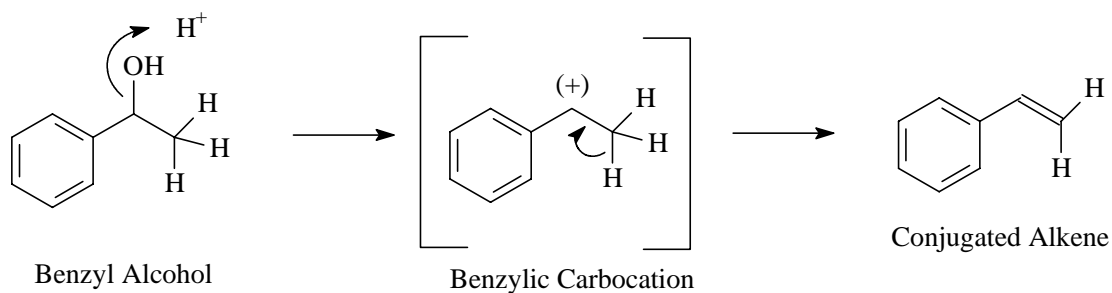
Reactions (3) and (4) are examples of "esterification" reactions which are very important in drug chemistry. In these examples the alcohols are functioning as a nucleophiles and a carboxylic acid (3) or acyl halide (4) is the electrophile. The esterification with the carboxylic acid in reaction (3) is catalyzed by acid to enhance the reactivity of the acid carbonyl and promote elimination to yield the final product. Yet this reaction may take days to complete. Acyl halides are very electrophilic and therefore reactive and when treated with alcohols they rapidly form esters (more rapidly than reaction (3)).



Alcohols and phenols can also react with carbonyl compounds such as aldehyde and ketones to form hemiacetals and ketals, and ketals and acetals as shown in reactions (5) and (6). These reactions are discussed in more detail in the Aldehyde and Ketone Tutorial.

D. Eliminations and Related Reactions:

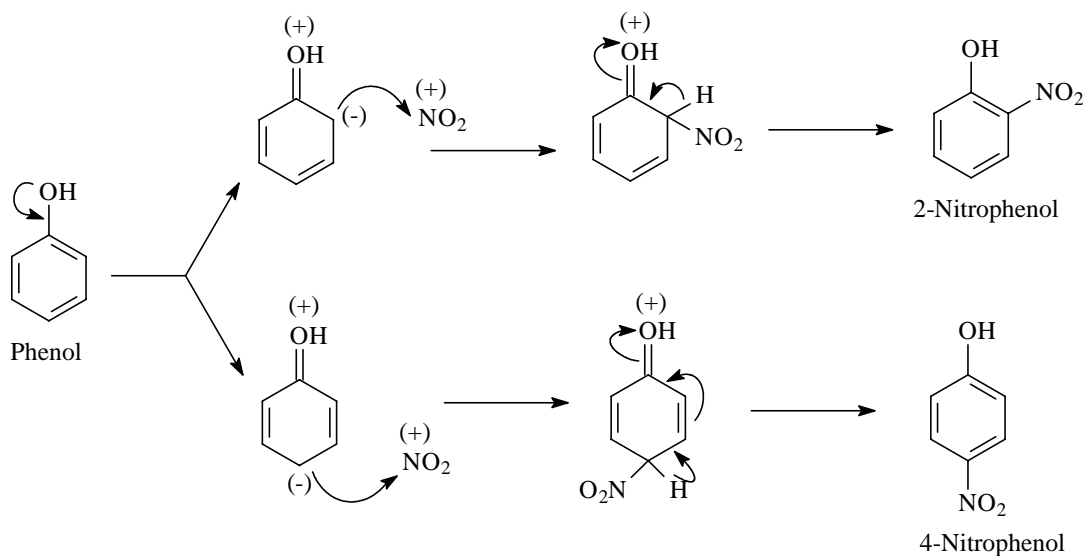
Because of the presence of an electronegative oxygen functionality, alcohols may also undergo "elimination" reactions under the appropriate chemical or metabolic conditions. For example, benzyl alcohols can undergo elimination reactions, particularly in acid, because the intermediate carbocation formed in the reaction can be stabilized by resonance contributions from the conjugated ring, AND the resulting product is a conjugated alkene: a C=C in conjugation with the aromatic ring. The ability of benzylic alcohols to ionize generally accounts for the greater reactivity of these compounds versus simple aliphatic alcohols. Note that for elimination reactions to occur with alcohols the carbon adjacent to the alcohol carbon must have at least one hydrogen atom to be abstracted:

E. Electrophilic Aromatic Substitution

A more complete discussion of electrophilic aromatic substitution reactions can be found in any organic chemistry textbook. Reactions of this type can simply be described as chemical processes whereby an electrophile is added to an electron rich aromatic ring with the loss of hydrogen (as a proton) at the position of electrophile attachment. Phenols are by definition electron rich aromatic systems and thereby can undergo such reactions. Consider the reaction of phenol with an electrophilic "nitronium ion". This reaction proceeds by the mechanism shown below, with the electron donating OH group contributing electron density to facilitate the reaction. Since electron donation by OH is greatest at the ring positions in direct conjugation with the OH (the 2-, 4- and 6-

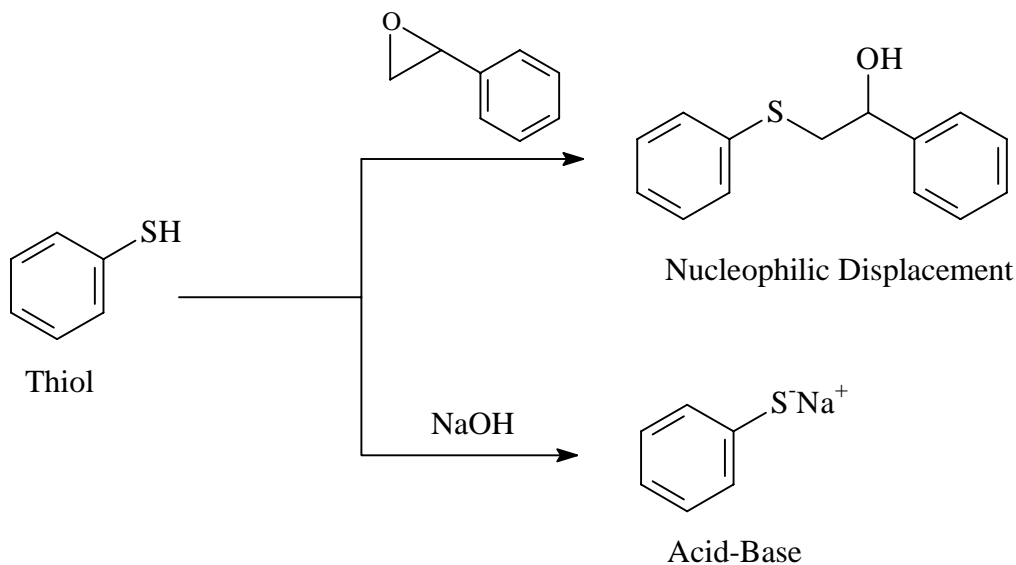
## Principles of Drug Action 1, Spring 2005, Alcohols

positions), these atoms are most likely to be substituted. In this example the phenol is "symmetrical", so substitution at position 2- yields the same product as substitution at position 6. Because there are multiple electron rich ring carbons, several substitution products may be possible, including the 2-nitro and 4-nitro isomers in the case of phenol:



## V. Thiols

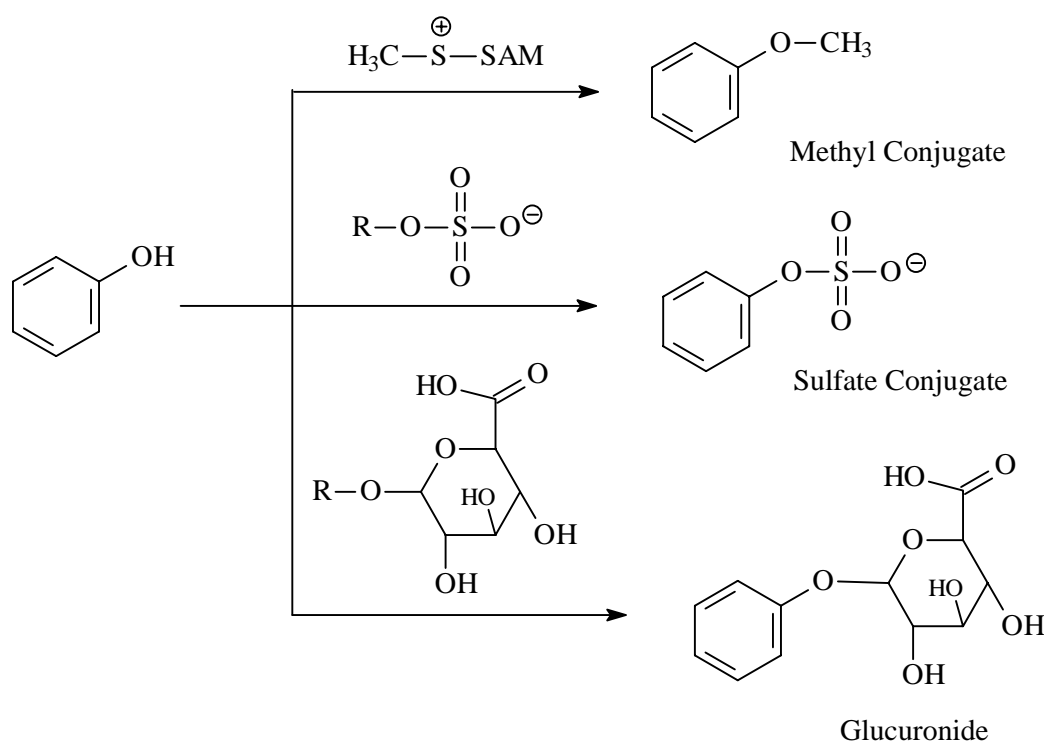
Thiols are derivatives or “isosteres” of alcohols where the hydroxyl oxygen atom has been replaced with a sulfur atom. Note that oxygen and sulfur are in the same family of the periodic table and thus have the same valence shell electronic configuration (six electrons in the valence shell). Thus oxygen in alcohols and sulfur in thiols display the same bonding order and similar chemical reactivities. However, sulfur is a larger atom (larger nucleus and valence electrons further from the nucleus) and this results in different relative reactivity with respect to oxygen. For example, since sulfur’s valence electrons are further from the nucleus and therefore less tightly held, the sulfur atom of thiols is more nucleophilic than the oxygen atom of alcohols. Also, because of the larger, more distant valence shell of sulfur, thiols are more acidic and ionize more readily than alcohols:



## VI. Alcohol and Phenol Metabolism

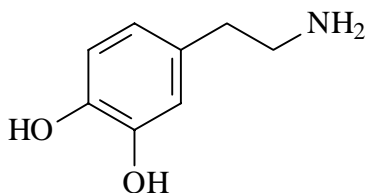
As discussed and shown in the “Reactions” section of this chapter, alcohols are metabolized by oxidation; primary alcohols are oxidized to aldehydes which may be further oxidized acids, secondary alcohols are oxidized to ketones, and tertiary alcohols are not capable of oxidation under normal conditions.

Phenols may also be metabolized by oxidation to yield catechols. Most commonly phenols are metabolized by “conjugation” reactions involving methylation, sulfonation or glucuronidation. These reactions are catalyzed by specific enzymes and take advantage of the nucleophilicity of phenols to react with an electrophilic conjugating species such as SAM (with an electrophilic methyl group) or activated glucuronic acid or sulfate:

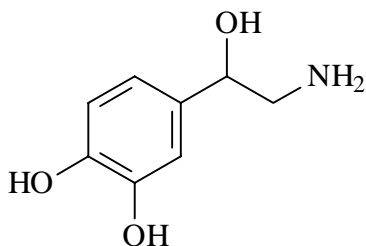


## VII. Hydroxyl Groups as Substituents

To understand the potential contributions of an hydroxyl substituent or functional group to the overall biological activity profile of a drug it is necessary to understand the physico-chemical and reactivity profiles of alcohols as described in the previous sections. Consider the example of Compounds A and B below. In this example, Compound B (the neurotransmitter and drug norepinephrine) differs structurally from Compound A (the neurotransmitter and drug dopamine) only in the presence of an additional hydroxyl substituent:



**A: Dopamine**



**B: Norepinephrine**

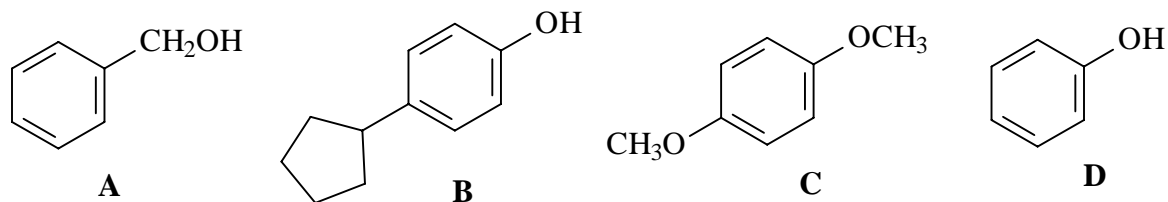
As a result of this structural difference, the physicochemical properties of Compound B differ significantly from those of Compound A including:

- Compound B is somewhat more polar (hydrophilic) than Compound A.
- The additional hydroxyl group present in compound B makes this compound a ligand for adrenergic receptors (alpha and beta-receptors). Compound A lacking the hydroxyl group is a preferential ligand (agonist) for dopamine receptors.
- The hydroxyl substituent present in Compound B creates another site of reactivity in this compound toward electrophiles.
- The hydroxyl substituent present in Compound B makes this carbon chiral so that R and S-enantiomers are possible. These enantiomers would have similar physicochemical properties relative to each other in achiral environments, but not a chiral environments such as adrenergic receptors. No site of chirality exists in Compound A.

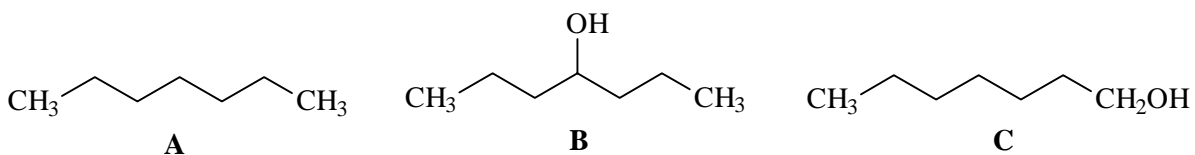


**VIII. Problems**

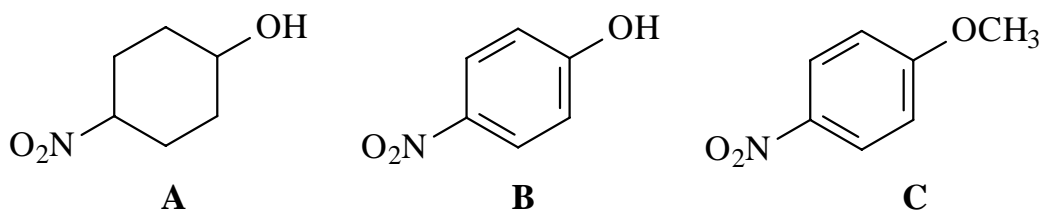
1. Which compound shown below is most acidic and why?



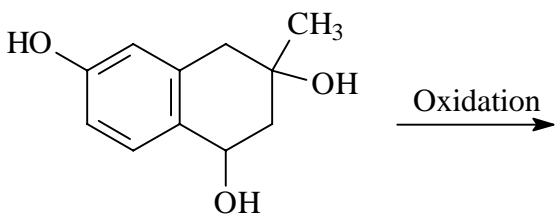
2. Rank each series of compounds shown below in terms of relative water solubility (hydrophilicity at pH 7. (1 = highest):



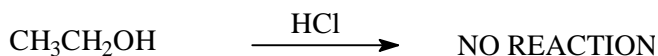
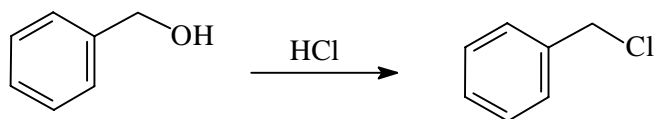
3. Rank each series of compounds shown below in terms of relative water solubility (hydrophilicity at pH 7. (1 = highest):



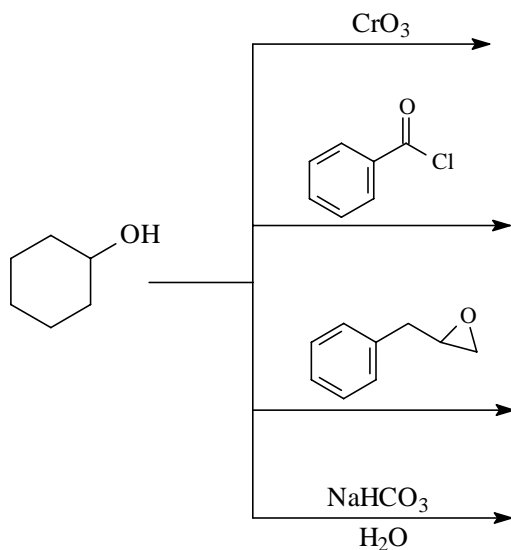
4. Which alcohol group is susceptible to oxidation?



5. Explain the difference in reactivity between the two alcohols shown below:

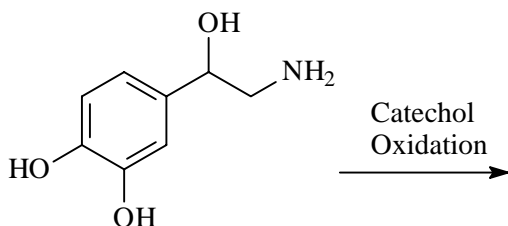


6. Show the reaction of cyclohexanol with the following reagents. If no reaction occurs, write

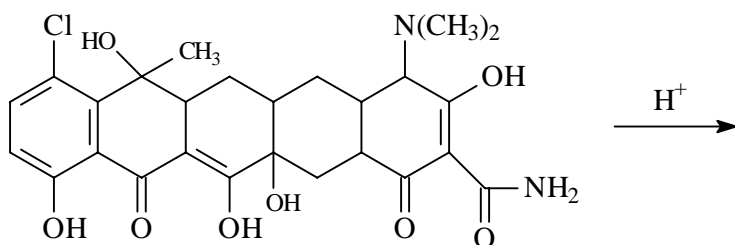


"NR":

7. Aqueous solutions of norepinephrine must be formulated with antioxidants to protect the drug from degradation by catechol oxidation. Show the catechol oxidation product of norepinephrine.



8. Tetracycline antibiotics may undergo acid-catalyzed elimination reaction reactions in the upper GI tract. Show the structure of the product that would form from such an elimination reaction with the following tetracycline.



*Tetracycline*