ETHERS AND THIOETHERS

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I. Introduction

Ethers are hydrocarbon derivatives containing a carbon-oxygen-carbon (C-O-C) fragment. Recall that carbon has a valence of four and thus requires four electrons or bonds to achieve an octet in its neutral state. Oxygen has a valence of six and thus requires two electrons or bonds to achieve an octet in its neutral state. In ethers there is a single oxygen atom bound to two carbons; in this bonding arrangement oxygen maintains two pairs of non-bonded electrons (NBEs) as is typical for oxygen in the neutral (uncharged) state:
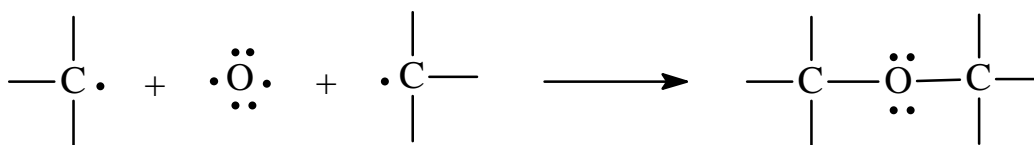
Ethers can be considered to structural analogues of alcohol in which the hydroxyl hydrogen has been replaced with a second hydrocarbon substituent. This structural difference results in significantly different properties. Ethers also are structurally related to amines which are hydrocarbons containing at least one C-N. However, because of the electronegativity difference between oxygen and nitrogen, ethers and amines have very different physico-chemical properties and reactivity profiles, as discussed below.

| Ether | Alcohol | Amine |
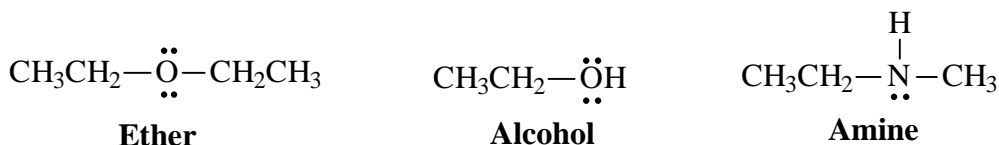
Ethers can be classified as aliphatic saturated or unsaturated, cycloaliphatic, aromatic, etc. as shown below. Thioethers are simple ether derivatives where the oxygen replaced by sulfur (note sulfur is in the same atomic "family" as oxygen). Thioethers display reactivity profiles similar to ethers, but generally are more reactive due to the presence of a less electronegative and "larger" (more polarizable) sulfur atom.

$CH_3CH_2-O-CH_2CH_3$

Saturated Aliphatic

$CH_2=CH-O-CH_2CH_3$
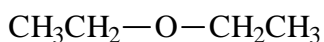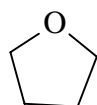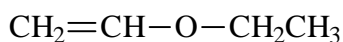
Unsaturated Aliphatic

$CH_3CH_2-S-CH_2CH_3$
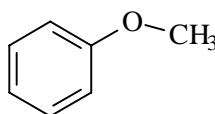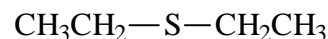
Saturated Aliphatic Thioether

Cycloaliphatic

Aromatic

II. Physicochemical Properties of Ethers
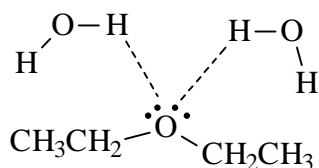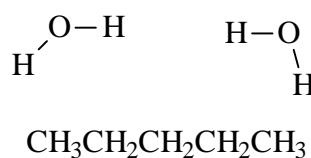
Since oxygen is significantly more electronegative than carbon, ether linkages are dipolar - a negative oxygen dipole linked to two positive carbon dipoles:
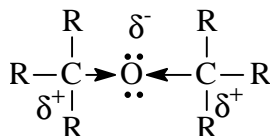
Because of the presence of this dipole, ethers have the ability to act as hydrogen bond acceptors and thus they display higher solubility in polar solvents such as water than corresponding hydrocarbons.


Ethers and H-Bonding   Alkanes: No H-bonding

Ethers are <u>less</u> water soluble than corresponding alcohols, acids or like compounds. Alcohols and acids can both donate and accept hydrogen bonds from water, and may form more hydrogen bonds with water due to the presence of both C-O and O-H dipoles. Ethers contain on C-O dipoles and thus can only accept hydrogen bonds from water and not donate hydrogen bonds. For these reasons ethers are less water soluble than alcohols and other organic compound containing more polar functionality:
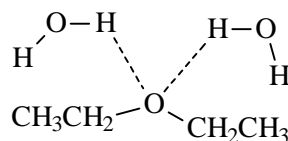
Ethers: H-Bond Acceptors
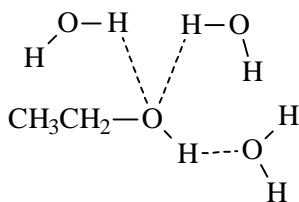
Alcohols: H-bond Donors and Acceptors   Acids: H-bond Donors and Acceptors
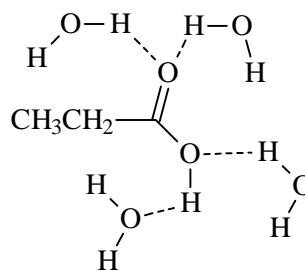
As is observed with other organic compounds containing a dipolar functional group, water solubility within a series of ethers is a function of overall structure. As would be expected, water

solubility rapidly decreases as the total hydrocarbon content of ethers increase. This is illustrated by comparison of the water solubilities of diethyl ether to diisopropyl ether:

$$CH_3CH_2-O-CH_2CH_3$$
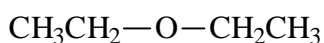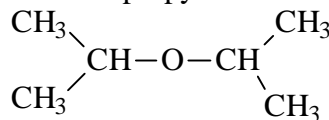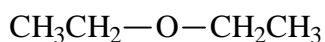

Diethyl Ether
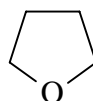Water Solubility: 8.4 g/100 mL

Diisopropyl Ether
Water Solubility: 0.002 g/100 mL

In addition to hydrocarbon content, steric factors and electronic factors also play a part in the relative solubilities of ethers. Note that the cyclic ether tetrahydrofuran (THF) is significantly more water soluble than diethyl ether, even though both compounds have approximately the same hydrocarbon content. In the case of THF, the hydrocarbon portion (alkyl groups on oxygen) are 'tied back" in the cyclic c structure, exposing the oxygen atom for optimal hydrogen bonding interactions with water with little interference form the non-polar, hydrocarbon portion of the molecule. In diethyl ether the two hydrocarbon chains (ethyl groups) can freely rotate about the carbon-oxygen bonds, and disrupt hydrogen bonding with water:

$$CH_3CH_2-O-CH_2CH_3$$

Diethyl Ether
Water Solubility: 8.4 g/100 mL

Tetrahydrofuran (THF)
Water Solubility: "Infinite"

The role of electronic factors in water solubility can be illustrated by comparing the water solubilities of THF and its aromatic counterpart, furan. In both structures the hydrocarbon portion is "tied back" in ring systems and does not sterically interfere with hydrogen bonding with water through rotation. But in furan, the NBEs of oxygen are in conjugation with the alkene (C=C) portions of the ring and can be delocalized into this system. This delocalization renders the NBEs of furans oxygen less available for hydrogen bonding with water. No such delocalization is possible in THF (oxygen is linked to fully saturated, sp^3 carbons), so its oxygen atom is 'free" to hydrogen bond with water (see Resonance Tutorial):

Tetrahydrofuran (THF)
Water Solubility: "Infinite"

Furan
Water Solubility: "Minimal"

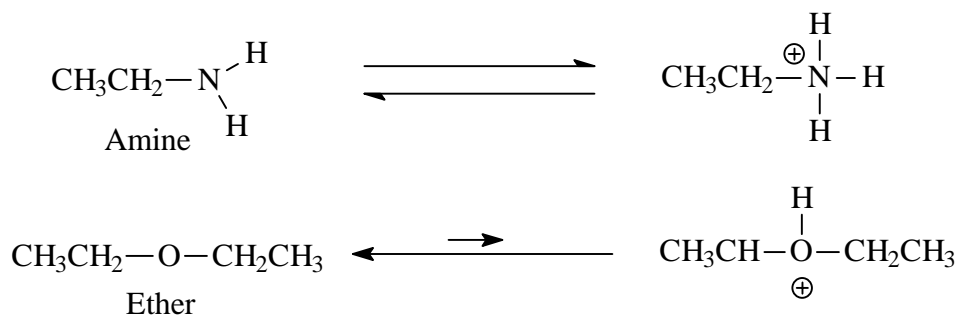## III. Ether Reactivity

In general, ethers are regarded as relatively unreactive compounds chemically. They do not possess acidic hydrogen atoms and thus do not donate protons to base over the pH range of 0-14 or under physiological conditions. Ethers contain only hydrogen atoms bound to carbon and there is no electron withdrawing functionality to stabilize negative charge that would form upon loss of a

proton. Contrast this carboxylic acids and carbonyl compounds (i.e. aldehydes and ketones) where certain hydrogen atoms are acidic since the charge formed in the base upon ionization can be stabilized by resonance (see Carboxylic Acid and Aldehyde and Ketone Tutorials):

$$CH_3CH_2 - C(=O)OH$$

Carboxylic Acid

$$CH_3CH_2 - C(=O)O^{\ominus}$$

Base: resonance stabilization!

$$CH_3CH_2 - C(=O)CH_3$$

Ketone

$$CH_3\overset{\ominus}{C}H - C(=O)CH_3$$

Base: resonance stabilization!

$$CH_3CH_2 - O - CH_2CH_3$$

Ether

$$CH_3\overset{\ominus}{C}H - O - CH_2CH_3$$

Unlikely!!!!
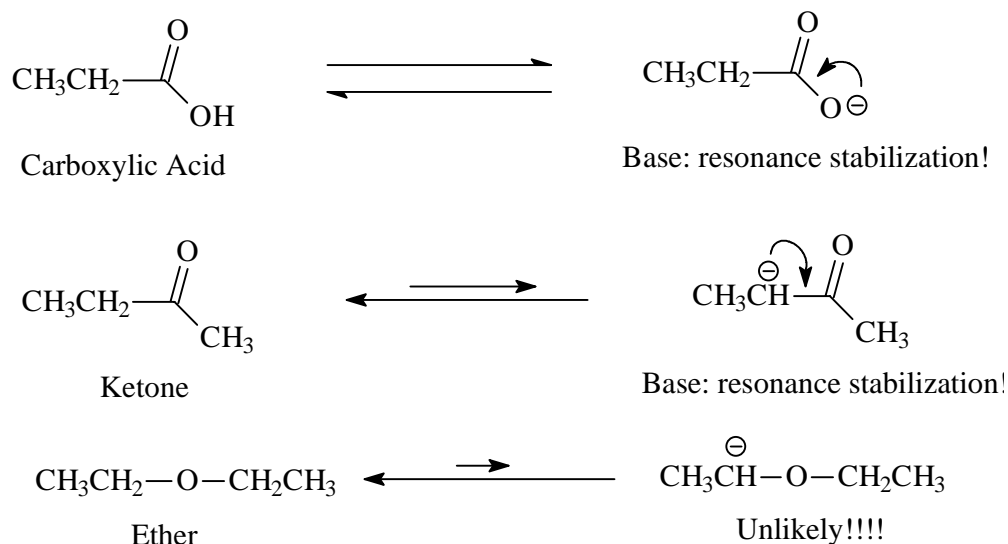
Ethers, like alcohols, also generally are not considered to be basic compounds since they do not contain an atom that readily donates a pair of electrons to a proton. This can be illustrated by comparing ethers to amines (see Amine Tutorial). Most amines contain a nitrogen atom with a non-bonded pair of electrons (NBEs). Since nitrogen has relatively low electronegativity, the amine nitrogen can share its NBEs with a proton in an acid-base reaction, and thus are basic. Ethers (and alcohols) also contain an atom with NBEs, the oxygen atom, but because of its relatively high electronegativity, oxygen does not readily share these electrons with a proton. As a result, ethers are significantly less basic than amines, and only act as bases in the presence of extremely strong acids (See any standard Organic Chemistry Text):

$$CH_3CH_2 - N(H)(H)$$

Amine

$$CH_3CH_2 - \overset{\oplus}{N}(H)(H) - H$$

$$CH_3CH_2 - O - CH_2CH_3$$
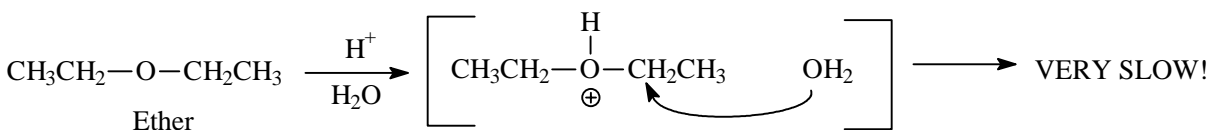
Ether

$$CH_3CH - \overset{\oplus}{O}(H) - CH_2CH_3$$

Ethers also do not readily undergo nucleophilic or electrophilic reactions typical of organic compounds such as aldehyde, ketones, esters, amides, alcohols, etc. In spite of the presence of an oxygen atom, ethers typically do not act as nucleophiles in displacement reactions. This is due a number of factors, most significant of which is the fact that the ether oxygen is already covalently bound to two carbon atoms. The illustration below compares ethers to alcohols as potential nucleophiles. As noted in the Alcohol Tutorial, the oxygen atom of an alcohol can displace leaving groups from an electrophilic carbon, yielding a displacement product as shown below. A key step

in this process is the loss of the hydroxyl group hydrogen as a proton that can occur readily. This proton loss allows the reaction to go to completion with alcohols. Ethers do not have a proton to loss in such a reaction, thus they cannot form a stable, uncharged displacement product:
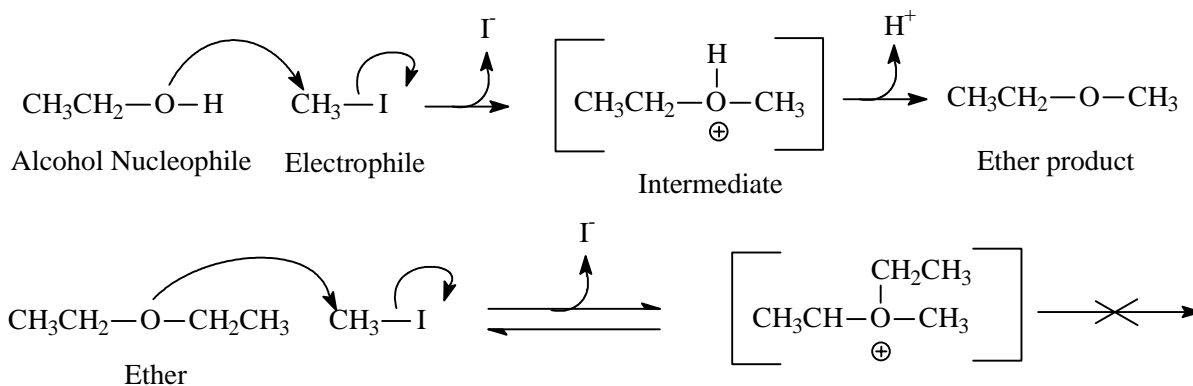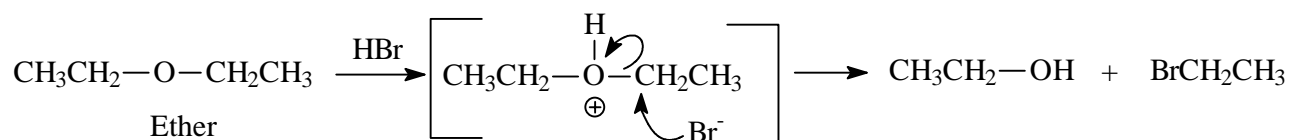
Ethers also do not function as electrophiles under mild reaction conditions. Ethers do possess two dipoles (C-O-C), and thus the carbon atoms attached to oxygen are somewhat electrophilic in nature (compared to a typical hydrocarbon C-C or C-H carbon). These dipoles are relatively weak compared to dipoles such as the carbonyl found in esters and amides (see Ester and Amide Tutorials). Thus ethers are "less electrophilic" than esters, amides and like compounds and are less likely to function as electrophiles in displacement reactions. These points are illustrated in the examples below, comparing the ability of esters, amides and ethers to undergo hydrolysis in mild aqueous acid. Esters have a polarized carbonyl and little electron donation by the other oxygen atom, thus they are readily attacked by nucleophiles such as water (see Ester Tutorial) and undergo hydrolysis. Amides also have a polarized carbonyl, but the amide nitrogen contributes electron density to the carbonyl by resonance, reducing its electrophilicity and therefore reactivity relative to esters (see Amide Tutorial). Ethers have simple carbon-oxygen single bond dipoles, and therefore these carbon atoms are only weakly electrophilic and not readily attacked by nucleophiles such as water. Thus ethers are not hydrolyzed as readily as esters or even amides:
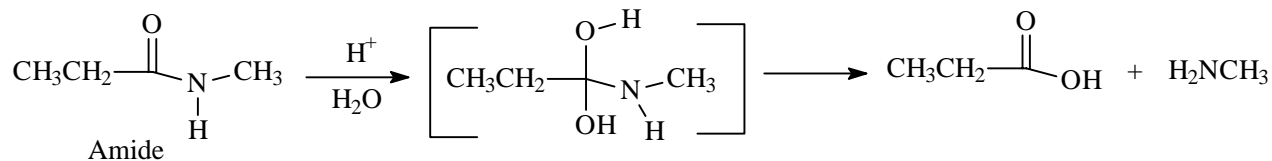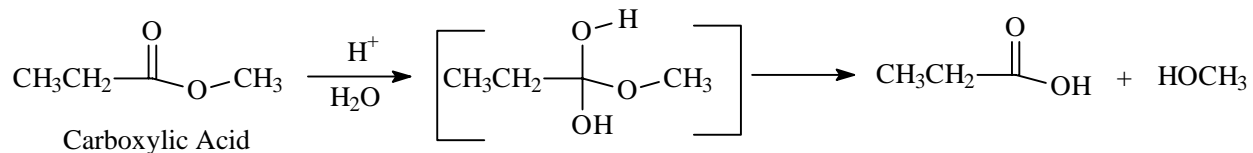
The stability of ethers, along with their modest polarity and the fact that many are liquids, makes them good solvents for chemical reactions. This, and the discussion above, however is not meant to imply that ethers are completely unreactive! Ethers can be cleaved in electrophile/nucleophile reactions, usually in the presence of strong acids that have nucleophilic conjugate bases, such as HBr. HBr is a sufficiently strong acid to partially protonate the ether oxygen, resulting in a charged intermediate.

This protonation renders the adjacent ether carbons more electrophilic and susceptible to attack by good nucleophiles such as Br$^-$, as shown below. Thus under more extreme reaction conditions, ethers will undergo bond cleavage reactions:

$$CH_3CH_2-O-CH_2CH_3 \xrightarrow{HBr} \left[CH_3CH_2-\overset{\overset{H}{|}}{\underset{\oplus}{O}}-CH_2CH_3 \right] \longrightarrow CH_3CH_2-OH \ + \ BrCH_2CH_3$$
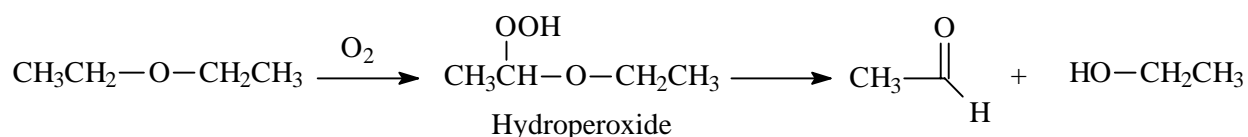
Ether

Also, the reactivity of ethers may be enhanced by the presence of other "activating" groups within the overall structure. For example, the simplest cyclic ethers, oxiranes or "epoxides", are among the most reactive ethers. This three-membered ring of oxiranes is highly strained since the carbon atoms in such a system cannot achieve the normal 109.5° bond angles. This strain and the dipole created by the carbon-oxygen bonding pattern allows oxiranes to react as electrophiles far more readily than typical aliphatic ethers. This is illustrated by the comparative nucleophilic displacement reactions shown below. Note that as ring size increases, reactivity declines rapidly:

Oxirane   "Fast"

Aliphatic Ether   "Extremely Slow" $CH_3CH_2-OH \ + \ RNHCH_2CH_3$
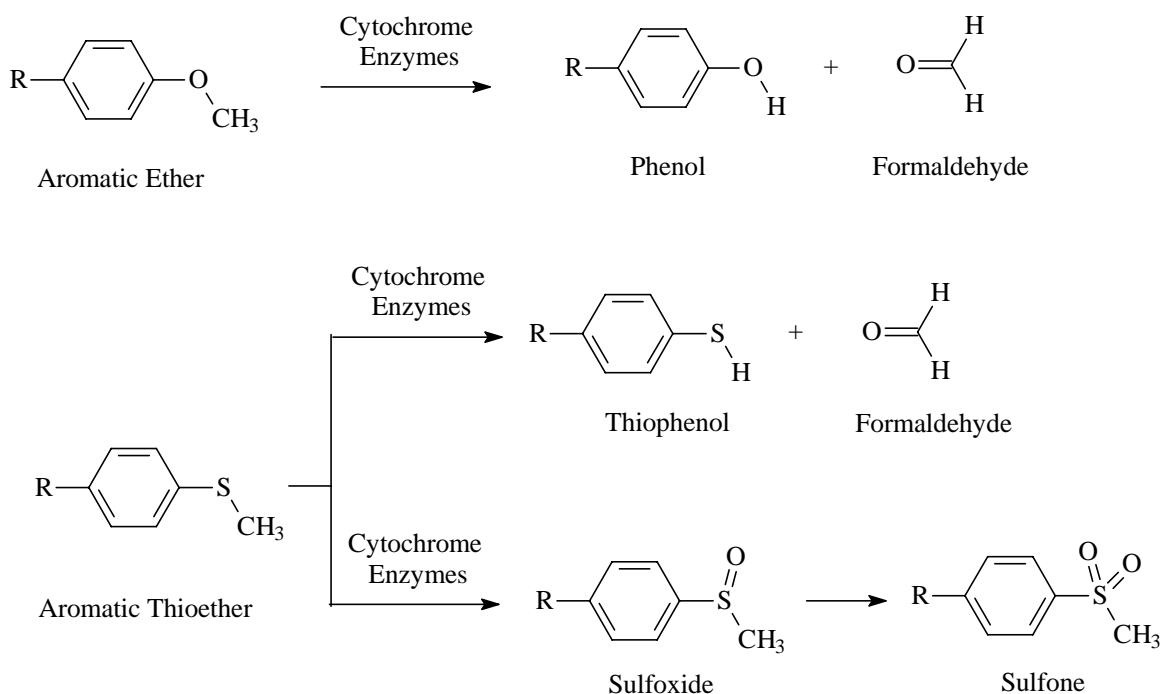
"Slow"
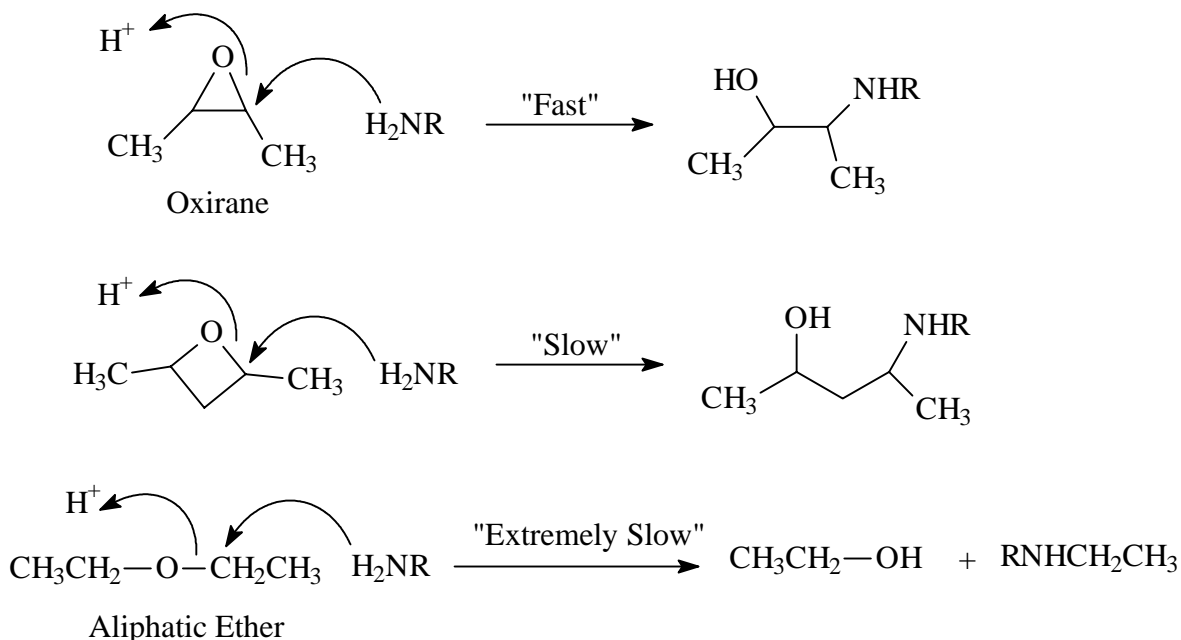
Based on the reactivity profiles discussed above, ethers in general are considered to be relatively unreactive under acid-base or nucleophilic-electrophilic reaction conditions. But note this discussion focused on the reactivity of ethers RELATIVE to other organic compounds containing dipolar functionality (alcohols, amines, esters, amides, aldehydes, ketones, etc.). It should also be

noted that thioethers display reactivity profiles similar to ethers, but generally are more reactive due to the presence of a less electronegative and "larger" (more polarizable) sulfur atom. Lastly it is important to realize that as hydrocarbon compounds, ethers are subject to free radical reactions including oxidative processes. In fact, ethers in contact with atmospheric oxygen may undergo radical-based oxidation to form peroxides and, even when present in small quantities, these peroxides are irritating to human tissues and may explore if concentrated. This is particularly a problem with ethers that are liquids and exposed to the environment:

$$CH_3CH_2-O-CH_2CH_3 \xrightarrow{O_2} \underset{\text{Hydroperoxide}}{\overset{\overset{\displaystyle OOH}{|}}{CH_3CH-O-CH_2CH_3}} \longrightarrow CH_3\overset{\displaystyle O}{\underset{\displaystyle H}{\parallel}}C \quad + \quad HO-CH_2CH_3$$

Also while ethers are considered be to relatively unreactive chemically, they may be quite reactive "metabolically". For example, ethers bearing at least one small alkyl group, such as methyl, are frequently cleaved by hepatic cytochrome enzymes in a process referred to oxidative O-dealkylation. This is a fairly common pathway of metabolism for ether drugs and is discussed in more detail in the Metabolism Tutorial. Also, thioethers may be metabolized by multiple pathways including oxidative S-dealkylation and/or sulfur oxidation to sulfoxide or sulfone metabolites; unlike oxygen sulfur is capable of "expanding it's valence" thus it can undergo oxidation:

Aromatic Ether → Cytochrome Enzymes → Phenol + Formaldehyde

Aromatic Thioether → Cytochrome Enzymes → Thiophenol + Formaldehyde

Aromatic Thioether → Cytochrome Enzymes → Sulfoxide → Sulfone

IV. Ether Substituents

To understand the potential contributions of an ether 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 ethers as described in the previous sections. Consider the example of Compounds A and

B below. In this example, Compound B (the methoxy metabolite of the neurotransmitter and drug norepinephrine) differs structurally from Compound A (the neurotransmitter and drug norepinephrine) only in the presence of an additional ether methyl substituent:
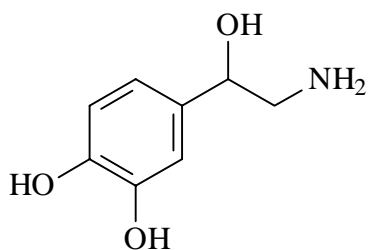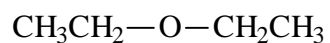

Compound A
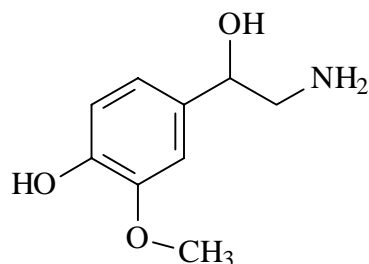
Compound B

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 less polar (less hydrophilic) than Compound A.

- The free dihydroxy (catechol) group present in compound A makes this compound a ligand for adrenergic receptors (alpha and beta-receptors). Compound B has the 3-hydroxyl group "masked" as an ether and thus has lower affinity for adrenergic receptors.

- The 3-ether substitutent present in Compound B eliminates one site of nucleophilic reactivity compared to compound A.

- Compound B could be formed from Compound A by methyl conjugation. Compound B could be metabolized to compound A by oxidative-O-dealkylation.

V. Problems

1. Explain why Compound B is hydrolyzed more readily than Compound A in the presence of HBr:
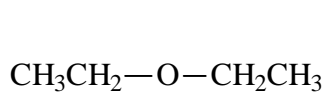
$$CH_3CH_2-O-CH_2CH_3 \qquad CH_2=CH-O-CH_2CH_3$$
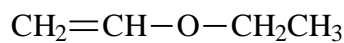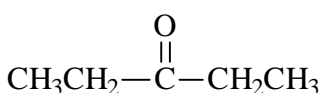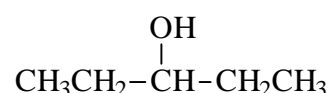
Compound A   **Compound B**

2. Rank the three compounds below in terms of their relative water solubility:

$$CH_3CH_2-O-CH_2CH_3 \qquad CH_3CH_2-\overset{\overset{O}{\parallel}}{C}-CH_2CH_3 \qquad CH_3CH_2-\overset{\overset{OH}{|}}{CH}-CH_2CH_3$$

A   **B**   **C**
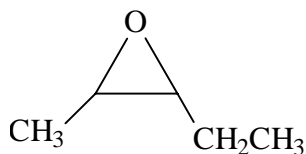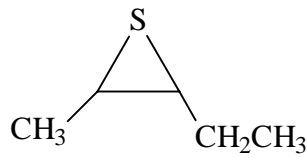
3. Which compound below, A or B, would undergo ring opening more readily in the presence of a nucleophile and why?

A   **B**

4. Explain how the metabolite shown below could be formed from the drug by a series of metabolic reactions.