HYDROCARBON STRUCTURE AND CHEMISTRY: AROMATICS

Jack DeRuiter

I. Introduction

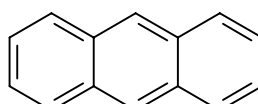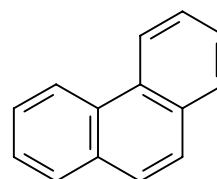Hydrocarbons are organic compounds consisting of C-C and C-H bonds. Carbon has a valence of four and thus requires four electrons or bonds to complete its octet in the neutral state. Hydrogen has a valence of one and thus requires a single electron or bond to complete its "duet" in the neutral state. Thus in hydrocarbons carbon can form neutral bonding arrangements by forming single bonds with hydrogen and single, double or triple bonds with other carbons (or other atoms). The nature of the carbon-carbon bonding arrangements in hydrocarbons is the basis for sub-classification of these compounds as alkanes, alkenes, alkynes or aromatics. The aromatic hydrocarbons are the subject of this tutorial.Hydrocarbons (Alkanes, Alkenes, Alkynes and Aromatics)
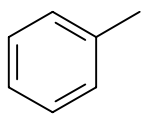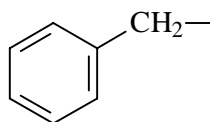
Benzene, the prototypical aromatic hydrocarbon is a six membered ring composed of six sp^2 hybridized carbon atoms in a plane and sharing 6 pi electrons. It can be represented by the "Kekule" structure shown below which suggests and "alternating" single bond-double bond bonding pattern. This representation does not really adequately reflect the true electronic character of benzene since, in reality, all six pi electrons are shared equally by the six carbons. Thus the "inscribed" circle representation may be more accurate (although it doesn't directly indicate the number of pi electrons):
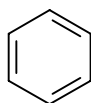
Kekule Structure
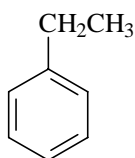of benzene
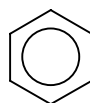
Inscribed circle
structure of benzene

A detailed presentation of the nomenclature of aromatic hydrocarbons is beyond the scope of this tutorial. The names and structures of some of the simpler aromatic hydrocarbons are shown below. It should be noted that a number of heterocyclic ring systems (conjugated ring systems containing one or more <u>non-carbon</u> atoms as members of the ring) are aromatic or "pseudo-aromatic", but these compounds are covered in a separate tutorial. Note that each name ends with the "ene" suffix (similar to the alkenes), while the prefix describes the nature and number of carbon atoms composing the aromatic ring:
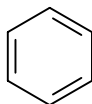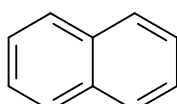
Benzene   **Naphthalene**   **Anthracene**   **Phenanthrene**

In addition to the individual compounds shown above, aromatic hydrocarbon "fragments" may be present as "substituents" of other molecules. When present as a substituent the "benzene" group is referred to as a "phenyl" substitutent. This substituent name should not be confused with the "benzyl" substitutent name that refers to a "phenylmethylene" substituent as shown below. Often in drug structures the phenyl substitutent may be abbreviated as "Ph" or "Ar" (if substituted):

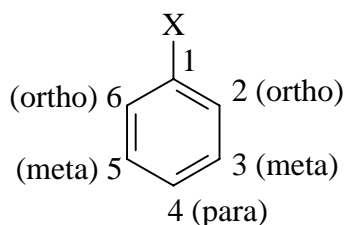**Phenyl Substituent**   **Benzyl Substituent**

Aromatic hydrocarbons with relative small, simple substituents typically are named using the ring system as the base name. For example, a benzene ring with a single ethyl group usually referred to as "ethylbenzene". However, when aromatic hydrocarbons are part of a larger, more complex organic structure, they may be referred to as substituents as illustrated in the example below:

Ethylbenzene
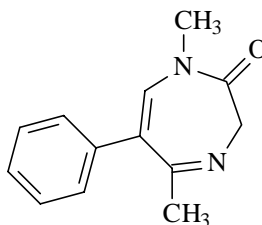
**6-phenyl-1,3-dihydro-1,5-dimethyl
2H-1,4-diazepin-2-one**

It should be noted that "mono-substituted" benzene derivatives often have trivial names that are used more commonly than the official IUPAC names. Several examples of such aromatic compounds are shown below. Most aromatic compounds of this type are discussed in other tutorials since the "substituent" rather than the aromatic ring often dominate their chemical properties. For example, phenol(s) is discussed in more detail in the *Alcohols and Phenols Tutorial* and aniline is discussed in more detail in the *Amines Tutorial:*
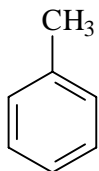
Toluene
(Methylbenzene)
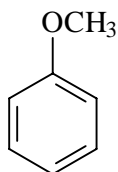
Anisole
(Methoxybenzene)
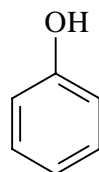
Phenol
(Hydroxybenzene)
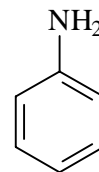
Aniline
(Aminobenzene)

In benzene all six ring carbon atoms are equivalent, thus numbering of ring positions has no real meaning. In monosubstituted aromatics, such as those shown above, the ring carbon bearing the substituent is assigned as position 1 and the other ring carbons numbered from this position as shown below. Historically the "other positions" have also been referred to as "ortho" (2 and 6-positions), "meta" (3 and 5 positions) and "para" (4 position):

Note that in monosubstituted benzene (phenyl) derivatives that a plane of symmetry exists through the 1 (substituent position) and 4 positions, and thus positions 2 and 6 (ortho positions) are equivalent, and positions 3 and 5 (meta positions) are equivalent. Thus monosubstituted benzene rings have four "non-equivalent" carbon atoms or positions (1, 4, 2 (=6) and 3 (=5)).

The presence of two substituents on an aromatic ring creates the potential for positional or regioisomerism. As shown in the example below, two substituents can be positioned 1,2- ("ortho"), 1,3- ("meta") or 1,4- ("para"), thus three possible positional isomers exist. Note that a "1,5-" arrangement would be equivalent to 1,3 (redundant), and "1,6" is equivalent (redundant) to 1,2-substitution:
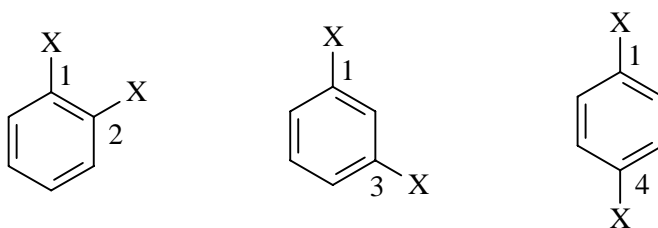

In the case of di- and multiply substituted aromatic compounds, ring carbon "'equivalency" or "non-equivalency" is dependent on the nature of the substituents (are they identical or different) AND their relative positions on the ring.

The phenyl and benzyl substituents are very common aromatic hydrocarbon functionalities in drug compounds. Larger aromatic hydrocarbons such as the naphthalene, anthracene and phenanthrene are also present in some drugs, but are not as common as the phenyl or benzyl substituent.

II. Configuration and Stereochemistry

Aromatic hydrocarbons are "conjugated" systems composed of planar sp^2 hybridized carbon atoms linked in cyclic structures. As a result conformational (rotational) and optical isomerism is not possible in these structures. Also, since aromatic hydrocarbons are linked in cycles, geometric ("cis/trans") isomerism also is not possible (see the *Stereochemistry Tutorial* for definitions and criteria). It should be noted, however, that aromatic hydrocarbons may possess **substituents** that may be asymmetrically substituted (chiral or geometric) and/or have rotational freedom to allow for conformational isomerism. This is illustrated in the example below. In this example, the carbon atoms of the benzene ring are not chiral (by definition), cannot give rise to geometric isomers (due to ring structure) and cannot rotate to yield differing conformers. The "substituent", however, contains a chiral center, an asymmetrically substituted C=C and has sp^3 hybridized carbon atoms that can exist in different conformational extremes.

cis/trans isomerism

H

CH₃

CH₃

OH

Conformational isomerism

Optical isomerism
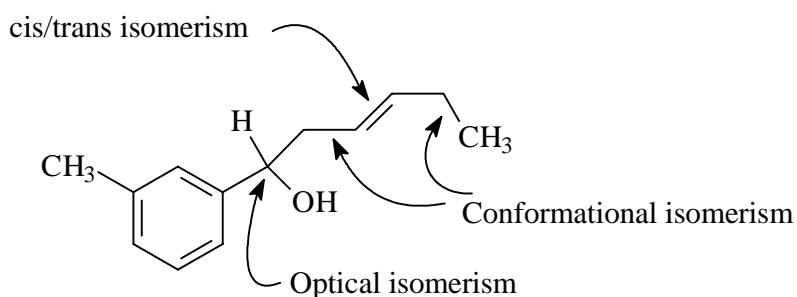
III. Physicochemical Properties

Aromatic hydrocarbons, like all hydrocarbons, are composed of carbon-carbon and carbon-hydrogen bonds. These atoms are of relatively low and similar electronegativity (2.1 for H, 2.5 for C) and thus no permanent dipole is established in hydrocarbon bonding arrangements. Aromatic hydrocarbons have a multiple, conjugated C=C with pi electron system, but this does not create a sufficient dipole for energetically favorable dipolar interactions with other molecules. Contrast this to alcohols where carbon and/or hydrogen are linked to an atom of significantly greater electronegativity - the oxygen atom (see Alcohol and Halogenated Hydrocarbon Tutorials).   In alcohols (and organic compounds with other atoms of electronegativity greater than carbon or hydrogen) permanent dipoles exist, created by the unequal sharing of bonding electrons between the more electronegative atom (O) and less electronegative atom (C, H). Thus partial ionic character is generated in dipolar compounds and this polarity determines the physicochemical properties and reactivity profiles of these compounds. In simple hydrocarbons such as the aromatics no such permanent dipoles and thus these compounds display physicochemical and reactivity profiles very different from dipolar compounds.

Because of their atomic composition, aromatic hydrocarbons are classified as "non-polar" compounds or substituents and the only significant intermolecular bonding possible are relatively weak van der Waals interactions (VDWs), or "induced dipolar" interactions created by temporary distortions in the electron distribution between atoms in the structure. The smallest stable aromatic hydrocarbon, benzene is a liquid at room temperature with a boiling point of about 80° C. As is observed for other hydrocarbons, as the size or number of carbon atoms increases, the total energy of VDWs between molecules increases and boiling points increase.   Thus naphthalene (10 carbons) has a higher boiling point than benzene, and anthracene (14 carbons) has a higher boiling point than naphthalene.

Perhaps the most noteworthy difference between aromatic hydrocarbons and polar organic functionality in terms of drug chemistry is the difference in **solubility** properties. As discussed in other tutorials, structurally similar or analogous compounds ("like" compounds) display overlapping solubility or "miscibility" profiles. Thus aromatic hydrocarbons are capable of "dissolving" other aromatic hydrocarbons (and are often used as solvents!), and other structurally related organic compounds are capable of dissolving aromatic hydrocarbons. For example, benzene is miscible in ether. However, as a result of their inability to establish significant

intermolecular interactions with H_2O and other polar compounds, aromatic hydrocarbons are considered to be **insoluble** in these media. Remember, water is a polar (H-O-H) substance that forms an ordered medium characterized by a high degree of intermolecular H-bonding. To dissolve in water, a "solute" must be able to break into this highly H-bond and ordered medium by "donating" and "accepting" H-bonds or ionic bonds of substantial energy. Since aromatic hydrocarbons do not possess ionic or dipolar functionality, they are not capable of such interactions. Thus when aromatic hydrocarbons are added to water they self-associate by VDWs interactions and "separate out" from the water, as discussed in the *Alkane Tutorial*.

IV. Reactions of Aromatic Hydrocarbons

A. Conjugation and Resonance

Although aromatic rings are often drawn with individual double bonds it should be remembered that this is somewhat misleading since the electrons represented by these bonds are actually delocalized over the ring. This **delocalization** occurs because of the apparent alternating arrangement of double bonds or **conjugation**. Resonance is therefore defined as the ability to represent a given structure by two or more forms that differ only in the arrangement of electrons. The concept of resonance is important since the ability of electrons to become delocalized can provide a great deal of stability to a compound or reaction intermediate. Remember the ability to form stable intermediates and products is important in deciding whether a given reaction will proceed. More details on resonance phenomena are covered in the *Resonance and Induction Tutorial*.

B. Electrophilic Substitution Reactions with Aromatic Hydrocarbons

Recall that alkenes are susceptible to electrophilic **addition** reactions since the carbon-carbon double bond present in these compounds can be polarized in the presence of an electrophile, allowing for both an electrophilic and nucleophilic atom or group to add across the double bond (see the *Alkene Tutorial*). The pi electrons of aromatic systems are less reactive than those of isolated double bonds present in alkenes, due to conjugative stabilization. However, the pi electrons of aromatic systems can participate in electrophilic reactions that result in **substitution**. Note the difference in the two types of reactions illustrated in the examples below. In the reaction with alkene, the electrophile H+ and the nucleophile Br- add across the double bond of the pi system, and the pi system is "consumed" in the reaction resulting in formation of a substituted **alkane**. In the aromatic system the pi system donates an electron pair to the electrophilic atom (Br+), but the conjugated pi system is regenerated by loss of a proton (energetically stable aromatic system). Thus a **substitution** (Br for H) rather than addition occurs in aromatic systems. Note also that the conjugated pi system in aromatic compounds helps to stabilize the positive charge in the reaction intermediate by resonance delocalization (see the composite structure below and the three resonance structures):

Alkene

Electrophilic Addition Product

Electrophilic Substitution Product
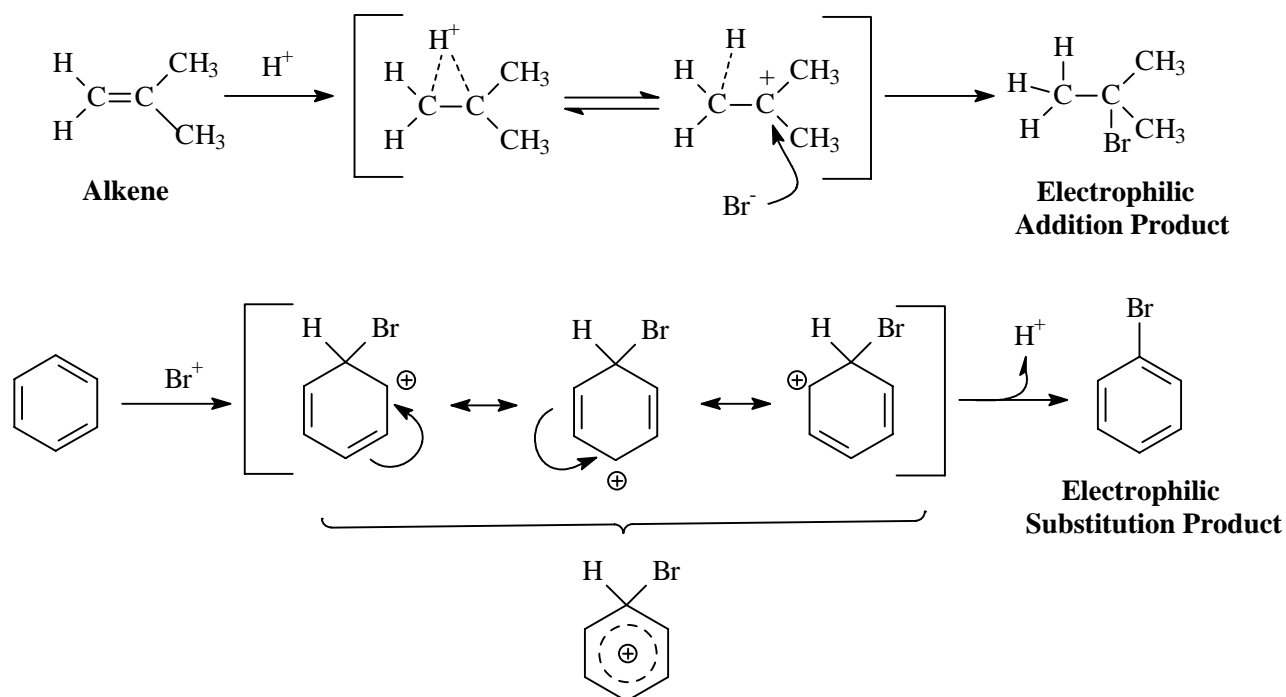
Based on the mechanism for electrophilic substitution shown above, it is not surprising that aromatic systems with **electron donating** substituents (by induction or resonance) are more susceptible (more reactive) to electrophilic substitution than aromatic rings with electron withdrawing substituents. Additionally, substituents on the ring may activate certain ring carbon positions for substitution over others based on their electronic properties. It is well known that electron releasing substituents activate the "ortho" and "para" positions to attack and substitution by electrophiles. Consider the example of phenol below. The OH group is a strong electron donating substituent by resonance (+R). Due to the conjugative pattern of the aromatic ring, the *greatest electron density* associated with the +R effects of the OH group occurs at positions 2 (ortho), 4 (para) and 6 (ortho) as shown by the resonance structures below. Thus these positions are most likely to be substituted. It is important to note that even though three positions are activated the OH group, only two products form - the 2-bromo and 4-bromo products. Remember, in the phenol structure the two "ortho" positions (2 and 6) are equivalent, and thus would give rise to a single product (2-bromophenol):


The +R effects of OH at positions 2, 4 and 6
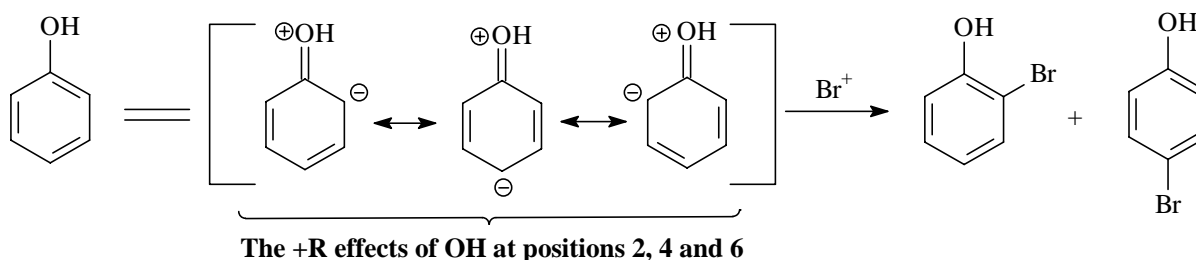
It should be noted that drugs possessing an aromatic substituent typically do not undergo **chemically catalyzed** electrophilic substitution reactions in formulations or in the biological environment. However, electrophilic substitution is relevant to the **enzyme-mediated metabolism**

of drugs containing an aromatic substitutent, as illustrated in the "Oxidation" section below and described in the *Metabolism Tutorial*.

## C. Nucleophilic Substitution Reactions with Aromatic Hydrocarbons

Typically substituted aromatic hydrocarbons are inert to nucleophilic substitution reactions due to the stabilization imparted by the conjugated pi electron system. Good leaving groups, such as halogen, can be displaced from aromatic ring systems, provided the ring is activated by the presence of appropriately positioned, strongly electronic withdrawing (by resonance (-R)) substituents. These concepts are illustrated in the examples below. Even though chlorine is a good leaving group, it cannot be displaced from it's position on the aromatic ring by the methylamine nucleophile, unless that ring is activated by two strong -R nitro groups positioned in conjugation with the site of reaction ("ortho" and "para"):
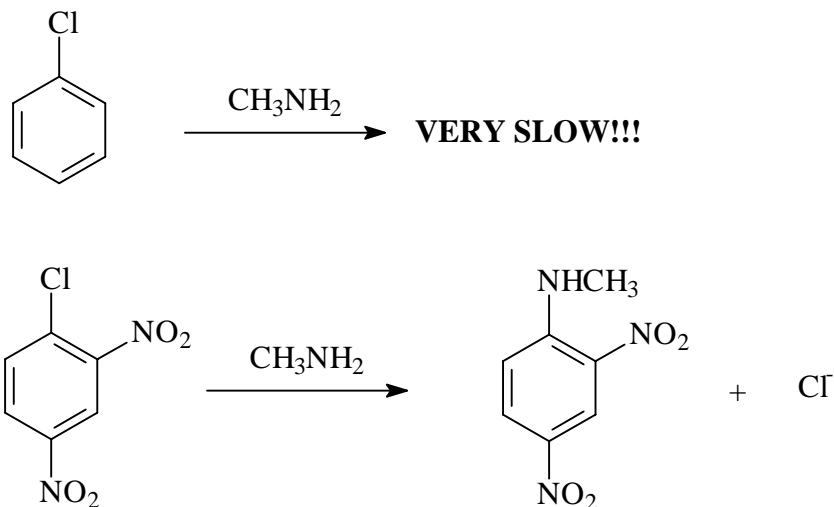
It should be noted that typically in the biologic environment such reactions do not occur by purely chemical means. However, there are aromatic systems (usually heterocyclic aromatic compounds) that can undergo such displacements with the aid of enzymes. Such reactions are discussed in more detail in other tutorials.

D. Oxidation of Aromatic Hydrocarbons

Typically aromatic hydrocarbons are somewhat resistant to chemical oxidation. However, under biologic conditions aromatic rings may be readily oxidized by cytochrome enzymes to phenol metabolites as illustrated by the example of the beta-blocker propranolol below. Note in this example that oxidation occurs primarily at the position para to the electron donating substituent.



Propranolol

Phenol Metabolite
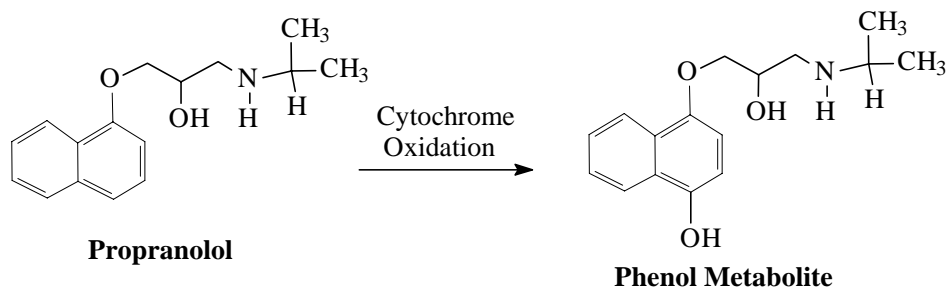
This is a position of high electron density (due to electron donation by resonance) and least sterically hindered (versus the "ortho" positions).

Also note that typically these metabolic oxidations do not occur readily on compounds with electron withdrawing substitutents as illustrated be the example below:

Cl — ⬡ — $SO_2NHCH_2CH_2CH_3$ ⟶ *No Aromatic Hydroxylation (electron withdrawing aromatic ring)*

Examples of Electrophilic Aromatic Substitution Reactions
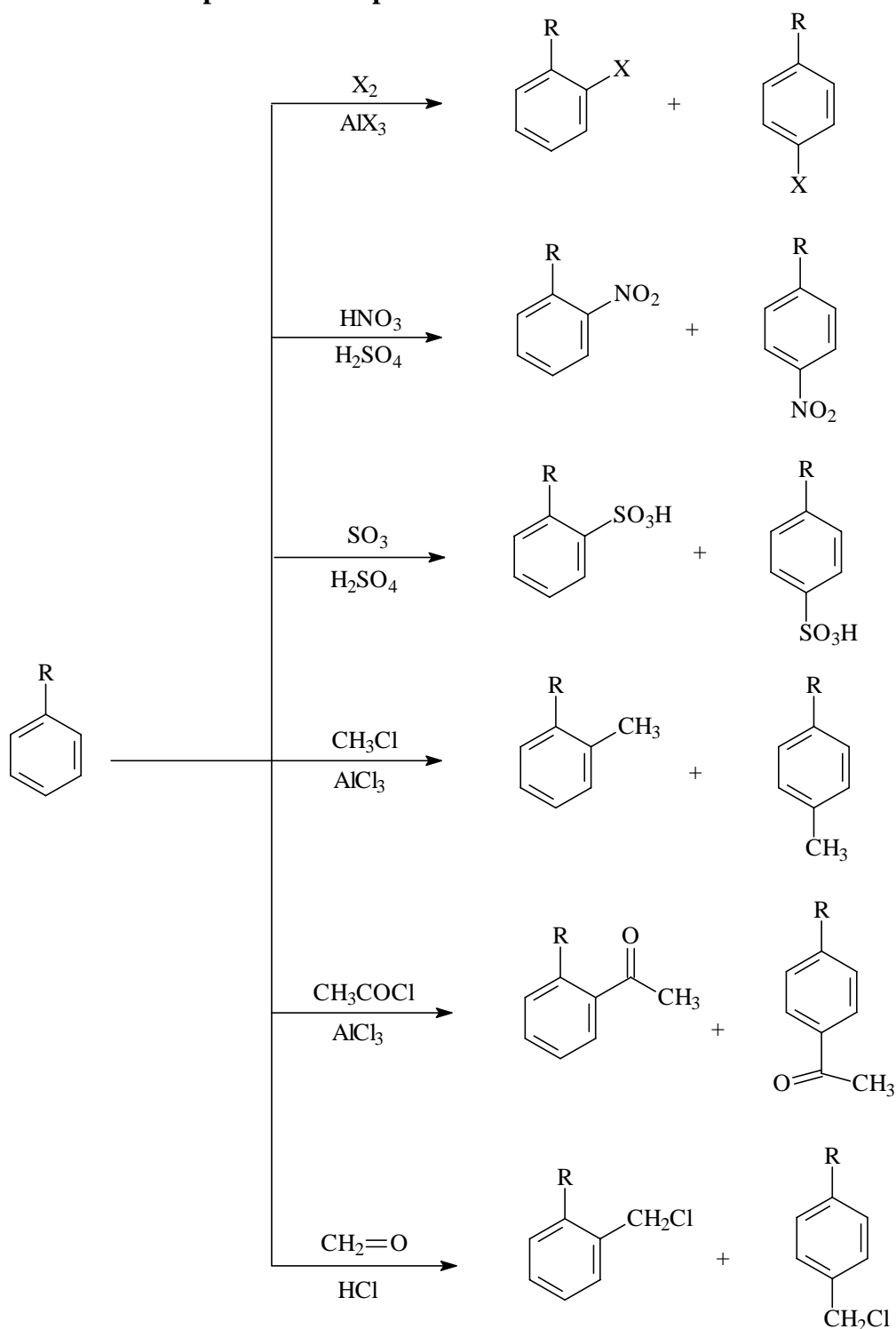
Notes: The "meta"-product may form as a minor product in these reactions. Reactions where the
an electron withdrawing group either will not occur or occur with low yields (and giving meta-pro

V. Problems

1. Answer questions a-e below for the following compounds:

CH₃ CH–CH₂–CH–CH₃ ... A

CH₃ C=CH–CH–CH₃ ... B

CH₃ CH–CH₂–CH–CH₃ ... C
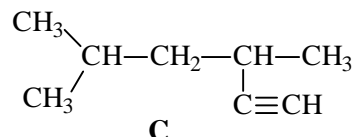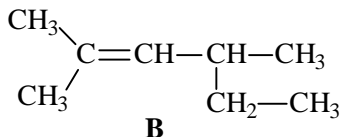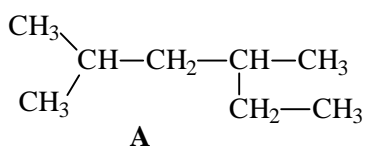
   a. Name the three compounds shown above.
   b. Which compound above (A-C) has the lowest boiling point?
   c. Which compound(s) above (A-C) have sites of asymmetry and can therefore exist in different stereoisomeric forms?
   d. Which of the compounds above (A-C) can undergo electrophilic addition reactions with Br₂?
   e. Which of the compounds above (A-C)can be reduced with H₂ and an appropriate metal catalyst?

2. Which compound below (A-C) would have the highest boiling point? Which would be most soluble in diethyl ether (ether)? Which compound below would penetrate biologic membranes most readily by passive diffusion?

HO—⬡—CH₃   HO—⬡—CH(CH₃)₂   HO—⬡—CH₂CH₂CH(CH₃)₂

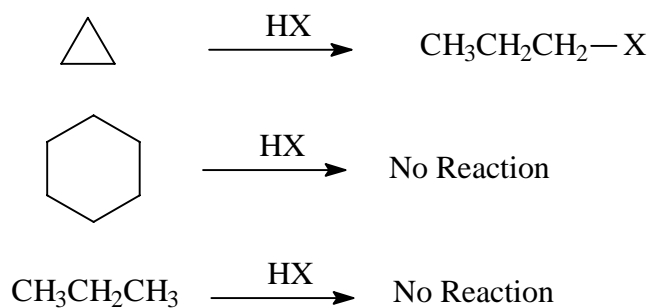   A   B   C
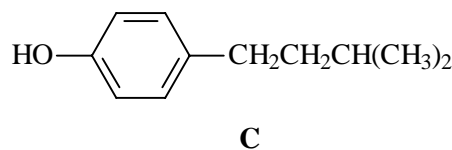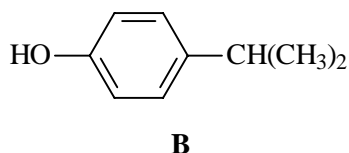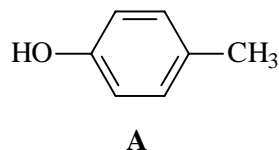
3. Classify each compound below by structural type (alkane, alkene, etc.). Also, which of these compounds would undergo <u>electrophilic</u> <u>addition</u> reactions with HCl?

   A   B   C
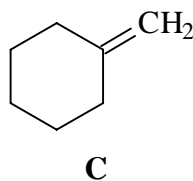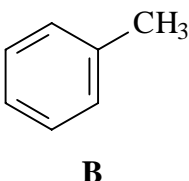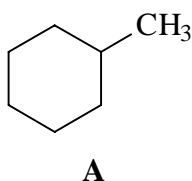
4. Rank the following compounds in terms of their ability to undergo addition a reaction with HBr (high, intermediate, low-None):

A   **B**   **C**
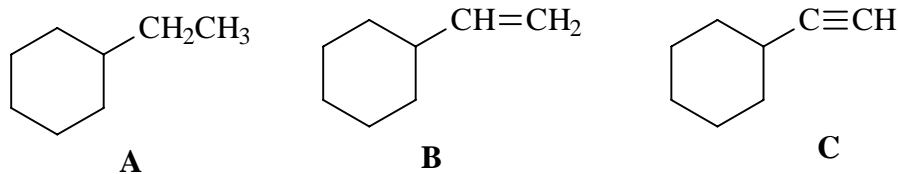
5. While alkanes and alkyl groups are regarded as relatively "unreactive", some cyclic alkanes such as cyclopropane will react and undergo ring opening as shown below. Explain why cyclopropane undergoes such reaction while propane and cyclohexane do not.


$\triangle$ $\xrightarrow{\text{HX}}$ $CH_3CH_2CH_2-X$

$\xrightarrow{\text{HX}}$ No Reaction

$CH_3CH_2CH_3$ $\xrightarrow{\text{HX}}$ No Reaction

6. Which compounds below contain a chiral center and therefore can exist in different stereoisomeric forms?
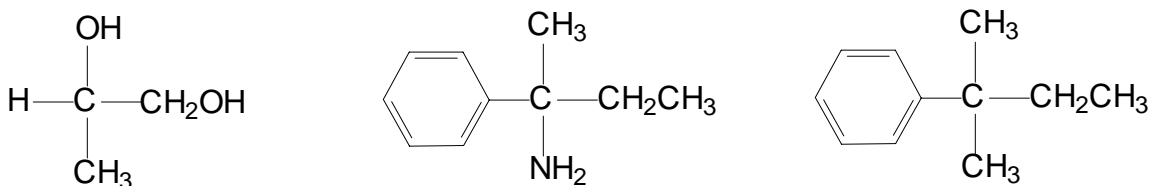

7. Would the two enantiomers of methamphetamine shown below be expected to show the same or different solubilities in water? Would they be expected to have the same or different affinities for a "receptor" (chiral protein)?
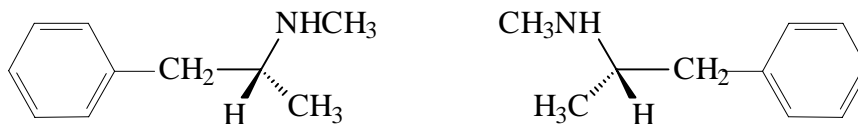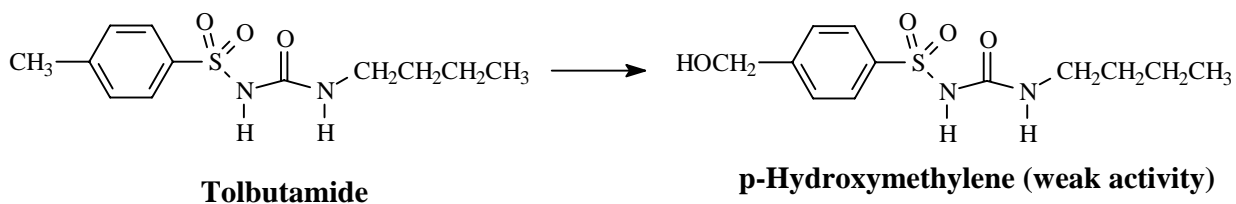

8. Draw all possible products that could form in the addition reaction shown below:
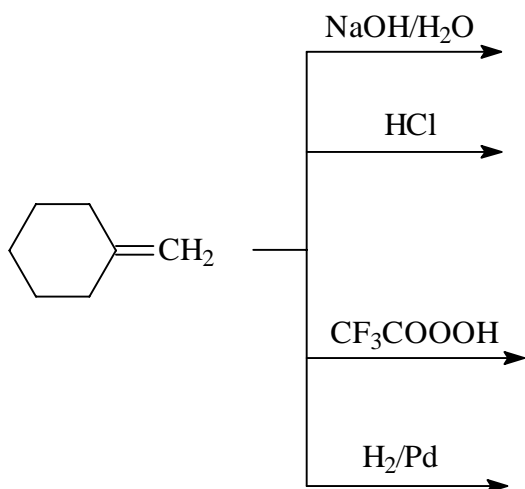

$\xrightarrow{\text{HBr}}$

11
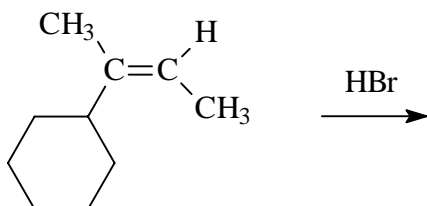
9. Compare the two drug molecules below in terms of their relative lipophilicity. Which compound would be more soluble in non-polar organic solvents? Which compound would passively diffuse across biologic membranes more readily?
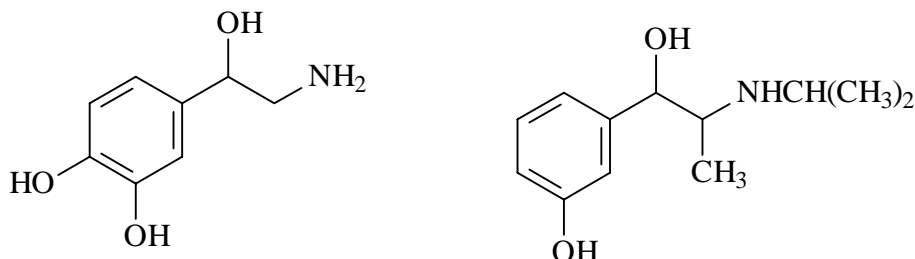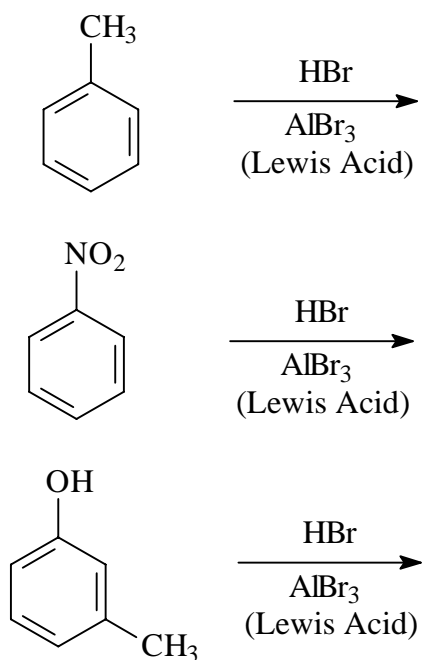

10. The oral hypoglycemic drug tolbutamide is rapidly metabolized after administration to yield the p-hydroxymethylene metabolite as shown below. What chemical (enzymatic) process is involved in this reaction?


Tolbutamide

p-Hydroxymethylene (weak activity)

11. Show all possible products (if any) that would form under the reaction conditions shown below:

$NaOH/H_2O$

HCl

CF_3COOOH

H_2/Pd

12. Show all possible products (if any) that would form under the reaction conditions shown below:

$$\underset{\text{(Lewis Acid)}}{\xrightarrow[\text{AlBr}_3]{\text{HBr}}}$$

$$\underset{\text{(Lewis Acid)}}{\xrightarrow[\text{AlBr}_3]{\text{HBr}}}$$

$$\underset{\text{(Lewis Acid)}}{\xrightarrow[\text{AlBr}_3]{\text{HBr}}}$$

13. How many stereoisomers (enantiomers and/or diastereomers) are possible for each compound shown below:

A

B

C

D
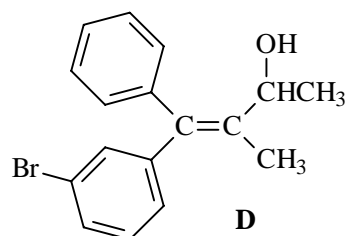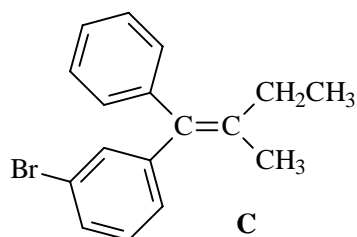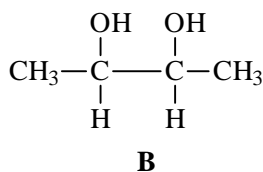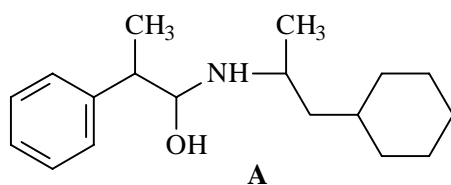
14. Show the structure of a phenol, benzylic alcohol, epoxide and diol that may form from oxidative metabolism of the compound shown below:

$$CH_2-CH=CH_2$$