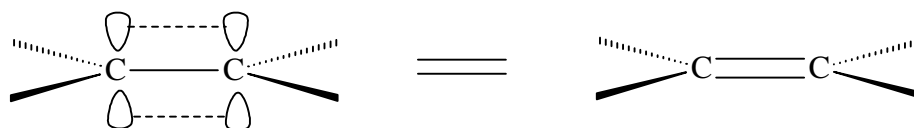


HYDROCARBON STRUCTURE AND CHEMISTRY: ALKENES*Jack DeRuiter***I. Introduction**

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 alkenes are the subject of this tutorial. Hydrocarbons (Alkanes, Alkenes, Alkynes and Aromatics)

Alkenes and simple organic hydrocarbons consisting of only of carbons bound to hydrogens or other carbon atoms with at *least one carbon-carbon double bond* (C=C). Carbon-carbon double bonds are formed as a result of hybridization involving one s orbital (2s) and 2p orbitals of each carbon to generate an sp^2 orbital, which possesses a trigonal geometry. The remaining p orbital of each carbon is aligned perpendicular to the plane of the carbon atoms to allow for sharing of the remaining electron pair by delocalization in a so-called (π) bond. Because of this bonding arrangement alkenes will always have the general formula represented by C_nH_{2n} .



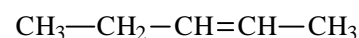
A detailed presentation of the nomenclature of alkenes is beyond the scope of this tutorial. The names and structures of some of the simpler, smaller alkenes are presented in the Table below. Note that each name ends with the "ene" suffix, denoting an alkene, and that they all "match" the general formula C_nH_{2n} . In addition to the individual alkene compounds, alkene "fragments" may be present as "substituents" of other molecules. When present as substituents they are referred to "alkenyl" groups and named using the parent prefix followed by "yl". The application of this nomenclature to alkene compounds, and alkyl substituents is illustrated in the example below, and the Table. Note that the position of the double bond may vary, thus it is necessary to designate where it occurs in the alkene structure.



1-Pentene

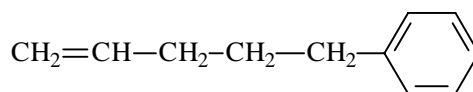


2-Pentene



3-Pentene

Alkenes: the "Pentenes"

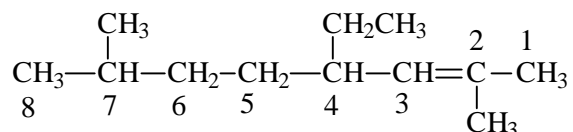


Alkenyl group: pentenyl

Alkenes and Alkenyl Groups

COMPOUND	NAME	GROUP	NAME
$\text{CH}_2=\text{CH}_2$	Ethene, ethylene	$\text{CH}_2=\text{CH}-$	Ethenyl, vinyl
$\text{CH}_2=\text{CH}-\text{CH}_3$	Propene, propylene	$\text{CH}_2=\text{CH}-\text{CH}_2-$ $-\text{CH}_2=\text{CH}-\text{CH}_3$	1-propenyl, allyl 2-propenyl
$\text{CH}_2=\text{CH}-\text{CH}_2\text{CH}_3$	1-Butene	$\text{CH}_2=\text{CH}-\text{CH}_2\text{CH}_2-$	1-butenyl
$\text{CH}_3-\text{CH}=\text{CH}-\text{CH}_3$	2-Butene	$\text{CH}_3-\text{CH}=\text{CH}-\text{CH}_2-$	2-butenyl

It should also be noted that more complex alkene structures require a systematic method of nomenclature. Official rules for naming all organic compounds have been developed by the International Union of Pure and Applied Chemistry (IUPAC). IUPAC nomenclature for alkenes requires that the **longest continuous carbon chain containing the C=C** be the “base” name for a structure (the “alkene”), and then that the chain be numbered to provide the lowest possible numbers for the C=C and then any substituents. An example of this nomenclature system is provided below. Note that the longest chain could be numbered in two possible directions, but the numbering used gives the lowest “net” numbers for the substituents. Also note that the methyl groups at positions 2 and 7 of this chain, and the ethyl at position 4 are named as alkyl substituents. More detailed discussion of IUPAC nomenclature can be found in any standard Organic Chemistry textbook:



2,7-Dimethyl-4-ethyl-2-octene (NOT 2,7-Dimethyl-5-ethyl-6-octene)

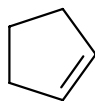
Alkenes and alkyl groups can be sub-classified as “aliphatic” (acyclic) or “cycloaliphatic” based on their general structure. Aliphatic alkenes are linear or branched structures as shown in the examples above. Cycloaliphatics or “cycloalkenes” contain the alkene or alkyl fragment as part of a carbon cycle. Cycloalkenes are named in a manner similar to the alkenes with the “cyclo” prefix. The primary cycloalkenes of interest are shown below:



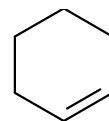
Cyclopropene



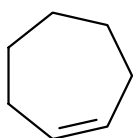
Cyclobutene



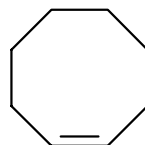
Cyclopentene



Cyclohexene

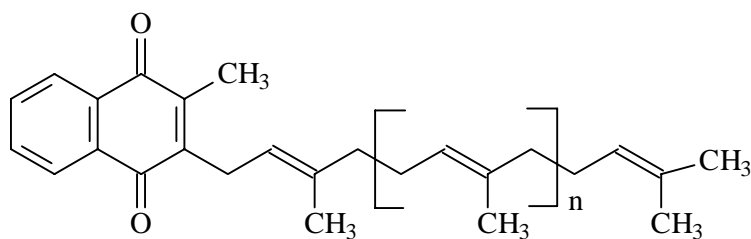


Cycloheptene



Cyclooctene

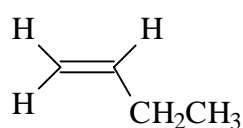
Sometimes alkenes have multiple C=C groups. These are referred to as "polyenes". The Vitamin K derivatives and polyene antifungal drugs (Amphotericin B) are examples of drugs that are polyenes:



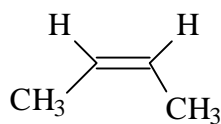
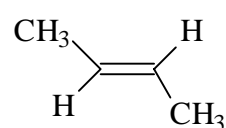
Vitamin K Derivative

II. Configuration and Stereochemistry

As mentioned in the Introduction, carbon assumes a trigonal shape in the sp^2 hybridized bonding state characteristic of alkenes, and the carbon atoms of the C=C exist in the same plane. Furthermore, the presence of the pi-bonding system **prevents** "free rotation" about the carbon-carbon double bonds of alkenes, so conformational isomerism at the C=C center is not possible. It is important to note that rotation and conformational isomerism may occur at the other sp^3 centers that may be present in an alkene. The restricted rotation at the C=C center of alkenes creates the *potential* for "geometric isomerism". Geometric isomerism is possible when **each** carbon atom of the double bond is asymmetrically substituted as illustrated for the examples of 1- and 2-butene below. In each case, the C=C restricts rotation, but only 2-butene is asymmetrically substituted at each carbon of the double bond. The restricted rotation and planar geometry of the double bond, along with the asymmetry, allow for two distinct stereoisomers or geometric isomers of 2-butene to exist. These isomers may be named as *cis* or *trans* or E or Z, as described in more detail in the *Stereochemistry Tutorial*.



1-Butene

*cis*-2-butene
[(Z)-2-butene]*trans*-2-butene
[(E)-2-butene]

Geometric isomers are nonsuperimposable, nonmirror images and therefore may be classified as diastereomers. Thus stereoisomers of this type have different physical and chemical properties. This is illustrated in more detail by the examples in the *Stereochemistry Tutorial*. A number of drugs contain asymmetrically substituted carbon-carbon double bonds and therefore can exist as two distinct geometric isomers.

III. Physicochemical Properties

Alkenes, like all hydrocarbons, are composed exclusively 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. Alkenes have a C=C with pi electrons, but this does not create a sufficient dipole for energetically favorable dipole-dipole interactions. Contrast this to halogenated hydrocarbons and alcohols where carbon and/or hydrogen are linked to atoms of significantly greater electronegativity (see Alcohol and Halogenated Hydrocarbon Tutorials). In halogenated compounds and 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 (Cl, 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 alkenes no such permanent dipoles and thus these compounds display physicochemical and reactivity profiles very different from dipolar compounds.



Because of their atomic composition, alkenes and alkenyl groups are classified as “non-polar compounds” 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. Compare the boiling points of the alkenes shown in the table below. Note that the smaller alkenes (less than 4 carbons) are gases at room temperatures. This is because the total energy of VDWs between these compounds is exceeded by the energy available at room temperature. As alkene size increases to 5 carbon atoms (1-pentene) and beyond, the total energy of VDWs between molecules increases to the point where it exceed the total amount of energy available at room temperature. These compounds are liquids at room temperature and, if sufficiently large, may be solids. Thus as alkene size increases, the total energy of VDWs attraction between molecules increase and boiling points increase. Note that the same trends are observed with the alkanes covered in the *Alkane Tutorial*. **In comparison, alkenes have lower boiling points than their corresponding alkanes!**

Alkene Boiling Points

COMPOUND	STRUCTURE	BOILING POINT (°C)
1-Propene	CH ₂ =CHCH ₃	-47.8
1-Butene	CH ₂ =CHCH ₂ CH ₃	-6.3
1-Pentene	CH ₂ =CHCH ₂ CH ₂ CH ₃	30.0
1-Hexene	CH ₂ =CHCH ₂ CH ₂ CH ₂ CH ₃	63.5

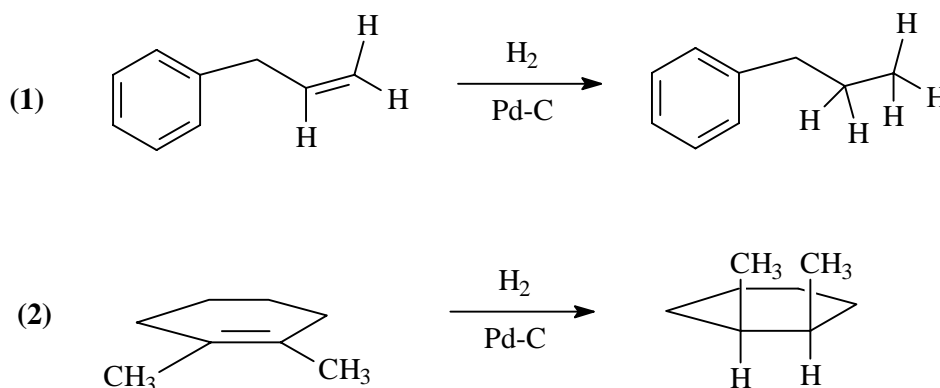
Perhaps the most noteworthy difference between alkenes/alkenyl groups and polar organic functionality in terms of drug chemistry is the difference in **solubility** properties. As discussed in other tutorials, structurally similar or analogous compounds ("like" compounds) display overlapping solubility or "miscibility" profiles. Thus alkenes are capable of "dissolving" other alkenes and other structurally related organic compounds are capable of dissolving alkenes. For example, ether can dissolve pentene. However, as a result of their inability to establish significant intermolecular interactions with H₂O and other polar compounds, alkenes 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 alkenes do not possess ionic or dipolar functionality, they are not capable of such interactions. Thus when alkenes are added to water they self-associated by VDWs interactions and "separates out" from the water, as discussed in the *Alkane Tutorial*.

IV. Reactions of Alkenes

The most significant difference between alkenes and alkanes is related to chemical reactivity. Alkenes are considerably more reactive than alkanes as a result of the additional electron density provided by the C=C pi bond. The pi bonding arrangement provides a site for reduction and interaction with a number of "electrophiles" and "nucleophiles" in ordered reactions as described below.

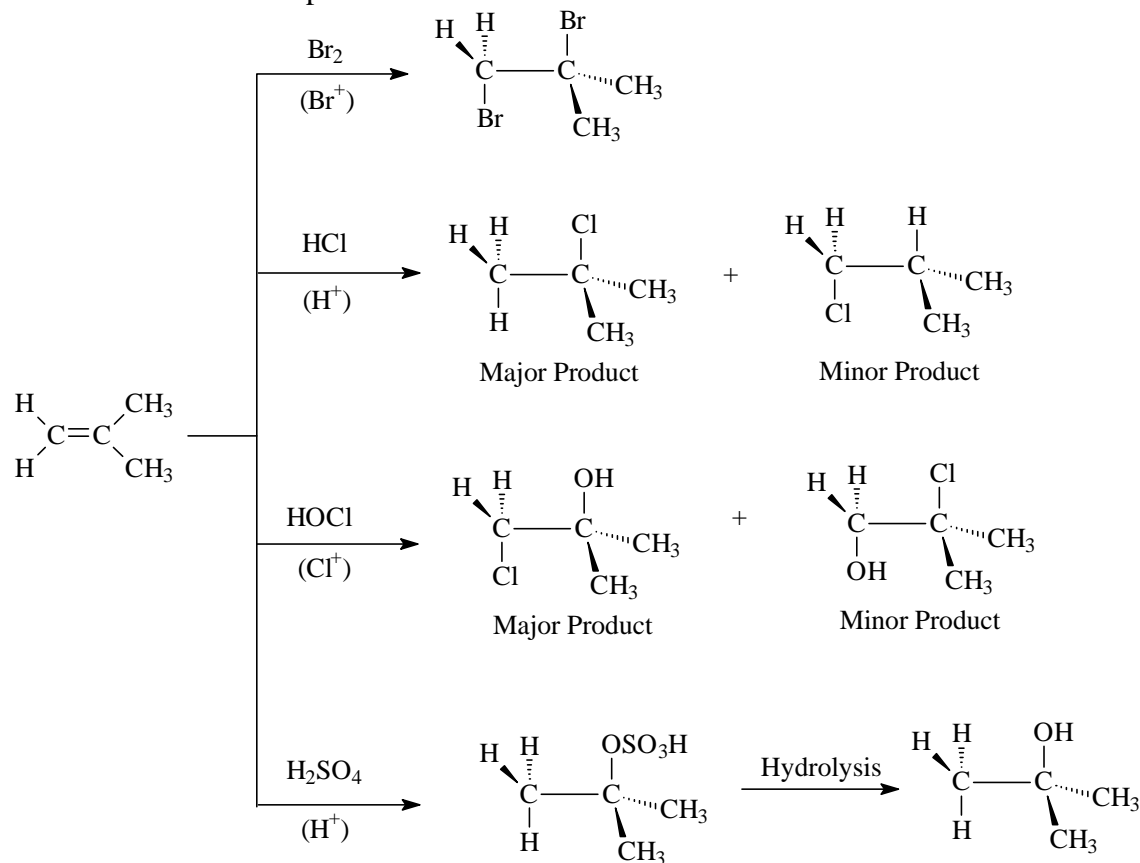
A. Alkenes and Reduction Reactions

In the presence of certain reducing metals (Ni, Pd, Pt, Cu, etc) and hydrogen alkenes undergo reduction to alkanes. In this reaction the alkene is believed to be bound by the metal catalyst and hydrogen added to "one side" ("cis" or suprafacial) of the C=C bond. The general reaction and mechanistic restrictions are illustrated in the two examples below. Note that alkenes are reduced more readily than aromatic rings (example 1) and that the addition of H₂ occurs to a common face of the original alkene C=C (example 2):

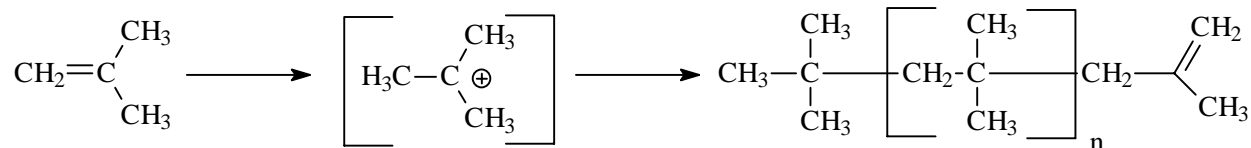


B. Alkenes and Electrophilic Addition Reactions:

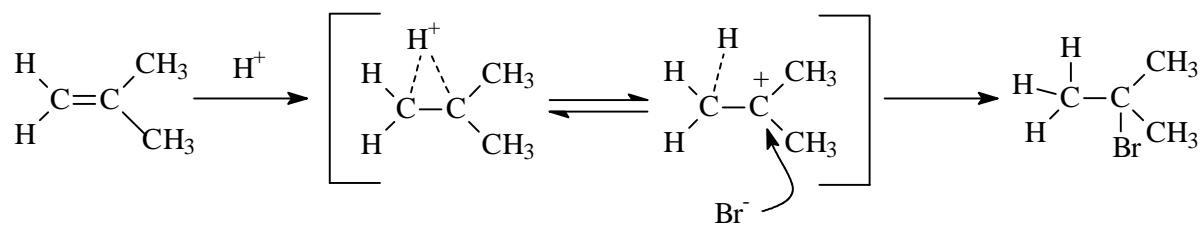
As a result of the pi bonding system present in alkenes these compounds may also undergo a variety of electrophilic addition reactions as illustrated in the examples below. Note that a host of chemical species can serve as electrophiles in these reactions including halogen (X_2), mineral acids (HX, sulfuric acid), hypohalous acids (HOX), etc. For each reaction below the "electrophile is identified below the reaction arrow in parentheses:



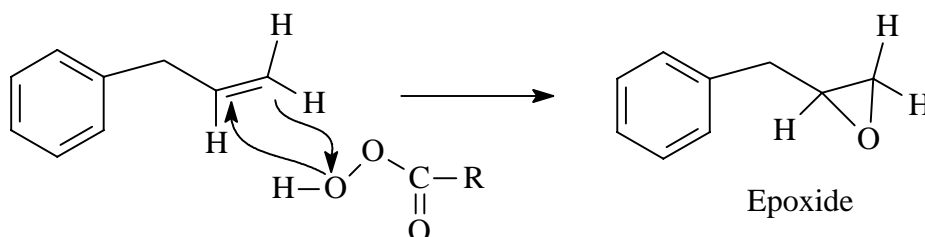
In an analogous reaction, alkenes that form stable carbocation intermediates can also undergo polymerization reactions in the presence of strong Lewis acids and water as illustrated for 2-methylpropene:



Note in the examples above that, in the major product, the electrophile adds to less substituted carbon atom of the alkene, while the nucleophile adds to the more substituted carbon atom. This regioselectivity is a result of the reaction mechanism. Mechanistically most of these reactions are believed to proceed through a cyclic "onium ion" intermediate formed from the original alkene and the electrophile. Such a mechanism would account for the observation that these reactions typically result in "anti" or antarafacial addition. Also in this mechanism "partial carbocation" character would develop to the greatest degree on the more substituted carbon atom (inductive stabilization) and this is where the nucleophile would add preferentially:

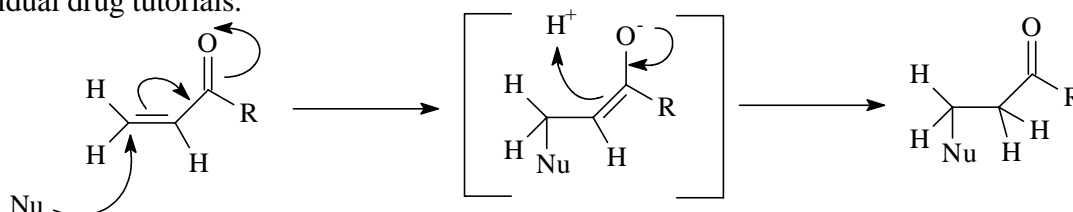


Alkene can also undergo "epoxidation" reactions in the presence of electrophilic oxidizing agents such as peroxides and the peracids as shown below:

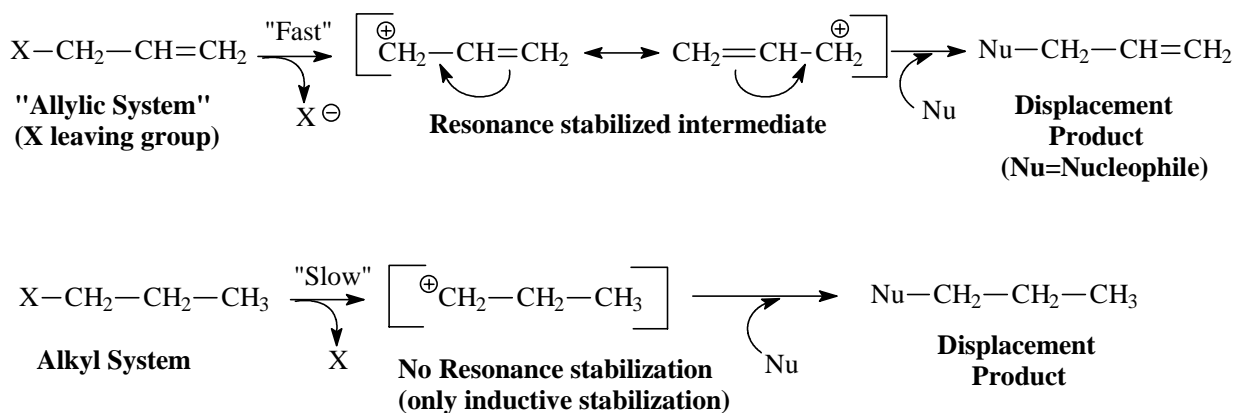


C. Alkenes and Nucleophilic Addition/Displacement Reactions and "Allylic Groups":

Because of their electronic character, direct nucleophilic addition reactions do not occur commonly with simple alkenes. However, if an alkenyl group is in direct conjugation with an electronic withdrawing functionality, then an alkenyl carbon may be sufficiently electrophilic to react. Such is the case in α, β -unsaturated carbonyl compounds (and isoelectronic analogues) as shown below. In this case the carbonyl moiety in conjugation with the alkene serves to further polarize (enhance the electrophilicity of) the alkene carbons - particularly the β -carbon, so that nucleophilic attack can occur. The conjugated system also stabilizes the intermediate anion in this reaction which further contributes to reactivity. This reaction is very important in biochemical systems and for a number of drug compounds. These reactions are discussed in more detail in the *Carbonyl Tutorial* and individual drug tutorials.

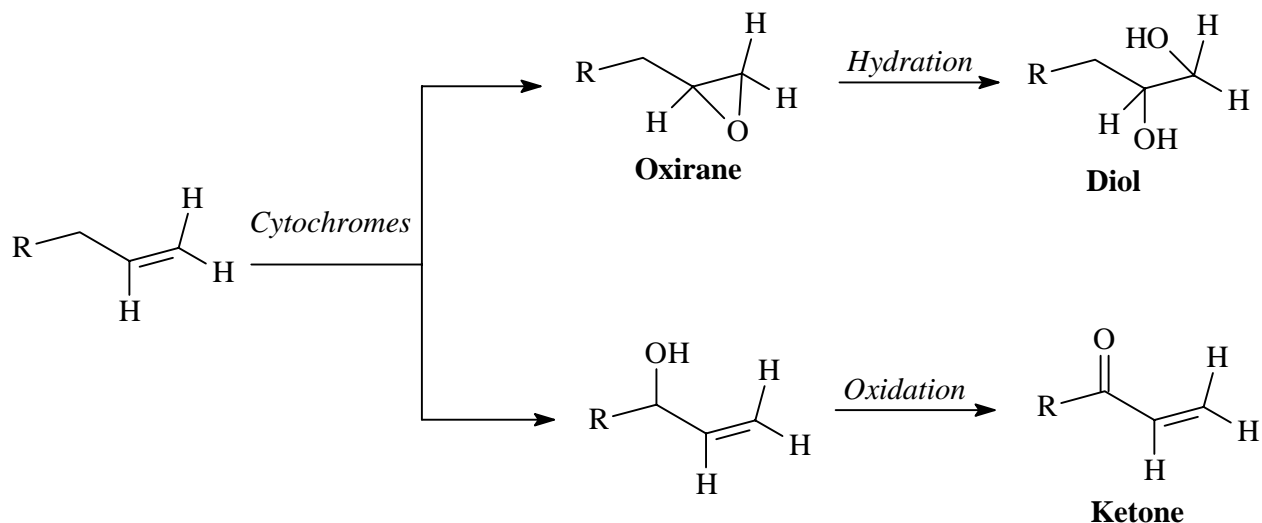


Alkenyl groups can also facilitate nucleophilic substitution reactions at adjacent or "allylic" carbon atoms as illustrated by the example below and discussed in more detail in the *Resonance and Induction Tutorial*. In such cases the allylic alkenyl group enhances the displacement reaction by resonance stabilization of the positive charge formed in the reaction intermediate; this positive charge forms as a result of departure of the leaving group. Alkyl groups are incapable of charge stabilization by resonance (they can only stabilize by weaker inductive effects), thus they do not facilitate displacement reactions to the same degree as alkenyl allylic groups:

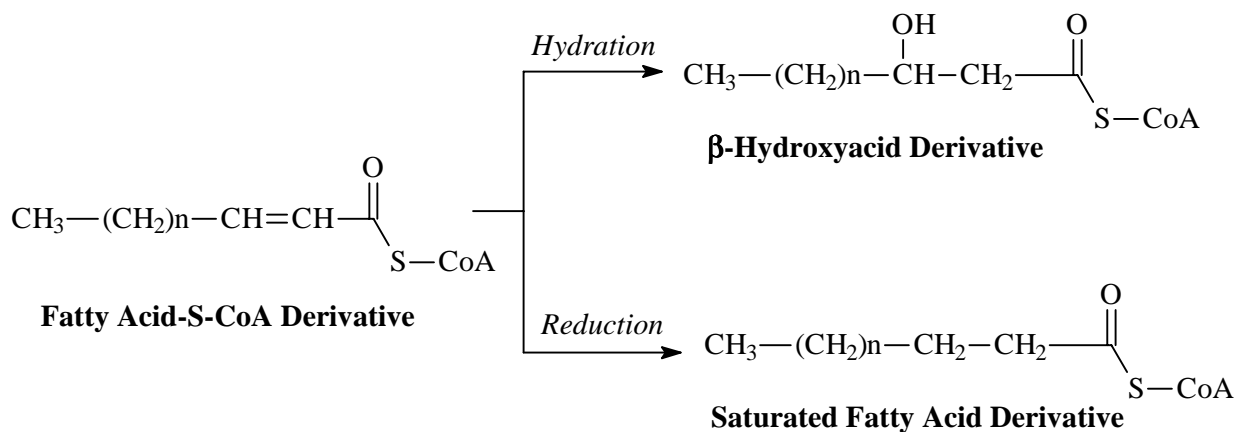


D. Alkenes and Metabolism:

Alkenes are also susceptible to a number of cytochrome-mediated metabolic reactions involving either the pi system or "allylic" carbon atoms. Enzymatic attack at the pi system results in oxirane (epoxide) formation, which may be further metabolized by hydrolysis catalyzed by hydrases to yield diols. Attack at the allylic carbon will yield allylic alcohols which may be further oxidized to ketones or aldehydes depending on the bonding state of carbon. Oxidation of primary allylic carbons results in aldehyde formation and the aldehyde may be further oxidized to the corresponding acid:

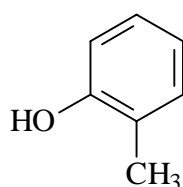


Alkenes present in fatty acid-like structures can undergo hydration and reduction reactions as shown below. These reactions are catalyzed by enzymes involved in fatty acid metabolism:

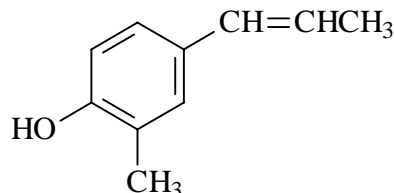
**V. Alkenyl Groups as Drug Substituents**

To understand the potential contributions of an alkenyl 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 alkenes as described in the previous sections. Consider the example of Compounds A and B below. In this example, Compound B differs structurally from Compound A only in the presence of an additional "alkenyl" (propenyl) substituent:



Compound A



Compound B

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

- The additional alkenyl group present on Compound B may have variable effects on affinity by the therapeutically relevant target (receptor, enzyme, etc.). If the target binds the additional alkenyl then Compound B may have higher affinity than Compound A. If the target does not bind the additional alkenyl group, the Compound B may have the same (bulk tolerance) or lower (steric interference with binding) than Compound A.
- Compound B is more lipophilic (non-polar) than Compound A and thus is more soluble in non-polar organic solvents (less soluble in water and polar solvents), and more readily partitions across biological membranes by passive mechanisms.
- The alkenyl substituent present in Compound B will alter the acidity and nucleophilicity of the hydroxyl group (OH) through direct resonance interactions (see *Alcohol Tutorial*).
- The particular alkenyl substituent present in Compound B contains asymmetrically substituted carbon atoms and thus "cis" and "trans"-stereoisomeric forms are possible for Compound B.
- The additional alkenyl group present in Compound B may undergo metabolic reactions involving alkene or allylic oxidations catalyzed by cytochrome enzymes.

VI. Problems: See end of "Aromatic" Chapter