**HYDROCARBON STRUCTURE AND CHEMISTRY: ALKYNES**

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

Alkynes are simple organic hydrocarbons consisting of only of carbons bound to hydrogens or other carbon atoms with at *least one carbon-carbon triple bond.* Carbon-carbon triple bonds are formed as a result of hybridization involving one s orbital (2s) and one 2p orbital of each carbon to generate an sp orbital which possesses a **linear** geometry. The remaining two p orbitals of each carbon are aligned perpendicular to each other to form two sets of pi bonding orbitals to allow for sharing of the remaining two electron pairs by delocalization. Because of this bonding arrangement alkynes will always have the general formula represented by C_nH_{n+1}.
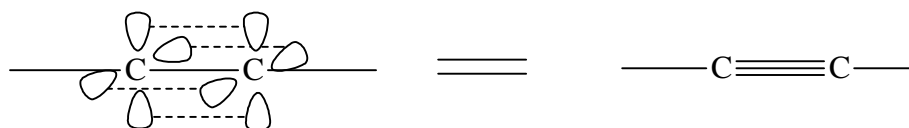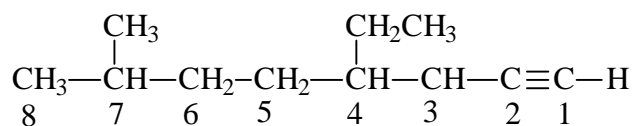

A detailed presentation of the nomenclature of alkynes is beyond the scope of this tutorial. The names and structures of some of the simpler, smaller alkynes are presented in the Table below. Note that each name ends with the "yne" suffix, denoting an alkyne. In addition to the individual alkyne compounds, alkyne "fragments" may be present as "substituents" of other molecules. When present as substituents they are referred to "alkynyl" groups and named using the parent prefix followed by "yl". The application of this nomenclature to alkyne compounds, and alkynyl 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 alkyne structure.

Alkynes and Alkynyl Groups

| COMPOUND	NAME	GROUP	NAME
$HC{\equiv}CH$	Ethyne, acetylene	$HC{\equiv}C$-	Ethynyl, acetylenyl
$HC{\equiv}C\text{-}CH_3$	Propyne	$HC{\equiv}C\text{-}CH_2$-	Propargyl
		$\text{-}C{\equiv}C\text{-}CH_3$	Propynyl

It should also be noted that more complex alkyne 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 alkynes

requires that the **longest continuous carbon chain containing the C≡C** be the "base" name for a structure (the "alkyne"), 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 numbers for the C≡C moiety and then numbers the substituents. Also note that the methyl groups at positions 4 and 7 of this chain are named as alkyl substituents. More detailed discussion of IUPAC nomenclature can be found in any standard Organic Chemistry textbook:
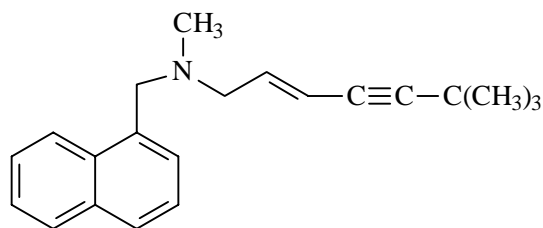
$$CH_3-\underset{8}{CH}-\underset{7}{CH}-\underset{6}{CH_2}-\underset{5}{CH_2}-\underset{4}{CH}-\underset{3}{CH}-\underset{2}{C}\equiv\underset{1}{C}-H$$

with CH₃ substituent on C7 and CH₂CH₃ substituent on C4

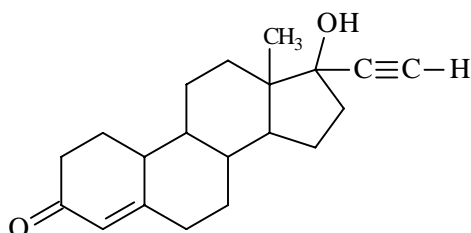**4-Ethyl-7-methyl-1-octyne**

The alkynyl group is present in a number of drugs including monoamine oxidase inhibitors (selegiline), antifungal agents (haloprogin, terbinafine), sedatives (ethchlorvynol) and synthetic female sex hormones (i.e. norethindrone):
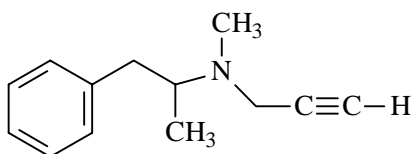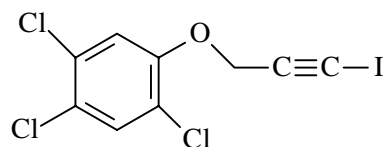
Selegiline

Terbinafine

Norethindrone

Haloprogin

II. Configuration and Stereochemistry

As mentioned in the Introduction, carbon assumes a linear shape in the sp hybridized bonding state characteristic of alkynes, and the carbon atoms of the C≡C exist in the same plane. The presence of the doubly 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). Also, the linear shape of alkynes eliminates the possibility of geometric or "cis"/"trans" isomerism.

III. Physicochemical Properties

Alkynes, 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 significant permanent dipole is established in hydrocarbon bonding arrangements. Alkynes have a C≡C with two pairs of 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 no such permanent dipoles and thus these compounds display physicochemical and reactivity profiles very different from dipolar compounds.

Because of their atomic composition, alkynes and alkynyl 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 alkynes shown in the table below. Note that, as is observed with alkanes and alkenes, the smaller alkynes (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 alkyne size increases to 5 carbon atoms (1-pentyne) 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 and alkenes covered in other tutorials. **In comparison, alkynes have <u>higher</u> boiling points than their corresponding alkanes!**

Alkyne Boiling Points

| COMPOUND	STRUCTURE	BOILING POINT (^{o}C)
Propyne	HC≡C-CH$_3$	-23.2
1-Butyne	HC≡C-CH$_2$CH$_3$	8.1
1-Pentyne	HC≡C-CH$_2$CH$_2$CH$_3$	40.2
1-Hexyne	HC≡C-CH$_2$CH$_2$CH$_2$CH$_3$	71

Perhaps the most noteworthy difference between alkynes/alkynyl 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 alkynes are capable of "dissolving" other alkynes and other structurally related organic compounds are capable of dissolving alkenes. For

example, alkanes, alkenes and even ethers can dissolve pentyne. However, as a result of their inability to establish significant intermolecular interactions with H_2O and other polar compounds, alkynes 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 alkynes do not possess ionic or dipolar functionality, they are not capable of such interactions. Thus when alkynes 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 Alkynes

A. Acid/Base Chemistry

Some alkynes - 1-alkynes - differ from other hydrocarbons in that they may possess a weakly acidic hydrogen atom. The terminal hydrogen atom of 1-alkynes is sufficiently acidic to be removed in the presence of very strong base as shown below. It should be noted that the acidity of these alkynes is to low to be of consequence at typical biologic pHs, and thus alkynes are regarded as neutral, non-ionizable substituents in the biologic environment:

$$CH_3-C\equiv C-H \xrightarrow{\quad NaH \quad} CH_3-C\equiv C^- \; Na^+$$
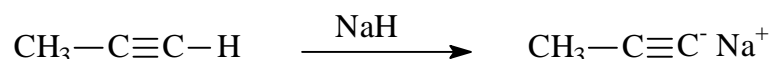
B. Alkyne Reduction

Alkynes are reduced **more readily** than alkenes, primarily because they are absorbed more readily on the surface of metal catalysts. Hydrogenation of alkynes proceeds in stages yielding first a "cis"-alkene followed by further reduction to provide an alkane. If the reduction (hydrogenation) catalyst is suitably deactivated (as Lindlar catalyst or Pd-Pb) the reaction can be stopped at the alkene stage:
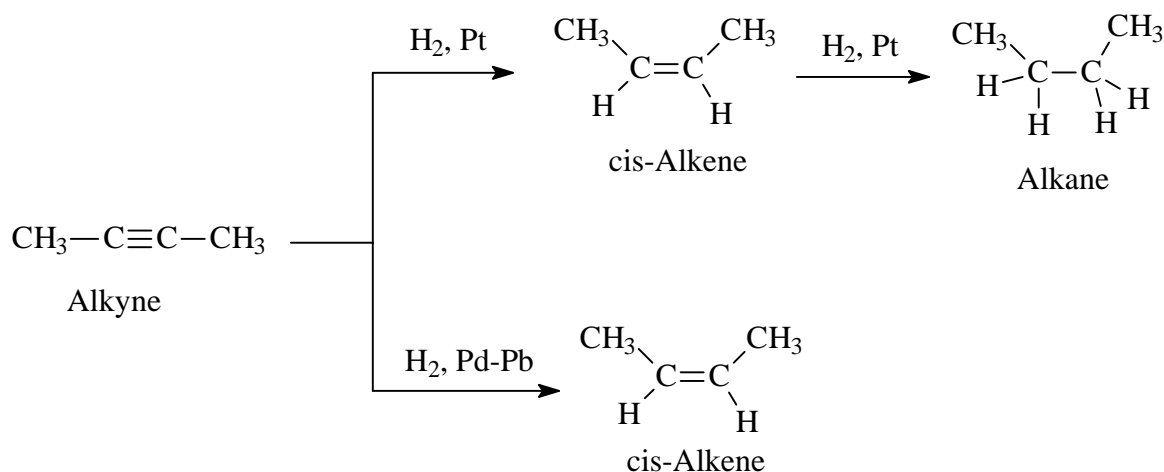
C. Alkynes and Electrophilic Addition:

Given the additional electron density in alkynes one might assume that alkynes were even more susceptible to electrophilic attack than alkenes; however, this is not the case. Alkynes are less susceptible to attack by electrophiles than alkenes. This is thought to be due to how tightly the pi electrons are held by alkynes and the fact that a relatively unstable vinyl carbocation would be formed upon attack of an electrophile. Nonetheless electrophilic attack can occur it just does so less readily than for alkenes. Below are several examples of addition reactions known to occur with alkynes. Note that in these reactions the product formed is a substituted alkene which can react further to produce a "di-addition" product:
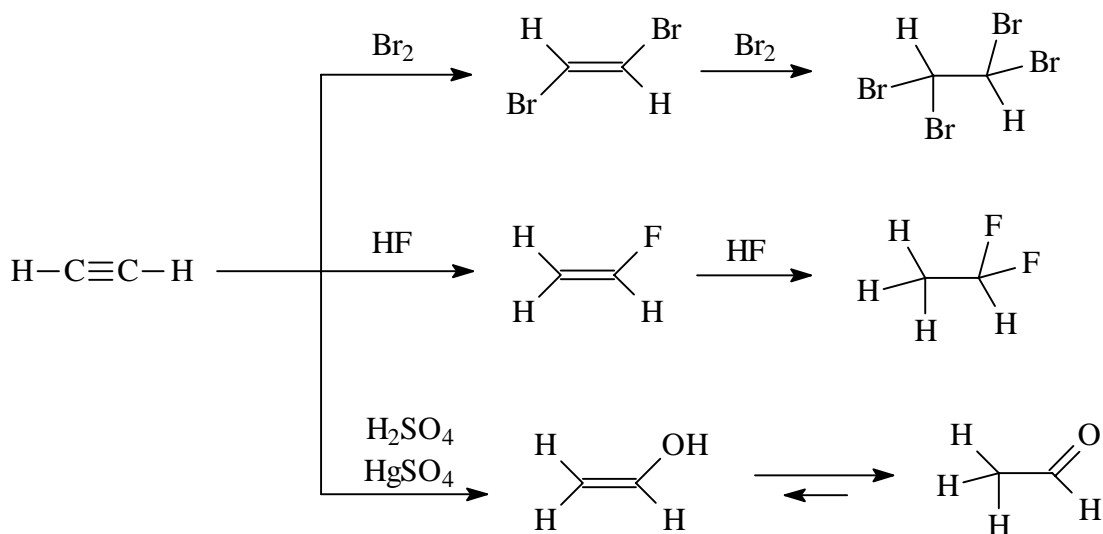
D. Alkynes and Nucleophilic Addition/Displacement Reactions

Like alkenes, alkynes do not commonly undergo direct nucleophilic because of their electronic configuration. However, similar to alkenes, if an alkynyl group is in direct conjugation with an electronic withdrawing functionality, then an alkynyl 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 alkyne serves to further polarize (enhance the electrophilicity of) the alkyne 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. These reactions are discussed in more detail in the *Carbonyl Tutorial* and individual drug tutorials.
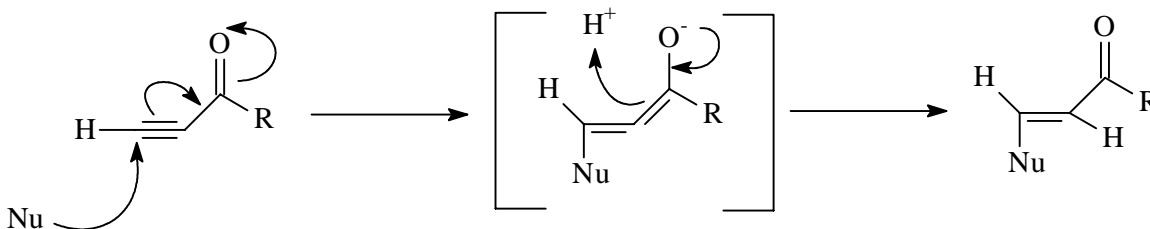
Like alkenes, alkynyl groups can facilitate nucleophilic substitution reactions at adjacent or "allylic" carbon atoms as discussed in more detail in the *Resonance and Induction Tutorial* and in the *Alkene Tutorial.* In such cases the allylic alkynyl group enhances the displacement reaction by resonance stabilization of the positive charge formed in the reaction intermediate; this positive charge forms as a result of departure of the leaving group.

V. Alkynyl Groups as Substituents

To understand the potential contributions of an alkynyl 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 alkynes 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 "alkynyl" (ethynyl) substituent:

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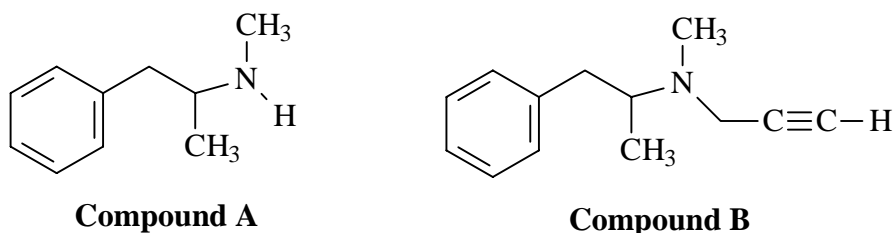
As a result of this structural difference, the physicochemical and pharmacological properties of Compound B differ significantly from those of Compound A including:

- The additional alkynyl group present on Compound B may have variable effects on affinity at therapeutically relevant targets (receptor, enzyme, etc.). If the target binds the additional alkynyl group then Compound B may have higher affinity than Compound A. If the target does not bind the additional alkynyl 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 alkynyl substituent present in Compound B is an electron donor by induction and therefore will alter the nucleophilicity of the amine nitrogen through direct inductive effects.

- The alkyny; substituent present in Compound B, like all alkynyl groups is linear and does not have different stereochemical forms (other than rotational forms about other atoms

- The additional alkenyl group present in Compound B may undergo metabolic reactions involving alkyne or allylic oxidations catalyzed by cytochrome enzymes.

VI. Problems: See end of the "Aromatics" Chapter