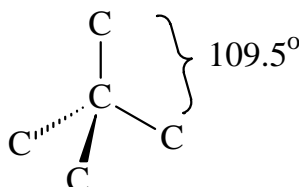


HYDROCARBON STRUCTURE AND CHEMISTRY: ALKANES*Jack DeRuiter***I. Introduction**

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

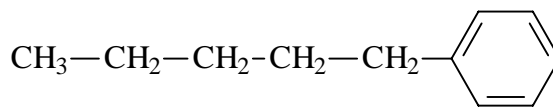
Alkanes or “saturated hydrocarbons” are simple organic hydrocarbons consisting of only of carbons bound to hydrogens or other carbon atoms by single bonds. In order to form four single bonds that are “equivalent”, carbon “hybridizes” the four electrons in its valence shell ($2s^2, 2p^2$), forming four equivalent bonding orbitals referred to as sp^3 orbitals; thus this type of hybridization is known as sp^3 . Each of the bonds formed by a carbon of this hybridization state are referred to as sigma (σ) bonds. Furthermore, according to the valence shell electron pair repulsion theory (VESPR), these bonds or electron pairs orient themselves as far away from each other as possible. This results in a tetrahedral geometry for carbon in the sp^3 hybridization state with bond angles of 109.5° between each C-C-C subunit. Also, since alkanes are composed exclusively of carbons and hydrogens in single (sigma) bonding arrangements, they will always have the general formula represented by C_nH_{2n+2} .



A detailed presentation of the nomenclature of alkanes is beyond the scope of this tutorial. The names and structures of some of the simpler, smaller alkanes are presented in the Table below. Note that each name ends with the “ane” suffix, denoting an alkane, and that they all “match” the general formula C_nH_{2n+2} . In addition to the individual alkane compounds, alkane “fragments” may be present as “substituents” of other molecules. When present as substituents they are referred to “alkyl” groups and named using the parent prefix followed by “yl”. The application of this nomenclature to alkane compounds, and alkyl substituents is illustrated in the example below, and the Table.



Alkane: Pentane

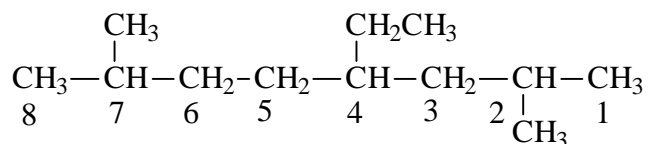


Alkyl group: pentyl

Alkanes and Alkyl Groups

COMPOUND	NAME	ALKYL GROUP	NAME
CH ₄	Methane	CH ₃ -	Methyl
CH ₃ CH ₃	Ethane	CH ₃ CH ₂ -	Ethyl
CH ₃ CH ₂ CH ₃	Propane	CH ₃ CH ₂ CH ₂ - CH ₃ CHCH ₃	n-Propyl iso-Propyl
CH ₃ CH ₂ CH ₂ CH ₃	Butane	CH ₃ CH ₂ CH ₂ CH ₂ - (CH ₃) ₂ CH ₂ CH- (CH ₃) ₃ C- CH ₃ CHCH ₂ CH ₃	n-Butyl iso-Butyl tert-butyl sec-butyl

It should also be noted that more complex alkane 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 alkanes requires that the longest continuous alkane chain be the “base” name for a structure (the “alkane”), and then that the chain be numbered to provide the lowest possible numbers for 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-ethyloctane (NOT 2,7-Dimethyl-5-ethyloctane)

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



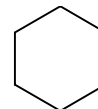
Cyclopropane



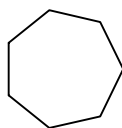
Cyclobutane



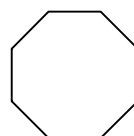
Cyclopentane



Cyclohexane



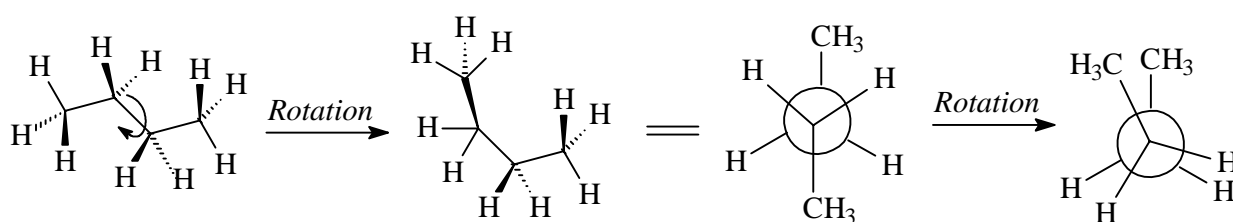
Cycloheptane



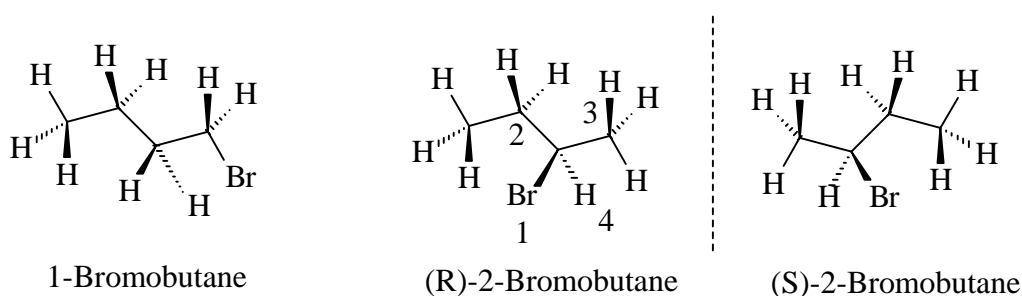
Cyclooctane

II. Configuration and Stereochemistry

As mentioned in the Introduction, carbon assumes a tetrahedral shape in the sp^3 hybridized bonding state characteristic of alkanes, and each carbon atom in an alkane lies at the center of a tetrahedron. Furthermore, there is “free rotation” about each carbon-carbon sigma bond in alkanes, so multiple rotation forms (conformers) are possible for an individual alkane as shown below for butane. Even in ring systems (cycloalkanes) where complete rotation is restricted by the presence of a ring, some rotation is possible, allowing for different conformational extremes. The conformational flexibility of alkanes and cycloalkanes is discussed in greater detail in the “Stereochemistry Tutorial” and is very important understanding overall molecular (and drug) structure and the interactions (i.e. receptor binding) and reactions of molecules with each other.



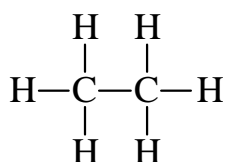
When the tetrahedral carbon atoms of alkanes are substituted with two, three or four like groups, there is no point or plane of asymmetry in the compound. However, if an alkane carbon atom is substituted with four different atoms or substituents, there is a point of asymmetry or “chirality” and different “stereoisomeric” forms are possible. Consider the examples of 1-bromobutane and 2-bromobutane below:



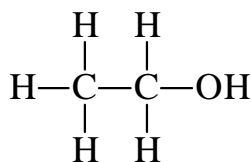
All the carbon atoms of 1-bromobutane contain at least two like substituents, so no carbon atom is chiral. In 2-bromobutane the second carbon atom contains four different substituents (a Br, H, methyl and ethyl) and thus is chiral. As a result of this chirality, there are two non-superimposable, mirror forms or enantiomers possible for 2-bromobutane and these are named as (R) or (S) depending on their relative clockwise or counter-clockwise orientation based on the Cahn-Ingold-Prelog priority rules. For a more detailed description of chirality and enantiomers, see the “Stereochemistry Tutorial”. The individual enantiomers of chiral alkanes typically display the same physico-chemical properties and chemical reactivities when placed in an “achiral” environment. However, in chiral environments, such those often encountered in drug science (proteins, DNA), enantiomers may display very different properties. These principles also are discussed further in the “Stereochemistry Tutorial”.

III. Physicochemical Properties

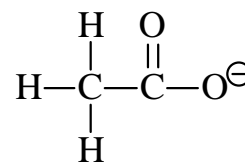
Alkanes, like all hydrocarbons, are composed exclusively of carbon-carbon and carbon-hydrogen bonds. These atoms are of relatively low and similar electronegativity (2.1 for H, 2.5 for C) and thus no significant permanent dipole is established in hydrocarbon bonding arrangements. Contrast this to halogenated 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 physico-chemical properties and reactivity profiles of these compounds. In simple hydrocarbons no such permanent dipoles and thus these compounds display physico-chemical and reactivity profiles very different from dipolar compounds. Because of their electronic nature, alkyl substituents are weak electron donors by induction as described in the "*Resonance and Induction Tutorial*".



Alkane
(Non-Polar)

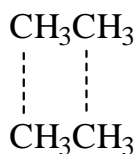


Alcohol
(Polar)

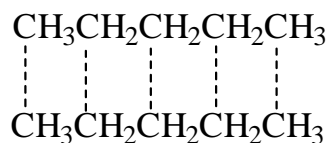


Acid
(Very Polar)

Because of their atomic composition, alkanes and alkyl 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 alkanes shown in the table below. Note that the smaller alkanes (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 alkane size increases to 5 carbon atoms (pentane) and beyond, the total energy of VDWs between molecules increases to the point where it exceeds 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 alkane size increases, the total energy of VDWs attraction between molecules increase and boiling points increase (see Table on next page).



Ethane (gas)
Few VDWs

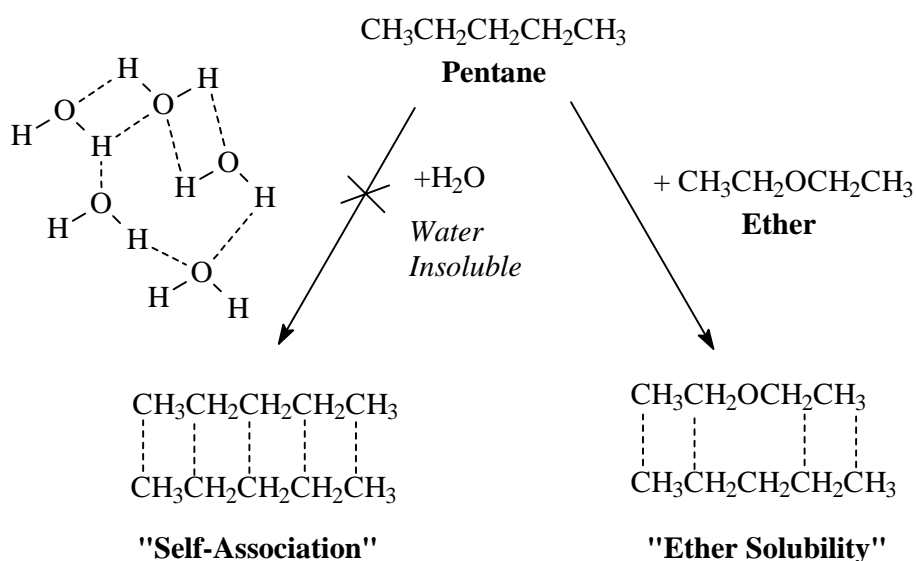


Pentane (Liquid)
More VDWs

Alkane Boiling Points

COMPOUND	STRUCTURE	BOILING POINT (°C)
Propane	CH ₃ CH ₂ CH ₃	-42
n-Butane	CH ₃ CH ₂ CH ₂ CH ₃	-0.5
n-Pentane	CH ₃ CH ₂ CH ₂ CH ₂ CH ₃	36.1
n-Hexane	CH ₃ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	69
n-Heptane	CH ₃ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	98
n-Octane	CH ₃ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	126

Perhaps the most noteworthy difference between alkanes/alkyl 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 alkanes are capable of “dissolving” other alkanes and other structurally related organic compounds are capable of dissolving alkanes. For example, ether can dissolve pentane. However, as a result of their inability to establish significant intermolecular interactions with water and other polar compounds, alkanes 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 alkanes do not possess ionic or dipolar functionality, they are not capable of such interactions. Thus when alkanes are added to water they self-associate by VDWs interactions and “separates out” from the water:

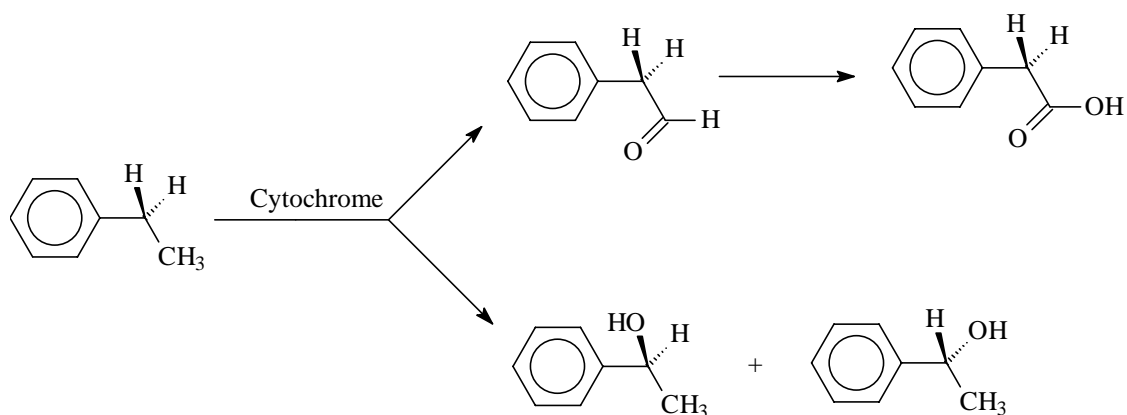


Because of their non-polar nature and resultant solubility properties, alkanes and alkyl groups are said to be "lipophilic" (lipid loving). This is discussed more at the end of this chapter.

IV. Reactions of Alkanes

In drug science alkanes are generally considered to be "relatively unreactive" molecules. Thus alkanes and drug with alkyl groups are relatively stable in the presence of air, light, water acid and base. It should be noted that in the presence of light and halogens or oxygen, alkanes can undergo halogenation or oxidation, but these reactions are not often significant in drug chemistry.

Also, as discussed in detail in the *Metabolism Chapter*, various carbon atoms of alkanes and alkyl groups are susceptible to metabolic oxidation by cytochrome enzymes (mainly in the liver) and this often has a significant impact on drug activity. Such metabolic oxidation reactions are illustrated below:



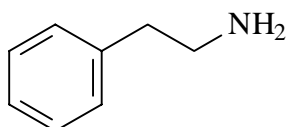
V. Alkyl Groups and Drug Analogues

The analysis of the relationships between drug structure and the various components of therapeutic and pharmacologic activity is a major focus of medicinal chemistry. Such structure-activity relationship (SAR) studies often involve investigating how altering the base structure of a drug will influence factors such as target binding (drug-receptor or drug-enzyme interactions), biodisposition (drug absorption, metabolism, distribution and elimination) as well as adverse reaction and drug interaction profiles. SAR studies are performed by designing and synthesizing "analogues" of a known drug, pharmacologic testing of the new analogues and, ultimately human clinical testing of those analogues with promising pharmacologic activity. In the design of new analogues, substituents may be added or removed from the parent drug, usually to accomplish some specific therapeutic goal such as improved receptor binding, or absorption from the GI tract, or reduced toxicity. These substituents may be an alkyl group, or some other organic functional group as detailed in the other Functional Group tutorials.

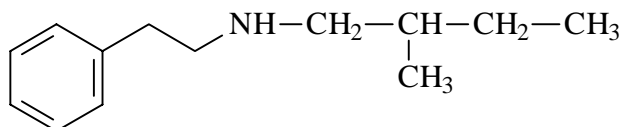
To understand the potential contributions of an alkyl substituent or functional group to the overall biological activity profile of a drug it is necessary to understand the physico-chemical and reactivity

profiles of alkanes 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 "alkyl" (branched pentyl) substituent and thus Compound B is an alkyl analogue (sometimes referred to as a "homologue") of Compound A:

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

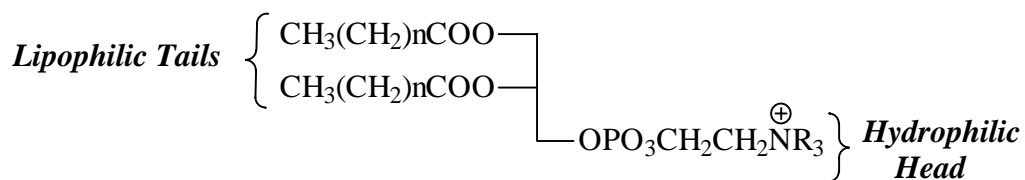


Compound A



Compound B

- The additional alkyl group present on Compound B may have variable effects on "intrinsic activity" which is the ability of the drug to bind to the therapeutically relevant target (receptor, enzyme, etc.). For example, the biologic target may be relatively small and not tolerate the additional steric bulk present in Compound B. In this case, Compound B would have lower intrinsic activity than Compound A. Alternatively, the biologic target may have a relatively large binding site with lipophilic functional groups capable of binding the additional pentyl group present on Compound B. In this case Compound B would have higher intrinsic activity than Compound A. Lastly it is possible that the biologic target may have a relatively large binding site but does not contain functional groups that actually bind the additional pentyl group present in Compound B. In this case the extra bulk of Compound B would simply be "tolerated" by the target and Compound B would not have lower or higher intrinsic activity 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. Recall that biological membranes are composed of a lipid bilayer (with interspersed proteins, etc.) and that each lipid component contains two lipophilic (long chain fatty acid esters) chains that "solubilize" non-polar substances more readily:



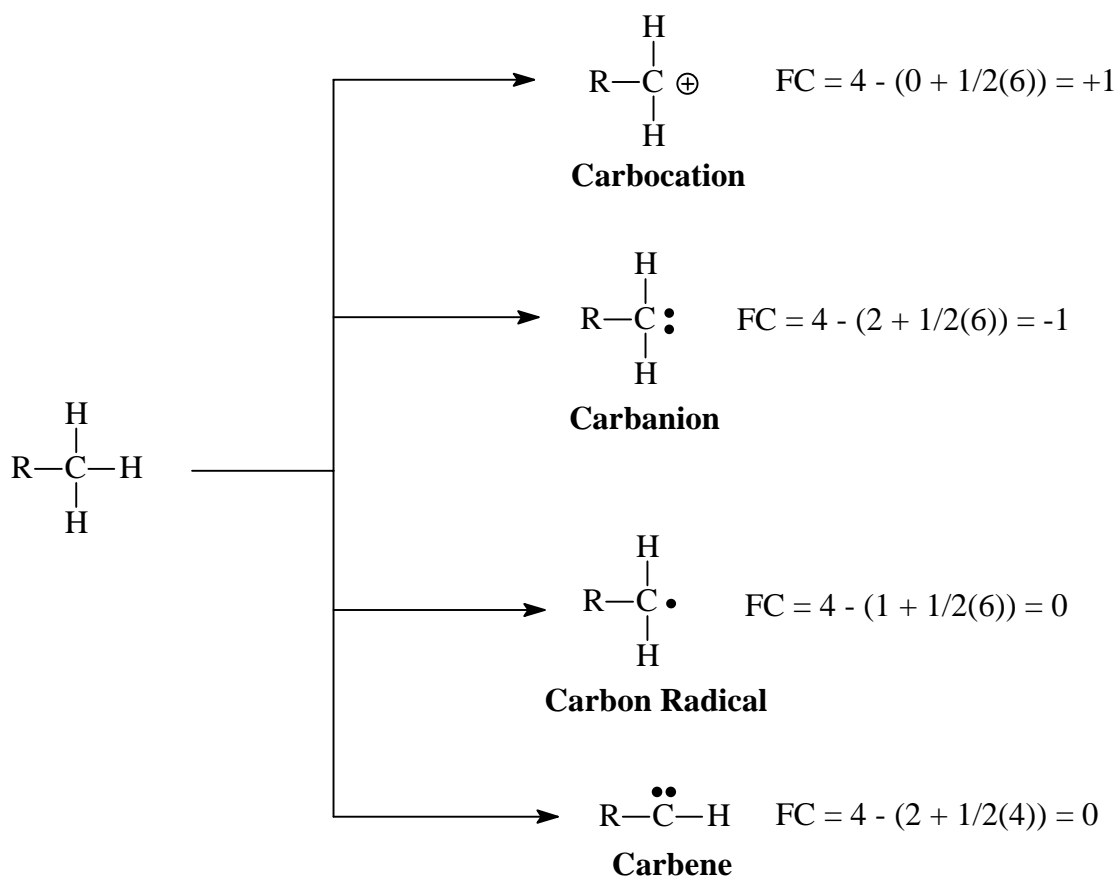
Membrane Phospholipid

- The alkyl substituent present in Compound B is an electronic donating group by induction, thus the amine group (N) present in this compound is more basic than the corresponding amino

group in Compound A (see *Amine Tutorial*). This can theoretically influence target binding, disposition properties, etc.

- The particular alkyl substituent present in Compound B contains a chiral carbon atom and thus R- and S-enantiomeric forms are possible. The two enantiomers would be expected to display similar solubility profiles, but may have different binding affinities for biologic targets and other proteins involved in distribution (plasma proteins), metabolism (enzymes), etc. Of course, conformational (rotational) isomerism is also possible in the additional pentyl side chain of Compound B and this may be important for target binding.
- The additional alkyl group present in Compound B may undergo metabolic reactions involving oxidation reactions catalyzed by cytochrome enzymes.

The Reactive Forms of Carbon and Formal Charge



VI. Problems: See end of the “Aromatics” chapter