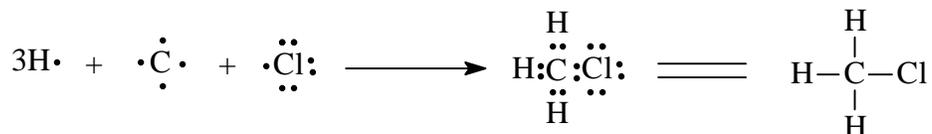
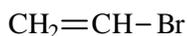
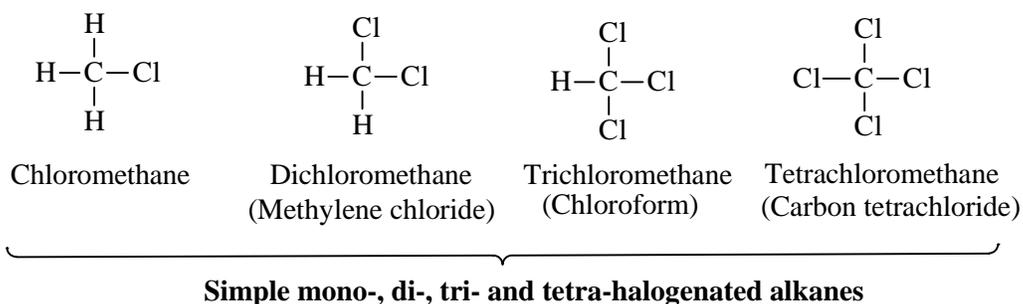
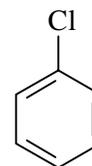


HALOGENATED HYDROCARBON STRUCTURE AND CHEMISTRY*Jack DeRuiter***I. Introduction**

Halogenated hydrocarbons are organic compounds consisting of C-C, C-H and C-X bonds where X is a halogen atom (F, Cl, Br, I). 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. Halogens have seven valence electrons and thus require a single electron or bond to complete its octet. Thus in halogenated hydrocarbons, carbon can form neutral bonding arrangements by forming single bonds with halogens, single bonds with hydrogen, and single, double or triple bonds with other carbons (or other atoms). This bonding order is illustrated for chloromethane shown below:

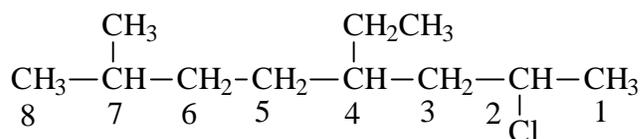


Halogenated hydrocarbons may be sub-classified based on the nature of the hydrocarbon fragment to which they are attached (alkane, alkene, alkyne, aromatic), and on the basis of the number of halogen atoms present (mono-, di- tri- tetra-, etc. halogenated compounds). The structures below show several examples of such sub-classification. In the simplest case, methane can be substituted with one, two, three or four halogens (chlorines, in the example below). These are examples of mono-, di-, tri- and tetra-halo substituted alkanes. Note that some of these halogenated methane derivatives also have trivial names that are commonly used (parentheses):

**Bromoalkene****Iodoalkyne****Chloroaromatic**

A detailed presentation of the nomenclature of halogenated hydrocarbons is beyond the scope of this tutorial. Briefly, the common names for mono-substituted halogenated hydrocarbons

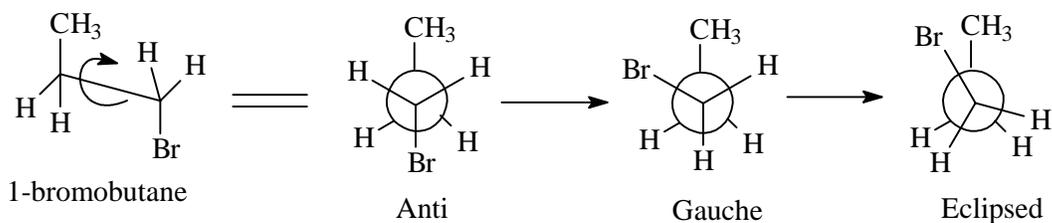
consists of the name of the alkyl (or alkenyl, alkynyl or aromatic) moiety followed by the name of the halogen. Thus, it may be necessary to review the other hydrocarbon tutorials to learn more about the nomenclature of these compounds. More complex halogenated hydrocarbons require a systematic method of nomenclature based on the official rules developed by the International Union of Pure and Applied Chemistry (IUPAC). IUPAC nomenclature requires that the longest continuous carbon chain be the "base" name for a structure (i.e. the "alkane"), and then that the chain be numbered to provide the lowest possible numbers for the **halide**. 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 halogen substituent. More detailed discussion of IUPAC nomenclature can be found in any standard Organic Chemistry textbook:



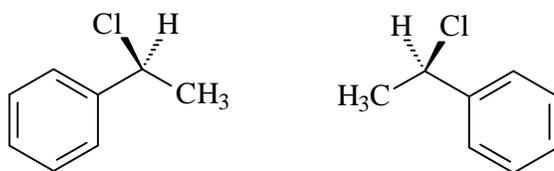
4-ethyl-7-methyl-2-chlorooctane (NOT 2-methyl-5-ethyl-7-chlorooctane)

II. Configuration and Stereochemistry

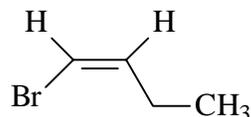
Halogen atoms may play a key role in the stereochemical potential (optical isomerism, geometric isomerism and conformational isomerism) of hydrocarbon compounds. For example, in 1-bromobutane there are a number of conformational energy extremes in which the bromine atom is in steric conflict (eclipsed and gauche forms) or steric relief relative to the terminal methyl group as shown by the following conformations drawn in Newman projection form:



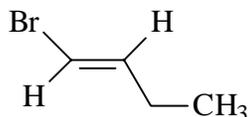
Halogen atoms may be one of the four differing substituents on a sp^3 hybridized carbon atom, resulting in chirality and optical isomerism with R and S enantiomers:



Halogen atoms also may be one of the differing substituents on an sp^2 hybridized carbon atom of an alkene, resulting in geometric isomerism with "cis" and "trans" isomers:



"cis"-isomer



"trans"-isomer

Note in these examples that the halogen atom is merely one of the substituent groups of the conformer, optical isomer or geometric isomer and that the hydrocarbon hybridization state and the overall substitution pattern on the hydrocarbon framework determines stereochemical potential. It may be useful to review the other hydrocarbon tutorials as well as the *Stereochemistry Tutorials* for a more detailed discussion of these subjects.

III. Physicochemical Properties

Although different in structure, the halogenated hydrocarbons are quite similar to simple hydrocarbons in many (but not all!) of their physicochemical properties. Recall that simple hydrocarbons (alkanes, alkenes, alkynes and aromatics) are composed exclusively of carbon-carbon and carbon-hydrogen bonds and these atoms are of relatively low and similar electronegativity (2.1 for H, 2.5 for C). Thus no significant permanent dipole is established in simple hydrocarbon bonding arrangements. Halogenated hydrocarbons contain at least one strongly electronegative halogen atom and thus have a permanent dipole (assuming multiple halogens are not present which have individual dipoles that cancel based on three-dimensional bonding arrangements). This permanent dipole does not, however, guarantee dipole-dipole interactions. Even though halogens are electron rich (3 pairs of non-bonded electrons in the bound state), there is no corresponding region of electron deficiency. Thus in halogenated hydrocarbons, like simple hydrocarbons, intermolecular bonding is dependent on van der Waals interactions (see *Alkane Tutorial*).

Because of their atomic and electronic composition, halogenated hydrocarbons 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. As is observed with the alkanes and other simple hydrocarbons (see *Alkane Tutorial*), as the number of carbon atoms (“size”) increases in the halogenated hydrocarbon series, the total energy of VDWs between molecules increases, and boiling points increase.

Perhaps the most noteworthy similarity between halogenated hydrocarbons and simple hydrocarbons is their solubility properties. As discussed in other tutorials, structurally similar or analogous compounds (“like” compounds) display overlapping solubility or miscibility profiles. Thus halogenated hydrocarbons are capable of “dissolving” other halogenated hydrocarbons as well as simple hydrocarbons. However, as a result of their inability to establish significant intermolecular interactions with H₂O and other polar compounds, halogenated 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 halogenated

hydrocarbons do not possess ionic or dipolar functionality, they are not capable of such interactions. Thus when halogenated hydrocarbons are added to water they self-associate by VDWs interactions and “separate out” from the water.

While similar to simple hydrocarbons in intermolecular bonding and solubility profiles, the halogenated hydrocarbons differ in several important respects:

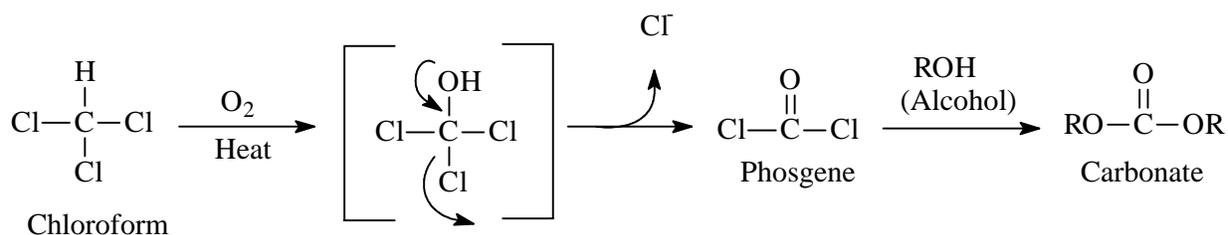
- They have higher boiling points than their corresponding alkanes. While small, mono-halogenated alkanes may be gases, even di-, tri- and tetra-halogenated methane derivatives are liquids at room temperature. Also, a number of halogenated ether derivatives are volatile liquids and used as inhalation anesthetics.
- While most simple hydrocarbons are very flammable, halogenated hydrocarbons are non-flammable. In fact, carbon tetrachloride has been used in fire extinguishers.

IV. Reactions of Alkanes

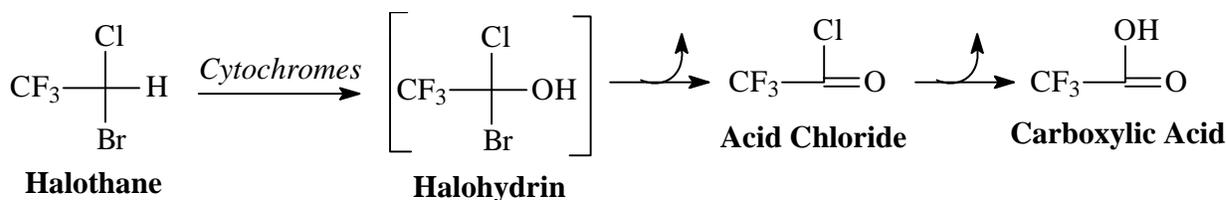
As drugs the halogenated hydrocarbons generally are considered to be relatively unreactive **chemically** (in formulations or the biologic environment). Under the appropriate conditions, however, halogenated hydrocarbons may undergo displacement, elimination, oxidation and other reactions are described generally below:

A. Oxidation Reactions:

Polyhalogenated compounds can undergo chemical oxidation in the presence of oxygen and thermal energy. For example, the solvent chloroform may undergo oxidation to yield phosgene a very reaction and toxic substance. This is why chloroform and other polyhalogenated compounds usually contain small amounts of alcohol. The alcohol (a nucleophile) "scavengers" the phosgene formed yielding an unreactive and non-toxic carbamate:

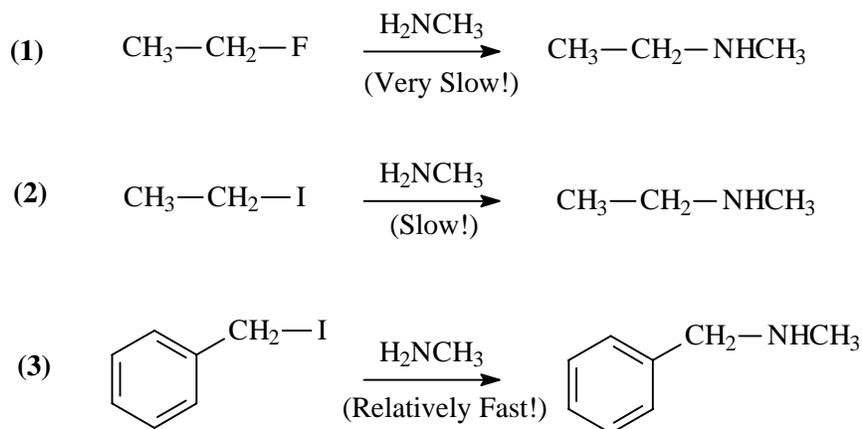


Halogenated compounds can also undergo oxidative metabolism catalyzed by human cytochromes. For example, the general anesthetic halothane is oxidized by liver enzymes and the intermediate halohydrin spontaneously eliminates halogen (Br-) to form an acid chloride, which then hydrolyzes to yield the acid (see the "Carboxylic Acid Tutorial" for more details on this chemistry):



B. Nucleophilic Displacement and Elimination Reactions:

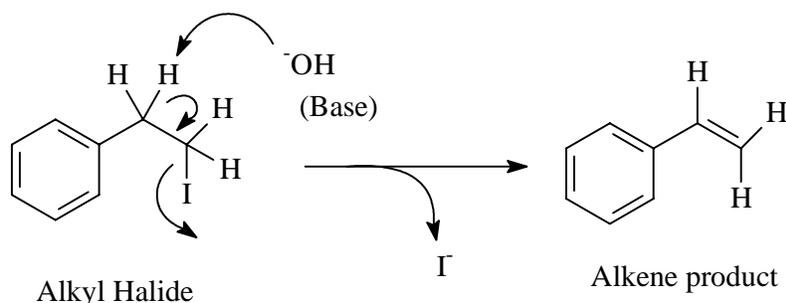
Suitably "activated" halogenated hydrocarbons may undergo nucleophilic displacement reactions in the presence of nucleophiles and elimination reactions in the presence of bases. As electronegative atoms, halogens are relatively good "leaving groups" - because of their electronegativity they can accommodate the negative charge resulting from heterolytic cleavage associated with displacement and elimination reactions. Also, the larger the halogen atom (further "down" the periodic table), the more "polarizable" (the greater the distance between the valence electrons and atomic nucleus) and therefore the more likely it is to function as a leaving group. Furthermore, when bound to a carbon atom that can yield a stabilized carbocation (tertiary carbon, benzylic carbon or allylic carbon), a halogen can leave more easily. Thus this carbon-halogen bond can be cleaved more readily than a carbon-halogen bond in which the carbon atom does not yield a stabilized carbocation. Each of these principles are illustrated in the examples below. Note in equation (1) a small, non-polarizable halogen atom is linked to a primary carbon atom. Thus it is difficult to displace this halogen with a nucleophile such as methylamine. In equation (2) the halogen is the larger, more polarizable iodide (better leaving group) and this is more readily displaced by the nucleophile, but still is a slow reaction. In equation (3) the halogen is a good leaving group (iodide) and it is attached to a benzylic carbon atom - a carbon atom that can yield a stabilized carbocation intermediate. In this case the reaction occurs quite readily:



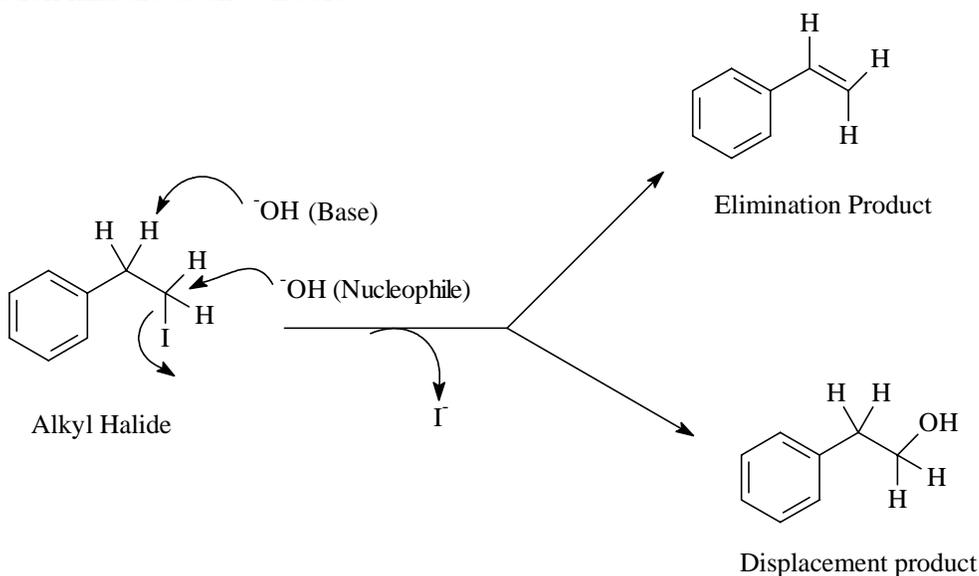
It may be necessary to review the *Resonance Tutorial* and *Amine Tutorial* for more details on displacement reactions such as these, and the structural requirements for reactivity.

Halogenated hydrocarbons can also undergo **elimination reactions** in the presence of strong base (HO^- , etc) to form alkenes. The general scheme for an elimination reaction is shown below. Note that the general criteria for reactivity here are very similar to those described above for

displacement reactions. To summarize, halogenated hydrocarbon with halogens that are good leaving groups (such as I⁻) linked to carbon atoms that can form stabilized (by resonance or induction) carbocations are more likely to undergo elimination reaction. Also, note that at least one hydrogen atom is required on carbon atom adjacent to the carbon bearing the halogen substituent for the elimination reaction to occur:



Based on the similarities in mechanism and structural requirements for reaction, and the fact that many nucleophiles are also good bases, it is not surprising that displacement and elimination reactions often compete with each other under certain conditions. In the example reaction shown above, hydroxide could function as a base to promote elimination, or compete as nucleophile to promote displacement. Thus it is possible to get mixtures of both mechanistic products from the same reaction mixture as shown below:

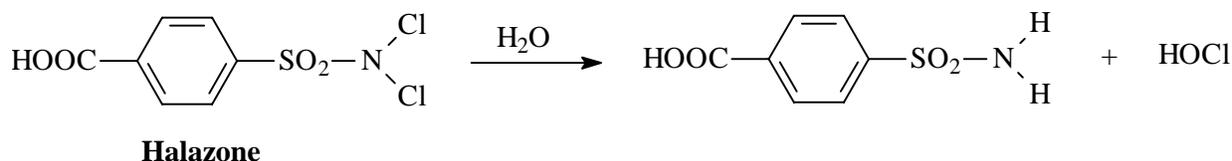
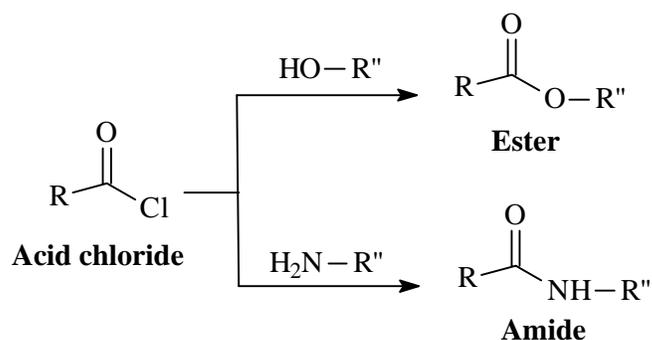


Note however, one key difference in the structural requirements of the halogenated hydrocarbon for displacement and elimination - that is, at least one hydrogen atom must be present on the carbon adjacent to the carbon bearing the halogen for elimination to occur. In other words, halogenated hydrocarbons lacking this structural requirement may be capable of displacement, but NOT elimination reactions. Such is the case for the benzyl halide in equation (3) illustrated displacement reactions. This compound will readily undergo displacement, but elimination is not possible (see above)! A more detailed discussion of the which products predominate in these reactions, or how reaction conditions can be controlled or modified to favor formation of one product over another is

beyond the scope of this tutorial. More information about these reactions can be obtained from any standard organic Chemistry Textbook.

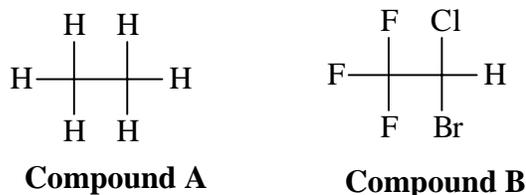
V. Other Halogenated Organic Compounds

In addition to simple hydrocarbons, halogens may also be present on other organic functionality as illustrated by the examples below. The acid chlorides are very reactive substances used in acylation reactions to form esters and amides. N-chloro compounds such as halazone are used as water disinfectants due to their ability to liberate hypochlorous acid (HOCl):



VI. Halogens as Substituents

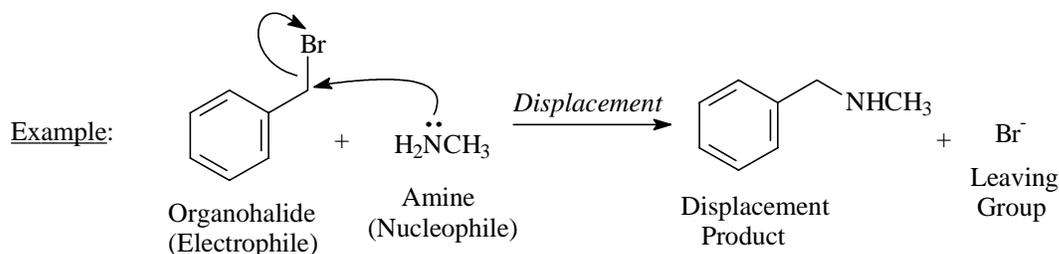
To understand the potential contributions of a halogen substituent or functional group to the overall biological activity profile of a drug it is necessary to understand the physico-chemical and reactivity profiles of halogens as described in the previous sections. Consider the example of Compounds A and B below. In this example, Compound B (the general anesthetic halothane) differs structurally from Compound A only in the presence of an additional halogen substituents:



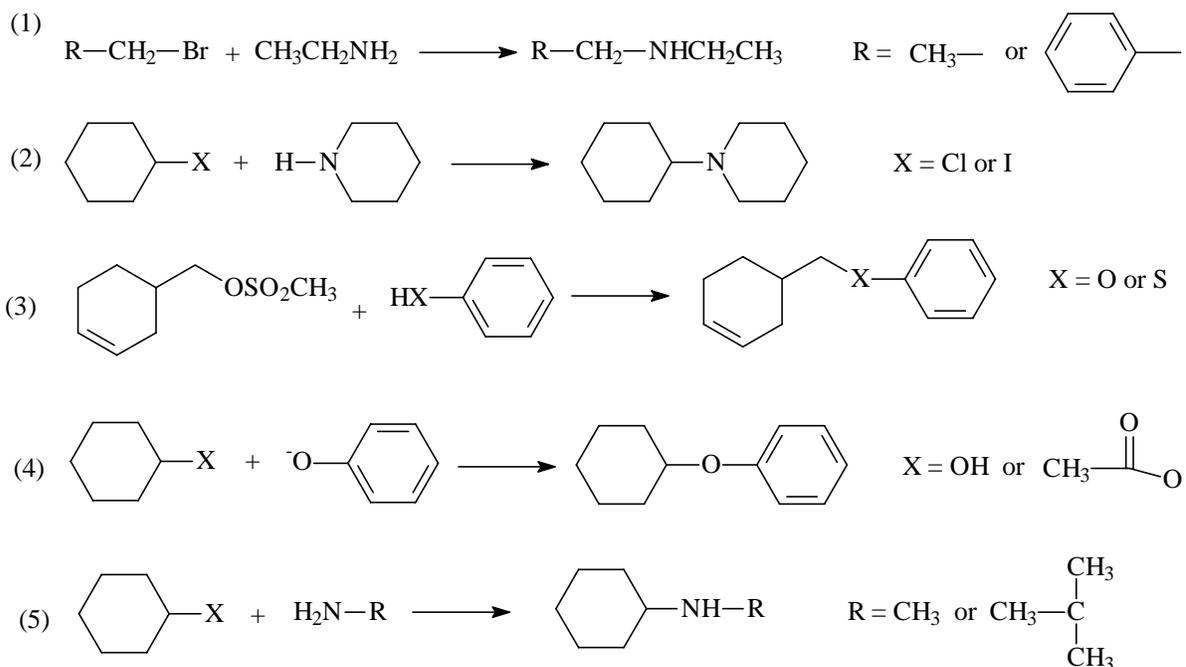
As a result of this structural difference, the physicochemical properties of Compound B differ significantly from those of Compound A including:

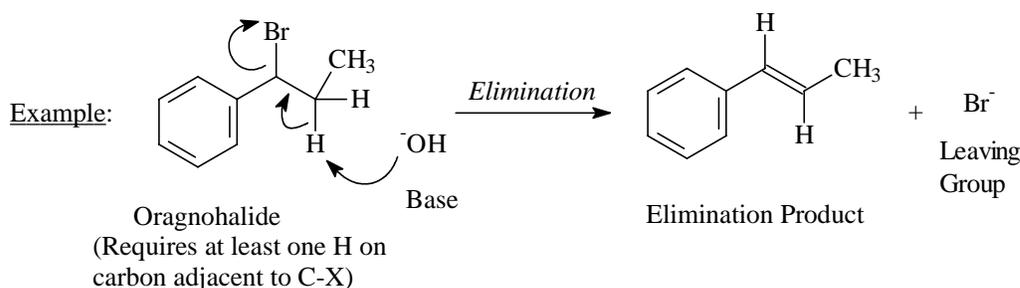
- Compound B is more lipophilic (non-polar) than Compound A and thus is more soluble in non-polar organic solvents (less soluble in water and polar solvents), and more readily partitions across biological membranes.
- The halogen substituents present in Compound B will alter the physical state (raise boiling point) and reduce flammability.
- The halogen substituents present in Compound B will alter the reactivity of the carbon atoms, making them more susceptible to displacement and elimination reactions.
- The different halogen substituents on one carbon atom of Compound B renders this site chiral and thus R and S-enantiomers of this compound are possible. These enantiomers would have similar physicochemical properties relative to each other in achiral environments.
- The presence of halogen substituents allow for unique metabolites to form (see example of Halothane above).

VII. Problems

Halogenated Hydrocarbon (Organohalide) Reactions1. Nucleophilic Displacement Reactions:**Rate of Nucleophilic Displacement Reactions dependent on:**

- Strength of the nucleophile: Less electronegative atoms more nucleophilic (assuming at least one pair NBEs)
Examples: $\text{N} > \text{O} > \text{F}$; $\text{S} > \text{O}$; $\text{I} > \text{Br} > \text{Cl} > \text{F}$
- Reactivity of the Electrophile: Benzylic and tertiary carbons > Secondary Carbons > Primary carbons
- Quality of the leaving group: More resonance stabilization, better leaving group ($\text{CH}_3\text{COO}^- > \text{HO}^-$).
Also, less electronegative atoms make better leaving groups: $\text{N} > \text{O} > \text{F}$; $\text{S} > \text{O}$; $\text{I} > \text{Br} > \text{Cl} > \text{F}$
- Steric factors: Increased steric bulk near atoms of reactions may slow reaction

Examples and Problems: Which Reaction is faster?

Halogenated Hydrocarbon (Organohalide) Reactions (Part 2)2. Elimination Reactions:**Rate of Elimination Reactions dependent on:**

- Strength of the base: For basic atoms (NBEs) Basicity decreases from left to right across the periodic table (N>O>F); for atoms in the same column of the periodic, basicity decreases as you move to higher atomic numbers (S > O; I > Br > Cl > F)
- Reactivity of the Organohalide: Benzylic and tertiary carbons > Secondary Carbons > Primary carbons. In compounds where elimination reactions may occur in "more than one direction", the more substituted alkene product will predominate as the thermodynamic product (see Examples below)
- Quality of the leaving group: More resonance stabilization, better leaving group (CH₃COO⁻ > HO⁻). Also, less electronegative atoms make better leaving groups: N>O>F; S > O; I > Br > Cl > F
- *NOTE: Elimination Reactions often compete with displacement reactions since some nucleophiles are also good bases!*

Examples and Problems: Which Reaction is faster?