

Alkyl Halides

Reading: Wade chapter 6, sections 6-1- 6-12

Study Problems: 6-44, 6-46, 6-48, 6-50, 6-56, 6-63, 6-64

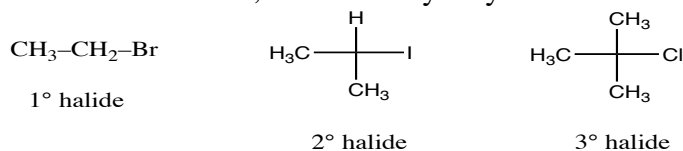
Key Concepts and Skills:

- Name and classify alkyl halides as primary (1°), secondary (2°) or tertiary (3°).
- Predict the products of SN2 reactions, including stereochemistry. Draw a mechanism for the SN2 reaction.
- Predict which substitutions will be faster based on differences in substrate, base/nucleophile, leaving group, or solvent.

Lecture Topics:

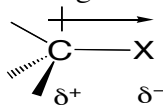
I. Nomenclature

Primary halide, secondary halide, tertiary halide: these terms specify the substitution of the halogen bearing carbon atom. If the halogen-bearing carbon atom is bonded to one other carbon atom, it is a primary alkyl halide; if the halogen-bearing carbon atom is bonded to two other carbons, it is a secondary alkyl halide; if the halogen-bearing carbon atom is bonded to three other carbons, it is a tertiary alkyl halide.



II. Structure of alkyl halides

The carbon-halogen bond of alkyl halides is highly polarized, with a partial positive charge on carbon and a partial negative charge on the halide:



Dipole moment: $\mu = 4.8 \times \delta \times d$

Both bond length and electronegativity must be considered. For the halides, these trends oppose one another:

Electronegativity: $\text{I} < \text{Br} < \text{Cl} < \text{F}$

Bond length: $\text{C-F} < \text{C-Cl} < \text{C-Br} < \text{C-I}$

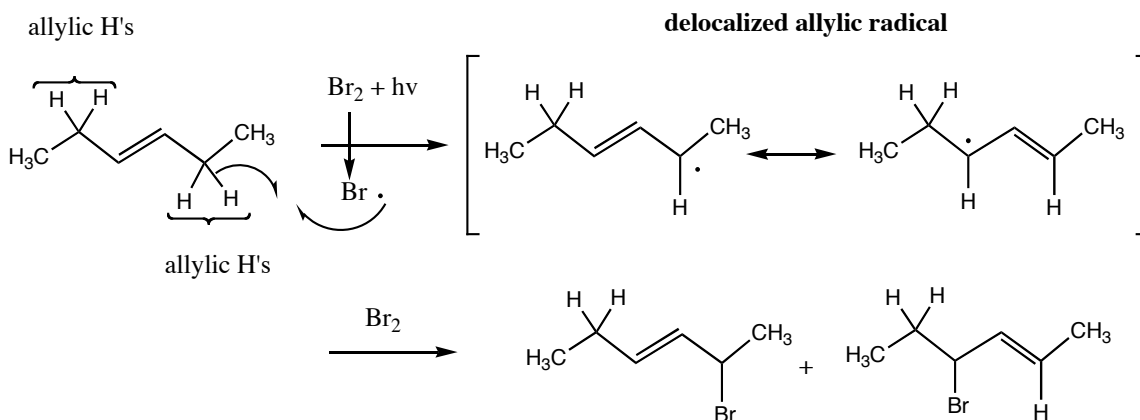
Dipole moment: $\text{C-I} < \text{C-Br} < \text{C-F} < \text{C-Cl}$

II. Synthesis of alkyl halides

Free radical halogenation is not a practical means of synthesis of alkyl halides because for normal alkanes, a mixture of products is obtained; however, formation of tertiary alkyl bromides is a practical process, since the tertiary radical (formed in the rate-determining step) is much more stable than the primary radical:



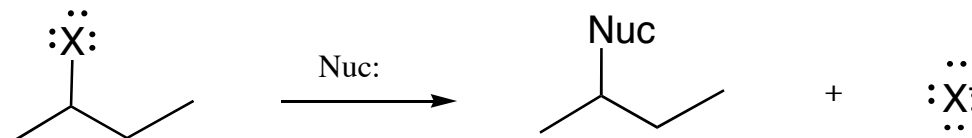
Allylic halogenation (the allylic position is the carbon atom neighboring a double bond) is also a practical process, since a delocalized, resonance-stabilized allylic radical is formed as an intermediate.



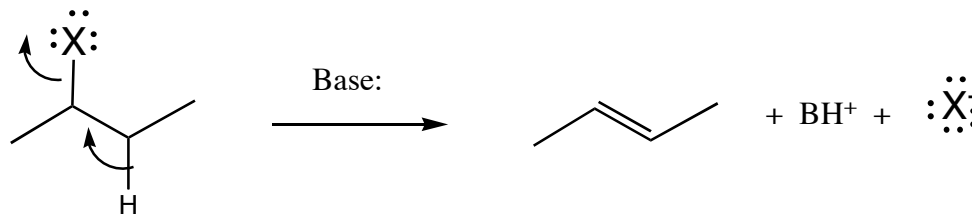
- Br_2 must be used in low concentrations since it will also add to double bonds
 - N-bromosuccinimide (NBS) is often used as a bromine source instead of Br_2 , since it generates a constant low concentration of Br_2 in solution.
- There are a variety of other methods of generating alkyl halides from alkenes, alkynes, and alcohols that will be studied in later chapters

III. Reactions of alkyl halides: substitution and elimination

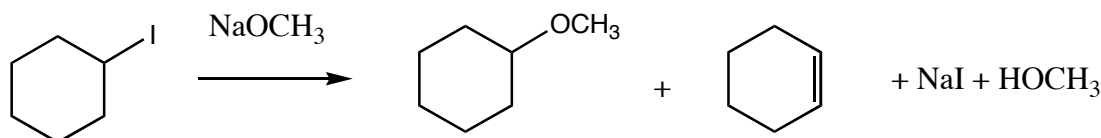
A. Substitution is the replacement of halide ion in a molecule by a nucleophilic species (an atom possessing a lone-pair.)



B. Elimination is the loss of H-X from an alkyl halide, resulting in the formation of an alkene. This is also called a dehydrohalogenation; a new pi bond is formed



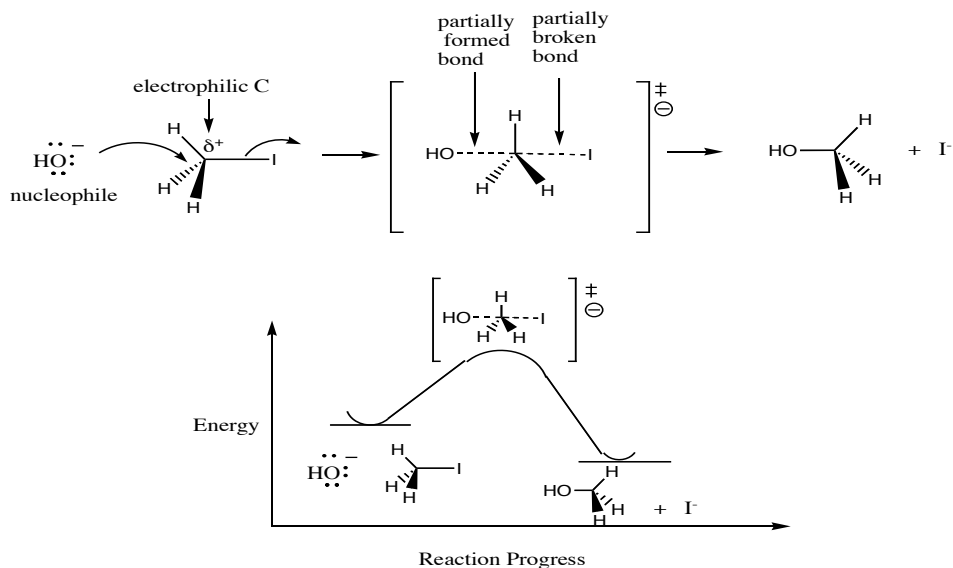
Most nucleophiles are basic and can engage in substitution or elimination depending on the alkyl halide and reaction conditions:



Bimolecular nucleophilic substitutions: SN2 reaction

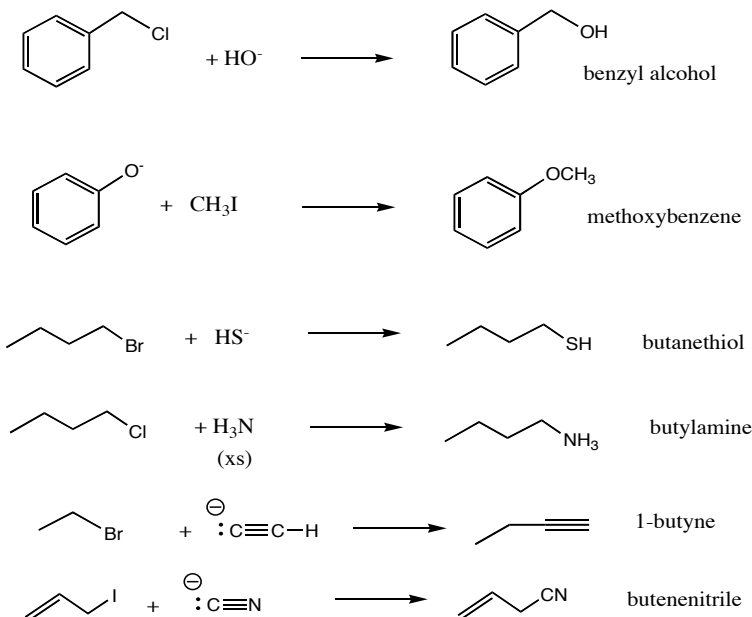
SN2 reactions are second order overall and involve a single concerted step (a bimolecular collision) in which a nucleophile approaches the alkyl halide 180° away from the halide **leaving group**. *Nucleophiles attack electrophiles*. For example, hydroxide ion is a strong nucleophile (donor of an electron pair) and iodomethane is a substrate with an electrophilic carbon atom (bearing a partial positive charge). The direction of the arrow shows the direction of electron flow: from nucleophile to electrophile:

The SN2 reaction is a single-step bimolecular collision of two molecules

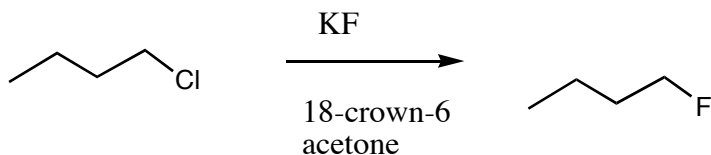
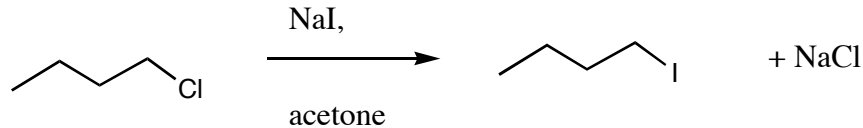


The reaction is second order overall; there are no intermediates, and the transition state (not a stable, isolable species) consists of a pentacoordinate carbon atom.

Typical examples:



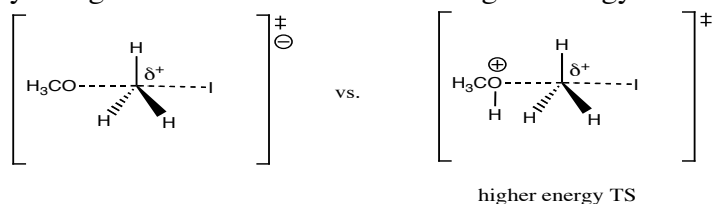
Halogen exchange is a substitution where one halogen atom replaces another; it is commonly used to form fluorides and iodides:



IV. Factors Affecting the Rate of SN2 Reactions

1. Strength of the nucleophile

•Negatively charged nucleophiles react faster than neutral, non-charged nucleophiles: compare CH_3O^- vs. CH_3OH (10^6 rate difference). Thus, $\text{HO}^- > \text{H}_2\text{O}$, and $\text{HS}^- > \text{H}_2\text{S}$, and $\text{H}_2\text{N}^- > \text{H}_3\text{N}$. For methanol as a nucleophile, there is a partial positive charge on the oxygen atom in the transition state. The electrostatic repulsion that ensues with the partially positively charged carbon atom results in a higher energy transition state:



•Basicity vs. Nucleophilicity

Basicity is measured as the equilibrium constant for abstracting an H atom, and **nucleophilicity** is the rate of attack on an electrophilic carbon atom. Most (but not all) good nucleophiles are also strong bases.

•Nucleophilicity decreases from left to right in the periodic table, following the increase in electronegativity: $\text{HO}^- > \text{F}^-$, $\text{H}_3\text{N} > \text{H}_2\text{O}$, $\text{R}_3\text{P} > \text{R}_2\text{S}$

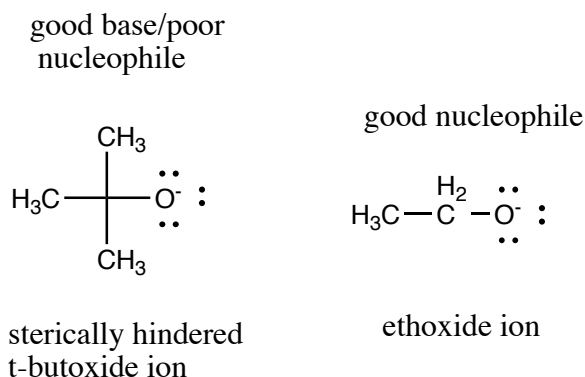
•Nucleophilicity increases down the periodic table, following the increase in size and polarizability.

$\text{I}^- > \text{Br}^- > \text{Cl}^- > \text{F}^-$; $\text{HSe}^- > \text{HS}^- > \text{HO}^-$; $\text{R}_3\text{P} > \text{R}_3\text{N}$:

The reason for this is that larger atoms are more polarizable, and their electrons can move more freely toward a positive charge in the transition state. The increased mobility of electrons enhances an atom's ability to form a bond at long distances. Consider the transition states involving substitution with F^- vs. I^- .

2. Steric Effects on Nucleophilicity

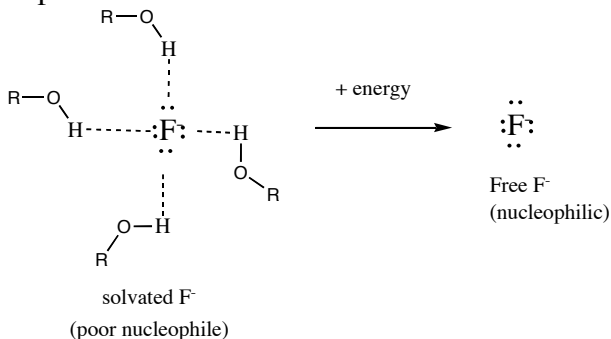
A nucleophile must get close to the substrate (electrophile) in order to achieve the overlap of orbitals required in the transition state. A sterically hindered nucleophile such as t-butoxide ion is a weak nucleophile because steric hindrance from the methyl groups around oxygen prevents close approach to the electrophilic carbon atom of an alkyl halide. While t-butoxide ion is still a strong base (a proton is relatively unhindered), ethoxide ion is a superior nucleophile because of a lack of steric hindrance.



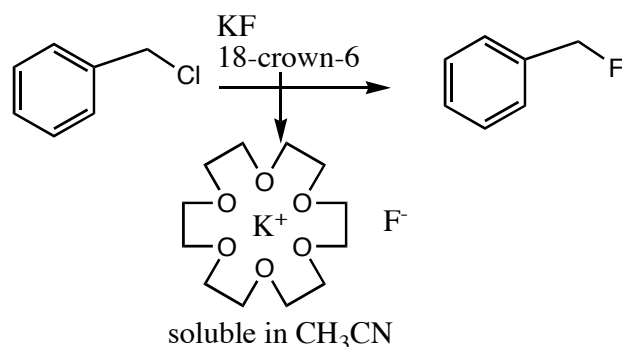
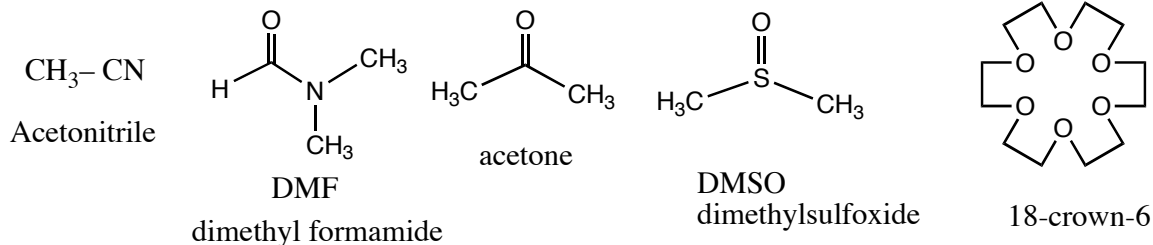
3. Solvent Effects

A protic solvent (H_2O , CH_3OH) will hydrogen bond to small, negatively-charged nucleophiles. Extra energy is required to “desolvate” these ions, thus their nucleophilicity is reduced in polar, protic solvents.

Nucleophilicity in polar protic solvents: $\text{F}^- < \text{Cl}^- < \text{Br}^- < \text{I}^-$



• **Aprotic solvents** enhance the nucleophilicity of anions but lead to decreased solubility. An anion is more reactive in an aprotic solvent because it is not so strongly solvated → no hydrogen-bonding. Polar aprotic solvents like acetone, **acetonitrile**, **DMF**, and **DMSO** have strong dipole moments to enhance the solubility of anions. **Crown ethers** are compounds which solvate positively charged ions, making them soluble in organic media; this process then enhances the solubility of the corresponding anion in polar aprotic solvents



4. Effects of substrate on reactivity in $\text{S}_{\text{N}}2$ reactions.

1. Leaving group, X

a. Must be electron-withdrawing, to polarize the C-X bond. *Halides are among the best leaving groups because of their electronegativity.*

b. Must be able to stabilize a negative charge once it has left: stability of X^- . Good leaving groups are weak bases, the conjugate bases of strong acids.

Good leaving groups: Cl^- , Br^- , I^- , RSO_2O^- , ROSO_2O^- , ROPO_2O^-

Poor leaving groups: HO^- , CH_3O^-

Neutral leaving groups: H_2O , ROH , R_3N , R_3P

Example: $\text{CH}_3\text{OH} + \text{HBr} \rightarrow [\text{CH}_3\text{OH}_2]^+ + \text{Br}^- \rightarrow \text{CH}_3\text{Br} + \text{H}_2\text{O}$

c. Must be polarizable to stabilize the transition state by engaging in more bonding at a distance; I^- is a good nucleophile and a good leaving group; F^- is a poor nucleophile and a poor leaving group.

2. Steric effects

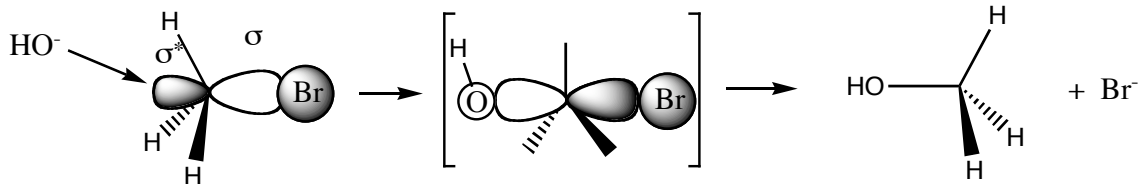
Rates for $\text{S}_{\text{N}}2$ substitution of alkyl halides: $\text{CH}_3\text{X} > 1^\circ > 2^\circ > 3^\circ \sim \text{neopentyl}$

- Crowding of the backside of electrophilic carbon atom drastically slows down the rate of attack. The steric bulk of alkyl groups hinder the rate.

- 3° alkyl halides **never** undergo substitution by an $\text{S}_{\text{N}}2$ mechanism

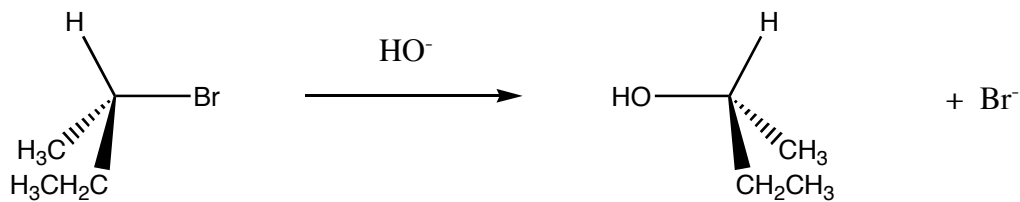
V. Stereochemistry of the SN2 reaction

Backside attack of the nucleophile, donating electron density to the σ^* orbital of the alkyl halide helps weaken the C-X σ bond. The tetrahedron is turned inside out (the “umbrella” effect) resulting in an inversion of configuration at carbon



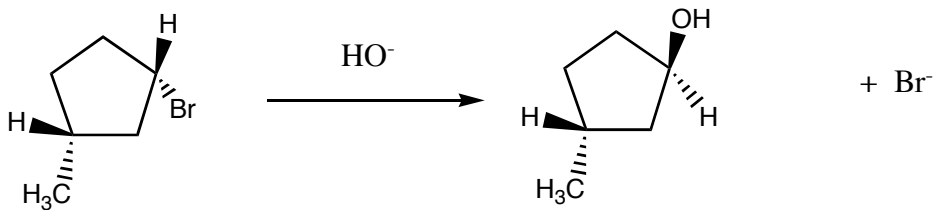
inversion of configuration

For an asymmetric carbon atom, backside attack gives the opposite configuration at the carbon atom. This is known as **Walden inversion**



S-2-bromobutane

R-2-butanol



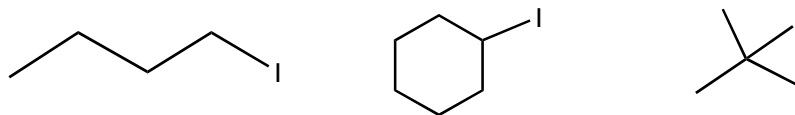
cis-1-bromo-3-methyl
cyclopentane

trans-3-methylcyclopentanol

The SN2 reaction is an example of a **stereospecific** reaction: the relationship between the stereochemical configuration of the reactants and products (at the reaction center) is one of inversion; that is, the product has inverted configuration relative to the starting material.

Additional Problems for practice:

- 1.) Which of the following compounds is the best SN2 substrate:



- 2.) Explain why an SN2 reaction proceeds more rapidly in a polar, aprotic solvent than in a polar protic solvent. Draw a reaction-energy diagram to illustrate your answer.
- 3.) Predict the product and give the stereochemistry resulting from the reaction of the following nucleophiles with R-2-bromooctane:
(a) NC^- (b) CH_3S^- (c) Br^- (d) I^-
- 4.) Which reagent in each pair will react faster in an SN2 reaction with hydroxide ion?
(a) CH_3Br or CH_3I (b) $\text{CH}_3\text{CH}_2\text{I}$ in ethanol or dimethyl sulfoxide
(c) $(\text{CH}_3)_3\text{CCl}$ or CH_3Cl
- 5.) Which reagent in each of the following pairs is more nucleophilic? Explain your answer?
(a) NH_2^- or NH^- (b) BF_3 or F^- (c) I^- or Cl^- (d) $(\text{CH}_3)_3\text{P}$ or $(\text{CH}_3)_3\text{N}$
(e) H_2O or CH_3COO^-