Chapter 7
Reactions of Haloalkanes, Alcohols, and Amines. Nucleophilic Substitution

from

Organic Chemistry

by
Robert C. Neuman, Jr.
Professor of Chemistry, emeritus
University of California, Riverside

orgchembyneuman@yahoo.com
<http://web.chem.ucsb.edu/~neuman/orgchembyneuman/>

Chapter Outline of the Book

****

I. Foundations

1. Organic Molecules and Chemical Bonding
2. Alkanes and Cycloalkanes
3. Haloalkanes, Alcohols, Ethers, and Amines
4. Stereochemistry
5. Organic Spectrometry

II. Reactions, Mechanisms, Multiple Bonds

6. Organic Reactions *(*Not yet Posted*)
7. Reactions of Haloalkanes, Alcohols, and Amines. Nucleophilic Substitution
8. Alkenes and Alkynes
9. Formation of Alkenes and Alkynes. Elimination Reactions
10. Alkenes and Alkynes. Addition Reactions
11. Free Radical Addition and Substitution Reactions

III. Conjugation, Electronic Effects, Carbonyl Groups

12. Conjugated and Aromatic Molecules
13. Carbonyl Compounds. Ketones, Aldehydes, and Carboxylic Acids
14. Substituent Effects
15. Carbonyl Compounds. Esters, Amides, and Related Molecules

IV. Carbonyl and Pericyclic Reactions and Mechanisms

16. Carbonyl Compounds. Addition and Substitution Reactions
17. Oxidation and Reduction Reactions
18. Reactions of Enolate Ions and Enols
19. Cyclization and Pericyclic Reactions *(*Not yet Posted*)

V. Bioorganic Compounds

20. Carbohydrates
21. Lipids
22. Peptides, Proteins, and α–Amino Acids
23. Nucleic Acids

****

**Note: Chapters marked with an (*) are not yet posted.*

7: Reactions of Haloalkanes, Alcohols, and Amines. Nucleophilic Substitution

Preview 7-4

7.1 Nucleophilic Substitution Reactions of Haloalkanes 7-5

Nucleophilic Substitution Mechanisms (7.1A) 7-5

The S_N1 Mechanism.

The Meaning of S_N1.

The S_N2 Mechanism.

S_N1 and S_N2 Reactions are Ionic.

Conversion of Haloalkanes to Alcohols (7.1B) 7-8

t-Butyl Alcohol ($(CH_3)_3C$-OH) from

t-Butyl Bromide ($(CH_3)_3C$-Br) (S_N1).

Solvent Stabilizes the Intermediate Ions.

Methanol (CH_3-OH) from Bromomethane (CH_3-Br) (S_N2).

H_2O versus $^-$:OH as a Nucleophile.

7.2 S_N1 versus S_N2 Mechanisms 7-10

Steric Sizes of R Groups in R_3C-Br (7.2A) 7-11

Relative S_N2 Rates for Different R_3C-Br.

Steric Crowding.

Carbocation Stabilization by R Groups in R_3C-Br (7.2B) 7-12

Relative S_N1 Rates for Different R_3C-Br.

Carbocation Stability.

S_N Mechanisms for Simple Haloalkanes (7.2C) 7-14

CH_3-Br and $(CH_3)_3C$-Br.

CH_3CH_2-Br and $(CH_3)_2CH$-Br.

Alkyl Group Stabilization of Carbocations (7.2D) 7-16

Carbocation Geometry and Hybridization.

Hyperconjugation.

Effects of Alkyl Group Substitution at a β-Carbon (7.2E) 7-17

S_N1 Mechanisms.

S_N2 Mechanisms.

7.3 Haloalkane Structure and Reactitvity 7-21

A Comparison of F, Cl, Br, and I as Leaving Groups (7.3A) 7-21

Relative S_N Rates for RI, RBr, RCl, and RF.

S_N Rates of R-X and H-X Acidity.

Leaving Group Ability.

Other Nucleophiles, Leaving Groups, and Solvents (7.3B) 7-22

The General Substrate R-L.

Preview. *(continued)*

7.4 Stereochemistry of S_N Reactions 7-23
Stereochemistry in the S_N2 Reaction (7.4A) 7-23
Inversion of Configuration.
The Need for a C-L Stereocenter.
S_N2 Reactions on 2-Chlorobutane.
Stereochemistry in the S_N1 Reaction (7.4B) 7-26
Inversion and Retention of Configuration.
Racemic Product.

7.5 Reaction Rates of S_N Reactions 7-28
Reaction Rates (7.5A) 7-28
S_N2 Reaction Rates.
S_N1 Reaction Rates.
Activation Energies (7.5B) 7-29
Energy Diagram for an S_N1 Reaction.
S_N1 Activation Energies.
Energy Diagram for an S_N2 Reaction.

7.6 Other Nucleophiles 7-32
ROH and RO^- as Nucleophiles (7.6A) 7-32
ROH Nucleophiles.
RO^- Nucleophiles (Williamson Ether Synthesis).
Limitations of the Williamson Ether Synthesis.
Alkoxide Ion Formation.
Formation of Cyclic Ethers (Epoxides).
R_2NH and R_2N^- as Nucleophiles (7.6B) 7-35
Amine Nucleophiles R_2NH.
The Amine Products React Further.
Two Different R Groups on N.
3∞ Amine (R_3N:) Nucleophiles.
Amide Nucleophiles R_2N^-.
S_N1 Mechanisms and Amine Nucleophiles.
RSH and RS^- as Nucleophiles (7.6C) 7-40
H_2S and HS^-.
RSH and RS^-.
Halide Ion Nucleophiles (X^-) (7.6D) 7-42
Formation of Fluoroalkanes.
Formation of Iodoalkanes.
The Nucleophiles N_3^- and $^-C{\equiv}N$ (7.6E) 7-43
Cyanide Ion.
Azide Ion. *(continued)*

7.7 Leaving Groups 7-44
The OH Group in Alcohols (R-OH) (7.7A) 7-44
R-OH is a Poor Substrate for S_N Reactions.
R-OH_2^+ is a Good Substrate for S_N Reactions.
Haloalkanes from Protonated Alcohols.
The OR Group in Ethers (R-OR) (7.7B) 7-47
Haloalkanes from Cleavage of Ethers.
Ring Opening of Cyclic Ethers (7.7C) 7-48
Epoxide Ring Opening.
Acid Catalysis.
Epoxide Ring Opening by Halide Ions.
A Summary of Leaving Groups (7.7D) 7-51
Some "Good" Leaving Groups.
Some "Poor' Leaving Groups.
Leaving Group Ability and K_a Values for H-L.

7.8 Nucleophilicity and Reaction Solvent 7-52
The Halide Ions (7.8A) 7-52
Solvent Dependence of Nucleophilicity.
Origin of Solvent Effect.
Solvation Changes during an S_N2 Reaction.
Solvation by Hydroxylic Solvents.
Polar Aprotic Solvents (7.8B) 7-55
Some Examples of Polar Aprotic Solvents.
Nucleophilic Substitution Mechanisms in Polar Aprotic Solvents.
Nucleophilicities of Other Nucleophiles (7.8C) 7-57
Nucleophiles and their Conjugate Bases.
Nucleophiles in the Same Row of the Periodic Table.
Nucleophiles in the Same Column of the Periodic Table.
Comparative Nucleophilicities in S_N2 versus S_N1 Reactions.

7.9 Carbon Nucleophiles 7-58
Organometallic Compounds give C Nucleophiles (7.9A) 7-59
Organomagnesium and Organolithium Compounds.
Carbon Polarity in Organometallic Compounds.
C-C Bond Formation Using Organometallic Compounds (7.9B) 7-61
Small Ring Formation.
Alkyl Group Coupling.
Reactions with Epoxides.
Positive, Negative and Neutral Carbon Atoms (7.9C) 7-62

7.10 Nucleophilic Hydrogen 7-62
The Polarity of H in Various Compounds (7.10A) 7-62
Metal Hydrides are Sources of Nucleophilic H (7.10B) 7-64

Appendix: Nucleophiles and Leaving Groups 7-66
Chapter Review 7-68

7: Reactions of Haloalkanes, Alcohols, and Amines. Nucleophilic Substitution

- *Nucleophilic Substitution Reactions of Haloalkanes*
- *S_N1 versus S_N2 Mechanisms*
- *Haloalkane Structure and Reactivity*
- *Stereochemistry of S_N Reactions*
- *Reaction Rates of S_N Reactions*
- *Other Nucleophiles*
- *Leaving Groups*
- *Nucleophilicity and Reaction Solvent*
- *Carbon Nucleophiles*
- *Nucleophilic Hydrogen*

Preview

This chapter describes **nucleophilic substitution reactions** of haloalkanes, alcohols, amines, and compounds related to them. These are **ionic reactions** in which one group on the molecule (a **leaving group**) is replaced by another group (a **nucleophile**). The transformation of *haloalkanes* (R-X) into *alcohols* (R-OH) where an OH group replaces the halogen (X) is an example of *nucleophilic substitution*.

Most *nucleophilic substitution* reactions take place by either the **S_N1** or the **S_N2** mechanism. The *S_N1* mechanism has an intermediate **carbocation** with a positive charge on a carbon atom. *Carbocation* intermediates are planar and stabilized by alkyl groups. The *S_N2* mechanism has no intermediates and occurs in a single step. We can distinguish *S_N1* and *S_N2* mechanisms by their **stereochemistry** and **reaction kinetics**.

Leaving groups and *nucleophiles* are often the same for both mechanisms, and the structure of the reactant with the leaving group (the **substrate**) usually determines the reaction mechanism. The relative reactivities of *nucleophiles* (**nucleophilicity**) and *leaving groups* (**leaving group ability**) depend on their *structures*, their *ionic charge*, and the *solvent*.

We illustrate these *nucleophilic substitution mechanisms* in this chapter using a variety of chemical reactions. Besides recognizing these reactions as *nucleophilic substitutions* you also need to learn them as individual reactions that perform specific chemical transformations such as the conversion of a *haloalkane* (R-X) into an *alcohol* (R-OH).

7.1 Nucleophilic Substitution Reactions of Haloalkanes

Nucleophilic substitution reactions are **ionic** reactions that break and make chemical bonds by transfers of pairs of electrons. We illustrate this using a general representation of a *nucleophilic substitution* reaction in which a halogen (X) is replaced by a new group (N).

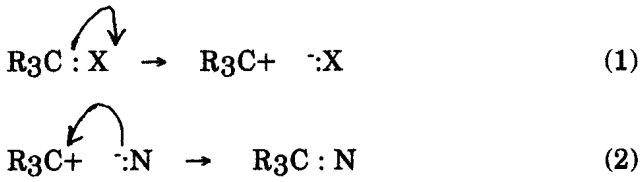
$$R_3C{:}X \;+\; {}^{-}{:}N \;\rightarrow\; R_3C{:}N \;+\; {}^{-}{:}X$$

The color coding shows that the electron pair in the original C:X bond remains with the halogen (X) as that bond breaks, while the electron pair on $^{-}$:N becomes the new C:N chemical bond.

Nucleophilic Substitution Mechanisms (7.1A)

The two major mechanisms for *nucleophilic substitution* are called $\mathbf{S_N1}$ and $\mathbf{S_N2}$. We describe them here using haloalkanes (R_3C-X) as the **substrates**.

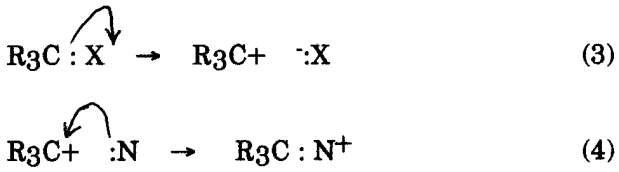
The S_N1 Mechanism. The *S_N1* mechanism has two steps and an intermediate **carbocation** R_3C^+.



In the first step, the C-X bond in R_3C-X breaks to give a negatively charged halide ion ($^{-}$:X) and positively charged *carbocation* (R_3C^+). The name *carbocation* signifies that it is a *carbon cation*. *Carbocations* are also called **carbonium ions**. In this *ionization reaction* (a reaction that forms ions), the electron pair in the C-X bond remains with the halogen (X) as the C-X bond breaks.

The intermediate *carbocation* reacts in the second step with an unshared electron pair on the species $^{-}$:N to form the new C:N bond. We use the letter N to signify that $^{-}$:N is a **nucleophile**. A *nucleophile* is a chemical species with an unshared pair of electrons that reacts with *electron deficient centers* such as the C+ atom in R_3C^+. *Nucleophile* is derived from a combination of the chemical word *nucleus* and the Greek word *philos* which means "loving". A *nucleophile* wants ("loves") to use one of its unshared electron pairs to bond to a positively polarized nucleus.

N*ucleophiles* always have an unshared electron pair that forms the new chemical bond, but they are not always negatively charged. When the nucleophile (:N) in an S_N1 reaction is electrically neutral (uncharged), it reacts with the intermediate carbocation to give a positively charged product.

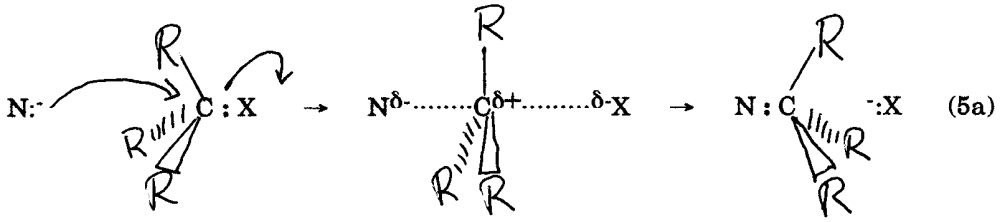


Arrows Show How the Electrons Move. We illustrate the movement of the C:X electron pair in reactions (1) and (3) above using curved arrows. The tail of the arrow begins at the electron pair in the C:X bond and the head of the arrow points to X to show that the electron pair remains with X as the bond breaks. In reactions (2) and (4) we use arrows to show that the electron pair on $^{-}$:N or :N binds to the C+ center of R_3C^+ to form the new C:N bond.

The Meaning of S_N1. *S_N1* stands for Substitution (*S*) Nucleophilic (*N*) Unimolecular (*1*) and organic chemists commonly refer to this mechanism as "*unimolecular nucleophilic substitution*". The term *substitution* indicates that one group (N) has taken the place of (substituted) another group (X). The term *nucleophilic* signifies that the new group N participates in the reaction as a *nucleophile*. The term *unimolecular* tells us that there is only one reactant molecule (R_3C-X) in the first reaction where the C-X bond breaks. We clarify the meaning of the term *unimolecular* later in the chapter, and in the next section where we describe the other major mechanism for *nucleophilic substitution*.

The S_N2 Mechanism. In contrast with the two-step *S_N1* mechanism, the *S_N2* mechanism has just one step and no intermediates.

The nucleophile $^{-}$:N interacts directly with the haloalkane R_3C:X by bonding to the C-X carbon while X is still bonded to C.

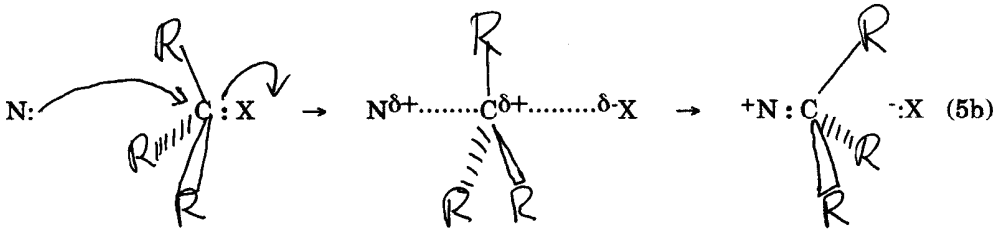


There is no carbocation intermediate such as the one we saw in the *S_N1* mechanism. The middle structure with dotted bonds that we show above is not an intermediate. We will learn that it is a high energy unstable molecular configuration that the reactants must attain as they change from the haloalkane (R_3C-X) to the product (R_3C-N). *S_N2* signifies that the reaction is **bimolecular** *nucleophilic substitution* (*S_N*). The number *2* in *S_N2* indicates that the C-X bond breaks in a

reaction that is *bimolecular* since it includes both the haloalkane (R_3C-X) and the nucleophile ($N:^-$) as reactants.

> ***A Caution***. You must be careful to distinguish between the two possible meanings of equation (5). You may see it used to illustrate the *overall chemical transformation* of R_3CX to R_3CN that occurs in any nucleophilic substitution reaction whether the mechanism is S_N1 or S_N2. However it may be the reaction that we write to specifically illustrate the S_N2 mechanism. You must interpret the meaning of that reaction in the context that it is given.

When nucleophiles in S_N2 reactions are electrically neutral (:N), the product is positively charged (R_3C-N^+) and we can represent the charge distribution during this S_N2 reaction as we illustrate here.



S_N1 and S_N2 Reactions are Ionic. The pictorial description of the S_N1 and S_N2 mechanisms above show that *nucleophilic substitution* reactions are ionic. We have seen that they may include ions such as *negatively* charged nucleophiles ($N:^-$), *positively* charged substitution products (R_3C-N^+), and *negatively* charged halide ions ($X:^-$). The S_N1 reaction has a *positively charged* intermediate carbocation (R_3C^+), while a partial positive charge develops on the C that is the site of bond making and bond breaking in the S_N2 reaction. In all cases, the new C:N bond comes from the pair of electrons on the nucleophile (N: or $N:^-$), and the pair of electrons in the original C:X bond ends up on the halide ion *leaving group* ($X:^-$).

These ionic nucleophilic substitution reactions of R_3C-X are facilitated by the polar character of their C-X bonds (Chapter 3). Halogen atoms (X) are more electronegative than the C to which they are bonded so the C-X bond has a positively polarized C and a negatively polarized X.

Figure 7.1

The ionic character of these reactions requires *reaction solvents* that can stabilize ions and polar species. We will learn more about these solvents later in the chapter.

Conversion of Haloalkanes to Alcohols (7.1B)

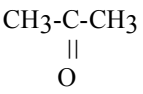
We illustrate the S_N1 and S_N2 mechanisms using examples of reactions where bromoalkanes (R_3C-Br) give alcohols (R_3C-OH).

t-Butyl Alcohol ($(CH_3)_3C$-OH) from t-Butyl Bromide ($(CH_3)_3C$-Br) (S_N1). If we reflux (heat to a boil) a mixture of *2-bromo-2-methylpropane* (*t-butyl bromide*) and water (H_2O), the reaction product *2-methylpropanol* (*t-butyl alcohol*) forms as we show here.

$$(CH_3)_3C\text{-Br} + H_2O \rightarrow (CH_3)_3C\text{-OH} + HBr \qquad (6)$$

(Since *t-butyl bromide* is relatively insoluble in water, we can facilitate the reaction by adding a solvent such as **acetone** that is miscible with water and helps dissolve the haloalkane).

Acetone. Acetone is a common organic solvent with the structure shown here.



It is a member of a class of organic compounds called *ketones* that have the general structure $R_2C{=}O$. While acetone is polar and dissolves a number of polar reactants used in nucleophilic substitution reactions, it is not nucleophilic. For this reason it is frequently used as a solvent in S_N2 reactions and sometimes in S_N1 reactions. We describe acetone in greater detail when we formally indtroduce *ketones* in Chapter 12.

The overall transformation of t-butyl bromide to t-butyl alcohol takes place by an S_N1 mechanism with an intermediate t-butyl carbocation.

$$(CH_3)_3C\text{-Br} \xrightarrow{H_2O} (CH_3)_3C^+ + Br^- \qquad (7)$$

$$(CH_3)_3C^+ + :OH_2 \rightarrow (CH_3)_3C\text{-}{}^+OH_2 \qquad (8)$$

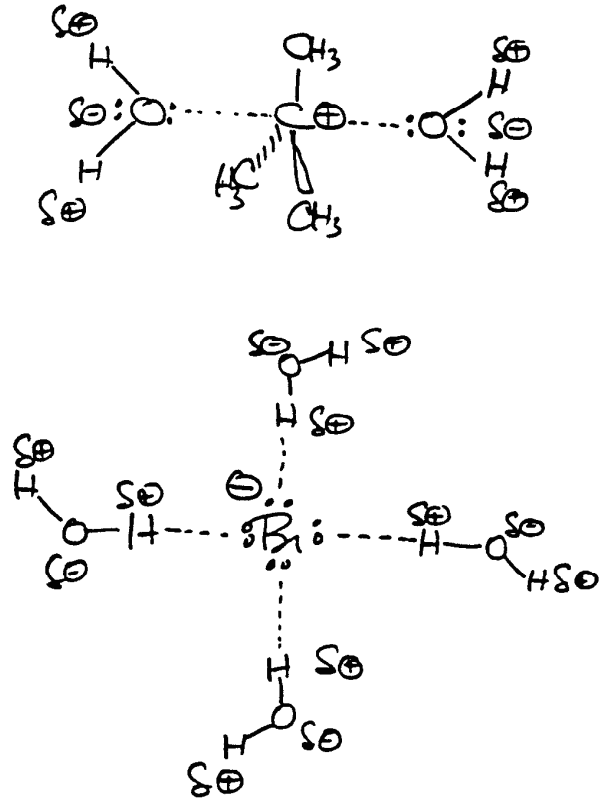
$$(CH_3)_3C\text{-}{}^+OH_2 + H_2O: \rightarrow (CH_3)_3C\text{-OH} + H_3O^+ \qquad (9)$$

The haloalkane ionizes (reaction (7)) to form the *t-butyl carbocation* and a *bromide ion* as we showed earlier in the general S_N1 mechanism (reactions (3) and (4)). We write H_2O above the reaction arrow to show that it is the reaction solvent. The intermediate *t-butyl carbocation* then reacts with one of the unshared electron pairs on the O of the *neutral nucleophile* H_2O forming a C-O bond to the C+ center (reaction (8)).

While the product of reaction (8) is the nucleophilic substitution product, it is not the final product. It loses a proton in reaction (9) that is <u>not</u> part of the S_N1 mechanism. Reaction (9) is an *acid/base reaction* (Chapter 3) in which the protonated alcohol product from reaction (8) transfers a proton (H^+) to a solvent water molecule. While we show HBr as a product in the overall transformation (reaction (6)), HBr actually exists in water as H_3O^+ and Br^- that we see are products of reactions (7) and (9).

Solvent Stabilizes the Intermediate Ions. The carbocation formed by ionization of the C-Br bond is stabilized by *dipolar interactions* with neighboring solvent water molecules, while the bromide ion is stabilized by hydrogen bonding to H_2O molecules (Figure [graphic 7.5]). We refer to these energetically favorable interactions between solvent molecules and any species in solution (a reactant, product, or intermediate) as **solvation** interactions.

Figure 7.5. Solvation of a Carbocation and a Halide Ion by Water.



Methanol (CH_3-OH) from Bromomethane (CH_3-Br) (S_N2). In contrast to what we have just seen for t-butyl bromide, no reaction occurs when we reflux a mixture of bromomethane

(CH_3Br) in water (or a mixture of acetone and water to improve solubility of CH_3Br)). CH_3Br cannot ionize in water to form the methyl carbocation.

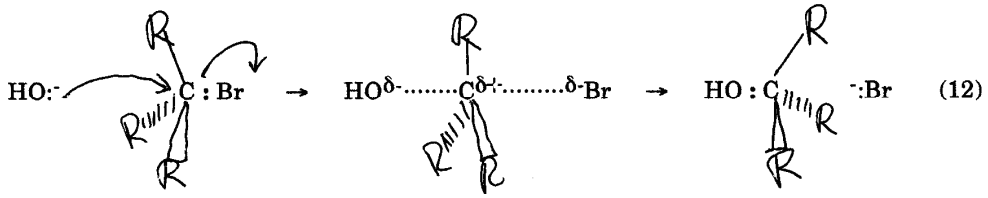
$$CH_3\text{-}Br \xrightarrow{H_2O} CH_3^+ + {}^-\!:Br \qquad (10)$$

If this ionization reaction occurred, H_2O would rapidly react with CH_3^+ to ultimately give CH_3-OH in steps analogous to reactions (8) and (9) that we showed for the S_N1 reaction of the t-butyl cation with H_2O.

However, we can form CH_3OH from CH_3Br by *nucleophilic substitution* if we add sodium hydroxide (NaOH) (or potassium hydroxide (KOH)) to our reaction mixture.

$$CH_3\text{-}Br + Na^+ {}^-\!:OH \xrightarrow{H_2O} CH_3\text{-}OH + Na^+ {}^-\!:Br$$

This reaction occurs by an *S_N2 mechanism* in which the nucleophile $^-$:OH *directly displaces* Br as a bromide ion ($^-$:Br) as we illustrated earlier in our general representation of S_N2 mechanisms. (The Na^+ cation does not directly participate in the reaction).



(12)

We will learn below that, because of the different structures of their alkyl groups, nucleophilic substitution on *bromomethane* (CH_3-Br) occurs only by *S_N2* mechanisms, while *t-butyl bromide (2-bromo-2-methylpropane)* (($CH_3)_3$C-Br) undergoes nucleophilic substitution only by S_N1 mechanisms.

H_2O versus $^-$:OH as a Nucleophile. While CH_3-Br reacts with $^-$:OH by an S_N2 reaction, it will not react with the nucleophile H_2O because H_2O is much less reactive (much less *nucleophilic*) than $^-$:OH. We will see later in this chapter that negatively charged nucleophiles are much more *nucleophilic* than neutral nucleophiles if they have the same nucleophilic atom. The nucleophilic atom is O in both H_2O and $^-$:OH.

7.2 S_N1 versus S_N2 Mechanisms

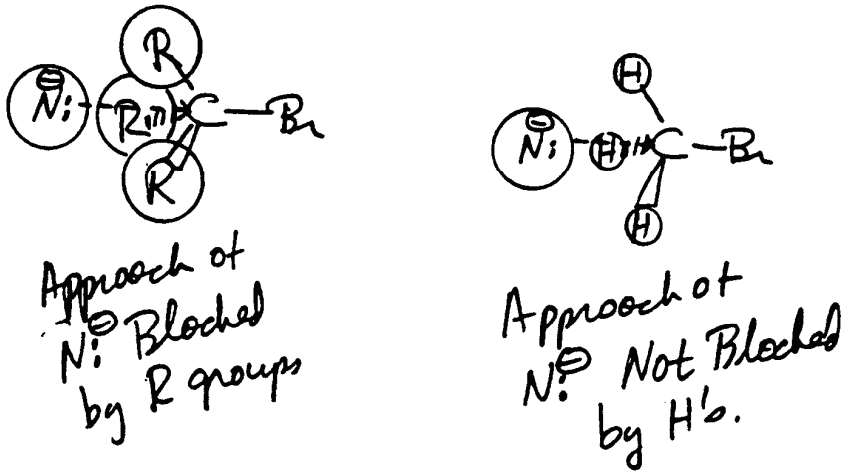
Why do the haloalkanes *bromomethane* (CH_3-Br) and *2-bromo-2-methylpropane* (($CH_3)_3$C-Br) undergo *nucleophilic substitution* by different mechanisms? We will see here that this is a result

of both the relative *steric sizes* of the alkyl groups in R_3C-Br, and the way that these alkyl groups *stabilize* carbocation centers.

Steric Sizes of R Groups in R_3C-Br (7.2A)

In the single step *S_N2 mechanism*, the attacking nucleophile assists the departure of $Br:^-$ by beginning to bond to the C-Br carbon on the side of the carbon opposite Br. R groups on R_3C-Br interfere with the required close approach of the nucleophile to the backside of C-Br when they are *alkyl groups* rather than *H atoms* as we illustrate in Figure [graphic 7.11].

Figure 7.11. Steric Hindrance to Approach of N: During an S_N2 Reaction.



Relative S_N2 Rates for Different R_3C-Br. The data in Table 7.1 show us how the rates of S_N2 reactions depend on whether the R's in R_3C-Br are H or CH_3.

Table 7.1. Relative Rates of S_N2 Reactions of Haloalkanes (R)(R')(R")C-Br

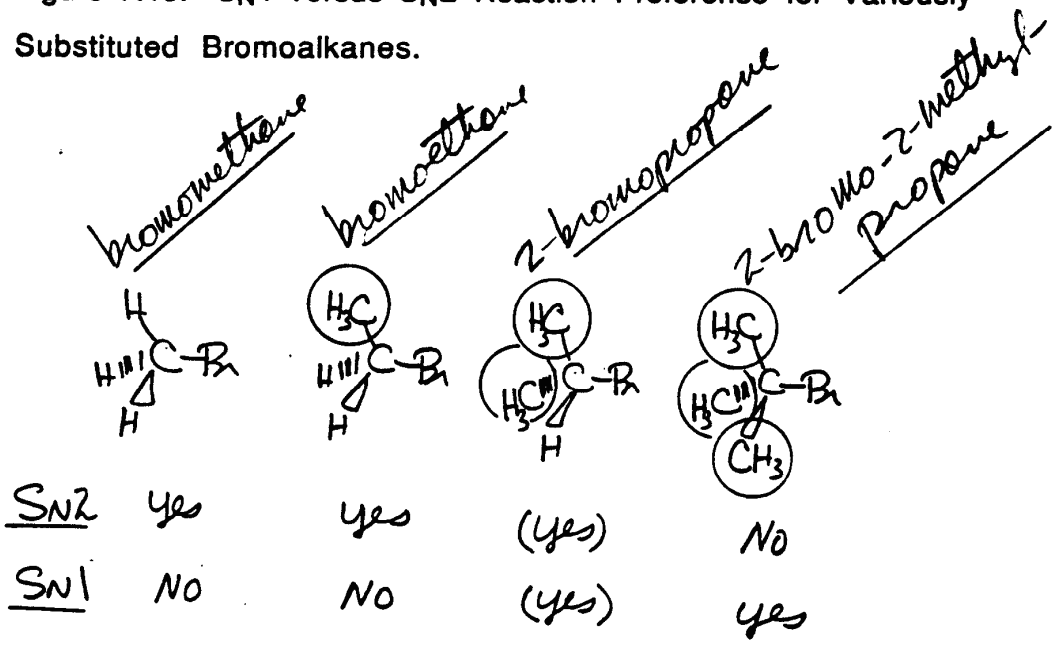
R	R'	R"	Relative Rate	Name
H	H	H	1,000	bromomethane
CH_3	H	H	30	bromoethane
CH_3	CH_3	H	1	2-bromopropane
CH_3	CH_3	CH_3	0	2-bromo-2-methylpropane

You can see that the S_N2 rates decrease as we substitute CH_3 for each H on CH_3Br. When all H's are substituted by CH_3, the S_N2 rate becomes zero (0).

Rates of Reactions. We will discuss rates of chemical reactions in more detail later in this chapter. At this point, you need to know that the relative reaction rates in Table 7.1 tell us the relative speed at which each of the haloalkanes reacts under identical conditions. The larger the relative rate, the faster the haloalkane reacts.

Steric Crowding. The decreases in S_N2 rates (Table 7.1) as we replace H's with CH_3's, result from **steric crowding** on the backside of the C-Br bond (see Figure [graphic 7.11]). Stepwise replacement of CH_3 for H makes backside bonding of a nucleophile in an S_N2 reaction less and less favorable. When all R's are CH_3 (as in 2-bromo-2-methylpropane), backside approach and bonding of a nucleophile is virtually impossible so the S_N2 rate becomes zero (0) (Figure [graphic 7.13]).

Figure 7.13. S_N1 versus S_N2 Reaction Preference for Variously Substituted Bromoalkanes.



Carbocation Stabilization by R Groups in R_3C-Br (7.2B)
While CH_3 groups on C-Br cause steric crowding in *S_N2 reactions*, they *stabilize* the carbocation intermediate in an *S_N1 reaction*.

Relative S_N1 Rates for Different R_3C-Br. The data in Table 7.1a show that <u>three</u> CH_3 groups on the C-Br carbon of R_3C-Br cause the S_N1 reaction rate to be much faster than when C-Br has one or two CH_3 groups.

Table 7.1a. Relative Rates of S_N1 Reactions of Haloalkanes (R)(R')(R")C-Br

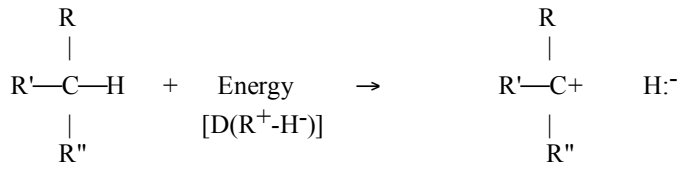
R	R'	R"	Relative Rate	Name
H	H	H	0	bromomethane
CH_3	H	H	0	bromoethane
CH_3	CH_3	H	1	2-bromopropane
CH_3	CH_3	CH_3	100,000	2-bromo-2-methylpropane

In fact, when R_3C-Br has fewer than two CH_3 groups, it does not react at all by the S_N1 mechanism (see Figure [graphic 7.13]). These changes in S_N1 rates result from the effect of alkyl groups such as CH_3 on the stability of R_3C^+ that forms in the first step of the S_N1 mechanism.

Carbocation Stability. The relative stability of simple methyl substituted carbocations is $(CH_3)_3C^+ > (CH_3)_2CH^+ > CH_3CH_2^+ > CH_3^+$. We call $(CH_3)_3C^+$ a **3°** (**tertiary**) carbocation since its C+ has *3* alkyl groups (methyl groups in this case). Similarly, $(CH_3)_2CH^+$ is a **2°** (**secondary**) carbocation because it has *2* alkyl groups on the C+ center, while $CH_3CH_2^+$ with *1* alkyl group on C+ is a **1°** (**primary**) carbocation. Using this general terminology, we can summarize this carbocation stability order as 3° > 2° > 1° > methyl.

Other simple alkyl groups (R) like *ethyl* (CH_3CH_2) or *propyl* ($CH_3CH_2CH_2$) have the same effect on carbocation stability as CH_3 groups. As a result, the general order of carbocation stability is $R_3C^+ > R_2CH^+ > RCH_2^+ > CH_3^+$ as long as we compare carbocations with similar R groups. The stabilizing effects of R groups on the C+ center is so important that it is virtually impossible for CH_3^+ or $CH_3CH_2^+$ to form from CH_3Br or CH_3CH_2Br by loss of $Br:^-$ in an S_N1 reaction. We explain why alkyl groups stabilize carbocations later in this chapter.

A Quantitative Measure of Carbocation Stability. The amount of energy required to break a C-H bond in R_3C-H to give R_3C^+ and $^-:H$ is a quantitative measure of the relative stabilities of R_3C^+ carbocations. We symbolize this energy as $[D(R^+\text{-}H^-)]$ as we show in this equation.



You can see in Table 7.2 that values of $D(R^+\text{-}H^-)$ decrease as we increase the number of CH_3 groups on R_3C-H. This energy decreases because the CH_3 groups increase the stability of the carbocation (R_3C^+) formed in this reaction.

Table 7.2. Energy Required to Break C-H Bond in Compounds of the Structure (R)(R')(R")C-H

R	R'	R"	$D(R^+-H^-)$ (kJ/mol)	Δ (kJ/mol)
H	H	H	1316	346
CH_3	H	H	1158	188
CH_3	CH_3	H	1043	73
CH_3	CH_3	CH_3	970	0

In order to more clearly show how substitution of CH_3 for H affects carbocation stability, we subtract the value of $D(R^+-H^-)$ for $(CH_3)_3C+$ from each $D(R^+-H^-)$ value and list those differences as the Δ values in the last column of this table. These Δ values show that when one H replaces a CH_3 group on $(CH_3)_3C$-H, the energy required to form the carbocation increases by 73 kJ/mol. Similarly, when two H's replace CH_3 groups the energy increases by 188 kJ/mol, and when H's replace all of the CH_3 groups, the energy for formation of the resultant carbocation CH_3+ is 346 kJ/mol higher than for $(CH_3)_3C+$.

S_N Mechanisms for Simple Haloalkanes (7.2C)

Now that we know that R groups in R_3C-Br can affect nucleophilic substitution reactions by *steric effects* in *S_N2* reactions, and by *carbocation stabilization* in *S_N1* reactions, we apply these ideas to nucleophilic substitution reactions of several simple bromoalkanes.

CH_3-Br and $(CH_3)_3C$-Br. The effects of CH_3 substitution on *steric crowding* and on *carbocation stability* provide a rationalization for the exclusive *S_N1* nucleophilic substitution mechanism for *2-bromo-2-methylbutane* ($(CH_3)_3C$-Br)), and the exclusive *S_N2* nucleophilic substitution mechanism for *bromomethane* (CH_3-Br). *Bromomethane* cannot form the carbocation of the S_N1 reaction, but it is very accessible to *backside bonding* of a nucleophile such as $^-$:OH in an S_N2 reaction. [graphic 7.12] On the other hand, S_N2 *backside bonding* is impossible for 2-bromo-2-methylpropane ($(CH_3)_3C$-Br)) because of its 3 CH_3 groups, but the carbocation resulting from its ionization in an S_N1 mechanism is stabilized by the three CH_3 groups.

CH_3CH_2-Br and $(CH_3)_2CH$-Br. *CH_3Br* with no CH_3 groups, and *$(CH_3)_3CBr$* with 3 CH_3 groups, are at extreme ends of the mechanistic possibilities for substitution reactions on bromoalkanes (R_3C-Br). What might we expect for the intermediate bromoalkanes *bromoethane* (CH_3CH_2-Br) and *2-bromopropane* ($(CH_3)_2CH$-Br) that have 1 or 2 CH_3 groups on the C-Br carbon? In fact, nucleophilic substitution reactions for CH_3CH_2Br are exclusively *S_N2* just like those for CH_3Br (Figure [graphic 7.13]). Even though backside attack of a nucleophile (such as $^-$

(2/94)(1-3/96)(10,11/97) Neuman Chapter 7

Figure 7.12

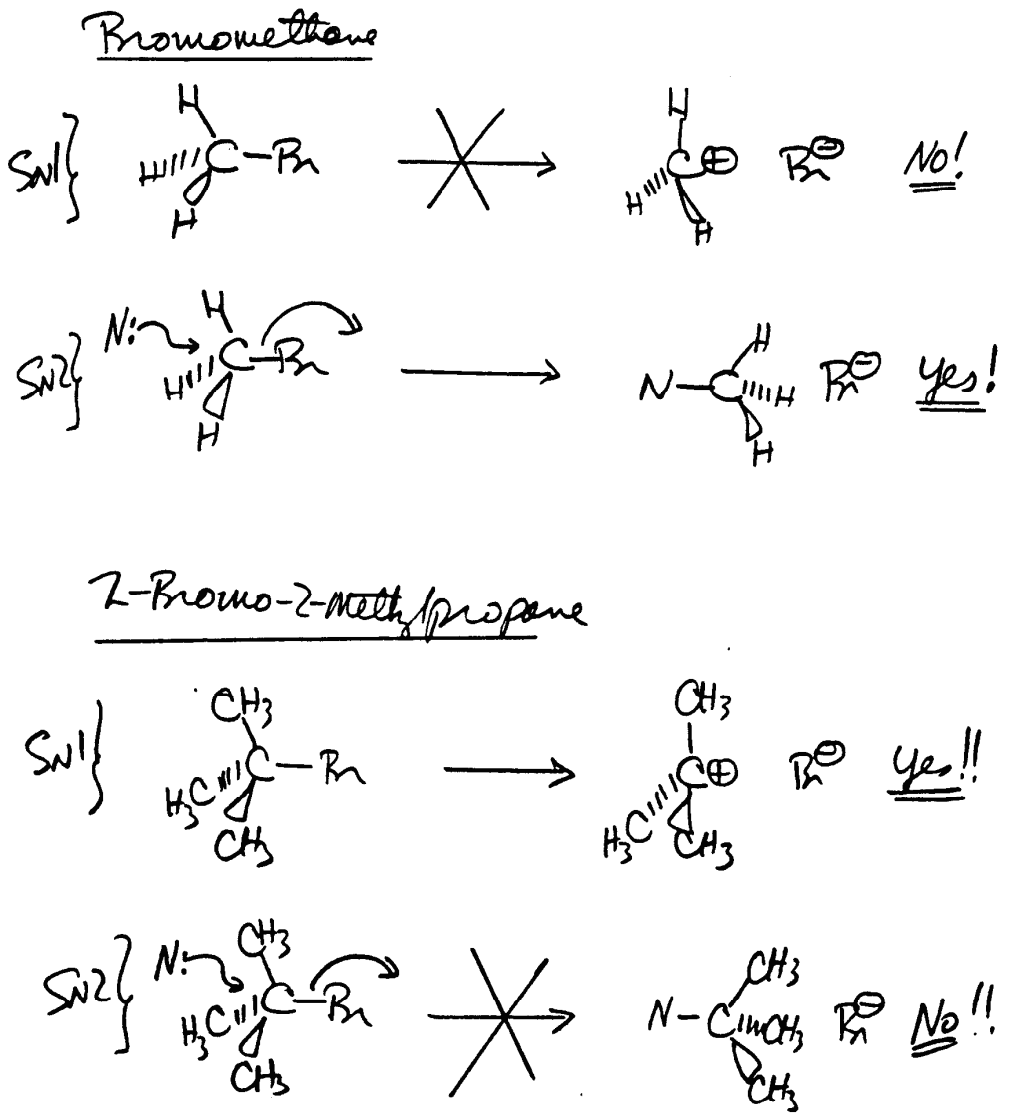


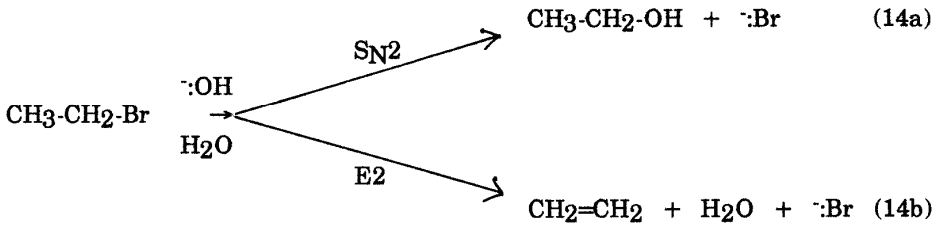
Figure 7.14. Compounds of the Structure R-CH_2-Br.

CH_3-CH_2Br	CH_3CH_2-CH_2Br	$(CH_3)_2CH$-CH_2Br	$(CH_3)_3C$-CH_2Br
R = CH_3	R = CH_3CH_2	R = $(CH_3)_2CH$	R = $(CH_3)_3C$

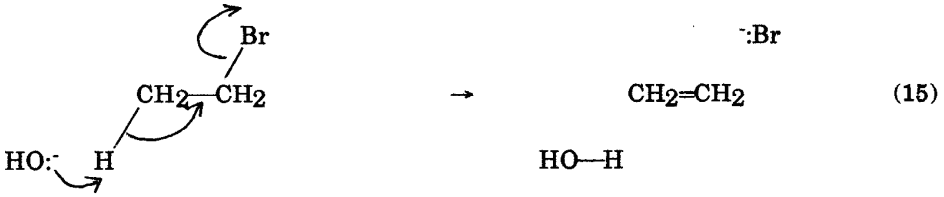
:OH) on CH_3CH_2Br is less favorable than on CH_3Br because one H is replaced by CH_3 (Table 7.1), CH_3CH_2+ is not stable enough to form from CH_3CH_2Br in an S_N1 reaction.

The second CH_3 of $(CH_3)_2CHBr$ further blocks a nucleophile such as $^-$:OH in backside S_N2 attack, but it increases the stability of the carbocation resulting from S_N1 ionization compared to CH_3CH_2Br. As a result, S_N1 and S_N2 mechanisms are sometimes competitive for $(CH_3)_2CHBr$.

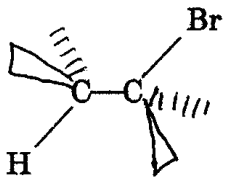
Elimination Reactions Compete with Nucleophilic Substitution. When CH_3CH_2-Br is refluxed in aqueous solutions containing $^-$:OH, the *alkene* $CH_2=CH_2$ forms simultaneously with the *alcohol* CH_3CH_2OH.



While CH_3CH_2OH forms by an S_N2 mechanism as we have just described, the alkene $CH_2=CH_2$ is the product of a competing **elimination reaction** with the mechanism that we show here.



We describe these *elimination reactions* and the factors that cause them to compete with nucleophilic substitution in Chapter 9. For now, it is only important to realize that a substrate that has a C-H bonded to C-Br, as we show here, often undergoes an *elimination reaction* to form an *alkene* competitively with *nucleophilic substitution*.



(16)

Alkyl Group Stabilization of Carbocations (7.2D)

Alkyl groups stabilize carbocations by donating *electron density* to the electron deficient C+ center.

Carbocation Geometry and Hybridization. *Carbocations* prefer to be *planar* with *bond angles* as close to 120° as possible (Figure [graphic 7.16]). This planar geometry causes the hybridization at C+ to be sp^2 (Chapter 1*). The resultant 2p orbital on C+ has no electrons and is perpendicular to the plane defined by the three R-C+ chemical bonds. When the carbocation R_3C+ forms from R_3C-Br, the C-Br carbon that is sp^3 in R_3C-Br changes (*rehybridizes*) to sp^2 as the C-Br bond breaks (Figure [graphic 7.17]).

Hyperconjugation. Carbocations are positively charged because they are *electron deficient*, and this is why they react so rapidly with unshared electron pairs of nucleophiles. Because of their electron deficiency, carbocations also seek *electron density* from any attached groups. Alkyl groups such as CH_3 share their electron density with the C+ by partially overlapping their C-H bonds (C-H bonding MO's)(Chapter 1) with the empty 2p orbital (Figure [graphic 7.18]).

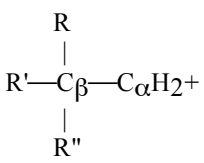
The CH_3+ cation is very unstable because it has no C-H's attached to C+ and such electron delocalization is impossible. As we add alkyl groups to C+, we increase the opportunities for C-H bond overlap with the empty 2p orbital as we illustrate in Figure [graphic 7.19]. This overlap between neighboring C-H bonds and the empty 2p orbital is called **hyperconjugation**. *Hyperconjugation* is generally limited to overlap between the 2p orbital on C+ and C-H bonds that are directly bonded to C+. More distant bonds usually do not interact significantly with a C+ center.

Effects of Alkyl Group Substitution at a β-Carbon (7.2E)

We have seen how alkyl groups substituted directly on the C-Br carbon affect nucleophilic substitution mechanisms. What about alkyl groups substituted at C's other than the C+ center?

S_N1 Mechanisms. In order to stabilize a carbocation, an alkyl group must be directly bonded to the C+ center (the α carbon). Alkyl substitution on a more distant carbon, such as C_β in the carbocation shown in Figure [graphic 7.14a], does not increase C+ stability

Figure [graphic 7.14a]. Carbocations with R Groups on Cβ.



The CH_3-CH_2+ carbocation is a specific example of the general structure in Figure [graphic 7.14a] where R = R' = R" = H. We learned earlier that CH_3-CH_2+ does not form by S_N1

(2/94)(1-3/96)(10,11/97) Neuman Chapter 7

Figure 7.16. Carbocation Structure.

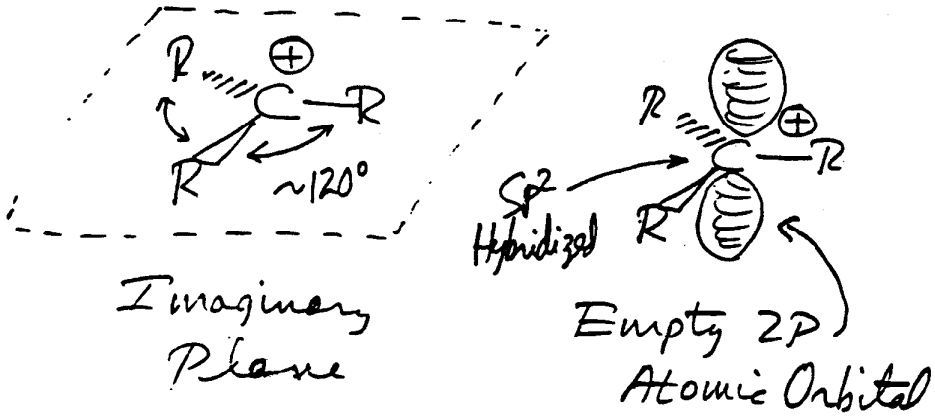
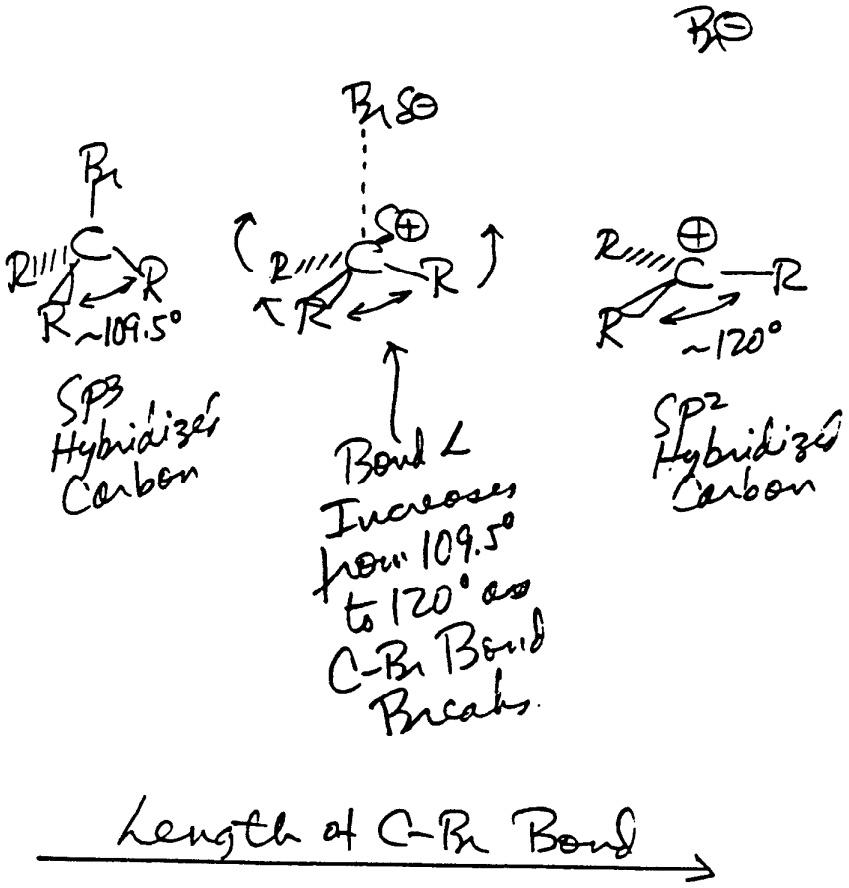


Figure 7.17. Changes in Substrate Structure During S_N1 Ionization.



(2/94)(1-3/96)(10,11/97) Neuman Chapter 7

Figure 7.18. C-H Electron Donation (Hyperconjugation) Stabilizing Neighboring C+ Center.

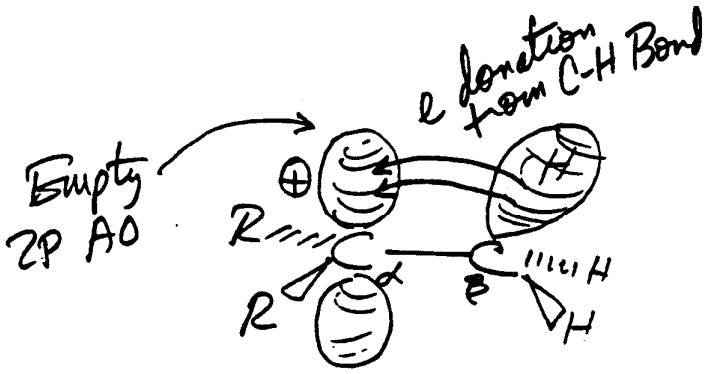
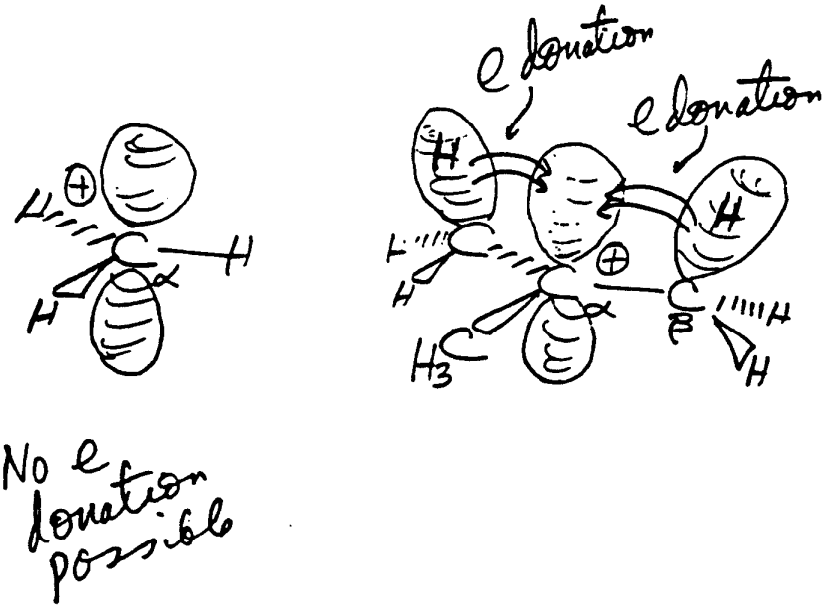


Figure 7.19. Effects of Alkyl Substitution on C+ Stabilization.



ionization of CH_3-CH_2-Br, and the same is true for other carbocations of this general structure even when the R's are alkyl groups such as CH_3. These carbocations (Figure [graphic 7.14a]) are all 1° carbocations so they do not form by ionization of bromoalkanes of the general structure R_3C-CH_2-Br.

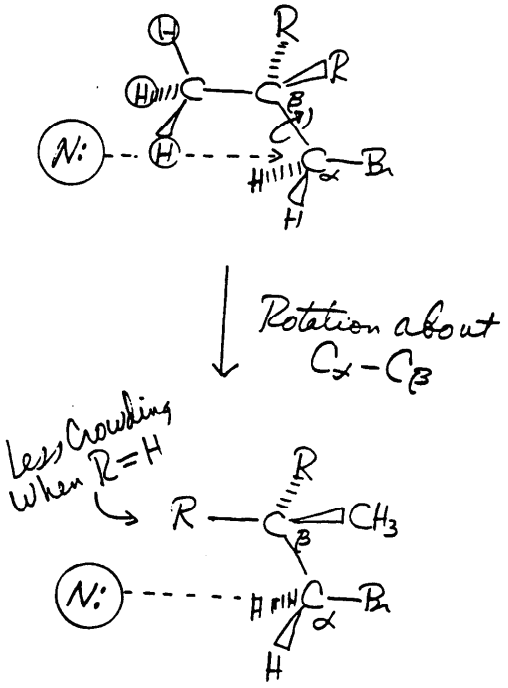
S_N2 Mechanisms. While they have little effect on S_N1 reactions, the number of methyl groups on C_β in RR'R"C_β-CH_2-Br markedly affects the rates of S_N2 reactions at -CH_2-Br (Table 7.3).

Table 7.3. Effect of CH_3 Substitution in RR'R"C_β-CH_2-Br on S_N2 Substitution Rates

R	R'	R"	Relative Rate	Name
H	H	H	30	bromoethane
CH_3	H	H	12	bromopropane
CH_3	CH_3	H	0.9	1-bromo-2-methylpropane
CH_3	CH_3	CH_3	0.0003	1-bromo-2,2-dimethylpropane

You can see that the S_N2 reaction rate at C-Br decreases as the number of CH_3 groups on C_β increases. Replacement of one H by a CH_3 has a relatively small effect, but the rate decreases are much greater when two or three of the R's become CH_3. This decrease in S_N2 reaction rates (Table 7.3), due to C_β-CH_3 groups, occurs because they interfere with the approach of a nucleophile to the backside of C_α (Figure [graphic 7.15]).

Figure 7.15. Steric Crowding by R Groups on C_β During Approach of N: to C_α.



The effect depends on the number of CH_3 groups on C_β. When there is only one CH_3 on C_β, rotation about the C_α-C_β bond relieves the *steric crowding* in the approach of :N so the effect on rate is small (Figure [graphic 7.15]). Rotation about C_α-C_β even provides some relief when two of the R's are CH_3. However when all three R groups are CH_3, rotation about C_α-C_β cannot relieve steric crowding and the S_N2 reaction rate is close to zero (Table 7.3).

7.3 Haloalkane Structure and Reactitvity

We have used *bromoalkanes* to introduce and describe *nucleophilic substitution* reactions. These reactions also occur with other haloalkanes.

A Comparison of F, Cl, Br, and I as Leaving Groups (7.3A)

F, Cl, Br, and I have different effects on rates of nucleophilic substitution reactions of their haloalkanes (R-X).

Relative S_N Rates for RI, RBr, RCl, and RF. For a particular R group and set of reaction conditions, the *rates* of both S_N1 and S_N2 reactions of R-X decrease in the order R-I > R-Br > R-Cl >>> R-F. *Iodoalkanes* (R-I) react more rapidly than *bromoalkanes* (R-Br), *chloroalkanes* (R-Cl) react more slowly than bromoalkanes (R-Br), while *fluoroalkanes* (R-F) usually do not react at all. These *relative reaction rates* have the same order as the *relative strengths* of the C-X bonds (Chapter 3*). They also have the same order as the *relative acidities* of the corresponding hydrogen halides H-X.

S_N Rates of R-X and H-X Acidity. Before we compare S_N reaction rates of haloalkanes (R-X) with acidities of H-X, lets review the acid-base reaction between water and the acids H-X.

(17)

In these reactions, the acid H-X transfers its proton to water (the base) forming the hydronium ion (H_3O^+) and a halide ion ($X:^-$). The H-X bond breaks in this reaction, so H-X bond strengths parallel the acidities of H-X. Since H-X and C-X bond strengths also have the same order, it is not surprising that the acidities of H-X and the rates of S_N reactions of R-X have the same order.

We show acid dissociation constants (K_a)* for H-X in Table 7.4 along with some relative S_N1 reaction rates in aqueous solution for the haloalkanes $(CH_3)_3C$-X.

Table 7.4. Acidity of H-X in Water (K_a) Compared to Relative S_N1 Rates of $(CH_3)_3C$-X.

X	K_a of HX	Relative S_N1 Rate for $(CH_3)_3C$-X
I	10^{10}	100
Br	10^{9}	40
Cl	10^{7}	1
F	10^{-3}	0

These K_a values are proportional to the equilibrium concentration ratio $[X:^-]/[H\text{-}X]$ so they reflect the extent of H-X bond breakage to form $^-$:X in aqueous solutions. *Strong acids* have large K_a values while *weak acids* have small K_a values so the relative acidities of HX are HI > HBr > HCl >>> HF. You can see that the HX acidity order is analogous to the order of S_N1 rates for $(CH_3)_3CX$ (RX) (RI > RBr > RCl >>> RF). The strong H-F bond (Chapter 3) causes HF to be a *weak acid* and this is consistent with the observation that C-F bonds do not break to form F^- in S_N1 reactions.

Leaving Group Ability. The relative rates in Table 7.4 are one example of many that show rates of C-X bond breaking to form X^- in S_N1 reactions have the order $I^- > Br^- > Cl^- >>> F^-$ that we say is their **leaving group ability**. The *leaving group ability* of X^- in S_N2 reactions is the same as that for S_N1 reactions.

Other Nucleophiles, Leaving Groups, and Solvents (7.3B)

We have used the nucleophiles $^-$OH and H_2O in aqueous solvents to illustrate nucleophilic substitution. In fact, many nucleophilic substitution reactions of haloalkanes involve other *nucleophiles* and *solvent systems*, and we will see that there are a variety of *leaving groups* besides halide ions (X^-).

The General Substrate R-L. Because there are many different *leaving groups* as well as *nucleophiles*, organic chemists often symbolize the reactant (**substrate**) in nucleophilic substitution reactions as **R-L** where *L* represents the *leaving group*. Using this general structure, we can write this overall equation for a nucleophilic substitution reaction.

$$R\text{-}L + :N \rightarrow R\text{-}N + :L$$

We have not included electrical charges since nucleophiles (:N) can be either uncharged (*eg.* H_2O:) or negatively charged (*eg.* $^-$:OH), and we will see that leaving groups (:L) can also have more than one type of electrical charge.

Preview. Before we explore more examples of leaving groups L: and nucleophiles N:, and examine the role of the solvent in more detail, we shall introduce two major features of nucleophilic substitution reactions that permit us to distinguish the S_N1 and S_N2 mechanisms. These are their reaction **stereochemistry** and **kinetics** that are very different for these two mechanisms.

7.4 Stereochemistry of S_N Reactions

The S_N1 and S_N2 mechanisms have very different reaction *stereochemistry*.

Stereochemistry in the S_N2 Reaction (7.4A)

The S_N2 mechanism is *stereospecific* because *nucleophiles* (N) displace the *leaving group* (L) by bonding to the C of C-L on the side opposite the leaving group L (**backside attack**) (Figure [graphic 7.20]).

Inversion of Configuration. As the *nucleophile* begins to bond to the C-L carbon of R_3C-L, and the C-L bond begins to break, you can see that R groups attached to C-L begin to move from a *tetrahedral* toward a *planar configuration*. As the nucleophile bonds more tightly, and L continues to leave as $L:^-$, these R groups pass through the *planar configuration* and continue on to a new *tetrahedral configuration*. As a result, the R groups in N-CR_3 end up on the opposite side of an imaginary plane through the molecule compared to their original location in R_3C-L because the new N-C bond is on the side of that plane opposite to the original C-L bond. We describe this change in *stereochemistry* that occurs in the S_N2 reaction as **inversion of configuration**.

The Need for a C-L Stereocenter. We cannot always experimentally observe *inversion of configuration* in S_N2 reactions. For example, S_N2 attack by $^-:OH$ on halomethanes (CH_3-X) occurs with *inversion of configuration*, but it is impossible for us to confirm this by examining the reaction product. Either *backside attack*, or <u>hypothetical</u> *frontside attack*, of ^-OH on CH_3-Br gives the same product (CH_3-OH) (Figure [graphic 7.21]).

In order to confirm the existence of *backside attack* in an S_N2 reaction, the *substrate* R-L must be a *chiral compound* with a *stereocenter* at the C-L carbon. In addition, the substrate should be a single stereoisomer with an *R* or *S* configuration at the C-L stereocenter as we will illustrate below using (S)-2-chlorobutane. Before proceeding to this section, you should review *chirality*, *stereocenters*, *stereoisomers*, and the terms *R* and *S*, in Chapter 4*.

(2/94)(1-3/96)(10,11/97) Neuman Chapter 7

Figure 7.20. Changes in Substrate Structure During S_N2 Displacement.

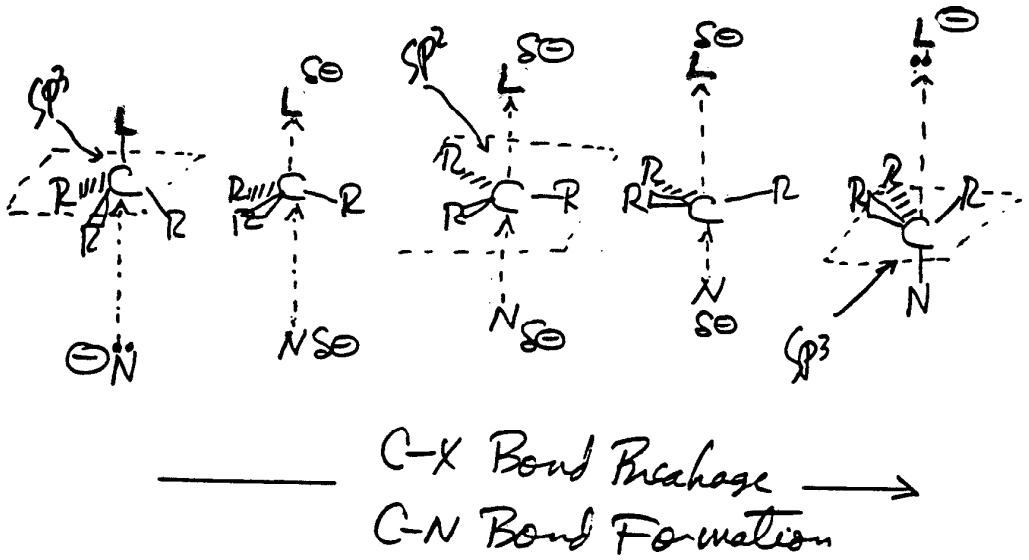
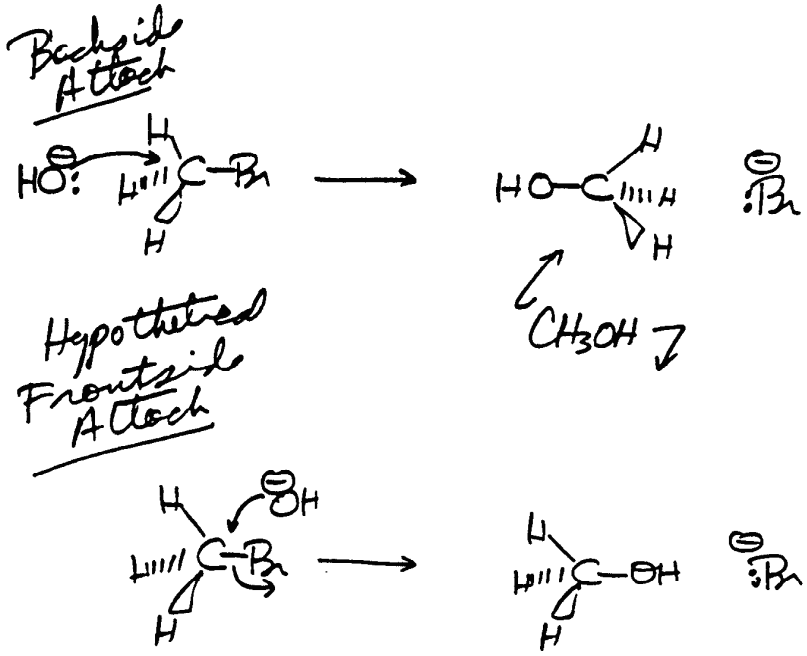
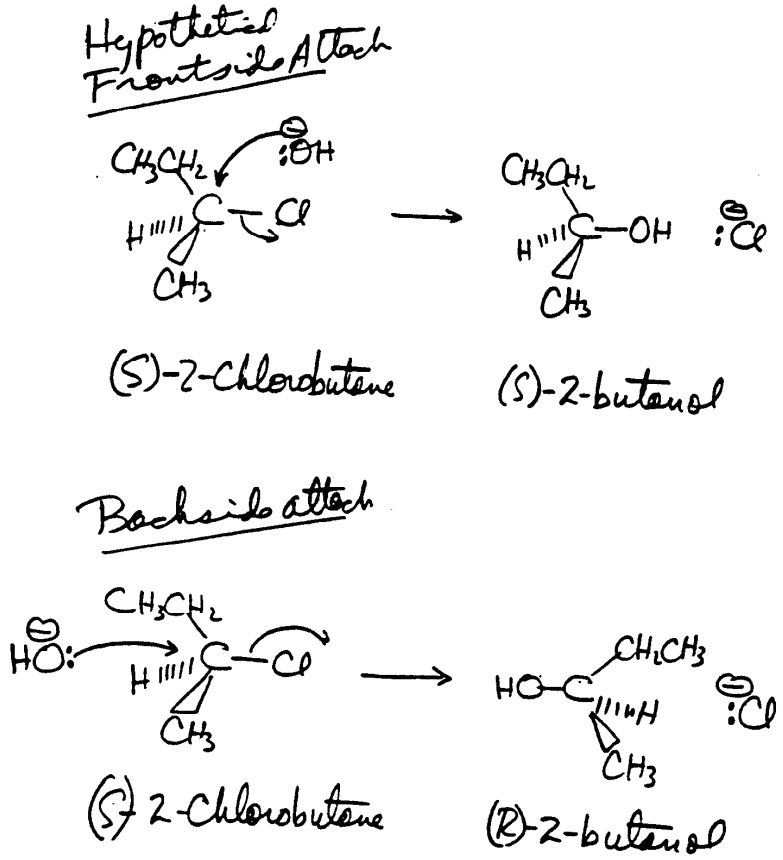


Figure 7.21. Backside versus Hypothetical Frontside Attack by Nucleophiles on CH_3Br.



S_N2 Reactions on 2-Chlorobutane. The stereochemical results of displacing Cl^- from the *frontside* or from the *backside* of the C-L stereocenter in 2-chlorobutane are quite different as we show in Figure [graphic 7.22]. If (*S*)-2-chlorobutane would react with ^-OH by a hypothetical *frontside* attack, the resulting alcohol would be *(S)-2-butanol*. In contrast, *backside* displacement of Cl^- by ^-OH gives (*R*)-2-butanol. Both of these reactions are **stereospecific**, but the different *stereochemical outcomes* allow a clear choice between these two possible mechanisms.

Figure 7.22. Backside versus Hypothetical Frontside Attack by Nucleophiles on $CH_3CH_2CH(CH_3)Cl$.



The exprimental result is that the S_N2 product is (*R*)-2-butanol in agreement with the *backside* displacement mechanism. Stereochemical results for a variety of S_N2 reactions on compounds with C-L stereocenters show that they occur by *backside* displacement of the leaving group by the nucleophile. There is always *inversion of configuration* at the C to which L and subsequently N are bonded.

Inversion of Configuration Does Not Always Change R to S. Inversion of configuration in an S_N2 reaction does not always change an *R* stereoisomer into an *S* stereoisomer, or *vice-versa*. We define *R* and

S configurations using priority rules that we outlined in Chapter 4* and L and N may have different priority rankings when they are bonded to a particular carbon stereocenter. As a result, backside attack by $^{-}$:N, and inversion of configuration, may convert an *R* stereoisomer of R_3C-L into an *R* stereoisomer of R_3C-N because of a difference in the priority rankings of L and N. Only when the relative priority rankings of nucleophiles and leaving groups are the same, do S_N2 reactions change *R* isomers of R_3C-L into *S* isomers of R_3C-N, and *vice-versa*.

Stereochemistry in the S_N1 Reaction (7.4B)

The *stereochemical outcome* of an S_N1 reaction is dramatically different from that of an S_N2 reaction.

Inversion and Retention of Configuration. As the leaving group departs from R_3C-L to form the intermediate carbocation, the R groups attached to C-L move from a tetrahedral to a planar configuration and the hybridization of the C changes from sp^3 to sp^2 (Figure [graphic 7.24]). In principle, a nucleophile can then approach the planar carbocation intermediate from either of its two sides (or **faces**) to give the substitution product R_3C-N.

When the nucleophile approaches from the *face* opposite that where L departed, R_3C-N has an *inverted* configuration at C-N. However, when the nucleophile approaches the carbocation from the same *face* from which L departed, R_3C-N has the same configuration at C-N as that of the C-L carbon in R_3C-L and we say that R_3C-N forms with **retention of configuration**.

Racemic Product. The actual stereochemical result that we observe for an S_N1 reaction depends on the *nucleophile*, the *leaving group*, and the *solvent system*. It usually is a mixture of R_3C-N *stereoisomers* that result from both *inversion* and *retention* of configuration. When C of C-L is the only stereocenter in the molecule, these *stereoisomeric* products are *enantiomers* (Chapter 4), and if they form in equal amounts we say that the reaction occurs with *racemization* to give a *racemic mixture*.

Often the product of an S_N1 reaction is not completely *racemic*, but has more of the *enantiomer* resulting from *inversion* of configuration than that resulting from *retention* of configuration. This occurs when the leaving group (L) partially blocks the *face* of R_3C+ from which it left. As a result, the nucleophile has easier access to the *backside* of the carbocation that is not blocked by the leaving group (Figure [graphic 7.25]).

An excess of the enantiomer from *inversion of configuration* can also occur if the reaction simultaneously occurs by both the S_N1 and S_N2 mechanisms. This is generally not the case,

Figure 7.24. Stereochemical Results of Attack of N: on Symmetrical Carbocation Intermediate.

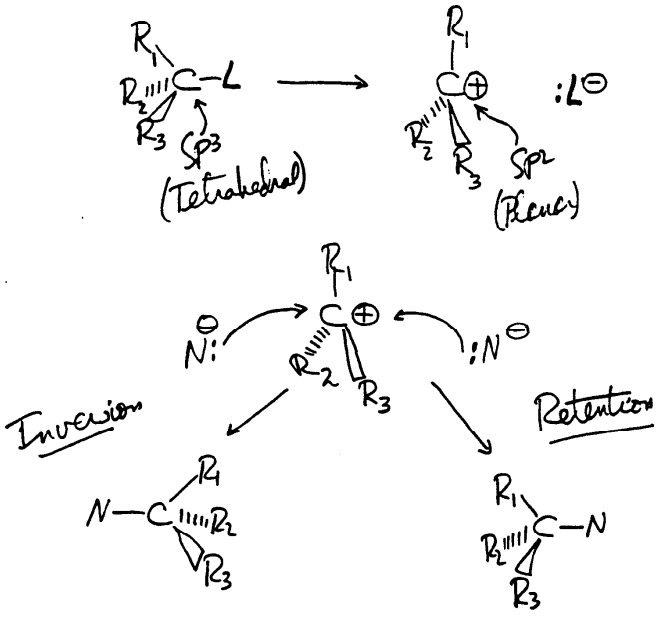
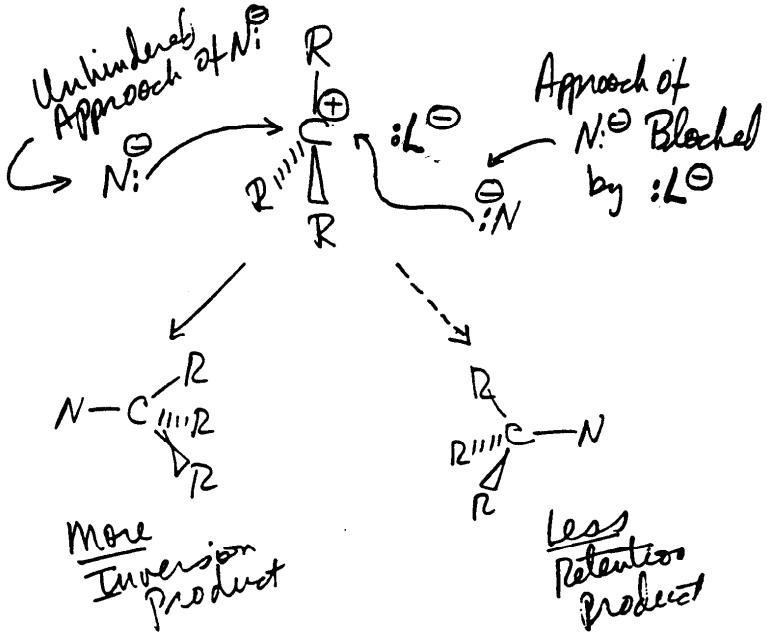


Figure 7.25. Stereochemical Results of Attack of N: on Carbocation Intermediate with One Face Blocked.



however we can test for this by determining how the *concentration* of the *nucleophile* affects the *rate* of nucleophilic substitution as we explain in the next section.

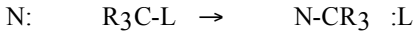
7.5 Reaction Rates of S_N Reactions

We can distinguish between S_N1 and S_N2 mechanisms by determining how the concentration of the nucleophile (:N) affects the **rate** of the nucleophilic substitution reaction.

Reaction Rates (7.5A)

The *rate* of a chemical reaction tells us the speed of that chemical reaction under a given set of reaction conditions. We can express the reaction rate as the change in concentration of a *reactant*, or of a *product*, in a specific period of time.

S_N2 Reaction Rates. The rate of an S_N2 reaction depends on both the concentration of the *substrate* [R_3C-L] and the concentration of the *nucleophile* [N:]. This is consistent with the S_N2 mechanism since the nucleophile directly attacks R_3C-L in a single step to give the nucleophilic substitution reaction product (R_3C-N) (we do not show electrical charges in this equation).



As we increase either the concentration of substrate [R_3C-L] , or nucleophile [N:], the reaction rate increases because the probability that the two reactants encounter each other in solution increases as their concentrations increase. We express this dependence of S_N2 reaction rate on these concentrations using the equation (**rate law**) that we show here.

$$S_N2 \text{ Reaction Rate} = d[R_3C\text{-}N]/dt = k[R_3C\text{-}L][N:]$$

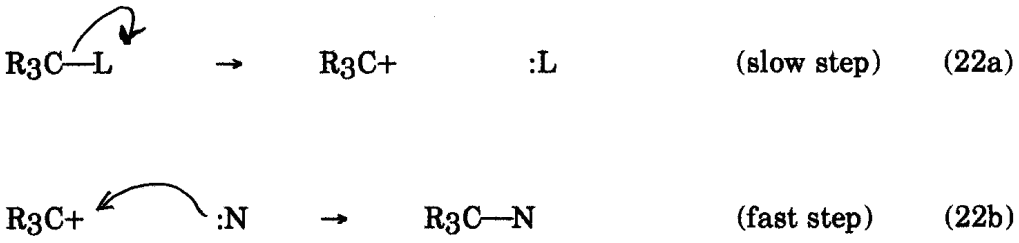
The term *d[R_3C-N]/dt* is a mathematical way of expressing "*the change in the concentration of the product R_3C-N per unit of time*" and typically has the units of *mol/L/sec*. We see that the magnitude of *d[R_3C-N]/dt* depends on the concentrations of both R_3C-L and N:, and additionally on a quantity **k** that is called the **rate constant**. The *rate constant k* is a proportionality constant that not only makes the units the same on both sides of the equation, but also is the actual rate of the reaction when both [R_3C-L] and [N:] are exactly equal to 1.0 mol/L.

S_N1 Reaction Rates. In contrast with what we have just seen for S_N2 reactions, the *rate law* for an S_N1 reaction does <u>not</u> include the concentration of the nucleophile.

$$S_N1 \text{ Reaction Rate} = d[R_3C\text{-}N]/dt = k[R_3C\text{-}L]$$

You can see from this expression that the only concentration that affects the rate is that of the substrate R_3C-L.

You recall that S_N1 mechanisms have two steps that include the ionization of the substrate R_3C-L to give a carbocation, followed by the reaction of that carbocation with the nucleophile (electrical charges are not completely shown in this equation) .



In the first step, the C-L bond breaks and this requires the input of a large amount of *energy*. However in the second step, the nucleophile forms a new bond to the unstable carbocation and this is accompanied by the release of a large amount of *energy*. Because the first step requires a *large energy input*, it is much *slower* than the second step. As a result, the overall rate of the S_N1 reaction depends only on that of the ionization step that forms the carbocation (the first step). Since the nucleophile is not involved in this first step, the rate of that step depends only on the concentration of R_3C-L.

Activation Energies (7.5B)
Reaction rates depend on energy changes that occur during the reaction.

Energy Diagram for an S_N1 Reaction. We explain the relative rates of the two steps of an S_N1 reaction using the **energy diagram** in Figure [graphic 7.26a]. It shows the energy changes that occur during each of the two steps of the overall S_N1 reaction that we wrote above.

Most carbocations (R_3C+) are very unstable, highly reactive, and have relatively high energies. In contrast, both the starting substrate (R_3C-L) and product (R_3C-N) are stable molecules with much lower energies as you can see from the relative energies of R_3C-L, R_3C-N, and R_3C+ in Figure [graphic 7.26a]. We show identical energies for R_3C-L and R_3C-N in this figure, but this is usually not the case. The important point is that their energies are much lower than that of R_3C+.

You can also see in Figure [graphic 7.26a] that while R_3C+ has a very high energy, it is not the highest energy point on this diagram. There is a molecular configuration of higher energy between

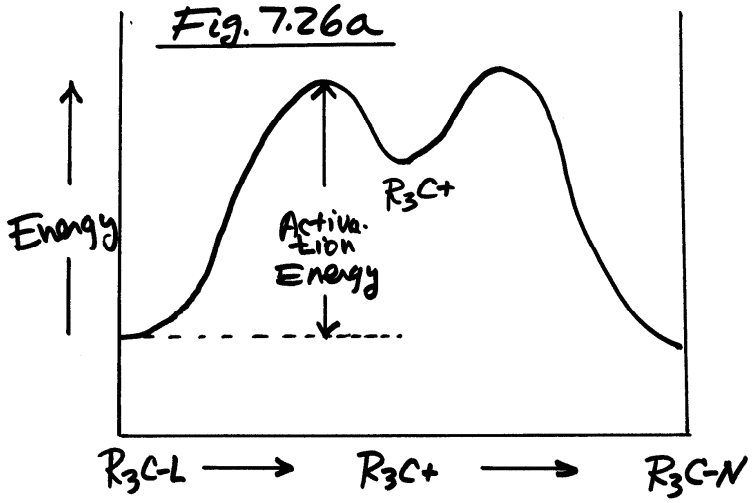


Figure 7.26. Generalized Energy Diagram for a One-Step Chemical Reaction.

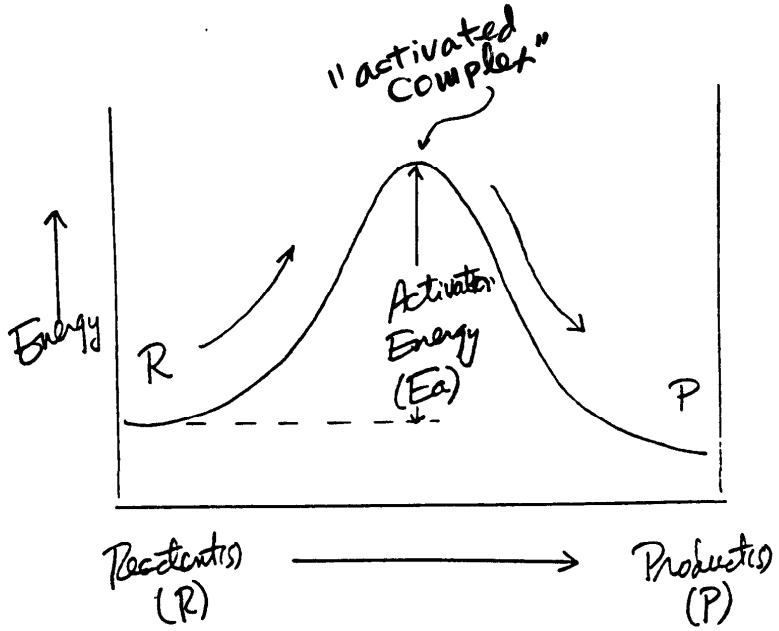
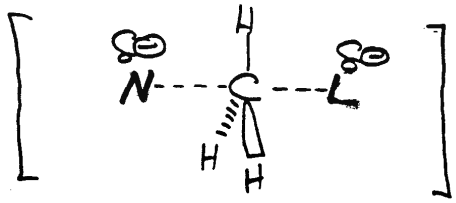


Figure 7.27. Transition State for S_N2 Reaction between N^- and CH_3L



R_3C-L and R_3C+, and another between R_3C+ and R_3C-N. These "highest energy" points are called **transition states** or **activated complexes**, and they represent the highest energy molecular configurations that molecules in each reaction must pass through as the reaction occurs.

S_N1 Activation Energies. The energy required to transform R_3C-L into the *activated complex* on the way to R_3C+ is called the **activation energy** for that reaction (Figure [graphic 7.26a]). Similarly, the energy required to form the *activated complex* from R_3C+ and :N, as they form R_3C-N, is the *activation energy* for the second step of the S_N1 reaction.

Rate constants k for chemical reactions depend on *activation energies*. As the *activation energy* for a reaction increases, the value of the *rate constant k* for that reaction decreases. Since the *activation energy* (**E_{a1}**) for the first reaction is much greater than that for the second reaction (**E_{a2}**), the rate constant for ionization of R_3C-L to form R_3C+ is much less than the rate constant for the second reaction where R_3C+ reacts with N:. As a result, the *first* reaction is much slower than the *second* reaction.

Energy Diagram for an S_N2 Reaction. In contrast to S_N1 reactions, the S_N2 mechanism has just one step so the energy diagram has just one *activated complex* (Figure [graphic 7.26]). We can represent that *activated complex* as a molecular configuration with a partially formed N···C bond and a partially broken C···L bond as we illustrate in Figure [graphic 7.27].

We showed this type of species in Figure [graphic 7.2] when we first described the S_N2 reaction. It is important to emphasize that it is not an *intermediate* in the S_N2 reaction. It is an *activated complex* (or *transition state*) that is the molecular configuration with the maximum energy between the substrate (R_3C-L), and the nucleophilic substitution product (R_3C-N). The *activation energies* for S_N2 reactions, (and their *rate constants k*) depend on the difference in energy between this *activated complex* and the energies of the reactants as we show in Figure [graphic 7.26].

> ***Determining Reaction Rates***. Chemists determine the rate of a chemical reaction by experimentally monitoring the change of concentration of a reactant (*eg*. RL) or a product (*eg*. RN) with time. The method used to measure the concentration of RL and/or RN may be chemical analysis involving *titrimetric* (determining concentrations by titration) or *gravimetric* (determining concentrations by weight) procedures such as those you may have studied in previous laboratory courses. These days, chemists measure concentrations using some type of spectrometry (Chapter 5).

7.6 Other Nucleophiles

We have considered *nucleophilic substitution* reactions that use $HO:^-$ or $H_2O:$ as nucleophiles and convert *haloalkanes* (R-X) into *alcohols* (R-OH) by substitution of OH for X. There are many other nucleophiles that we can also use in S_N reactions. We list common examples in Table 7.5 and show others in Appendix 7.1 at the end of this chapter.

Table 7.5. Common Nucleophiles (:N) for Nucleophilic Substitution Reactions

Neutral	Negative
ROH	RO^-
R_2NH	R_2N^-
RSH	RS^-
	X^-
	N_3^-
	NC^-

ROH and RO⁻ as Nucleophiles (7.6A)

The alcohol (ROH), and alkoxide ions ($RO:^-$) nucleophiles are analogous to water (HOH) and hydroxide ion ($HO:^-$). HOH and $HO:^-$ are specific examples of ROH and $RO:^-$ where R is H. We introduced alcohols (ROH) in Chapter 3* and you may wish to review that discussion again at this time.

ROH Nucleophiles. The S_N1 reaction between *ethanol* (CH_3CH_2OH) and the *substrate* 2-iodo-2-methylpropane is an example where an alcohol (ROH) is the nucleophile. [graphic 7.33] This mechanism is analogous to that for the S_N1 reaction of water (HOH) with 2-bromo-2-methylpropane that we showed in section 7.1B. The first two steps, common to all S_N1 reactions, are carbocation formation, and its subsequent reaction with the nucleophile CH_3CH_2OH. The product of the second step then loses a proton in an *acid/base* reaction to give an *ether* (ROR).

Alcohols (ROH), like water (HOH), primarily serve as nucleophiles in S_N1 reactions. They are generally not reactive enough to displace a leaving group such as a halide ($^-:X$) ion from a haloalkane (R-X) by an S_N2 mechanism. When nucleophiles such as ROH or HOH also serve as the reaction *solvent*, we refer to their S_N1 reactions as **solvolysis reactions**. *Solvolysis reactions* of haloalkanes (R-X) in *water* give *alcohols* as products, while those of haloalkanes in *alcohols* give *ethers* (Chapter 3*).

RO⁻ Nucleophiles (Williamson Ether Synthesis). Alkoxide ion (RO^-) nucleophiles react by an S_N2 mechanism with haloalkanes (R-X) to also give *ethers* (R-OR) as we illustrate here using the formation of *ethyl methyl ether* from *bromomethane* and *ethoxide* ion. [graphic 7.34] This

Figure 7.33

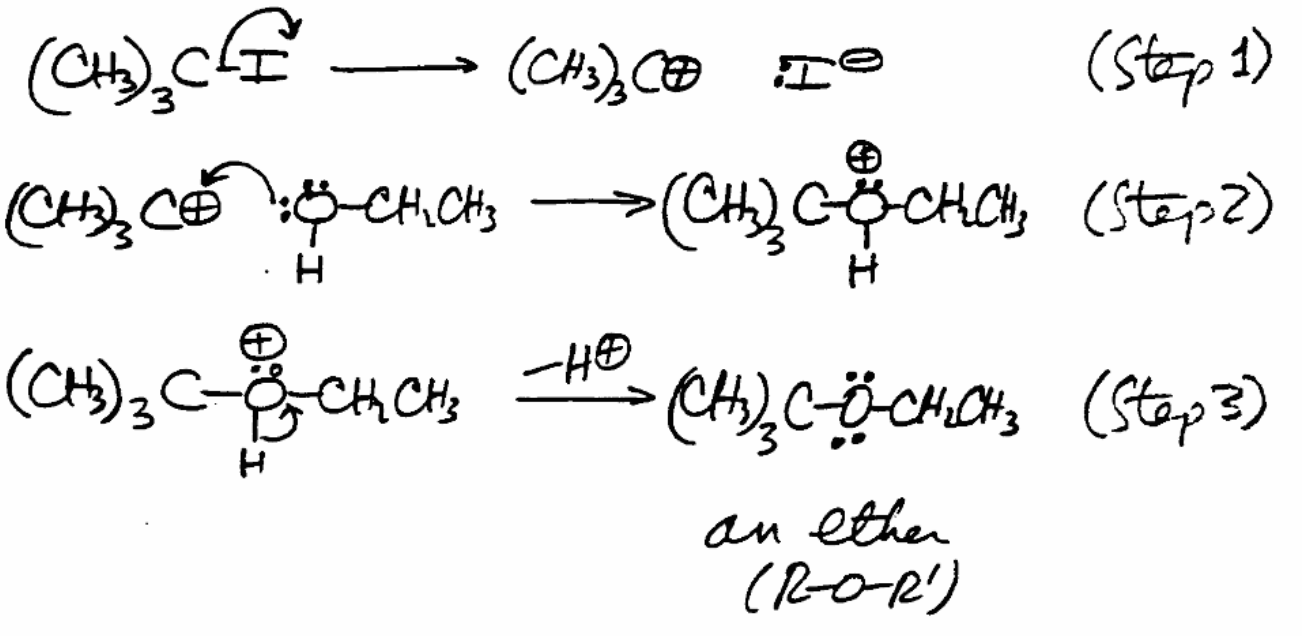


Figure 7.34

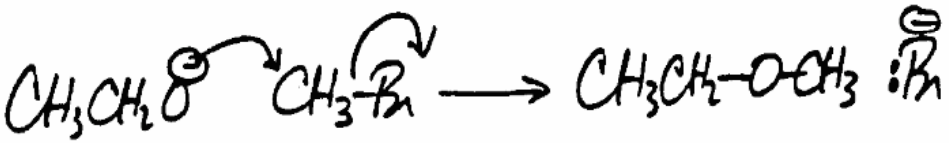
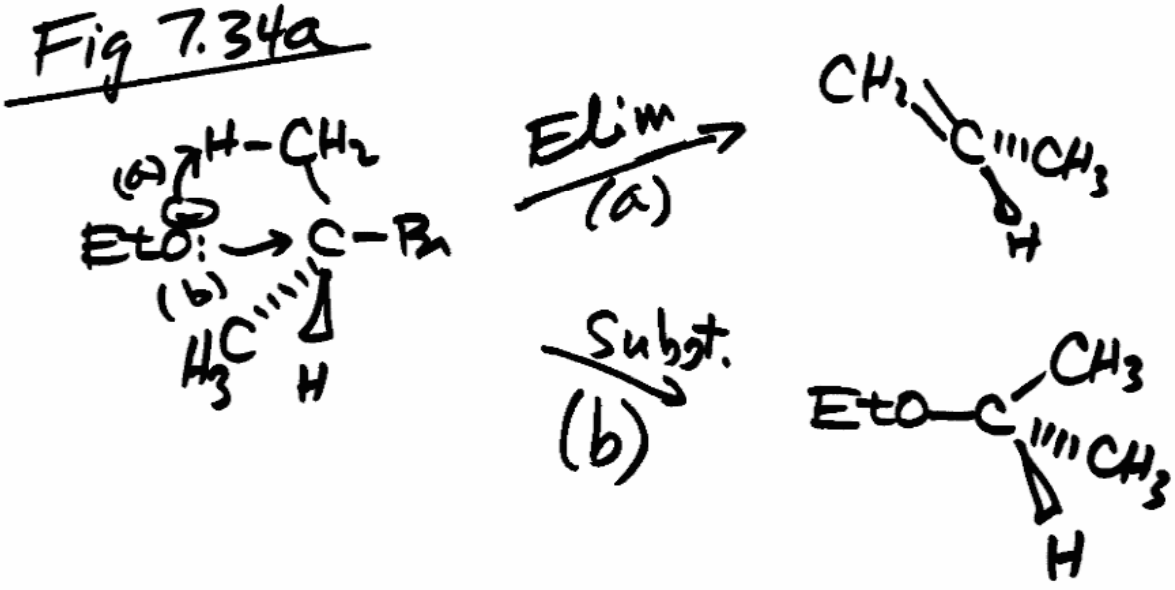


Fig 7.34a

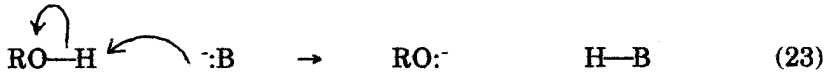


type of reaction is often referred to as the **Williamson ether synthesis** and the solvent is often the alcohol (ROH) that corresponds to the alkoxide ion (RO^-) nucleophile.

Limitations of the Williamson Ether Synthesis. The *Williamson Ether Synthesis* is a convenient way to make certain *ethers*, but there are limitations on the haloalkane. Since the mechanism is S_N2, the best substrates are *halomethanes* (CH_3-X) and *1° haloalkanes* (R-CH_2-X), where R is an alkyl group such as methyl, ethyl, propyl, or other 1° alkyl group. 3° haloalkanes (R_3C-X), are not appropriate for the Williamson Ether Synthesis since S_N2 reactions are impossible for 3° substrates because of *steric hindrance* to approach of the nucleophile.

While 2° substrates are less favorable then 1° substrates for the same reason, another important consideration is that *elimination* reactions frequently compete with S_N2 reactions if the nucleophile is a strong base such as $^-$:OR as we illustrate in here using *ethoxide* ion and *2-bromopropane*. [graphic 7.34a] We mentioned *elimination* reactions earlier in this chapter and will describe them in detail in Chapter 9. We will see there that 3° substrates are also excellent substrates for *elimination* reactions.

Alkoxide Ion Formation. Alkoxide ions (RO^-), such as those in the *Williamson ether synthesis*, are the *conjugate bases* of alcohols (ROH). We form them by removing a proton from the OH group of the alcohol using another base ($^-$:B).



(23)

The acidity of alcohols (K_a approximately 10^{-16}) is comparable to the acidity of water (K_a = 1.8 x 10^{-16}) *, so a base ($^-$:B) that can remove the ROH proton to form RO^- must be at least as basic as hydroxide ion (HO^-). In order to form significant amounts of RO^- from alcohols (ROH), the base ($^-$:B) should be a much stronger base than $^-$OH. We can also generate RO^- in the alcohol solvent (ROH) by carefully adding elemental sodium (Na) or elemental potassium (K) to the alcohol. We must carefully control these reactions, because they generate a large amount of heat as well as the flammable gas H_2.

$$2\ RO\text{-}H \quad 2\ Na \quad \rightarrow \quad 2\ RO^-\ Na^+ \quad H_2\uparrow$$

Simple alkoxides are commercially available as their sodium or potassium salts (RO^-Na^+ or RO^-K^+) . These include sodium or potassium salts of *methoxide ion* (*eg.* $NaOCH_3$), *ethoxide ion* (*eg.* $KOCH_2CH_3$), *isopropoxide ion* (*eg.* $NaOCH(CH_3)_2$), or t-*butoxide ion* (*eg.* $KOC(CH_3)_3$). We can sometimes use these alkoxide salts in solvents other than the corresponding alcohol ROH.

Formation of Cyclic Ethers (Epoxides). When an OH group and a halogen atom (X) are located on adjacent carbon atoms in the same molecule, treatment of that compound with a base such as $^{-}$:OH or $^{-}$:OR leads to the formation of a three-membered *cyclic ether* (an *epoxide*). [graphic 7.35] These bases ($^{-}$:OH or $^{-}$:OR) remove a proton from OH and give a low concentration of the intermediate anion (Step 1). It rapidly reacts to give an *epoxide* by **intramolecular** displacement of X^- (X^- by O^- in the same molecule) (Step 2).

You may wonder why $^{-}$:OH or $^{-}$:OR do not directly displace $^{-}$:X to give products like those shown here. [graphic 7.35a] These reactions do not efficiently compete with epoxide formation shown above because proton removal from the OH group (Step 1) is much faster than nucleophilic displacement of $^{-}$:X from the β-haloalcohol. The intermediate β-haloalkoxide anion then reacts very rapidly to give an epoxide (Step 2) since the nucleophilic O^- atom and the C-X carbon that it attacks are in the same molecule.

R_2NH and R_2N^- as Nucleophiles (7.6B)

Amines (R_2NH) and *amide ions* (R_2N^-) are nucleophiles that appear at first glance to be analogous to alcohol (ROH) and alkoxide ion (RO^-) nucleophiles. However, there are important differences in the ways that we can use them in nucleophilic substitution reactions. We introduced *amines* in Chapter 3* and you may wish to review that material before you proceed to the following sections.

Amine Nucleophiles R_2NH. The simplest R_2NH nucleophile is ammonia (NH_3) where both R groups are H. NH_3 reacts with haloalkanes by nucleophilic substitution to form *amines* by the sequence of two reaction steps shown below for the conversion of *bromoethane* to *ethaneamine*.

$$CH_3\text{-}CH_2\text{-}Br + :NH_3 \rightarrow CH_3\text{-}CH_2\text{-}NH_3^+ + Br^- \quad \text{(Step 1)}$$

$$CH_3\text{-}CH_2\text{-}NH_3^+ + :NH_3 \rightarrow CH_3\text{-}CH_2\text{-}NH_2 + NH_4^+ \quad \text{(Step 2)}$$

Step 1 is an *S_N2 reaction* where the nucleophile NH_3 displaces the bromide ion by *backside attack* at the C-Br carbon (Figure [graphic 7.37]). Step 2 is an *acid/base reaction* in which *ammonia* acts as a base and removes the proton from the protonated *aminium ion* formed in Step 1.

We see from these reactions that *ammonia* (NH_3) must be a much stronger nucleophile than *water* (H_2O). While H_2O does not displace bromide ion from bromoalkanes by an S_N2 mechanism, NH_3 readily reacts with bromoalkanes in such a reaction (Step 1). Similarly, *amines* (R_2NH) are always stronger nucloeophiles than their analogous *alcohols* (ROH). Because NH_3

Figure 7.35

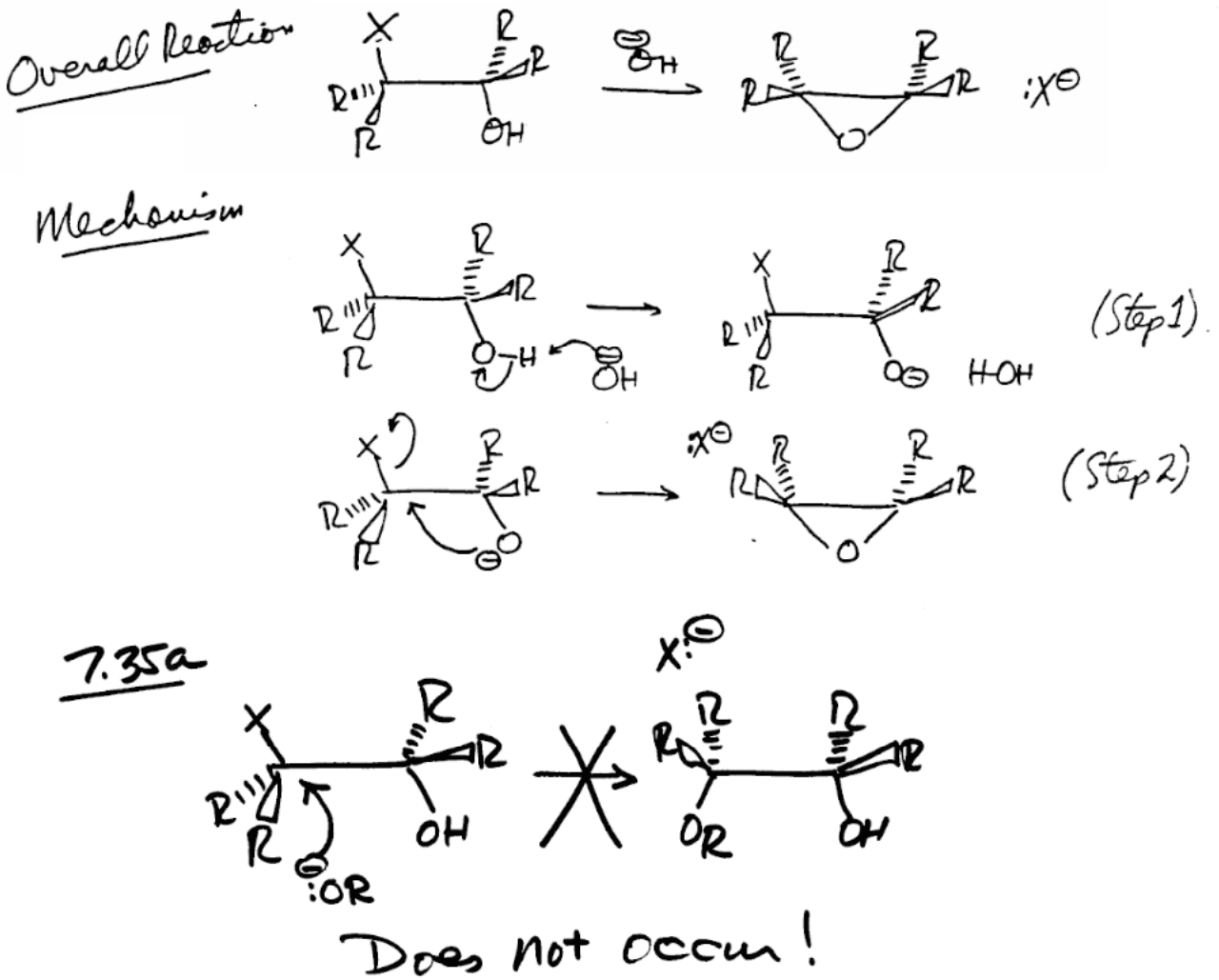
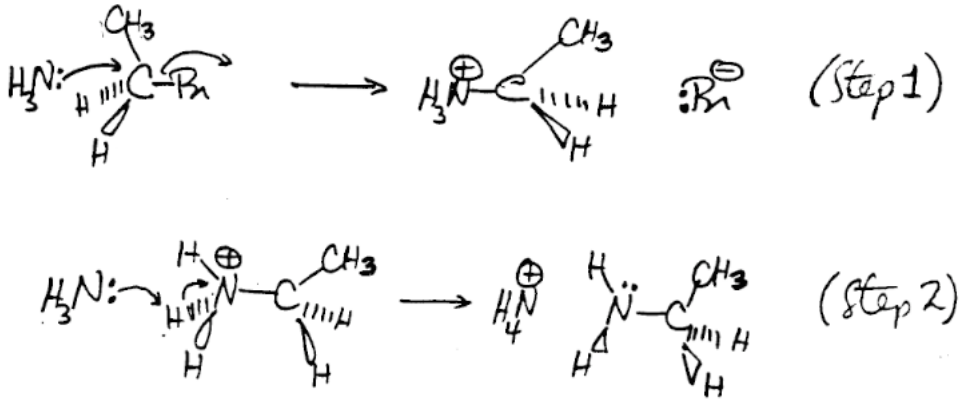


Figure 7.37. S_N2 Mechanisms for Reaction of Ammonia with 1-Bromoethane.



and amines (R_2NH) are much stronger nucleophiles than H_2O or ROH, we can use water or alcohols as solvents for S_N2 reactions involving NH_3 or R_2NH nucleophiles without fear that they will compete as nucleophiles with NH_3 or R_2NH.

The Amine Products React Further. While the reaction between $:NH_3$ and CH_3CH_2Br to give $CH_3CH_2NH_2$ occurs rapidly and is easy to carry out, it is usually accompanied by subsequent side reactions. Since $CH_3CH_2NH_2$ is itself a nucleophile, it readily reacts with unreacted CH_3CH_2Br in the reaction mixture to give the 2° amine $(CH_3CH_2)_2NH$.

$$CH_3CH_2\text{-}Br + H_2N\text{-}CH_2CH_3 \rightarrow CH_3CH_2\text{-}\overset{+}{H_2}N\text{-}CH_2CH_3 + Br^- \quad \text{(Step 1)}$$

ethanamine

$$CH_3CH_2\text{-}\overset{+}{H_2}N\text{-}CH_2CH_3 + H_2N\text{-}CH_2CH_3 \rightarrow CH_3CH_2\text{-}HN\text{-}CH_2CH_3 + \overset{+}{H_3}N\text{-}CH_2CH_3 \quad \text{(Step 2)}$$

N-ethylethanamine

Step 1 is an S_N2 reaction while Step 2 is an acid/base reaction. The product *N-ethylethanamine* (abbreviated Et_2NH) can react even further with *bromoethane* (EtBr) by two more successive S_N2 reactions ultimately giving the *tetraethylammonium ion* (*tetraethylaminium ion*) (Et_4N^+). [graphic 7.38]

To minimize the formation of subsequent products during the reaction of an amine such as $CH_3CH_2NH_2$ with a haloalkane such as CH_3CH_2Br, we can use a large excess of the amine nucleophile ($CH_3CH_2NH_2$) in Step 1. As a result, the reaction product $(CH_3CH_2)_2NH$ is always present in low concentration compared to $CH_3CH_2NH_2$ and this minimizes the side reaction between the product $(CH_3CH_2)_2NH$ and reactant CH_3CH_2Br.

Two Different R Groups on N. We can use the sequence of the reactions in Steps 1 and 2 to put two different alkyl groups on the same nitrogen. For example, if we react a 1° amine such as *$CH_3CH_2NH_2$* with *bromocyclohexane*, we obtain the 2° amine *N-ethylcyclohexaneamine*. [graphic 7.39]

This reaction is subject to the same side reactions that we described above. As a result, we must take precautions like those we described to minimize further reaction of the desired product with *bromocyclohexane* that could give a *3° amine* or a *quaternary aminium ion* (see next section)

Figure 7.38

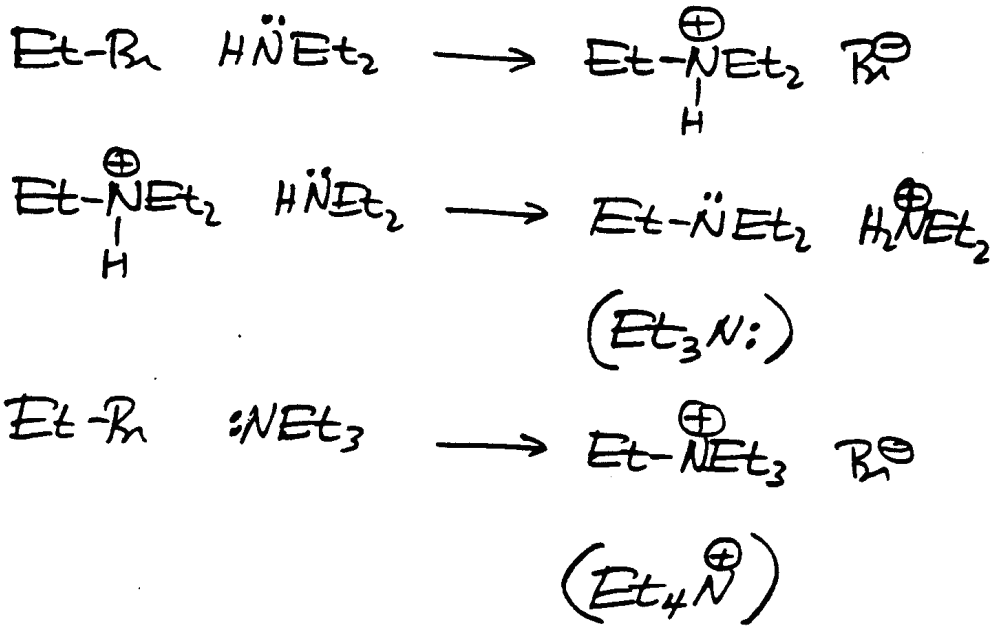
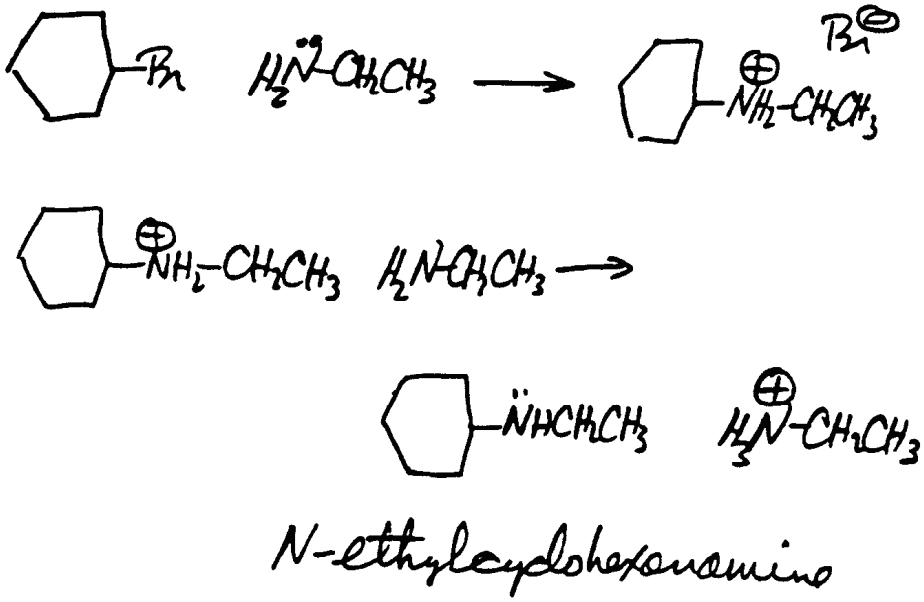


Figure 7.39



3° Amine (R_3N:) Nucleophiles. When the amine nucleophile has three R groups (R_3N:) (a 3° amine), the product of its reaction with a haloalkane is a *quaternary aminium salt* that has 4 alkyl groups bonded to N.

$$\underset{\text{3° amine}}{R_3N:} + R'X \rightarrow \underset{\text{quaternary aminium salt}}{R_3N^+R'\ X:^-}$$

Since R_3N^+R' has no H's on N, it cannot form a neutral amine by loss of a proton.

Amide Nucleophiles R_2N^-. The *amide ion* $^-NH_2$ is the conjugate base of ammonia (NH_3) and we can form it by reacting NH_3 with elemental sodium (Na), potassium (K), or lithium (Li) as we show here using Na.

$$2\ Na + 2\ NH_3 \rightarrow 2\ Na^+\ ^-NH_2 + H_2\uparrow$$

Just as R_2NH is more nucleophilic than ROH, $^-NH_2$ (the amide ion) is more nuclephilic than $^-$OH. However, while we frequently use $^-$OH as a nucleophile in S_N2 reactions because H_2O is much less reactive, the high reactivity of NH_3 as a nucleophile makes it unneccesary to use $^-NH_2$ as a nucleophile in S_N2 reactions.

All of the comparisons of $^-NH_2$ with $^-$OH are also true for R_2N^- and RO^-. We can synthesize the alkyl amide ions (R_2N^-) by reacting amines (R_2NH) with Na, K, or Li as we show here using K and R_2NH.

$$2\ K + 2\ R_2NH \rightarrow 2\ R_2N^-\ K^+ + H_2\uparrow$$

As is the case with $^-NH_2$, alkylamide ions (R_2N^-) are not usually used as nucleophiles because the parent amines (R_2NH) are sufficiently nucleophilic to react directly with substrates. Although they are not generally used in nucleophilic substitution reactions, amide ions ($^-NH_2$ and R_2N^-) are strongly basic and we will see later in the text that they are used as strong bases in a variety of other organic reactions.

S_N1 Mechanisms and Amine Nucleophiles. All of the reactions that we have described between amine nucleophiles (R_2NH) and haloalkanes (RX) are S_N2 reactions. While amines can react with 3° haloalkanes by S_N1 mechanisms, these reactions are usually accompanied by undesired reactions of the intermediate carbocation with other nucleophiles present in the reaction mixture.

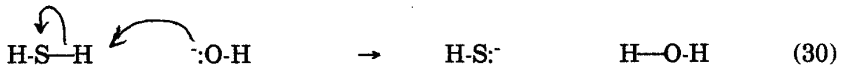
In order to form carbocations from haloalkanes, we must use highly polar solvents such as water, alcohols, and alcohol/water mixtures. Even if amines are present in the reaction mixture, the

intermediate carbocations will rapidly react with solvents such as H_2O or ROH to give other products besides the desired amine (Figure [graphic 7.40]). In contrast, we can use H_2O or ROH as solvents for S_N2 reactions of *haloalkanes* and *amines* since amines are much more nucleophilic than H_2O or ROH.

RSH and RS⁻ as Nucleophiles (7.6C)

S atoms are nucleophilic centers in the compounds RSH and RS^-.

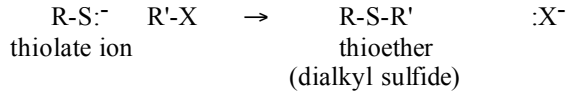
H_2S and HS^-. H_2S and $HS:^-$ are nucleophiles analogous to H_2O and $HO:^-$, as well as to NH_3 and $H_2N:^-$. Their nucleophilic substitution products from reaction with haloalkanes (RX) are **thiols** (R-SH) that are structurally analogous to alcohols (ROH). [graphic 7.41] HS^- is more synthetically useful than H_2S and we can prepare its sodium salt (Na^+SH^-) by bubbling gaseous H_2S into a solution of NaOH. H_2S is a stronger acid than H_2O so the H_2S/HS^- equilibrium in aqueous NaOH favors HS^-.



(30)

The reaction of HS^- with *haloalkanes* occurs by an S_N2 mechanism, so 1° haloalkanes (RCH_2X) are better substrates than 2° haloalkanes (R_2CHX), while 3° haloalkanes (R_3CX) do not react.

RSH and RS⁻. *Thiols* (RSH) and their conjugate bases, the **thiolate ions** (RS^-), are also nucleophilic. The negatively charged *thiolate ions* are used much more frequently as nucleophiles than *thiols*. Reactions of *thiolate ions* with haloalkanes give **thioethers** (RSR') that are also commonly named **dialkyl sulfides**.



This reaction is analogous to the *Williamson ether synthesis*.

Thiols and Thioethers. Thiols (RSH) are systematically named ***alkanethiols***. As an example, CH_3SH is named **methanethiol**. Thiols are also commonly referred to as **mercaptans** so the common name for CH_3SH is *methyl mercaptan*. Since thioethers (RSR') are commonly referred to as **dialkyl sulfides**, the common name for $(CH_3)_2S$ is *dimethyl sulfide* while that for $CH_3SCH_2CH_3$ is *ethyl methyl sulfide*.

Thiols (RSH) form much weaker hydrogen bonds than alcohols (ROH). As a result, they have much lower boiling points than alcohols with the same R group even though they have greater molar masses as is apparent in the comparison of CH_3CH_2SH and CH_3CH_2OH in Table 7.5a.

Figure 7.40. Carbocations React with All Nucleophiles Present in the Reaction Mixture.

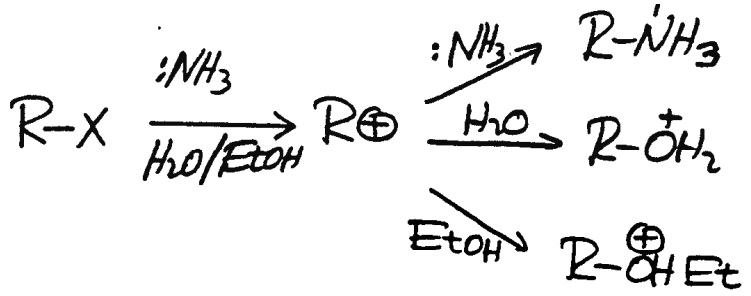


Figure 7.41

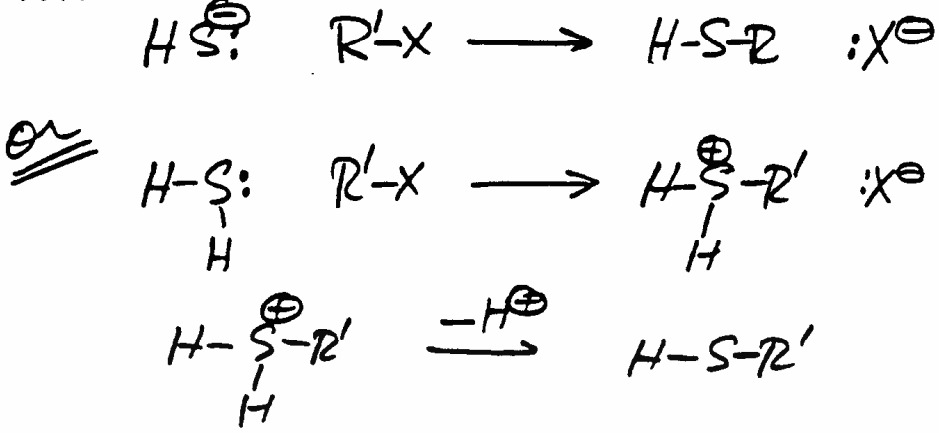


Figure 7.42 These reaction do not occur.

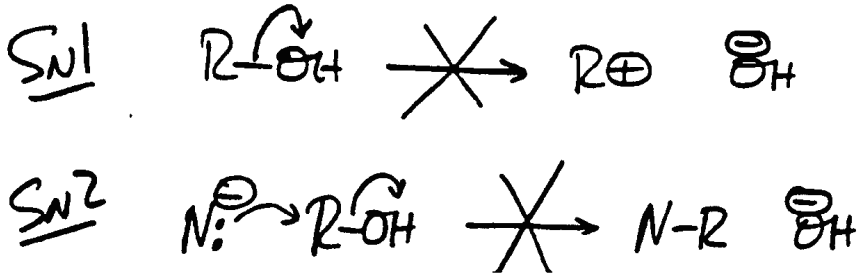


Table 7.5a. Boiling Point Comparisons for ROR' and RSR'.

Compound	Molecular Mass	B.p. (°C)
CH_3CH_2SH	62	+35
CH_3CH_2OH	46	+79
CH_3SCH_3	62	+37
CH_3OCH_3	46	-25

Ethanol (CH_3CH_2OH) has a lower molecular mass than *ethanethiol* (CH_3CH_2SH), but it has a substantially higher b.p. because of strong H-bonding in *ethanol*. In contrast, the b.p. of the *ether* CH_3OCH_3 (molar mass 46) and *thioether* CH_3SCH_3 (molar mass 62) reflect their relative molar masses since H bonding is not possible for either CH_3OCH_3 or CH_3SCH_3. Note that the b.p.'s of CH_3CH_2SH and CH_3SCH_3 (both with molar mass 62) are almost the same even though one has an SH group. This provides further support for the absence of SH hydrogen bonding in *thiols*.

Thiols and *thioethers* are highly toxic and have very unpleasant odors. *Butanethiol* ($CH_3CH_2CH_2CH_2SH$) is added in very low concentration to odorless *natural gas* so that you can detect *natural gas* leaks. Skunks expel a mixture of thiols when they are alarmed.

Halide Ion Nucleophiles (X^-) (7.6D)

We have shown many examples of halide ion *leaving groups*, and all four halide ions (I^-, Br^-, Cl^- and F^-) are also *nucleophiles*. Organic chemists have designed reaction conditions where the **halide exchange reaction** shown below can occur for each of the halide ion nucleophiles (X^-) when R-X' is an *iodoalkane*, a *bromoalkane*, or a *chloroalkane*.

$$X^- \quad R\text{-}X' \quad \rightarrow \quad X\text{-}R \quad X'^-$$

However R-X' cannot be a fluoroalkane (R-F) because you may remember that F^- is a very poor leaving group (see Table 7.4).

Formation of Fluoroalkanes. The *halide exchange reaction* shown above is actually an equilibrium when X^- is I^-, Br^-, or Cl^-. The halide ion (X'^-) that leaves can react with the new haloalkane product R-X to regenerate R-X'. However, there is no equilibrium when the nucleophile is F^-. F^- is such a poor leaving group that formation of R-F is irreversible. Since R-F does not react with halide ions, *halide exchange* where $F:^-$ attacks R-I, R-Br, or R-Cl, is a good method for making fluoroalkanes (R-F). The F^- is brought to the reaction mixture in the form of commercially available salts such as AgF or KF.

Formation of Iodoalkanes. We can use the *halide exchange reaction* to form chloroalkanes, bromoalkanes, and iodoalkanes, but we will also see other methods for forming *chloroalkanes* and bromoalkanes in Chapters 10 and 11. However, these alternative reactions generally do not give iodoalkanes, so halide exchange is an important reaction for making iodoalkanes.

A convenient way to replace Cl or Br by I, is the reaction between a chloroalkane or bromoalkane and sodium iodide in *acetone*.

$$\text{R-Cl or R-Br} + \text{Na}^+\text{I}^- \xrightarrow{\text{acetone}} \text{R-I} + \text{NaCl}\downarrow \text{ or NaBr}\downarrow$$

Iodide ion comes from sodium iodide (NaI) that is soluble in the solvent *acetone* (see description earlier in the chapter). Neither sodium chloride (NaCl) nor sodium bromide (NaBr) are soluble in acetone, so these salts precipitate from the reaction mixture preventing the reverse reaction of Cl^- or Br^- with the reaction product R-I.

Halide exchange reactions can be either S_N1 or S_N2 reactions, however S_N2 reactions provide the greatest control over the reaction products since there is no intermediate carbocation to react with other nucleophiles that might be present. The S_N2 mechanism requires that the reactant haloalkane is methyl, 1° or 2° for the steric reasons that we described earlier.

The Nucleophiles N_3^- and $^-C{\equiv}N$ (7.6E)

The last two nucleophiles that we describe in this section are *azide ion* (N_3^-) and *cyanide ion* ($^-C{\equiv}N$). While good nucleophiles, we will learn later in this chapter that $^-C{\equiv}N$ and $^-N_3$ are very poor leaving groups. As a result, nitriles (R-C≡N) and azides (R-N_3) are stable products of S_N reactions.

Cyanide Ion. *Cyanide ion* ($^-C{\equiv}N$) is an important nucleophile because it forms a C-C bond when it replaces the leaving group as we show here using a haloalkane (R-X) substrate.

$$\text{R-X} + {}^-\text{:C}{\equiv}\text{N} \rightarrow \text{R-C}{\equiv}\text{N} + {}^-\text{:X}$$

This reaction has an S_N2 mechanism so it requires requires a methyl, 1° or 2° haloalkane. The product R-C≡N is a **nitrile** that we describe in Chapters 14 and 15. We will see in Chapter 15 that we can convert the nitrile functional group (C≡N) into a variety of other organic functional groups, and that is why $^-C{\equiv}N$ is such an important nucleophile. Cyanide ion ($^-C{\equiv}N$) is readily available in the very poisonous inorganic salts *sodium cyanide* (NaC≡N) and *potassium cyanide* (KC≡N).

Azide Ion. The *azide ion* (N_3^-), available as *sodium azide* or *potassium azide* ($Na^{+-}N_3$ or $K^{+-}N_3$), reacts with haloalkanes in S_N1 or S_N2 reactions to give organic azides that are precursors precursors to a variety of other organic compounds including 1° amines ($R\text{-}NH_2$).

$$R\text{-}X \quad + \quad N_3^- \quad \rightarrow \quad R\text{-}N_3 \quad + \quad X^-$$

Electronic Structures of N_3^- and R-N_3. We show the electronic structures of the azide ion (N_3^-) and azide functional group in $R\text{-}N_3$ here.

$^-\!:N{=}N^+{=}N\!:^-$	$R\text{-}N{=}N^+{=}N\!:^-$
(Charge of -1)	(No electrical charge)

The number of bonds to each N, the number of unshared pairs on each N, and the resultant formal charges on the atoms, satisfy the bonding rules for nitrogen. The sum of the charges on the *azide ion* is -1, while the sum of the charges on the *azide functional group* in $R\text{-}N_3$ is zero (0).

7.7 Leaving Groups

We have seen that halogens in haloalkanes (R-X) can leave as halide ions ($^-\!:X$) in nucleophilic substitution reactions, but that they differ in their *leaving group ability*. In this section we will consider other possible leaving groups and their *leaving group ability* in S_N1 and S_N2 reactions.

The OH Group in Alcohols (R-OH) (7.7A)

The OH group in alcohols (R-OH) is a very poor leaving group, but we can adjust reaction conditions so that alcohols become good substrates for nucleophilic substitution reactions.

R-OH is a Poor Substrate for S_N Reactions. We have seen that *alcohols* are products of S_N1 and S_N2 reactions, and that we can use *alcohols* as solvents for these reactions. Both of these situations are possible because nucleophiles <u>cannot</u> displace $^-\!:OH$ in S_N2 reactions, and alcohols do not ionize to form $^-\!:OH$ in S_N1 reactions (Figure [graphic 7.42]).

We can rationalize this on the basis of the acidity of H-OH that is the conjugate acid of $^-\!:OH$. Earlier we showed that relative *leaving group abilities* of halide ions ($^-\!:X$) correlated with the acidities of their conjugate acids (H-X). We saw that H-I, H-Br, and H-Cl are strong acids ($K_a >> 1$), and that $^-\!:I$, $^-\!:Br$, and $^-\!:Cl$ are good leaving groups. In contrast, H-F is a weak acid ($K_a = 10^{-4}$), and $^-\!:F$ is a poor leaving group. The very weak acidity of H-OH ($K_a = 10^{-16}$) is consistent with the observation that $^-\!:OH$ is a very poor leaving group.

R-OH_2^+ is a Good Substrate for S_N Reactions. If we add a strong acid to a reaction mixture containing R-OH, the acid protonates the OH group to form R-OH_2^+. This acid/base reaction is analogous to the protonation of H_2O by strong acid. [graphic 7.43]

The resultant OH_2^+ group is a very good leaving group that leaves as OH_2 (*ie*., H_2O) in both S_N1 and S_N2 reactions depending on the structure of the R group. H-OH_2^+ (*ie*., H_3O^+) is the conjugate acid of the OH_2 (*ie*., H_2O) leaving group and it has a K_a value about 10^2. The large K_a value of H-OH_2^+ is consistent with the fact that OH_2 is a good leaving group.

Haloalkanes from Protonated Alcohols. We can use the good leaving group of protonated alcohols to make haloalkanes by reacting alcohols with HCl, HBr, or HI.

R-OH + H-X → R-OH_2^+ + X^- (Step 1)
R-OH_2^+ + X^- → R-X + H-O-H (Step 2)

HX protonates the alcohol, while $^-$:X serves as the nucleophile that replaces OH_2^+ by either an S_N1 or an S_N2 mechanism. Since an acid (H-X) transforms the poor leaving group OH into the good leaving group OH_2^+, we refer to Step 1 as **acid catalysis**.

If the mechanism is *S_N2*, "Step 2" is a single reaction in which $^-$:X displaces OH_2^+ by *backside attack*. If the mechanism is *S_N1*, "Step 2" is actually two separate steps. The OH_2^+ group leaves to give an intermediate carbocation (R+) (Step 2a) that then reacts with $^-$:X (Step 2b).

R-OH_2^+ → R+ + $:OH_2$ (Step 2a)
R+ + X^- → R-X (Step 2b)

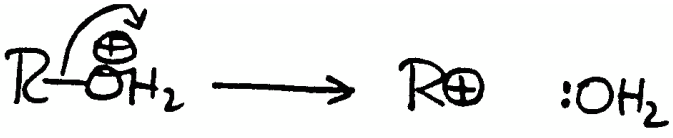
When the mechanism is *S_N2*, the best nucleophiles are the more nucleophilic Br^- or I^- ions from H-Br or H-I. When the reaction is *S_N1*, haloalkanes readily form from H-Cl, H-Br, or H-I since the carbocation is highly reactive. That intermediate carbocation can also react with other nucleophiles that may be present decreasing the yield of the desired haloalkane product. Since HF is a weak acid (Table 7.7), it does not protonate alcohols so we cannot use it in this reaction. (HF is also a very corrosive reagent that reacts with glass reaction vessels).

Haloalkanes from Alcohols Using $SOCl_2$ or PBr_3. Although we can form *chloroalkanes* and *bromoalkanes* from alcohols and HCl or HBr, organic chemists most often use the reagents *$SOCl_2$* or *PBr_3* for these transformations. [graphic 7.44] They react with the OH group of the alcohol to give an OS(=O)Cl group or $OPBr_2$ group. [graphic 7.45]

Figure 7.43

These reactions can occur!

SN1



SN2

Figure 7.44

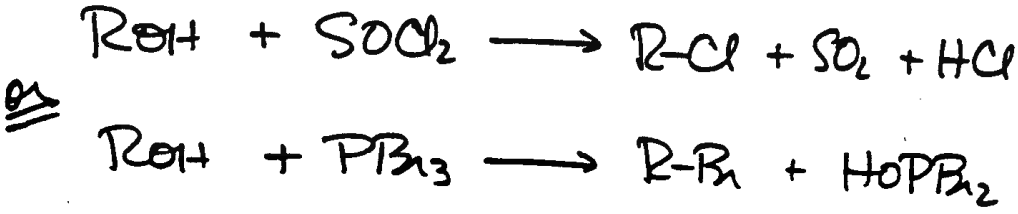


Figure 7.45

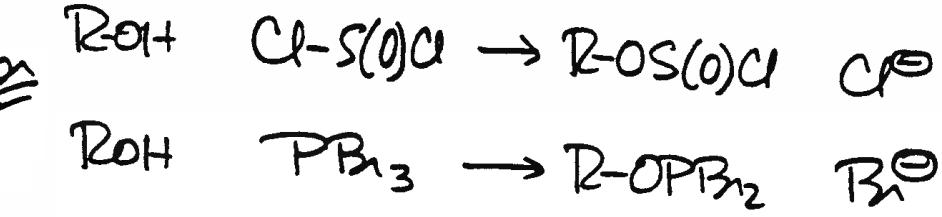
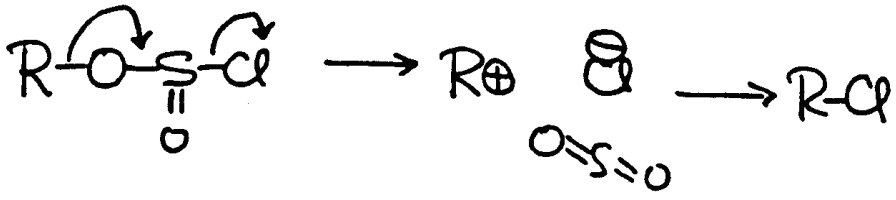


Figure 7.46



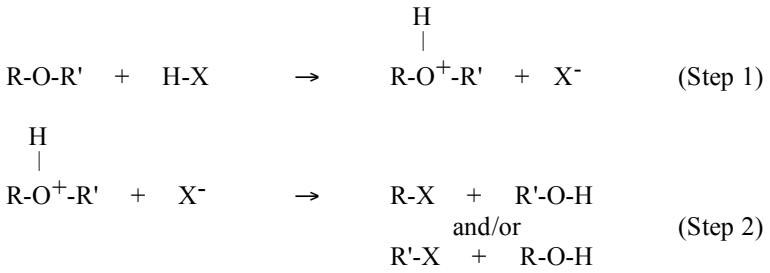
When the alcohol is 1° or 2°, the Cl^- or Br^- formed in the reaction directly displaces the new leaving groups by S_N2 mechanisms. When the alcohol is 3°, the OS(=O)Cl or $OPBr_2$ groups leave as anions to form a carbocation that subsequently reacts with Cl^- or Br^-.

When we use $SOCl_2$, the R+ intermediate in an S_N1 reaction reacts with Cl^- from its "frontside". [graphic 7.46] Organic chemists describe this "frontside" reaction as an **S_Ni mechanism** (Substitution, Nucleophilic, internal) and it gives chloroalkanes with *rentention of configuration* at the C-OH carbon.

The OR Group in Ethers (R-OR) (7.7B)

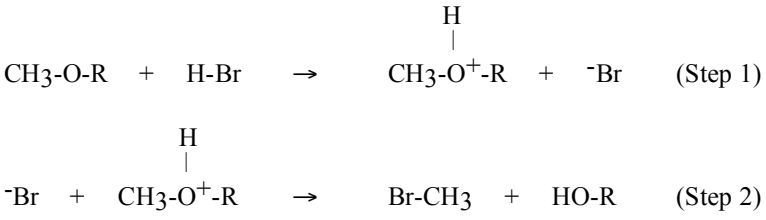
While the OR group of ethers (R-OR) is a poor leaving group like OH in alcohols (R-OH), the ORH^+ group is a good leaving group just like OH_2^+ in protonated alcohols.

Haloalkanes from Cleavage of Ethers. Ethers (R-O-R) react with H-Br or H-I in the same way that we have shown for alcohols (R-OH), however this reaction does not work well with H-Cl. A protonated ether intermediate forms in Step 1 so that the leaving group in Step 2 is a neutral alcohol molecule.



The leaving group of the protonated ether intermediate can be either ROH or R'OH so that the reaction may give a mixture of all four possible products RX, R'X, R'OH, and ROH. We can simplify the product mixture if we use a large excess of H-X that converts ROH and/or R'OH into RX and R'X as we showed in the previous section.

We can further simplify the product mixture from the ether cleavage reaction if one of the ether R groups is CH_3.



Ethers with the structure R-O-CH_3 react with HBr or HI to give either CH_3Br or CH_3I, and the alcohol ROH. This is because in Step 2, S_N2 attack of $Br:^-$ or $I:^-$ preferentially occurs at the least

sterically hindered CH_3 carbon. [graphic 7.47] Since $Br:^-$ or $I:^-$ attacks the CH_3 group in preference to the R group in CH_3-O-R, we say that the reaction is **regiospecific**.

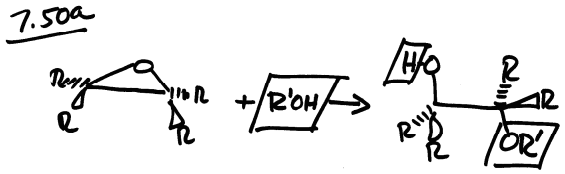
Ring Opening of Cyclic Ethers (7.7C)

Cyclic ethers can also be substrates in nucleophilic substitution reactions and those with 4-membered or largr rings ring react in the same way that we have just shown for *acyclic ethers*. In contrast, 3-membered cyclic ethers (**epoxides**) have different reactivities.

Epoxide Ring Opening. In addition to undergoing reactions like those we have just seen, the strain that is present in the 3-membered rings of *epoxides* allows them to react with nucleophiles even when the ether oxygen is unprotonated. For example, simple epoxides react with $HO:^-$ or $RO:^-$ (and even with H_2O or ROH) by S_N2 mechanisms. [graphic 7.48] These nucleophiles attack the epoxide at the least substituted C-O carbon consistent with the general observation that S_N2 reactions are more favorable at less sterically crowded C's.

Acid Catalysis. These *epoxide* ring opening reactions go even faster with an *acid catalyst*, however the *regiochemistry* is different than that for the uncatalyzed reactions. In acid catalyzed reactions of epoxides with nucleophiles such as HOH or ROH, the nucleophile adds to the more highly substituted C. [graphic 7.49] This is consistent with an S_N1 mechanism in which ring opening gives the most highly substituted C+ (Step 2), that subsequently reacts with the nucleophile (Step 3) (Figure [graphic 7.50]).

> ***These Ether Cleavage Reactions are also Addition Reactions***. While we refer to the reactions of cyclic ethers that we have just shown as *nucleophilic substitutions*, the leaving group remains part of the product so we can also view them as **addition reactions** where the components of the nucleophile "add" to the substrate as we show below. [graphic 7.50a] We will describe other addition reactions in later chapters.



Epoxide Ring Opening by Halide Ions. HX opens epoxide rings giving products with X bonded to the most highly substituted C. [graphic 7.52] Although this is what you expect for an S_N1 reaction (see Figure [graphic 7.50]), organic chemists believe that epoxide reactions with HX actually occur by an S_N2 mechanism. They rationalize this contradiction in X substitution by arguing that the protonated epoxide intermediate is a polarized intermediate as we show below rather than an "open" carbocation . [graphic 7.51]

Figure 7.47

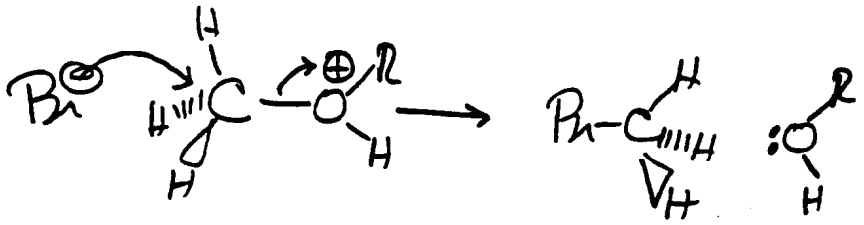


Figure 7.48

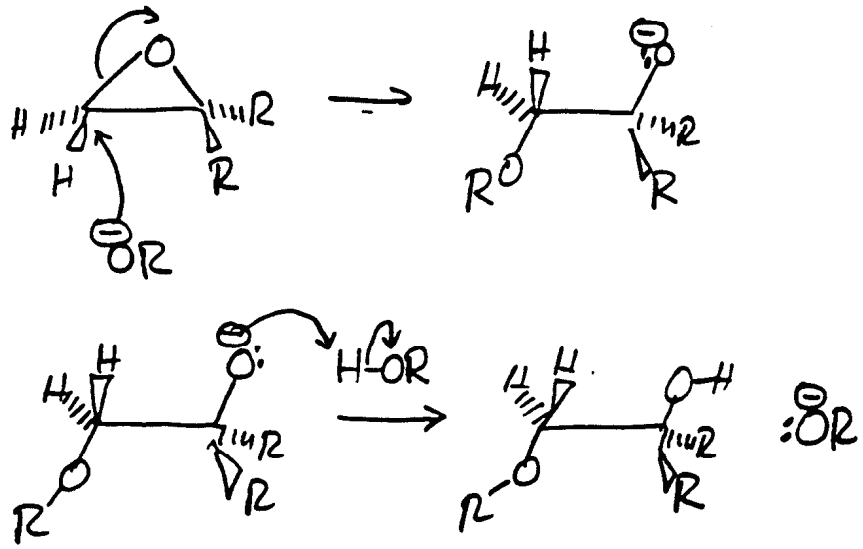


Figure 7.49

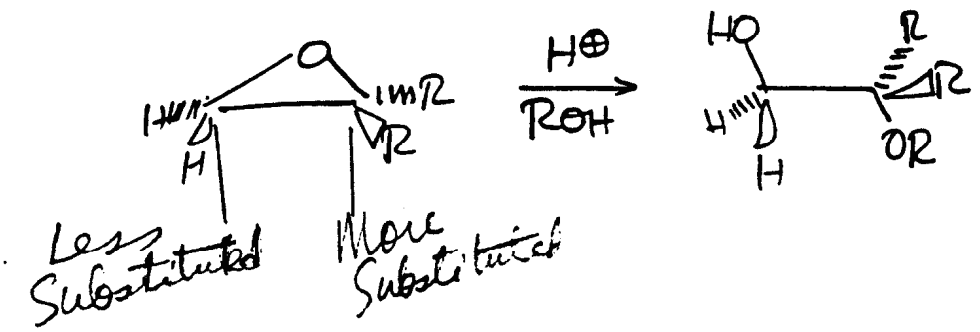


Figure 7.50

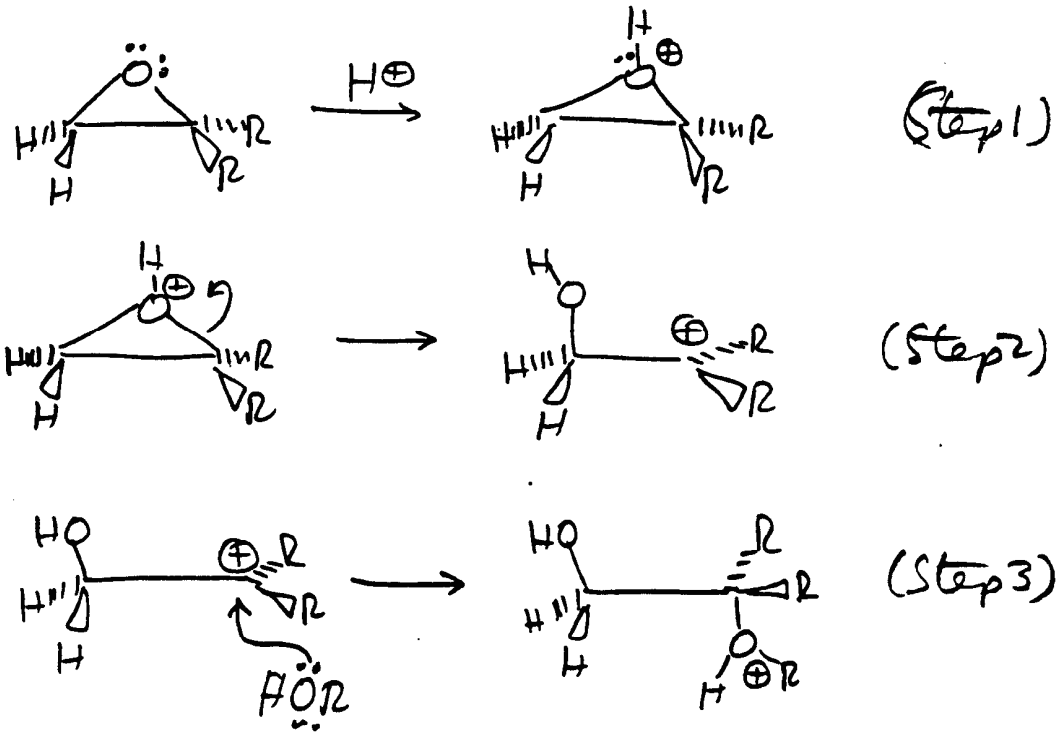


Figure 7.51

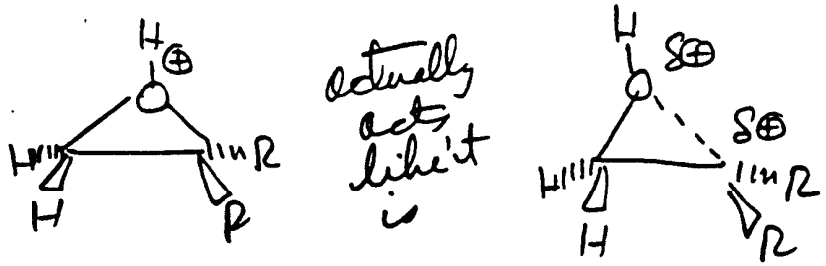
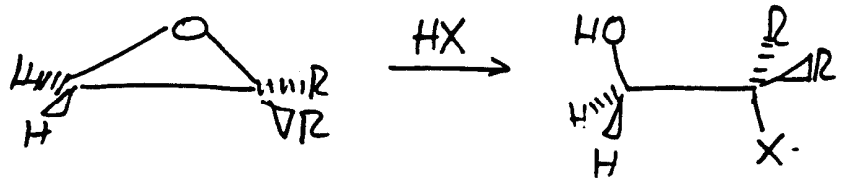


Figure 7.52



Nucleophilic attack by S_N2 displacement is more favorable at the more positively polarized C that is also the most highly substituted C. H-F is sometimes used to open epoxides, but the reaction between epoxides and HX is most successful with H-Cl, H-Br, and H-I.

A Summary of Leaving Groups (7.7D)

In this section, we summarize the leaving groups (:L) that we have already discussed and others that we have not yet mentioned. We also review the basis for the use of K_a values of their conjugate acids H-L to predict whether they are "good" or "poor" leaving groups

Some "Good" Leaving Groups. We show examples of substrates with "good" leaving groups in Table 7.6.

Table 7.6. Some Common Leaving Groups (L) in Nucleophilic Substitution Reactions

R-L	:L	K_a of H-L
R-I	$^-$I	10^{10}
R-Br	$^-$Br	10^9
R-Cl	$^-$Cl	10^7
R-$^+$OR'H	R'-O-H	10^2
R-$^+OH_2$	H-O-H	10^2
R-$^+SR'_2$	R'-S-R'	10^7

These include the now familiar halogens I, Br, and Cl that leave as their corresponding halide ions ($X:^-$). They also include positively charged leaving groups that leave as neutral molecules (:L). We show some additional *good leaving groups* in the Appendix at the end of this chapter.

Some "Poor' Leaving Groups. We summarize examples of *poor leaving groups* in Table 7.7 along with the K_a values of their conjugate acids H-L.

Table 7.7. Poor Leaving Groups in Nucleophilic Substitution Reactions

Substrate R-L	Leaving Group :L	K_a of H-L
R-F	$^-$F	10^{-3}
R-OH	$^-$OH	10^{-16}
R-OR	$^-$OR	10^{-16}
R-NH_3^+	NH_3	10^{-11}
R-NH_2	$^-NH_2$	10^{-38}
R-SH	$^-$SH	10^{-7}
R-CN	$^-$CN	10^{-9}
R-N_3	$^-N_3$	10^{-5}

We have discussed many of these in previous sections of this chapter.

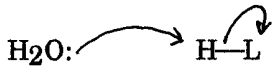
Leaving Group Ability and K_a Values for H-L. The common difference between the leaving groups in Tables 7.6 and 7.7 is the K_a values for their conjugate acids H-L. All good leaving groups (Table 7.6) have conjugate acids (H-L) with K_a values that are much greater than 1. In contrast, poor leaving groups (Table 7.7) all have K_a values for H-L that are much smaller than 1. This direct correlation between *leaving group ability* and *H-L acidity* occurs because both reflect the strength of the bond between L and another atom.

The *leaving group ability* of L reflects the ease with which a C-L bond breaks in the rate determining *transition state* ([ ]*) for an S_N1 or an S_N2 reaction as we depict here.

S_N1 Reaction: R-L → [R·····L]* → R+ :L

S_N2 Reaction: N: R-L → [N·····R·····L]* → N-R :L

The rates of these reactions depend on the C-L bond strength as well as the relative stabilities of R-L and :L. Similarly, the relative acidities of H-L (their K_a values for the equilibrium shown below) depend on the H-L bond strength and the relative stabilities of :L and H-L.



(42)

We showed an example of this correlation earlier in this chapter for the haloalkane substrates R-X. Although the *leaving group ability* order $I^- > Br^- > Cl^- > F^-$ is the same as the order of the *K_a values* for H-X (K_a(HI) > K_a(HBr > K_a(HCl) > K_a(HF)), the *leaving group ability* order of the full set of groups in Tables 7.6 and 7.7 does not correlate exactly with specific K_a values of H-L.

7.8 Nucleophilicity and Reaction Solvent

We have described a number of "good" *nucleophiles* such as $HO:^-$, $RO:^-$, $^-:CN$, and $^-:N_3$ that we have also said are "poor" *leaving groups* (Table 7.7). Does this mean that the strength of a *nucleophile* (its **nucleophilicity**) and its willingness to leave as a *leaving group* (its *leaving group ability*) have the opposite order? While there are many examples of this *inverse* correlation between *nucleophilicity* and *leaving group ability*, we will see that there are important examples where this is not true.

The Halide Ions (7.8A)

One example is I^- that is both a very good *nucleophile* and a very good *leaving group*. In solvents such as water or alcohols, the *nucleophilicity order* of the halide ions is $I^- > Br^- > Cl^- > F^-$ and this is identical to their order of *leaving group ability*.

Solvent Dependence of Nucleophilicity. While the orders of *nucleophilicity* and *leaving group ability* of the halide ions are $I^- > Br^- > Cl^- > F^-$ in H_2O or alcohols (ROH), there are other solvents where halide ion *nucleophilicity* order is $F^- > Cl^- > Br^- > I^-$ even though their *leaving group ability* order remains as $I^- > Br^- > Cl^- > F^-$. Organic chemists have also found that the halide ion *nucleophilicity* order $F^- > Cl^- > Br^-$ (data for I^- are not available) applies to reactions in the *gas phase* where no solvent is present.

The nature of the solvent (or whether there is a solvent at all) is of crucial importance to *nucleophilicity order*. We will see in the next section that the solvent dependence of *nucleophilicity*, and the solvent independence of *leaving group ability*, reflects differences in the way solvents interact with *nucleophiles* and *leaving groups* during a reaction.

Origin of Solvent Effect. *Nucleophilicity* order and *leaving group ability* order both refer to the order of *reaction rates*. A "good" nucleophile *reacts faster* than a "poor" nucleophile with a particular substrate under the same reaction conditions. A leaving group with "greater" leaving group ability causes an S_N reaction of R-L to be *faster* than one with "lesser" leaving group ability under the same reaction conditions. As a result, to understand *nucleophilicity* order and *leaving group ability* order, we need to understand the way that solvents interact with the reactants as they proceed to the *activated complex*.

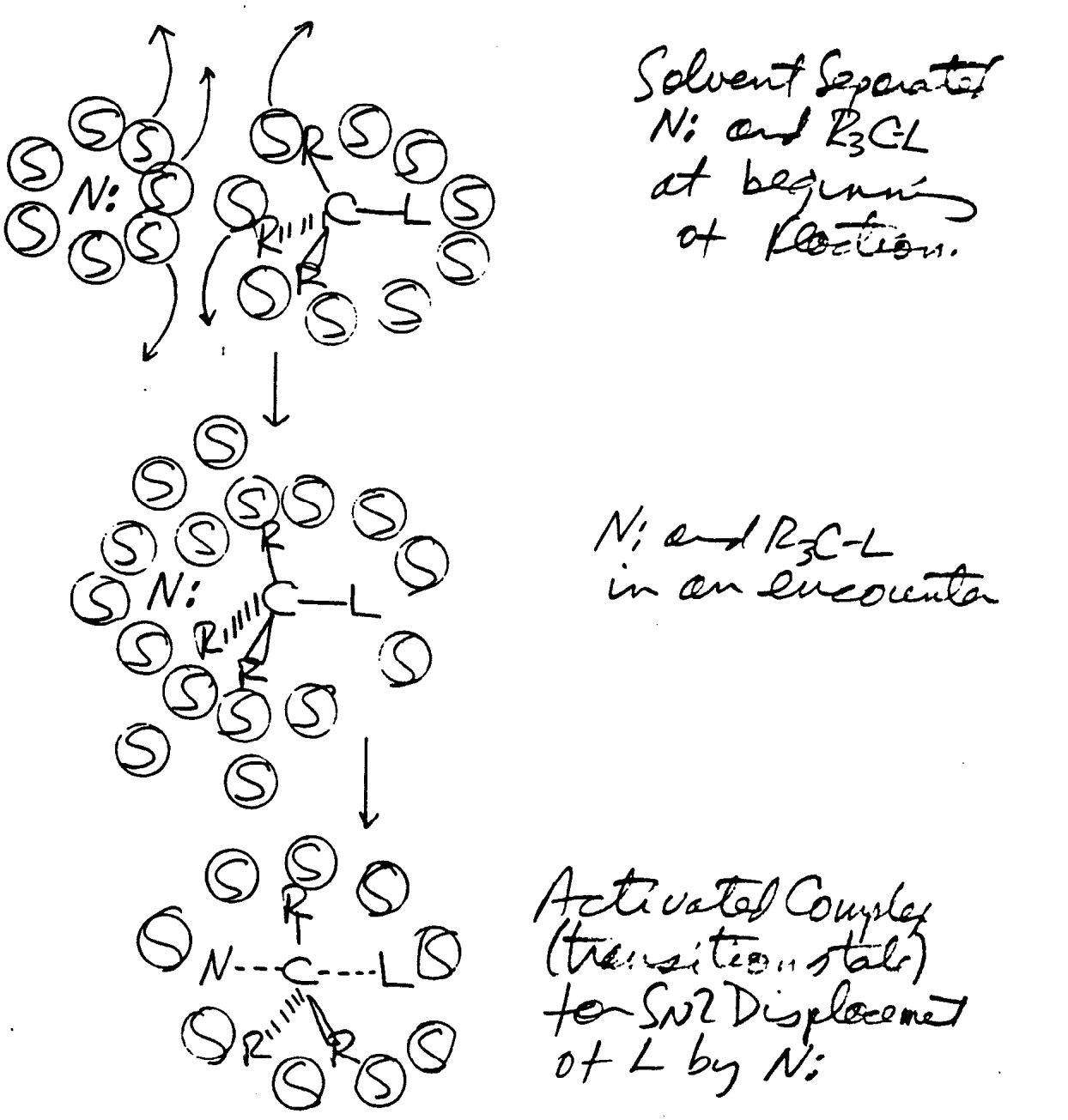
Solvation Changes during an S_N2 Reaction. We provide an illustration of changes in solvation interactions during an S_N2 reaction in Figure [graphic 7.53] where we represent solvent molecules with the letter "S". The nucleophile N: must get very close to the backside of the C to which L is attached, so we expect major changes in the solvation of N: as it and the substrate R-L come together.

Initially, both N: and the substrate R_3C-L are each completely surrounded by solvent molecules. In order for N: to get close to the C-L carbon, solvent molecules must move away from N: and

from R_3C-L so that tthey can get close to each other. You can see that major changes in solvation of both N: and R_3C-L occur as they move into an "encounter" that precedes their actual chemical reaction.

At the same time that N: approaches the backside of C-L and begins to bond to the C, the C-L bond begins to break. However that C-L breakage is only partially accomplished in the activated complex. As a result, while we also expect changes in the interaction of the solvent with L during

Figure 7.53. Solvation Changes During an S_N2 Reaction.



C-L breakage, these changes are often relatively minor compared to changes in solvation that occur around the nucleophile N:. As a result, it is not surprising that *nucleophilicities* of N: are much more sensitive to the the solvent than *leaving group abilities* of L.

Solvation by Hydroxylic Solvents. We described in Chapter 3* how water or alcohols solvate negative ions such as halide anions ($X:^-$). Their OH groups interact strongly with these anions by *hydrogen bonding* as we illustrate again in Figure [graphic 7.54] using H_2O.

The strength or "tightness" of this *hydrogen bonding* depends on the size of $^-:X$. The small F^- ion is "tightly" solvated (*hydrogen bonded*) by H_2O or ROH, but this solvation becomes "looser" as the size of the ion increases from F^- to Cl^- to Br^- and finally to I^-. This means that I^-, with relatively "loose" solvation, requires a smaller amount of solvent reorganization (see Figure [graphic 7.53]) in order to bond to the C of C-L compared to the "tightly" solvated F^- ion leading to the observed nucleophilicity order $I^- > Br^- > Cl^- > F^-$.

The opposite order ($F^- > Cl^- > Br^- > I^-$) that we observe in the absence of solvent as we mentioned earlier, reflects the *inherent* desire of $^-:X$ nucleophiles to form an X-C bond as they displace L. We also observe this *inherent* order ($F^- > Cl^- > Br^- > I^-$) in solvents where $^-:X$ is not solvated by *hydrogen bonding* as we illustrate in the next section.

Polar Aprotic Solvents (7.8B)

A number of polar solvents do not have OH groups and therefore cannot solvate $^-:X$ by *hydrogen bonding*. Because these solvents are *polar*, but do not possess an OH group, organic chemists call them **polar aprotic solvents**.

Some Examples of Polar Aprotic Solvents. One example of a *poal aprotic solvent* is *acetone* that we mentioned earlier. We show others in Figure [graphic 7.55]. These solvents contain functional groups that we have not yet discussed. While we will learn more about them later in the text, the important point for now is that each of them has a strong *dipole* that lies along the multiple bond. In each case, the negative end of the dipole is the oxygen or nitrogen atom of the multiple bond that is more *electronegative* than the other atom to which it is attached.

Nucleophilic Substitution Mechanisms in Polar Aprotic Solvents. *Polar aprotic solvents* are particularly useful for *S_N2 reactions*. They dissolve salts such as metal halides (*eg.* K^+Cl^- or Na^+I^-) or metal alkoxides (*eg.* $NaOCH_3$ or $KOC(CH_3)_3$) because they solvate the metal cation (*eg.* K^+ or Na^+). However they do not strongly solvate the anionic nucleophile (*eg.* X^- or ^-OR) because they have no OH group and cannot form hydrogen bonds. As a result, negatively

Figure 7.54. Solvation of Halide Ions by H-Bonding with H_2O.

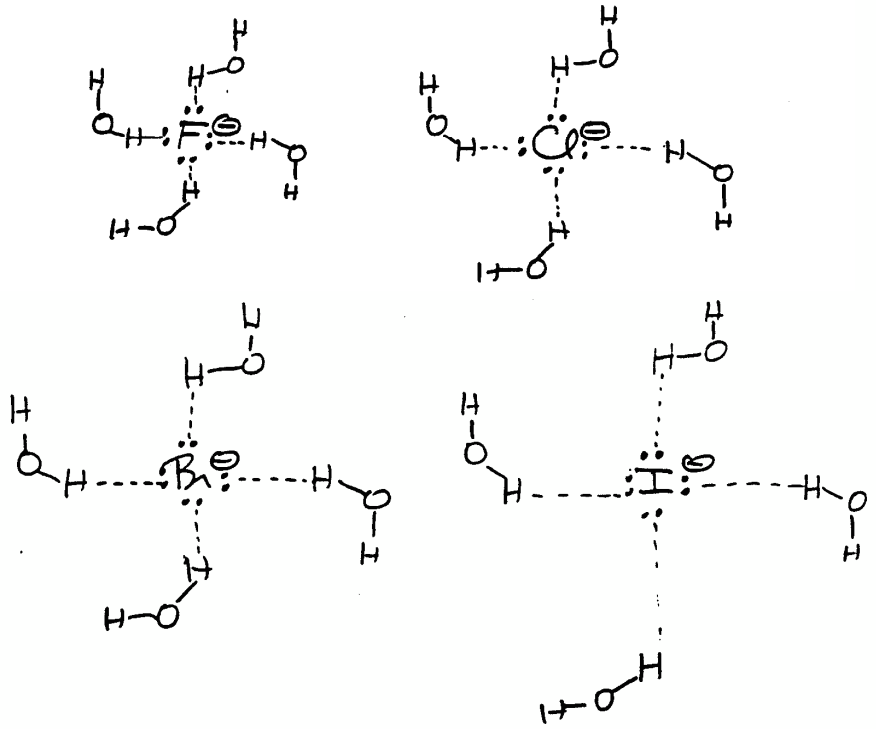
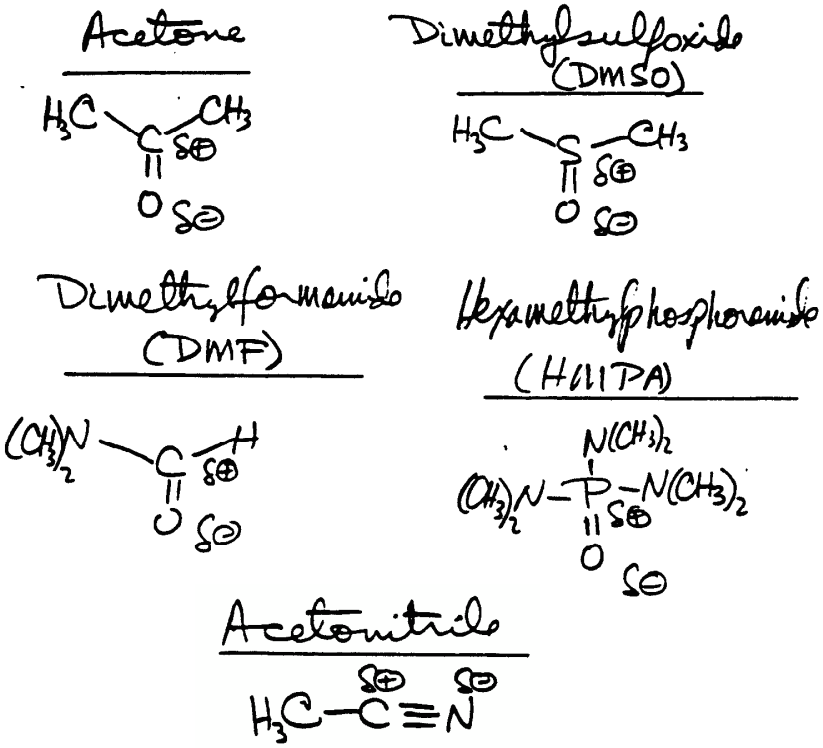


Figure 7.55. Several Polar Aprotic Solvents.



charged nucleophiles are much more reactive in polar aprotic solvents than in **polar protic solvents** (solvents with OH groups) like alcohols and water.

Although they favor S_N2 reactions, *polar aprotic solvents* are not polar enough to allow ionization of a substrate R-L by an S_N1 mechanism. They do not provide stabilization of the intermediate R+. As a result, S_N1 reactions are usually limited to *polar protic solvents* such as *alcohols*, *water*, or solvent mixtures that contain both a *polar aprotic solvent* and an *alcohol* or *water*. Organic chemists also use the polar aprotic solvents that we have shown here in a wide variety of organic reactions other than nucleophilic substitution. We illustrate some of these applications in later parts of this text.

Nucleophilicities of Other Nucleophiles (7.8C)

We have already shown examples of nucleophiles other than halide ions, and have qualitatively described their order of nucleophilicity. We review these results here along with additional important trends in nucleophilicity order.

Nucleophiles and their Conjugate Bases. We have stated that $RO:^-$ is more nucleophilic than ROH. $RO:^-$ is the *conjugate base* of ROH and we see the same trends in nucleophilicity order for other nucleophiles and their conjugate bases (Table 7.7a).

Table 7.7a. Relative Nucleophilicities of Conjugate Acid/Base Pairs

Base Form		Acid Form
$HO:^-$	>>	H O H
$RO:^-$	>>	R O H
$H_2N:^-$	>>	H_3N
$R_2N:^-$	>>	R_2NH
$RS:^-$	>>	R S H

Conjugate bases of nucleophiles $N:^-$ are always more nucleophilic than their protonated forms N-H independent of the solvent that we use in the reaction.

Nucleophiles in the Same Row of the Periodic Table. Another important trend is that the nucleopilicity order of nucleophilic atoms in the same *row* of the periodic table increases from left to right as we show here.

Table 7.7b. **Relative Nucleophilicities**

$$R_3C:^- > R_2N:^- > RO:^- > F:^-$$

$$H_3N: > H_2O:$$

You can compare these nucleophiles and their nucleophilicities with the location of the nucleophilic atoms in the partial periodic table in Figure [graphic 7.56].

Figure [graphic 7.56]. A Partial Periodic Table

H						
Li	Be	B	C	N	O	F
Na	Mg	Al	Si	P	S	Cl
						Br
						I

We have not yet discussed the $R_3C:^-$ nucleophile, but we consider it briefly later in the chapter. The relative *basicities* of these nucleophiles have the same order as their *nucleophilicities*.

Nucleophiles in the Same Column of the Periodic Table. The halide ions F^-, Cl^-, Br^-, and I^- are all in the same *column* of the periodic table and we have shown that their nucleophilicity order depends on the reaction solvent. This is also true for other negatively charged nucleophilic atoms in the same *column* of the periodic table such as O and S.

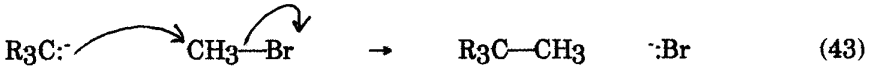
$RS:^-$ is more nucleophilic than $RO:^-$ in *hydrogen bonding* solvents (polar *protic* solvents), but $RO:^-$ is more nucleophilic than $RS:^-$ in solvents where hydrogen bonding is not possible (polar *aprotic* solvents). In contrast, the nucleophilicity order RSH > ROH is independent of solvent. Uncharged nucleophiles are usually not affected by solvation interactions to the same extent as negatively charged nucleophiles.

Comparative Nucleophilicities in S_N2 versus S_N1 Reactions. While the nucleophilicity orders described here are for S_N2 reactions, they are probably the same for S_N1 reactions. However, the nature of S_N1 reactions makes nucleophilicity order unimportant.

All S_N1 reactions have carbocation intermediates that react rapidly with all nucleophiles that are present. As a result, relative yields of products from reaction of the carbocation with different nucleophiles depends not on their nucleophilicity, but on their relative concentrations (see Figure [graphic 7.40]).

7.9 Carbon Nucleophiles

We showed a nucleophile with a nucleophilic C atom ($R_3C:^-$) in the previous section (Table 7.7b). Although we have not discussed them yet, carbon-centered nucleophiles are among the most important nucleophilic reagents in organic chemistry because they form C-C bonds.



(43)

In this example, the nucleophilic carbon species $R_3C:^-$ reacts with CH_3-Br by an S_N2 reaction. Species such as $R_3C:^-$ do not exist in solution as free anions. They are "tightly associated" with metal cations and solvent molecules as we describe below.

Organometallic Compounds give C Nucleophiles (7.9A)
Organometallic compounds are sources of *nucleophilic carbon* species and we can form them by reacting *haloalkanes* with various *metals*.

Organomagnesium and Organolithium Compounds. Two metals that readily react with haloalkanes are *magnesium* (*Mg*) and *lithium* (*Li*). We show them reacting with *iodoethane* to give **organomagnesium** and **organolithium** compounds that contain a CH_3CH_2 group (an ethyl group) bonded to Mg or Li (Figure [graphic 7.56a]).

Figure [graphic 7.56a]

$$CH_3\text{-}CH_2\text{-}I + Mg \xrightarrow{\text{ether}} CH_3\text{-}CH_2\text{-}Mg\text{-}I$$

$$CH_3\text{-}CH_2\text{-}I + 2\ Li \xrightarrow{\text{ether}} CH_3\text{-}CH_2\text{-}Li + Li\text{-}I$$

You can see that these two reactions have different stoichiometry. <u>One</u> molecule of *iodoethane* reacts with <u>one</u> atom of *Mg*, but it reacts with <u>two</u> atoms of Li. This is because *Mg* is a <u>di</u>valent metal in its compounds (it acts like it is Mg^{+2}), while *Li* is a <u>mono</u>valent metal in its compounds (it acts like it is Li^{+1}), consistent with their locations in the periodic table (see Figure [graphic 7.56]).

Organomagnesium compounds, such as CH_3CH_2-Mg-I, are called **Grignard reagents** after the Nobel laureate (1912) French chemist (Francois A. V. Grignard, 1871-1935). His last name is approximately pronounced *"grin-yard"*. In contrast, *organolithium* compounds do not have a common name.

Carbon Polarity in Organometallic Compounds. The metal in an *organometallic* compound dramatically affects the polarity of its bonded C. [graphic 7.57] We learned in Chapter 3 that the higher *electronegativities* of halogens (X) compared to C lead to a $^+C\text{-}X^-$ bond polarity in haloalkanes. In contrast, the lower *electronegativities* of Mg and Li compared to C lead to $^-C\text{-}M^+$ (M = Mg or Li) bond polarities. The negative polarity of C in C-M bonds of organometallic compounds makes those C's nucleophilic.

Figure 7.57

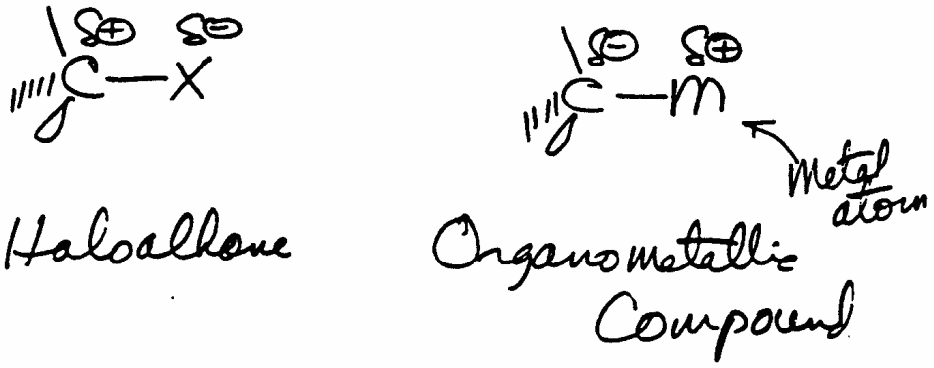


Figure 7.58

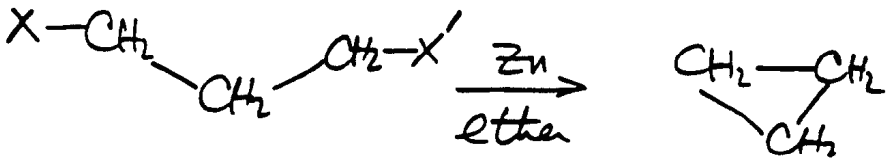
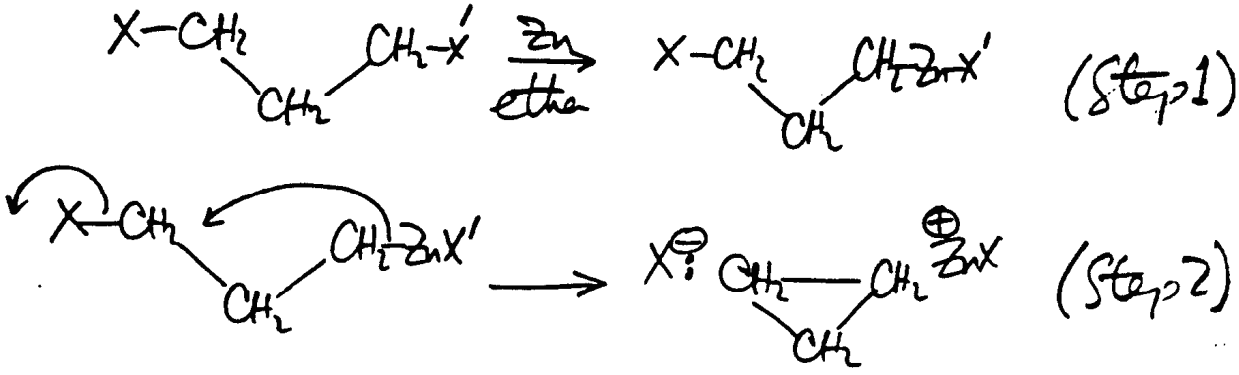


Figure 7.59



Properties of Organometallic Compounds. *Organolithium* and *organomagnesium* compounds must be kept in solution because their stability depends on the presence of a solvent that is usually the one in which they are prepared. They are very reactive, so organic chemists often prepare them just before they are used in a chemical reaction. Some organolithium compounds are commercially available packaged in solvents and protected from water and oxygen with which they rapidly react.

Mechanisms of their formation reactions (eg. Figure [graphic 7.56a]) are not clearly defined since they occur at interfaces between solutions and metal surfaces. They are **oxidation/reduction** reactions (Chapters 13 and 17) in which the metal is **oxidized** while the C is **reduced**, and frequently involve intermediate free radicals (Chapter 11).

C-C Bond Formation Using Organometallic Compounds (7.9B)

This section shows some specific examples of the C-C forming reaction that we described earlier between haloalkanes and organometallic compounds. We will learn about other important C-C bond forming reactions that use *organometallic* compounds later in the text.

Small Ring Formation. *Cyclopropane* ring formation is a special example of C-C bond formation between the C's of two C-X groups that involves intermediate organometallic compounds. Treatment of *1,3-dihaloalkanes* or *1,3-dihalocycloalkanes* with *zinc (Zn)* metal leads to *intramolecular* C-C formation to give a three-membered *cyclopropane* ring. [graphic 7.58]

The reaction occurs by the initial formation of an *organozinc* intermediate (Step 1) that then undergoes *intramolecular* C-C bond formation (Step 2). [graphic 7.59] *Diethyl ether* ($CH_3CH_2OCH_2CH_3$) is frequently used as a solvent for these reactions and we indicate its presence below the reaction arrows as "ether". Diethyl ether is a *polar aprotic* solvent that dissolves haloalkanes and solvates intermediate organometallic compounds, but it is unreactive toward the reactants and their products.

In these examples, the two C-X centers are in the same molecule. While two C-X centers that we wish to couple can also be in separate molecules, such *intermolecular* reactions (called **Wurtz** reactions) usually give complicated mixtures of products. [graphic 7.60]

Alkyl Group Coupling. Although *Wurtz* reactions do not efficiently couple alkyl groups from separate haloalkanes, we can couple 1° alkyl groups using **Gilman's** reagents prepared from *organolithium* reagents (R-Li) and *cuprous iodide* (CuI).

$$2\ R\text{-}Li + CuI \rightarrow R_2Cu\text{-}Li + LiI$$

An R group in R_2Cu-Li will couple with an alkyl group in a haloalkane (R'-X) to give R-R'.

$$R_2Cu\text{-}Li + R'\text{-}X \rightarrow R\text{-}R' + R\text{-}Cu + LiX$$

This reaction is successful for 1° alkyl groups, but not for 2° or 3° alkyl groups.

Reactions with Epoxides. Our focus in this section has been on reactions of organometallic reagents with haloalkanes, but organometallic reagents also react with epoxides to form alcohols. [graphic 7.61] This reaction is analogous to the nucleophilic substitution reactions of epoxides that we described earlier in this chapter except that the nucleophilic atom is C.

Positive, Negative and Neutral Carbon Atoms (7.9C)

We have just seen examples of compounds and intermediates that contain C that is negatively polarized. Earlier we saw intermediates and compounds where C is positive (carbocations), or positively polarized (eg. haloalkanes). In Chapter 11, we will see intermediate **carbon free radicals** where a C atom, although electrically neutral, has an unshared electron.

These different charge types or polarities for C result from its location in the middle of the first row of the periodic table (see Figure [graphic 7.56]). The *electronegativity* of C is greater than those of the *metals* to its left and less than those of *halogens* to its right. As a result, the polarization or charge type of C depends on the atoms directly bonded to it. We will continue to see examples of all three of these different charge types of C throughout this text.

7.10 Nucleophilic Hydrogen

It may surprise you to learn that *nucleophilic H* "($H:^-$)" is a very important reactant in organic chemistry. We will provide only a brief introduction in this section because we consider *nucleophilic H* in Chapter 17 where we discuss organic *reduction reactions*.

The Polarity of H in Various Compounds (7.10A)

The intermediate electronegativity of H, like C, allows it to have *positive*, *negative*, or *neutral* polarity. While we find H at the top of the far left column of most periodic tables, this location does not properly reflect all of its properties. H has almost the same electronegativity as C (Chapter 3*) that lies between between *low electronegativity* atoms such as *metals*, and *high electronegativity* atoms such as *halogens*. While we are accustomed to seeing *positively* polarized H in mineral acids H-X, or in *protic* compounds like H_2O, H is negatively polarized in **metal hydrides** such as *Li-H* (Chapter 3*).

Figure 7.60

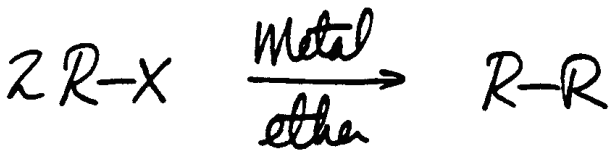


Figure 7.61

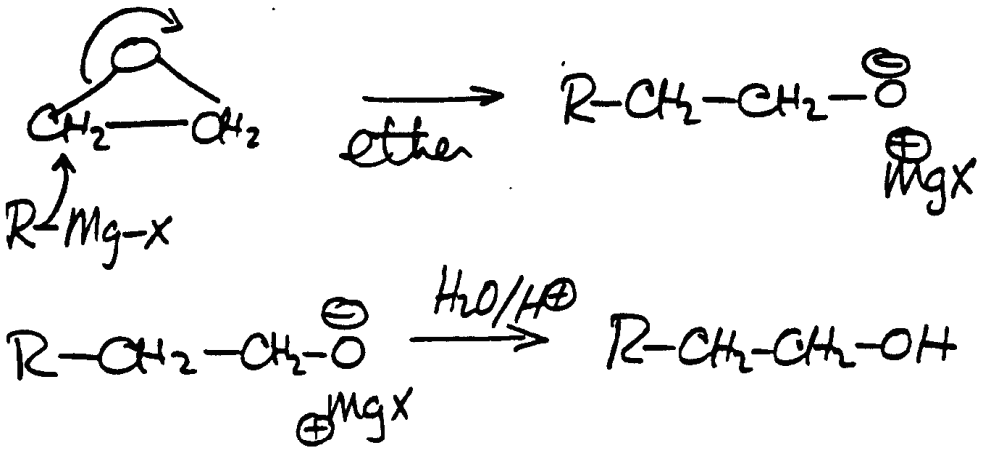
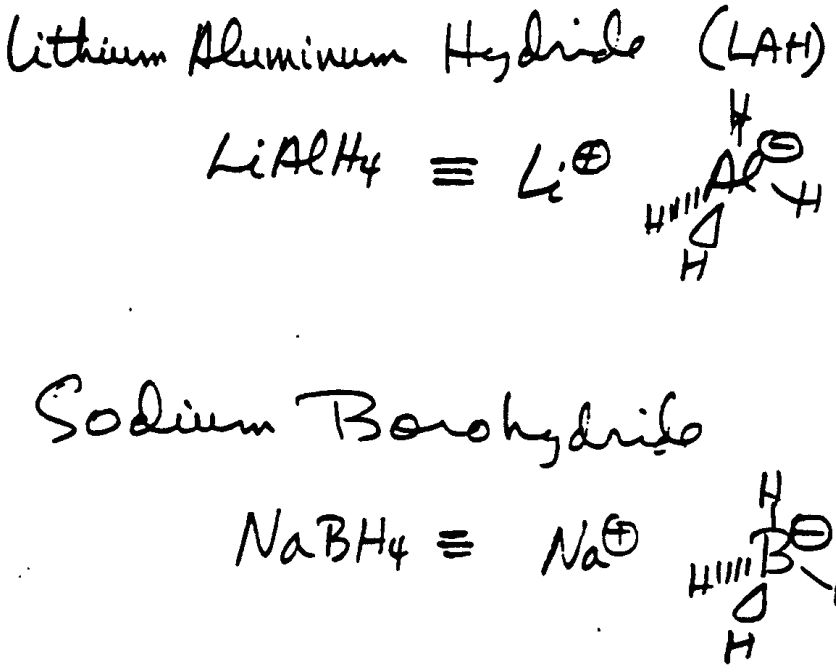


Figure 7.62



Compounds with metal-H bonds include not only the **simple metal hydrides** *Li-H*, *Na-H*, and *K-H*, but **complex metal hydrides** such as $LiAlH_4$ (*lithium aluminum hydride*) and $NaBH_4$ (*sodium borohydride*). [graphic 7.62]

Metal Hydrides are Sources of Nucleophilic H (7.10B)

In all metal hydrides, H reacts as if it is the negatively charged *hydride ion* ($H:^-$). However, just as protons (H^+) do not exist freely in solution, the same is true of *hydride ions* ($H:^-$). Metal hydrides *transfer* H as $H:^-$ to other reactants. Since $H:^-$ brings along the pair of electrons that forms the new chemical bond in these reactions, we say that H acts as a *nucleophile*.

The most important reactions involving **hydride transfer** (*nucleophilic H*) utilize reactants that we describe in later chapters. However, we show two reactions here that are examples of *hydride transfer* that occur by S_N2 mechanisms. [graphic 7.63] In the first reaction, 1° or 2° *haloalkanes* react with $LiAlH_4$ to give *alkanes*. In the second reaction, $LiAlH_4$ converts an *epoxide* into an *alcohol*.

We can write the mechanisms of the hydride transfer steps as S_N2 reactions. [graphic 7.64] We obtain the final reaction products in these reactions by treating the reaction mixtures with aqueous acid.

Figure 7.63

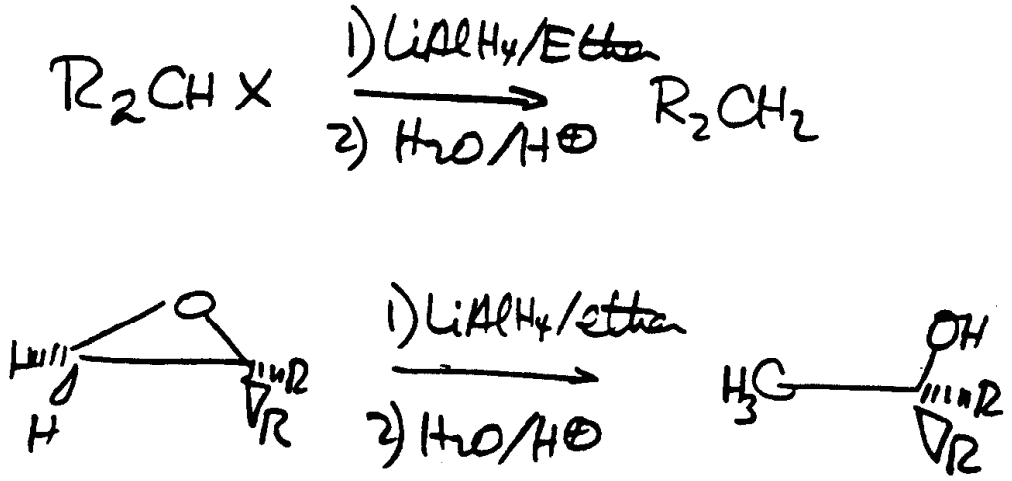
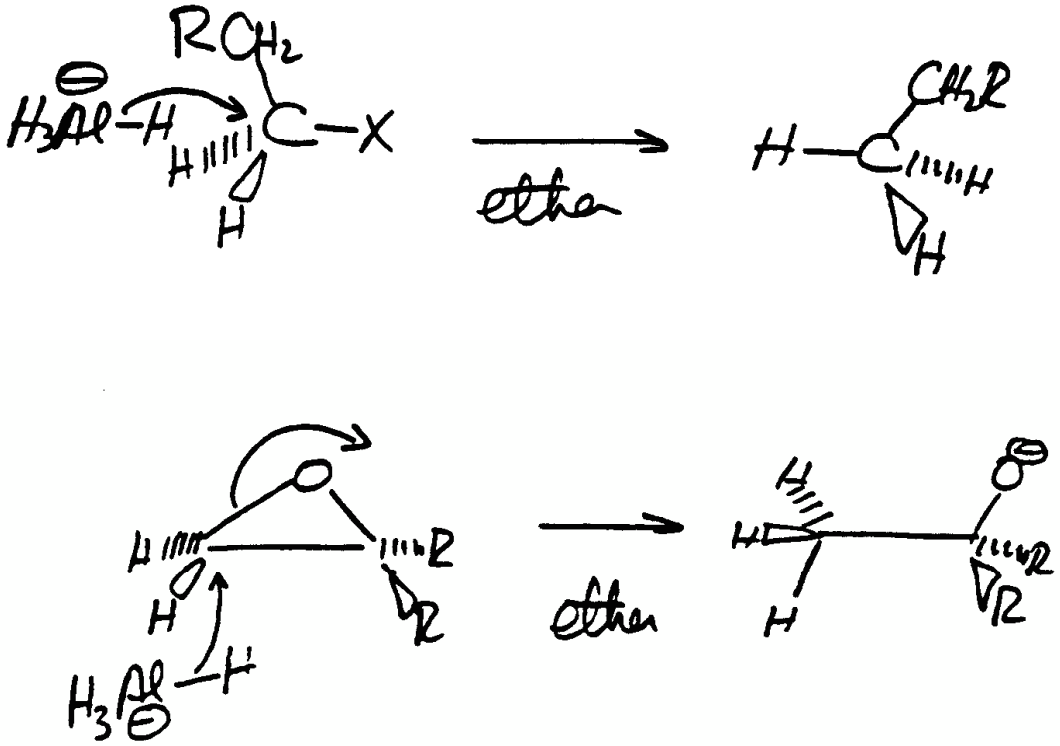


Figure 7.64



Appendix: Nucleophiles and Leaving Groups

Nucleophiles

Table 7.8. Nucleophiles (N:) in Increasing Order* of Nucleophilicity and their S_N Products (R-N)**

N:	R-N
$CF_3C(=O)OH$	$R\text{-}^{+}OHC(=O)CF_3$
H_2O	$R\text{-}^{+}OH_2$
R'C(=O)OH	$R\text{-}^{+}OHC(=O)R'$
R'OH	$R\text{-}^{+}OHR'$
ONO_2^- (NO_3^-)	$R\text{-}ONO_2$ ($R\text{-}NO_3$)
F^-	R-F
OSO_3^{-2}	$R\text{-}OSO_3^-$
$R'C(=O)O^-$	$R\text{-}OC(=O)CR'$
Cl^-	R-Cl
$O{=}NO^-$	R-ON=O
NH_3	$R\text{-}^{+}NH_3$
R'_2S	$R\text{-}^{+}SR'_2$
N_3^-	$R\text{-}N_3$
Br^-	R-Br
$R'O^-$	R-OR
R'_3N	$R\text{-}^{+}NR'_3$
CN^-	R-CN
R'_3P	$R\text{-}PR'_3{}^{+}$
R'_2NH	$R\text{-}NHR'_2{}^{+}$
I^-	R-I
HS^-	R-SH
SO_3^{-2}	$R\text{-}SO_3^-$
$S_2O_3^{-2}$	$R\text{-}S_2O_3^-$

*In polar protic solvents. Order is from least nucleophilic to most nucleophilic.

**Taken from Tables 4.2 and 4.11 in T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry,* 3rd Ed., Harper and Row, Publishers, N.Y., 1987.

Appendix (continued)

Leaving Groups

Table 7.9. Leaving Groups (L:) in Decreasing Order* of Leaving Group Ability and their S_N Substrates (R-L)**

R-L	:L
R-N_2^+	N_2
R-OR'$_2^+$	R'OR'
R-OS(=O)$_2$CF$_3$	$^-$OS(=O)$_2$CF$_3$
R-OS(=O)$_2$F	$^-$OS(=O)$_2$F
R-OS(=O)$_2$OR	$^-$OS(=O)$_2$OR
R-OS(=O)$_2$R	$^-$OS(=O)$_2$R
R-I	$^-$I
R-Br	$^-$Br
R-OH_2^+	OH_2^+
R-Cl	-Cl
R-OR'H$^+$	ROH
R-ON(=O)$_2$	$^-$ON(=O)$_2$
R-SR'$_2^+$	R'SR
R-NR_3^+	NR_3
R-F	$^-$F
R-OC(=O)R	$^-$OC(=O)R
R-NH_3^+	NH_3

*Order is from best to worst leaving group.

**Taken from Table 10.10 in J. March, *Advanced Organic Chemistry*, 4th Ed., John Wiley and Sons, Inc., N.Y., 1992

Chapter Review

Nucleophilic Substitution Reactions of Haloalkanes

(1) Nucleophilic substitution reactions transform haloalkanes (R_3C-X) into other compounds (R_3C-N) by replacing the leaving group (X) with the nucleophile (N:). (2) N: uses an unshared electron pair to form the new C-N bond, while the C-X bonding electron pair becomes an unshared electron pair on the leaving group $X:^-$. (3) Nucleophilic substitutions usually occur by S_N1 or S_N2 mchanisms. (4) S_N1 mechanisms have two steps in which an intermediate carbocation (R_3C+) forms by loss of $X:^-$ and then reacts with N:. (5) S_N2 mechanisms have one step where N: displaces $X:^-$ by "backside attack" on the C-X bond. (6) The the nucleophiles H_2O: or $HO:^-$ transform haloalkanes (R_3C-X) into alcohols (R_3C-OH) by S_N reactions.

S_N1 versus S_N2 Mechanisms

(1) R groups in R_3C-X sterically hinder attack of N: on the backside of C-X so S_N2 reactivity order is CH_3X > RCH_2X > R_2CHX >> R_3CX. (2) Reactivity order is reversed for S_N1 reactions (R_3CX > R_2CHX > RCH_2X >> CH_3X) because R groups stabilize C+ centers. (3) CH_3X and RCH_2X react by S_N2, R_3CX reacts by S_N1, while R_2CHX may react by S_N1 or S_N2. (4) Alkyl groups R stabilize the planar R_3C+ by hyperconjugation. (5) Alkyl substitution on C_β in C_β-C_α-X inhibits S_N2 reactions due to steric crowding.

Haloalkane Structure and Reactitvity

(1) Leaving group ability order of halide ions is I^- > Br^- > Cl^- >> F^-. (2) This order for $X:^-$ parallels acidity (K_a values) of the corresponding conjugate acids (H-X). (3) Acidity order of H-X, and leaving group ability order for $X:^-$, reflect C-X and H-X bond strengths. (4) S_N reactions have other leaving groups besides $X:^-$so substrates are often symbolized R_3C-L.

Stereochemistry of S_N Reactions

(1) Backside displacement of L from R_3C-L.by N: in S_N2 reactions inverts configuration at C of C-N compared to C of C-L. (2) In S_N1 reactions N: can attack planar R_3C+ from either side leading to both inversion and retention of configuration at C-N. (3) L: sometimes partially blocks the side of the C+ from which it departs in S_N1 reactions, so inversion of configuration at C-N may exceed retention .

Reaction Rates of S_N Reactions

(1) S_N2 reaction rates depend on concentrations of both R-L and N:. (2) S_N1 reaction rates depend only on the concentration of R-L. (3) Carbocation (R_3C+) formation in S_N1 reactions is slow while reaction of R_3C+ with N: is fast. (4) Reaction rates depend on activation energy (E_a) that is the difference in energy between reactants and activated complex (transition state). (5) S_N2 energy diagrams have a single activated complex that includes both R-L and N:. (6) S_N1 energy diagrams have one activated complex for R_3C+ formation, and one for reaction of R_3C+ with N:. (7) The activation energy for R_3C+ formation is much greater than for R_3C+ reaction with N:.

Other Nucleophiles

(1) RO^- and ROH nucleophiles react with haloalkanes (R_3C-X) to give ethers (R_3C-OR). (2) ROH nucleophiles are used in S_N1 reactions while RO^- nucleophiles are used in S_N2 reactions such as the Williamson Ether Synthesis. (3) RO^- ions are formed by treating ROH with strong bases or with metals such as Na or K. (4) When a molecule contains the atomic grouping X-C-C-OH, three-membered cyclic ethers (epoxides) form when OH reacts with a base to give O^-. (5) R_2N^- and R_2NH are nucleophiles analogous to RO^- and ROH, but much more nucleophilic. (6) R_2NH can be used in both S_N1 and S_N2 reactions, but often gives more than one product. (7) RS^- and RSH are analogous nucleophiles that react with haloalkanes to give thioethers. (8) I^-, Br^-, Cl^-, and F^- are nucleophiles that react in halide exchange reactions with all haloalkanes (R-X) except fluoroalkanes (R-F). (9) N_3^- and $^-C{\equiv}N$ ions are good nucleophiles.

Leaving Groups

(1) Alcohols (R_3C-OH) and ethers (R_3C-OR) have poor leaving groups, but strongly acidic solutions protonate them to give $R_3C\text{-}OH_2^+$ or $R_3C\text{-}OHR^+$ with good leaving groups. (2) HCl, HBr, and HI transform R_3C-OH and R_3C-OR into R_3C-X (X = Cl, Br, or I). (3) Epoxides undergo both acid-catalyzed and uncatalyzed ring opening reactions with the nucleophiles R-OH or $X:^-$ because of ring strain. (4) Good leaving groups (L) (I^-, Br^-, Cl^-, OR_2, and SR_2) have conjugate acids (H-L) that are strong acids ($K_a >> 1$). (5) Poor leaving groups (F^-, RO^-, NH_3, $^-NH_2$, ^-SH, ^-CN, and $^-N_3$) have conjugate acids (H-L) with $K_a << 1$. (3) Alcohols (R-OH) and ethers (ROR) have poor leaving groups, but undergo nucleophilic substitution in strongly acidic solutions because protonation gives $R\text{-}OH_2^+$ or $R\text{-}OHR^+$. (4) Epoxides undergo ring opening by nucleophilic substitution with or without acid catalysis because of ring strain.

Nucleophilicity and Reaction Solvent

(1) Halide nucleophilicity order is $I^- > Br^- > Cl^- > F^-$ in H_2O and ROH (polar protic solvents), but opposite in polar aprotic solvents. (2) Polar aprotic solvents are good for S_N2 reactions, but polar protic solvents are best for S_N1 reactions. (3) Negative nucleophiles ($N:^-$) are more nucleophilic than their conjugate acids (N:H). (4) Nucleophiles in the same row of the periodic table (with the same charge) decrease in nucleophilicity from lower to higher atomic number. (5) Neutral nucleophiles in the same column of the periodic table increase in nucleophilicity from top to bottom, but the relative nucleophilicity of negative nucleophiles in the same column depends on the solvent.

Carbon Nucleophiles

(1) C in C-M bonds is negatively polarized ($^-C\text{-}M^+$) and nucleophilic in organometallic compounds such as organolithium (R_3C-Li) and organomagnesium (R_3C-Mg-X) compounds. (2) Organometallic compounds are used in nucleophilic substitution reactions to make small ring compounds, couple alkyl groups, and react with epoxides to make alcohols.

Nucleophilic Hydrogen

(1) H is negatively polarized in simple and complex metal hydrides such as Li-H or $LiAlH_4$. (2) Metal hydrides can transfer nucleophilic hydride ion ("H^-") to substrates such as haloalkanes and epoxides and form C-H bonds.

A Biological S_N1 Reaction: Lysozyme Cleavage of Bacterial Cell Walls

Virtually every reaction mechanism that has been discovered by organic chemists takes place in biochemical reactions of living systems. Biological molecules are primarily organic molecules and the reactions of organic molecules take place by mechanisms that are essentially the same whether they are in a laboratory reaction vessel or in an organism. As a result, you will encounter most of the mechanisms that we discuss in this text in biochemistry courses. The nucleophilic substitution mechanisms in this chapter are no exception since cleavage of bacterial cell walls by the enzyme **lysozyme** includes an S_N1 reaction as a key step.

Lysozyme

Lysozyme is an enzyme and enzymes are relatively large protein molecules that catalyze biochemical reactions. Lysozyme specifically causes the cell walls of certain types of bacteria to "dissolve" because it cleaves ("lyses") bonds between sugar molecules that make up these cell walls.

Alexander Fleming, a British bacteriologist who later discovered penicillin, noted in 1922 that mucus from an accidental sneeze dissolved cultures of bacteria. He finally concluded that this was due to the presence in mucus of the substance lysozyme also found in other bodily secretions including tears. He hoped that lysozyme might be useful as an antibiotic, but it did not prove to be effective against many bacteria responsible for disease. Biochemists now believe that lysozyme is responsible for disposal of bacterial debris that remains after bacteria are killed by other means.

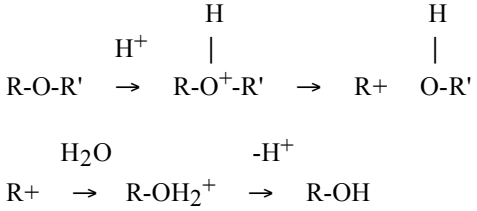
Bacterial Cell Walls

The cell walls of bacteria are complex structures made up of long chains of sugar molecules (**carbohydrate chains**) held together by intermittent short chains made up of amino acids (**peptide chains**) (Figure [graphic 7.65]). The circles in the carbohydrate chains represent six-membered ring sugar molecules that we show here in more detail (Figure [graphic 7.66]).

These six-membered ring sugar units are attached to each other by way of O atoms between the rings. The R-O-R' bonds between the sugar units (R and R' represent six-membered sugar rings) are called **glycosidic bonds**, and it is these glycosidic bonds that are cleaved by lysozyme in a series of reactions that includes the S_N1 reaction.

Cleavage of Glycodidic Bonds by an S_N1 Reaction

We can write general reactions for a glycoside bond cleavage reaction catalyzed by lysozyme as we show here where R-O-R' represents a part of the carbohydrate chain of the cell wall that we showed above.



This sequence of reactions is the same as we wrote for the acid catalyzed S_N1 solvolysis by water of a substrate of the structure R-O-R' !

In the lysozyme catalyzed cleavage reaction, the enzyme binds to the bacterial cell wall, and then transfers an H^+ to the O of the glycoside bond (R-O-R') using one of its acidic groups called **glutamic acid 35**. We will learn about the amino acid glutamic acid in Chapter 22. It is numbered "35" indicating its position as the 35^{th} amino acid in the protein chain of the enzyme molecule.

After the enzyme transfers the proton to oxygen, the protonated substrate R-$^+$OHR' loses HOR' (glycoside bond cleavage) so that the carbocation center is on the C that is attached to the ring O atom as we show here (Figure [graphic 7.67]). This C+ center is stabilized by the presence of the attached O in the ring in a way that we will learn about later in this text.

The C+ center is also stabilized by the presence of a negatively charged group that hovers over the face of the six-membered ring opposite to the face from which the H-O-R' group left. Because one face of the carbocation is blocked by this stabilizing group, the new water molecule that reacts with the C+ center can only approach from the side of the six-membered ring from which HOR' left. As a result, this S_N1 reaction takes place by retention of configuration at the C-L carbon.

This mechanism was proposed in 1965 by David Phillips based on X-ray crystallographic studies in which he determined the structure of lysoyme. It certainly illustrates the importance of basic concepts of organic chemistry in explaining biochemical processes in living systems.