

**CHEM 321 Organic Chemistry I - Professor Kathleen Kilway**  
**"Organic Chemistry" by Maitland Jones, 3rd edition**

Chapter 7 – 1, 4, 5, 11, 12, 17, 19, 21, 22, 23, 25, 27, 28, 32, 35, 36, 38, 39, 40, 42, 48, 49,  
50, 51, 54, 57, 60, 61, 62, 63, 66, 67, 69.

**CHAPTER 7: SUBSTITUTION AND ELIMINATION REACTIONS:  
THE S<sub>N</sub>2, S<sub>N</sub>1, E2, AND E1 REACTIONS**

**Section 7.1**

**I. Preview**

**Section 7.2**

**II. Review of Lewis Acids and Bases**

**A- The Curved Arrow Formalism**

- 1- Only sketches what happens during a reaction.
- 2- Arrow formalism does not constitute a full reaction mechanism.
  - a- Reaction mechanism: "a determination in terms of structure and energy of the stable molecules, reaction intermediates, and transition states involved in the reaction, along with a consideration of how the energy changes as the reaction progresses".
- 3- See Figure 7.3 on page 274 for an example of the arrow formalism.

**B- Lewis Acids and Lewis Bases**

- 1- **Lewis acid** - anything that reacts with a Lewis base (empty orbital).
- 2- **Lewis base** - a species with a reactive pair of electrons (filled orbital).

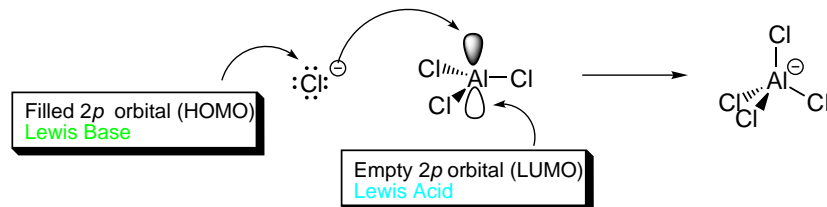


Figure 1

**C- HOMO-LUMO Interactions**

- 1- **HOMO** - Highest Occupied Molecular Orbital - can be filled nonbonding, 2s, 2p, or  $\pi$  orbital of a double bond.
- 2- **LUMO** - Lowest Unoccupied Molecular Orbital - can be empty 2s, 2p or  $\sigma^*$  orbital.
- 3- Figure 2 shows the interaction of HOMO and LUMO based on Figure 1.

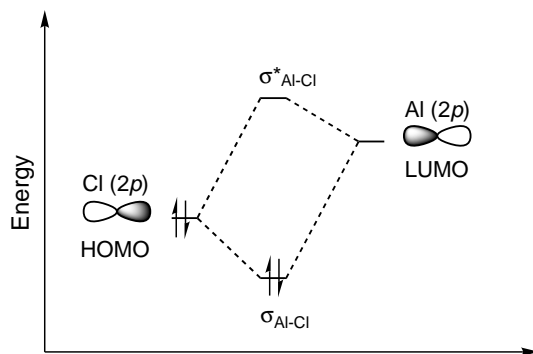


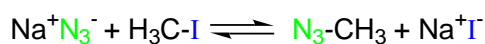
Figure 2

### Section 7.3

### III. Reactions of Alkyl Halides: Substitution Reaction

#### A- Substitution Reactions

- 1- **Nucleophile** - displacing or substituting group.
- 2- **Leaving group** - displaced group.



HOMO - filled nonbonding orbital of  $\text{N}_3^-$ .

LUMO - empty  $\sigma^*$  orbital of  $\text{H}_3\text{C-I}$ .

- 3- This reaction lies to the right (i.e., it's exothermic and will go to completion).
- 4- See Figure 7.9 on page 277 for some examples of substitution reactions.

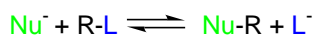
### Section 7.4

### IV. Substitution, Nucleophilic, Bimolecular: The $\text{S}_{\text{N}}2$ Reaction

(See your CD for mechanisms.)

#### A- Rate Law

- 1- Substitution, Nucleophilic, bimolecular (2), or  $\text{S}_{\text{N}}2$  reaction  
Rate ( $v$ ) =  $k [\text{R-L}][\text{Nu}^-]$



- a- Rate ( $v$ ) is proportional to the concentration of both nucleophile  $[\text{Nu}^-]$ , and the substrate  $[\text{R-L}]$ .
- b- First order in both  $\text{Nu}^-$  and  $\text{R-L}$ , second order overall.

#### B- Stereochemistry of $\text{S}_{\text{N}}2$ Reaction

- 1- Retention of stereochemistry - stereochemistry of starting material is preserved.



Figure 3

- 2- Inversion of stereochemistry - the configuration of the starting material is reversed (*R*) to (*S*) and vice versa.



Figure 4

- 3- Racemization - loss of stereochemistry (50:50 mixture).

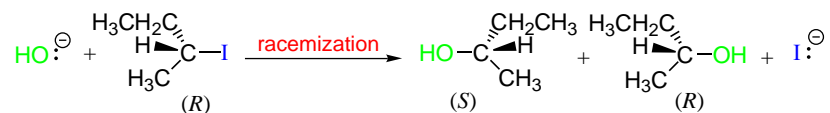


Figure 5

- 4- Normally this reaction goes with **inversion of configuration** (See Figure 4).
- Nucleophile must approach the substrate from the rear of the departing atom.
  - See Figure 7.16 on page 281.
- 5- Why inversion preferred?
- A filled nonbonding orbital "n" on the nucleophile interacts with an orbital on the substrate, R-L, involved in the bond from R to the leaving group L.
  - It's more stabilizing for a filled orbital to interact with an empty orbital; therefore, the filled orbital must overlap with the empty antibonding orbital of R-L.
  - See Figure 7.19a on page 283 for an illustration.
  - For retention, frontside substitution would have to occur.
    - Reduced interactions by poor overlap with the smaller lobe of the antibonding orbital.
    - Offsetting bonding and antibonding interactions.
    - See Figure 7.20 on page 283 for an illustration.
- 6- **Transition state** - half energy point between starting material and product. It is an energy maximum and cannot be isolated.

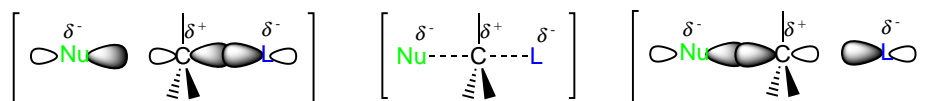


Figure 6

- 7- **Activation energy** - energy difference between starting material and transition state (See Figure 7.23 on page 285).

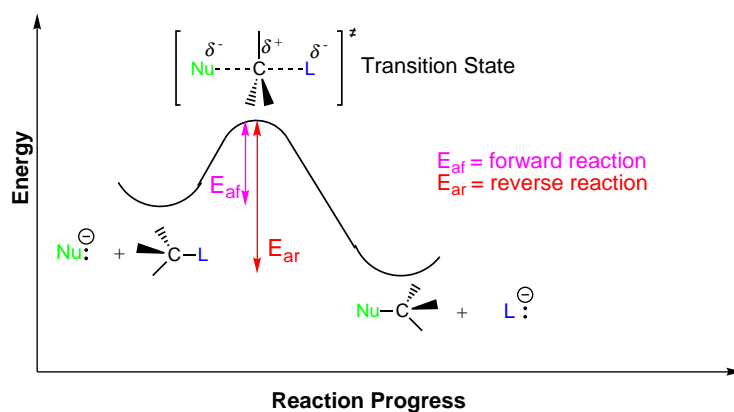


Figure 7

### C- Effects of Substrate Structure: The R Group

- 1- In general, methyl substrates react faster than primary substrates, which react faster than secondary.
- 2- Tertiary substrates do not react under  $S_N2$  conditions, because the alkyl groups hinder approach from the rear.
- 3- Exception - neopentyl groups  $(\text{CH}_3)_3\text{CCH}_2^-$ .
  - a- Primary substrate, but *tert*-butyl group blocks pathway for rearside displacement.
  - b- Very slow substitution.
  - c- See Figure 7.25 on page 287.
- 4- Ring compounds.
  - a- Small rings are slow due to ring strain in the transition state.
  - b- Cyclohexane is slow due to the steric interactions of the axial hydrogens.

### D- Effect of the Nucleophile

- 1- A good nucleophile has a good match in energy with the  $2p$  orbital on carbon.
- 2- In general, a good base is a good nucleophile.
- 3- See Table 7.3 on page 291 for a list of nucleophiles.

### E- Effect of the Leaving Group

- 1- Best leaving group is the weakest base:  
 $\text{R-F} \ll \text{R-Cl} < \text{R-Br} < \text{R-I}$

### F- How to Play "Change the Leaving Group"

- 1- Convert an alcohol into a new compound Nu-R.
  - a- Problem:  $^-OH$  is a poor leaving group.
    - i- Transfer a proton to the alcohol with a strong acid to give  $\text{R-O}^+\text{H}_2$ .
    - ii- The poor leaving group  $-OH$  is converted into a good leaving group  $^+OH_2$ .
    - iii- See Figure 7.39 on page 294 for an example.
- 2- Ether Cleavage.
  - a- In strong halogenated acids such as HI or HBr, ethers can be cleaved into the corresponding alcohol and halide.

- i- Ether is first protonated to turn the leaving group from alkoxide,  $^-\text{OR}$ , into the better leaving group HOR.
  - ii- See Figure 7.40 on page 294 for an example.
- 3- Sulfonate.
- a- In a two-step process alcohols are first converted into sulfonates, which can be displaced in a second step by all manners of nucleophiles.
  - b- See Figure 7.41 on page 295 for an example.
- 4- Thionyl Chlorides ( $\text{SOCl}_2$ ).
- a- Treatment of an alcohol with thionyl chloride ( $\text{SOCl}_2$ ) leads to the conversion of the alcohol into a chloride (see Figure 8).
  - b- See Figure 7.42 on page 296 for an example.

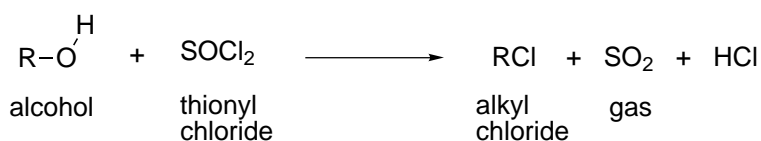


Figure 8

- 5- Phosphorus Reagents.
- a- Alcohols treated with phosphorus halides,  $\text{PX}_3$  or  $\text{PX}_5$ , are converted into alkyl halides (see Figure 9).
  - b- See Figure 7.44 on page 297 for an example.

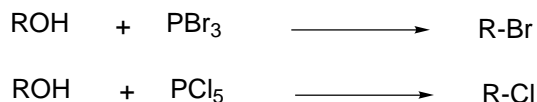


Figure 9

## 6- Effect of Solvent

- 1- As the solvent polarity is increased, some  $\text{S}_\text{N}2$  reactions go faster, some slower.
  - a- If the products of a reaction are charged, a more polar solvent will act to stabilize the charged products and the polar charge-separated transition state.
    - i- The activation energy is decreased, and the reaction will go faster.
    - ii- See Figure 7.48 on page 299 for an example.
  - b- If the starting material bears full charges, a more polar solvent will stabilize the starting material.
    - i- The activation energy is increased, and the reaction slows.
    - ii- See Figure 7.49 on page 299 for an example.

## Section 7.5

### V. The $\text{S}_\text{N}2$ Reaction in Biochemistry

- A- DNA.
- B- S-adenosylmethionine.

## Section 7.6

VI. Substitution, Nucleophilic, Unimolecular: The  $S_N1$  Reaction

(See your CD for mechanisms.)

## A- Rate Law

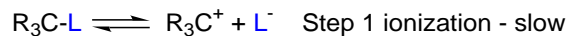


Figure 10

- 1- Two-step mechanism.
  - a- Step 1: Leaving group is lost, producing a carbocation.
  - b- Step 2: Nucleophilic solvent adds to carbocation.
  - c- See Figure 7.53 on page 302.
- 2- Presence of carbocation intermediate means that there are two transition states.
  - a- See Figure 7.54 on page 303 for a diagram representation.
- 3- The second step determines the structure of the product, but not the rate of the reaction.
- 4- Rate ( $v$ ) =  $k [R-L]$ .
  - a- Rate of  $S_N1$  reaction is irrelevant to the concentration of the nucleophile  $[Nu^-]$  in solution, but depends only on the concentration of the substrate  $[R-L]$ .
  - b- First order reaction.

B- Stereochemistry of  $S_N1$  Reaction

- 1- Intermediate carbocation is planar.
- 2- Therefore, the  $Nu^-$  can attack from **above** or **below** the planar carbocation.



Figure 11

- 3- Reaction proceeds with a mixture of retention and inversion of stereochemistry (Racemization).
  - a- Usually there is an excess of inversion.
    - i- The leaving group hasn't completely diffused away from the carbocation, and hinders the retention pathway.
- 4- When a carbocation is formed optical activity is lost.

## C- Effects of Substrate Structure: The R Group

- 1- Carbocation formation is the rate-determining step in  $S_N1$  reaction.
- 2- Rate is much greater for tertiary than secondary carbocations.
- 3- Primary and methyl halides do not react under these conditions.
- 4- Roughly follows the stability of carbocations:
 
$$\text{Tertiary } R_3C-L > \text{Secondary } R_2HC-L > \text{Primary } RH_2C-L > \text{Methyl } H_3C-L$$

**D- Effect of the Nucleophile**

- 1- Rate-determining step - step that has the highest activation energy.
- 2- Product-determining step - step that determines structure(s) of product(s).
- 3- Concentration of nucleophile does not effect the rate of the reaction, but does effect products.
- 4- Nucleophile will probably be more reactive towards carbocation than solvent.

**E- Effect of the Leaving Group**

- 1- Best leaving groups give weakest bases as products.
  - a- The more stable the leaving group compared to its corresponding anion is, the more easily it is lost.

**F- Effect of Solvent**

- 1- Reactions are accelerated by polar, protic, donor solvents.
- 2- This is because the ions formed (cations and anions) are stabilized by polar solvents.

**Section 7.7****VII. Summary and Overview of the S<sub>N</sub>2 and S<sub>N</sub>1 Reaction****A- Complement each other; therefore have to compare substrates & solvents.**

- 1- S<sub>N</sub>2 - works better for:
  - a- Methyl and primary- less steric hindrance.
  - b- Weak nucleophiles.
  - c- Apolar solvents.
- 2- S<sub>N</sub>1 - works best for:
  - a- Tertiary substrates- because the most stable carbocation is formed.
  - b- Strong nucleophiles.
  - c- Polar, protic, donor solvents.
- 3- Secondary substrates - depends on solvent.
  - a- Polar solvent favors S<sub>N</sub>1.

**B- In almost all S<sub>N</sub>1 and S<sub>N</sub>2 reactions, there are some elimination products.****Section 7.8****VIII. The Unimolecular Elimination Reaction: E1**

(See your CD for mechanisms.)

**A- Rate Law**

- 1- Rate determining step is ionization of substrate.
  - a- Same as for S<sub>N</sub>1, Rate (v) = k [R-L].
  - b- First order reaction.
  - c- First step yields carbocation intermediate (same as in S<sub>N</sub>1 reaction).
- 2- Instead of adding a nucleophile as is done during the second step of a S<sub>N</sub>1 reaction, the substrate is deprotonated. An alkene is formed.
  - a- The nucleophile is acting as Brønsted base.

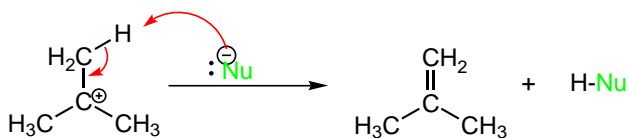
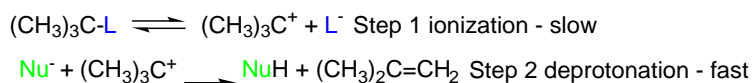


Figure 12

- 3- Mixture of E1 and  $\text{S}_{\text{N}}1$  products depends on nucleophile's basicity.
- Strong Brønsted bases - E1.
  - Good nucleophiles favor  $\text{S}_{\text{N}}1$ .

### B- Orientation in the E1 Reaction

- More stable alkene is favored, thus more substituted.
- Saytzeff elimination - produces the most substituted alkene possible.
- Competes with the  $\text{S}_{\text{N}}1$  reaction.
- See Figure 7.72 on page 313 for an example.

## Section 7.9

### IX. The Bimolecular Elimination Reaction: E2

(See your CD for mechanisms.)

#### A- Rate Law

- Second order process, dependent on substrate and nucleophile.
- Rate ( $v$ ) =  $k [\text{R-L}] [\text{Nu}^-]$

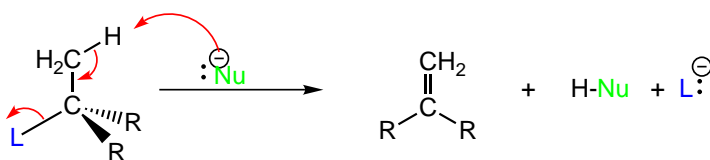


Figure 13

- Strong base attacks proton attached to  $\beta$ -carbon (carbon adjacent to the carbon bearing the leaving group).
- E2 competes with  $\text{S}_{\text{N}}2$ .

#### B- Effect of Substrate Branching on the E2- $\text{S}_{\text{N}}2$ Mix

- The more branching of substrate, the more likely reaction will proceed E2.
- Tertiary substrates only undergo E2 reactions under E2- $\text{S}_{\text{N}}2$  conditions.

#### C- Stereochemistry of the E2 Reaction

- Only syn ( $0^\circ$ ) and anti ( $180^\circ$ ) arrangements of substrate can lead to  $\pi$ -bond formation.
- Syn elimination - elimination where the dihedral angle between C-H and C-L is  $0^\circ$ .

- 3- **Anti-elimination** - elimination where the dihedral angle between C-H and C-L is  $180^\circ$ .
- 4- Anti elimination is favored over syn elimination (See Figure 7.83 on page 320).
- 5- Formation of the more substituted alkene is also favored.

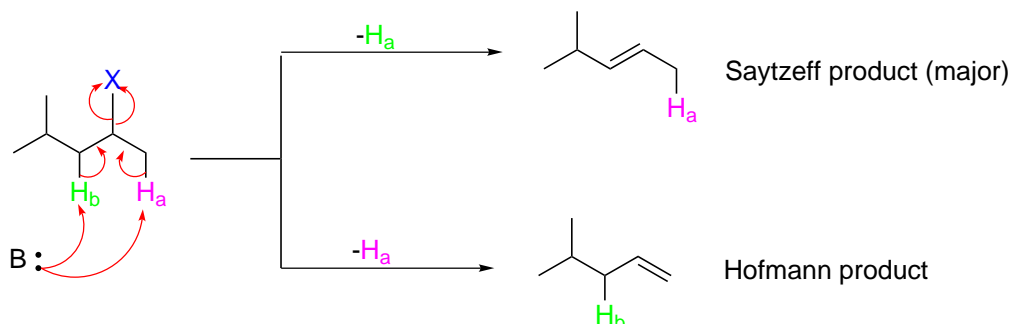


Figure 14

#### D- Orientation of the E2 Reaction

- 1- The larger the size of the base the more likely 1:1 (Hofmann/ Saytzeff) product ratio.
- 2- **Regiochemistry** - refers to the outcome of the reaction in which more than one orientation of substituents is possible in the product.
- 3- **Hofmann elimination** - formation of the less stable alkene and is favored when:
  - a- The leaving group is fluoride, ammonium ( $R_3N^+$ ), and sulfonium ( $R_2S^+$ ).
  - b- The base is a strong one like an alkoxide ( $RO^-$ ).
  - c- For  $R_3N^+$  and  $R_2S^+$  as leaving groups, the Hofmann product formed is due to a steric effect.
  - d- See Figure 7.88 on page 324 for an example.

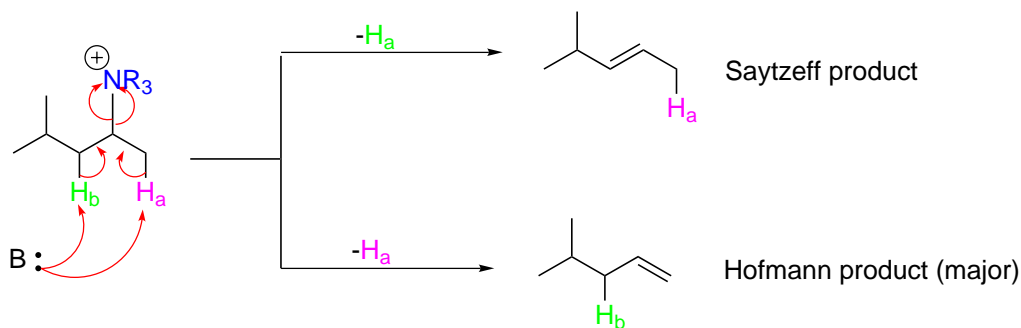


Figure 15

### Section 7.10

#### X. What Can We Do with These Reactions? How to Do Organic Synthesis

Both Substitution and elimination products.

Acetylide Formation.

With a terminal alkyne,  $NH_2^-$  in  $NH_3$  deprotonates the terminal hydrogen to form an excellent nucleophile.

### A- Sulfur as Nucleophile

1- Converting isopropyl bromide into propane-2-thiol.

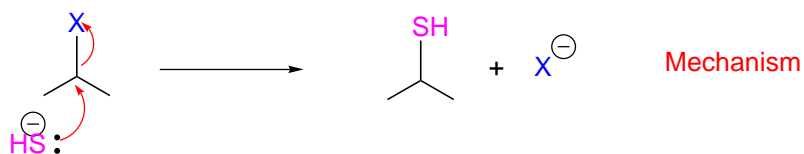
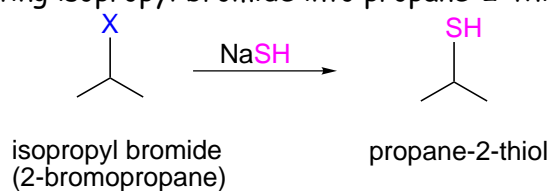


Figure 16

2- Converting propene into propane-2-thiol.

a- Requires two steps.

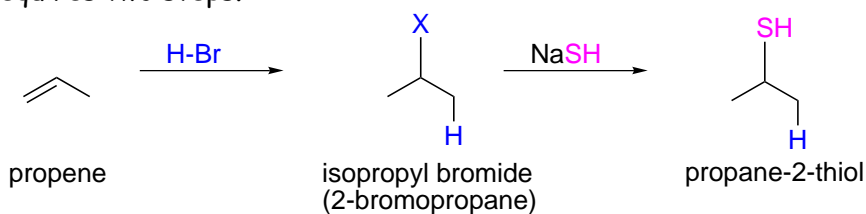


Figure 17

3- Converting propyl bromide into propane-2-thiol.

a- Requires three steps.

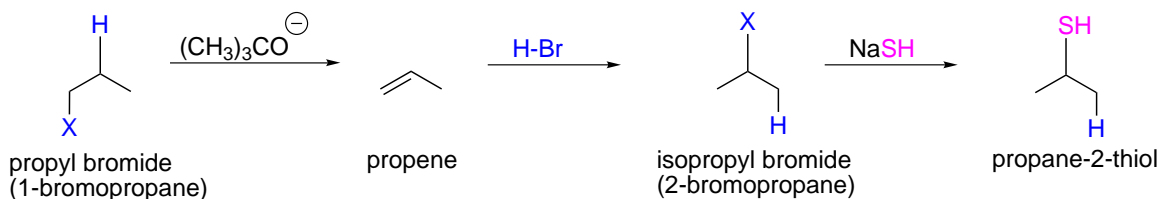


Figure 18

4- Try to work backwards on the synthesis problems.

### B- Oxygen as Nucleophile: The Williamson Ether Synthesis

1- Converting propyl bromide into an ether.

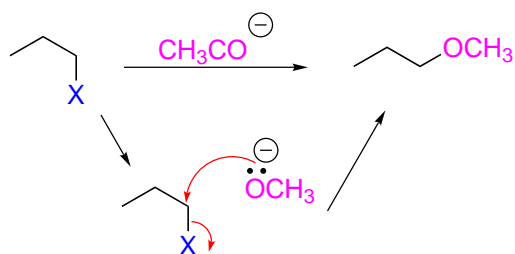


Figure 19

- a-  $S_N2$  reaction.
- b- See Figure 7.103 on page 331 for the arrow formalism.
- c- Sodium hydride (NaH) is a good agent to convert the alcohol into the alkoxide.
  - i- Hydrogen gas is produced, which can easily be removed.

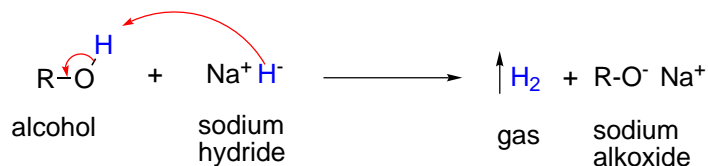


Figure 20

- 2- Alkoxides are named after the starting alcohol as metal alkoxides, (e.g.: sodium methoxide).
- 3- Williamson Ether Synthesis only works for  $S_N2$  reactive alkyl halides.
  - a- Tertiary halides cannot be used ( $R_3C-X$ ).
  - b- Even secondary halides lead to a mixture of the ether and the elimination product.
- 4- Williamson Ether Synthesis can also form intramolecular rings.

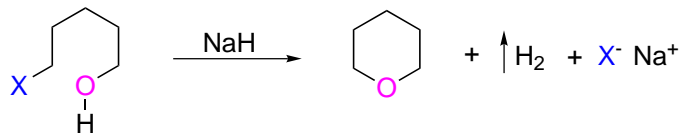


Figure 21

- a- Oxiranes (ethers with the oxygen atom in a three-membered ring) can be produced.
- b- Oxiranes are also called epoxides.
- c- See Figure 7.110 on page 334 for an example of an epoxide synthesis.

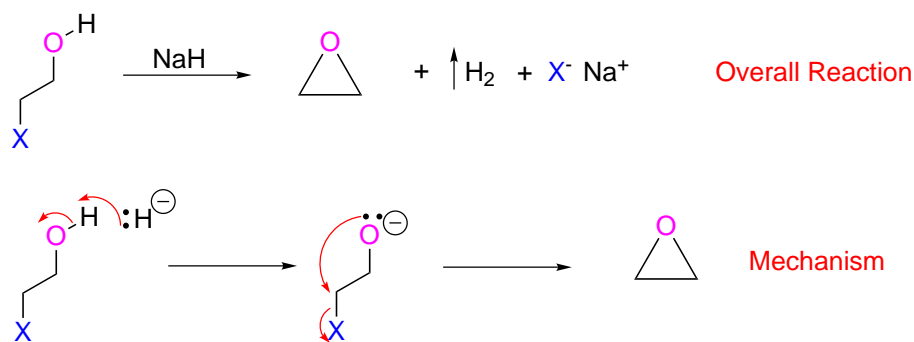


Figure 22

### C- Nitrogen as Nucleophile: Alkylation of Amines

- 1- Amines can be used as nucleophiles to displace leaving groups in a  $S_N2$  reaction.
  - a- Limitations of  $S_N2$  reaction apply.
  - b- Products are primary, secondary, and tertiary amines, and quaternary ammonium ion.

- c- Difficult to stop reaction.
- d- See Figure 7.111 and 7.112 on pages 334 and 335 for an example.

#### D- Summary and a Few "Real-World" Difficulties

- 1- Challenges of Synthesis are great.
  - a- Find a reaction or sequence of reactions that produces the desired compound without other isomers.
  - b- Make synthesis economical.

### Section 7.11

#### XI. Summary

A-  $S_N1$  Reaction competes with E1 Reaction ( $3^\circ$  and some  $2^\circ$  Carbons)

B-  $S_N2$  Reaction competes with E2 Reaction ( $2^\circ$ ,  $1^\circ$ , and methyl Carbons)

C- In order to decide which reaction is favored, follow the following flow chart:

- 1- Is the R of the alkyl halide methyl (a), primary (b), secondary (c), or tertiary (d)?
- 2- Is the nucleophile a good base?  
Yes or no?
- 3- Is the solvent polar?  
Yes or no?

#### D- Flow Chart

- (a) methyl carbon, no - not a good base, no - not a polar solvent =  $S_N2$  only  $S_N2$  possible
- (b), yes, no = E2
- (b), no, no =  $S_N2$
- (c), yes, no = E2
- (c), no, no =  $S_N2$
- (c), no, yes =  $S_N1$
- (d), yes, yes = E1
- (d), no, yes =  $S_N1$

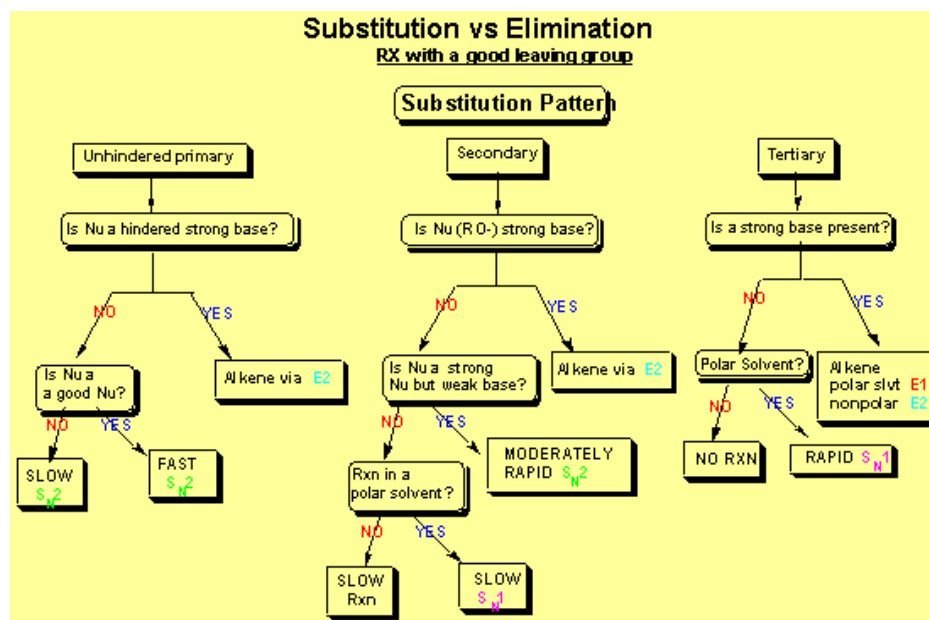


Figure 20