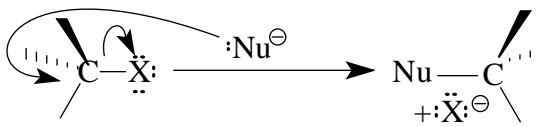
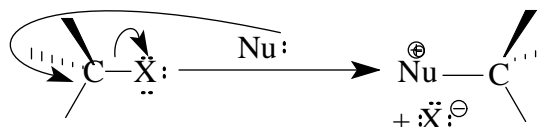
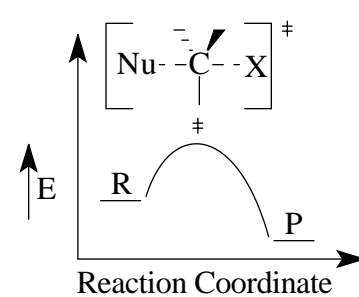
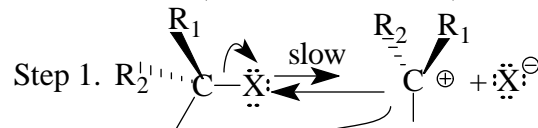
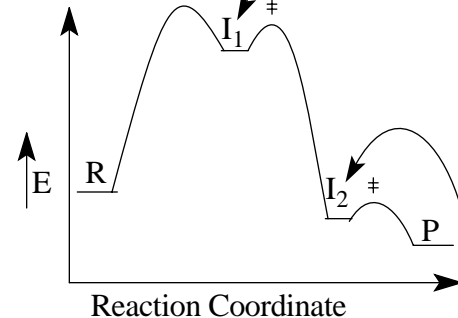
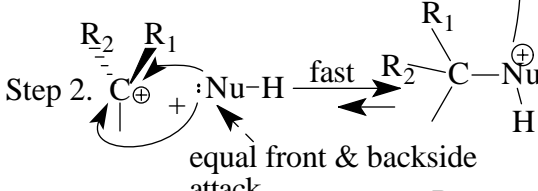
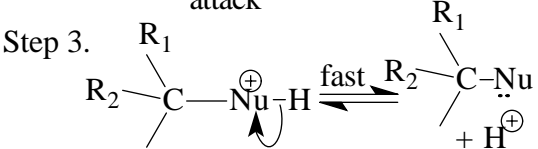


| <b>SUBSTITUTION REACTION CHARACTERISTICS</b>  | <b>Chemistry 118A Workshop</b><br>Jim Hollister, Doug Kent, Rolf Unterleitner<br>Learning Skills Center; UC Davis  |
|---|--|
| <b>S<sub>N</sub>2: Substitution Nucleophilic, Bimolecular: Characteristics</b>  | <b>S<sub>N</sub>1: Substitution Nucleophilic, Unimolecular: Characteristics</b>  |
| 1) The 2 means <b>Bimolecular</b> (or 2 <sup>nd</sup> order) in the rate-determining (slow) step:<br>rate = k [Nu: <sup>-</sup> ] [R-X] or<br>rate = k [Nu:] [R-X] if the Nu is neutral.  | 1) The 1 means <b>Unimolecular</b> (or 1 <sup>st</sup> order) in the rate-determining (slow) step:<br>rate = k [R-X]. The Nu is not in the rate law.   |
| 2) S <sub>N</sub> 2 reactions are <b>One Step and Concerted</b> ( <i>Concerted</i> means bond making and breaking at the same time):<br><br> <p>If the nucleophile is neutral;</p>   | 2) <b>Two (or Three) Steps:</b><br>Step 1. Dissociation of halide from haloalkane. (I <sub>1</sub> = Intermediate 1)<br>  <p>Step 2. Nucleophilic Attack forms Intermediate 2 (I<sub>2</sub>).</p>  <p>Step 3. Deprotonation step forms the Product.</p>  |
| 3) There is a <b>Transition State (TS)</b> but <b>no Intermediate</b> (The symbol ‡ indicates a TS) (See above).  | 3) Has <b>Intermediate Carbocation</b> (sp <sup>2</sup> carbon) and <b>Transition States</b> (See above).  |

|   |  |
|---|--|
| <p>4) <b>Backside Attack- get Inversion</b><br/>       (and, if the electrophilic carbon is chiral, usually get a change in absolute configuration, as from R to S, but not necessarily, because it depends on the priorities of the attaching nucleophile and the leaving group relative to the other groups attached to the chiral carbon.)</p> | <p>4) <b>Equal Front and Backside Attack;</b><br/>       not stereospecific; if start with chiral carbon, get racemic mixture.</p>                       |
| <p>5) <b>Enhanced by aprotic polar solvents</b><br/>       which make the nucleophile unhindered, or "naked."</p>   | <p>5) <b>Enhanced by protic, polar solvents,</b> as H<sub>2</sub>O, R-O-H, and small carboxylic acids, which stabilize the carbocation by H bonding.</p> |
| <p>6) <b>Sensitive to steric hindrance.</b></p>   | <p>6) <b>Solvolysis:</b> Solvents as H<sub>2</sub>O, R-O-H, and small carboxylic acids, can act as nucleophiles.</p>                                     |
| <p>7) <b>Occurs in methyl &gt; 1° &gt; 2° haloalkanes substrates. Reacts best in order indicated.</b></p>   | <p>7) Occurs <b>best in 3° haloalkanes</b> substrates and <b>slowly in 2° haloalkanes.</b></p>   |

## Four Factors For Finding Products of $S_N1$ , $S_N2$ , $E1$ & $E2$

### 1) Substrate

**Steric Hindrance:** The more groups around the reactive center (the C with the leaving group), the harder it is to get to, therefore the less reactive via  $S_N2$ .

**Order of Steric hindrance; methyl < 1° < 2° < 3°**  
**Order of reactivity via  $S_N2$ ; methyl > 1° > 2° > 3°**

**Carbocation stability:** The more alkane groups around a reactive center (the C with the leaving group), the more stable it will be.

**Order of stability of carbocations; 3° > 2° > 1° > methyl**  
**Order of reactivity via  $S_N1$ ; 3° > 2° > 1° > methyl**

### 2) Nucleophile

#### A) 3 Trends

1) nucleophilicity (and basicity) increase with incr. neg. charge.

e.g.  $OH^- > H_2O$ ;  $NH_2^- > NH_3$ ;  $SH^- > SH_2$ ;  $Cl^- > HCl$

2) Nucleophilicity (and basicity) decr. within a period from left to right

e.g.  $NH_3 > H_2O > FH$ ;  $CH_3^- > NH_2^- > OH^- > F^-$  (note: no  $CH_4$  in the first group because if you don't have any lone pairs, it isn't nucleophilic or basic).

3) Nucleophilicity incr., but basicity decr., as you go down the periodic table within a group e.g.  $I^- > Br^- > Cl^- > F^-$  \*;  $H_2Se > H_2S > H_2O, HSe^- > HS^- > OH^-$  (trend 3 due to polarizability: bigger p orbitals can reach out better than smaller ones, 4p is bigger than 3p .....) \* in protic solvents, due in large part to solvation.

In aprotic solvents the trend for halogens is the same as basicity  $F^- > Cl^- > Br^- > I^-$ .

#### B) General Rules

1) Strong bases are usually good nucleophiles (trends 1 and 2 above), but always look out for  $E2$  with all strong base nuc.'s especially with "bulky ones" like  $^-OC(CH_3)_3$ .

2) Weak bases can be good nuc.'s if they have big p orbitals (trend 3 above)

### 3) Leaving Group

**The more stable it is by itself, the better it is as a leaving group**

1) Weak bases are good leaving groups (strong bases are bad)

2) Halogens:  $I^- > Br^- > Cl^- > F^-$  ( $F^-$  is a poor leaving group)  
weakest base, best leaving group

3) Strong bases ( $OH^-$ ,  $RO^-$ ) can be made into a good leaving groups ( $H_2O$ ,  $ROH$ ) by adding a strong acid.

4) If the negative charge can be delocalized, the ion will be more stable, therefore, it will be a better leaving group ( $RSO_3^-$ ;  $CH_3-C_6H_4-SO_3^-$ )

### 4) Solvent

**Polar like polar:** If you have a polar, or a charged species or intermediate, then you need a polar solvent which will help stabilize these species.

**Polar protic (have H-bonding) ( $H_2O$ ,  $ROH$ ...):** Lowers the reactivity of the nuc. because of H-bonding to nuc., so it is bad for  $S_N2$ . Stabilizes carbocation intermediates, so it is good for  $S_N1$ .

**Polar aprotic (have NO H-bonding) (acetone, DMSO, HMPA...):** Leaves nucleophiles naked and ready to react, also helps to stabilize reactants so it is good for  $S_N2$ .

**S<sub>n</sub>2 substitution rxns**Factors favoring S<sub>n</sub>2

- 1) **Substrate:** methyl > 1° > 2° (never 3°)  
Can't have things in the way or the nucleophile won't make it in.
- 2) **Good nucleophile needed.** Nuc. has to go after the reactive center or no rxn.
- 3) The substrate needs to have a **good leaving group**. Good LG's are very weak bases which can accommodate their negative charge by high electronegativity &/or delocalization.
- 4) **Best with aprotic polar solvents.** They leave the nuc. free to react, and help to stabilize the polar species.

**Mechanism: Backside attack.** In the transition state, the nucleophile is coming in as the leaving group is coming off. Inversion changes R/S configurations most of the time.

**E2 Elimination rxns**

Factors favoring E2

- 1) **Nucleophile** □ **strong bases.** The nuc. acts like what it is, a strong base. It tears a □-H off a □-carbon, which is next to the carbon with the leaving group on the substrate (called the □-carbon).
- 2) **Needs a good leaving group in anti-position** to a neighboring □-hydrogen. When the □-H is being removed, the leaving group needs to be free to come off. A double bond forms.
- 3) **Solvent** is often the conjugate acid of basic nuc., as NaOH in H<sub>2</sub>O (but could also be in CH<sub>3</sub>OH), CH<sub>3</sub>CH<sub>2</sub>O<sup>-</sup>K<sup>+</sup> in CH<sub>3</sub>CH<sub>2</sub>OH, etc. (Strong bases are looking for H's. You need the base to remove the H's from the substrate and not the solvent).
- 4) **Substrate** not as important, but they should not be methyl and 1° unbranched (which with small, strong bases will favor S<sub>n</sub>2 product). Needs a leaving group, which is anti to the □-H being removed.

**Mechanism: Anti-elimination.** Base removes a □-H 180° to leaving group on neighboring carbon.

**S<sub>n</sub>1 substitution rxns**Factors favoring S<sub>n</sub>1

- 1) **Substrate:** 3° > 2° (never 1° and methyl) More alkyl groups help to stabilize the carbocation intermediate.
- 2) The substrate needs to have a **good leaving group (LG)**. To fall off and leave a carbocation behind, the LG has to be stable on its own. Good LG's are very weak bases which can accommodate their negative charge by high electronegativity &/or delocalization [as I<sup>-</sup>, or RSO<sub>4</sub><sup>-</sup> (sulfates) or RSO<sub>3</sub><sup>-</sup> (.sulfonates)]
- 3) Works with **poor nucleophiles as H<sub>2</sub>O or ROH**. Once the carbocation is formed in the rate determining step, it is very, very reactive; anything with a lone pair will do.
- 4) **Best with aprotic polar solvents.** The carbocation is a charged (+1) species, so polar solvents help stabilize it (H-bonds).

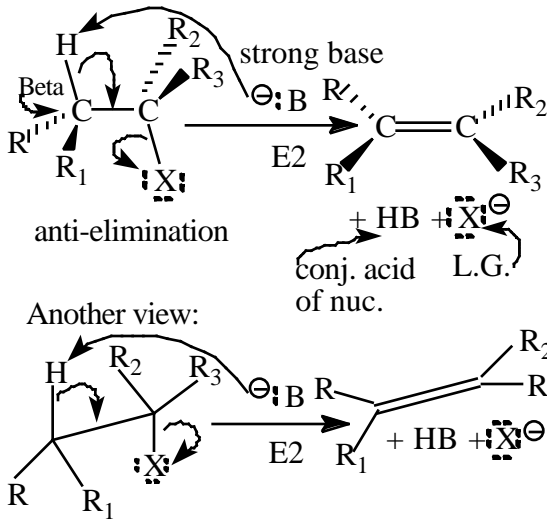
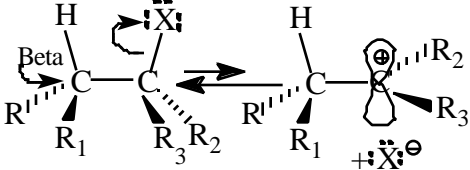
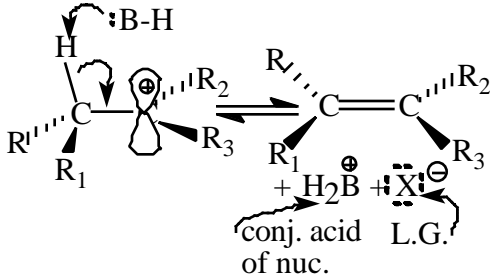
**Mechanism: Carbocation intermediate.** You get a mixture of both R and S. Beware of rearrangements.

**E1 Elimination rxns**

Factors favoring E1

- 1) **Substrate** 3° > 2° (never 1° and methyl) More alkyl groups help to stabilize the carbocation intermediate.
- 2) The substrate needs to have a **good leaving group (LG)**. To fall off and leave a carbocation behind, the LG has to be stable on its own (needs to accommodate its negative charge by high electronegativity &/or delocalization [as I<sup>-</sup>, or RSO<sub>4</sub><sup>-</sup>, or RSO<sub>3</sub><sup>-</sup> (sulfonates)])
- 3) **Best with aprotic polar solvents.** As with S<sub>n</sub>1, the carbocation is a charged (+1) species; polar solvents help stabilize it.
- 4) **Poor nucleophiles as H<sub>2</sub>O or ROH.**

**Mechanism: Carbocation intermediate.** The product that comes from the most substituted (most alkyl groups around it) carbocation is usually the major product. Beware of rearrangements too.

|   |  |
|---|--|
| <p><b>ELIMINATION REACTIONS FORM ALKENES.</b></p> <p><b>THEY ARE FAVORED BY STERICALLY HINDERED MOLECULES, EITHER HALOALKANES, NUCLEOPHILES, OR BOTH.</b></p>   | <p><b>Chemistry 118A Workshop</b></p> <p>Jim Hollister, Doug Kent, Rolf Unterleitner<br/>Learning Skills Center; UC Davis</p>  |
| <p><b>E2: Elimination, Bimolecular: Characteristics</b></p>   | <p><b>E1: Elimination, Unimolecular: Characteristics</b></p>   |
| <p>1) The 2 means <b>Bimolecular</b> (or 2<sup>nd</sup> order) in the rate-determining (slow) step:<br/>rate = k [Nu:-] [R-X] or<br/>rate = k [Nu:] [R-X] if the Nu is neutral.</p>   | <p>1) The 1 means <b>Unimolecular</b> (or 1<sup>st</sup> order) in the rate-determining (slow) step:<br/>rate = k [R-X]. The Nu is not in the rate law.</p>  |
| <p>2) E2 reactions are <b>One Step Concerted Acid/Base reaction with elimination of the LG:</b><br/>(Acid/Base reactions happen faster than nucleophilic/electrophilic reactions.)<br/><b>Alkene forms.</b></p>  <p>The diagram shows two views of the E2 mechanism. In the first, a strong base (B:) attacks a beta-hydrogen (H) on a carbon (C) bonded to a leaving group (X). Simultaneously, the C-X bond breaks, and the C-H bond electrons form a C=C double bond. The products are an alkene, a conjugate acid (HB), and a leaving group (X-). The transition state is shown with partial bonds and partial negative charge on the base. The second view shows the same reaction from a different perspective, emphasizing the anti-periplanar arrangement of the H and X groups.</p> <p>anti-elimination</p> <p>Another view:</p> | <p>2) E1 reactions are <b>Two Steps: Alkene forms.</b></p> <p><b>Step 1.</b> Dissociation of halide</p>  <p>The diagram shows a haloalkane (R1-CH2-CH(R2)-X) dissociating into a carbocation (R1-CH2-CH+(R2)) and a halide ion (X-). Curved arrows show the movement of electrons from the C-X bond to the X atom.</p> <p><b>Step 2.</b> Acid/Base Reaction. A poor nuc. acts as a base to remove the acidic H. <b>Alkene forms.</b></p>  <p>The diagram shows a carbocation (R1-CH2-CH+(R2)) reacting with a base (B-H). The base removes a proton from the beta-carbon, and the C-H bond electrons form a C=C double bond. The products are an alkene, a conjugate acid (H2B+), and a leaving group (X-). The transition state is shown with partial bonds and partial positive charge on the carbocation carbon.</p> |
| <p>3) <b>Concerted Mechanism-No Intermediate</b></p>  | <p>3) <b>Carbocation Intermediate</b></p>  |
| <p>4) <b>Anti-Elimination:</b> The base takes the H of the TS which is in anti-conformation (180°) to the Leaving Group (LG). (The carbon with the LG on it is called the carbon and the carbon(s) with the acidic H on it is called the carbon.).</p>  | <p>4) The <b>H is removed from the Carbocation Intermediate in the second step</b> (the LG left when the intermediate was formed by dissociation in the first step. Therefore, the LG and the acidic H are <b>not in anti-conformation.</b>)</p>   |

|  |   |
|--|---|
| <p>5) <b>Enhanced by sterically hindered, strongly basic nucleophiles</b> as LDA or tert-butoxide.</p>   | <p>5) <b>E1 product usually seen as a minor product along with a major S<sub>N</sub>1 product</b>; the solvent, usually H<sub>2</sub>O or an R-O-H, acts as a base to deprotonate the carbocation. (E1 can be a minor product with a major E2 also, but do not worry about this.)</p> |
| <p>6) <b>Can have more than one type of alkene product</b> if the haloalkane has more than one different type of carbon with H's on them. (Chapter 11 in Vollhardt and Schore)</p> | <p>6) <b>Same as E2.</b></p>  |
| <p>7) <b>Occurs with 2° and 3° haloalkanes and 1° haloalkanes branched near the α carbon.</b></p>  | <p>7) <b>Best with 3° haloalkanes.</b></p>  |

## Likely Mechanisms by Which Haloalkanes React with Nucleophiles of Varying Basicity

Modified From Schore and Vollhardt, Table 7.4

| Type of Haloalkane | Type of Nucleophile and its Basicity  |   |   |  |
|--------------------|---|---|---|--|
|                    | Very, very poor base; Poor nucleophile (e.g., H <sub>2</sub> O, or small alcohols or organic acids) | Weakly basic, GOOD nucleophile (e.g., I <sup>-</sup> , Br <sup>-</sup> , NH <sub>3</sub> , CH <sub>3</sub> COO <sup>-</sup> ) | Strongly basic, unhindered nucleophile (e.g., <sup>-</sup> OH, CH <sub>3</sub> O <sup>-</sup> , <sup>-</sup> NH <sub>2</sub> , <sup>-</sup> H, <sup>-</sup> CH <sub>3</sub> ) | Strongly basic, hindered nucleophile (e.g., (CH <sub>3</sub> ) <sub>3</sub> CO <sup>-</sup> , LDA) |
| Methyl             | No reaction   | S <sub>N</sub> 2  | S <sub>N</sub> 2  | S <sub>N</sub> 2   |
| Primary unhindered | No reaction   | S <sub>N</sub> 2  | S <sub>N</sub> 2  | E2   |
| Primary branched   | No reaction   | S <sub>N</sub> 2  | E2  | E2   |
| Secondary          | Slow S <sub>N</sub> 1, E1   | S <sub>N</sub> 2  | E2  | E2   |
| Tertiary           | S <sub>N</sub> 1, E1  | S <sub>N</sub> 1, E1  | E2  | E2   |

