

## 8.4: Comparison and Competition Between S<sub>N</sub>1, S<sub>N</sub>2, E1 and E2

For a certain substrate, it may have chance to go through any of the four reaction pathways. So it seems rather challenging to predict the outcome of a certain reaction. We will talk about the strategies that can be applied in solving such problem, and explain the reasonings behind.

It is very important to understand that the **structural nature of a substrate** (primary, secondary or tertiary) is the most critical factor to determine which reaction pathway it goes through. For example, primary substrates never go with S<sub>N</sub>1 or E1 because the primary carbocations are too unstable. If the substrate could go with a couple of different reaction pathways, then the reaction conditions, including the basicity/nucleophilicity of the reagent, temperature, solvent etc., play the important role to determine which pathway is the major one. Our discussions therefore will start from the different type for substrates, then explore the condition effects on that substrate.

### Methyl

This is the easiest case. Methyl substrate only go with S<sub>N</sub>2 reaction, if any reaction occurs. Elimination is not possible for methyl substrates, and no S<sub>N</sub>1 reaction either because CH<sub>3</sub><sup>+</sup> is too unreactive to be formed, so the only possible way is S<sub>N</sub>2.

### Primary (1°)

Primary (1°) substrates cannot go with any unimolecular reaction, that is no S<sub>N</sub>1/E1, because primary carbocations are too unstable to be formed. Since primary substrates are very good candidates for S<sub>N</sub>2 reaction, so **S<sub>N</sub>2 is the predominant pathway when good nucleophile is used**. The only exception is that when big bulky base/nucleophile is used, E2 becomes the major reaction.

Examples of reactions for primary substrates:

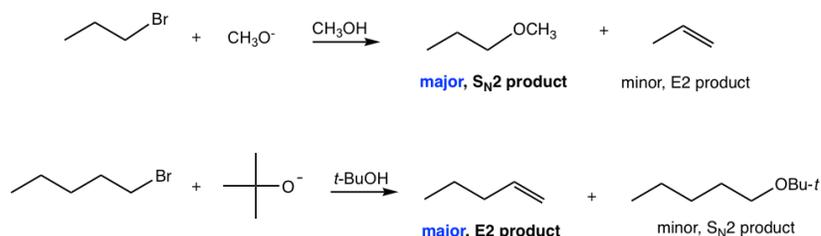


Figure 8.4a Reactions for primary substrates

### Secondary (2°)

It is most complicated or challenging to predict the reaction of a secondary substrate (2°), because all the pathways are possible. The reaction conditions then become very key factor. The total four types of reactions can be separated into 3 pathway, that is:

- **E2**: favored by a strong base
- **S<sub>N</sub>2**: favored by a good nucleophile (relatively weaker base)
- **S<sub>N</sub>1/E1**: It is hard to separate S<sub>N</sub>1 and E1 completely apart, because they both go through carbocation intermediates, and are favored by poor nucleophile/weak base, for example, H<sub>2</sub>O or ROH (solvolysis). Under such neutral condition, S<sub>N</sub>1 and E1 usually occur together for secondary substrates, and **increasing the reaction temperature favors E1 over S<sub>N</sub>1**.

It is relatively easy to separate S<sub>N</sub>2 and E2 pathways from S<sub>N</sub>1/E1, since both S<sub>N</sub>2 and E2 require strong nucleophile or strong base that are usually negatively charged species, while S<sub>N</sub>1/E1 require neutral conditions.

In order to distinguish S<sub>N</sub>2 from E2, we need to be able to determine whether a negatively charged anion is a strong nucleophile (for S<sub>N</sub>2) or a strong base (for E2)? All nucleophiles are potential bases, and all bases are potential nucleophiles, because the reactive part of both nucleophile and base is *lone pair electrons*. Whether an anion is a better nucleophile or a better base depends on its basicity, size and polarizability. Generally speaking, the relative stronger bases have the stronger tendency to act as base; and relative weaker base, with small size and good polarizability, have the better tendency to act as nucleophile, see the list given below.

Strong bases: OH<sup>-</sup>, RO<sup>-</sup>(R: small size alkyl group), NH<sub>2</sub><sup>-</sup>

Good nucleophiles (relatively weaker bases): Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>, RS<sup>-</sup>, N<sub>3</sub><sup>-</sup>, CN<sup>-</sup>, RCO<sub>2</sub><sup>-</sup>, RNH<sub>2</sub>

Please note that bulky bases, such as  $t\text{-BuO}^-$  and LDA, always favor E2 and generate elimination products that follow Hofmann rule, because they are too big to do back-side attack in  $\text{S}_{\text{N}}2$ .

Examples of reactions for secondary substrates:

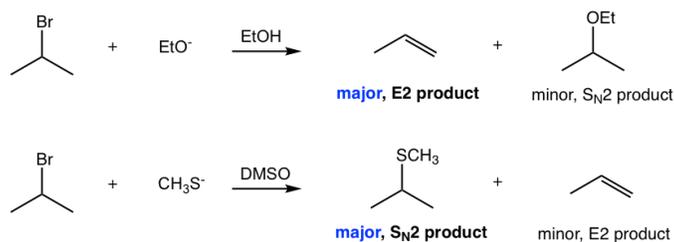


Figure 8.4b Reactions for secondary substrates

### Tertiary ( $3^\circ$ )

Tertiary ( $3^\circ$ ) substrates do not go with  $\text{S}_{\text{N}}2$  reactions because of steric hindrance. So E2 reaction is the choice when strong base applied, or  $\text{S}_{\text{N}}1/\text{E}1$  pathway with neutral condition (poor nucleophile/weak base). Theoretically speaking, E2 and E1 supposed to give the same elimination product. However, in order to synthesize an alkene from a tertiary substrate, it is a better choice to use a strong base that encourage E2 process rather go with E1. This is because that E1 always combine together with  $\text{S}_{\text{N}}1$ , and it is almost impossible to avoid the substitution product.

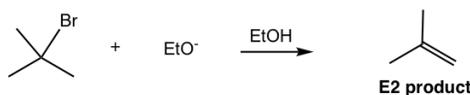


Figure 8.4c Reaction for tertiary substrates

The above discussions can be briefly summarized in the table below, followed by several examples. To predict the reaction outcome, or to design synthesis route for a certain case, it is highly recommend that you **do the analysis by following the logics mentioned above**, instead of just refer to the table. Also, practice makes perfect!

Substrate	Preferred Reaction Pathways
Methyl	$\text{S}_{\text{N}}2$ reaction
Primary	Predominantly $\text{S}_{\text{N}}2$ reaction; Exception: E2 reaction for bulky base
Secondary	

$\text{S}_{\text{N}}2$  reaction with good nucleophile (e.g.,  $\text{RS}^-$ ,  $\text{RCO}_2^-$ , etc)

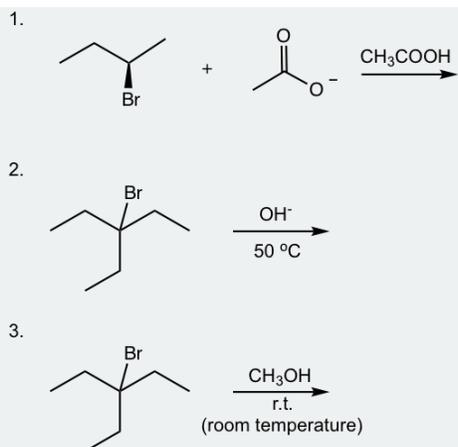
E2 reaction with strong base (e.g.,  $\text{OH}^-$ ,  $\text{OR}^-$ )

$\text{S}_{\text{N}}1/\text{E}1$  with neutral condition (e.g.,  $\text{H}_2\text{O}$ ,  $\text{ROH}$ )

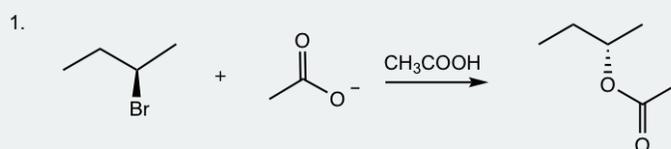
Tertiary E2 reaction with strong base (e.g.,  $\text{OH}^-$ ,  $\text{OR}^-$ )

$\text{S}_{\text{N}}1/\text{E}1$  with neutral condition (e.g.,  $\text{H}_2\text{O}$ ,  $\text{ROH}$ )

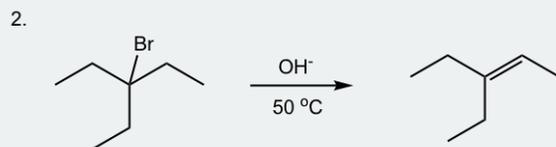
Show major organic product(s) for following reactions. Examples:



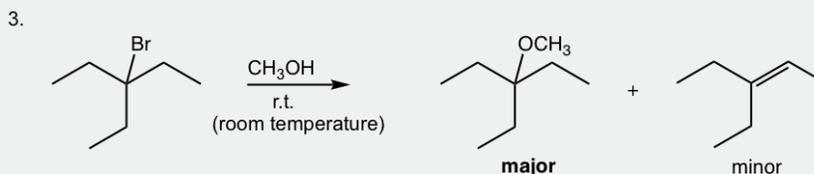
Solutions:



Secondary substrate, with good nucleophile, acetate, which is weak base, so  $S_N2$  is the major pathway. Configuration inverted at the chirality center.



Tertiary substrate with strong base  $OH^-$ , therefore  $E2$  is the major pathway. The high temperature facilitates the  $E2$  reaction.



Tertiary substrate in neutral condition, this is solvolysis.  $CH_3OH$  is weak nucleophile/weak base and the solvent, so the possible reactions are  $S_N1$  and  $E1$ . At this low temperature,  $S_N1$  is the major pathway, with bit  $E1$  product obtained.

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