Learning Guide for Chapter 10 - Alkyl Halides II

I. Elimination Reactions of Alkyl Halides

Introduction

Describe the result of a substitution reaction. Give an example.

halide is replaced by a Nu

How is an elimination reaction different? Give an example.

halide and H are removed, C=C remains

What does it mean to say that substitution and elimination reactions are competing reactions?

they occur under similar conditions

one or the other may be favored, or both may occur
Mechanisms

What are the two mechanisms by which elimination may occur?  E2 and E1

Consider the following mechanisms:

\[ \text{E2:} \]

\[
\begin{array}{c}
\text{acid} \\
\text{Br} \\
\text{H}
\end{array}
\quad + 
\begin{array}{c}
\text{base} \\
\text{O}^{-} \\
\text{K}^+
\end{array}
\rightarrow
\begin{array}{c}
\text{H} \\
\text{Cyclohexene}
\end{array}
+ 
\begin{array}{c}
\text{base} \\
\text{OH} \\
\text{K}^+ : \text{Br}^{-}
\end{array}
\]

Draw in the arrows to show how this reaction occurred.

What type of Lewis acid/base reaction is this?  **displacement**

How could this mechanism be described?  **deprotonate-push off**

Identify the acid and the base.

Why can the alkyl halide behave as an acid?  **halogen can leave, so e- can come in**

Why is the alkoxide a good base?  **negative charge, lone pair of e-, hindered, so it won't act as a Nu**

\[ \text{E1:} \]

\[
\begin{array}{c}
\text{acid} \\
\text{Br} \\
\text{H}
\end{array}
\rightarrow
\begin{array}{c}
\text{base} \\
\text{O}^{-} \\
\text{Br}^{-}
\end{array}
\rightarrow
\begin{array}{c}
\text{H} \\
\text{Cyclohexene}
\end{array}
+ 
\begin{array}{c}
\text{base} \\
\text{OH}
\end{array}
\]

Draw in the arrows to show how this reaction occurred.

What types of Lewis acid/base reactions occur?  **dissociation, displacement**

How could this mechanism be described?  **fall off  deprotonate-fall in**

Identify the acid and the base.

Why can the carbocation behave as an acid?  **there is an empty orbital, so e- can come in**
Beta hydrogens, constitutional isomers, and stereoisomers

What is the relationship between the halogen and the H that is removed? Why?

\[ \text{Br} : \text{base} \rightarrow \text{H} + \text{Br} : + \text{H-base} \]

on two C's that are next to each other (neighbors)

C=C can only be formed between 2 C's next to each other

Why can't the H on the same carbon as the halogen be removed?

\[ \text{can't happen} \quad \text{not stable} \]

only thing you could do - but won't happen - C- not stable

e- can't go in to form C=C
the other C already has 4 bonds

What is the relationship between the carbocation and the H that is removed?

\[ \text{H} + \text{base} \rightarrow \text{H} + \text{H-base} \]

on neighboring C same reason!

What is this relationship called?

carbons are labeled alpha, beta, etc
these are the beta hydrogens

Is it possible for there to be more than one set of beta hydrogens? yes!

all the same two different sets three different sets
What two elimination products could be formed from the following compounds? What is their relationship?

Not all isomers will be formed in equal amounts. Which are favored?

- **the most substituted**
- **the ones with the most C attached the to C=C**

Zaitsev's rule

What two elimination products could be formed from the following compounds? What is their relationship?

Which isomer will be favored? **E or trans > Z or cis**

Give all products of the following reactions. Indicate which is favored.

**no rxn! no beta H's**
E2 vs. E1

How are the E2 and E1 reactions the same? both need a leaving group and a base both lose an X and an H, both give a C=C

What are the two bases used in the examples? Which do you think is stronger, and why?

E2 stronger base - negatively charged

E1 weaker base - neutral

What are the two acids used in the examples? Which do you think is stronger, and why?

E2 weaker acid stable compound

E1 stronger acid incomplete octet very unstable

pK_a unknown

pK_a -2

How do the strengths of the acid and base go together?

E2 - stronger base, weaker acid

E1 - weaker base, stronger acid

Scenario A: strong base added to alkyl halide

base attacks! - E2

Scenario B: weak base added to alkyl halide

base can't attack, sits around waiting until alkyl halide dissociates, then attacks carbocation - E1

Following the pattern of the reactions given previously, draw the mechanisms for the following reactions:

1 step: deprotonate-push off

E2

step 1: fall off

E1

step 2: deprotonate-fall in
**Strong and Weak Bases**

What do nucleophiles and bases have in common? a pair of electrons that can attack

What is the difference between how the base attacks and how the nucleophile attacks?

- base attacks H's
- Nu attacks C's

Could one molecule act as both a nucleophile and a base? yes!

What do S_N2 and E2 have in common? 1 step, strong Nu or base

What do S_N1 and E1 have in common? more than one step, weak Nu or base carbocation formation

What factors make a nucleophile stronger?

- NaOH vs H_2O negative charge
- H_C≡CNa vs NaOH less EN atom
- NaSH vs NaOH bigger atom
- CH_3CH_2ONa vs (CH_3)_3COK less steric hindrance

How do these same factors affect the strength of bases?

- NaOH vs H_2O negative charge - stronger base same
- H_C≡CNa vs NaOH less EN atom - stronger base same
- NaSH vs NaOH bigger atom - weaker base opposite
- CH_3CH_2ONa vs (CH_3)_3COK less steric hindrance - no effect

Which reactions will the following molecules participate in?

- NaOH strong Nu or base - E2 and S_N2
- H_2O weak Nu or base - E1 and S_N1
\[ \begin{align*}
\text{E2 only - strong, steric hindrance, so no } S_N2 \\
\text{E1 only - weak, steric hindrance, so no } S_N1 \\
\text{E2 and } S_N2 \text{ - strong Nu or base} \\
\text{E2 and } S_N2 \text{ - strong Nu or base} \\
\text{ } S_N2 \text{ only - strong Nu but poor base - large atom} \\
\text{S_N2 only - strong Nu but poor base - large atoms} 
\end{align*} \]

**Rate laws**

Consider the following E2 reaction.

\[ \begin{align*}
\begin{array}{c}
\text{Br}^- \\
\text{K}^+ \\
\text{O}^-
\end{array}
\rightarrow
\begin{array}{c}
\text{C} \\
\text{H} \\
\text{C}
\end{array}
+ \\
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{Br}
\end{array}
+ \text{KBr}
\end{align*} \]

Draw the energy diagram for this reaction.

What is the rate-limiting step? What reagents are involved?  
the only step; both alkyl halide and base

Draw the structure of the transition state.

What would happen to the rate of the reaction if you  
doubled the concentration of the alkyl halide? rate would double  
doubled the concentration of the base? rate would double

What is the order of the alkyl halide? the base? the reaction?  
1st order in both  
2nd order overall

Write the write law: \[ \text{rate} = k[RX][\text{base}] \]

What does E2 stand for? elimination 2nd order
How does the halogen affect the reaction rate? Larger atoms have longer bonds which are easier to break, so they react faster

\[
\text{RI} \quad \text{> RBr} \quad \text{> RCl} \quad \text{> RF}
\]

How does the structure of the alkyl halide affect the rate?

- methyl
- \( \text{CH}_3\text{Cl} \)

No beta H's

Steric hindrance doesn't affect the ability to take a H

More substituted alkyl halides form more stable alkenes

Consider the following E1 reaction.

\[
\begin{align*}
\text{C}_7\text{H}_{15}\text{Br} & \quad \text{+ OH}^- \\
\rightarrow & \quad \text{C}_7\text{H}_{15}\text{H} + \text{Br}^- \\
\end{align*}
\]

Draw the energy diagram for this reaction.

Which is the rate limiting step?

- fall off - creating a C+

Which reagents are involved in the rate limiting step?

- only the alkyl halide

Draw the structure of the transition state for this step.

What would happen to the reaction rate if you

- doubled the concentration of the alkyl halide? rate would double
- doubled the concentration of the nucleophile or base? nothing!

What order is the alkyl halide? the base? the reaction?

- alkyl halide 1st order
- base 0th order
- 1st order overall

Write the rate law: \( \text{rate} = k[\text{RX}] \)

What does E1 stand for? Elimination 1st order
How does the halogen affect the reaction rate? longer bond is easier to break
RI  >  RBr  >  RCl  >>  RF  
(same for E2, E1, S_N1, S_N2)

How does the structure of the alkyl halide affect the rate?

- methyl
- CH_3Cl

no beta H's

more substituted alkyl halides form more stable carbocations

**Rearrangements**

Which elimination reaction has the possibility of rearrangements?  **E1**

Which alkyl halides are most likely to rearrange?  2° 3° - already as stable as it can get; 1° - don't usually form

What kinds of rearrangements can occur? alkyl shifts (usually methyl), hydride shifts

What rearrangement will occur in the following reactions? Draw the carbocation and the elimination products.

**hydride shift**

- weak, hindered base - E1 only

**methyl shift**

- no rxn
Stereochemistry

What types of stereoisomers can be formed in an elimination reaction?

\[ \text{E2} \quad (\text{CH}_3)_2\text{CO} \\
\text{or } (\text{CH}_3)_2\text{COH} \]

C=C diastereomers

What orientation is required in order for an E2 reaction to occur?

halide, H must be anti to each other

Which stereoisomer will be formed from the following alkyl halides?

What product would the enantiomer of the SM give?

same

Which stereoisomer will be formed from the following alkyl halide?

not a stereocenter

Since the Br can be opposite both H's, both products will form.

Under what conditions will an E2 reaction give only one stereoisomer?

if both C's are chiral, only one position in which H is anti to X
What orientation is required for an E1 reaction to occur? p orbital, H must be anti

either side of p orbital will work; both stereoisomers

How many stereoisomers will result from the following reactions?

- E1: two diastereomers
- E2: two diastereomers (plus rearrangements)
- E2: two diastereomers (plus rearrangements)
- E2: two diastereomers (plus rearrangements)
- E2: two diastereomers (plus rearrangements)
- E2: only one which? - use models!
- E2: only one same as above
- E2: only one opposite one
- E2: only one opposite one
Solvents

What kinds of solvents were best for $S_N2$ reactions? polar, aprotic

Why? solvent needs to dissolve ionic reactants, H-bonding with Nu slows it down

What kinds of solvents were best for $S_N1$ reactions? polar, protic

Why? H-bonding can help stabilize C+

Which of these is E2 most like? What kind of solvents would be best?

$S_N2$ - polar aprotic: acetone, acetonitrile, dimethylformamide (DMF)

Which of these is E1 most like? What kind of solvents would be best?

$S_N1$ - polar protic: water, alcohols

Eliminations of aryl and vinyl halides

Can aryl and vinyl halides undergo $S_N2$ or $S_N1$ reactions? nope!

Can aryl and vinyl halides undergo elimination? yes - but only with a much stronger base

- $\text{CH}_2=\text{CHCl}$: no reaction
- $\text{PhCl}$: no reaction
- $\text{CH}_2=\text{CHCl}$: (CH$_3$)$_3$COH → no reaction (CH$_3$)$_3$COH pKa 18
- $\text{PhCl}$: (CH$_3$)$_3$COH → no reaction NH$_3$ pKa 36
- $\text{CH}_2=\text{CHCl}$: NaNH$_2$ → + NH$_3$ Ch 13 - alkynes
- $\text{PhCl}$: NaNH$_2$ → unstable! Ch 18 - aromatic rings
## Summary of Elimination Reactions

<table>
<thead>
<tr>
<th>E2 reactions:</th>
<th>E1 reactions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>result: halide and H removed alkene formed</td>
<td>result: halide and H removed alkene formed</td>
</tr>
<tr>
<td>mechanism: 1 step</td>
<td>mechanism: 2 steps</td>
</tr>
<tr>
<td>deprotonate-push off</td>
<td>fall off deprotonate-fall in</td>
</tr>
<tr>
<td>reagent: strong base</td>
<td>reagent: weak base (often the solvent)</td>
</tr>
<tr>
<td>stereochemistry: anti elimination</td>
<td>stereochemistry: none</td>
</tr>
<tr>
<td>rate law: rate = k[RX][base]</td>
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<td>alkyl halides: 3° &gt; 2° &gt;&gt; 1° &gt;methyl RI &gt; RBr &gt; RCl &gt;&gt; RF</td>
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</tr>
<tr>
<td>rearrangements? no</td>
<td>rearrangements? yes</td>
</tr>
<tr>
<td>solvent: polar, aprotic</td>
<td>solvent: polar, protic (usually base)</td>
</tr>
</tbody>
</table>
II. Elimination vs Substitution

What does it mean to say that elimination and substitution are competing reactions?

they can both happen under the same conditions

you have to figure out which is fastest, or if there will be a mixture

What reagents does substitution require? alkyl halide, Nu

What reagents does elimination require? alkyl halide, base

Can some molecules act as nucleophiles or bases? yes

The following criteria can help us decide:

1) How can we choose between 1st and 2nd order reactions?

   strong Nu or base - $S_N^2$ or E2

   weak Nu or base - $S_N^1$ or E1

\[
\begin{align*}
\text{strong Nu/base} & : \quad \text{NaOH} \quad \rightarrow \quad S_N^2 \text{ or E2} \\
\text{weak Nu/base} & : \quad \text{H}_2\text{O} \quad \rightarrow \quad S_N^1 \text{ or E1}
\end{align*}
\]

   both substitution and elimination may occur; but one may be faster than the other

2) How can we choose between substitution and elimination reactions?

   A) use reaction rates

   $S_N^2$: $1^\circ > 2^\circ >> 3^\circ$ less steric hindrance reacts faster

   E2: $3^\circ > 2^\circ > 1^\circ$ more substituted alkene is formed faster

\[
\begin{align*}
1^\circ & \quad \text{Cl} - \quad \text{NaOH} \quad \rightarrow \quad \text{OH} & \quad S_N^2 \text{ only - faster than E2 with } 1^\circ \text{ RX}
\end{align*}
\]
S\(_N\)1: \(3^\circ > 2^\circ >> 1^\circ\) more stable C+ is faster

E1: \(3^\circ > 2^\circ >> 1^\circ\) more stable C+ is faster

B) Watch out for special cases

\(2^\circ\) \hspace{1cm} \begin{align*} \text{Na}^+ & \quad \overset{\text{strong Nu}}{\rightarrow} \quad \overset{\text{SN2 only}}{\text{good Nu, poor base, too large}} \quad \text{also thiolates} \end{align*}
Would it be possible to have a reaction in which no product was formed?

Summary:

<table>
<thead>
<tr>
<th></th>
<th>strong Nu</th>
<th>weak Nu</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;o&lt;/sup&gt; RX</td>
<td>$S_{N2}$</td>
<td>no rxn</td>
</tr>
<tr>
<td>2&lt;sup&gt;o&lt;/sup&gt; RX</td>
<td>$S_{N2}$ and E2</td>
<td>$S_{N1}$ and E1</td>
</tr>
<tr>
<td>3&lt;sup&gt;o&lt;/sup&gt; RX</td>
<td>E2</td>
<td>$S_{N1}$ and E1</td>
</tr>
</tbody>
</table>

exceptions: tert-butoxide or tert-butyl alcohol - elimination only
halides and thiolates - substitution only
no beta H's - substitution only
benzylic RX - 1<sup>o</sup> C+ ok
III. Synthesis Using Elimination

What kinds of functional groups can be made using substitution reactions?

nitriles, alkynes, alcohols, ethers, thiolates, other alkyl halides

What kinds of functional groups can be made using elimination reactions?

alkenes

What starting materials and reagents could be used to make the following compounds?

In order to have a good synthesis, what must be true?

reaction should be fast
no other major products formed

What will go wrong in the following examples? What can be done about it? Rewrite the reaction so that it will work (if possible).

interference from substitution - use hindered reagents
too hindered for $S_N2$
2) constitutional isomers - choose alkyl halide carefully
stereoisomers - nothing (yet)

3) rearrangements - avoid E1 mechanism by using a strong base

4) slow - 1° alkyl halide - choose a different one

Write a good synthesis for the following compounds, or explain why you can't.

2 products :)
correct product :)

2 products :
1° - too slow
neither is a good synthesis