Alkyl Halides

Substitution and Elimination

• halides mainly undergo **SUBSTITUTION** and **ELIMINATION** reactions

\[
\text{LB: } \begin{array}{c}
\text{C} \quad \text{C} \\
\text{X} \quad \text{X} \\
\end{array} \rightarrow \begin{array}{c}
\text{LB} \\
\text{C} \\
\end{array} + \begin{array}{c}
\text{X} \\
\text{X} \end{array}
\]

\[
\text{LB: } \begin{array}{c}
\text{C} \quad \text{C} \\
\text{X} \quad \text{X} \\
\end{array} \rightarrow \begin{array}{c}
\text{LB} \\
\text{H} \\
\end{array} + \begin{array}{c}
\text{CC} \\
\text{H} \\
\end{array} + \begin{array}{c}
\text{X} \\
\text{X} \end{array}
\]

1 Nomenclature

• Look for the longest chain that **CONTAINS** the MAXIMUM NUMBER of functional groups, in this case the halogen is the functional group and so even though the cyclohexane has more carbon atoms, the main chain is the two carbon ethane chain

\[
\begin{array}{c}
\text{Br} \\
\text{C} \\
\end{array}
\]

• named as a substituted alkyl bromide

2 Second Order Nucleophilic Substitution (SN2) Reaction

**SUBSTITUTION** by **making a new bond AT THE SAME TIME as breaking the old bond**

• substitution requires a bond to be broken AND a new bond to be formed

• the LOWEST energy way of doing this (unless precluded by steric or other effects, see later) is to **MAKE THE NEW BOND** (getting some energy "back") at the same time as **BREAKING THE OLD BOND**, this is **SN2**

Example

\[
\begin{array}{c}
\text{HO} \\
\text{Et} \\
\text{Me} \\
\end{array} \rightarrow \begin{array}{c}
\text{C} \\
\text{Br} \\
\end{array}
\]

• This is fundamentally just a Lewis acid/base reaction of the kind we saw when we were learning about Lewis acid/base reactions, the Lewis base has the high energy chemically reactive electrons, which are used to make a new bond to the Lewis acid, and a stronger bond is formed (C-O in the example above) and a weaker bond is broken (C-Br above)

• HO– is the Lewis Base and **Nucleophile**

• the halides is the Lewis acid/electrophile

• the Br– anion is the **Leaving Group**

• The reaction "goes" because....

1) a weaker bond is converted into a stronger bond
2) A stronger base (–OH) is converted into a weaker base (Br–).

3) In this way higher energy electrons are converted into lower energy electrons.
   - Reactions in which all bonds are made and broken at the same time are called **concerted**.
   - The reaction also proceeds with inversion (i.e., backside attack, think about an umbrella turning inside out in the wind!), called a Walden inversion. Often this will lead to a change in absolute configuration, i.e., R to S or vice versa, but not necessarily!

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**Why the Name Second Order Nucleophilic Substitution (SN2)?**

**SN** - Substitution reaction

**N** - Nucleophile does the substitution (like a Lewis base, but see below)

2- kinetically 2nd order, because both the nucleophile and the halide are involved in the *rate determining step*.
   - In this reaction, there is only one step, it is **concerted**, and both the halide and the nucleophile are involved in this step, and so the reaction rate depends upon the concentration of both, the reactions is kinetically second (2nd) order.

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**What is a Nucleophile and How is it Different from/Same as a Base?**

---

**Visualize the Walden Inversion**
**Definition of a BASE**

\[
\text{H}_3\text{C}^- + \text{H}^+ \rightleftharpoons \text{H}_3\text{C}^+ \tag{1}
\]

- **Lewis/Bronsted base** strength measured by size of \(K_{eq}\) (thermodynamic definition)
- **stronger base** means stronger new bond means **more exothermic reaction** larger \(K_{eq}\)
- **weaker base** means weaker new bond means **less exothermic** (or more endothermic) smaller \(K_{eq}\)

**Definition of a NUCLEOPHILE**

\[
\text{H}_3\text{C}^- + \text{H}_3\text{C}^- \rightleftharpoons \text{H}_3\text{C}^- \tag{2}
\]

- **Nucleophile** strength measured by size of rate constant \(k\) (kinetic definition)
- **stronger nucleophile** means smaller \(E_a\) (stronger partial bonds), larger \(k\), **faster reaction** rate
- **weaker nucleophile** means larger \(E_a\) (weaker partial bonds), smaller \(k\), **slower reaction** rate

**All nucleophiles are Lewis bases**, the Hammond postulate says that strong bases should also be strong nucleophiles, and this is generally true, although we will meet a few important exceptions later.....

**Nucleophile (nucleus loving), donates electrons**

**Electrophile (electron loving), accepts electrons**

Why are we concerned with kinetics now? We have already seen that when there is a competition between reactions the fastest reaction “wins” (e.g. the most stable intermediate is formed fastest), in other words MOST organic reactions are controlled by kinetics, they are KINETICALLY CONTROLLED. For this reason it makes sense to start talking about nucleophiles and electrophiles, because their definition is based on kinetics. Of course, most strong nucleophiles react fast BECAUSE they are also strong bases and have very exothermic reactions (although there are some exceptions). We will often use the terms nucleophile/electrophile and Lewis base/acid interchangeably.

**Examples of SN2 Reactions**: Give the major organic product in the following reactions

- we understand these SN2 reactions a simple Lewis acid/base processes
- identify the Lewis base/NUCLEOPHILE as the reactant with the high energy electrons
- the Lewis acid/nucleophile must react with the Lewis acid/ELECTROPHILE

\[
\text{Br}^- + \text{Na}^+ \text{C} = \text{N}^- : \text{DMF (solvent)} \tag{3}
\]

\[
\text{Br}^- + \text{Na}^+ \text{C} = \text{CCH}_3^- : \text{CH}_3\text{CN (solvent)} \tag{4}
\]

\[
\text{Br}^- + \text{Na}^+ \text{O}^- : \text{acetone (solvent)} \tag{5}
\]
• IMPORTANT POINT: SN2 reactions are one of the most important ways of MAKING NEW BONDS, i.e. of transforming one organic molecule into another one

2.1 Factors Controlling SN2 Reactivity: Leaving Group Ability
Good leaving groups are:
• stable as an anion
• generally weak bases (stable as an anion, have weak X-H bonds)
• polarize the C–LG bond (and are polarizable to make strong partial bonds in transition state)

![Chemical structures and equations]

Example: tosylate as a leaving group:

![Chemical structure and reaction]

2.2 Factors Controlling SN2 Reactivity: Solvent Effects
Nucleophile strength (ability of the nucleophile to donate electrons in transition state depends upon SOLVENT
• Solvent effects on reactions are often DRAMATIC, the possible crucial role of solvent is a new concept for us
• A complication: solvent effects are different for nucleophiles of different sizes (see below)

<table>
<thead>
<tr>
<th>Polar Protic (Hydrogen-bonding) Solvents</th>
<th>dielectric constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>water</td>
<td>78</td>
</tr>
<tr>
<td>methanol</td>
<td>33</td>
</tr>
<tr>
<td>ethanol</td>
<td>24</td>
</tr>
<tr>
<td>i-propanol</td>
<td>18</td>
</tr>
</tbody>
</table>

* dielectric constant measures solvent "polarity" but not H-bonding ability
* PROTIC SOLVENTS can undergo HYDROGEN-BONDING
* polar protic solvents solvate small anions VERY WELL, but solvate larger anions LESS WELL
* anion reactants and products tend to be solvated well, BUT, the transition state is LARGE, and is thus much less solvated
• there is often a LARGE solvation energy difference between reactants and the transition state, particularly when using small anionic nucleophiles in a polar protic solvent
• you NEED TO KNOW the polar protic solvents, but this is easy because they are essentially all alcohols
• even though polar protic solvents are not the best for SN2 and E2, SN2 reactions can be performed in these solvents if convenient

**Polar Aprotic (NON Hydrogen-bonding) Solvents**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Dielectric Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetonitrile</td>
<td>36</td>
</tr>
<tr>
<td>dimethylformamide (DMF)</td>
<td>37</td>
</tr>
<tr>
<td>hexamethylphosphoramide (HMPA)</td>
<td>30</td>
</tr>
<tr>
<td>dimethylsulfoxide (DMSO)</td>
<td>49</td>
</tr>
<tr>
<td>acetone</td>
<td>21</td>
</tr>
</tbody>
</table>

• **APROTIC SOLVENTS** do NOT have hydrogen atoms that undergo Hydrogen Bonding
• polar aprotic solvents solvate anions well, but particularly for ANIONS, NOT AS WELL as POLAR PROTIC solvents
• For this reason, there is a usually a SMALLER energy difference between reactants and the transitions state when SN2 reactions are performed in polar APROTIC solvents, SN2 reactions in polar APROTIC solvents are usually faster than in polar protic solvents (but see further below)
• you NEED TO KNOW the polar APROTIC solvents, this is not easy because they are different structures, learn them by working with them

**Medium and Nonpolar Solvents**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Dielectric Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>hexane</td>
<td>1.9</td>
</tr>
<tr>
<td>chloroform</td>
<td>4.7</td>
</tr>
<tr>
<td>benzene</td>
<td>2.3</td>
</tr>
<tr>
<td>ethyl acetate</td>
<td>6</td>
</tr>
<tr>
<td>diethyl ether</td>
<td>4</td>
</tr>
<tr>
<td>carbon tetrachloride</td>
<td>2.2</td>
</tr>
<tr>
<td>cyclohexane</td>
<td>2.0</td>
</tr>
</tbody>
</table>

• Medium and in particular non-polar solvents are commonly used in organic chemistry, but not so much for SN2 reactions, since these often involve ionic reactants that will simply not dissolve in non-polar solvents

**Example**

\[
\begin{align*}
\text{H}^- & \quad \text{H}_3\text{C}^-\text{Br} & \xrightarrow{\text{CH}_3\text{CN}} & \text{H}_3\text{C}^-\text{OH} + \text{Br}^- \\
\text{H}^- & \quad \text{H}_3\text{C}^-\text{Br} & \xrightarrow{\text{MeOH}} & \text{H}_3\text{C}^-\text{OH} + \text{Br}^-
\end{align*}
\]
• explain the difference in reaction rates using a reaction energy diagram

![Reaction energy diagram](image)

• here we have TWO reactions on one diagram. The ABSOLUTE energies of the two systems are very different, thus we need to NORMALIZE the energies and plot RELATIVE ENERGY. Where to normalize? In general we will want to emphasize the places where the energies are different and where they are similar. In this case the energies at the start and end are different due to large differences in anionic solvation, and the energies at the transition states are more similar due to small differences in solvation, thus we normalize at the transition state

2.3 Factors Controlling SN2 Reactivity: Nucleophilicity

**Good nucleophiles:**
• donate electrons
• make strong partial bonds in the transition state

**Comparing same atom (charged versus non-charged), anions make stronger nucleophiles than neutrals**

\[
\begin{align*} 
\text{H}_3\text{C}-\overset{\ominus}{\text{O}}: & \quad \text{H}_3\text{C}-\text{Br} \\
\text{H}_3\text{C}-\overset{\ominus}{\text{O}}: & \quad \text{H}_3\text{C}-\text{Br} 
\end{align*} 
\]

• higher energy electrons on negatively charged oxygen, more reactive, faster

**Comparing similarly sized atoms (across the periodic table), electronegative atoms make poor nucleophiles**

\[
\begin{align*} 
\text{H}-\overset{\ominus}{\text{O}}: & \quad \text{H}_3\text{C}-\text{Br} \\
\text{F}-\overset{\ominus}{\text{F}}: & \quad \text{H}_3\text{C}-\text{Br} 
\end{align*} 
\]

• lower energy electrons on electronegative fluorine, the fluorine "holds" its electrons, less reactive

**Comparing differently sized atoms (down the periodic table)**
• A NEW CONCEPT. Larger atoms have more polarizable electrons, they do not have to "get so close" too make a bond, can make "longer" bonds, and thus can make stronger PARTIAL BONDS in the transition state
4. Large atomic size over small atomic size in protic solvents
3. Small atomic size over large atomic size in aprotic solvents
2. Less electronegative over more electronegative
1. Anion over neutral

Nucleophilicity order: $I^-$

Example: compare halide anions in polar aprotic solvent (or even gas phase!)
• Nucleophilicity order: $F^-$ > $Cl^-$ > $Br^-$ > $I^-$ (same order as basicity)

- Larger, more polarizable iodide forms stronger partial bonds in $\ddagger$, which is opposite to basicity effect
- But basicity still wins; iodide simply doesn't make a strong enough bond in the product
- Nucleophilicity follows (Lewis) basicity here, the stronger base is the better nucleophile
- To emphasize the difference due to basicity, the curves are normalized to show difference in exothermicity

Example: compare halide anions in polar protic solvent
• Nucleophilicity order: $I^-$ > $Br^-$ > $Cl^-$ > $F^-$ (Reversed order compared to basicity!)

- The larger more polarizable iodide forms stronger partial bonds in $\ddagger$, opposite to basicity
- And, the large iodide anion is not solvated well (not stabilized) by the polar protic solvent, more reactive
- Here nucleophilicity is opposite to basicity, solvation and polarization effects "win" over exothermicity
- To curves emphasize the difference in solvation of the nucleophilic ions

Summary: Nucleophilicity order is sometimes difficult to remember, but favored by.....
1. Anion over neutral
2. Less electronegative over more electronegative
3. Small atomic size over large atomic size in aprotic solvents
4. Large atomic size over small atomic size in protic solvents

Example
2.4 Factors Controlling SN2 Reactivity: F.M.O. Theory and Steric Effects

First, take a closer look at how reaction occurs, where do the electrons from the nucleophile "go" (at first)?
- We will use a more detailed form of Lewis acid/base theory, Frontier Molecular Orbital (F.M.O.) theory
- FMO theory is an advanced topic that we will return to later in the course, but a simple version is useful here
- We need to make a BOND between two molecules
- We learned that making bonds between ATOMS requires overlap of ATOMIC orbitals IN PHASE to generate a new BONDING molecular orbital
- Here we will make a bond between MOLECULES by overlapping MOLECULAR orbitals IN PHASE to generate a new BONDING molecular orbital
- F.M.O. theory looks at the overlap between MOLECULAR orbital with the highest energy electrons (the HOMO) of nucleophile, with the lowest energy MOLECULAR orbital of the electrophile (the LUMO)
- The HOMO is where the reactive Lewis basic electrons "are", the anti-bonding LUMO is the only orbital that the electrons can "go to" in the electrophile, all of the bonding orbitals are full of electrons

\[
\text{Nu} \quad \text{Nu} \\
\text{Nu} \quad \text{Nu}
\]

- The provides the BEST explanation for "backside attack", HOMO/LUMO overlap best at the carbon "end" of the halide LUMO
- for this reason, reaction suffers "steric hindrance" when R1, R2, R3 are large

\[
\begin{align*}
\text{C} & \quad \text{C} \\
\text{CH}_2 & \quad \text{CH}_2
\end{align*}
\]

- SN2 reactions get slower with increasing steric hindrance at the backside of the carbon of the electrophile
- To the extent that there is NO SN2 REACTION at a TERTIARY halide
- SN2 reactions at METHYL and ALLYLIC carbons are particularly facile (see below)

\[
\text{Nu} : \quad \text{Nu} ; \quad \text{Nu} ;
\]

- There is also NO SN2 at a tertiary or vinyl carbons because the nucleophile cannot get close enough to form reasonable partial bonds in the transition state due to a steric effect at the other alkyl substituents on the C atoms
- The vinyl C(sp2)-X sigma* orbital is smaller than a C(sp3)-X sigma* orbital, weakens any potential partial bond
- The vinyl C(sp2)-X bond is stronger than a corresponding C(sp3)-X bond
- SN2 at the allylic position is FASTEST because the transition state is resonance stabilized, lowering the energy of the electrons in the transition state
A lower energy transition state means a smaller activation energy which results in a faster reaction.

ANOTHER example of a steric effect is provided by the nucleophile

\[
\begin{align*}
\text{H}_3\text{C}^- & > \text{H}_3\text{CH}_2\text{C}^-\text{O}^- > \text{H}_3\text{C}^-\text{H}^-\text{O}^- > \text{H}_3\text{C}^-\text{C}^-\text{O}^- \\
\end{align*}
\]

A good example of difference between basicity and nucleophilicity, t-butoxide is a very strong base (it forms a strong bond to a small proton), but a weak nucleophile, since it can't form a strong partial bond in the transition state with carbon. SN2 is not possible using the t-butoxide anion.

3 First Order Nucleophilic Substitution (SN1) Reaction

- What happens if we try to do an SN2 reaction with a very weak (e.g. neutral) nucleophile Lewis base? Example

\[
\begin{align*}
\text{H}_3\text{C}^- \text{C}^-\text{Br}^- + \text{H}_3\text{C}^-\text{O}^- (\text{solvent}) & \xrightarrow{\Delta} \text{H}_3\text{C}^-\text{C}^-\text{O}^- \text{H}^- \\
\end{align*}
\]

- here we have a nucleophilic substitution reaction BUT......
- we have a 3° halide which is a weak electrophile (backside attack is not possible), can't do SN2
- H₂COH is a weak nucleophile (no negative charge on the oxygen), shouldn't do SN2
- H₂COH is also a PROTIC solvent, which should be slow for SN2
- here the solvent "helps" to break the C–Br bond, the reaction is a solvolysis reaction (lysis - bond breaking)

We need a new substitution MECHANISM to account for this: The SN1 Mechanism

- although the alcohol is a weak LB/Nucleophile, the first cation intermediate is a STRONG LA/Electrophile, and so nucleophilic addition at this step in the mechanism is fast
- the SN1 reaction requires a polar protic solvent to stabilize the ionic (cation and halide) intermediates
- usually requires heat (energy) to break the C–X bond unimolecularly
• ONLY the halide (not the nucleophile) involved in the R.D.S., thus **SN1** (1 means only 1 reactant in the R.D.S.)
• requires a stable intermediate cation, NO SN1 for methyl or primary halides

![Cation Rearrangements in SN1 Reactions](image)

• No SN1 (OR SN2) at sp2 hybridized carbons, the C-X bond is too strong and the cations are too unstable
• In general, SN1 will always occur in preference to SN1 since this makes a bond at the same time the bond is broken, unless SN2 is impossible (e.g. at a 3° carbon)

**3.1 Stereochemistry of SN1 Reactions: Racemization (?)**

**Example**

![Example Reaction](image)

• We expect racemization, or at least some loss of stereochemistry for SN1 compared to SN2
• depending upon conditions/reactants, attack on the same side as the leaving group may be hindered, resulting in a slight excess of the inversion product
• in reality, however, it is not easy to predict exactly how much stereochemistry will be lost, and so we will use the "rule" in this course that if the reaction goes via SN1 we will assume that racemization always occurs

**3.2 Cation Rearrangements in SN1 Reactions**

**Example**

![Example Reaction](image)

• Once the cation is made it will react the same as any other cation, and so this cation will rearrange
3.3 Distinguishing SN1 and SN2 Reactions

$S_N2$ favored by:

$S_N1$ favored by:

- NOTE: the factors above favor the reactions by making them go faster, e.g. SN2 is FASTER at a primary carbon, SN1 is faster at a tertiary carbon, SN1 is faster in polar protic solvents etc.
- However, weak nucleophiles do not favor SN1 because they make Sn1 reactions faster, they don’t, but they do make competing SN2 reactions SLOWER
- SN2 reactions are not precluded by polar protic solvents, they are just faster in aprotic solvents

Examples: assign the mechanism of the following reactions to $S_N1$ or $S_N2$

\[
\begin{align*}
\text{H}_3\text{C}\text{Br} & \quad \text{Na}^+\text{CN}^- \quad \text{DMF} \quad \text{H}_3\text{C}\text{C}=\text{N}^- + \text{Na}^+\text{Br}^- \\
\text{CH}_3\text{OH} & \quad \text{heat} \quad \text{MeO}^- \\
\text{Na}^+\text{SPh} & \quad \text{CH}_3\text{CN} \quad \text{SPh} \\
\end{align*}
\]

Example Problems: Give the major organic product of reactions

\[
\begin{align*}
\text{:Cl} & \quad \text{:Br} \quad \text{K}^+\text{SCH}_3 \quad \text{CH}_3\text{CN} \\
\end{align*}
\]

- polar aprotic solvent, strong nucleophile, SN2, Br- better leaving group
- 1 equivalent means exactly the same number of nucleophiles as organic reactants, which in this context means that there is only enough nucleophile to substitute one of the halide leaving groups

\[
\begin{align*}
\text{EtOH} & \quad \text{boil} \\
\end{align*}
\]

- polar protic solvent and heat, no strong nucleophile and allylic halide, must be SN1. Need to draw the mechanism to be sure of the product!
- polar aprotic solvent, strong nucleophile, SN2, allylic position more reactive
- 1 EQUIVALENT will ONLY REACT at the carbon where SN2 will be fastest

### 4 E2 Elimination Reaction

**Here is a reaction that we now know.....**

- what about this one? SN2 is not possible here (3° bromide), yet there certainly IS a reaction

- does E2 instead!!
- breaks weak C–Br bond and strong C–H bond, makes strong O-H bond and C=C pi bond
- not as exothermic as SN2, but... converts 2 molecules into 3, favored by entropy AND "converts" strong -OH base into weak -Br base, this lowers the energy of these electrons, which also helps
- Just like SN2, all bonds made and broken at the same time (all four!)
- Concerted reaction, no intermediates, 1 transition state
- the -OH acts as a Brønsted base, a STRONG base is required for E2! Really, we are using the chemical potential energy (reactive electrons) in the string base to "drive" this reaction, to make it "go"
- The reaction is CONCERTED (all bonds are made and broken at the same time)

### 4.1 Product Selectivity in E2: Saytzeff Rule (Or Zaitzev, etc.)

- **Saytzeff Rule**: Most substituted alkene formed, if possible

**Example**
• When more than one alkene isomer can be formed in an E2 elimination, the more substituted, more stable alkene isomer is usually formed (see an exception below), this more substituted alkene is called the Sayetzeff alkene, after the Russian chemist of the same name
• His name was translated differently from the Cirillic into Roman alphabet in different countries, hence Sayetzeff can be spelled multiple ways, Zaitsev is another common spelling
• consider how these two E2 products are formed

Recall: The most substituted alkene is always the most stable alkene isomer
• the Sayetzeff alkene is the most substituted of all possible structurally isomeric alkenes that can be formed in an elimination reaction
• E2 eliminations will always form the Sayetzeff alkene unless there are severe steric inhibitions, see further below

### 4.2 Reactivity Order for E2
• decreasing reactivity order: $3^\circ > 2^\circ > 1^\circ$ halide

**Example**

```
\[ \text{Br} \quad \text{Br} \quad \text{Br} \]
\[ \text{Na}^+ \quad \text{OMe} \quad \text{DMF} \]
\[ \text{Br} \quad \text{Br} \quad \text{Br} \]
\[ \text{Na}^+ \quad \text{O-t-Bu} \quad \text{DMF} \]
\[ \text{Br} \quad \text{Br} \quad \text{Br} \]
\[ \text{Na}^+ \quad \text{O-t-Bu} \quad \text{DMF} \]
```

• elimination from a $3^\circ$ halide tends to give a more substituted alkene product, tends to be faster
• this is one way that we can easily distinguish the possibilities of SN2 versus E2, there is simply no SN2 at a tertiary halide, but E2 eliminations tend to be facile (assuming a strong enough base)

### 4.3 Stereochemistry of E2 Reaction
• Again, F.M.O. theory provide a very informative picture
• We need to make and break ALL FOUR bonds at the same time, the reaction is concerted
• We need to make the new bonds by **overlapping the HOMO and the LUMO IN PHASE to make new bonding molecular orbital**
the 2 sigma M.O.s on the central carbons (associated with the breaking C-H and C-Br bonds) become the pi M.O.s (bonding and antibonding)
• the 2 sigma M.O.s therefore must be parallel in order to be able to make the new pi-bond
• the H and leaving group (Br) must be coplanar (periplanar), and preferably "anti"
• the electrons in the breaking C-H sigma bond are used to make the new pi-bond, overlap occurs with the anti- bonding M.O. associated with the breaking C-Br bond best as shown, i.e. analogous to "backside attack" in the SN2 reaction, this is the origin of the requirement for ANTI- in addition to co-planar
• Only One conformation will tend to be reactive in an E2 Reaction

![Diagram](image)

• the reactive conformation must be attained BEFORE reaction can occur

Example: give the major products of the E2 reactions of:
(1R)-bromo-(1,2R)-diphenylpropane AND (1R)-bromo-(1,2S)-diphenylpropane

![Structure](image)

unreactive conformation

anti-coplanar conformations

E2

• The reaction is STEREOSELECTIVE, different isomeric halides give different isomeric alkenes because the reaction is CONCERTED

Example: give the major product of the E2 reaction of (1R)-iodo-(2S)-methylcyclohexane

![Structure](image)
Example: give the major product of the E2 reaction of the following compound

\[
\begin{array}{c}
\text{Me}_3\text{C} - \text{Br} \\
\end{array}
\]

\[
\text{t-Bu} = \begin{array}{c}
\text{t-Bu} \\
\text{HO}^{-} \\
\text{Me}
\end{array}
\]

Example: give the major product of the following reaction......

\[
\begin{array}{c}
\text{Me}_3\text{C} - \text{Br} \\
\end{array}
\]

\[
\text{EtO}^{-} \text{Na} \rightarrow \text{acetone}
\]

\[
\begin{array}{c}
\text{Me}_3\text{C} - \text{Br} \\
\text{t-Bu}
\end{array}
\]

• Br is "locked" equitorial because of the t-butyl group, NO E2, only SN2 possible, E2 NOT possible in this case

5 E1 Elimination Reaction

• elimination initiated by 1st-order heterolysis
Example: a 3° halide with a poor nucleophile, poor Brønsted base and in a polar protic solvent

\[
\begin{array}{c}
\text{CH}_3 \\
\text{H}_3\text{C}-\text{C} - \text{Br} \\
\text{CH}_3
\end{array}
\]

\[
\text{H}_2\text{O} \rightarrow \text{heat}
\]

• the intermediate cation is a strong electrophile AND strong Brønsted acid
• SN1 and E1 are often competitive
• Difficult to select for E1 (high temperature can help due to entropy effect), i.e. not useful "synthesis" reaction

Example: Give the expected ELIMINATION products (ignore substitution) under the following conditions

\[
\begin{array}{c}
\text{Ph} \\
\text{Me}
\end{array}
\]

\[
\text{EtOH/heat} \rightarrow \text{E1 Conditions}
\]

\[
\text{Ph} \\
\text{Me}
\]

\[
\text{Cl} \\
\text{Na}^{+} \text{-O-t-Bu} \rightarrow \text{DMF (E2 conditions)}
\]
6 Distinguishing E1, E2, SN1 and SN2 Reactions

- Reality - the mechanisms are often mixed: However, favored conditions are........
  
  S\(_{\text{N2}}\) - 1° halide, aprotic solvent, strong nucleophile, weak base
  
  S\(_{\text{N1}}\) - 3° halide, protic solvent, weak nucleophile, weak base
  
  E2 - 3° halide, aprotic solvent, weak nucleophile, strong base
  
  E1 - 3° halide, protic solvent..... difficult to favor!

Strong Base but Weak Nucleophile? What is this?

- The tert-butoxide anion makes a strong bond to (for example) a proton, just as strong a bond as the methoxide anion, they are equally strong bases
- However, the t-butoxide anion is not a strong nucleophile, it undergoes SN2 reactions very slowly (remember the definition of nucleophilicity is based on how FAST a reaction is, not how exothermic it is) due to steric interactions associated with the t-butyl group, SN2 reactions are sterically hindered, it is a BULKY BASE
- t-butoxide is a strong bulky base that is a weak nucleophile, this can be used to direct E2 reactions over competitive SN2 reactions, we will see other bulky bases as we work through the course

Examples: What was the mechanism that resulted in the PROVIDED organic product? (there may be other reaction products, but the questions ask about the provided ones only)

Example: give the major products of the following reactions and identify the reaction mechanisms
• there is no REQUIREMENT for an SN2 reaction to be in a polar aprotic solvent, they are faster in aprotic solvents but in reality many are actually performed in protic solvents for convenience

![SN1 and E1 reaction](image)

• secondary halides don't favor any mechanism in particular and often undergo more than one reaction

![Secondary halide reaction](image)

• it is usually a good idea to draw out at least a partial mechanism when carbocation intermediates are involved to avoid missing any rearrangements
• SN1 and E1 are often competitive, unless elimination is not possible because there are no adjacent hydrogen atoms

![SN1 and E1 reaction with carbocation](image)

• elimination is not possible in this case

![Elimination reaction](image)
• note the use of the t-butoxide anion BULKY BASE to force E2 elimination for E2 eliminations where there is stereochemistry in the reactant, you will usually have to setup the correct conformation for elimination (anti-coplanar) in order to get the correct stereochemistry in the alkene product

7 Elimination Using Bulky (Sterically Hindered) Bases
• The products of E2 eliminations can be different for 2 versus 3° halides with or without bulky bases

Examples

Transition states explain product distribution
• the FASTEST reaction occurs, the reaction is KINETICALLY CONTROLLED

• the transition state for formation of the MAJOR product has CH₃-H electron repulsion/steric effects, which costs LESS energy that CH₃-CH₃ electron repulsions/steric effects below, the transition state is thus lower in energy, the reaction is faster and this reaction forms the MAJOR product

• the transition state for formation of the minor product has CH₃-Ch₃ electron repulsion/steric effects, which costs MORE energy that CH₃-H electron repulsions/steric effects in the reaction that forms the major product, the transition state is thus higher in energy, the reaction is slower and this reaction forms the minor (Hoffman) product
Summary:
• a NON-BULKY with a 3° halide forms the MOST substituted alkene (normal Saytzeff product)
• BUT, a BULKY BASE with a 3° HALIDE forms the LEAST SUBSTITUTED alkene (Hofmann product) for
  steric reasons

8 Elimination in Alcohols: E1 and E2 in a new Context
• E1 and E2 eliminations are observed in systems other than alkyl halides with strong bases
  The reaction

\[
\text{H : OH} \quad \xrightarrow{\text{conc. H}_2\text{SO}_4, \text{heat}} \quad \text{H}_2\text{O} \quad \text{C} = \text{C} = \text{C} \quad \xrightarrow{\text{conc. H}_2\text{SO}_4, \text{heat}} \quad \text{H}_2\text{O} \quad \text{C} = \text{C} = \text{C} \\
\]

• note a special kind of SOLVENT EFFECT here! In an aqueous medium, acid catalyzes water ADDITION to the
  alkene to make an alcohol. In conc. sulfuric acid medium, the acid helps to REMOVE water from an alcohol to
  make an alkene (the sulfuric acid DEHYDRATES the alcohol)
• Alternate reagents and conditions are H2SO4/P2O5, and others....

Mechanism: you already know it - either an E1 or an E2 elimination!
• in the mechanism, H2O is the leaving group, −OH is a poor leaving group (this is an important general principle
  that we will return to again later....)

\[
\text{H : OH} \quad \xrightarrow{\text{conc. H}_2\text{SO}_4, \text{heat}} \quad \text{H}_2\text{O} \quad \text{C} = \text{C} = \text{C} \quad \xrightarrow{\text{conc. H}_2\text{SO}_4, \text{heat}} \quad \text{H}_2\text{O} \quad \text{C} = \text{C} = \text{C} \\
\]

• in general, small neutral molecules such as water make excellent leaving groups, since they tend to contain low
  energy electrons, we will see this again

Example: Secondary (2°) and Tertiary (3°) Alcohols: E1 elimination (with rearrangement...)

\[
\text{Sayetzeff major} \quad \xrightarrow{\text{conc. H}_2\text{SO}_4, \text{heat}} \quad \text{Sayetzeff major} \quad \xrightarrow{\text{conc. H}_2\text{SO}_4, \text{heat}} \quad \text{Sayetzeff major} \\
\]
With 3° and 2° alcohols the elimination mechanism is almost always E1, the protonated water is a very good leaving group, so good that E1 is quite fast even at a secondary carbon to make a secondary cation
• carbocation intermediates means rearrangements
• the sulfuric acid is the initial acid, the bisulfate anion is a likely base to deprotonate, recovering the acid catalyst
• The alkene formed will be the Sayetzeff (Zaitsev), there are no stereochemical constraints in the E1 mechanism and the most stable alkene will form

Example: Primary (1°) Alcohols: E2 elimination (with rearrangement…)

With a primary alcohol the mechanism must be E2, formation of a primary carbocation does not occur
• BUT, even though the elimination does not involve a rearrangement, the final alkene product is usually the same one that would have been formed via an E1 reaction due to protonation followed by deprotonation (isomerization) of the primary alkene into a final more stable product

Look AGAIN at the second part of the mechanism, the rearrangement

ADD SOME hydrogen atoms back to the organic structure to solve this simple mechanism problems, the H atoms tell you exactly where you need to protonate and deprotonate
• in the presence of acid, PROTONATION will occur first, followed by deprotonation
• a less substituted/less stable alkene is converted into a more substituted/more stable alkene
• this is a REARRANGEMENT, the acid is only the catalyst (no atoms are overall added or subtracted)
• In a strong acid, especially with heat, protonation and deprotonation can OFTEN occur, and if this can result in formation of a more stable alkene, then the more stable alkene will form, and you should always include this step when doing acid catalyzed dehydrations of alcohols

The final product is the SAME MOST SUBSTITUTED ALKENE, whether the mechanism is SN1 followed by cation rearrangement (2° and 3° alcohols) or SN2 followed by protonation/deprotonation (1° alcohols)
9 Summary of Nucleophiles and Bases

Some of the influences on nucleophility CAN be confusing. In fact, the definition of nucleophilicity is complicated by the fact that it can depend upon what the nucleophile is actually reacting with! Trends going down the periodic table are particularly complicated. Nucleophilicity can be difficult, but students deserve guidelines and "rules" to systematize studying.

Most of the time basicity (LB) and nucleophilicity (Nuc) exhibit the same trends that we already understand, although there are some dramatic exceptions. Here is a summary:

**Cases where basicity and nucleophilicity exhibit SAME BEHAVIOR (stuff you already know!)**
- Negatively charged species are stronger bases and stronger nucleophiles than their neutral counterparts
  \[
  \begin{array}{c}
  \text{common strong LB/BB/Nuc.} \\
  \text{common moderate/weak LB/BB/Nuc.}
  \end{array}
  \]

- Basicity and nucleophilicity decrease with resonance delocalization

  \[
  \begin{array}{c}
  \text{stronger LB/BB and Nuc.} \\
  \text{weaker LB/BB and Nuc.}
  \end{array}
  \]

- Basicity and nucleophilicity decrease going across the periodic table

  \[
  \begin{array}{c}
  \text{increasing nucleophilicity} \\
  \text{increasing BB/LB strength}
  \end{array}
  \]

**Cases where basicity and nucleophilicity exhibit MIXED BEHAVIOR**
- Basicity and nucleophilicity for anions follow the SAME trend down the periodic table, but ONLY IN APROTIC SOLVENTS

  \[
  \begin{array}{c}
  \text{in acetone} \\
  \text{DMF} \\
  \text{acetonitrile} \\
  \text{etc.}
  \end{array}
  \]

  \[
  \begin{array}{c}
  \text{increasing BB/LB strength} \\
  \text{increasing nucleophilicity}
  \end{array}
  \]

- Basicity and nucleophilicity for anions follow the OPPOSITE trend down the periodic table IN PROTIC SOLVENTS, in protic solvents the small anions are highly solvated which decreases their kinetic reactivity and nucleophilicity

  \[
  \begin{array}{c}
  \text{in MeOH} \\
  \text{EtOH} \\
  \text{etc.}
  \end{array}
  \]

  \[
  \begin{array}{c}
  \text{increasing BB/LB strength} \\
  \text{increasing nucleophilicity}
  \end{array}
  \]

**Cases where basicity and nucleophilicity exhibit OPPOSITE BEHAVIOR**
basicity and nucleophilicity for neutrals follow the OPPOSITE trend down the periodic table IN ALL SOLVENTS. Neutrals are not as affected by solvent and the large size and polarizability of the electrons on the larger atom wins out over electronegativity

**increasing BB/LB strength**

- **increasing nucleophilicity OPPOSITE TO BASICITY**

• strong bases that are sterically hindered are weak nucleophiles, these are the so-called "bulky" bases

- **most common "bulky" base**

  - methoxide: strong LB/BB, strong Nuc.
  - ammonia: moderate LB/BB, moderate Nuc.
  - tert-butoxide: strong LB/BB, WEAK Nuc.
  - di-isopropyl amine: moderate LB/BB, WEAK Nuc.

• We will make considerable use of t-butoxide as a bulky base in elimination reactions where we need to avoid substitution