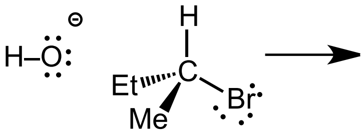
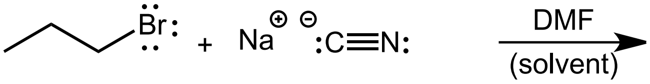
1.1 SN2 Reactions

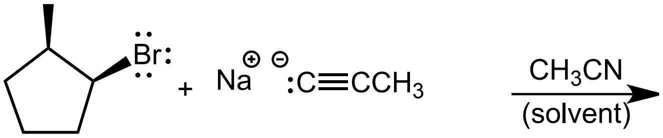


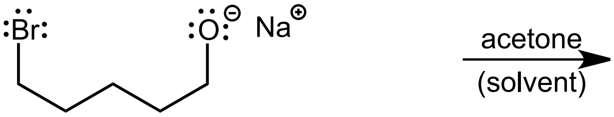
- **CONCERTED reaction**: all bonds are broken and made at the same time.
- This is fundamentally just a Lewis acid/base reaction of a kind we have seen previously, the Lewis base has the high energy chemically reactive electrons, which are used to make a new bond to the Lewis acid, and a stronger bond is formed (C-O in the example above) and a weaker bond is broken (C-Br above)
- HO^- is the Lewis Base/**Nucleophile**, the halide is the Lewis acid/**Electrophile**, Br^- is the **Leaving Group**
- A weaker bond is converted into a stronger bond:

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

- We understand these SN2 reactions a simple Lewis acid/base processes
- We can identify the Lewis base/**nucleophile** as the reactant with the high energy electrons.
- The Lewis acid/nucleophile must react with the Lewis acid/**electrophile**.

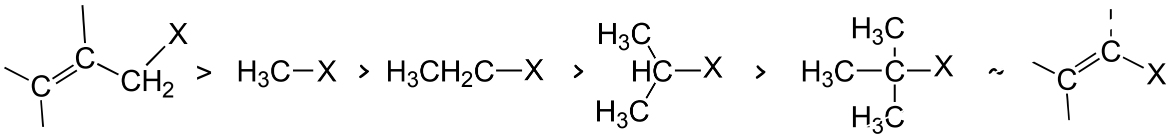






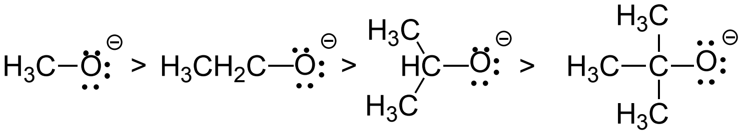
- **SN2** reactions proceed with **INVERSION**

Reactivity order for SN2, halide structure...



- SN2 reactions get slower with increasing steric hindrance at the backside of the carbon electrophile
- To the extent that there is **no SN2 at a tertiary carbon**
- **SN2** reactions at **methyl and allylic carbons** are particularly **favorable**
- There is **no SN2 at a tertiary or vinyl carbons** because the nucleophile cannot get close enough to form reasonable partial bonds in the transition state, and the bond to the leaving group is stronger.

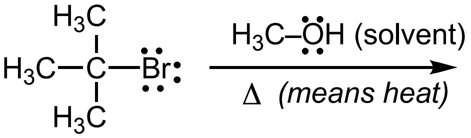
and, nucleophile structure



- SN2 gets slower with increasing steric bulk of the nucleophile, to the extent that there is **no SN2 for the t-butoxide anion.**

1.2 SN1 Reactions

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



- 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.
- H_3COH is a weak nucleophile (no negative charge on the oxygen), shouldn't do SN2.
- H_3COH 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)

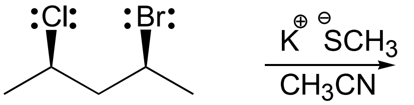
1.3 SN1 versus SN2 Reactions

S_N2 favored by:

S_N1 favored by:

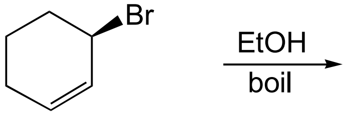
Example Problems

Give the major organic product of reaction:



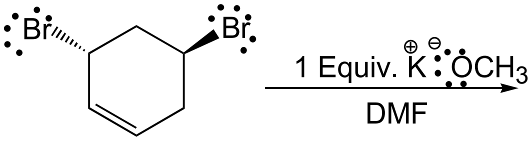
- Polar aprotic solvent, strong nucleophile, SN2, Br- better leaving group
- **1 equivalent means exactly the same number of nucleophiles as organic reactants**, which in this context means that there is only enough nucleophile to substitute one of the halide leaving groups

Give the major organic product of reaction:



- 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!

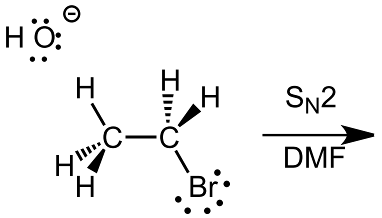
Give the major organic product of reaction:



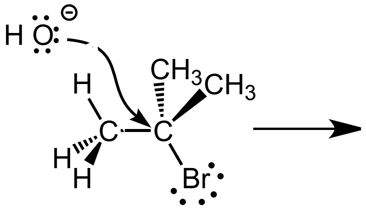
- Polar aprotic solvent, strong nucleophile, SN2, allylic position more reactive.
- 1 **equivalent** will **only react** at the carbon where SN2 will be fastest, there is only enough reagent to react once.

4 E2 Elimination Reaction

Here is a reaction that we now know, straightforward S_N2 at a primary bromide......



- What about this reaction? SN2 is not possible here (3° bromide), yet there certainly **is a reaction.**

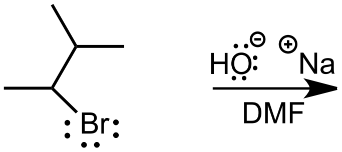


- The reaction does E2 instead!
- It breaks weak C–Br bond and strong C–H bond, makes strong O-H bond and C=C pi bond
- E2 is not as exothermic as S_N2, but the reaction converts 2 molecules into 3, favored by entropy AND "converts" strong -OH base into weak -Br base, this lowers the energy of these electrons, which also helps
- Just like S_N2, all bonds made and broken at same time *(all four!)*
- The ^{-}OH acts as a Brønsted base, a **strong base is required for E2!** What we are doing here is using the chemical potential energy (reactive electrons) in the strong base to "drive" this reaction, to make it "go"
- **The reaction is concerted (all four bonds are made and broken at the same time)**

4.1 Product Selectivity in E2: Saytzeff Rule (or Zaitsev, etc.)

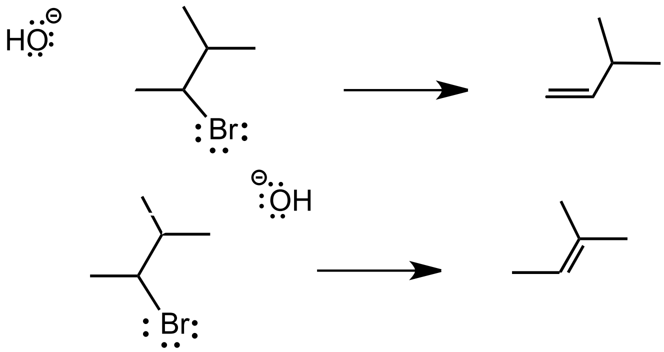
The Saytzeff Rule: Most substituted alkene is formed in an E2 reaction, if possible

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
- Sayetzeff's name was translated differently from the Cyrillic 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:



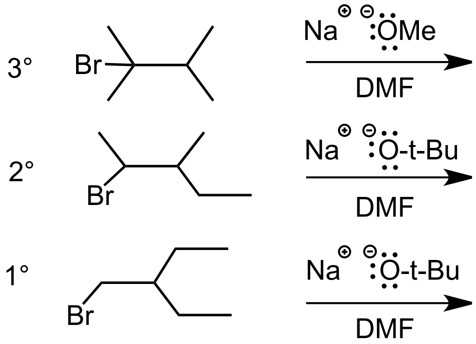
Recall, the most substituted alkene is always the most stable alkene isomer.

- the Sayetzeff/Zaitsev 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/Zaitsev alkene unless there are steric inhibitions, see below.

4.2 Reactivity Order for E2

•Decreasing reactivity order: 3° > 2° > 1° halide

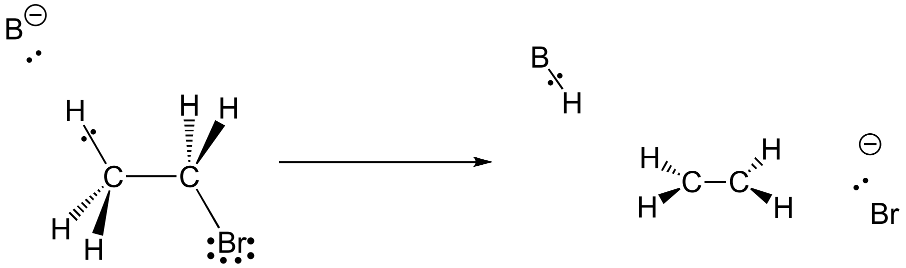
Example



- Elimination from a 3° 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)

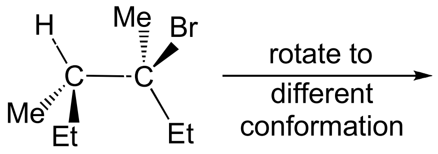
4.3 Stereochemistry of E2 Reaction

- Again, Molecular Orbital 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 two 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".

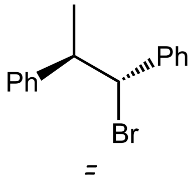
- The electrons in the breaking C-H sigma bond are used to make the new pi-bond, overlap occurs with the anti-bonding M.O. associated with the breaking C-Br bond best as shown, i.e. analogous to "backside attack" in the SN2 reaction, this is the origin of the requirement for ANTI- in addition to co-planar
- **Only One conformation will tend to be reactive in an E2 Reaction:**

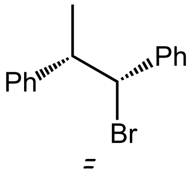


- The reactive conformation must be attained **before** reaction can occur.

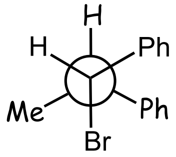
Example: give the major products of the E2 reactions of:

(1R)-bromo-(1,2R)-diphenylpropane AND (1R)-bromo-(1,2S)-diphenylpropane

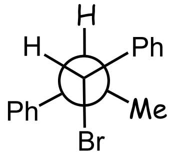




unreactive
conformations



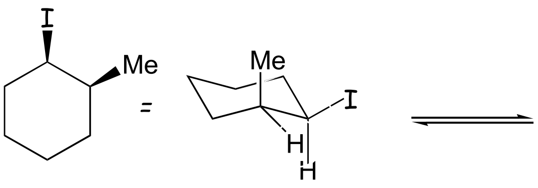
anti-coplanar
conformations



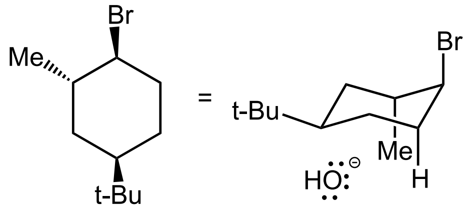
E2

- **The reaction is stereospecific, 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

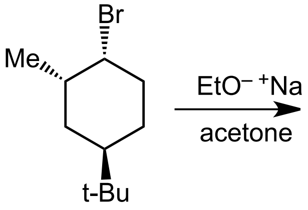


Example: give the major product of the E2 reaction of the following compound



- The cyclohexane is "locked" into the chair that has the **large** t-butyl substituent in the equatorial position, i.e., the energy difference between the two chairs is so large that the one with the axial t-butyl is present at such low concentration that it can be ignored.
- In this conformation, the C-H bond that is anti-coplanar to the C-Br bond **must** give the Anti-Sayetzeff alkene.

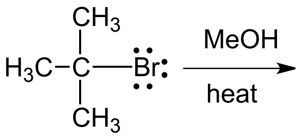
Example: give the major product of the following reaction:



- Again, the Br is "locked" into an equitorial position because of the **large** t-butyl group.
- In this conformation (chair) that are **no** anti-coplanar C-H bonds, therefore E2 is **not possible** and SN2 is the only reasonable reaction.

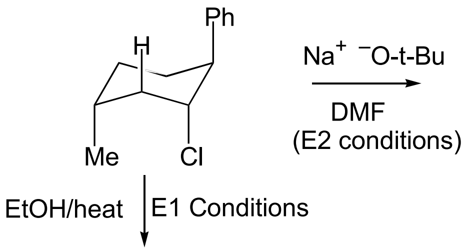
5 E1 Elimination Reaction

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



- The intermediate cation is a strong electrophile that can react with the weak nucleophile MeOH via SN1
- The intermediate cation is **also** a **very strong** Brønsted acid, stronger than hydrochloric acid (pKa < -10)
- The intermediate cation can, therefore, react with the weak Bronsted base MeOH in a Bronsted acid/base reaction to give an alkene **elimination** product.
- E**1** elimination because **one molecule** is involved in **the rate determining step** (kinetically first order)
- SN1 and E1 are often competitive, they have the **same** rate determining step, the reactions "partition" at the cation intermediate.
- It is difficult to select conditions that favor E1 (high temperature can help due to the temperature dependence of entropy), i.e. not useful "synthesis" reaction - see later.

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

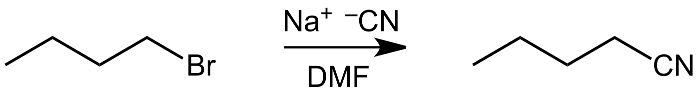


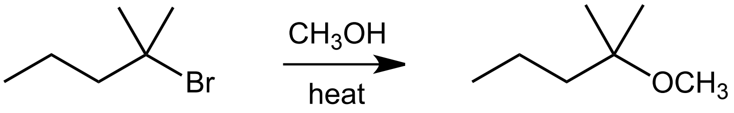
6 Distinguishing E1, E2, SN1 and SN2 Reactions

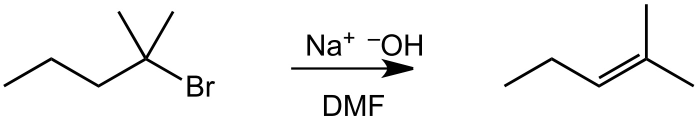
- Reality - the mechanisms are often mixed : However, favored conditions are........

SN2 - 1° halide, aprotic solvent, strong nucleophile, weak base
SN1 - 3° halide, protic solvent, weak nucleophile, weak base
E2 - 3° halide, aprotic solvent, weak nucleophile, strong base
E1 - 3° halide, protic solvent, but in reality they are difficult to favor!

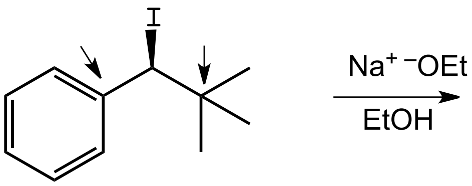
Examples: What was the mechanism that resulted in the PROVIDED organic product? (there may be other reaction products, but the questions ask about the provided ones only)



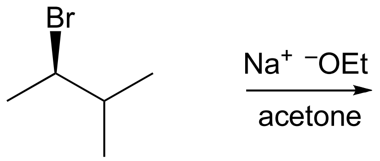




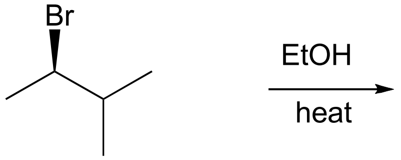
Example: give the major products of the following reactions and identify the reaction mechanisms



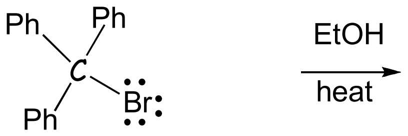
- There is no REQUIREMENT for an SN2 reaction to be in a polar aprotic solvent, they are faster in aprotic solvents but in reality many are actually performed in protic solvents for convenience



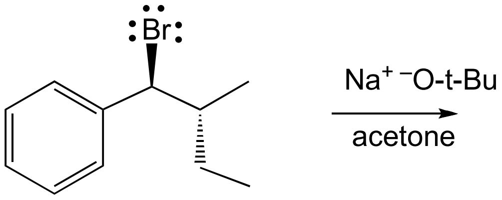
- Secondary halides don't favor any mechanism in particular and often undergo more than one reaction.



- 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.



- Elimination is not possible in this case

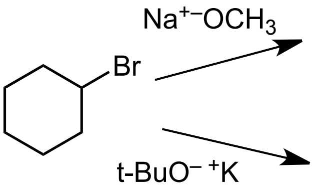


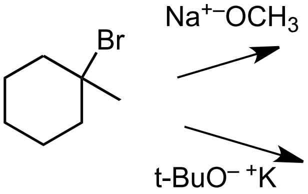
- Note the use of the t-butoxide anion **bulky base** to force E2 elimination.
- For E2 eliminations where there is stereochemistry in the reactant, you will usually have to setup the correct conformation for elimination (anti-coplanar) in order to get the correct stereochemistry in the alkene product.

7 Elimination Using Bulky (Sterically Hindered) Bases

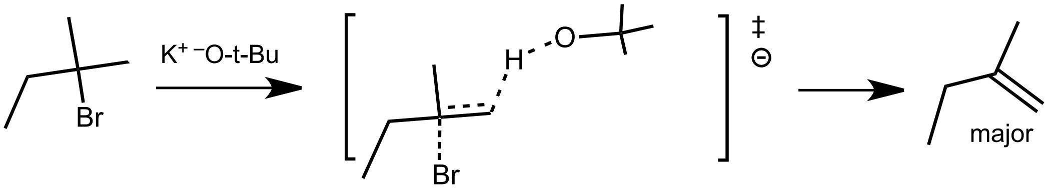
- The products of E2 eliminations can be different for 2 versus 3° halides with or without bulky bases

Examples:



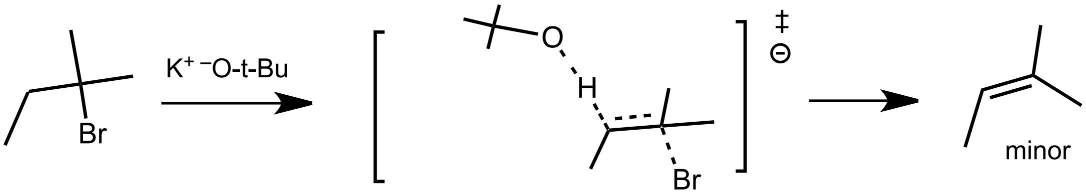


- Looking at the **Transition States** can explain these product distributions.
- The **fastest** reaction occurs, the reaction is **kinetically controlled:**



transition state for MAJOR product

- 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.



transition state for MINOR product

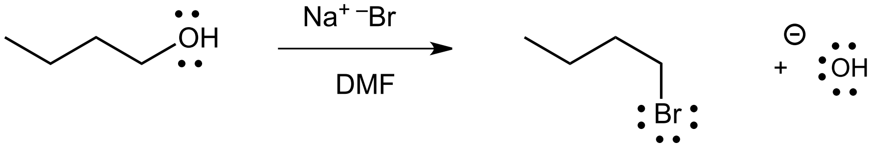
- The transition state for formation of the minor product has CH3-Ch3 electron repulsion/steric effects, which costs MORE energy that CH3-H electron repulsions/steric effects in the reaction that forms the major product, the transition state is thus higher in energy, the reaction is slower and this reaction forms the minor (Hoffman) product.

In 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.

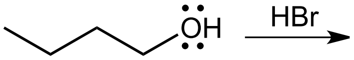
8 Water as a Leaving Groups

- Substitution and elimination reactions are **not limited** to alkyl halides with halide anions as leaving groups
- It is a good idea to look at some other leaving groups now, not to create more stuff to learn, but to facilitate learning of these new reaction types in different contexts.
- **Good leaving groups are stable as anions.**
- **Leaving groups** that are **stable neutral molecules** therefore should be expected to be **even better!**
- A classic example is water, consider the following reaction that converts an alcohol into an alkyl bromide.



- This reaction doesn't work! In fact, goes in reverse $^-$OH will substitute for X$^-$ (think about a standard SN2 reaction that has **-OH as the nucleophile** and **Br- as the Leaving group**), this reaction has the **opposite**!
- **$^-$OH is too poor a leaving group**, we need to make a better leaving group.

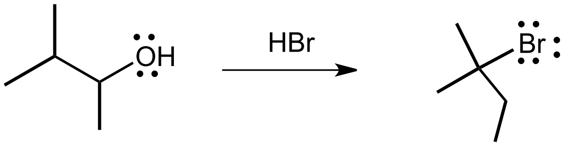
Consider the following reaction instead:



- The first step is a standard Bronsted acid/base reaction, with H-Br as the strong Bronsted acid
- **Now,** we have a very good potential leaving group, H_2O, the next step is standard SN2 and it works well, even though the bromide anion is a poor nucleophile.

Example Problem:

- Give the mechanism of the following substitution reaction:

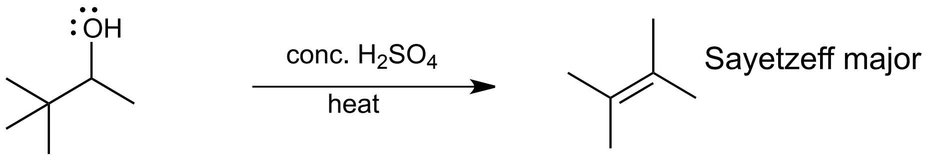


- **First**, standard Bronsted acid base reaction between the -OH and the strong Bronsted acid H-Br, **this converts the -OH from a poor leaving group into a very good leaving group.**
- After that it is **standard SN1 mechanism** with an expected rearrangement of the cation intermediate.

Elimination of Water

- E1 and E2 eliminations are also observed where water can be a good leaving group.
- Again, the reactions start by protonating the -OH of an alcohol to form a good leaving group, and then standard E1 and/or E2 mechanisms after that.

Example Problem. Give the product AND Mechanism for the following elimination reaction:

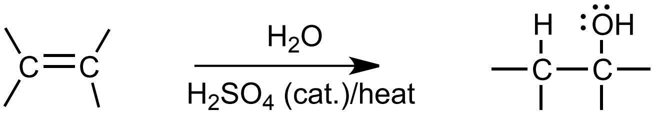


Sayetzeff major

- Sulfuric acid protonates the -OH in a Bronsted acid/base reaction to convert the -OH into a good leaving group.
- Water is such a good leaving group that the elimination is almost always **E1 with 3° and 2° alcohols.**
- Water is such a good leaving group that E1 is occurs even at a secondary carbon to make a secondary cation
- **carbocation intermediates mean rearrangements!** (that hasn't changed, of course).
- the conjugate base anion of the sulfuric acid, the bisulfate anion, is the most likely base to deprotonate the carbocation intermediate, thus regenerating 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.

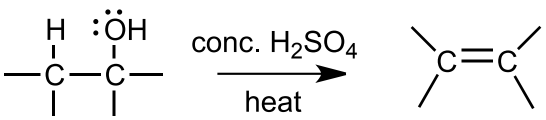
Why does the alcohol make an alkene + water when previously we learned that water + alkene gives an alcohol?

- **This** is what we learned previously:



- The addition reaction "goes" because the weaker π-bond is converted into a stronger σ-bond.
- The reagents/conditions have a **large quantity of water** and a **small quantity of sulfuric acid.**

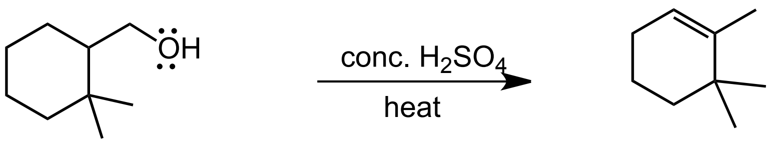
- **This** is what now learned:



- The reagents have **zero water** and a **high concentration of sulfuric acid** (opposite of previous reaction).
- The elimination reaction "goes" because the water is highly solvated in the concentrated sulfuric acid.
- 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).

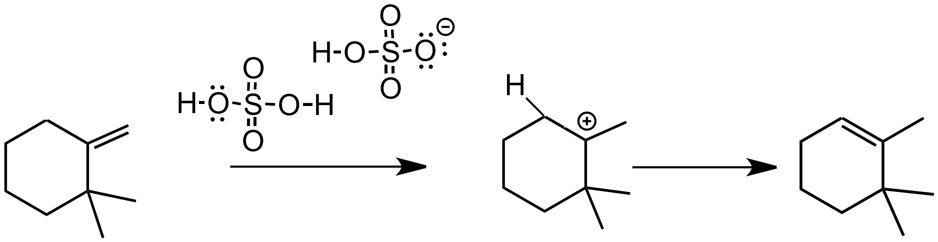
- Alternate reagents and conditions are H_2SO_4/P_2O_5, and others….

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



- With a **primary alcohol** the **mechanism must be E2, formation of a primary carbocation can't 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:



- This effectively converts a less stable less substituted alkene into a more stable more substituted alkene, this is why this **isomerization** reaction "goes".
- To solve the mechanism problem, **add some hydrogen atoms back to the line-angle structure**, 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, whether the mechanism is E1 followed by cation rearrangement (2° and 3° alcohols) or E2 followed by protonation/deprotonation (1° alcohols).

10 Reaction Summary

Do not start studying by trying to memorize these reactions!
Work as many problems as you can with this list of reactions in front of you, if necessary, so that you can get through as many problems as you can without getting stuck on the reagents/conditions. **After** you have worked all of the problems, just before an exam, then do the following:

- Cover the entire page of reagents/conditions with a long vertical strip of paper, see if you can write down the reagents/conditions for each reaction, check to see which you get correct, if **completely** correct, circle Y, if incorrect or even slightly incorrect, circle N. In this way you keep track of what you know and what you don't know.
- Keep coming back to this list and so the same thing only for those reactions you circled N, until all are circled Y.
- Knowing the reagents/conditions on this page is **insufficient** to do well on an exam since you will **also** need to recognize how to use and solve reaction problems in different contexts, this page **only** helps you to learn the reagents/conditions that you have **not yet** learned by working problems.

Also, SN2 reactions in particular can occur in **many different contexts**, knowing the reactions summarized here is **insufficient** for you to solve substitution and elimination reaction problems.