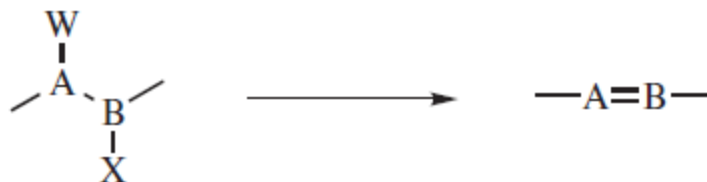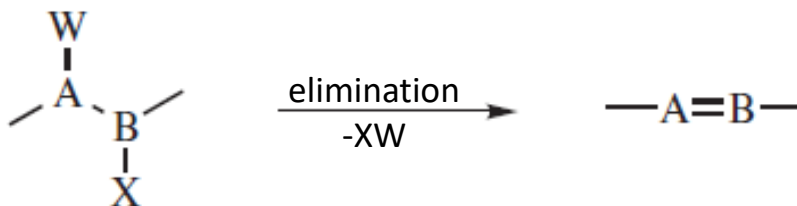Elimination Reactions

Elimination reactions involve the loss of fragments or groups from a molecule to generate multiple bonds.
Used for the generation of double and triple bonds in compounds from a saturated precursor molecule.

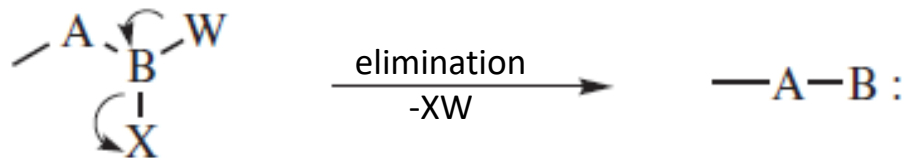$$\underset{\underset{X}{|}}{\overset{\overset{W}{|}}{\underset{B}{A}}} \longrightarrow \quad -A{=}B-$$

Types of elemination (*Three major types of elimination reactions are:*)

1. β-elimination: loss of atoms or groups on adjacent atoms. It is also known as 1,2-elimination.

$$\underset{\underset{X}{|}}{\overset{\overset{W}{|}}{\underset{B}{A}}} \xrightarrow[\text{-XW}]{\text{elimination}} \quad -A{=}B-$$

2. *α-elimination: two atoms or groups are removed from the same atom. It is also known as* 1,1-*elimination.* Example: Generation of a carbene (or a nitrene)

$$\xrightarrow[\text{-XW}]{\text{elimination}}$$

$$-A-B:$$

3. *γ-elimination: loss of atoms or groups from the 1st and 3rd positions. Generally such elimination reactions result in cyclic compounds.*

1,3 elemination

More details on β-eliminations

β-eliminations can be further subdivided into three categories depending upon the mechanistic pathway. The important aspect is to establish the number of molecules taking part in the elimination step (molecularity of the reaction)

More details on β-eliminations

The types of β-eliminations are

1. *E2*

2. *E1*

3. *E1cB*

These are read as "Elimination bimolecular E2", "Elimination unimolecular"and "Elimination unimolecular conjugate base"

1. *E2 eleminations*

<u>*Key mechanistic features in this family are*</u>

➢ *Two groups depart simultaneously*

➢ *Involves one step (in other words, no intermediates are involved)*

➢ *bimolecular reaction i.e., both substrate and nucleophile participate in a single step*

➢ *The base abstracts the β hydrogen and leaving group simultaneously leaves such that it forms a multiple bond between αand βcarbon atoms.*

E2 eleminations

Propene
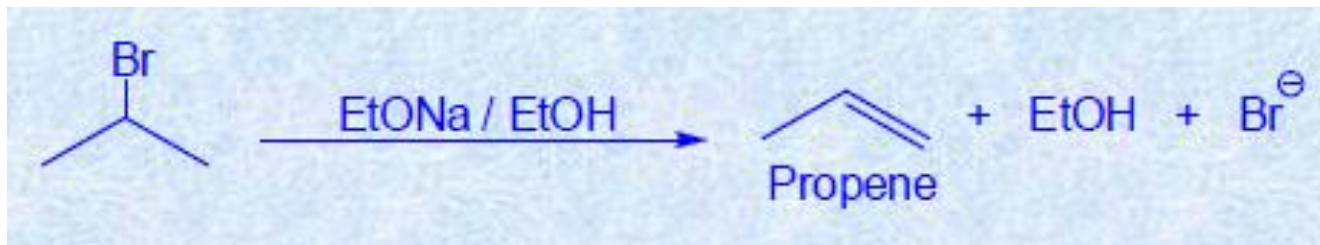
In the example given above, sodium ethoxide acts as the base, abstracting β-hydrogen. Bromine is the leaving group.

An illustration of a common elimination reaction is given below,
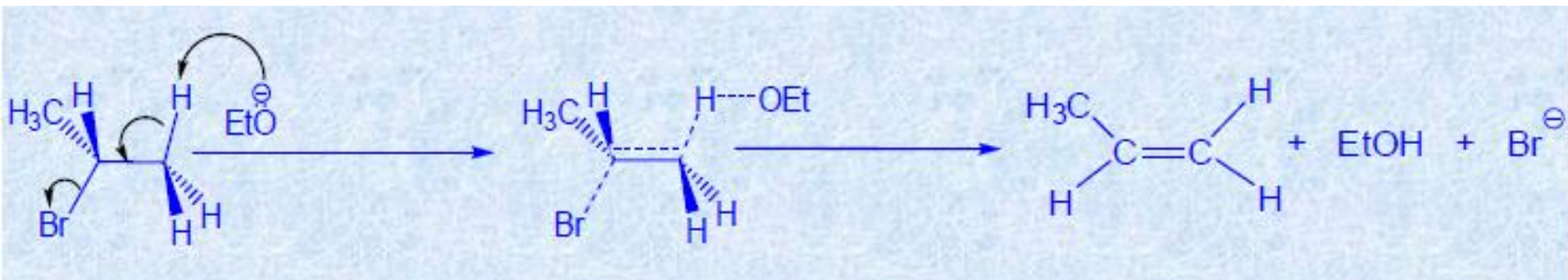

The sequence of events involved are,
(i) The attack of ethoxide on β hydrogen and its abstraction as a proton is the first event. This will leave two electrons of the C-H bond available for the formation of a new double bond between the carbon atoms.
(ii) As the new double bond is created, the C-Br bond begins to break away (leaving group). This will result in the departure of the bromide ion.

Note: Often times, E2 *elimination competes with SN2 reactions. This is due to the inherent propensity of the incoming nucleophile also to attack the carbon atom bearing the leaving group. Such situations will lead to substitution products.*
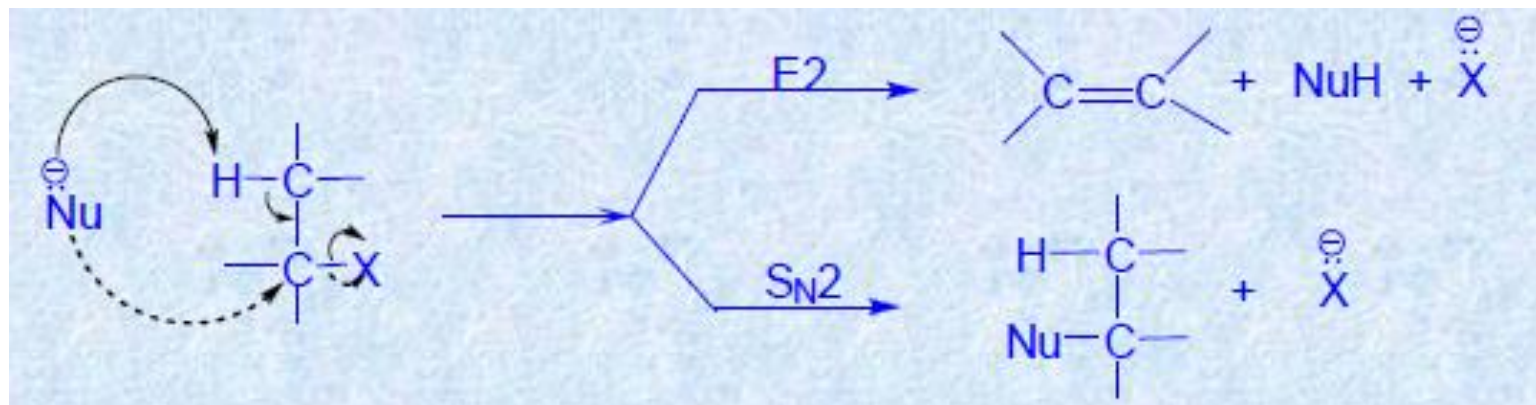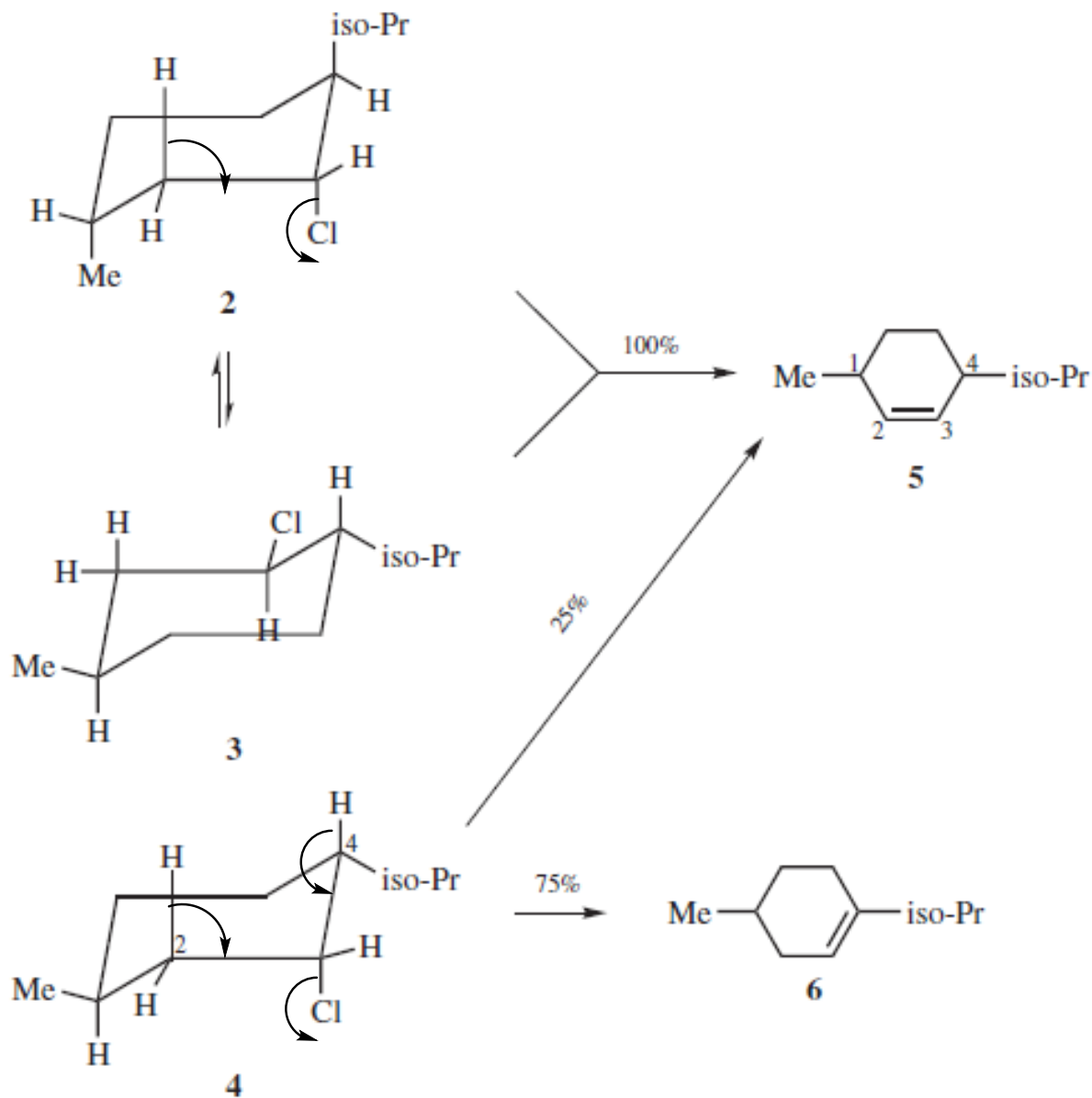

Examples for E2 elimiations
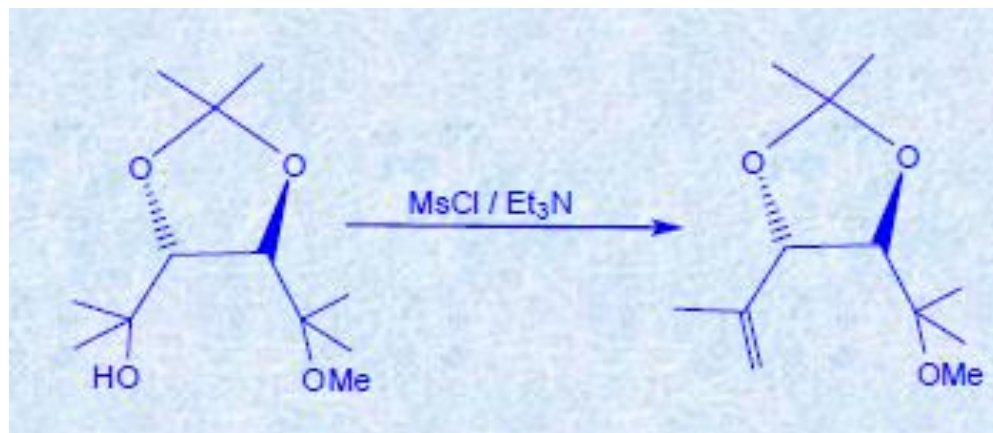
Et3N is the base, and 'OH-group'should be removed. Now, note that OH is a poor leaving group and conversion to O-mesyl is required here (achieved through the use of mesyl chloride, MsCl).

Anti-periplanarity of the leaving groups requires that they be diaxial, even if this is the conformation of higher energy.

(2) *E1 Eliminations*
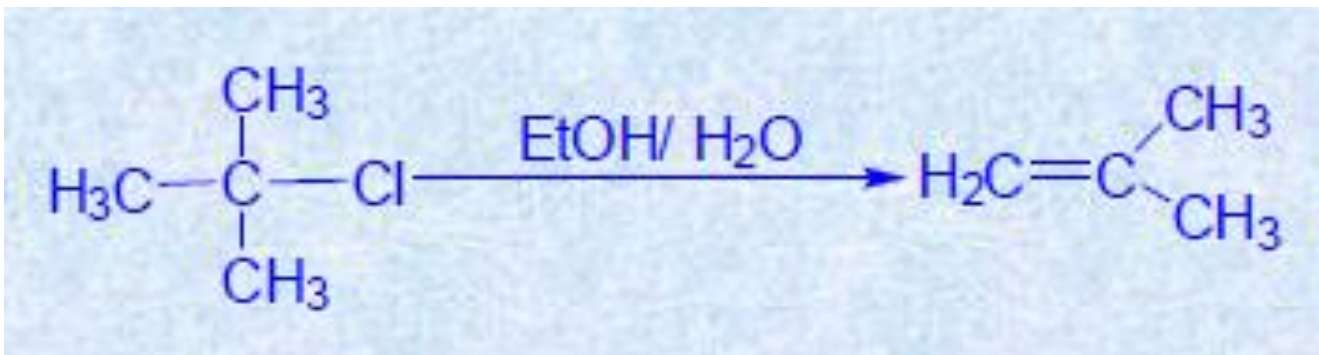
Important characteristics include,

it is two step reaction.

First step is similar to that of SN1*reaction i.e., the generation of carbocation intermediate.*
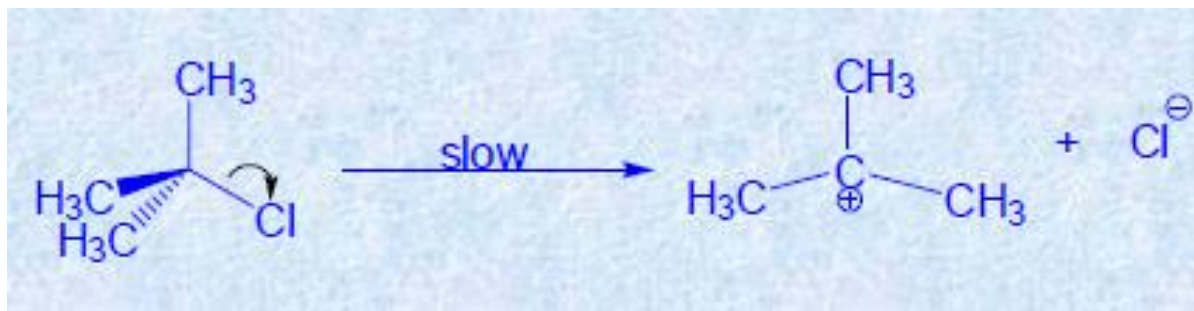
Subsequently, hydrogen is abstracted by the base rather than attack on the carbocation as in

SN1

only one of the substrates is involved in the rate determining step i.e., unimolecular reaction.

Step 1 :

departure of chlorine with bonding electron pair

stable carbocation (tertiary)

Step 2 :
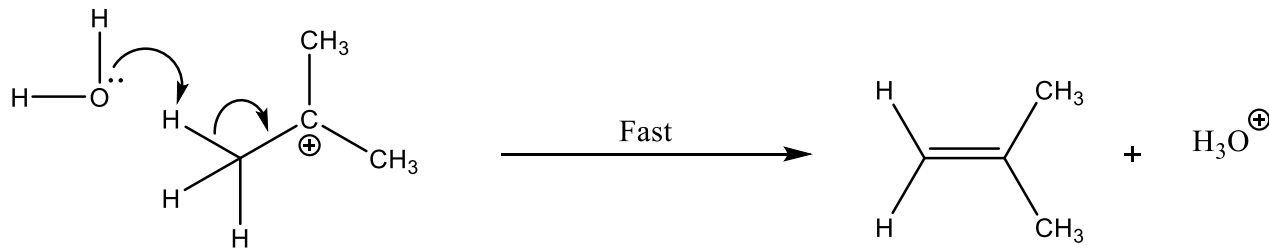
Attack of water or solvent molecule on the βhydrogen and subsequent movement of electron pair to the developing carbon carbon double bond.

Note: Even though a sp3 C-H bond is not acidic in a general sense, the presence of a carbocationic center adjacent to it renders increased acidity such that even a weak base such as water can deprotate.

E2 *vs* SN2 *and* E1 *vs* SN1

Similar to the competition between E2 and S_N2 pathways, E1 mechanism competes with S_N1.

Formation of carbocation is a slower process, as compared to the reaction between a 'reactive-carbocation' and a base/solvent. Hence, carbocation formation is the rate determining step.

Ideal conditions are for E1 mechanism are (a) highly substituted carbon atom for the carbocation center, such as a tert-carbon atom, (b) use of polar solvents (which can stabilize the resulting carbocation in addition to stabilizing a polar transition state involved in the heterolytic bond cleavage.

E1cB Eliminations

This is a two step base-induced β*-elimination.*

➢ *In this reaction base first abstracts the* β*hydrogen, giving rise to a carbanion or* **conjugate base** *of the substrate from which the leaving group departs subsequently to form the product.*

➢ *An interesting comparison can be done with the E1 pathway. The timing of departure of the groups is reversed as compared to that in* E1 *reaction. In E1cB, the deprotonation occurs ahead of leaving group departure*

➢ *Reaction usually follows second order kinetics but is designated as* E1cB *to indicate that the departure of the leaving group is from the initially formed conjugate base (i.e., carbanion).*

Illustration of E1cB mechanism

Step 1 :
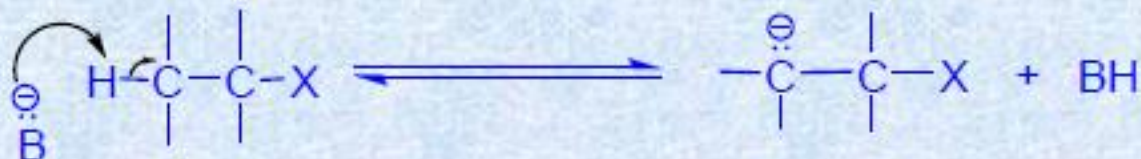
attack of the base on the β hydrogen.

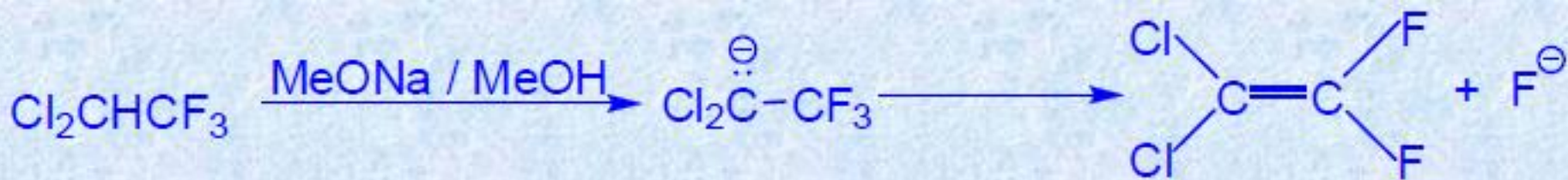*β hydrogen leaves without its carbon electron pair forming a carbanion.*

The electron pair then move towards the new C-C double bond to be generated.

Step 2

departure of the leaving group to give product.

These reactions require substrate which contain groups that can stabilize carbanions i.e., presence of electron withdrawing group

$$Cl_2CHCF_3 \xrightarrow{MeONa\ /\ MeOH} Cl_2\overset{\ominus}{\underset{..}{C}}-CF_3 \longrightarrow \underset{Cl}{\overset{Cl}{>}}C=C\underset{F}{\overset{F}{<}} + F^{\ominus}$$

Additional Details on E1cB:

Depending on the nature of the rate-determining step, there are different ways by which reaction can proceed,

✓ *Carbanion returns to the starting material faster than the product formation. Step 1 is reversible and step 2 is slow. It is designated as* (E1cB)R.

✓ *Product formation is faster as compared to return of proton to carbanion. Step 2 is irreversible and step 1 is slow. It is designated as* (E1cB)I.

Elimination Reaction

Elimination reactions involve the loss of elements from the starting material to form a new π bond in the product.

Alkyl halides (RX) undergo elimination with bronsted bases. The elements of HX are lost and alkene are formed.

General elimination reaction
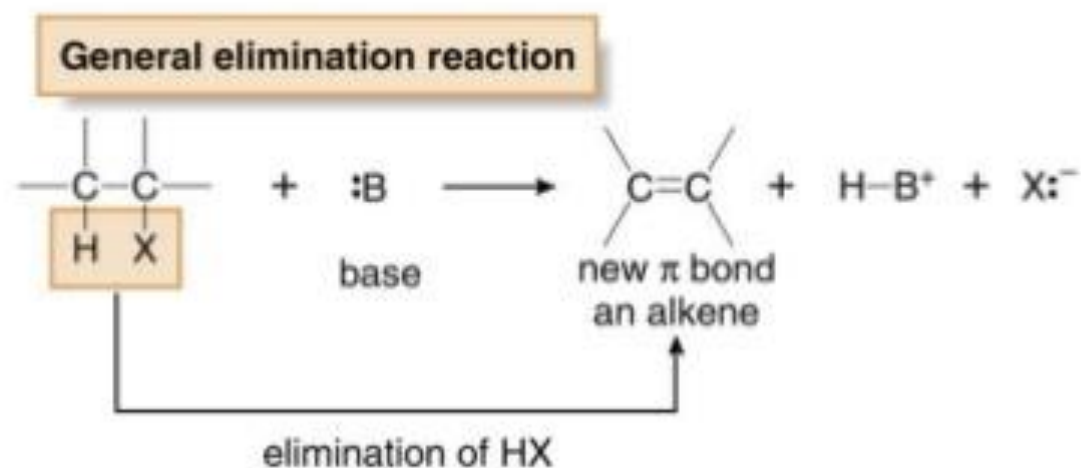
elimination of HX

Leaving groups

X, OH, OR, N_2^+, N_3, H_2O+, NR_3^+ and SR_2^+

Classification   **β- elimination**

➢ α-elimination (1,1)   E1
➢ β- elimination (1,2)   E2
➢ γ- elimination (1,3)   E1CB

Elimination Reactions (1): Introduction And The Key Pattern

As you've probably noticed by now, organic chemistry is a lot different from physics. When we're looking to predict what reaction might occur in a given situation, we don't have a handy series of equations we can simply refer to.

No, it's messier than that. **We take the experimental results, work backwards, and then try to rationalize what is happening in terms of the key concepts at work.**

Furthermore, to use an analogy, organic chemistry isn't "digital". **It's extremely uncommon that one set of conditions will give you 100% yield of one product, and a different set of conditions will give you 100% yield of another**.

Rather, organic chemistry is "analog". Think of each reaction as having a series of knobs we can turn, which can "tune" a reaction toward a different result. (Some examples of "knobs" – temperature, solvent, type of substrate, type of leaving group, type of nucleophile….).

I say this because this post is the first in a series on **elimination reactions**, the third of the "four most important" reactions in first semester organic chemistry. Elimination reactions often occur under similar conditions to substitution reactions, which means that we will have to learn how to think about how these reactions compete with each other.

# Elimination Reactions Often Accompany Substitution Reactions

Let's start with a concrete example. In these two reactions, substitution is the major product. However, the yield of substitution products is not 100% . As it turns out there are actually some minor byproducts in this reaction that are **not** substitution products.

Alkenes Are Byproducts In Some S_N1 and S_N2 Reactions

This substitution reaction (S_N1) also forms an alkene:

Substitution product   +   minor Alkene   + H_3O^{+} Br^{-}
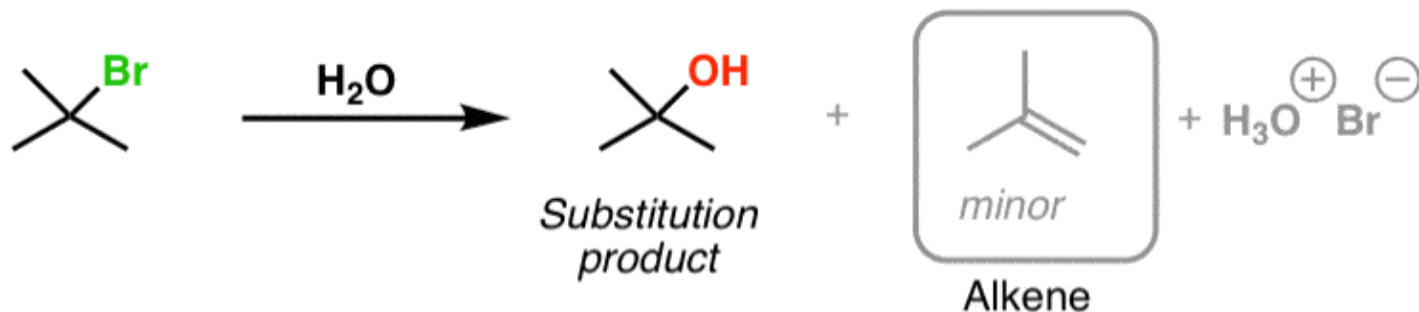
So does this substitution reaction (S_N2)

Substitution product   +   Alkene   + H_2O + Na^{+} Cl^{-}

15
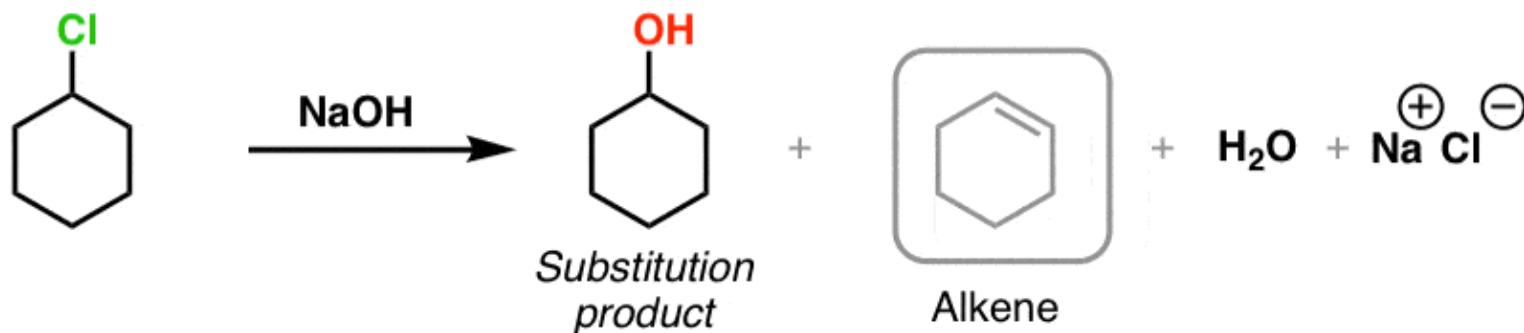
Remember that the key pattern of bond forming/bond breaking in a substitution reaction is a simple swap of a C-(leaving group) bond for a C-(nucleophile) bond? Clearly, in the boxed products, this isn't occurring here. Let's break down these patterns in more detail.

Alkenes From Alkyl Halides: What Bonds Form And Break?

Form	Break
C_1–C_2 (π)	C_1–H
O–H	C_2–Br

Form	Break
C_1–C_2 (π)	C_2–H
O–H	C_1–Cl
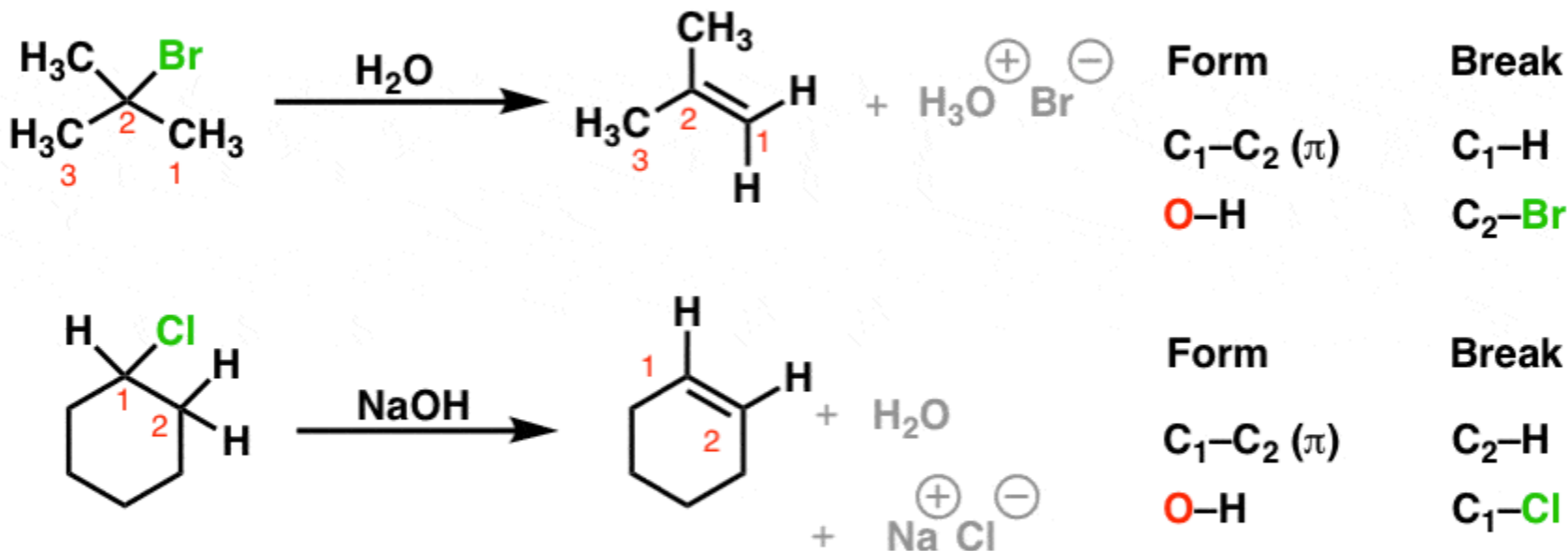
A new carbon-carbon pi bond formed, and a C-H and C-(leaving group) bond broke
These are both **Elimination Reactions**

Elimination Reactions: The Key Bond Forming/Breaking Pattern

Note the key pattern here. In each case, we're **forming a new C–C π bond, and breaking two single bonds to carbon.** So this is a completely different pattern than acid-base reactions or substitution reactions, because it involves two **adjacent** carbon atoms. This class of reactions are called "elimination" reactions.

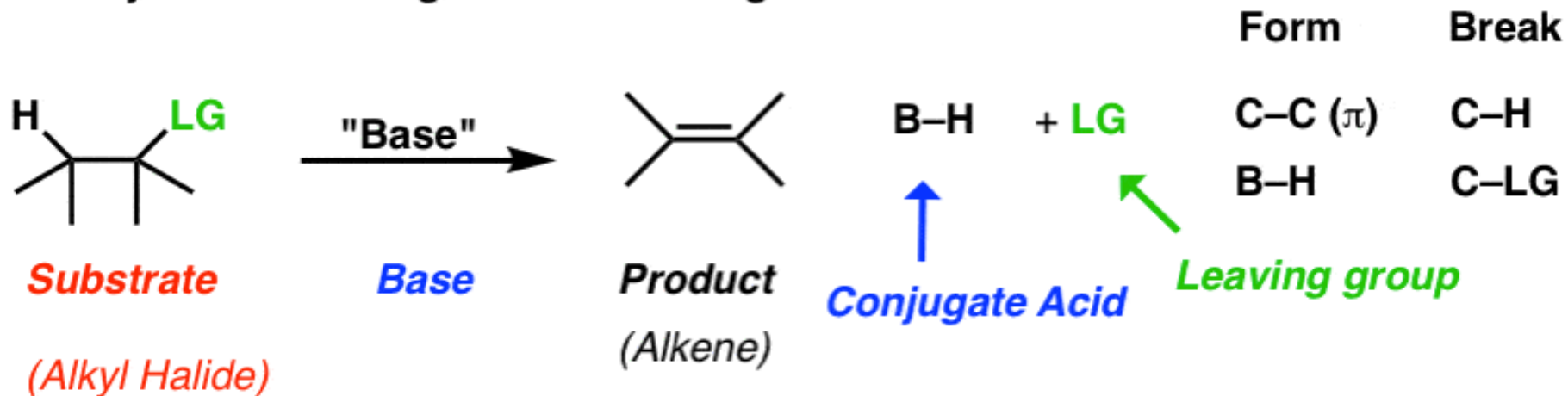However, it's not *completely* without comparison to reactions we've seen before:

1. Note how we're breaking a C-H bond and forming a new base between H and something else (in the case above, oxygen). We've seen this before. **This is an "acid-base" reaction**. So one component of the elimination reactions we will see is the involvement of a strong base.

2. In addition, **we're breaking a bond between carbon and a leaving group**. We're familiar with leaving groups by now; remember how good leaving groups are weak bases? The same principle applies to elimination reactions as well.

What's slightly new here is that we're forming a C-C π bond in addition to the above.
So when you add up the number of species in solution, we're going from **two** species in solution (base and substrate) to **three** species (product, conjugate acid, and leaving group)

Elimination Reactions!

The Key Bond Forming / Bond Breaking Pattern

	Form	Break
	C–C (π)	C–H
	B–H	C–LG

H   LG

"Base" →

Substrate   Base   Product   B–H   + LG   Leaving group
(Alkyl Halide)   (Alkene)   Conjugate Acid

That's the simple pattern for this reaction. As we'll see, there are going to be a lot of little wrinkles with the mechanics of how this reaction works. But as I've said before, knowing "what" [what bonds formed, what bonds broke] is the <u>most important question</u> you can ask yourself when learning a new reaction. In the coming few posts, we can then start to make more observations and start to ask "why"?

Elimination Reactions (2): The Zaitsev Rule

Elimination Reactions: The Zaitsev Rule

So far, we've only looked at some simple elimination reactions where only one product is possible. Now we'll look at some examples where we start to see some of the extra "wrinkles" that can be present in elimination reactions.

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1. **In Elimination Reactions, The "More Substituted" Alkene Tends To Be The Major Product**

2. **The Stability Of Alkenes Increases As C-H Bonds Are Replaced With C–C Bonds**

3. **The "Zaitsev Rule": Elimination Will Occur Such That The Hydrogen Is Removed From The Beta-Carbon With The Fewest Hydrogens**

In Elimination Reactions, The "More Substituted" Alkene Tends To Be The Major Product

For example, if we heat the alcohol below with a strong acid (like sulfuric acid, H_2SO_4) we will obtain one major product (an alkene) and a minor product (also an alkene).

This elimination reaction *can* give two different alkenes

But the major product is the alkene with most carbons directly attached

major

(a tetrasubstituted alkene)

minor

(a disubstituted alkene)
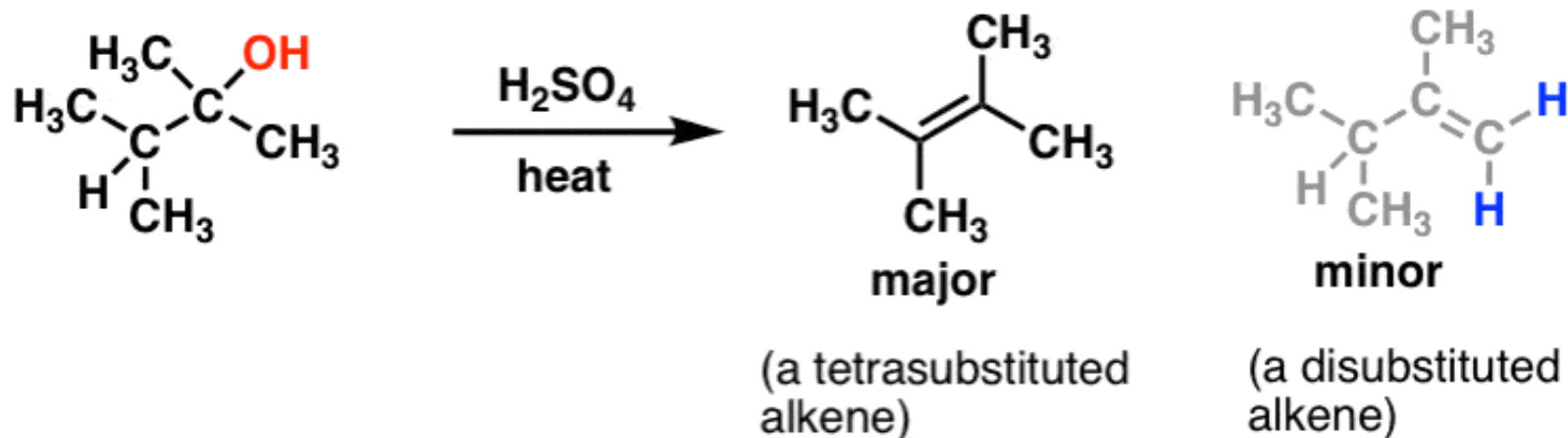
What's interesting about this? Well, if you look closely you should see that actually two elimination products are possible here, but only one is formed as the major product.

The alkene which is "tetrasubstituted" – that is, attached to four carbon atoms – is the major product, and not the "disubstituted" alkene, which is attached to two carbon atoms and two hydrogen atoms.

(The fact that we're forming a new C-C π bond at the expense of sigma bonds on adjacent carbons is characteristic of elimination reactions.)

Similarly, look at the product of this next reaction. Taking an alkyl bromide and adding a strong base, we again get a "major" product and a "minor product".

In this elimination reaction the trisubstituted alkene is formed preferentially vs. the disubstituted alkene
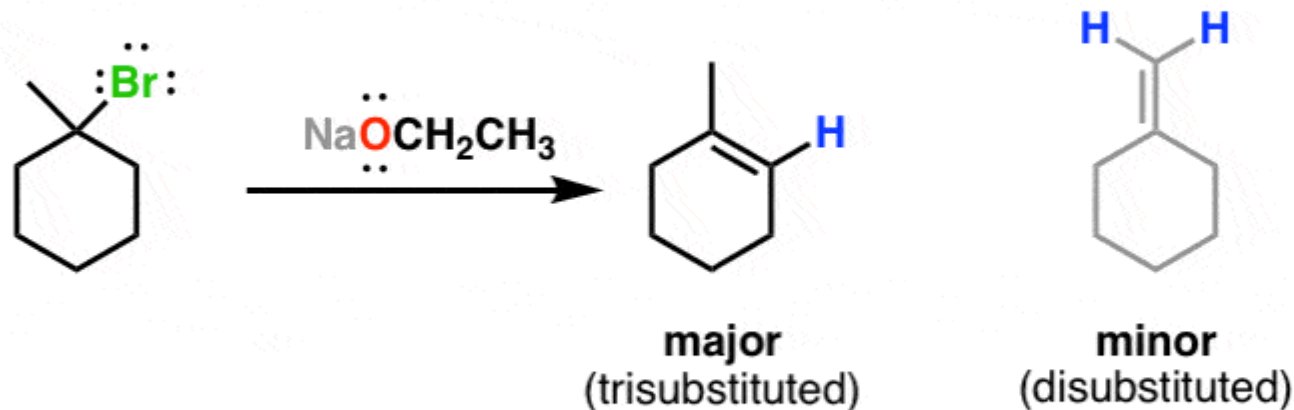
Ratio is about 80:20

Again, the major product is "more substituted" than the minor product. Of the 4 atoms directly attached to the alkene in the major product, 3 of them are carbon and 1 is hydrogen. In the minor product, 2 carbon atoms and 2 hydrogen atoms are directly attached to the alkene.

So what's responsible for this preference for the "more substituted" alkene in elimination reactions?

2. The Stability Of Alkenes Increases As C-H Bonds Are Replaced With C–C Bonds

Well, this correlates nicely with an observation that's been made regarding the heats of formation of various alkenes. **As an alkene becomes more substituted (i.e. more carbons attached, fewer hydrogens attached) it becomes more thermodynamically stable**. [This observation comes from measuring the enthalpy of hydrogenation for various alkenes

Relevant Observation

Alkene stability* increases with the number of attached carbons
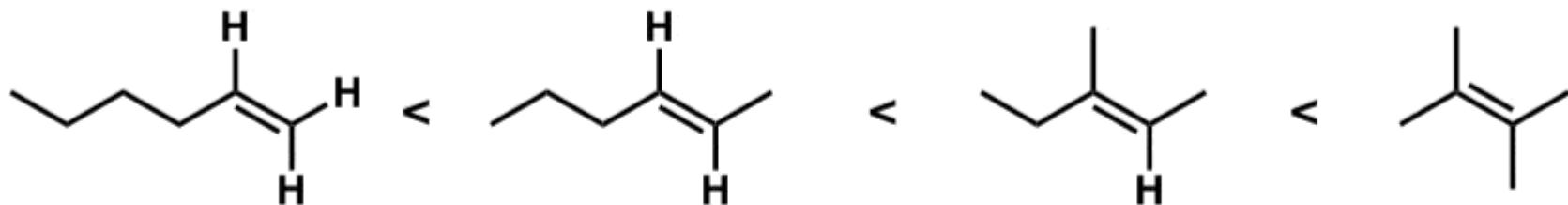
Monosubstituted
(least stable)   **Disubstituted**   **Trisubstituted**   **Tetrasubstituted**
(most stable)

* as determined by measuring the ΔH (enthalpy) for hydrogenation of alkenes

So the observed preference for "greater substitution" reflects the fact that formation of the more thermodynamically stable alkene is favored

This agrees nicely with the trend that's observed for elimination reactions. **The major**

product of an elimination reaction tends to be the more substituted alkene. This is

because the transition state leading to the more substituted alkene is lower in energy and

therefore will proceed at a higher rate.

3. The "Zaitsev Rule": Elimination Will Occur Such That The Hydrogen Is Removed From The Beta-Carbon With The Fewest Hydrogens

It was a Russian chemist named Alexander Zaitsev who published a paper making this observation back in the late 19th century, and therefore this observation has become known as [Zaitsev's Rule](). Formally, the rule is that an elimination will occur such that a hydrogen is removed from the "β-carbon" with the fewest hydrogens. [Organic chemists and their terms: the "α-carbon" is the carbon attached to the leaving group, while "β-carbons" are all carbons attached to the alpha carbon.]

Zaitsev's Rule

"The alkene formed in greatest amount is the one that corresponds to removal of the hydrogen from the β-carbon having the fewest hydrogen substituents"

Alexander M. Zaitsev, 1875

alpha (α) **carbon**: the carbon attached to the leaving group

beta (β) **carbon**: the carbon **adjacent** to the carbon attached to the leaving group

In this case the **blue** β carbon has the fewest hydrogens, and therefore the alkene formed from this alkyl halide in an elimination reaction would be **this:**

beta carbon with three hydrogens

beta carbon with one hydrogen

fewest

base

beta carbon with two hydrogens
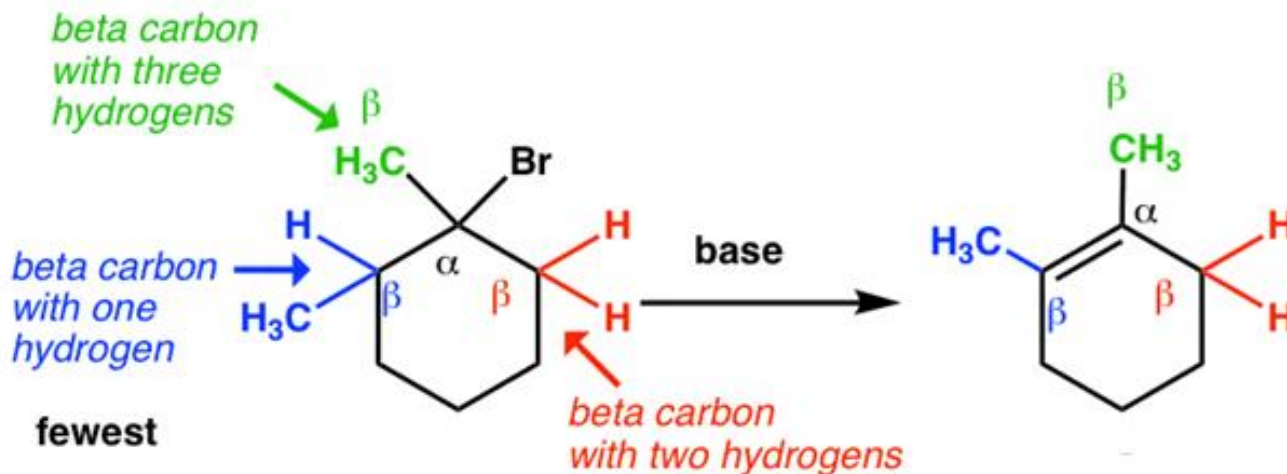
Elimination Reactions Are Favored By Heat

A few posts back we saw how [elimination reactions are often in competition with substitution reactions](#).

How do we know when one reaction pathway is going to be preferred over another? As we'll see, there are going to be several components to answering this question fully, but today we'll talk about one simple rule of thumb going forward.

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1. All Else Being Equal, Elimination Reactions Are Favored Over Substitution Reactions With Increasing Heat.

2. Heating Results In A Gradual Increase In Elimination Versus Substitution.

3. Elimination Reactions Result In An Increase In The Number Of Species In Solution; Substitution Reactions Do Not.

4. Increasing Number Of Species In Solution Means Greater Entropy, Which Means That The $-T\Delta S$ Term In The Gibbs Equation Increases In Value As Temperature (T) Is Increased

1. All Else Being Equal, Elimination Reactions Are Favored Over Substitution Reactions With Increasing Heat

Let's say you have a reaction like this one. It's possible for substitution or elimination products to be formed. [I'm keeping the identity of the base, substrate vague here since I don't have a concrete experimental example to provide (although I'd greatly appreciate one)].

Substitution and Elimination Reactions Can Compete With Each Other

B = base or nucleophile
LG = leaving group

Substitution product

Elimination Product
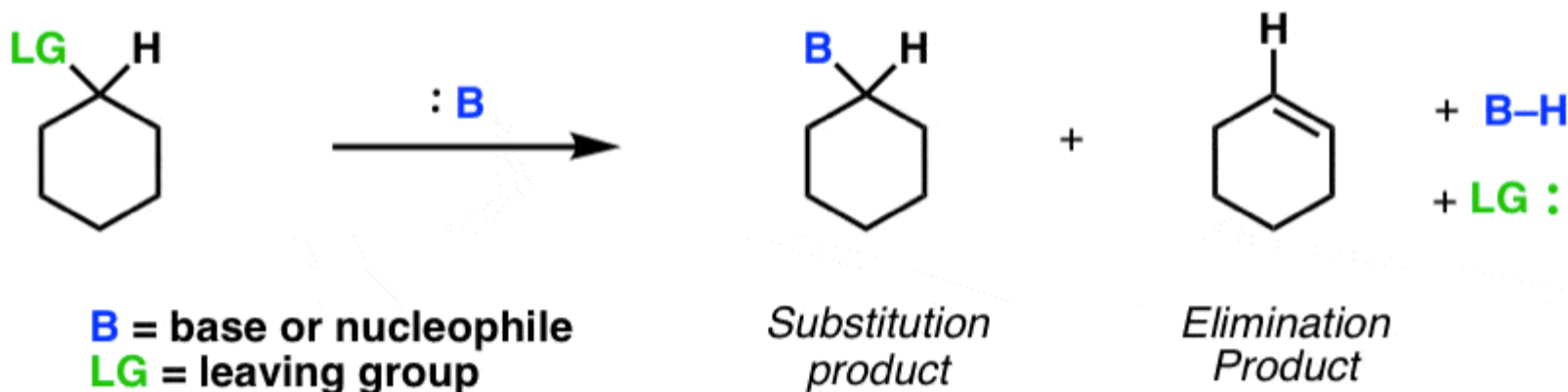
Lower temperatures tend to favor substitution versus elimination

As temperature is increased, the relative amount of elimination products will increase relative to substitution products. You can imagine it looking like this.

All else being equal, the proportion of elimination products will increase with temperature
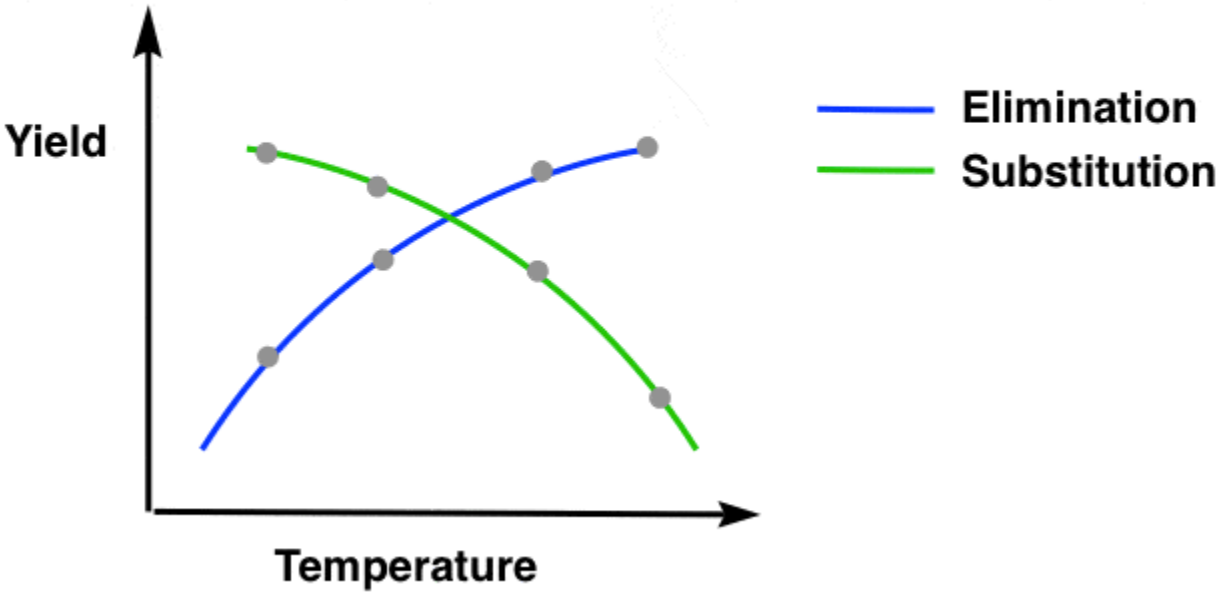
2. Heating Results In A Gradual Increase In Elimination Versus Substitution

Notice again how organic chemistry works. It's not as if applying heat is an on/off switch that results in a reaction going from 100% substitution to 100% elimination. Instead, increasing temperature results in a **gradual** increase in elimination products relative to substitution. That's because temperature is gradually leading to an increase in the rate constant for elimination versus rate constant for substitution.

So what's going on here?

Here's one thing we can say with confidence: at *low temperatures*, the activation energy for the substitution reaction is lower than that for the elimination reaction. Remember that *the lower the activation energy, the higher the rate of the reaction*. This might help to explain our product distribution: as we increase the temperature, more energy is available, so that the starting materials can ascend the activation barrier to provide elimination reactions also. This fits with what is observed.

However, there's an even more fundamental reason why we might see more elimination products as heat is increased, and it has to do with some properties we know about thermodynamics that make rate constants (and activation energies) temperature dependent.
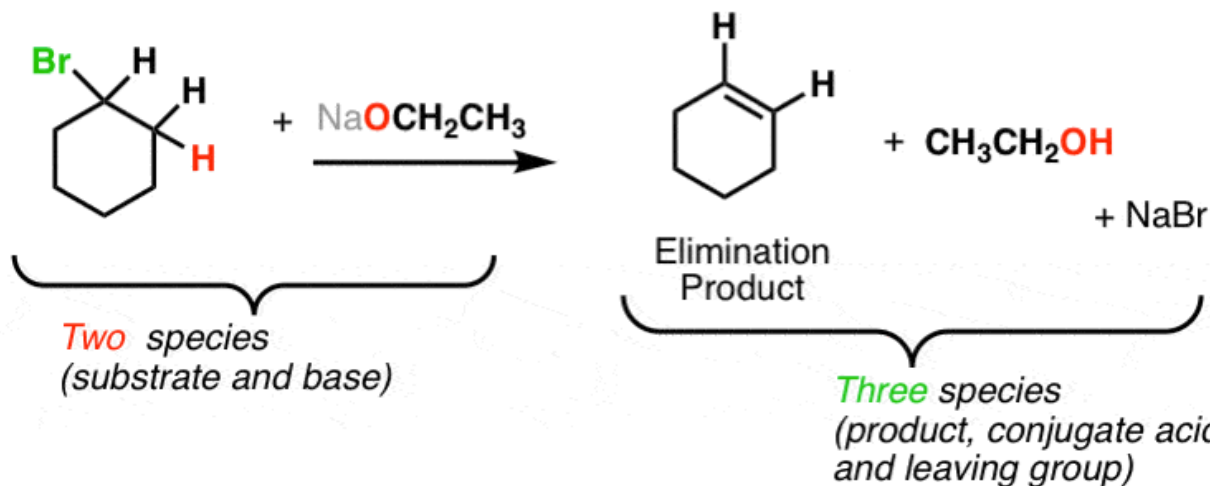
3. Elimination Reactions Result In An Increase In The Number Of Species In Solution; Substitution Reactions Do Not

What do we notice here? Notice that the substitution reaction we're going from 2 species in the starting material to 2 species in the product. But in the elimination reaction, **we're going from 2 species in the starting material to 3 species in the product**. An increase!

In Substitution Reactions The Number Of Species In Solution Generallly Remains Constant

Br H

+ NaOCH₂CH₃ → OCH₂CH₃ + NaBr

Two species
(substrate and nucleophile

Two species
(product and leaving group)
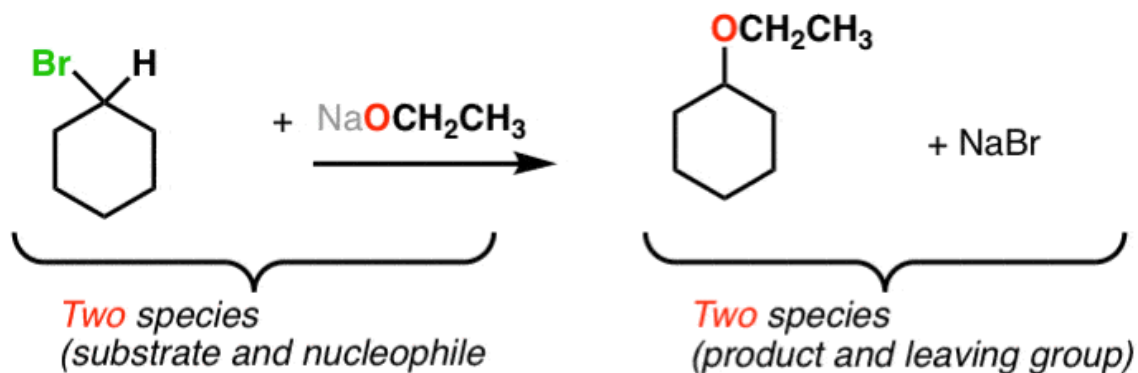
Elimination Results In An Increased Number of Species In Solution

Br H H H

+ NaOCH₂CH₃ → + CH₃CH₂OH + NaBr

Elimination Product

Two species
(substrate and base)

Three species
(product, conjugate acid, and leaving group)

4. Increasing Number Of Species In Solution Means Greater Entropy, Which Means That The −TΔS Term In The Gibbs Equation Increases In Value As Temperature (T) Is Increased

Since we're birthing a new species in solution here, that's going to result in an **increase in entropy**. And if you think waaay back to general chemistry, the Gibbs equation told us this relationship:

$\Delta G = \Delta H - T\Delta S$

Remember that the more negative ΔG is, the more favorable the reaction. As temperature increases, that $T\Delta S$ term is going to start getting bigger and bigger; this will make ΔG more and more negative. At some point, as temperature is increased, the ΔG for elimination will become more negative than delta G for substitution. **In other words, more favorable.**

The ΔS term in the Gibbs equation will increase more with heat for elimination than it will for substitution

As T increases, this term starts getting **big**

This will make ΔG more negative

making the reaction more favorable

$\Delta G = \Delta H - T\Delta S$

Therefore, all else being equal, heating tends to favor elimination over substitution

One thing to be careful about though! When we're discussing ΔG, we really should be talking about the ΔG of the **transition state**, not that of the final product. [Why not? Because the stability of **products** isn't related to reaction rate (if it was, our bodies would have combusted to CO_2 and H_2O a long time ago!)]. We give a special designation to thermodynamic terms of the transition state – we put a little double-dagger on them. Like this: $\Delta G^{\ddagger}$. This "Gibbs energy of activation" is how we define the activation energy of a reaction.

So you can see by analyzing this term that activation energy can change with temperature!

At low temperatures, the Gibbs energy of activation for substitution $(\Delta G^{\ddagger})$ is lower in energy (more negative) than that for elimination. But **at high temperatures**, the Gibbs energy of activation ($\Delta G^{\ddagger}$) for elimination starts to be **lower** in energy than that for substitution reactions, and hence we get an increase in the amount of elimination product.

$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$

Again, **the bottom line is that, all else being equal, heat will tend to favor elimination reactions.**

A Tale of Two Elimination Reaction Patterns

Like I said in the introduction to substitution reactions, organic chemistry is an empirical, experimental science. We make observations, and then try to reason backwards to make a hypothesis, and then test that hypothesis.

The results of the experiments below weren't predicted by those who did them in the first place! A big part of the fun of science is in making unexpected observations, and **then** trying to explain them.

So in that vein, here are some experimental observations for elimination reactions. As you'll see, they seem to divide nicely into two classes.

How do we explain what is going on in each case? See if you can figure it out.

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1. Two Elimination Reaction Patterns. Observation #1 : One Elimination Is Accompanied By S_N2, The Other By S_N1

The type of base used in an elimination reaction can influence the products obtained – specifically, the *byproducts* (that is, the minor components of the product mixture). In the first example, we take a sample of 2-bromobutane as a **single enantiomer**. Treatment with the strong base sodium ethoxide (NaOEt) gives two alkenes (*trans* and *cis*) which follow Zaitsev's rule. The trans product dominates over the cis product (due to less steric crowding), but what's really interesting is the byproduct obtained: 2-ethoxy butane, obtained with *inversion* of stereochemistry. This is the product of a substitution reaction – specifically, an SN2 reaction.

Elimination reactions can vary in the type of byproducts that are obtained

Example 1:

Elimination products (major)
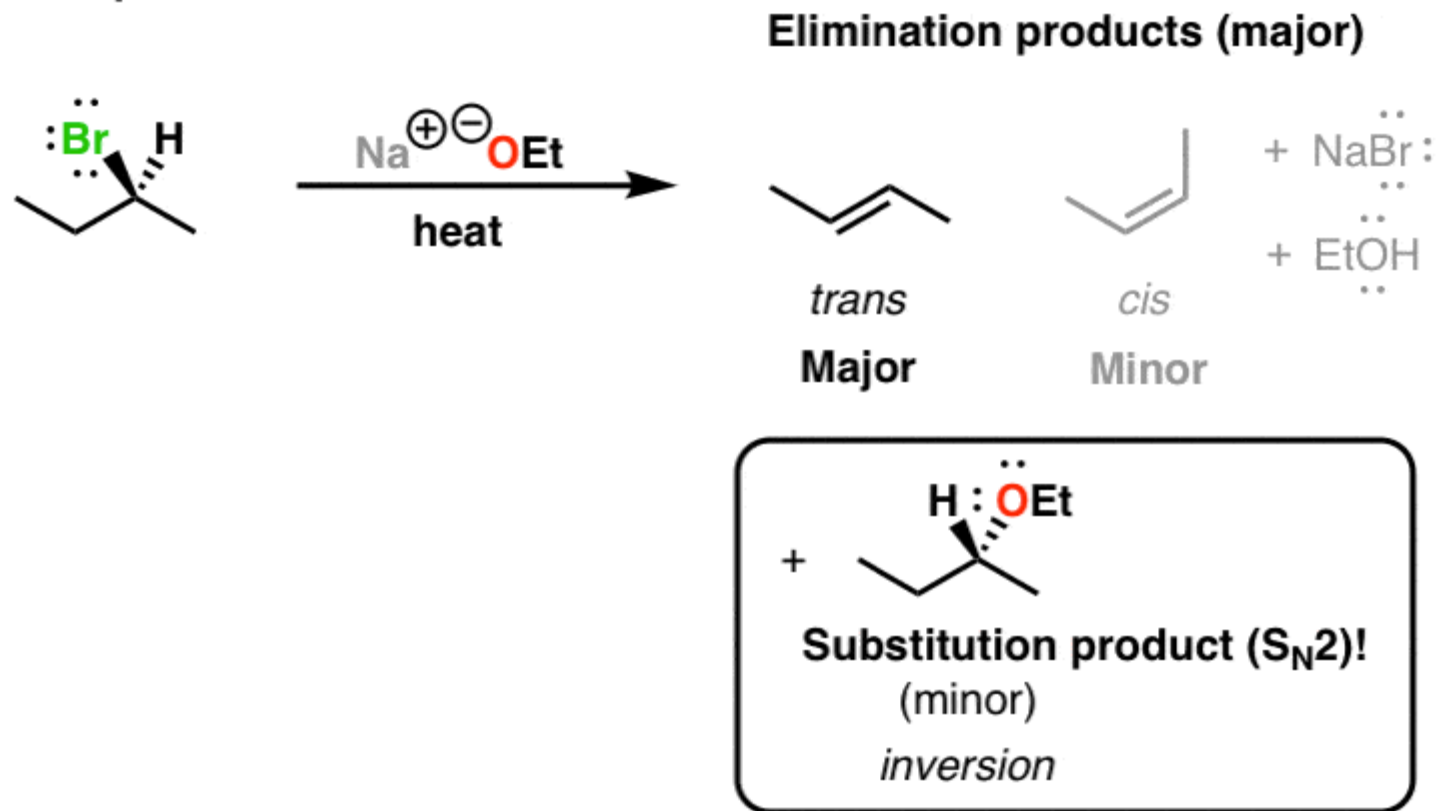
Now, if the same starting material is treated with water (a weaker base) and heated, we also obtain elimination products. However, the substitution product that is formed (2-butanol) is obtained as a **mixture of enantiomers**. In other words, we have a mixture of retention and inversion of the stereocenter. This is recognizable as an SN1 process.

Example 2:

Elimination products (major)

Major	Minor

$+ H_3O^{\oplus}$ $:Br:^{\ominus}$

Substitution products (S$_N$1)
(minor)
inversion + retention
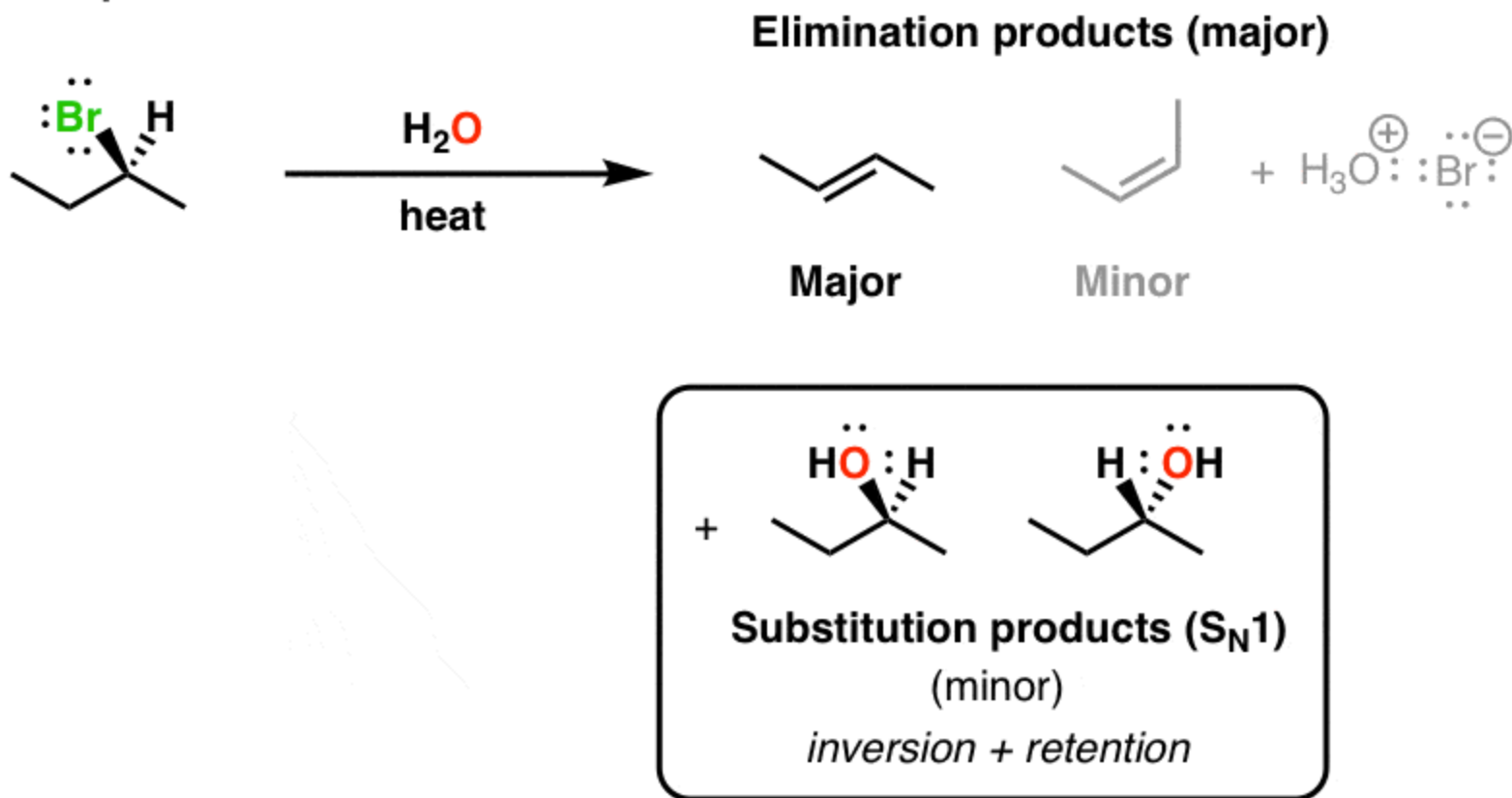
So one type of elimination (with strong bases) tends to compete with S$_N$2 reactions, while the other (with weak bases) tends to compete with the S$_N$1 pathway.

2. Two Elimination Reaction Patterns, Observation #2: One Elimination Is Sensitive To Stereochemistry, And The Other Is Not

Here's a quirky example of an elimination reaction. If you treat this substituted cyclohexane with the strong base NaOEt, you might expect to get the more substituted (tetrasubstituted) alkene with double bond between C_1 and C_2. But that's not what we actually get! In this case we only get the trisubstituted alkene shown below.

Stereochemistry

In some situations, the stereochemistry of the substrate can have quirky effects on the product obtained.

The first elimination reaction below produces only this product - which seems to violate Zaitsev's rule!

Only product!
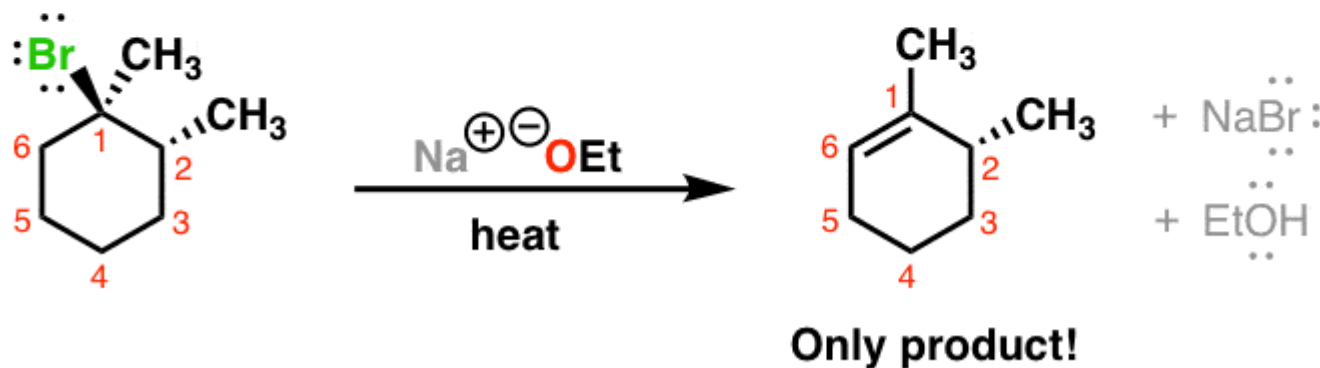
However, if you dissolve this same alkyl bromide in water, and heat it, you do obtain the tetrasubstituted alkene. The trisubstituted alkene is formed too, albeit only to a minor extent.

Major product   Minor product
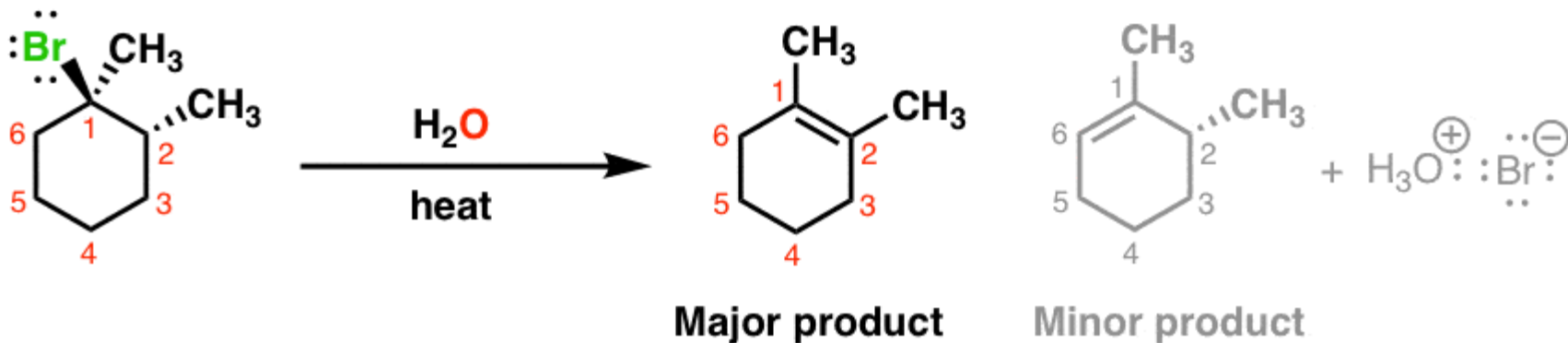
So clearly the stereochemistry of the starting material has some influence on the product of the first reaction, but seemingly not the second.

3. Two Elimination Reaction Patterns, Observation #3: One Elimination Has A Second-Order Rate Law, The Other Has A First-Order Rate Law

Finally, we can measure the rates of each of these reactions and determine their dependence on the concentration of substrate and base.

Looking at the first reaction below, the rate is dependent on the concentration of both the substrate and also of the base. Note how if we double the concentration of either the substrate or the base, the rate also doubles. **(Has A Second-Order Rate Law}**

Rate Laws

Some elimination reactions are sensitive to the concentration of both substrate and base:
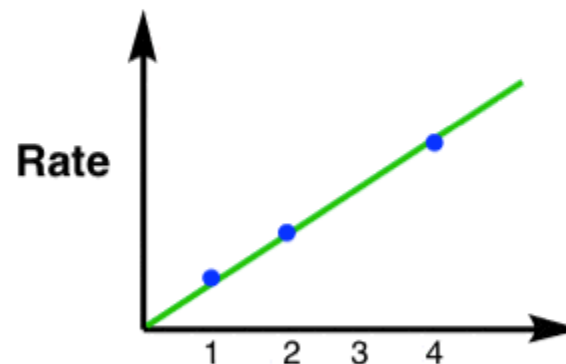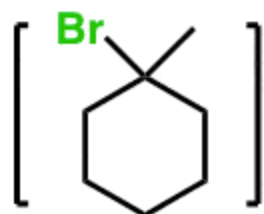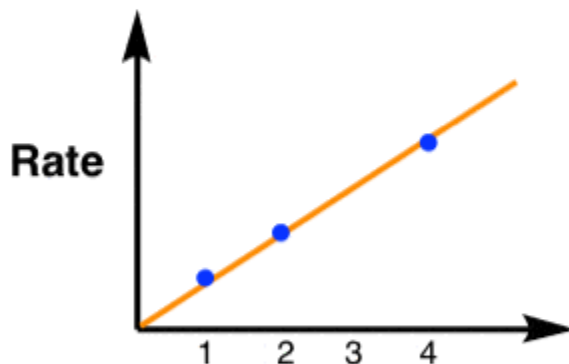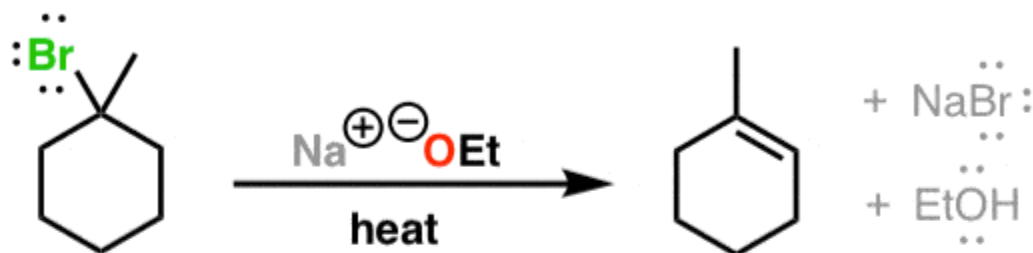
Contrast that with the second reaction, where the reaction rate is dependent *only* on the concentration of the substrate, but not on the base.

Others are only sensitive to the concentration of substrate
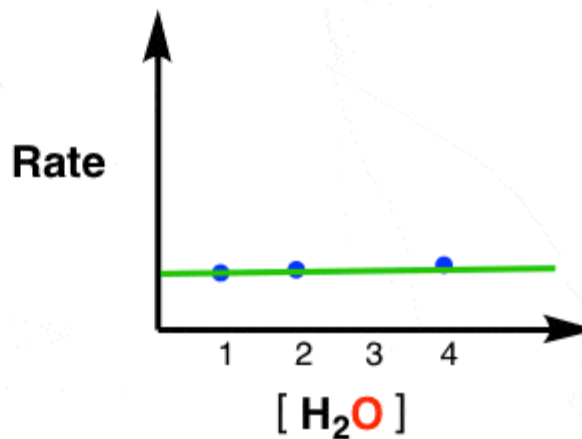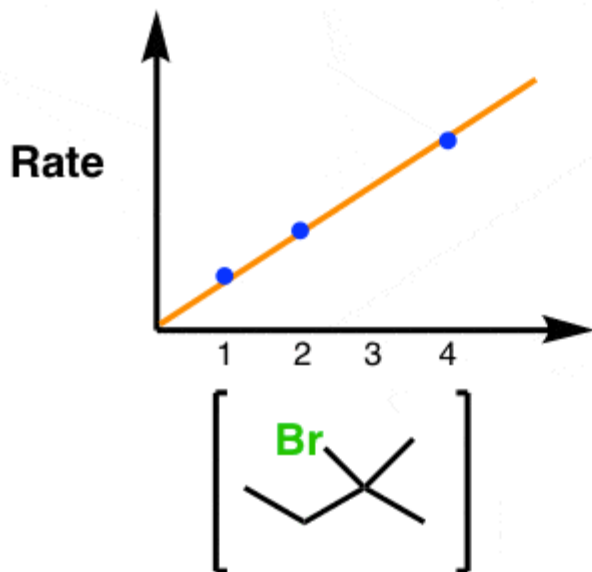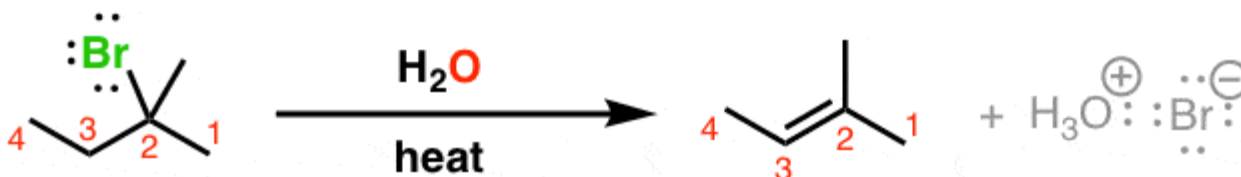
(Has A First-Order Rate Law)

4. What Mechanisms Could Explain The Results We Obtain For Each Of These Two Elimination Reactions?

The E1 Reaction

The E1 Reaction – Three Key Pieces of Evidence, and a Mechanism

Last time in this walkthrough on elimination reactions, we talked about two types of elimination reactions. In this post, we're going to dig a little bit deeper on one type of elimination reaction, and based on what experiments tell us, come up with a hypothesis for how it works.

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1. How Do We Explain What Happens In This Elimination Reaction (Which We Will Call, "E1")

2. First Clue About The Mechanism of the "E1 Elimination": The Rate Only Depends On Concentration of Substrate (Not Base)

3. The Second Clue About The Mechanism Of The E1 Elimination Reaction – Rate Is Fastest For Tertiary Substrates

4. The Third Clue About The Mechanism Of The E1 Elimination Reaction: It Competes with the SN1 Reaction

5. Putting It Together: The E1 Mechanism Proceeds Through Loss Of A Leaving Group, Then Deprotonation

1. How Do We Explain What Happens In This Elimination Reaction (Which We Will Call, "E1")

Here's the reaction. First, look at the bonds that are being formed and broken. This is a classic elimination reaction – we're forming a new C–C(π) bond, and breaking a C–H and C–leaving group (Br here) bond.

How do we explain what happens in this reaction?
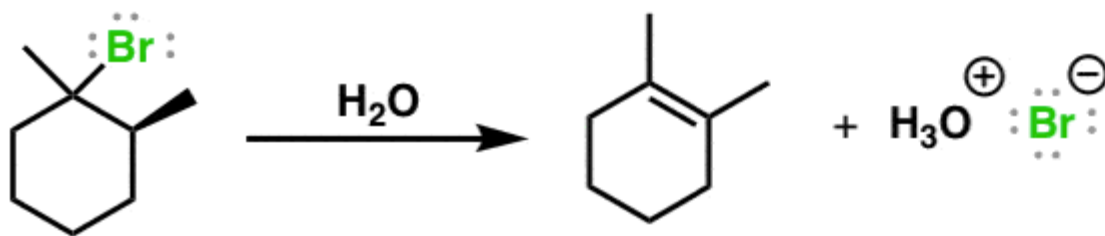
| Form	Break
C–C (π)	C–Br
O–H	C–H

But now we want to know more than just "what happens". We want to understand **how** it happens. What's the sequence of bond-forming and bond breaking? To understand HOW it happens, we need to look at what the data tells us. That's because chemistry is an empirical science; we look at the evidence, and then work backwards.

2. First Clue About The Mechanism of the "E1 Elimination": The Rate Only Depends On Concentration of Substrate (Not Base)

Let's look at the first important clue for this reaction. We can measure reaction rates quite readily. When we vary the concentration of the substrate, the reaction rate increases accordingly. In other words, there is a "first-order" dependence of rate on the concentration of substrate.
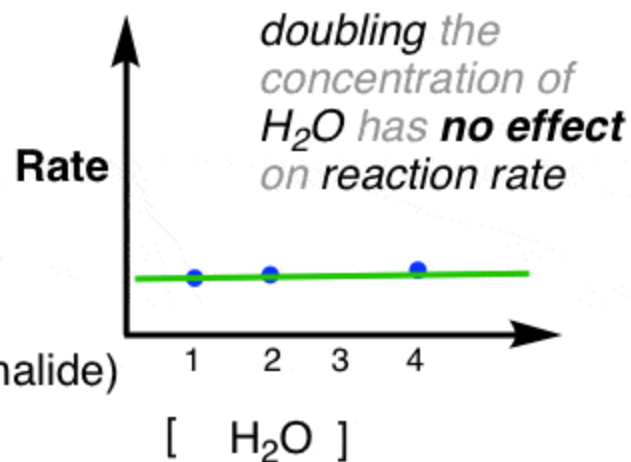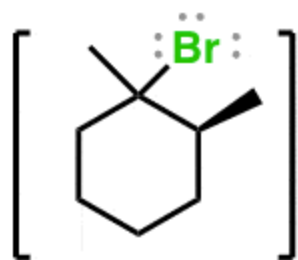
However, if we vary the concentration of the base (here, H_2O) the rate of the reaction doesn't change at all.

The reaction rate depends ONLY on the concentration of substrate
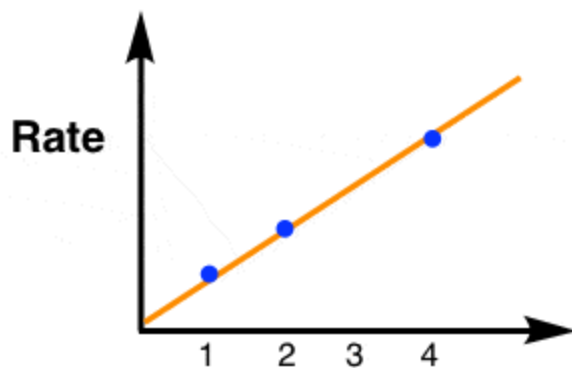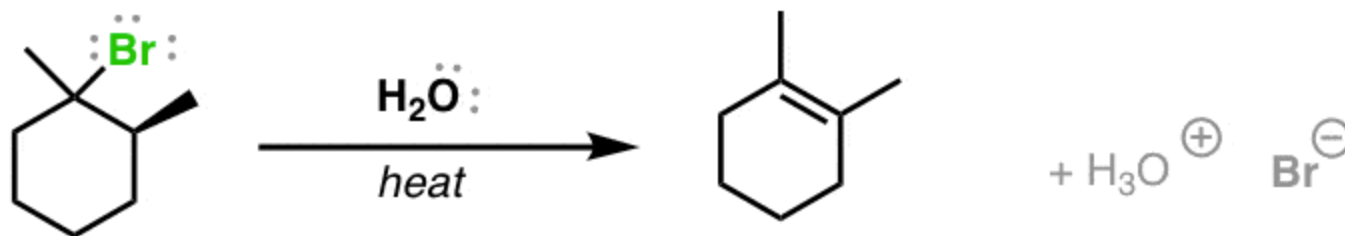
Rate

doubling *the concentration of alkyl halide* **doubles** *the reaction rate*

("First-order" in alkyl halide)

Rate

doubling *the concentration of* H_2O has **no effect** *on reaction rate*

$[\ H_2O \ ]$

What information can we deduce from this? The rate determining step for this reaction (whatever it is) therefore does **not** involve the base. Whatever mechanism we draw will have to account for this fact.

3. The Second Clue About The Mechanism Of The E1 Elimination Reaction – Rate Is Fastest For Tertiary Substrates

Another interesting line of evidence we can obtain from this reaction is through varying the **type** of substrate, and measure the rate constant that results. So if we take the simple alkyl halide on the far left (below) where the carbon attached to Br is also attached to 3 carbons (this is called a **tertiary** alkyl halide), the rate is faster than for the middle alkyl halide (a **secondary** alkyl halide) which is itself faster than a **primary** alkyl halide (attached to only one carbon in addition to Br).

So the rate proceeds in the order **tertiary (fastest) > secondary >> primary (slowest)**

The rate of the reaction depends greatly on the substitution pattern of the alkyl halide:

tertiary > secondary >> primary

fastest   slowest
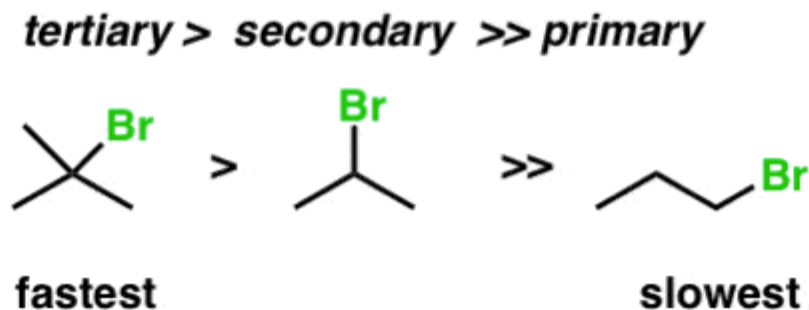
Any mechanism we draw for this reaction would likewise have to account for this fact. What could be going on such that tertiary substrates are faster than primary?

4. The Third Clue About The Mechanism Of The E1 Elimination Reaction: It Competes with the SN1 Reaction

A final interesting clue about the mechanism of this reaction concerns the by-products that are often obtained. For instance, when the alkyl halide below is subjected to these reaction conditions, we do obtain the expected elimination product. *However*, we also get substitution reactions in the product mix as well. Remember – substitution reactions involve breakage of C-(leaving group) and formation of C-(nucleophile). What makes this particular starting alkyl halide particularly interesting is that the carbon attached to Br is a **stereocenter.** And if we start with a single enantiomer of starting material here, we note that the substitution product formed is a **mixture of stereoisomers.** Note that both inversion **and** retention of stereochemistry at the stereocenter has occurred.

We've seen this pattern before – it's an S$_N$1 reaction!

The competing products of this reaction are S$_N$1

elimination
product

note two substitution products
with opposite stereochemistry
(a mix of retention and inversion)
This is an S$_N$1 reaction!
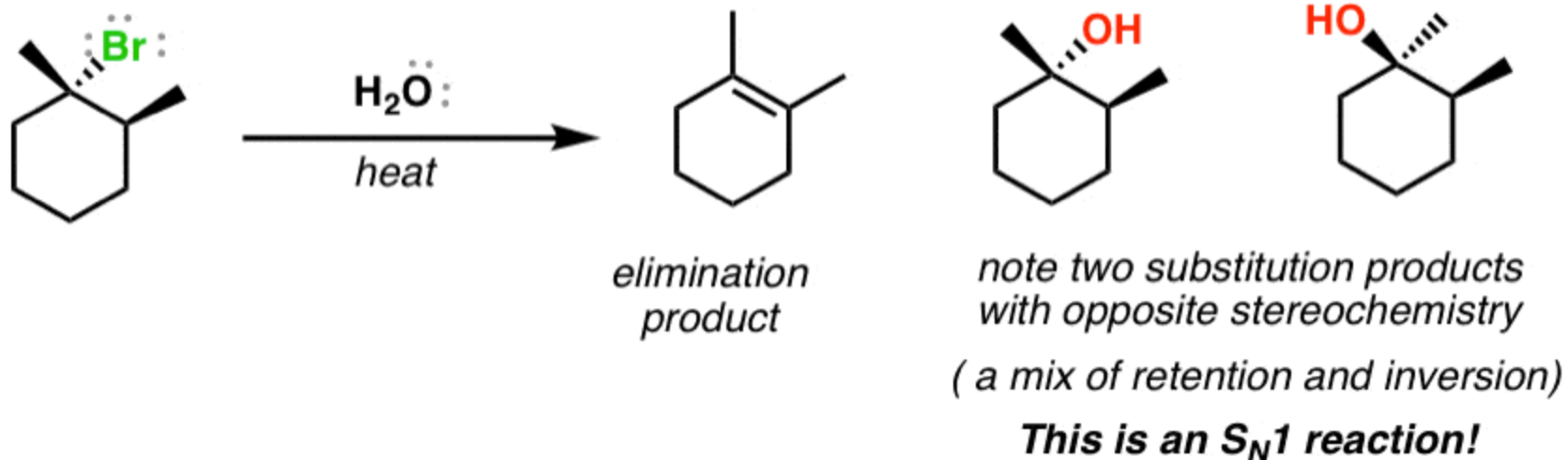
This last part is a very important clue. If an SN1 reaction is occurring in the reaction mixture, looking back at the mechanism of the SN1 could help us think about what type of mechanism might be going on in this case to give us the elimination product.

5. Putting It Together: The E1 Mechanism Proceeds Through Loss Of A Leaving Group, Then Deprotonation

Taking all of these clues into account, what's the best way to explain what happens? This:

How best to explain these results?

The best theory we have is that the reaction proceeds through two steps.

First, the leaving group leaves to form a carbocation:

Loss of leaving group
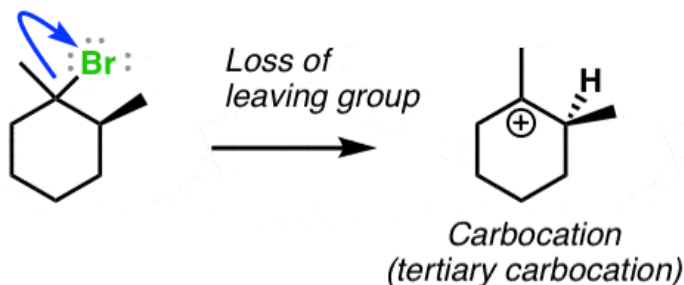
Recall that this is also the first step in the S_N1 reaction!

Carbocation (tertiary carbocation)

Second, a proton is removed by base to give the alkene:

Carbocation (tertiary carbocation)

$+ H_3O^{\oplus}$ $Br^{\ominus}$
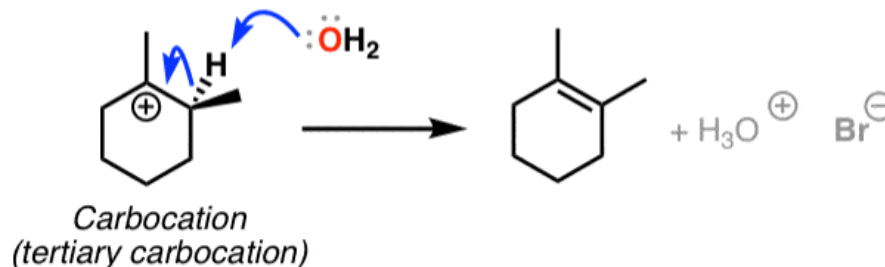
This explains several key facts!

1) the **rate determining step** (slow step) is loss of leaving group to form the carbocation
   This explains why the reaction only depends on the substrate concentration

2) the **rate** is proportional to **carbocation stability** (tertiary > secondary >> primary)

3) Recall that **loss of the leaving group** is also the first step in the **S_N1 reaction**.
   This is why S_N1 byproducts can also be observed

This is called the **E₁ mechanism**   **[Elimination, unimolecular]**

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The reaction is proposed to occur in two steps: **first, the leaving group leaves,** forming a carbocation. **Second, base removes a proton**, forming the alkene. This nicely fits in with the three clues mentioned above. [Also note that the more substituted alkene is formed here, following Zaitsev' rule].

Similar to the S_N1 mechanism, this is referred to as the **E1 mechanism** (elimination, unimolecular).

So what's going on in the other type of elimination reaction? That's the topic for the next post!

The E2 Mechanism

2 Mechanism – How The E2 (Elimination, Biomolecular) Reaction Works

Having gone through the [E1 mechanism for elimination reactions](#), we've accounted for one way in which elimination reactions can occur. However, there's still another set of data that describes some elimination reactions that we haven't adequately explained yet.

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1. Example Of An "E2" Reaction: How Do We Explain What Happens In This Reaction?

Here's an example of the reaction I'm talking about:

How do we explain what happens in this reaction?

	Form	Break
	C–C (π)	C–Br
	O–H	C–H

+ HOCH$_3$

+ NaBr
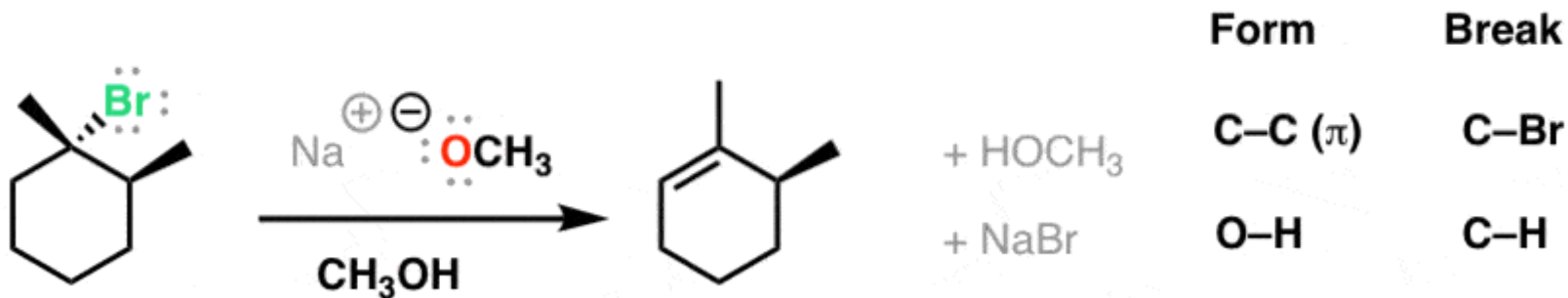
What's interesting about this reaction is that it doesn't follow the same rules that we saw for the E1 reaction. We'll talk about two key differences here.

2. Clue #1 About The Mechanism Of The E2 Reaction: The Rate Depends on Concentration of Both Substrate and Base

Remember that the E1 reaction has a "unimolecular" rate determining step (that is, the rate **only** depends on the concentration of the substrate?)

Well, when we look at the rate law for this reaction, we find that it depends on two factors. It's dependent on the concentration of **both** substrate **and** the base.

That means that whatever mechanism we propose for this reaction has to explain this data.

By the way, see how **useful** chemical kinetics can be? They're such simple experiments – measure reaction rate versus concentration – and you get these nice graphs out of it. I can't even begin to stress how important this data can be in understanding reaction mechanisms. So simple, so elegant, and so useful.

Another note – you might notice that the base here (CH_3O^-) is a stronger base than we see for the E1 reaction (more on that later).

First Clue - The Rate Laws

The Reaction rate depends on the concentration of BOTH base and substrate (first order in alkyl halide + first order in base = second order overall)
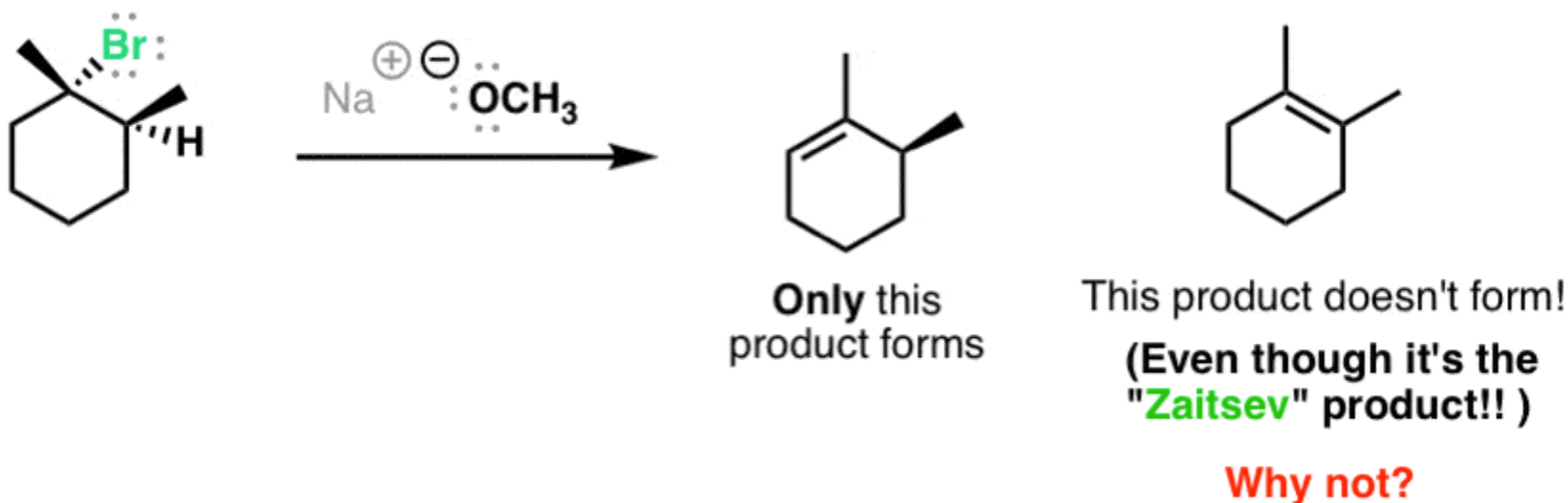

doubling the concentration of alkyl halide *doubles* the rate

Rate

First order in alkyl halide
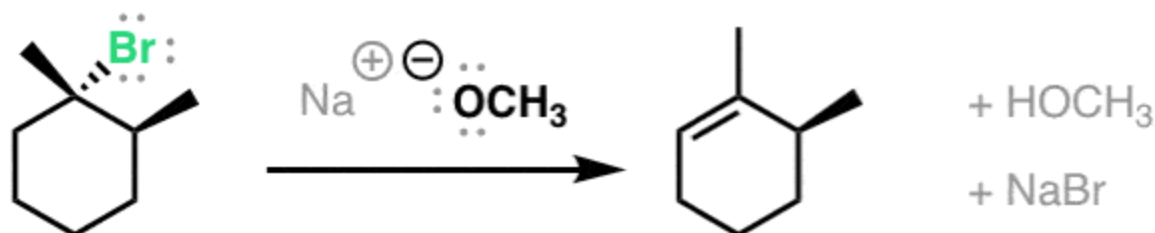
doubling the concentration of base *doubles* the rate

Rate
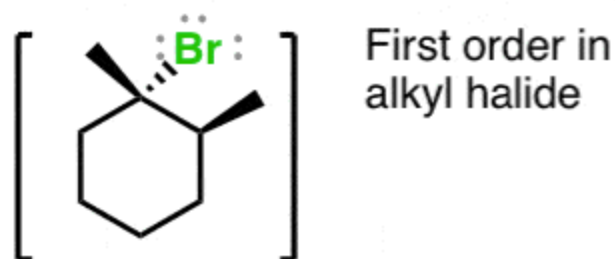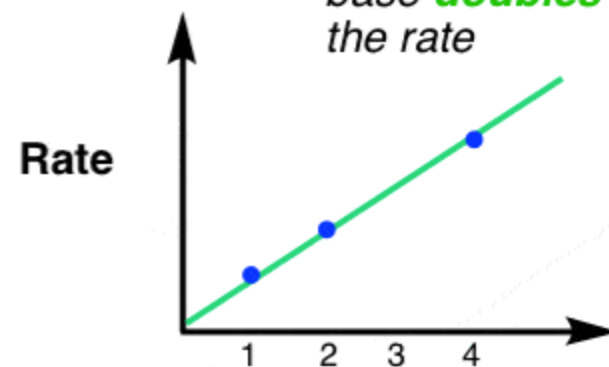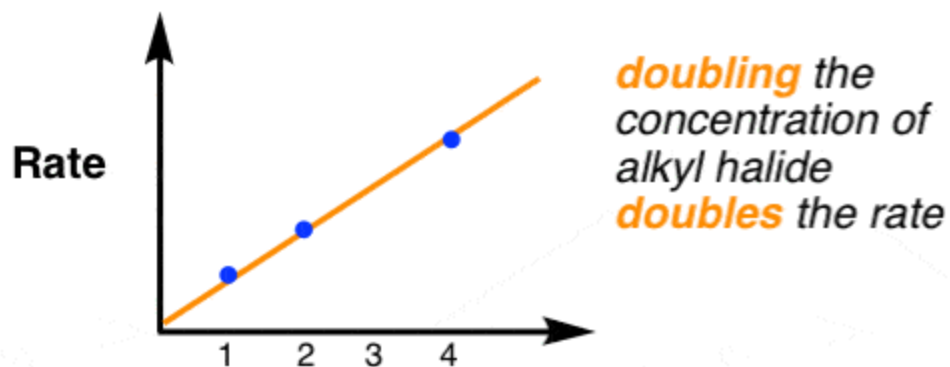
[NaOCH$_3$]

First order in base

3. Clue #2 About The Mechanism Of The E2 Reaction: Stereochemistry Of The C–H Bond And The Leaving Group Is "Anti"

Here's the second key piece of information – and we didn't talk about this for the E1. **The reaction below is very dependent on the stereochemistry of the starting material.**
When we treat this alkyl halide with the strong base, CH_3ONa, look at this interesting result. What's weird about this? Well, this seems to fly in the face of Zaitsev's rule, right? Why don't we get the tetrasubstituted alkene here?

Second Clue To The Mechanism: The Stereochemistry

Only this product forms

This product doesn't form!

(Even though it's the "Zaitsev" product!!)

Why not?

The mystery gets a little deeper. If, instead of starting with the alkyl halide above, we "label" it with deuterium – that is, we replace one of the hydrogens with its heavy-isotope cousin that has essentially identical chemical properties – we see this interesting pattern:

Using isotopically 'labelled' products makes it even more interesting

D stands for deuterium, a heavy isotope of hydrogen

Only the deuterium is removed in this case.

Here, the deuterium remains behind!
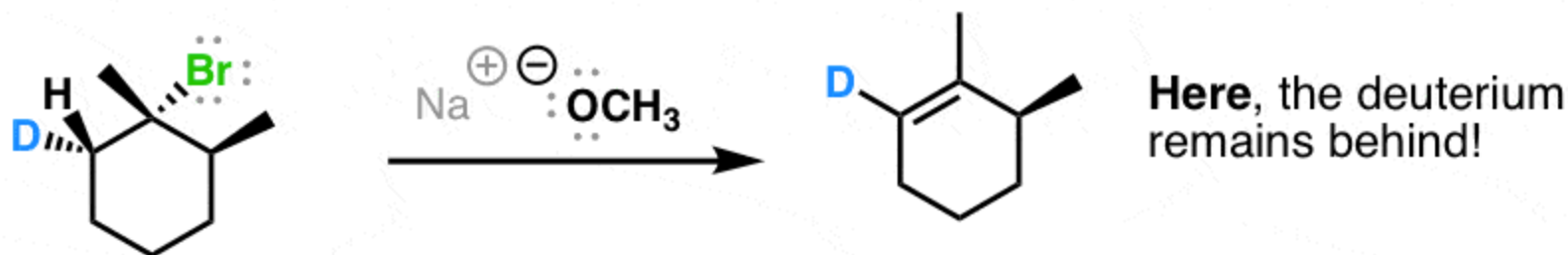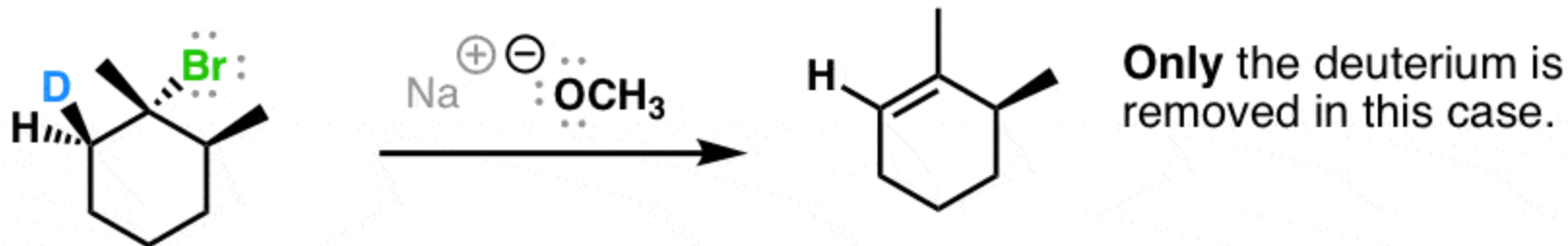
Note that in each case only the H/D that is *anti* to the Br is removed !

Note how the group that is on the opposite face of the cyclohexane ring to the leaving group (Br) is always broken.

In fact, if we use the molecule above and make just one modification, now we actually **do** get the Zaitsev product!

Making one small change DOES give us the Zaitsev product!
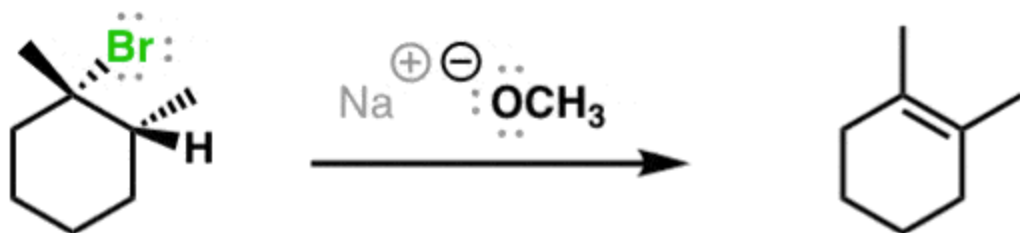
In this molecule,
note that the **H**
and **Br** are **anti**
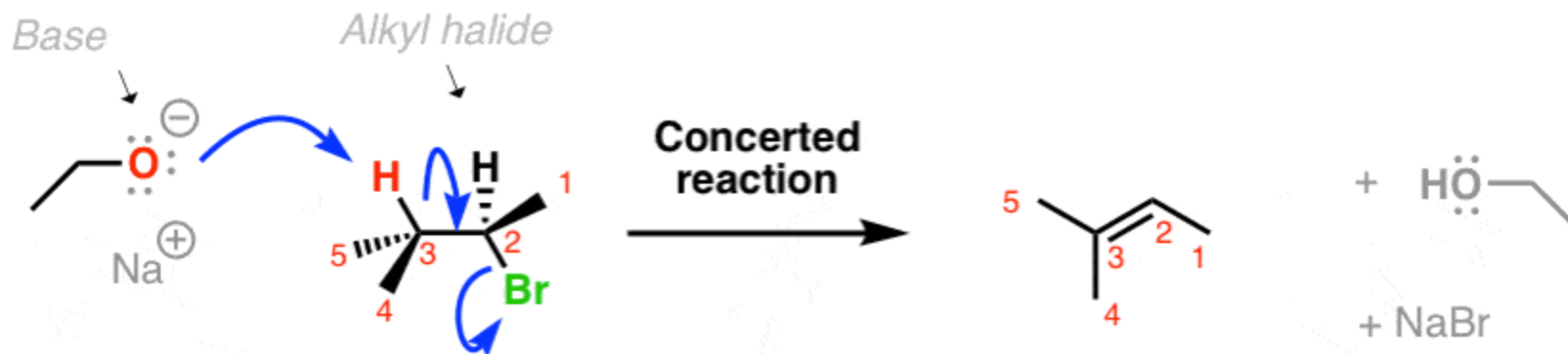to each other

Now the Zaitsev
product is major!

See what's going on? The hydrogen that is broken is always opposite, or "anti" to the leaving group.

So how do we explain these two factors?

4. Putting It Together: The Mechanism Of The E2 Reaction

Here's a hypothesis for how this elimination reaction works. It accounts for all the bonds that form and break, as well as the rate law, and – crucially – the stereochemistry.

A Mechanism That Incorporates All The Evidence

Explains the observed rate law

- First order in base, first order in alkyl halide, second order overall
- Concerted mechanism

Explains the observed *stereochemistry* of this reaction

- Note that the **H** and **Br** are oriented at 180° to each other ("anti")
- Imagine the pair of electrons from C3–H doing a "backside attack" on the C2–Br bond, forming the new π bond.

This is called the E_2 mechanism (Elimination, bimolecular)

In this mechanism, the base removes the proton from the alkyl halide that is oriented **anti** to the leaving group, and the leaving group leaves – **all in one concerted step.**

Since it's an elimination reaction, and the rate law is "bimolecular", we call this mechanism the **E2**.

E1 versus E2 : Comparing The E1 and E2 Reactions

Now that we've gone through the mechanisms of the E1 and E2 reactions, let's take a moment to look at them side by side and compare them.
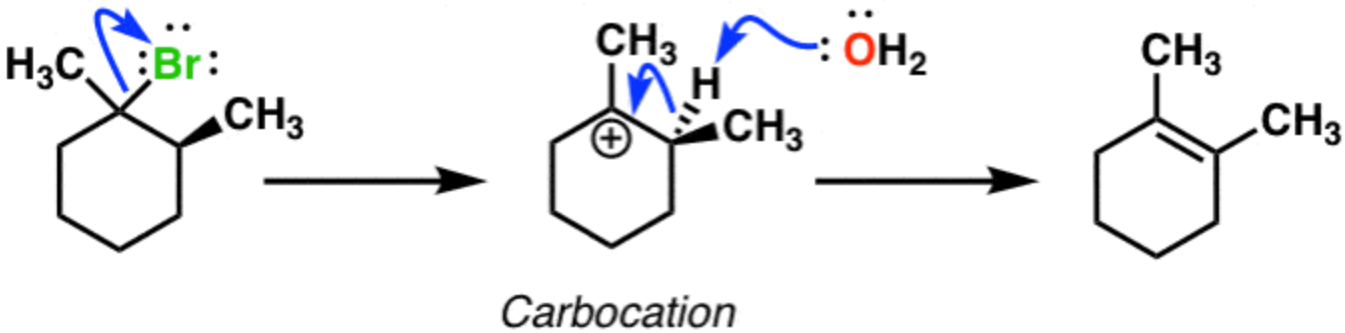
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1. Comparing The Mechanism Of The E1 and E2 Reactions

Here's how each of them work:

The E$_1$ Mechanism

Step 1: Loss of leaving group *Step 2: Deprotonation*

Carbocation

The E$_2$ Mechanism
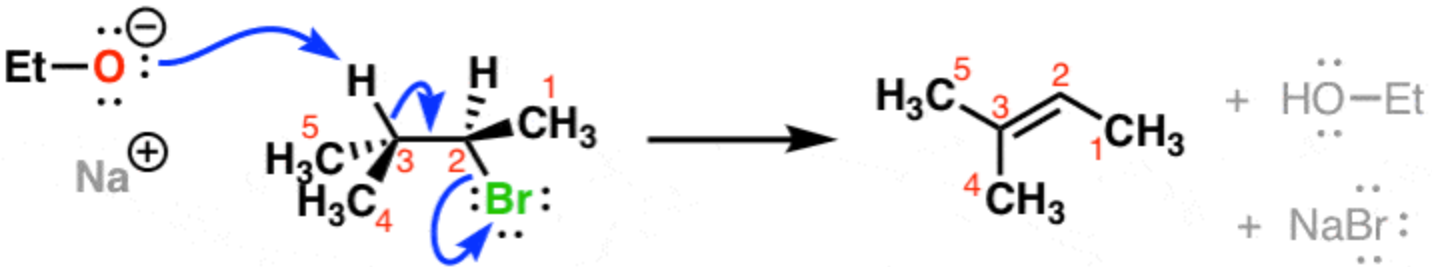
One step! Hydrogen removed must be "anti" to the
leaving group (dihedral angle 180°)

2. What Do The E1 and E2 Reactions Have In Common?

Here's what each of these two reactions has in common:

- in both cases, we form a new C-C π bond, and break a C-H bond and a C–(leaving group) bond

- in both reactions, a species acts as a base to remove a proton, forming the new π bond

- both reactions **follow Zaitsev's rule** (where possible)

- both reactions are **favored by heat**.

3. How Are The E1 and E2 Reactions Different?

Comparing the E1 and E2 mechanisms

	E1	E2
Rate Law	Unimolecular (depends on concentration of substrate)	Bimolecular (depends on concentration of both substrate and base)
"Big Barrier"	Formation of carbocation 3° > 2° >> 1°	None
Requires strong base?	No	Yes
Stereochemistry	No requirement	Leaving group must be *anti* to hydrogen removed

The rate of the E1 reaction depends **only on the substrate**, since the rate limiting step is the **formation of a carbocation**. Hence, the more [**stable**](#) that carbocation is, the faster the reaction will be. Forming the carbocation is the "slow step"; a strong base is **not** required to form the alkene, since there is no leaving group that will need to be displaced (more on that in a second). Finally there is no requirement for the stereochemistry of the starting material; the hydrogen can be at any orientation to the leaving group in the starting material [although we'll see in a sec that we **do** require that the C-H bond be able to rotate so that it's in the same plane as the empty p orbital on the carbocation when the new π bond is formed].

The rate of the E2 reaction depends on **both substrate and base**, since the rate-determining step is **bimolecular** (concerted). A **strong base** is generally required, one that will allow for displacement of a polar leaving group. The stereochemistry of the hydrogen to be removed **must be *anti*** to that of the leaving group; the pair of electrons from the breaking C-H bond donate into the antibonding orbital of the C-(leaving group) bond, leading to its loss as a leaving group.

Now we're in a position to answer a puzzle that came up when we first looked at elimination reactions. Remember this reaction – where one elimination gave the "Zaitsev" product, whereas the other one did not. Can you see why now?

Now we can solve a puzzle

Remember how this elimination reaction seemed to violate Zaitsev's rule?

Only product!
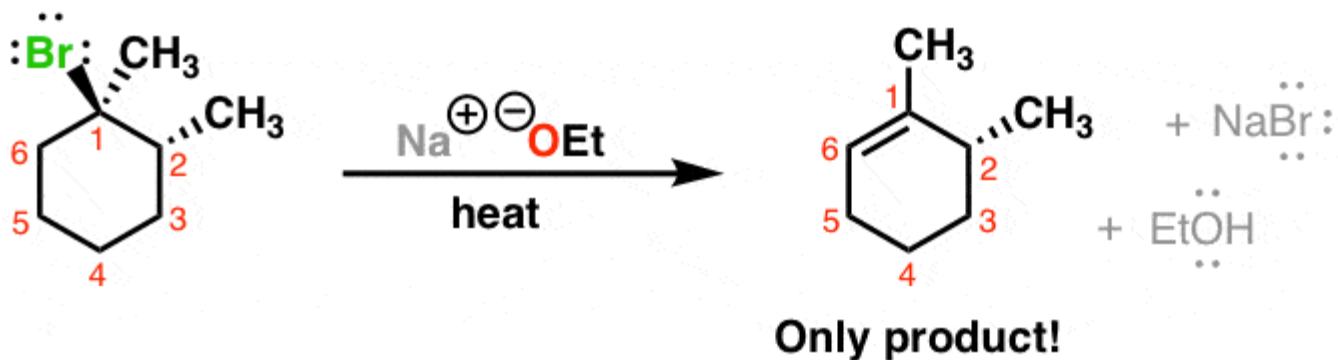
Whereas the elimination below produces the Zaitsev product (more substituted) as major.

Major product   **Minor product**
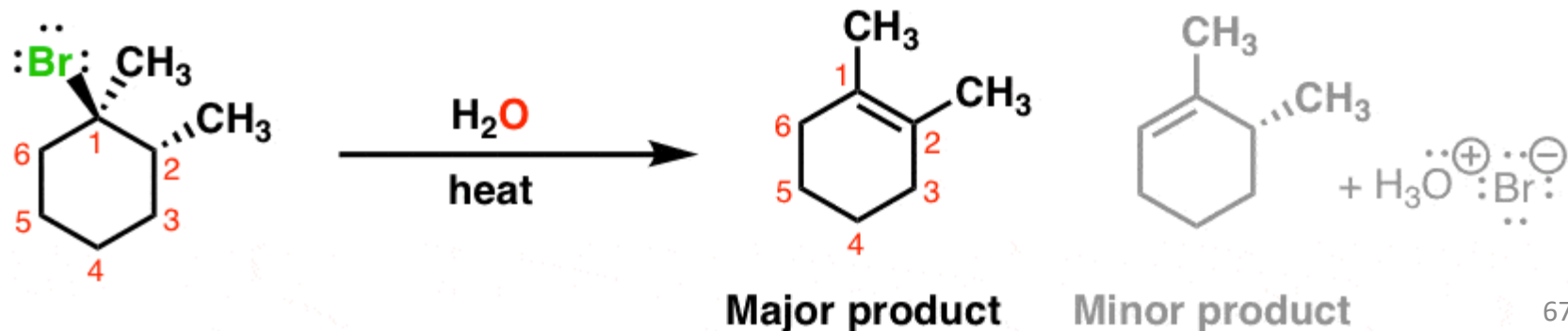
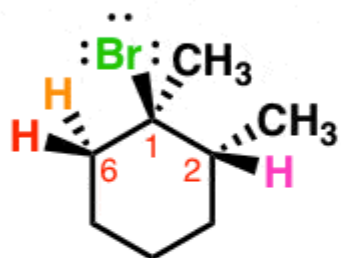# 5. The Key Requirements Of Stereochemistry In The E2 Reaction

So what's going on here?
The first case is an E2 reaction. The leaving group **must** be *anti* to the hydrogen that is removed.
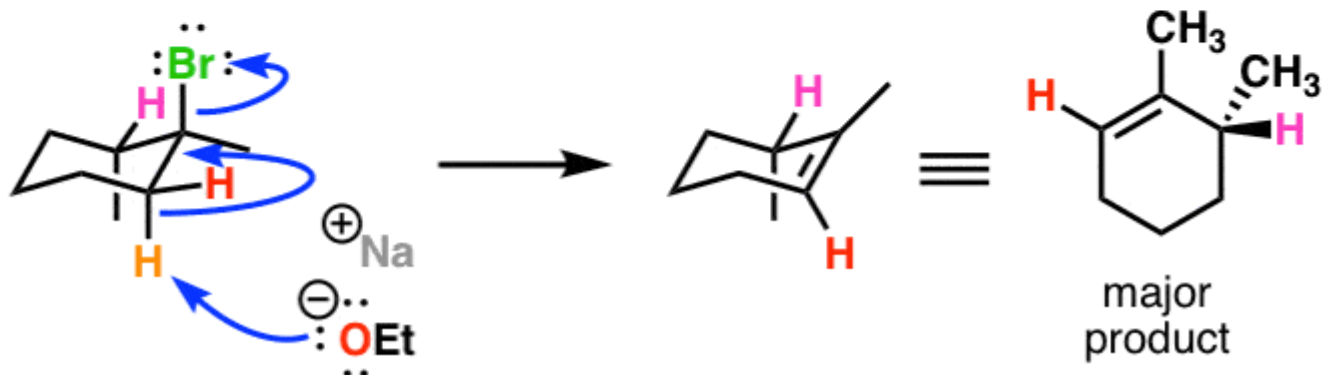
Why? (Part 1)

The first case is an E2 reaction.

The leaving group **must** be anti to the hydrogen that is removed.

The hydrogen on C_2 (H) can never be *anti* to the Br, because it is on the same side of the ring. So we can't form a double bond between C_1 and C_2! (i.e. we can't get the Zaitsev product)

We must remove the hydrogen from C_6 (H) that is *anti* to the Br
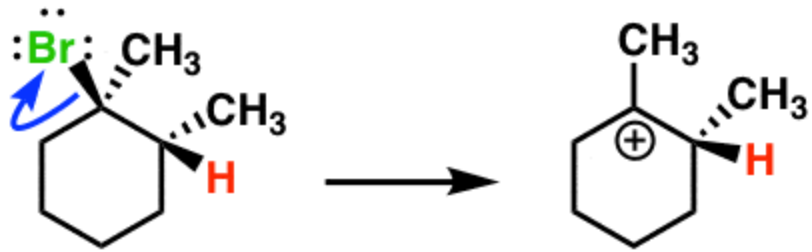
major
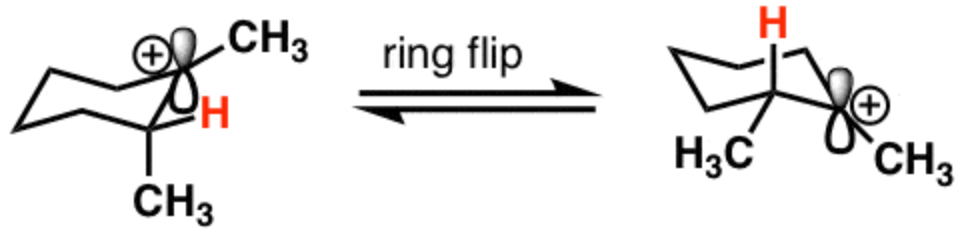product

The second case is an E1 reaction.

Why? (Part 2)

The second case is an **E1 reaction**

The first step is formation of a carbocation

As long as the C-H bond is aligned with the empty p-orbital of the carbocation, the double bond can form. There will always be a ring conformation where this is possible.

ring flip

H not aligned with p-orbital
(elimination **not** possible)

H aligned with p-orbital
(elimination **is** possible!)

Note how the H is axial!

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In our cyclohexane ring here, the hydrogen has to be axial. That's the only way we can form a π

bond between these two carbons; we need the p orbital of the carbocation to line up with the

pair of electrons from the C-H bond that we're breaking in the deprotonation step. We can

always do a ring flip to make this H axial, so we can form the Zaitsev product.

Here's that deprotonation step:

The second step of the E1 is removal of the proton and formation of the double bond:
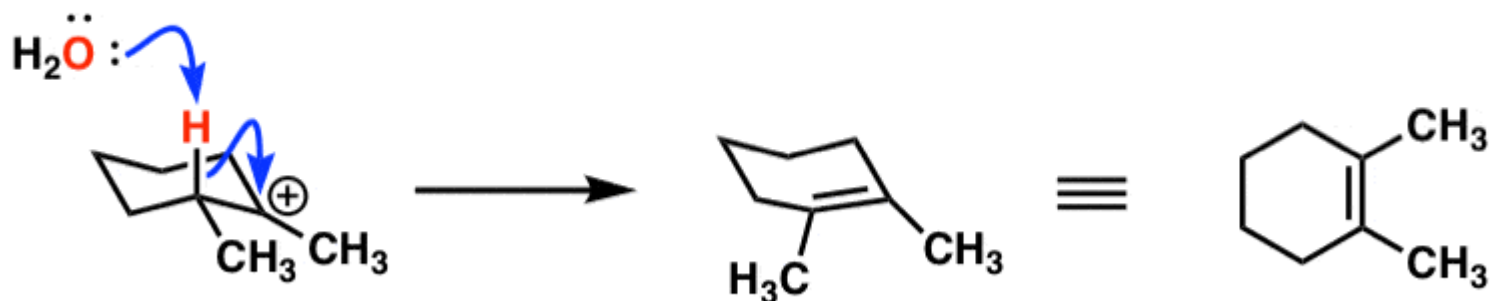
As you can see, cyclohexane rings can cause some interesting complications with

elimination reactions! In the next post we'll take a detour and talk specifically about E2

reactions in cyclohexane rings.

Antiperiplanar Relationships: The E2 Reaction and Cyclohexane Rings

Antiperiplanar Relationships Between C-H And The Leaving Group: The E2 Reaction and Cyclohexane Rings

Here we come to a very *testable* application of the E2 reaction – how to draw the products of E2 reactions in cyclohexane rings!

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1. In The E2 Reaction, The Leaving Group Is Always "Anti-Periplanar" To The Hydrogen That Is Removed On The Adjacent Carbon ("Beta-Carbon")

2. In Cyclohexane Rings, E2 Reactions Can Only Occur When The Leaving Group Is Axial

3. In E2 Reactions Of Cyclohexane Rings, The Only Way The Leaving Group And C-H Bond Can Be Anti-Periplanar Is If They Are On Opposite Faces Of The Ring

4. Some Examples: What Would Be The Major E2 Product In Each Case?

5. Cyclohexane Substituents Can Affect The Rate Of E2 Elimination Reactions In Cyclohexane Rings

6. The Higher The Concentration Of The Conformer With An Axial Leaving Group, The Faster The Elimination Will Be

7. Notes

1. In The E2 Reaction, The Leaving Group Is Always "Anti-Periplanar" To The Hydrogen That Is Removed On The Adjacent Carbon (i.e. the "Beta-Carbon")

Last time we [compared the E1 and E2 reactions](#) and mentioned one of the key differences was the stereochemistry of the E2 reaction. Remember that in the E2, the leaving group is always "anti" to the hydrogen that is removed on the adjacent carbon. [That means that they're directly opposed to each other, or 180°; kind of like the minute hand and the hour hand when a clock reads 6:00].

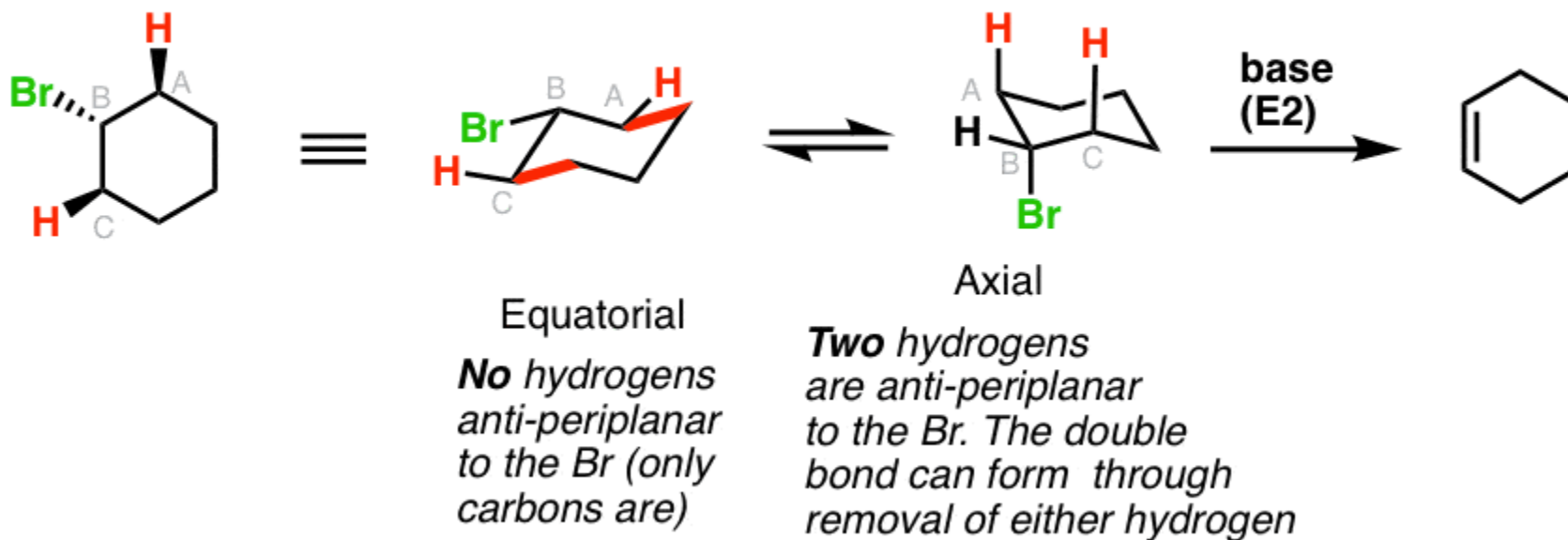This is an extremely important detail to be able to apply in reactions.

2. In Cyclohexane Rings, E2 Reactions Only Occur When The Leaving Group Is Axial

One way this often comes up is in discussions of cyclohexane rings. If you'll recall, in the cyclohexane chair conformation, groups can either be axial (pointing straight up or down) or equatorial (pointing "somewhat up" or "somewhat down").

In order for a hydrogen to be "anti" to a leaving group, it's required that **both groups be axial.** Look closely at the cyclohexane ring on the left, where the leaving group is equatorial – see how the group that is "anti" is the C-C bond [highlighed in red]?
That E2 is never gonna work!

In a cyclohexane, the E2 can only occur when the leaving group is axial:

Equatorial
No hydrogens anti-periplanar to the Br (only carbons are)

Axial
Two hydrogens are anti-periplanar to the Br. The double bond can form through removal of either hydrogen

So if you draw the leaving group equatorial in a cyclohexane chair, **you'll have to do a chair flip so that the leaving group is axial.** That's shown in the right hand example, where an E2 can actually happen.

3. In E2 Reactions Of Cyclohexane Rings, The Only Way The Leaving Group And C-H Bond Can Be Anti-Periplanar Is If They Are On Opposite Faces Of The Ring

This brings us to the second point. If the leaving group is, let's say, on the "top" face of the cyclohexane, you can **only** form an alkene to adjacent carbons where the hydrogen is on the **opposite face.**

You might remember the example from last time where we couldn't form the "Zaitsev" alkene because the Br was a wedge and there was an alkyl group on the carbon next door that was on the opposite face. In this case we can only form the less substituted alkene. If the methyl group is switched, however, then the E2 to give the Zaitsev product becomes possible:

## How Cyclohexane Stereochemistry Affects Elimination

• Elimination can't occurr when there is no **H** "anti-periplanar" to the leaving group (**Br**)

anti-periplanar to leaving group Br ✓

Br Equatorial

Br Axial

base (E2)

(not IUPAC numbering)
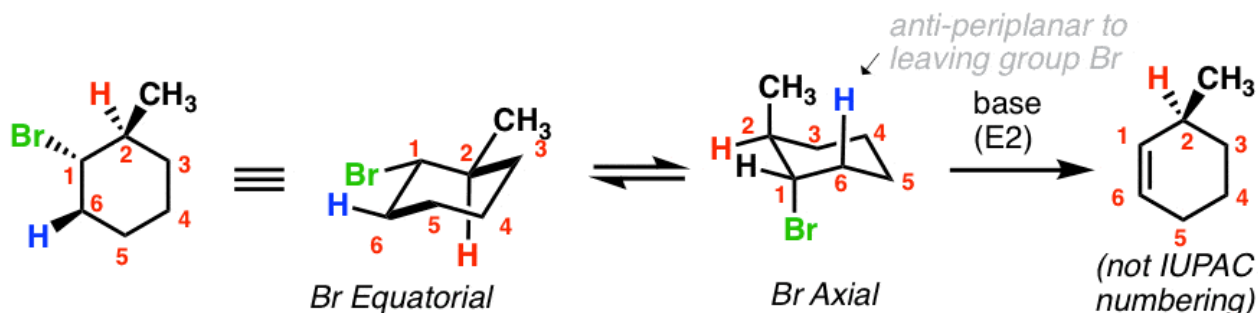
Note how elimination between C_1 and C_2 is **not possible**, since there is no **H** at C_2 that is anti-periplanar to the leaving group **Br**

Elimination can only occur between C_1 and C_6 here (removal of **H**)

• When multiple eliminations are possible, the one forming the more substituted alkene is favored (Zaitsev's rule)

Br Equatorial

Br Axial

base (E2)

(not IUPAC numbering)
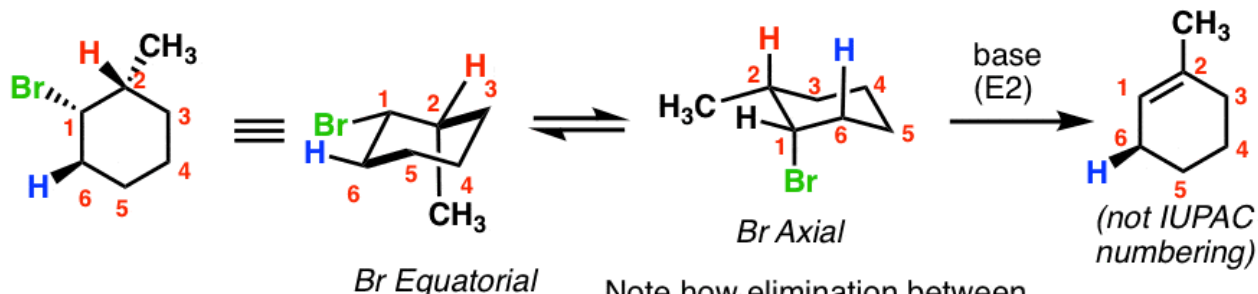
Note how elimination between C_1 and C_2 **is possible**, since there is now an **H** at C_2 that is anti-periplanar to the leaving group

Elimination can occur between C_1 and C_2 here (favored due to Zaitsev's rule) and also between C_1 and C_6 (not favored)

The bottom line here [and trust me, this comes up in tests, *a lot*!] is that you always want to pay attention to what side of the ring your leaving group is on, and make sure that the E2 you draw is indeed possible.

4. Some Examples: What Would Be The Major E2 Product In Each Case?

Here are some more examples to think about. What would be the major E2 product in each case?

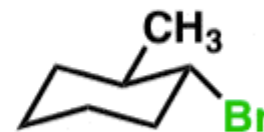**What would be the major E2 product for each of these 4 substrates?**
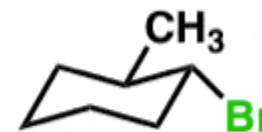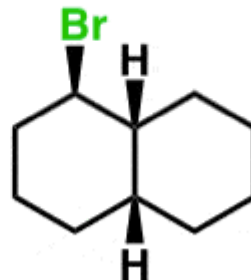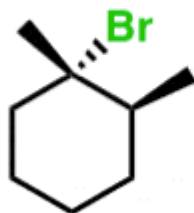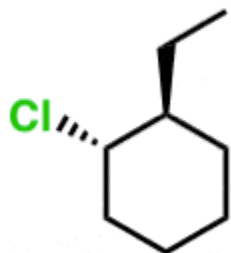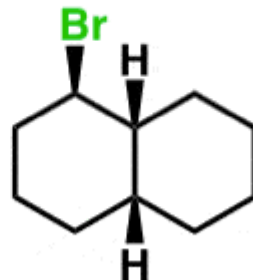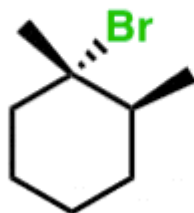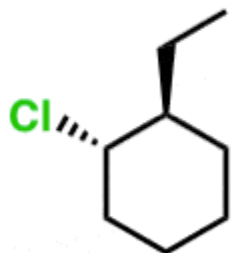

Now, let's talk about a very interesting application of what we just discussed. This is a little more advanced, but see if you can follow it through. It ties together what we've discussed about the E2 with what you've previously learned about cyclohexane chair flips.
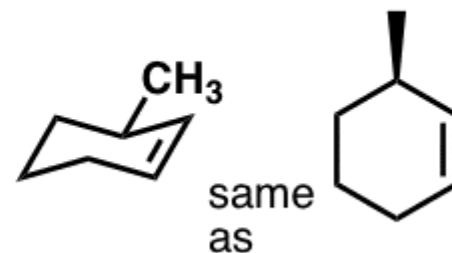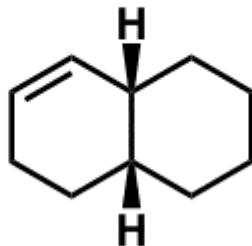
4. Some Examples: What Would Be The Major E2 Product In Each Case?

Here are some more examples to think about. What would be the major E2 product in each case?

What would be the major E2 product for each of these 4 substrates?

Now, let's talk about a very interesting application of what we just discussed. This is a little more advanced, but see if you can follow it through. It ties together what we've discussed about the E2 with what you've previously learned about cyclohexane chair flips.
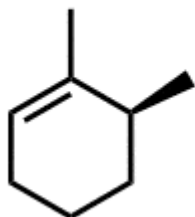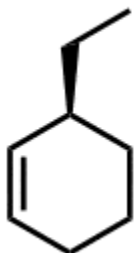
5. Cyclohexane Substituents Can Affect The Rate Of E2 Elimination Reactions In Cyclohexane Rings

Imagine you've got two alkyl halides, and they've got slightly different structures. We make the following observation: E2 with the second starting material is significantly faster than E2 with the first product. Question: why might this be?

Application: Explain the difference in rate in these two cyclohexanes!

strong base (E2)

SLOWER

(+ enantiomer)

strong base (E2)

FASTER

(+ enantiomer)
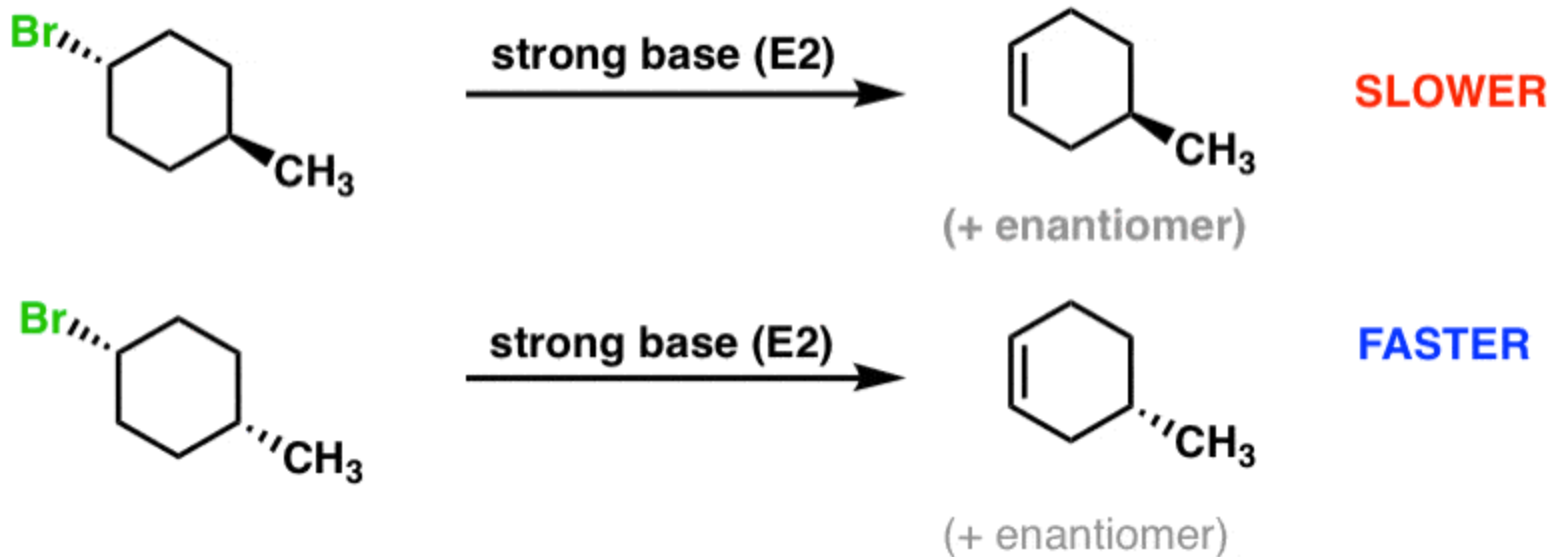
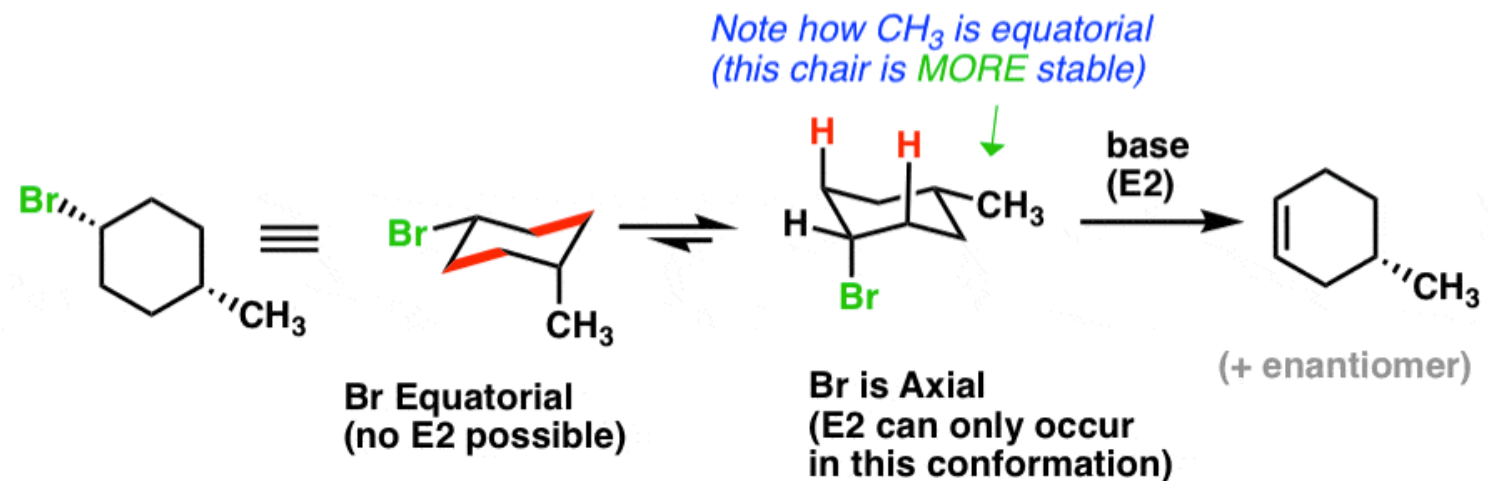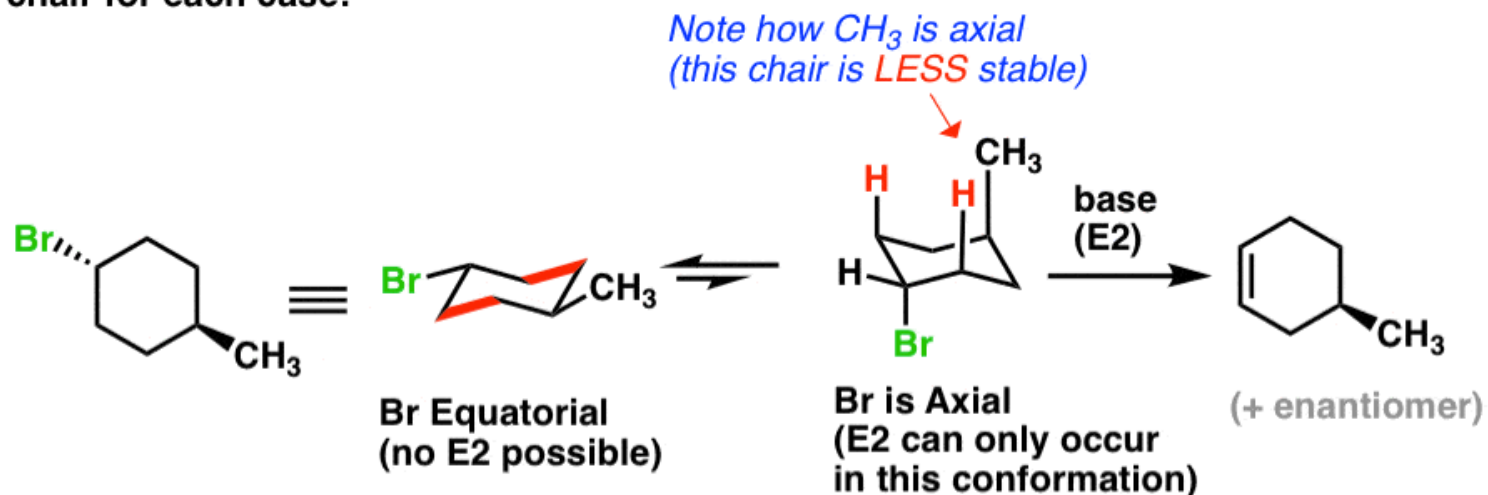In order to understand what's going on, it would help to draw the cyclohexane chair forms of both of these molecules. So let's do that and then have a closer look.

Knowing that the elimination <u>must</u> occur when Br is axial, draw the corresponding chair for each case:

Note how CH_3 is axial (this chair is LESS stable)

Br Equatorial (no E2 possible)

Br is Axial (E2 can only occur in this conformation)

(+ enantiomer)

Note how CH_3 is equatorial (this chair is MORE stable)

Br Equatorial (no E2 possible)

Br is Axial (E2 can only occur in this conformation)

(+ enantiomer)

• The bottom reaction will occur more quickly because it goes through a **more stable** chair conformation (when Br is axial, CH_3 is equatorial)

What's going on? Each molecule will have an equilibrium between two chair forms. In the top molecule, the left-hand conformation is favored, because the bulky methyl group* [CH_3 is actually bulkier than Br] is equatorial. So equilibrium will favor the left hand molecule.

In the bottom molecule, the rightmost conformation is favored, because the bulky methyl group is equatorial. So equilibrium will favor the right-hand molecule.

6. The Higher The Concentration Of The Conformer With An Axial Leaving Group, The Faster The Elimination Will Be

Notice something interesting? Remember that in order for E2 to occur, the leaving group must be axial. So there's only one conformation where this will be possible for each ring. However, in the top example, Br is axial only in the **least stable** conformation, whereas in the bottom example, Br is axial in the **most stable** conformation. Since the bottom example will have a **higher concentration where Br is axial, it will be faster.**

Isn't it interesting how it all ties together? Concepts you learn in one chapter can come back and be applied in later chapters!

In the next post we'll talk about another example where Zaitsev's rule doesn't apply.

Bulky Bases in Elimination Reactions

Elimination Reactions Using "Bulky Bases" – When The Zaitsev Product Is Minor
We've recently talked about Zaitsev's rule in elimination reactions, and how the transition state leading to the more substituted alkene is lower in energy. This covers reactions involving "bulky bases" where less of the Zaitsev product is obtained.

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1. "Normal" E2 Reactions Follow Zaitsev's Rule, Giving The "More Substituted" Alkene

2. "Bulky Bases" Tend To Give A Higher Proportion Of "Non-Zaitsev" Products

3. Bulky Bases Give More "Non-Zaitsev" Products Due To Steric Interactions With The Alkyl Halide

4. Two Common Bulky Bases Are The t-Butoxide Ion And Lithium Di-Isopropyl Amide (LDA)

1. "Normal" E2 Reactions Follow Zaitsev's Rule, Giving The "More Substituted" Alkene

Most elimination reactions follow Zaitsev's rule : you should expect that the "more substituted" alkene will be formed if at all possible. Like in the elimination reaction below, for instance, we get 80% of the tetrasubstituted alkene ["Zaitsev" – more substituted because there are 4 carbons attached to the alkene] and 20% of the disubstituted "non-Zaitsev" product.


80%

Zaitsev product

20%

non-Zaitsev product
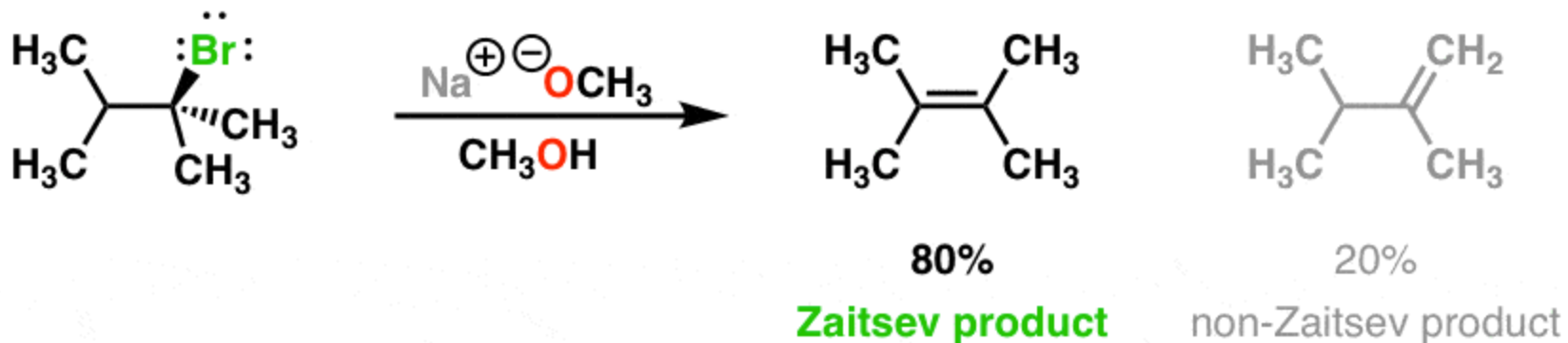
However, today we'll talk about one interesting exception to this "rule" and how under certain conditions we actually end up with the "non-Zaitsev" alkene product instead.

2. "Bulky Bases" Tend To Give A Higher Proportion Of "Non-Zaitsev" Products

For instance, instead of using sodium methoxide, (NaOCH$_3$) if you use the base NaOC(CH$_3$)$_3$ [or KOC(CH$_3$)$_3$, changing sodium for potassium doesn't really matter here] you end up with an interesting reversal of products!

### Changing the base can change the product distribution

25% Zaitsev product

75% non-Zaitsev product
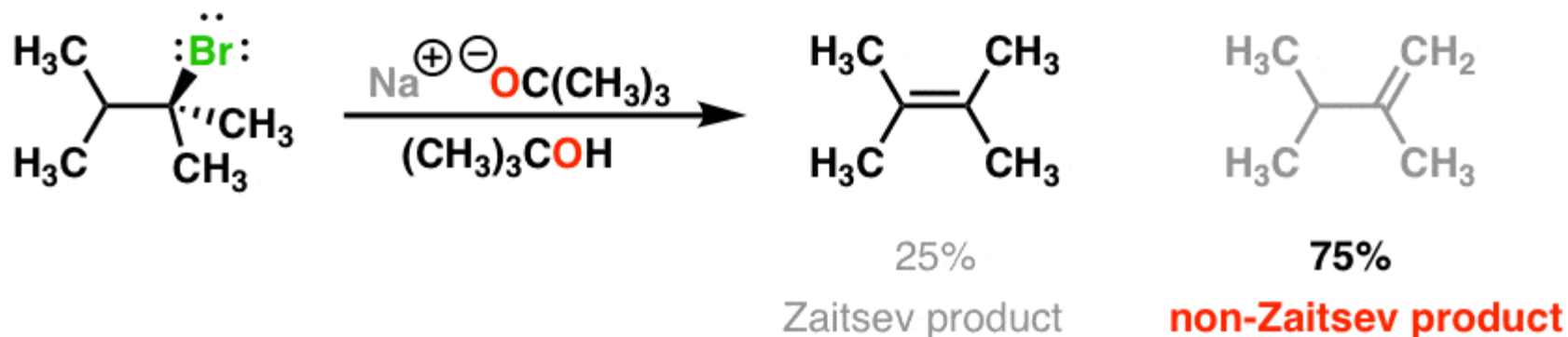
So what's going on here? Why might we get less of the Zaitsev product here and more of the "non-Zaitsev" product?

3. Bulky Bases Give More "Non-Zaitsev" Products Due To Steric Interactions With The Alkyl Halide

Well, if we draw out what the structure of the reactants might look like in their transition state, we can start to see why. [Note: this is not technically a transition state since we're not drawing partial bonds, but you can at least see how the reactants are assembled]. The base in this instance – potassium t-butoxide – is an extremely **bulky** base, and the proton we remove to form the Zaitsev product is on a tertiary carbon. As the oxygen from the base draws nearer to this proton, a **steric clash** occurs. In essence the electron clouds around the methyl groups are interacting with each other, and the repulsion between these clouds will raise the energy of the transition state [remember – opposite charges attract, like charges repel]. This will slow down the reaction.

Why the reversal?
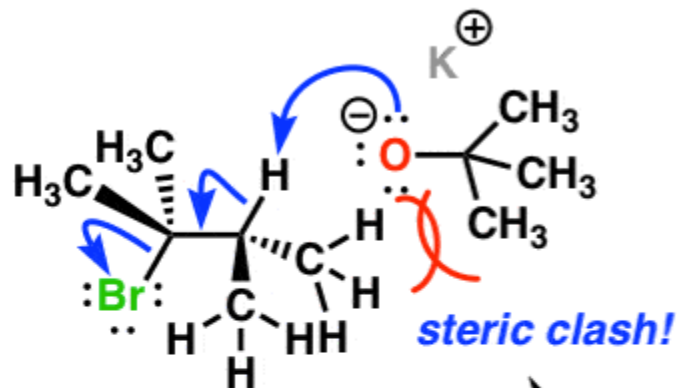
"Zaitsev" mechanism
(disfavored)

steric clash!
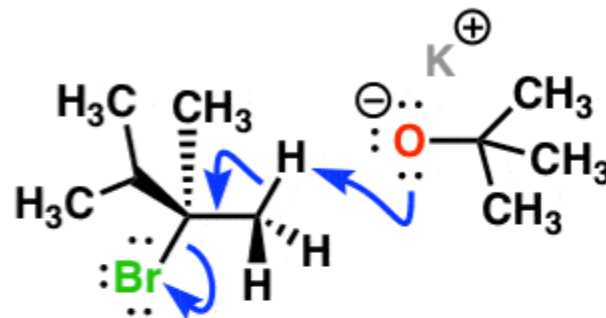
"Non-Zaitsev" mechanism
(favored)

the bulky base has severe steric interactions with the substrate, increasing the energy of the transition state (and lowering the yield of Zaitsev product)

Looking at the reactant assembly that produces the non-Zaitsev product, the bulky base is removing a proton from a primary carbon. Steric clash is considerably reduced in comparison to that for the Zaitsev product. Elimination is faster, and we therefore end up with the less substituted alkene as our major product. Note: for an excellent set of 3D models that show the differences in excellent detail, visit this page on Reusch's site. This is one example of a reaction where the more thermodynamically stable product is not formed [recall that alkene stability increases with the number of carbons directly attached to the alkene].

4. Two Common Bulky Bases Are The *t*-Butoxide Ion And Lithium Di-Isopropyl Amide (LDA)

So the bottom line for this post is that **when performing an E2 reaction, using a bulky base will produce a greater proportion of non-Zaitsev alkene products relative to a less bulky base**.

As far as we'll see, the most common "bulky base" we need to consider is the t-butoxide ion, which can be drawn in many forms [see diagram]; occasionally you might see lithium di-isopropyl amide (LDA) used as well. For our purposes this completes the roster of bulky bases.
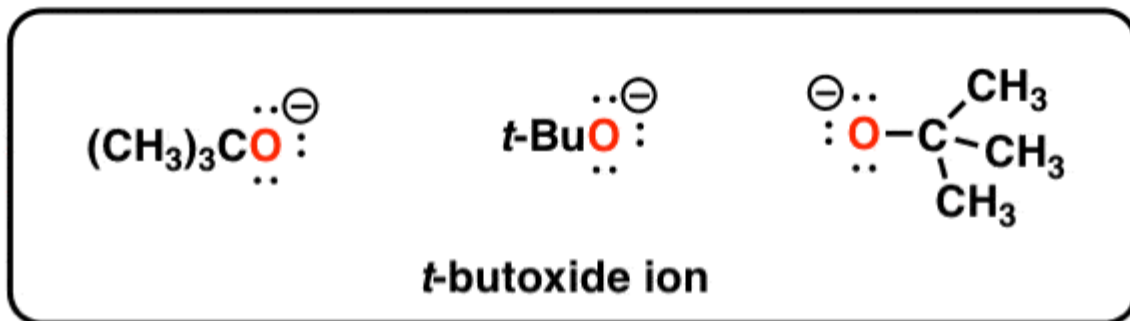
t-butoxide ion

The *tert*-butoxide ion is considered a "bulky" base. It will give a higher yield of the "less substituted" alkene (i.e. the non-Zaitsev product)

Lithium diisopropyl amide [LDA] is another base with this property.
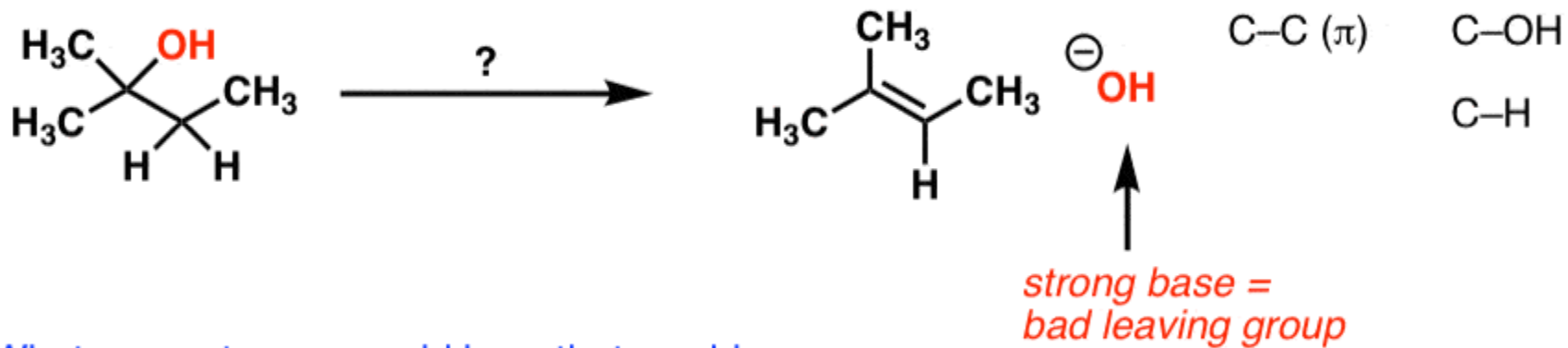
Comparing the E1 vs SN1 Reactions

The Important Role of The Counter-Ion In Determining E1 vs SN1

1. Alcohols Don't Undergo Elimination Reactions Until OH Is Converted To A Better Leaving Group
2. Adding Acid To Alcohols Results In A Better Leaving Group'
3. When Elimination And Substitution Compete: E1 vs SN1
4. In Order To Get E1 To Predominate vs SN1 In The Reaction Of Alcohols Use H_2SO_4, TsOH, or H_3PO_4 (And Heat)

1. Alcohols Don't Undergo Elimination Reactions Until OH Is Converted To A Better Leaving Group

Imagine you're starting with the alcohol on the left and you'd like to get to the alkene on the right.

This elimination reaction won't happen by itself

Form	Break
C–C (π)	C–OH
	C–H

H_3C OH
H_3C CH_3
H H

? →

CH_3
H_3C CH_3 $\ominus OH$
H

strong base = bad leaving group

What reagent can we add here that would facilitate this elimination reaction?

What bonds are formed and broken here? We're forming C-C (π), we're breaking C-H, and we're breaking C-OH. It's an elimination reaction.

Notice a problem here? We need to have HO(-) as a leaving group. If you'll recall, strong bases [like HO(-)] are terrible leaving groups – which makes the E1 pathway unlikely. So what if we tried to use a strong base, maybe trying to promote an E2 reaction? Well, that would be even worse – we'd likely deprotonate OH before the C-H, and you can imagine that we'd have to have O^{2-} as a leaving group here. Not good!

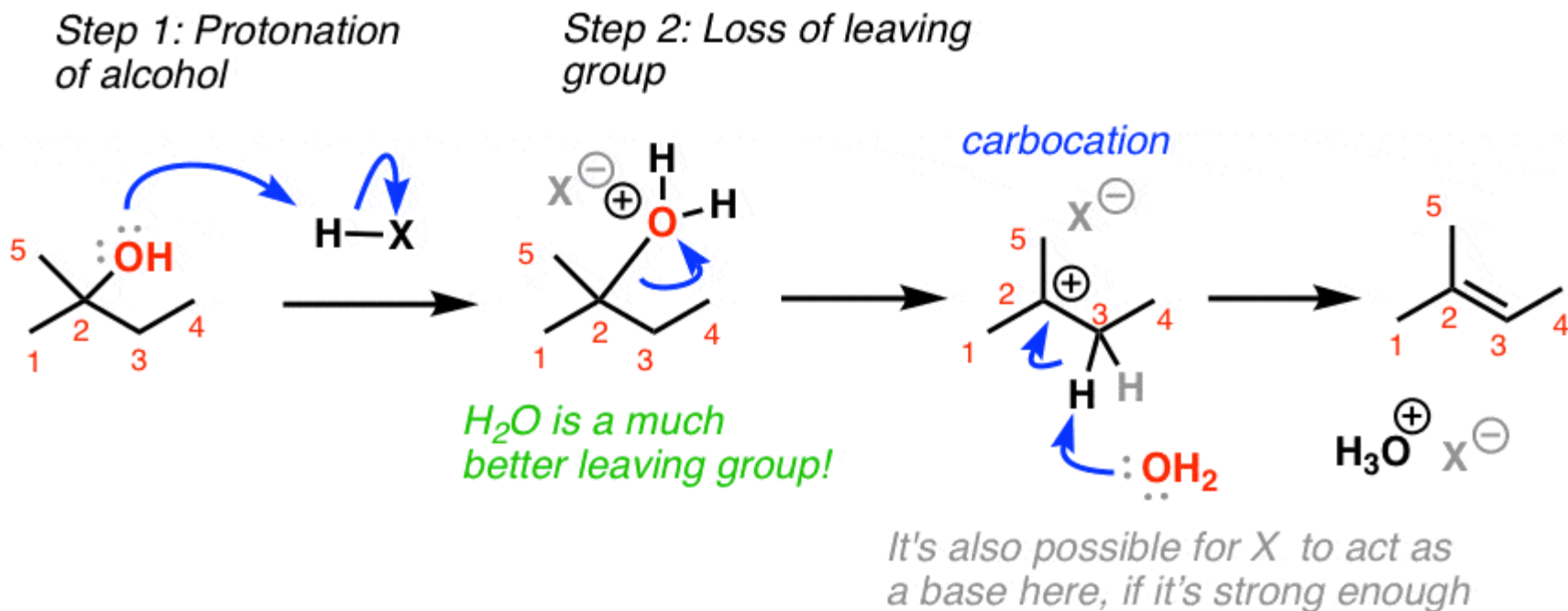That means that the reaction, as written, is very unlikely to happen.

2. Adding Acid To Alcohols Results In A Better Leaving Group

Yet, there is something very simple that we can do to make this reaction work. We'd need to have a better leaving group (a weaker base). How can we do this?
Add acid!

Acid-Catalyzed Elimination Of Alcohols

• Acid makes OH a better leaving group (its conjugate acid, H_2O) facilitating the elimination reaction

Step 1: Protonation of alcohol

Step 2: Loss of leaving group

carbocation

H_2O is a much better leaving group!

It's also possible for X to act as a base here, if it's strong enough

If we add a strong acid, we turn OH into H_2O^+, <u>the conjugate acid is a better leaving group.</u> Now, water can leave, forming a carbocation; and then a base can break the C-H bond, forming the alkene.

Notice that this is now a classic E1 reaction. The rate is going to be dependent on the stability of the carbocation. This one is tertiary, so it should proceed at a reasonably high rate.

A question arises here. What's going to act as the base? As it stands, a C-H bond adjacent to a carbocation has an extremely high acidity (at least below -2, if you follow pKa). That means that just about any weak base (water, or the conjugate base of the acid) is sufficient to deprotonate the carbon. It's possible that more than one species can act as a base here. I've shown water removing the proton, but it's not unreasonable to show the conjugate base of the acid removing the proton in most circumstances.

3. When Elimination And Substitution Compete: E1 vs SN1

Now comes one of the things about organic chemistry that often causes trouble for students. For one of the first times in our discussions here, we're dealing with a situation where we can have **competing** reactions.

Let's back up. The E1 reaction goes through a carbocation, correct? Well, if you'll recall, so does the S_N1 reaction.

We've already seen examples where a carbocation was formed from an alcohol by adding a strong acid like HCl, HBr, or HI, and we ended up with the alkyl halide.

Why? The halide ions (Cl- , Br-, I-) are decent nucleophiles under the reaction conditions. So how can we stack the deck in favor of the E1 process?
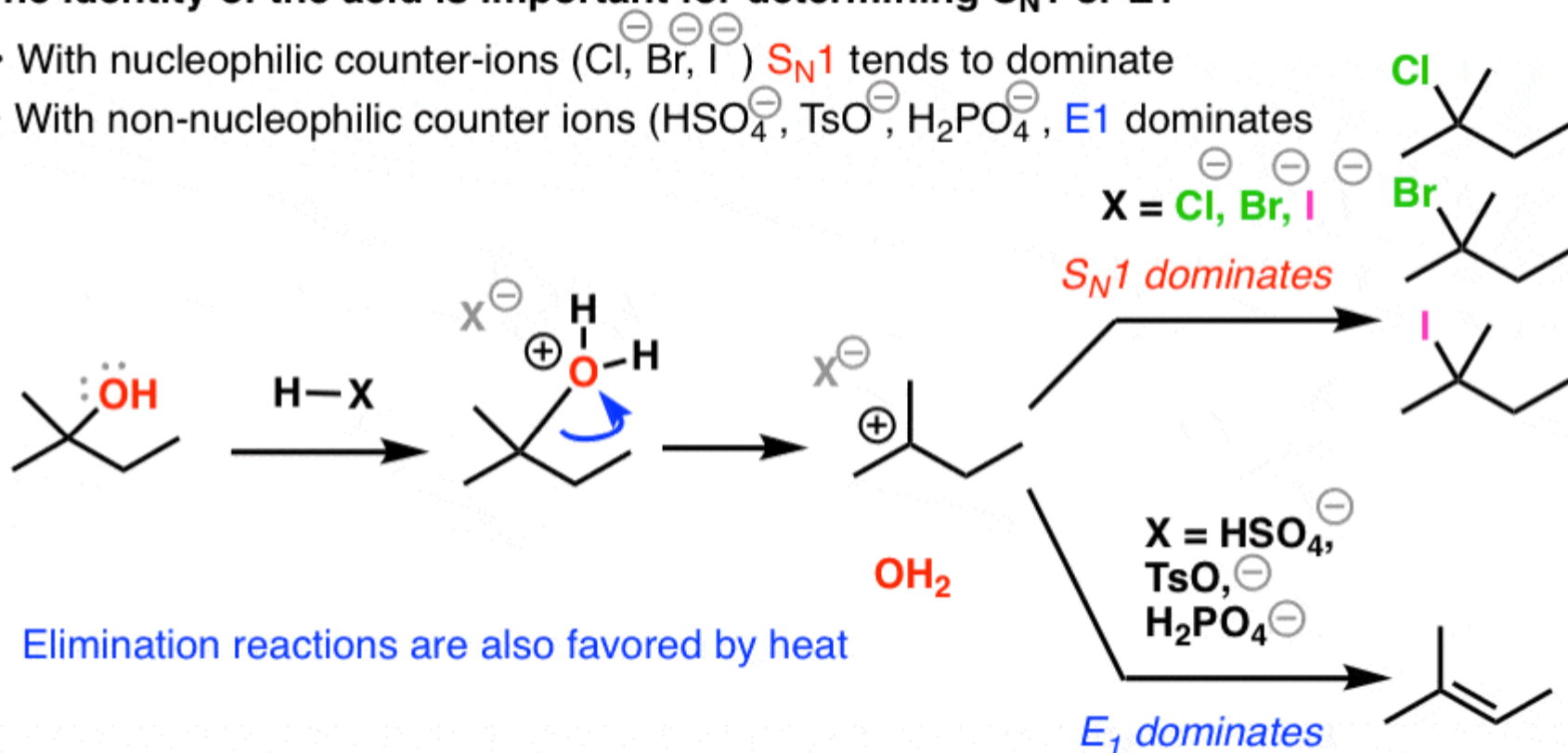
Use a strong acid with a conjugate base that is a **poor nucleophile.**

The usual choice is H_2SO_4. The $HSO_4(-)$ ion is a relatively poor nucleophile due to the negative charge of the oxygen being distributed throughout the molecule (resonance). Two other acids you might see for this purpose are p-toluenesulfonic acid (p-TsOH), which is essentially a cousin of H_2SO_4, and phosphoric acid (H_3PO_4).

Also, don't forget that elimination reactions are favored by heat.

The identity of the acid is important for determining S_N1 or E1

- With nucleophilic counter-ions (Cl⁻, Br⁻, I⁻) S_N1 tends to dominate
- With non-nucleophilic counter ions (HSO_4^-, TsO^-, $H_2PO_4^-$, E1 dominates

X = Cl, Br, I

S_N1 dominates

X = Cl, Br, I

S_N1 dominates

X = HSO_4, TsO⁻, $H_2PO_4^-$

Elimination reactions are also favored by heat

E_1 dominates

4. In Order To Get E1 To Predominate vs S$_N$1 In The Reaction Of Alcohols Use H$_2$SO$_4$, TsOH, or H$_3$PO$_4$ (And Heat)

In summary, if you'd like E1 to predominate over SN1: choose an acid with a weakly nucleophilic counterion [H$_2$SO$_4$, TsOH, or H$_3$PO$_4$], and heat.

If you'd like SN1 to predominate over E1, choose an acid like HCl, HBr, or HI.

We're almost done talking about elimination reactions. Next post – we'll talk about rearrangements.

Elimination (E1) Reactions With Rearrangements

Elimination Reactions (E1) That Occur With Rearrangements – Hydride Or Alkyl Shifts

Where there are carbocations (see last post), rearrangement reactions are never far behind. Our old friends have come back for a short visit in this chapter on elimination reactions.

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1. What's Weird About This Elimination Reaction?

2. Elimination (E1) With Hydride Shift

3. Elimination (E1) With Alkyl Shift

1. What's Weird About This Elimination Reaction?

One last (weird) reaction to show you with respect to elimination reactions. Can you see what's weird about it?

An Elimination Reaction. But something is weird about it!

How did the double bond get **here**?
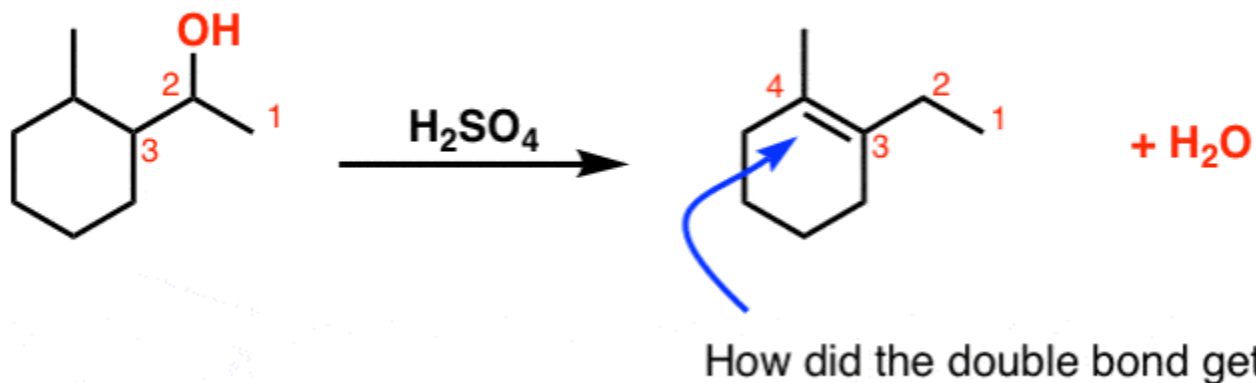
How did that double bond get over **there?** Normally when elimination occurs, we remove a hydrogen from the carbon adjacent to the leaving group. But here, something extra has taken place.

2. Elimination (E1) With Rearrangement: Hydride Shift

Let's look at all the bonds that form and the bonds that break so we can track down **exactly** what happens:

Eliminations (E1) Can Occur With Rearrangement!
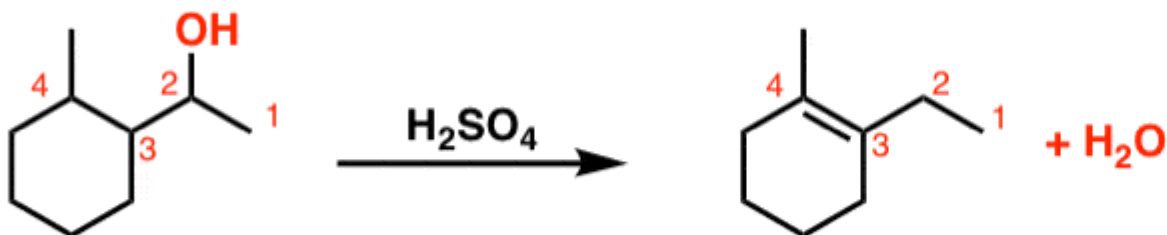
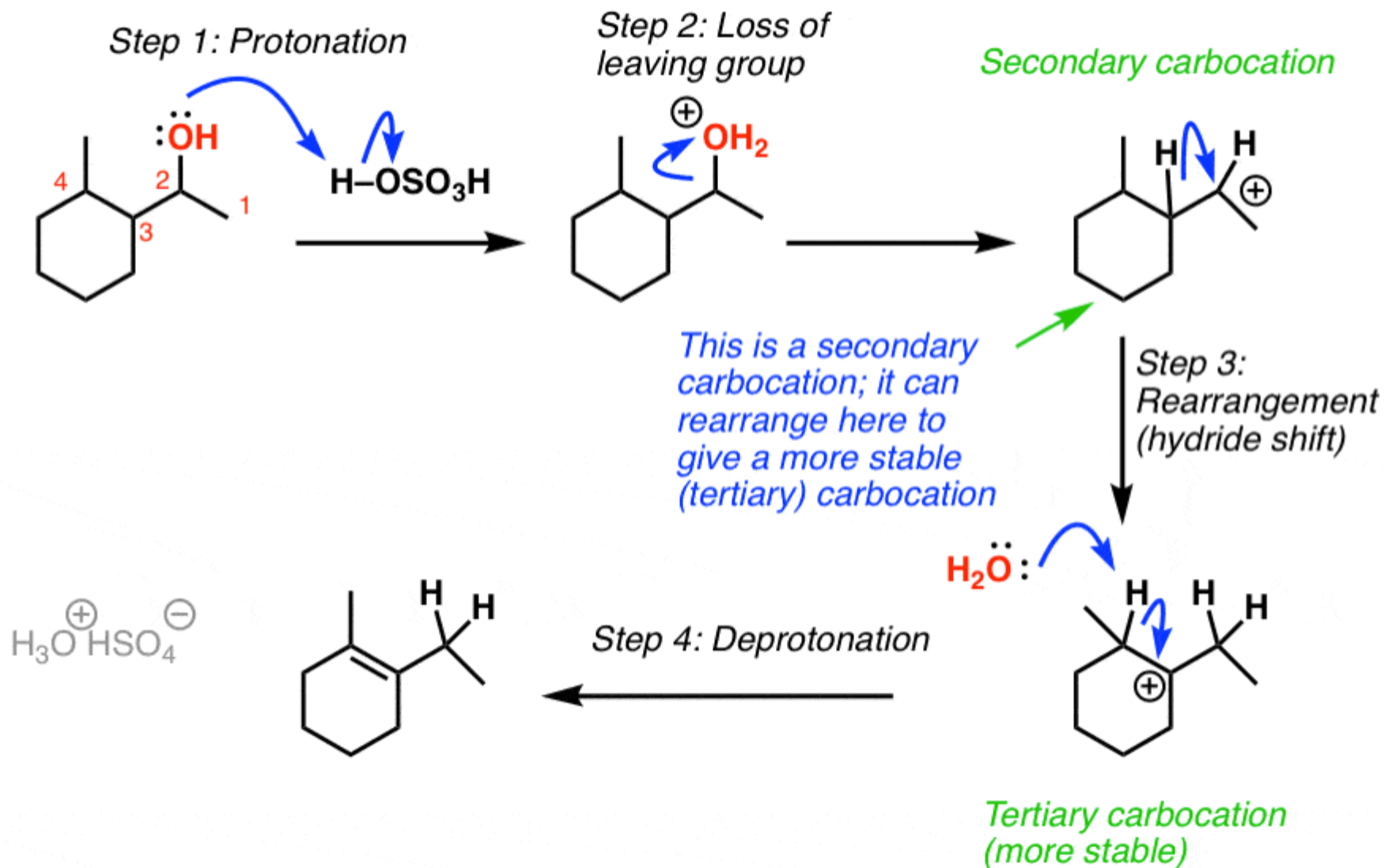| Form	Break
C_3–C_4 (π)	C_2–OH
O–H	C_4–H
C_2–H	C_3–H

notice the extra set

Notice how it differs from a typical elimination reaction? Sure, we're forming C-C (π), and breaking C-H and C-OH, but we have an extra C-H that forms and an extra C-H that breaks. This is a sure sign of a rearrangement step!

o what's going on here?

Well, we start by protonating the alcohol. This allows for water to leave in the next step, which is going to form a carbocation. **Here's the thing:** the carbocation is **secondary**, and we're adjacent to a **tertiary** carbon. So if the hydrogen (and its pair of electrons) were to migrate from C3 in our example to C-2, we'd now have a tertiary carbocation, which is **more stable**. Then, a base (water in this example) could remove C-H, forming the more substituted alkene (the Zaitsev product in this case). And that's how the alkene ends up there.

# Elimination With 1,2-Hydride Shift: Mechanism

Step 1: Protonation

Step 2: Loss of leaving group

Secondary carbocation

This is a secondary carbocation; it can rearrange here to give a more stable (tertiary) carbocation

Step 3: Rearrangement (hydride shift)

Step 4: Deprotonation

Tertiary carbocation (more stable)

OK. So that's one mystery solved.

3. Elimination (E1) With Rearrangement: Alkyl Shift

You might remember that these types of rearrangements can occur in SN1 reactions too. And if you read that post, you might recall that in addition to shifts of hydrogen ("hydride", because there's a pair of electrons attached) we can also have alkyl shifts. Here's a final example. Note – I've also made a video of this, you can watch it here.
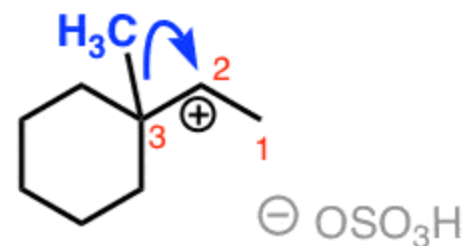
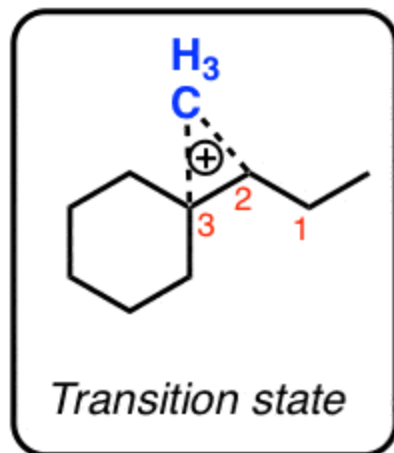# Elimination (E1) With Alkyl Shift: Mechanism
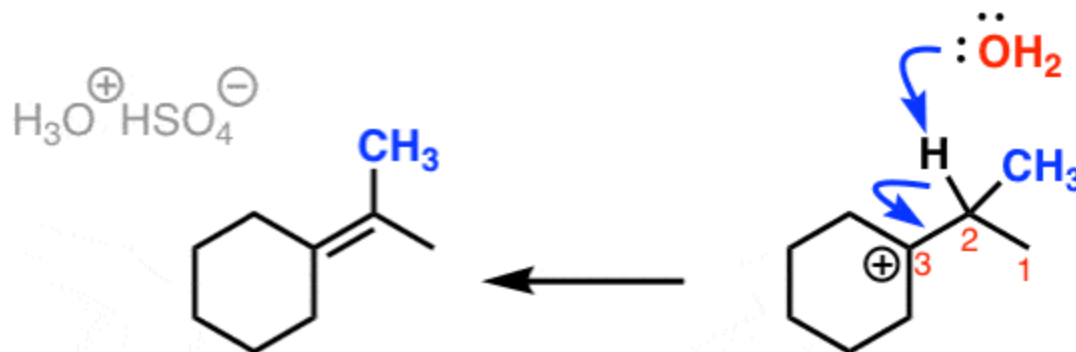
Step 1: Protonation of leaving group
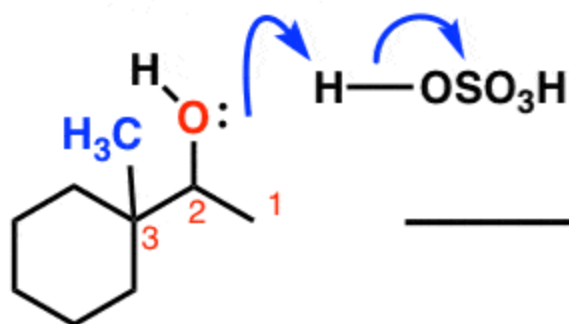
Step 2: Loss of leaving group to give carbocation
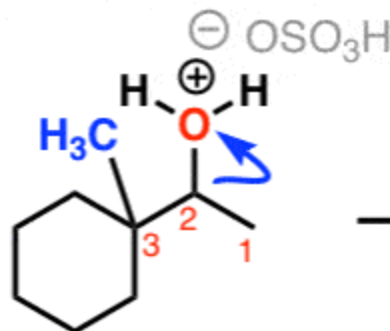
Step 3: 1,2-alkyl shift

Transition state
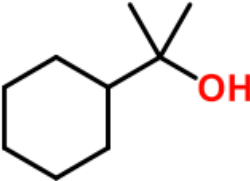
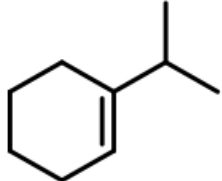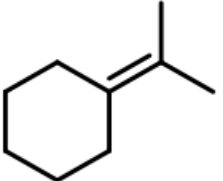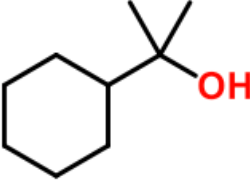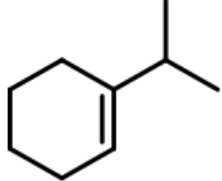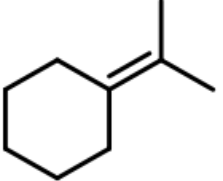Step 4: Deprotonation to give alkene

This pretty much does it for elimination reactions.

In the next series of posts, let's go though one of the biggest questions students struggle with. Okay, now that we've gone through substitution and elimination reactions, HOW DO WE DECIDE WHICH ONE IS GOING TO OCCUR IN EACH SITUATION?

Starting Material	Reagent	Total Yield (%)	Product 1 (% of total)	Product 2 (% of total)
	$BF_3 OEt$	61	90	10
	TsOH/PhH	28	88	12

Tf$_2$O (1 equiv.)
DMAP (3 equiv)

CH$_2$Cl$_2$ (5 mL)
0 °C
2 h
70%

(1 mmol)

Ratio: 1.2   1.1   0.4
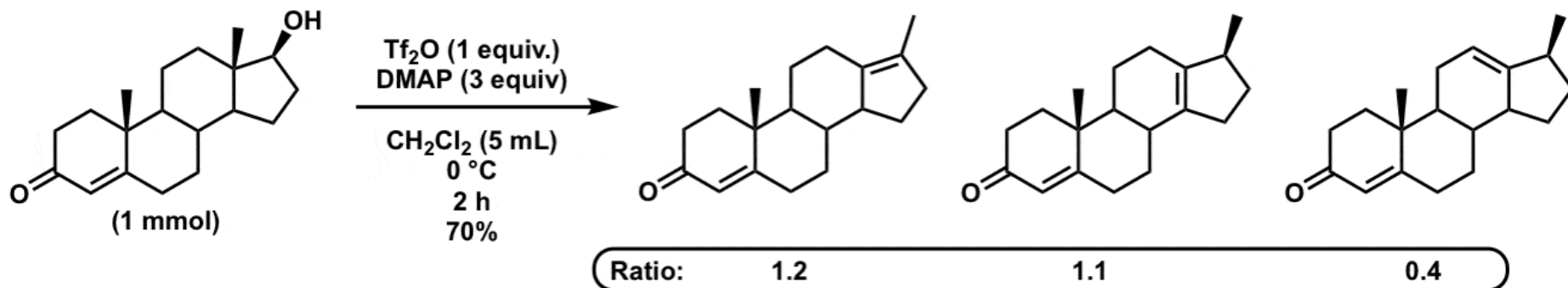
E1cB – Elimination (Unimolecular) Conjugate Base
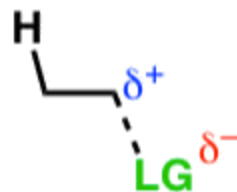
The E1cB Elimination Mechanism Is Awesome

The E1cB (Elimination, Unimolecular, Conjugate Base) mechanism is a third mechanistic pathway for elimination reactions. In many ways it is the exact opposite of the E1 mechanism, as the first step is deprotonation to form a carbanion, followed by elimination in the second step. It does occasionally come up in introductory organic chemistry courses, particularly in the mechanism of the aldol condensation, aryne formation, and elimination of alkenyl halides to give alkynes.

Comparing the E1, E2, and E1cB Mechanisms

E1	E2	E1cB
Two steps	**One** step	**Two** steps
1) C–LG breaks	C–H breaks, C–C (pi) forms	1) C–H breaks

2) C–H breaks
   C–C (pi) forms
	C–LG breaks, all at same time	2) C–LG breaks
		   C–C (pi) forms

Carbocation intermediate	**No** intermediate (concerted)	**Carbanion** intermediate
Carbocation stabilized by electron **donating** groups		Carbanion stabilized by electron **withdrawing** groups
Assisted by **good** leaving groups		Assisted by **poor** leaving groups
No strict requirement on stereochemistry of C–H and C–LG	C–H and C–LG are **anti**	No strict requirement on stereochemistry of C–H and C–LG

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Table of Contents

1. Elimination To Give Alkenes: The E1 and E2 Pathways

Elimination reactions are one of the most common and powerful methods we've learned to make alkenes (carbon-carbon pi bonds) from alkyl halides.

In elimination reactions giving new C-C pi bonds, the same general pattern of bond-forming and bond-breaking is always observed!
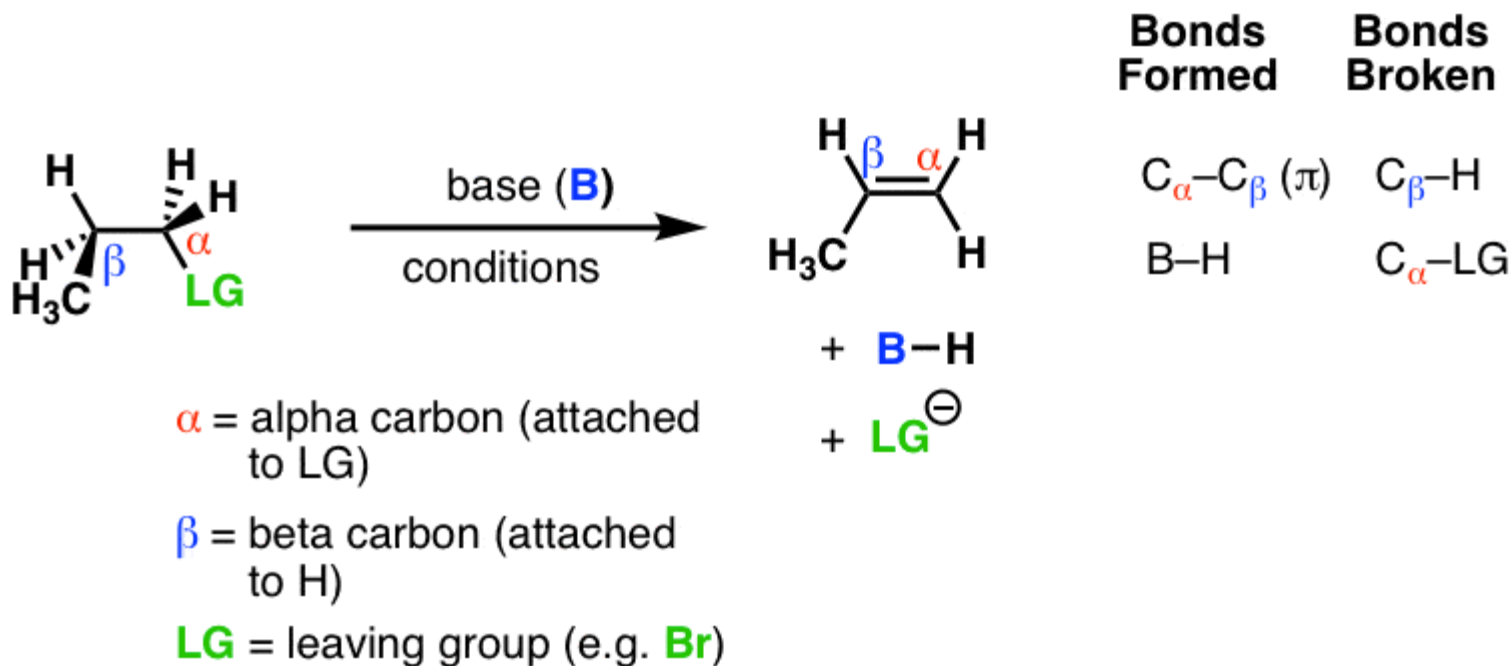
A single bond between the carbon and a leaving group breaks (C-LG). The **carbon** attached to the **leaving group** (LG) is referred to as the "**alpha**"(α) carbon.

A single bond between the carbon and a hydrogen breaks. The **carbon** bearing this hydrogen is referred to as the "**beta**" (β)carbon.

A new **pi bond** forms between the alpha carbon and the beta carbon.

Review: A Typical Elimination Reaction Forming A New C–C Pi Bond

Bonds Formed | **Bonds Broken**

C_α–C_β (π) C_β–H

B–H C_α–LG

α = alpha carbon (attached to LG)

β = beta carbon (attached to H)

LG = leaving group (e.g. Br)

We've seen eliminations proceed through E1 (leaving group leaves first, followed by elimination) or E2 (concerted elimination) pathways

Everyone agrees on *what* happens. The key question we'd really like to know, however, is "*how* did it happen?".

[Film directors know this. They give away the endings to movies all the time – often in the first 5 minutes. But what keeps you watching is trying to understand *how* something happened. Why else would people sit through a six hour movie trilogy if they already know Anakin is going to become Darth Vader in the end?]

The sequence in which these bonds form and break is the "mechanism" of a reaction, or if you will, the "story" of how this reaction happens.

We've seen **two** of these patterns so far for elimination:

1. In the **E1 mechanism**, elimination happens in **two steps**. The C-LG bond breaks first, leaving behind a carbocation. This is the **slow step**. In the second step, a base deprotonates the beta carbon, breaking C-H. The lone pair of electrons from the C-H bond forms the new pi bond with the empty p orbital from the carbocation. The rate law is unimolecular (hence E1) since it depends only on the substrate.

2. In the **E2 mechanism**, the C-H bond and C-LG bond break **at the same time** that the new C-C pi bond is formed. This is a **concerted mechanism**. The rate law is bimolecular (hence E2) since the reaction rate depends both on the concentration of base and of substrate.
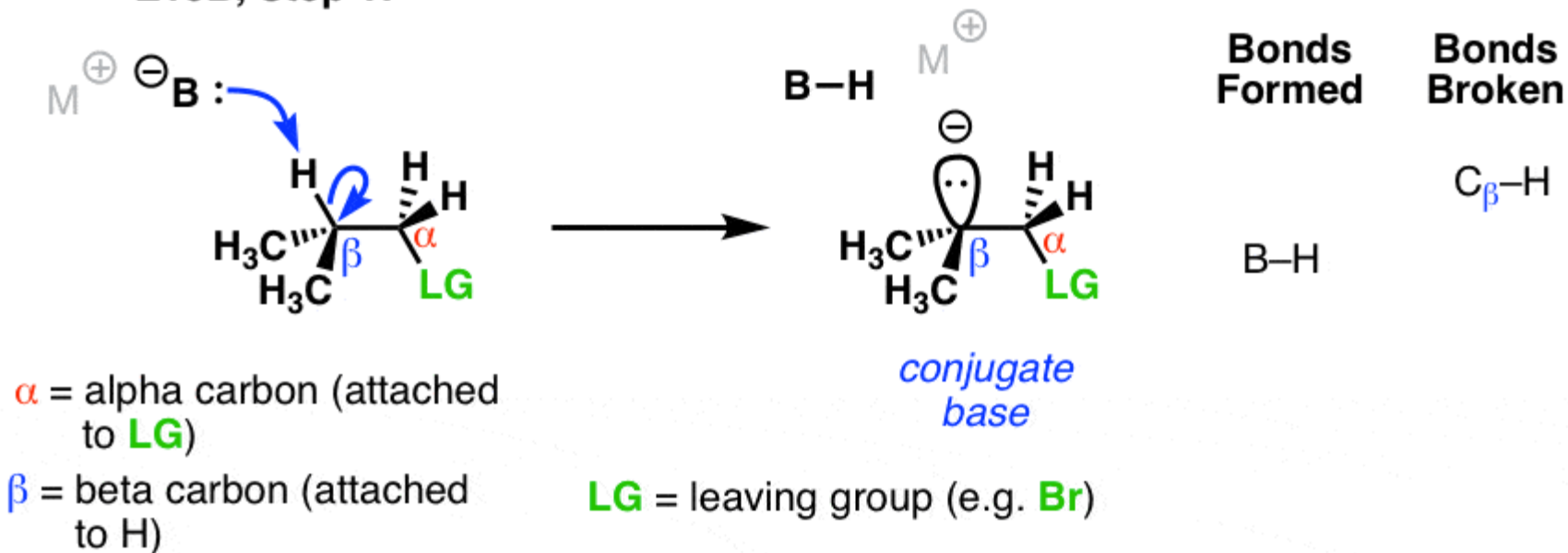
There is actually a third possibility, and that's what we're going to talk about today.

2. The E1cB Mechanism

The third possibility is that the **beta carbon is deprotonated first** (form B–H, break C–H). In the limiting case, this would give an anionic intermediate, the "conjugate base" of the substrate.

In the E$_1$cB Mechanism of Elimination, The β-Carbon Is Deprotonated First, To Give The "Conjugate Base" Of The Substrate

E1cB, Step 1:

α = alpha carbon (attached to **LG**)

β = beta carbon (attached to H)

LG = leaving group (e.g. **Br**)

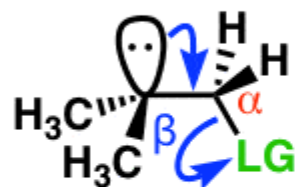| Bonds Formed	Bonds Broken
	C$_\beta$–H
B–H	

Since the first step is deprotonation to give an anion, then you would be right to guess that **this mechanism is more likely to occur when the C–H bond is relatively acidic**, as when the alpha carbon is adjacent to an electron withdrawing group like a ketone, nitrile (CN), or nitro group (NO_2). These groups stabilize negative charge

In the **second step,** the pair of electrons from the conjugate base then displaces the leaving group, forming a pi bond [form C–C pi, break C–LG].

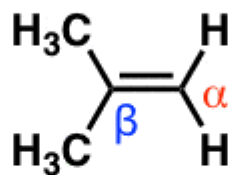**In the second step of the E₁cB mechanism, a new C–C pi bond is formed and the C–LG bond breaks**

E1cB, Step 2:

	Bonds Formed	Bonds Broken
	$C_\alpha\text{–}C_\beta\ (\pi)$	
		$C_\alpha\text{–LG}$

conjugate base → *alkene product* + **B–H** + LG⁻

α = alpha carbon (attached to **LG**)

LG = leaving group (e.g. **Br**)

β = beta carbon

In the (many) cases of the E1cB where the second step is the slow step, you can imagine that this step would be made slower by a relatively poor leaving group like (HO-), (CH_3O-) or even (believe it or not!) fluorine.

3. The E1cB Mechanism And The E1 Mechanism Are Two Extremes, With The E2 Mechanism Lying In The Middle

It's helpful to think of the E1cB mechanism and the E1 mechanisms as two extremes, or mirror images, and the E2 cutting exactly in between. It's kind of like the continuum between "quitting" and "being fired", with "mutually agreeing to part ways" somewhere in the middle.

The first step in the E1 mechanism is loss of a leaving group (break C-LG) to give a **carbocation** intermediate, and this step is promoted when there are electron-donating groups adjacent to the alpha carbon (making the carbocation more stable).

The first step in the E1cB mechanism is deprotonation (break C-H) to give a **carbanion** intermediate, and this step is promoted when there are electron-withdrawing groups adjacent to the alpha carbon (making the carbanion more stable).

The E2 mechanism is in between these two extremes, where everything happens at once.

Comparing the E1, E2, and E1cB Mechanisms

E1	E2	E1cB
Two steps	**One** step	**Two** steps
1) C–LG breaks	C–H breaks, C–C (pi) forms	1) C–H breaks
2) C–H breaks	C–LG breaks, all at same time	2) C–LG breaks
C–C (pi) forms		C–C (pi) forms

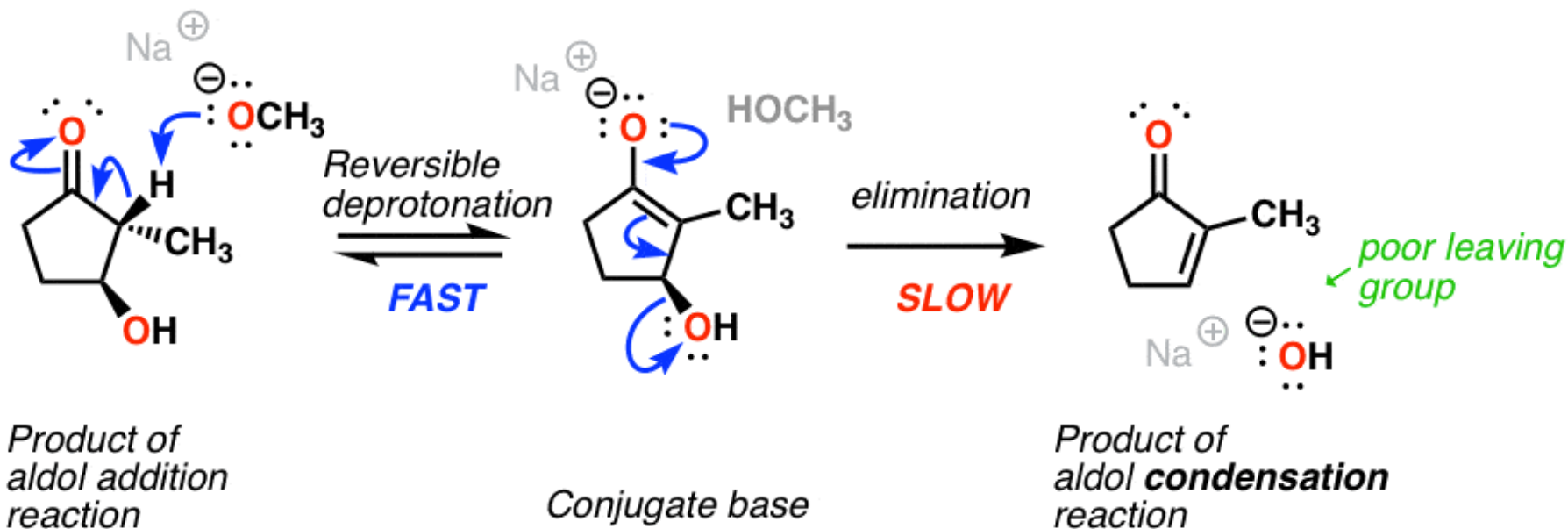| **Carbocation** intermediate	**No** intermediate (concerted)	**Carbanion** intermediate
Carbocation stabilized by electron **donating** groups		Carbanion stabilized by electron **withdrawing** groups
Assisted by **good** leaving groups		Assisted by **poor** leaving groups
No strict requirement on stereochemistry of C–H and C–LG	C–H and C–LG are **anti**	No strict requirement on stereochemistry of C–H and C–LG

So does this mechanism actually occur in reactions we see in introductory organic chemistry?
Yes it does!

4. Examples Of The E1cB Mechanism In Introductory Organic Chemistry: The Aldol Condensation

Probably the most commonly encountered example of the E1cB mechanism in introductory organic chemistry is in the **aldol condensation reaction**, specifically the last step where the new C-C double bond is formed.

Below, left, is the product of an alcohol addition reaction. If this is heated with base (like NaOCH$_3$), it loses water, giving the alkene. (Loss of water = "condensation")

Example of an E$_1$cB Mechanism: Formation of an Aldol Condensation Product

Na⊕ ⊖:OCH$_3$

Reversible deprotonation
FAST

Na⊕ ⊖:O: HOCH$_3$

elimination
SLOW

Na⊕ ⊖:OH

poor leaving group

Product of aldol addition reaction

Conjugate base

Product of aldol **condensation** reaction

Wait a minute, you may say. "I thought the hydroxyl ion (HO-) was a poor leaving group? What's going on here?"

Exactly! If there was a really good leaving group (like OTs or Br) present instead of OH, an E2 (or even E1) mechanism would be more likely. [Note] The bad leaving group (HO-) makes the elimination step is **slow**, which is largely responsible for this being a two-step mechanism.

Another (very subtle) point is stereochemistry. If you look really closely you'll notice in the drawing above that the C–H bond and the C–OH bond are not anti to each other (a requirement for the E2) but instead are syn.

So unlike the E2, the E1cB mechanism doesn't have a strict requirement that the C-H and C-LG bonds be anti to each other.

5. Another Example: Formation Of Alkynes From Alkenyl Halides

Another example of the E1cB is in the formation of alkynes from alkenyl halides with $NaNH_2$ in liquid ammonia (NH_3).

When alkenyl halides are treated with $NaNH_2$ in NH_3 as solvent, elimination to give the alkyne occurs. This reaction works even if the H and Cl are *cis* to each other, which would seem to rule out the E2 mechanism. [*The elimination when H and the halide are trans is much faster, though!* _note_]

$NaNH_2$ is an extremely strong base. Being sp^2 hybridized, the C-H bond of the alkenyl halide is reasonably acidic (pKa about 40) and able to stabilize negative charge.

In this case a two-step mechanism likely operates, where 1) a carbanion intermediate is formed by deprotonation, followed by 2) loss of the leaving group.

Another Example of an E1cB process: Elimination Of Alkenyl Halides To Alkynes

Step 1: Deprotonation of alkenyl halide

Step 2: Elimination to give alkyne

fast

slow

Conjugate base

(a relatively stable anion)
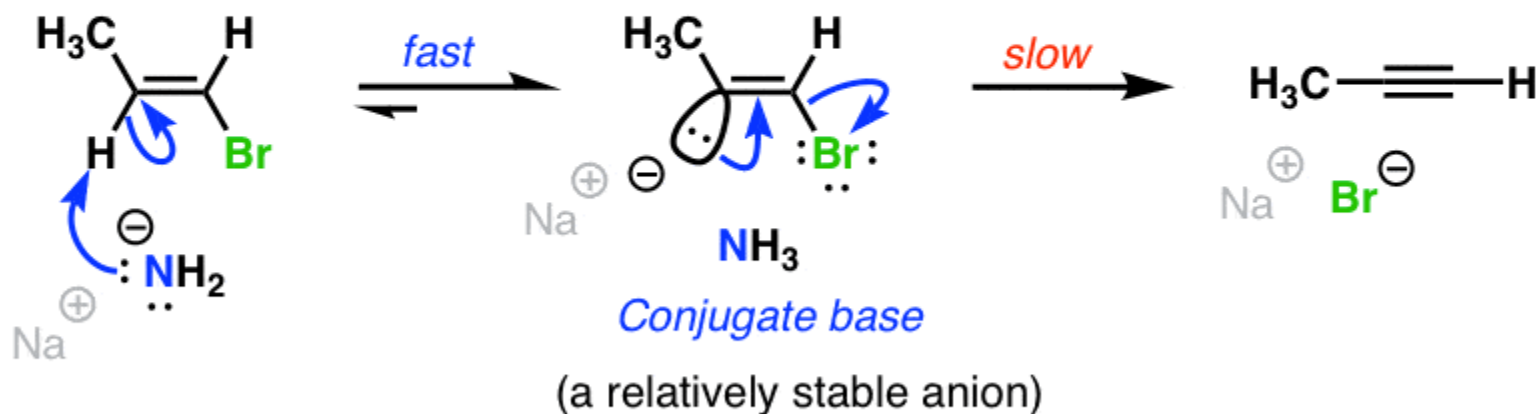
*note: elimination of the *trans* alkenyl halides is *much* faster

6. Formation Of Arynes From Phenyl Halides

A related situation to alkenyl halides where the E1cB mechanism can arise is in the formation of benzyne and other "arynes"

Although benzyne does not have a "true" pi bond, many of the same principles of the E1cB still apply.

Deprotonation of the aryl fluoride by the strong base ($NaNH_2$) occurs first, giving a carbanion. In this specific case, the second step is loss of the bad leaving group, fluorine. [Note]

Formation of "Benzyne" - Another Example of an E1cB Process

Step 1: Deprotonation of C–H   *Step 2: Elimination*
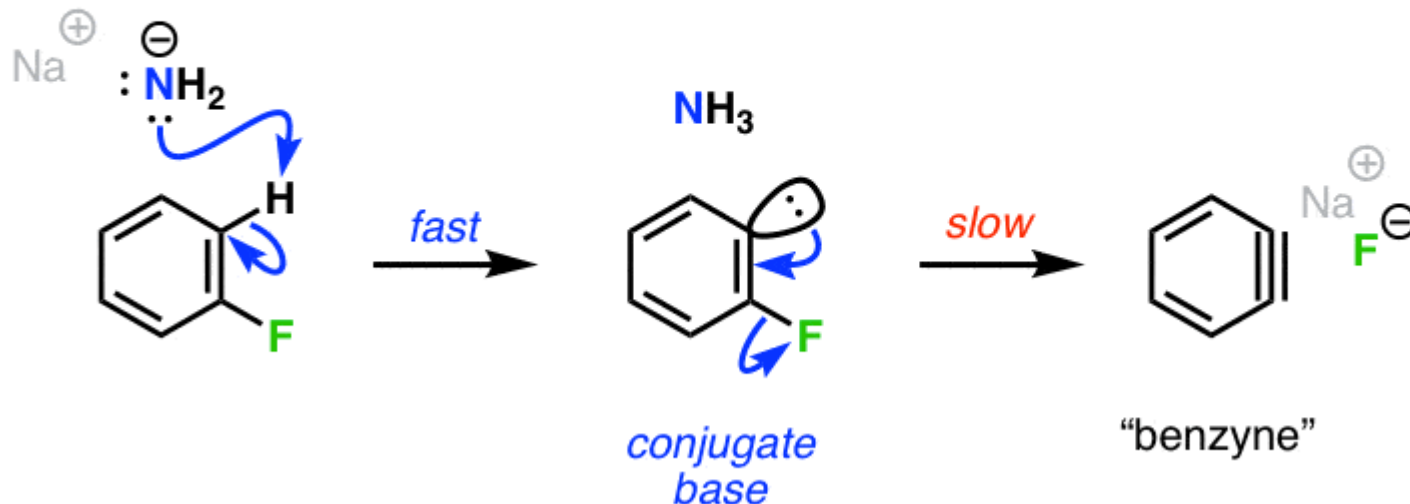
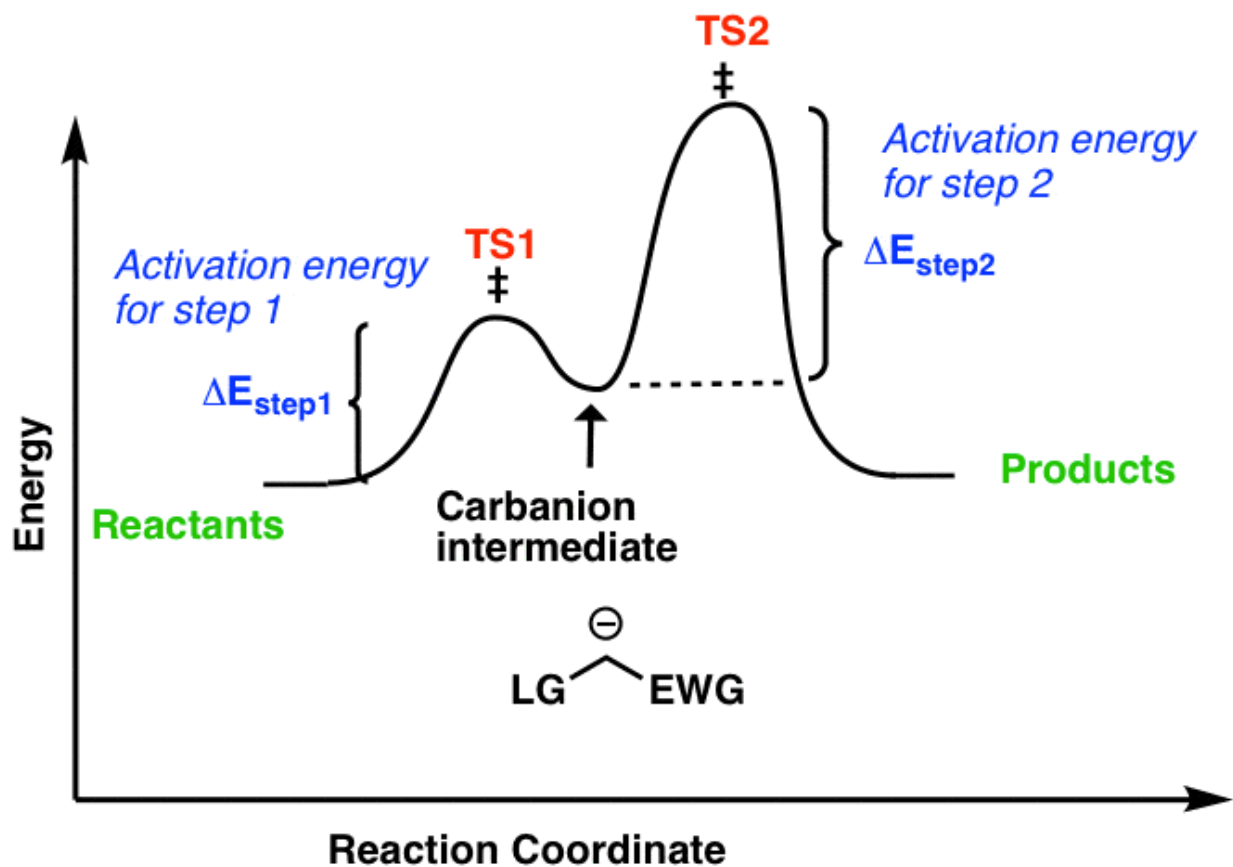*[Note – apparently, when F or Cl is the leaving group, deprotonation is the slow step. However, when the leaving group is Br, or I, deprotonation is rate-determining and breakage of C-X is fast. Note that both of these still qualify as E1cB so long as the reaction proceeds through the carbanion intermediate!]*

7. The Reaction Coordinate Diagram Of The E1cB Reaction

So what does the reaction coordinate diagram of the E1cB look like? If we assume that the **first step is fast** and the **second step is slow (rate-determining)**, and there is an anion **intermediate,** then the reaction coordinate diagram of the E1cB should look roughly like this:

Reaction Coordinate Diagram For An E_1cB Reaction

•for a case where deprotonation is fast, and elimination is slow

TS2

‡

Activation energy for step 2

ΔE_{step2}

TS1

‡

Activation energy for step 1

ΔE_{step1}

Reactants

Carbanion intermediate

Products

$\ominus$

LG⌃EWG

Energy

Reaction Coordinate

· **Step 2 is rate determining.** The activation energy for Step 2 (elimination, ΔE_{step2}) is greater than that for Step 1 (deprotonation to give carbanion, ΔE_{step1})

For example
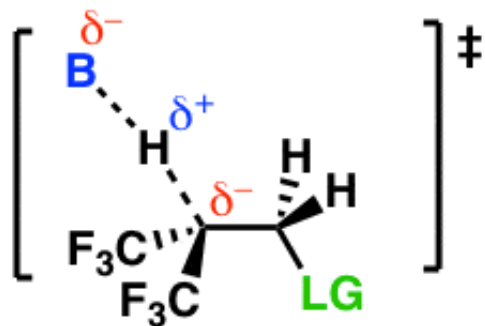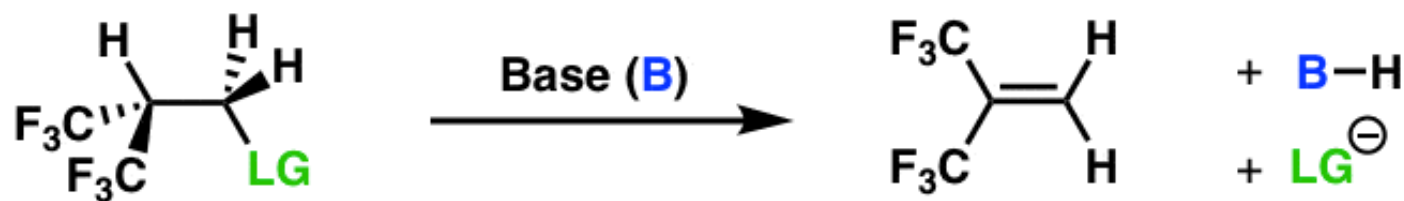
Transition state 1 (**TS1**)
Deprotonation to give
carbanion (fast step)
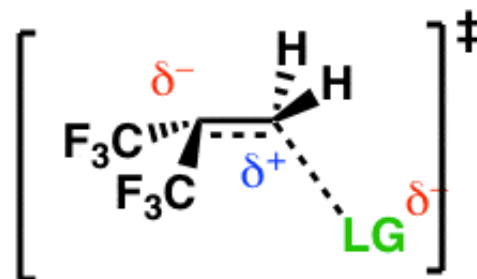
Transition state 2 (**TS2**)
Formation of pi bond with loss
of leaving group
 (**rate determining step**)

We've drawn a small hump going from reactants to TS$_1$ with activation energy (ΔE_{Step1}) equal to [$\Delta E_{TS1} - \Delta E_{reactants}$].
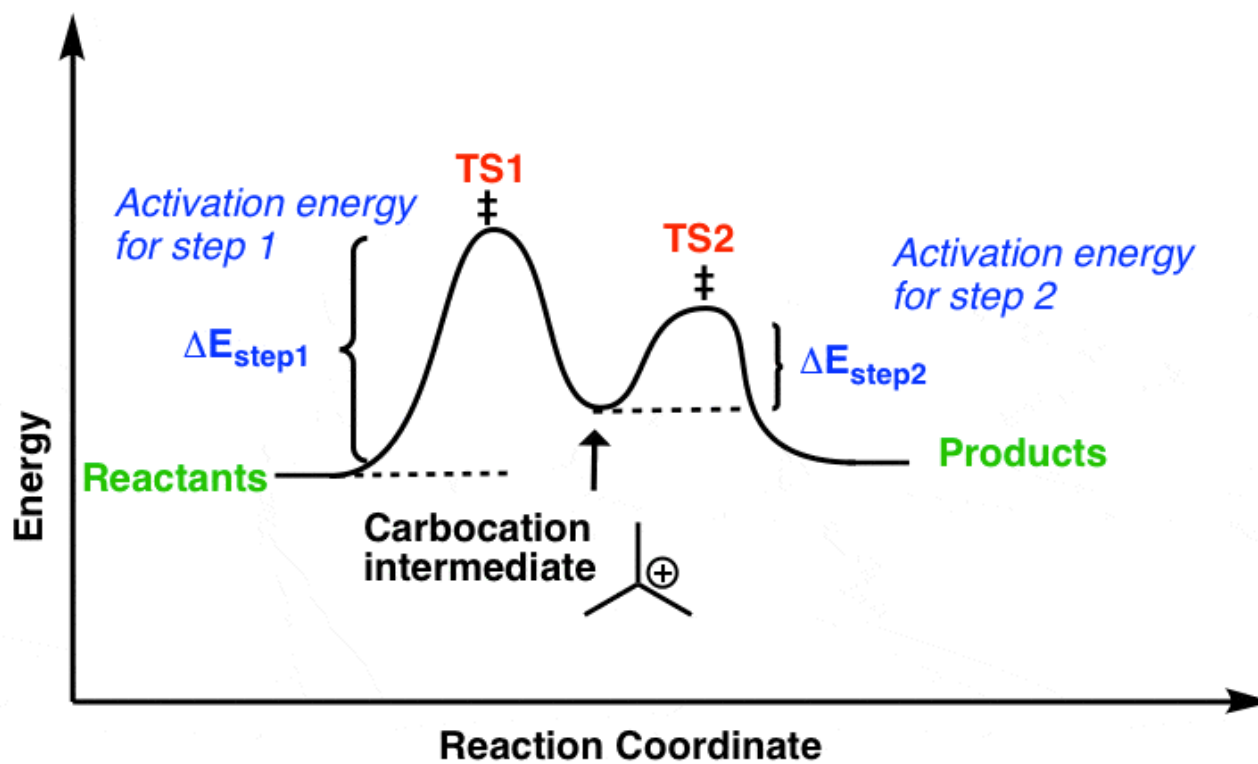
This then proceeds to the anionic intermediate (the "well" in the middle)

Which in turn proceeds through TS$_2$ with activation energy (ΔE_{Step2}) equal to [$\Delta E_{TS2} - \Delta E_{intermediate}$]

Since $\Delta E_{Step2} > \Delta E_{Step1}$, the second step is rate determining

Compare that to the reaction coordinate of the **E1 elimination**, which is the mirror image.

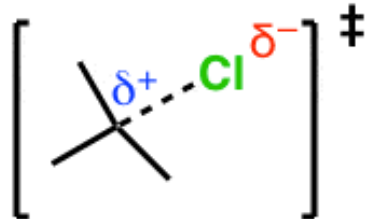**Reaction Coordinate Diagram For An E1 Reaction**

• **Step 1 is rate determining.** The activation energy for Step 1 (loss of leaving group to give the carbocation, ΔE_{step1}) is greater than that for Step 2 (elimination, ΔE_{step2})
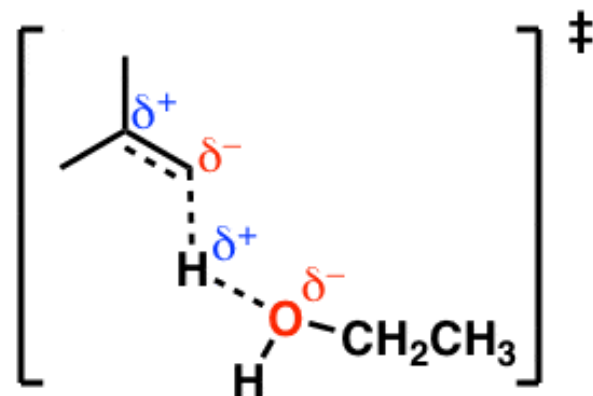
for example:

Transition state 1 (TS1)
Loss of leaving group
*(**Rate determining step** (slow))*

Transition state 2 (TS2)
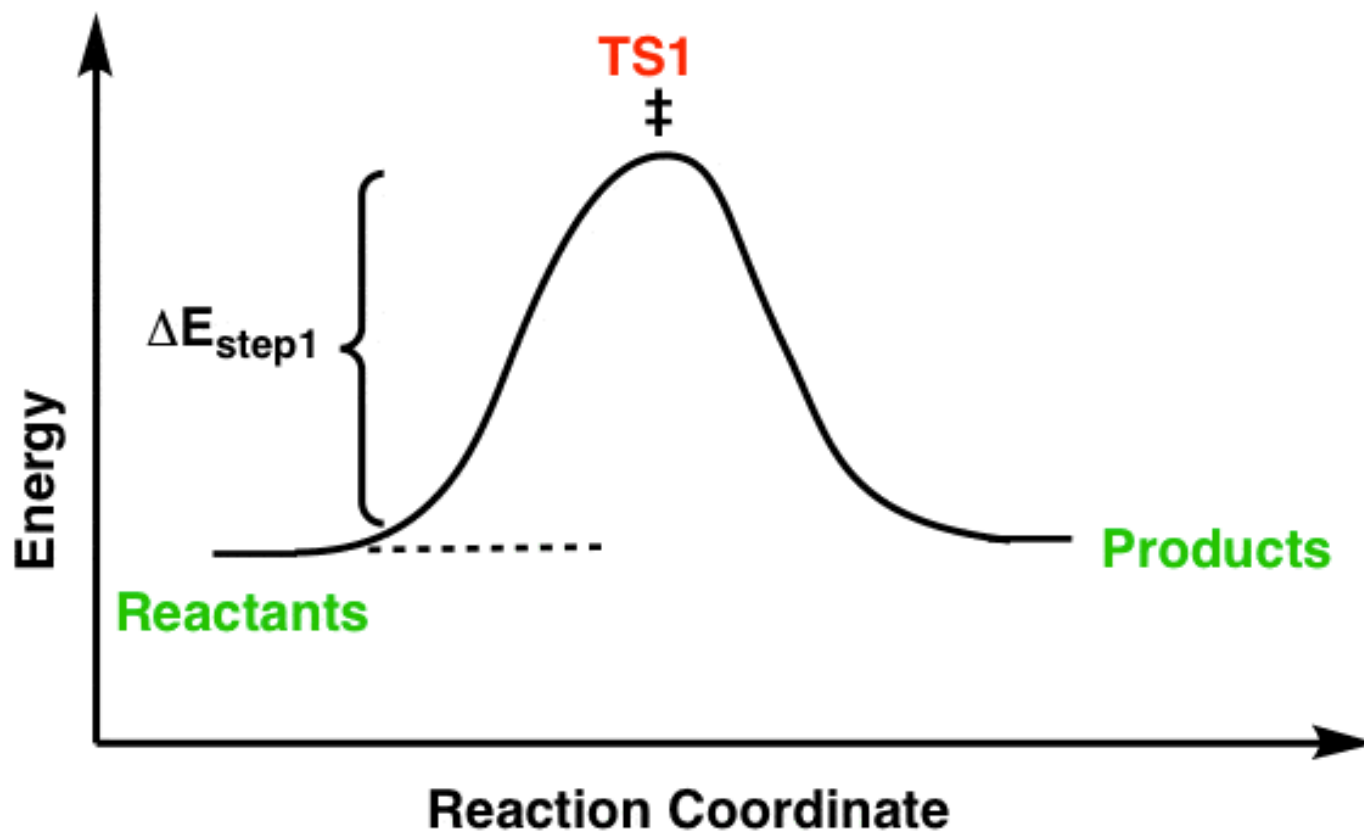*Elimination reaction*
(fast step)

In the E1 mechanism, the energy barrier (activation energy, ΔE_{Step1}) for the first step (loss of leaving group) is higher than the energy barrier (ΔE_{Step2}) for the second step (elimination).
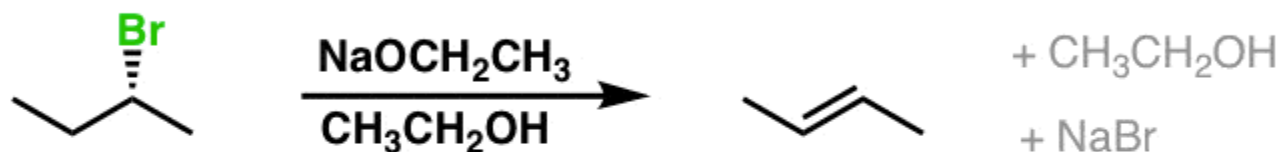
The reaction coordinate in the E2 case shows both of these steps happening at the same time.

Reaction Coordinate Diagram for an E2 Reaction

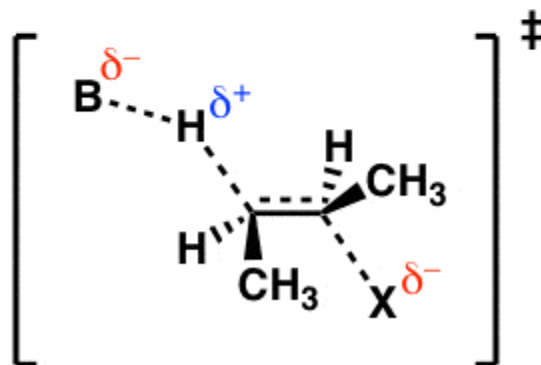- **There is only one step**. The reaction proceeds from reactants to products through the transition state TS1 with activation energy ΔE_1

for example:

$$+ CH_3CH_2OH$$

$$+ NaBr$$

Transition state 1 (TS1)
Concerted elimination

8. Summary: When Is a Reaction Likely To Go Through An E1cB Mechanism?

So, to summarize, in the E1cB mechanism, elimination occurs in two steps:

Deprotonation of the substrate to give an anion (its conjugate base), followed by

Loss of a leaving group to give a new C-C pi bond.

The E1cB mechanism is not very commonly encountered in introductory organic chemistry, but when it is observed, expect to see several of these characteristics:

The presence of an electron-withdrawing group which helps to stabilize an intermediate **anion**

A relatively poor **leaving group** (which will slow down the second step)

Here's one last classic _example_ of an E1cB, where deprotonation leads to a very stable anion (it's _aromatic_) which slowly loses the poor leaving group (hydroxide ion) forming a new C-C pi bond.

Another Example of An E1cB Mechanism:

Step 1: Deprotonation to give a stable anion
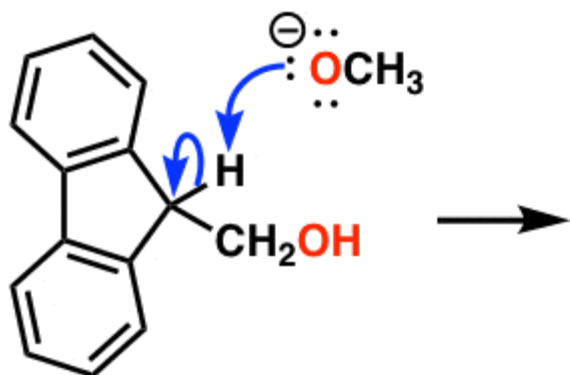
Step 2: Loss of leaving group (slow)
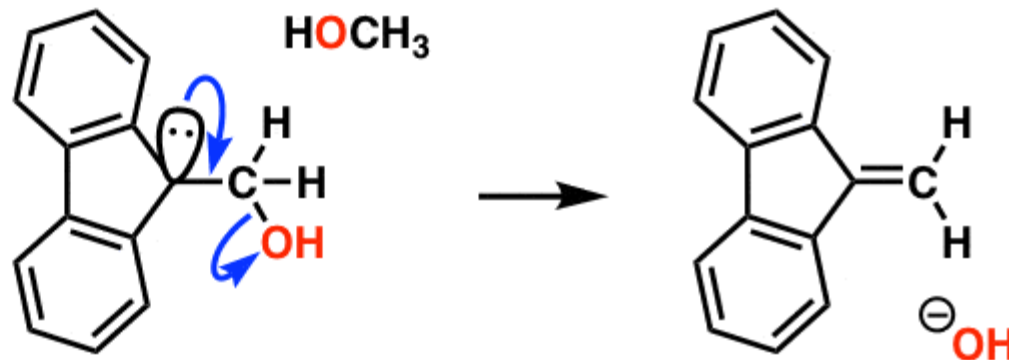
Conjugate base

Stabilized due to aromaticity and presence of electron withdrawing OH group

Notes

1. We never consider F(–) as a leaving group for S_N2 reactions, but under certain conditions it can be a leaving group in various types of substitution and elimination reactions. One example is in nucleophilic aromatic substitution, another example of a mechanism that proceeds through a relatively stable anion.

2. How might we determine that some reactions follow an E1cB mechanism versus an E2 mechanism? How do you know the difference?

That is a great question.

These studies always begin with experimental observations, followed by applied curiosity. For example, consider the reaction below.[Note] We might naively begin by considering this an E2 reaction. After all, there's a strong base, a leaving group (bad though it may be) and the stereochemistry of the C-H and C-OH bonds are capable of being anti to each other.

Elimination of OCH₃ To Give A New Alkene
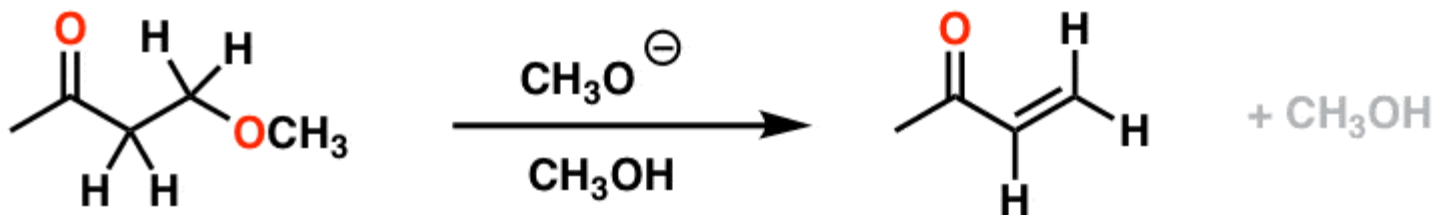
should be E2, right? why wouldn't it be?

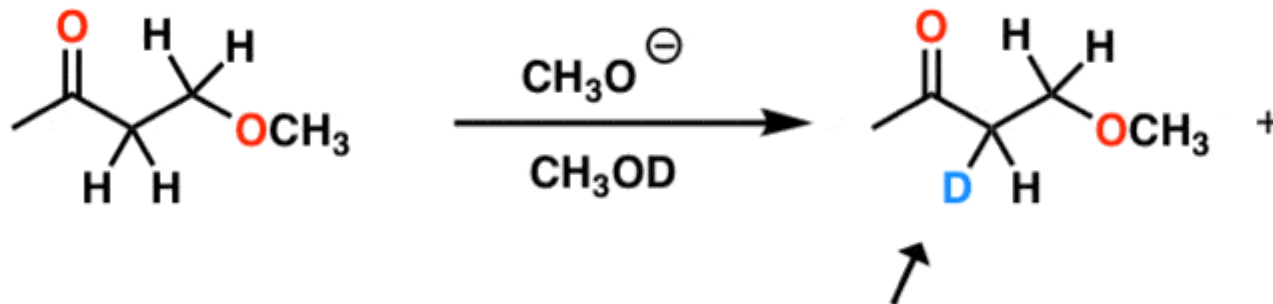E2, right? However, it turns out that if you run this reaction in a deuterated solvent, and stop it halfway, you end up with a lot of this:

However, in the presence of deuterated solvent , stopping the reaction halfway gets you lots of deuterated product!

The starting ketone is incorporating deuterium without undergoing elimination to the alkene. This isn't consistent with a "concerted" E2 reaction!

We don't see this in E2 reactions, since the C-H bonds can only break when they are *anti* to the leaving group.

In this example, C-H bonds are clearly breaking, but elimination does not always happen. **So what is going on?**

The best explanation for what's happening here is that the base forms the *conjugate base* of the substrate, and this can react with the deuterated solvent (as an acid), resulting in *deuterium exchange* at that position.

It turns out that exchange is 220 times faster than elimination.

That's very interesting. But, how important is the conjugate base in the elimination? Just because we know it's being formed doesn't *prove* it's involved in the elimination.

Maybe formation of the anion is just a "dead end", and a slower E2 reaction is responsible for formation of the alkene?

Perhaps. It actually takes quite a lot of work to answer that question, but the clear evidence that an anion is formed should at least plant the seeds of doubt that the E2 is the only possibility here.

Kinetic Isotope Effects

In theory, one way to tell the difference between the E1cB and the E2 is by studying rate laws. It turns out that this is generally difficult in the case of the E1cB [note] , so chemists have had to resort to other methods.

A key strategy for studying organic reaction mechanisms is to measure kinetic isotope effects, which take advantage of the subtle differences in bond strengths between isotopes. For example C-D (deuterium) bonds are slightly shorter (and stronger) than comparable C-H bonds. If C-H bond breaking occurs in the rate determining step, then the rate for the reaction of the C-H compound (k_H) should be slightly faster than the rate of the deuterium labelled analog with a C-D bond *(k_D)*. This difference, termed the primary kinetic isotope effect, has been experimentally determined to have a range k_H/k_D of about 2-8 in most cases for the E2.

So if C-H is broken in the rate determining step, then we should see a primary kinetic isotope effect in the range of 2-8. If it is not, then there should be no difference between the two. Right?

E1cB_{reversible}

In the case of the reaction above, the kinetic isotope effect is about 1.0 . **That is a clear indication that the C-H bond is not broken in the rate determining step**, which rules out the E2 (concerted) mechanism.

These types of E1cB reactions are referred to as E1cB_{reversible} indicating a reversible deprotonation step followed by (slow) loss of leaving group.

E1cB_{reversible}

In the E1cB_{reversible} mechanism, there is **reversible** formation of the conjugate base, followed by a slow elimination

Primary kinetic isotope effects are not observed, since C-H bond breaking is not implicated in the rate determining step
However, changing the identity of the leaving group can have a dramatic effect on rate
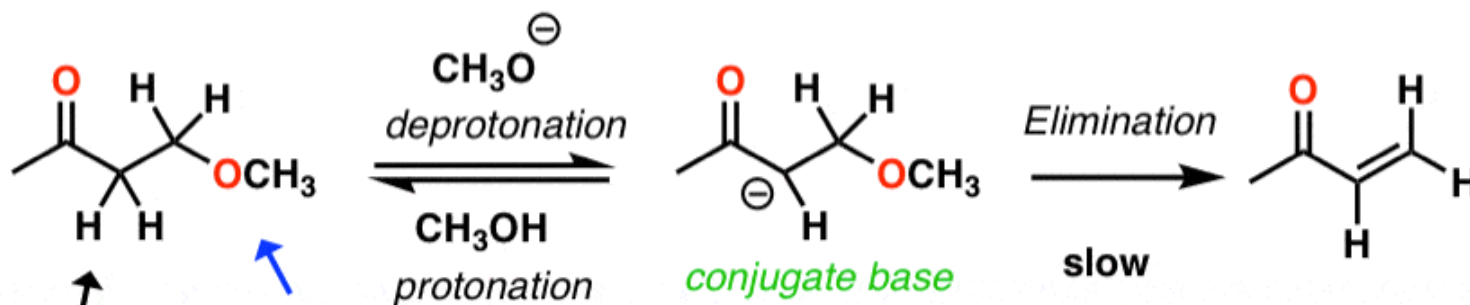
switching
H for D does
not change
rate-determining
step (no isotope effect)

changing the
identity of the leaving
group has a dramatic
effect on the rate

Since loss of the leaving group is slow, one should expect to see big effects on the reaction rate by tweaking the identity of the leaving group. For example, leaving group ability can be greatly modified by the identity of the group X on the phenyl group (shown). Changing the X group to a strong electron withdrawing group like NO2 should make the leaving group much less basic (and a better leaving group) and hence increase the rate. That's exactly what happens.

E1cB IRR

So is that it? Just measure kinetic isotope effects, and we can tell the difference between E2 and E1cB?

Not necessarily!

For example, this reaction below shows a large primary kinetic isotope effect, meaning that C-H is broken in the rate determining step.

E1cB$_{Irreversible}$

This reaction has a large primary kinetic isotope effect, meaning that C-H is broken in the rate-determining step. Is this enough to classify it as E2? Not quite!
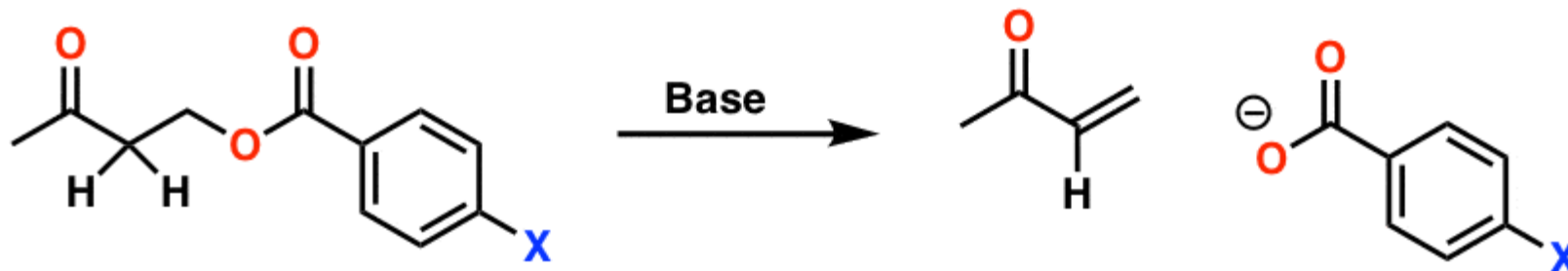
Significant k_H/k_D deuterium isotope effects are observed, since this is the rate determining step

Does that mean that we can safely classify this reaction as E2? Not yet.

It's possible that this is a case of an E1cB reaction where deprotonation to give the conjugate base is the **slow** step, and loss of the leaving group is **fast**. This is called the E1cB irreversible

If that's the case, there is a fairly simple way to test this: **change the leaving group.**

Breaking the C–LG bond is part of the rate determining step in the E2, but wouldn't be a rate determining step in the E1cB.

As it turns out, changing the leaving group didn't lead to any significant change in the reaction rate.

This reaction actually proceeds through a slow, rate-determining, irreversible deprotonation followed by fast elimination.
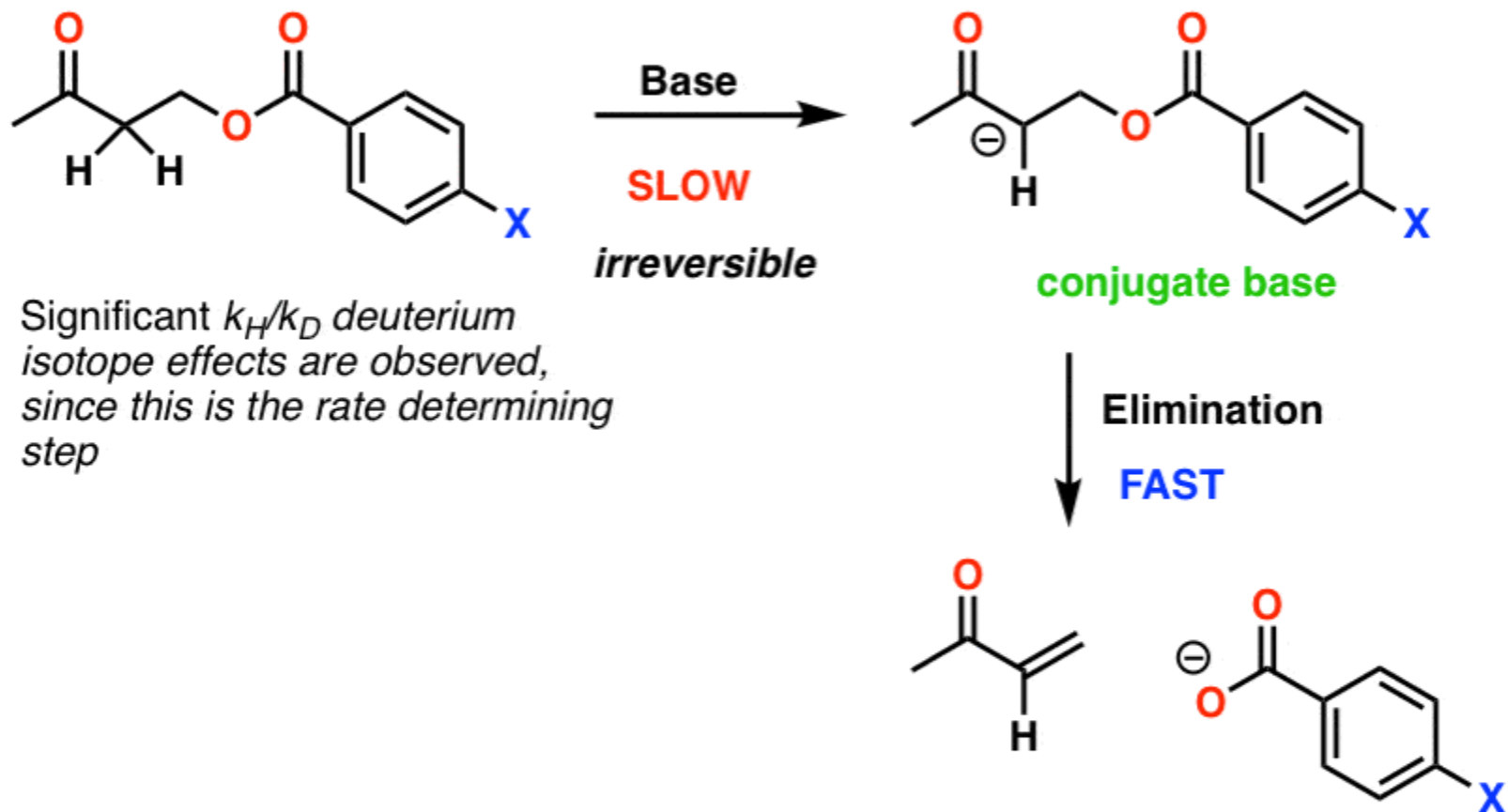
Base

SLOW

irreversible

conjugate base

Significant k_H/k_D deuterium isotope effects are observed, since this is the rate determining step

Elimination

FAST

*Changing the group X can have large effects on basicity (and leaving group ability). However in this case, since elimination is not the rate-determining step, **no large rate differences are detected.***

Changing the leaving group and seeing no large change in rate is how this mechanism is differentiated from the E2.

That would rule out an E2.

E1cbAnion
There's one major possibility left, and it's probably the easiest to visualize: fast, irreversible deprotonation, followed by slow elimination.

This would also **not** show a primary isotope effect, since C-H bond breaking is not in the rate determining step. The reaction rate would be very sensitive to the identity of the leaving group, however.

This flavor of the E1cB is called the E1cB anion. Here is an example.

E1cB$_{anion}$

Fast, irreversible deprotonation, followed by slow elimination
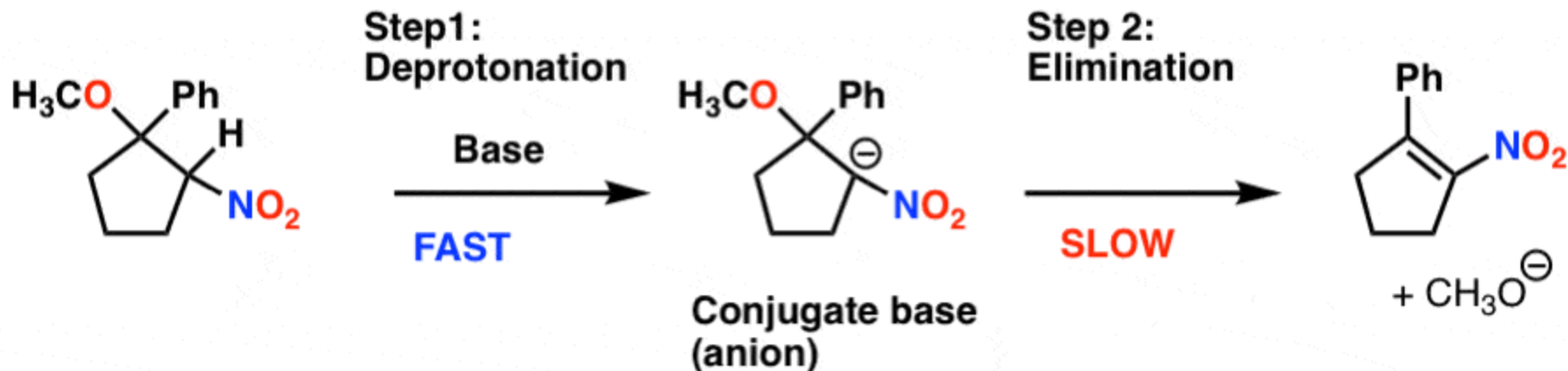
- No primary kinetic isotope effects observed
- Strong influence of identity of leaving group on reaction rate

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Summary: Three Flavors of E1cB

These three examples follow three possibilities for the three rate constants: k_1 (deprotonation), its reverse (k_{-1}), and elimination (k_2)

E1cB reversible (reversible, fast deprotonation followed by slow elimination)

E1cB irreversible (irreversible, slow deprotonation followed by fast elimination)

E1cB anion (irreversible, fast deprotonation followed by slow elimination)

The experimental differentiation of these different "flavors" of the E1cB from the E2 can be determined by studying kinetic isotope effects and making subtle changes to the identity of the leaving group.

There is also a variant of the E1cB called the E1cB ion pair which I haven't discussed here, it's discussed in this reference.

What About Stereochemistry?

The E2 has a strict stereochemical requirement that the C-H and C-X bond are anti to each other. The C-H bond must be *anti*-periplanar to the C-LG bond so that the pair of electrons from the breaking C-H bond is aligned with the C–LG sigma* (antibonding) orbital.

In layman's terms, you need that C-H bond to be lined up with the C-LG so that its pair of electrons can **push out** the leaving group (while forming the new pi bond).

No orbital alignment? No deprotonation.

In the E1cB, however, both "syn" and "anti" elimination reactions can occur (also true of the E1, if you'll recall)

The E1cB mechanism operates when the C-H bond is reasonably acidic. Although the substrate might be tetrahedral (sp^3) to start, once the conjugate base (anion) is formed, it generally adopts a flat (trigonal planar, sp^2) structure that has electron density on both "faces". The orientation of the leaving group with respect to the anion does not matter at that point, so long as the C–LG antibonding orbital is aligned with the pi system.

That's because the pair of electrons from the breaking C-H bond have to donate into the antibonding orbital of the C-X sigma * bond .

That isn't the case in the E1cb. Nor is it the case in the E1.

In the case of the aldol dehydration you get an anion. lone pair in a p orbital. p orbital can be thought to have electron density on either face of the molecule, and since there is electron density on either face, the C-X bond can be broken no matter what.

Why isn't "anti" stereochemistry required in the E1cB ?

e.g. *the conjugate base of this ketone*
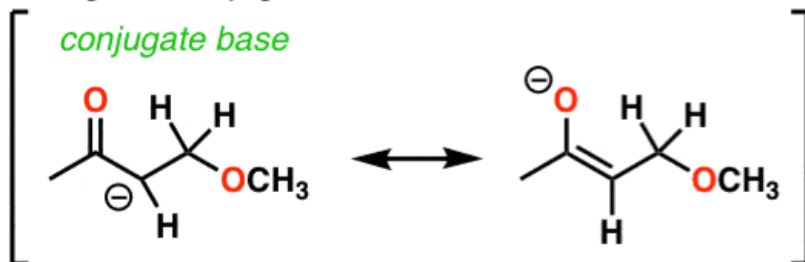
conjugate base

Drawing out the orbitals in the conjugate base "pi-system": all conjugated atoms can be considered to be sp² hybridized (flat)

• In order to break the C–LG bond, orbital overlap must occur between the sigma* of the C-LG bond and the pi system of the conjugate base

• Electron density can be considered to be on either "face" of pi system, so "syn" and "anti" doesn't really exist here

← *alignment between p-orbitals in pi system and σ* of the C–LG bond*

new C–C π bond