

Reactions of Alkyl Halides

This is probably the most confusing chapter in the first semester of organic chemistry, the reactions of alkyl halides. Alkyl halides undergo two basic types of reactions in organic chemistry, including substitutions and eliminations. There are two types of substitution reactions and two types of elimination reactions. We will look at each individually and then try to compare and contrast so you know what identifying characteristics to look for, to help you recognize which reaction is most likely to occur. Remember though, that there are exceptions to most rules. As defined and black and white as we might wish life to be, sometimes we have to deal in grey.

Substitutions:



There are two types of Substitutions reactions.

1. The S_N2 reaction

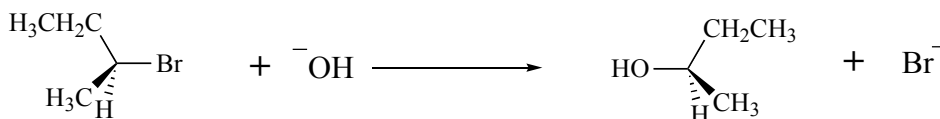
Substitution : one species replaces another (self-explanatory)

Nucleophilic : the substitution occurs as the result of attack by an electron-rich species

Bimolecular : two species are involved in the rate-determining step (the slowest of the mechanism)

Bimolecular: Dealing with the rate of the reaction. The rate of any S_N2 reaction is directly linked to the concentration of two species, the Nucleophile (Nuc) and the alkyl halide (RX) undergoing substitution. Both of these species are involved in the rate-determining (thus slowest) step. The rate equation would be: Rate = k[Nuc][RX], where k is a constant based on what species are actually involved. It is important to remember that, as a result, if you double the concentration of either, you double the reaction's rate. If you cut the concentration in half for either, the rate will also be cut in half. The rate of the reaction is directly linked to the number of times these two species can collide to react together. Change the concentration and you change the number of possible collisions!

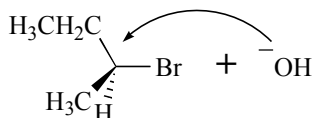
An example of an S_N2 reaction:



Mechanism of S_N2:

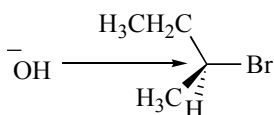
There are actually two potential ways the nucleophile could attack:

Frontside attack:

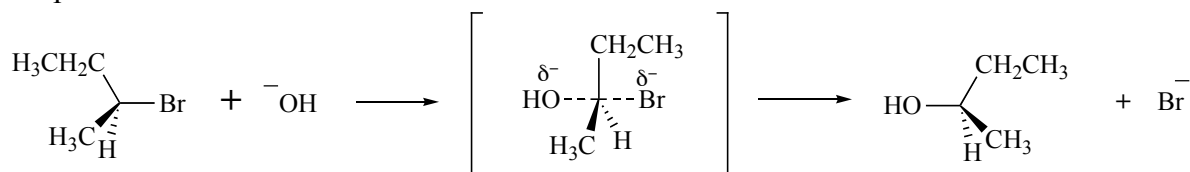


The attack from the frontside (the side the leaving group is on) is disfavored for two reasons. First, there's **sterics** – the nucleophile is trying to attack in the same space the leaving group is trying to leave. Second, there's **electronics** – the nucleophile is trying to attack bearing a full negative charge and the leaving group is trying to leave with a full negative charge, and they will repel each other (a.k.a. electrostatic repulsions)

Backside attack:



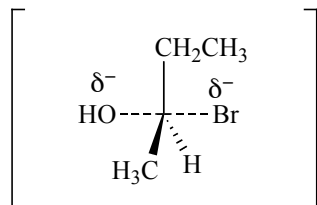
Attack from the backside, where the nucleophile comes in from the opposite side of the leaving group, alleviates both the electronic and steric issues seen in the frontside attack. This is a one-step concerted (i.e. happens all at once) process where all the bond formations and breakages occur simultaneously. There aren't any intermediates formed (no anions, cations, etc) and it is surmised based on the results that the following is an accurate depiction of the transition state of the process:



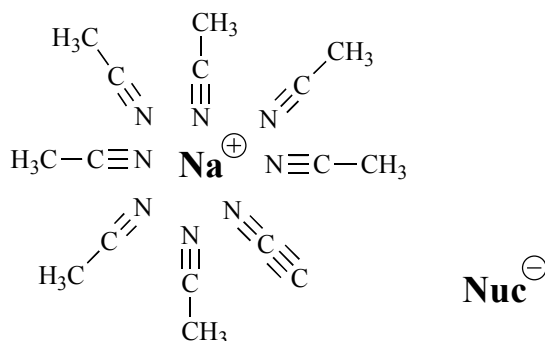
Any chiral center that was once perhaps the “S” configuration, as shown in the starting material here, winds up inverting its stereochemistry and becoming the “R” configuration. Centers that are not chiral cannot “show” this inversion but the inversion process is still occurring.

Transition State of S_N2 : The original starting material was sp^3 hybridized but note that the transition state resembles sp^2 hybridization (turned on its side – with the nucleophile, OH, and the group that's leaving, Br, where the perpendicular p orbital might once sit). It is this planar geometry and the need to put the other groups through the inversion into this “planar” state that define what alkyl halides can undergo the S_N2 reaction.

Transition State:



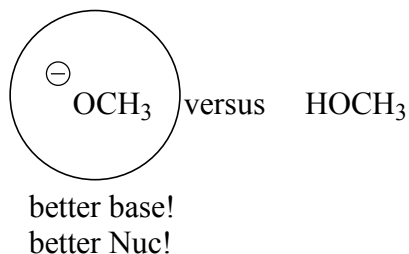
b. **Aprotic (Polar) Solvents:** Every nucleophile with a full negative charge is in the reaction with some sort of metal counterion (typically Na, Li or K). Aprotic, polar solvents cause solvation of the counterion, exposing the nucleophile, with its anionic charge, to need to react even more. The nucleophile is destabilized and faster to react. Examples of aprotic polar solvents might be DMSO [dimethylsulfoxide ($\text{CH}_3\text{S}(\text{O})\text{CH}_3$)], DMF [(dimethylformamide, $(\text{CH}_3)_2\text{NCHO}$)] or acetonitrile, CH_3CN . Notice how the acetonitrile, with its partial positively negative nitrogen atom is totally surrounding the sodium counterion. That Nucleophile NEEDS to find something to react with!



4. Nucleophiles:

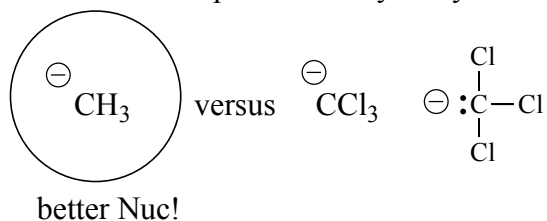
a. Strong bases are strong nucleophiles, and vice versa. Full negative charges are always more basic and also more nucleophilic. (Hint: Look for Na, K, Li : they always are positively charged counterions that are associated with full negative charges)

Ex.



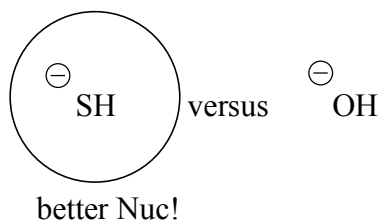
b. The strength of a nucleophile is reduced by the presence of electron-withdrawing groups (EWG). Electron density is removed from the attacking atom, reducing its strength.

Ex. The chlorine atoms pull e^- density away from the attacking carbon – weaker nucleophile.



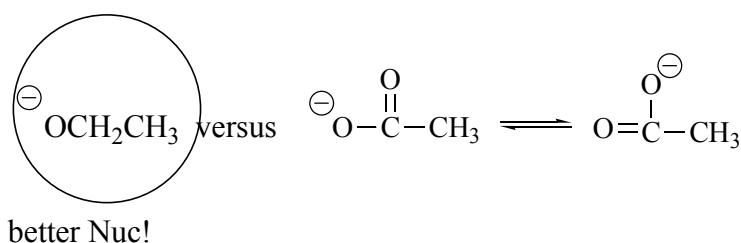
c. The strength of a nucleophile increases for atoms down the column of the periodic table

Ex:



d. Resonance stabilization results in spreading out the anion of the nucleophile, making it less concentrated, thus weaker. Notice that in the two resonance forms below, the anion is located on both oxygens, effectively splitting the negative charge between the two atoms. Its not concentrated on a single atom, thus it's a weaker nucleophile.

Ex:



2. The $\text{S}_{\text{N}}1$ reaction

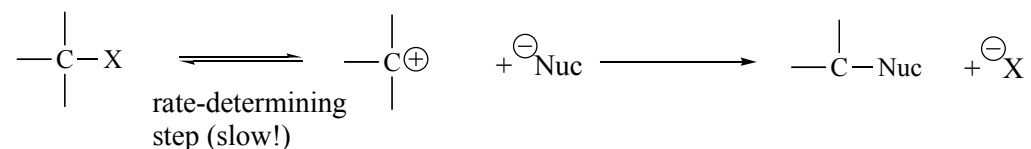
Substitution : one species replaces another (self-explanatory)

Nucleophilic : the substitution occurs as the result of attack by an electron-rich species

Unimolecular : one species are involved in the rate-determining step (the slowest of the mechanism)

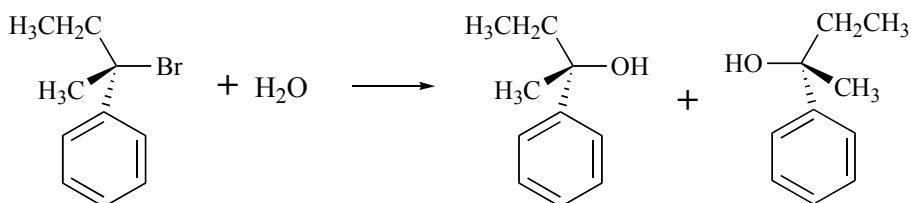
Unimolecular: Dealing with the rate of the reaction. The rate of any $\text{S}_{\text{N}}2$ reaction is directly linked to the concentration only one species, the alkyl halide (RX) undergoing substitution. This is the only species involved in the rate-determining (thus slowest) step. The rate equation would be: $\text{Rate} = k[\text{RX}]$, where k is a constant based on what species is actually involved. It is important to remember that, as a result, if you double the concentration of the nucleophile, there will be NO EFFECT on the rate of the reaction. Go ahead – add as much as you want – it won't make the reaction any faster! But cut the concentration of the alkyl halide in half and the reaction will slow down by half – only half as many alkyl halides are undergoing reaction!

An example of an $\text{S}_{\text{N}}1$ reaction:



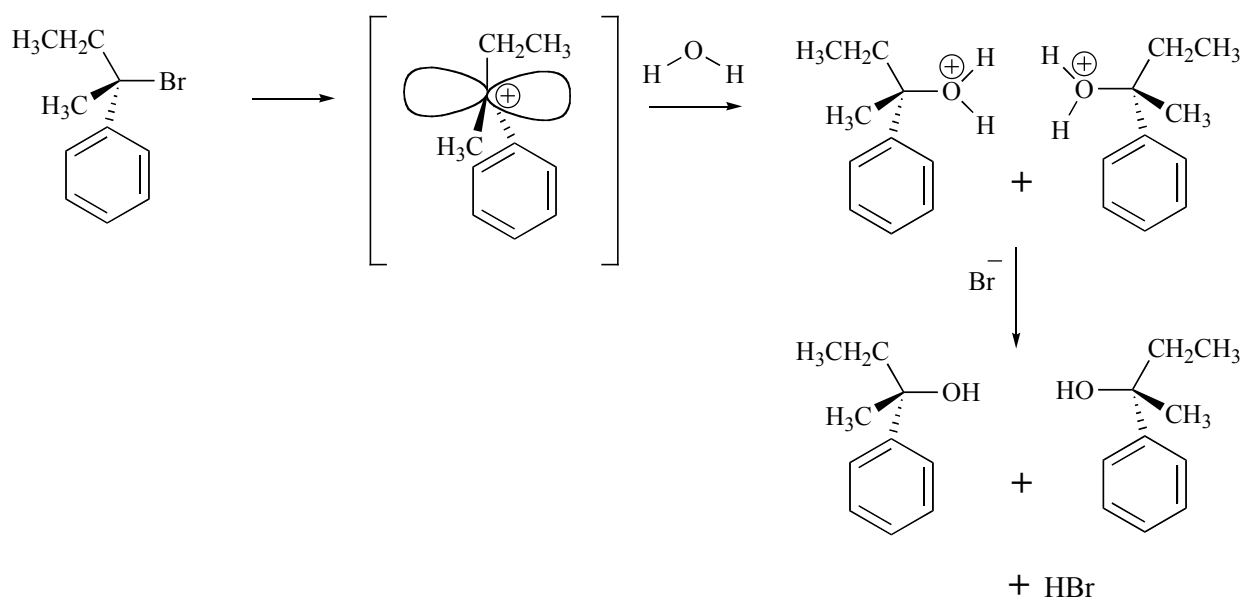
The rate of reaction is dependent on the formation of a carbocation intermediate from the alkyl halide. It is the rate of the “spontaneous dissociation” of the leaving group that determines how fast this reaction goes.

Specific example:



Notice how one of the products looks almost exactly like the starting material but the other is its mirror image. When chiral compounds undergo S_N1 reaction, they form a racemic mixture of enantiomers!

Mechanism of S_N1 :



In the first step, a carbocation forms. This results in an empty p orbital that can be attacked by the nucleophile from either the right side or the left side. As a result, a mixture of two possible chiral centers occurs. In the last step, the bromide anion scavenges the extra proton from the oxygen, to produce the final products.

Both retention and inversion of configuration = formation of racemic mixture from chiral material (loss of optical activity)

Factors that affect the S_N1 :

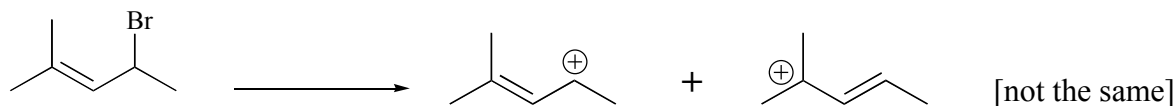
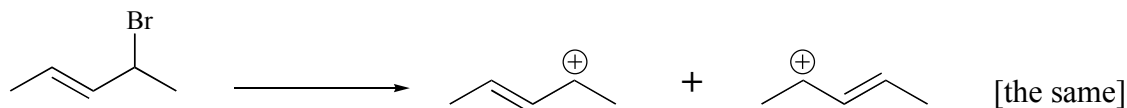
1. **Alkyl Halide:** the more stable the carbocation, the faster it can form. (Recall: both hyperconjugation and the inductive effect allow alkyl groups to stabilize carbocations). The

more stable carbocation intermediate has a lower activation barrier, so the S_N1 reaction occurs faster.

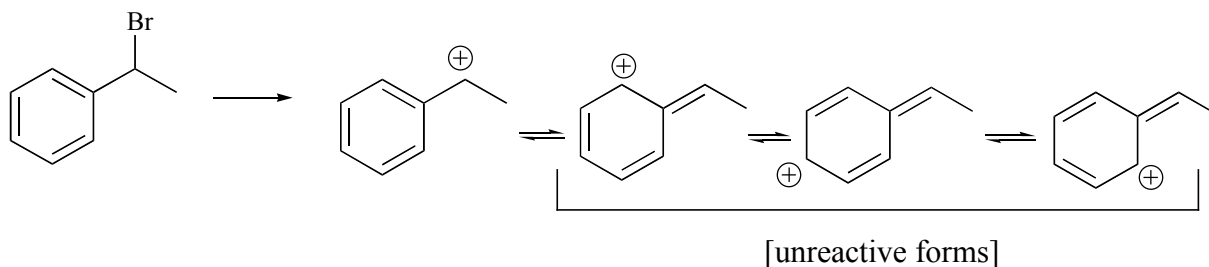
Order of reactivity: At a first glance:

3° carbocations > 2° carbocations >>>>>>>>> 1° carbocations or methyl carbocations

Add in resonance stabilization and these carbocations become even more stable! If the allylic carbocation can form two different resonance forms, both react:



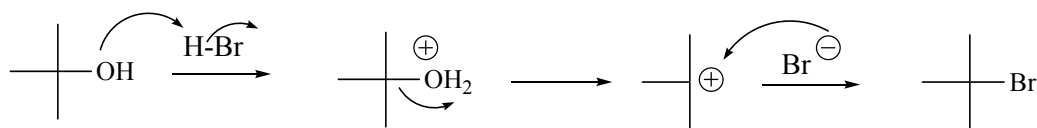
If there is a benzylic carbocation, it is also resonance stabilized but only the carbocation on the benzylic position is reactive (retain the aromatic ring):



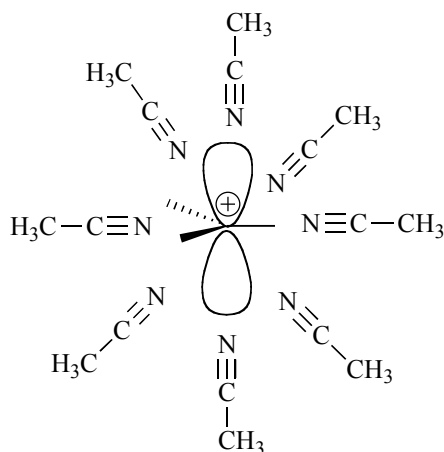
2. Leaving Group: The leaving group is almost always expelled with a full negative charge. As a result, the best leaving groups are those that can best stabilize an anion (i.e. a weak base). In S_N1 reactions, it is not uncommon for water to also be considered a leaving group.

Best: ⁻OMs, ⁻OTos > I⁻, Br⁻ > H₂O ≈ Cl⁻ > F⁻ (⁻OH, ⁻NH₂) (Worst)

Example of water as a leaving group:



3. **Solvent:** The rate of the reaction can be affected by the energy level of the reagents. Solvation of the carbocation allows the carbocation to be surrounded by more electron density, making the positive charge more stable. The solvent can be protic or aprotic, but it must be polar.



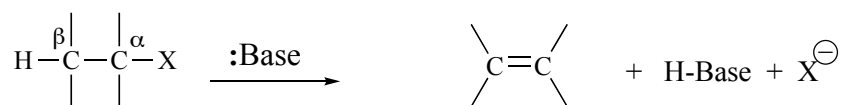
4. **Nucleophiles:** those nucleophiles that do the SN1 mechanism are those that are weak, neutral molecules (ex. H₂O, ROH). Any nucleophile that is stronger than this is generally also a strong base and will result in elimination reactions instead.

One further comment: Remember that carbocations can undergo rearrangements (hydride or methide shifts or even evil ring contractions) in order to become MORE stable.

Eliminations:

Absolute Requirement– must have a β-hydrogen atom in order for elimination to occur. The carbon the leaving group is attached to is labeled as the α (alpha) carbon and the carbon attached next is the β (beta) carbon. The rest of the Greek alphabet falls into place beyond that. This keeps you from confusing relative positions with the IUPAC numbering.

Ex.



There are two types of Elimination reactions.

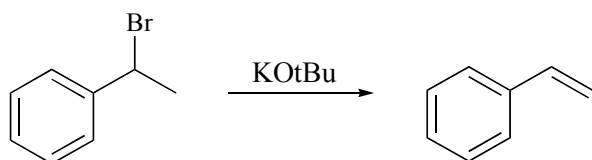
1. The E2 reaction

Elimination: one species splits into two or more (alkene formation)

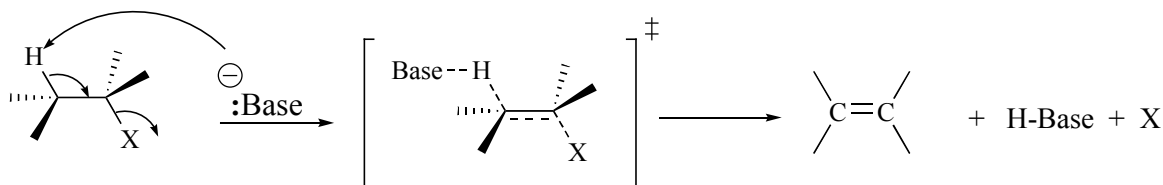
Bimolecular : two species are involved in the rate-determining step (the slowest of the mechanism)

Bimolecular: Dealing with the rate of the reaction. The rate of any E2 reaction is directly linked to the concentration of two species, the Base and the alkyl halide (RX) undergoing substitution. Both of these species are involved in the rate-determining (thus slowest) step. The rate equation would be: $\text{Rate} = k[\text{Base}][\text{RX}]$, where k is a constant based on what species are actually involved. It is important to remember that, as a result, if you double the concentration of either, you double the reaction's rate. If you cut the concentration in half for either, the rate will also be cut in half. The rate of the reaction is directly linked to the number of times these two species can collide to react together. Change the concentration and you change the number of possible collisions!

An example of an E2 reaction:



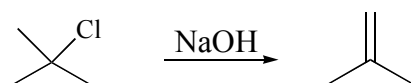
Mechanism of E2:



The E2 reaction utilizes a strong base and an alkyl halide. Strong bases are those with full negative charges (ex. OH^- , OR^- , NH_2^- , etc). All the strong nucleophiles used for the $\text{S}_{\text{N}}2$ are also strong bases for the E2, with the exception of the halide anions (these are non-basic). There are also some bases out there that are strong, NON-nucleophilic bases because they are very sterically hindered. An example of a base like this is KOtBu. The anion of tert-butyl alcohol is a huge base. And cannot be a nucleophile. This can be useful sometimes.

There are three types of alkyl halides that we work with:

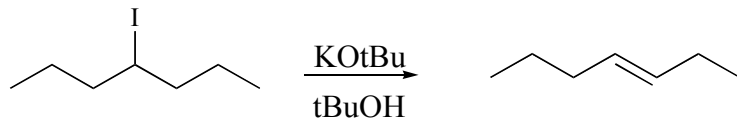
3° alkyl halides – E2 occurs with any strong base. Even if the strong base is a strong nucleophile, it won't be a problem. 3° halides can't undergo $\text{S}_{\text{N}}2$ reactions. No competition.



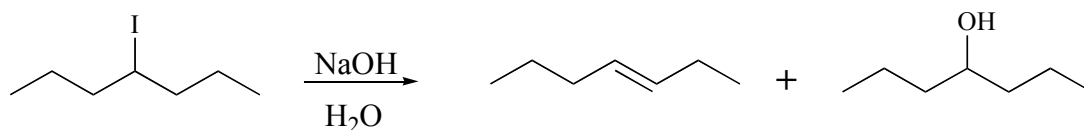
1° alkyl halides – E2 occurs with any strong NON-nucleophilic base. If you use a base that is a strong nucleophile also, the $\text{S}_{\text{N}}2$ reaction actually predominates!



2° alkyl halides – If you want E2 only, you MUST use a strong NON-nucleophilic base.

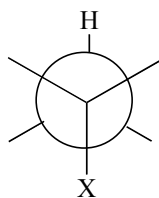
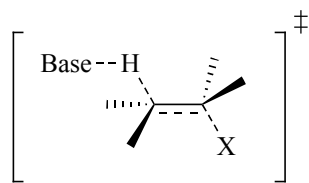


2° alkyl halides will do both $\text{S}_{\text{N}}2$ and E2 in competition if the strong base is a strong nucleophile. See what happens when you use a strong base that's a strong nucleophile??

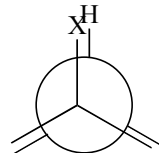
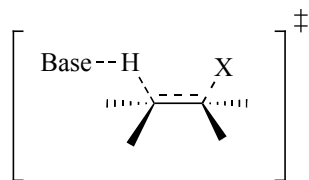


Stereochemistry:

Transition State of E2: The original starting material has two sp^3 hybridized carbons which must rehybridize to form two sp^2 hybridized carbons. The C-X bond and the C-H bond must line up in the same plane (periplanar) and will face in opposite directions (anti) to each other. The “antiperiplanar” arrangement is required for all E2 eliminations. If the molecule were “syn periplanar” it would be a higher energy state.



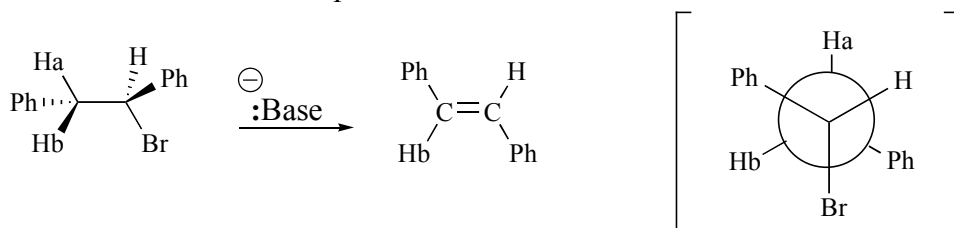
Antiperiplanar results in a staggered transition state. STABLE!!



Syn periplanar results in an eclipsed transition state. UNSTABLE!!

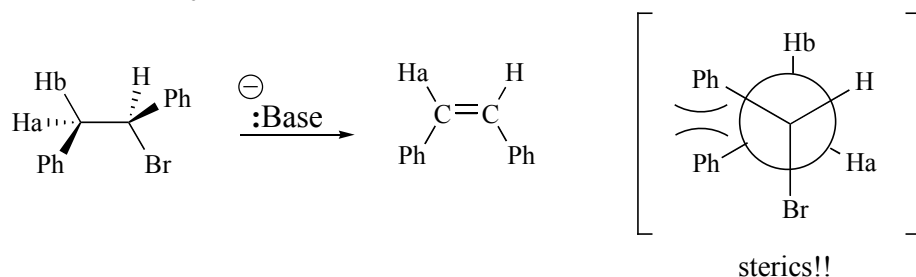
Keep antiperiplanar in mind, when working with chiral carbons. You may need to rotate and set up the “anti periplanar” arrangement. Sometimes you have options though and you will need to think which product will predominate:

Eliminate H_a in this example:



Note that the two phenyl groups are on opposite sides. (A phenyl group is an unsubstituted aromatic ring.)

Elimination H_b now:



Phenyls are on the same side! Sterics going on... If you have a choice – always form the **Trans (or E) double bond** product.

Regiochemistry : A regiochemical reaction is one which potentially could product two different products but in fact forms one preferentially. You saw this concept back when we discussed Markovnikov and Non-Markovnikov reactions with you. This also applies to some reactions that form C=C.

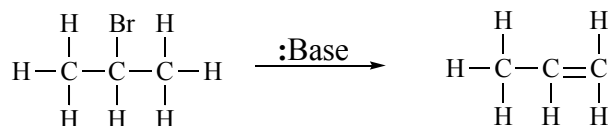
Let's start simple:

a.



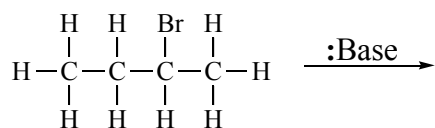
This is NOT a regioselective reaction – there's only one possibility.

b.

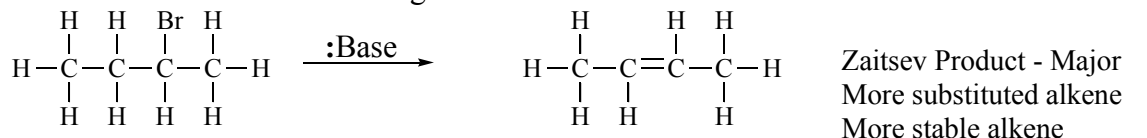


This is also not a regioselective reaction – the two β-carbons are symmetrical.

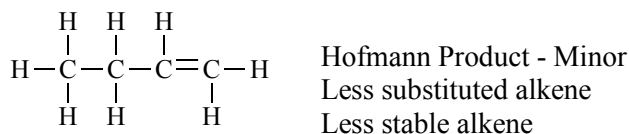
But what if there are two possible β-carbons with hydrogens that were different?



Elimination to the left side or right?



+



Remember that increasing the alkyl groups on an alkene results in a more stable alkene product. The E2 reaction almost always favors the Zaitsev product, with almost every base/solvent pair. Common base/solvent pairs would include: ^-OH in H_2O , (NaOH in water), $^-\text{OCH}_3$ in CH_3OH (or any NaOR in its corresponding alcohol, ROH) or $^-\text{OCH}_3$ in DMSO (NaOCH_3 , DMSO).

There is one solvent/base pair exception to the Zaitsev-always rule. If you use KOtBu in tBuOH solvent, you will always favor the formation of the Hofmann product. How so you ask? Recall what protic solvents do to anionic species. They solvate them. They create the solvent “cage” around them. Now, think of the really REALLY big base tert-butoxide (the anion of tert-butyl alcohol) and SOLVATE IT with a really, REALLY big solvent (and it has to be THAT one). This thing just became Gargantuan...! So – can it really even be possible that this can pull off protons from the middle of the molecule? Nope. This solvent/base pair can only react at the easiest protons to get to, those on the end of the molecule, those that lead to the Hofmann product.

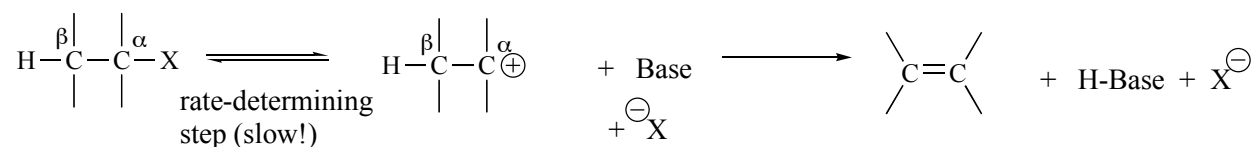
4. The E1 reaction

Elimination: one species splits into two or more (alkene formation)

Unimolecular : one species are involved in the rate-determining step (the slowest of the mechanism)

Unimolecular: Dealing with the rate of the reaction. The rate of any E1 reaction is directly linked to the concentration only one species, the alkyl halide (RX) undergoing elimination. This is the only species involved in the rate-determining (thus slowest) step. The rate equation would be: $\text{Rate} = k[\text{RX}]$, where k is a constant based on what species is actually involved. It is important to remember that, as a result, if you double the concentration of the base, there will be NO EFFECT on the rate of the reaction. Like the $\text{S}_{\text{N}}1$, the amount of base does not increase the rate of the reaction. But cut the concentration of the alkyl halide in half and the reaction will slow down by half – only half as many alkyl halides are undergoing reaction!

An example of an E1 reaction:



Same spontaneous dissociation as the $\text{S}_{\text{N}}1$. Same formation of a carbocation intermediate. Like the E2 reaction, the E1 favors the **Zaitsev** product (always) and **Trans/E** always.

Factors that affect the E1: all the factors that cause the $\text{S}_{\text{N}}1$ also cause the E1 to occur. Weak nucleophiles are also weak bases and cause the E1 to occur. As long as there is a β -hydrogen to be abstracted by the weak base, both the $\text{S}_{\text{N}}1$ and E1 will occur simultaneously.

