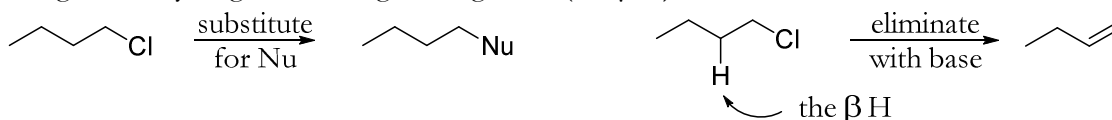


# Loudon Chapter 9 Review: Reactions of Alkyl Halides

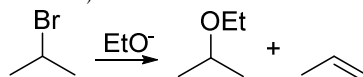
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Chapter 9 covers reactions you can do with alkyl halides. For the most part, these break down into two categories: substitution and elimination. Substitution results in replacing the halogen with some other group. Elimination results in removing the halogen, along with a hydrogen on a neighboring atom (the  $\beta$  H), to create a new double bond.



There are several terms that are useful to know here:

- The **substrate** is the molecule having this reaction performed on it.
- The **leaving group** or LG is the group that dissociates from the substrate. In this chapter, all the leaving groups are halogens.
- The **base/nucleophile** is the molecule that attacks the substrate. If it performs substitution, then it's acting as a nucleophile (because it's attacking a C atom); if it performs elimination then it's acting as a base (because it's attacking an H atom). Often it can do a mixture of both jobs:



## Reaction Kinetics

The reactions we'll see can be subdivided based on kinetics (how fast the reaction occurs, or the reaction rate). Reaction rate is defined as:

$$\text{rate} = \frac{\text{change in product concentration}}{\text{time}}$$

The rate is often set by the concentrations of one or more reactants; concentrations are usually given in square brackets. For a reaction like  $A + B \rightarrow C$ , the rate can be measured at various concentrations of each reactant. For example, if double the concentration of A or the concentration of B doubles the rate, then the rate law would be  $\text{rate} = k[A][B]$ . For a different reaction, perhaps doubling the concentration of A quadruples the rate but doubling the concentration of B has no effect. In this case the rate law would be  $\text{rate} = k[A]^2$ . **Overall kinetic order** is the sum of the powers in the rate law for a reaction. For  $\text{rate} = k[A][B]$ , it's second-order overall (first-order in A, and first-order in B). For  $\text{rate} = k[A]^2$ , it would also be second-order overall (second-order in A, and zeroth-order in B). The order is determined by how many molecules are involved in the rate-determining step. First-order reactions involve only one molecule and are unimolecular, second-order reactions involve two and are bimolecular, and third-order reactions involve three and are termolecular.  $k$ , the rate constant, varies from reaction to reaction. A bigger  $k$  gives a faster reaction. It's controlled by the activation energy,  $\Delta G^\ddagger$  - a smaller activation energy gives bigger  $k$ . It's also controlled by temperature - higher temperature gives a bigger  $k$ .

The substitution and elimination reactions in this chapter each have one unimolecular and one bimolecular option. They are:

$S_N1$ : First-order substitution	$E1$ : First-order elimination
$S_N2$ : Second-order substitution	$E2$ : Second-order elimination

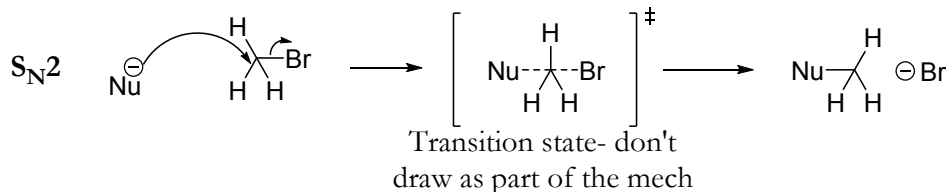
Looking at the mechanism for each one will explain why it behaves the way it does.

# Loudon Chapter 9 Review: Reactions of Alkyl Halides

Jacque Richardson, CU Boulder – Last updated 5/1/2016

## $S_N2$

The attacking nucleophile forms a bond to the substrate at the same time the leaving group is dissociating. This is a concerted, one-step reaction.



Since both the substrate and the nucleophile are involved in the RDS, the reaction is second-order. This reaction has several interesting characteristics, as a result of its mechanism being what it is.

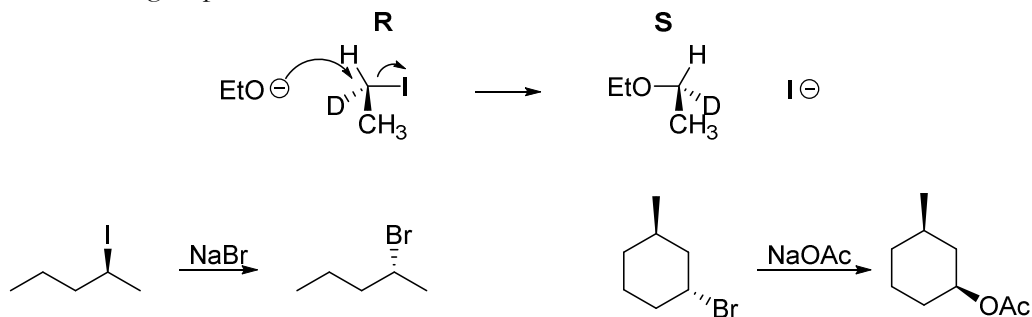
- Since the carbon has bonds or partial bonds to five atoms at once during the transition state, space is at a premium. The fewer R groups and the more Hs there are on the central carbon (in other words, the less sterically hindered the carbon is), the faster this reaction will go. The trend is  $\text{Me} > 1^\circ > 2^\circ > 3^\circ$ . Some examples of relative  $S_N2$  rates are given below – these are just examples under a very specific set of conditions, but the same general trends hold for all  $S_N2$  reactions.

Substrate	Relative Rate	Substrate	Relative Rate
	145		145
	1		0.82
	0.0078		0.036
	0.0005		0.000012

This list of compounds has increasing substitution at the  $\alpha$  carbon - it goes from Me, to  $1^\circ$ , to  $2^\circ$ , to  $3^\circ$  alkyl halides.  $S_N2$  is good on Me and  $1^\circ$ , mediocre on  $2^\circ$ , and NR (no reaction) on  $3^\circ$ .

This list of compounds has increasing substitution at the  $\beta$  carbon, although they're all Me or  $1^\circ$ . The last compound, commonly named neopentyl bromide, is so slow at  $S_N2$  that it's also NR. This is called the neopentyl effect.

- Since the nucleophile attacks from the side opposite to the leaving group, **inversion** of stereochemistry occurs. We've seen this before in the opening of bromonium rings – it's similar to an umbrella turning inside-out. If the leaving group had a bold bond before, then the new group will have a dashed bond or vice-versa.

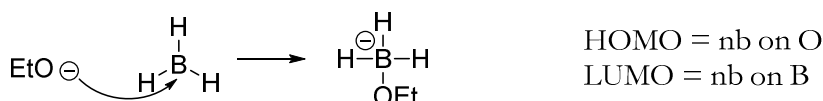
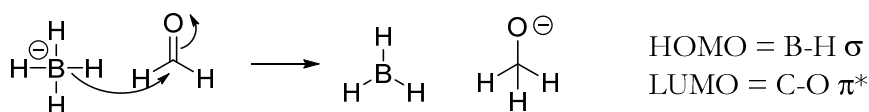
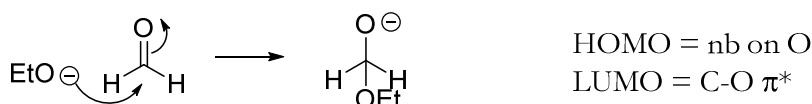
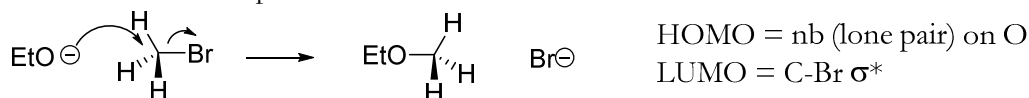


# Loudon Chapter 9 Review: Reactions of Alkyl Halides

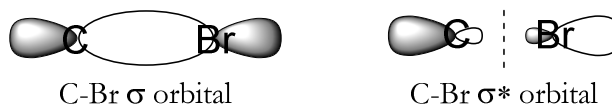
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This also means that as long as the leaving group and the incoming group have the same priority ranking in CIP rules, the molecule will convert from R to S or vice-versa at the attacked carbon.

Why does  $S_N2$  happen this way? It has to do with the orbitals involved and their shapes. This is getting a little bit into Frontier Molecular Orbital (FMO) Theory. Whenever a mechanistic step occurs, electrons are being transferred from one orbital to another during the attack. The orbital where electrons are attacking from is the **highest occupied molecular orbital (HOMO)** and the orbital that is being attacked is the **lowest unoccupied molecular orbital (LUMO)**. Often the HOMO is a lone pair (nonbonding or nb) orbital, but it can also be a sigma bond or pi bond. The LUMO will often be an antibonding orbital – in the first example below, the C-I  $\sigma$  bond breaks as a result of the attack, so this means the incoming electrons must have gone into the  $\sigma^*$  orbital to reduce its bond order to zero. This can also happen to  $\pi$  bonds, as in the second and third examples.



The first of these examples is what happens during an  $S_N2$  reaction – the HOMO is a lone pair on the attacking nucleophile, and the LUMO is a  $\sigma^*$  orbital between a carbon and a halogen. For the reaction to occur, these orbitals must overlap each other. The shapes of the C-Br  $\sigma$  and  $\sigma^*$  orbitals are shown here:



The largest lobe of the  $\sigma^*$  orbital is on C, pointing in the opposite direction from the Br. For the lone pair on the nucleophile to overlap with this, it must perform backside attack from  $180^\circ$  away from the leaving group.

- The  $S_N2$  mechanism looks very similar to an acid-base reaction:

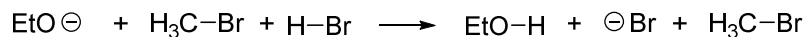


The only difference is that an alkyl group is getting transferred, instead of a proton. The rates for these reactions, though, are very different. Acid-base occurs almost

# Loudon Chapter 9 Review: Reactions of Alkyl Halides

Jacque Richardson, CU Boulder – Last updated 5/1/2016

instantaneously, while  $S_N2$  takes minutes to hours. This means that if both reactions are a possibility (as determined by relative  $pK_a$  values, like we saw in Ch. 3), acid-base will happen faster.

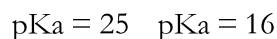
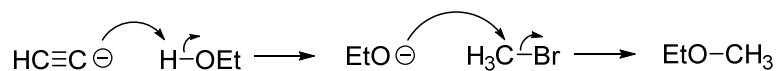


If all reagents are present in equal amounts,  
no  $S_N2$  occurs - only acid-base

However, the product of the acid-base reaction can often go on to do its own  $S_N2$  reaction on the substrate, giving an unexpected side product.



Instead, the base/Nu does acid-base reaction with EtOH first, creating  $\text{EtO}^-$ . This goes on to perform  $S_N2$  on  $\text{CH}_3\text{Br}$



- Nucleophilicity vs. Basicity: Basicity is how good something is at forming new bonds to H, and nucleophilicity is how good something is at forming new bonds to something other than H (in this case, C). We can use  $pK_a$  values to compare basicity. There's not a single number that describes nucleophilicity, but we can get an estimate of it by comparing  $S_N2$  rates under the same conditions. It turns out that nucleophilicity follows different trends in protic vs. aprotic solvents. In **protic solvents**:
  - If the charge-bearing atoms are within the same row of the periodic table, more basic = more nucleophilic.
  - If the charge-bearing atoms are within the same column of the periodic table, more basic = less nucleophilic.

Here are some examples within the same row. The  $S_N2$  rate constants are all for a reaction with  $\text{CH}_3\text{I}$  in  $\text{CH}_3\text{OH}$ .

Base/Nu	$pK_a$	$S_N2$ rate
$\text{CH}_3\text{O}^-$	15.1	$2.5 \times 10^{-4}$
$\text{Ph}_3\text{O}^-$	10	$7.9 \times 10^{-5}$
$\text{Ac}_3\text{O}^-$	4.76	$2.7 \times 10^{-6}$
$\text{F}^-$	3.2	$5.0 \times 10^{-8}$

Note that even though three of these have the same charge-bearing atom, they all have different  $pK_a$  values and therefore different nucleophilicities.

Here are some examples within the same column. The  $S_N2$  rates are all for the same reaction again.

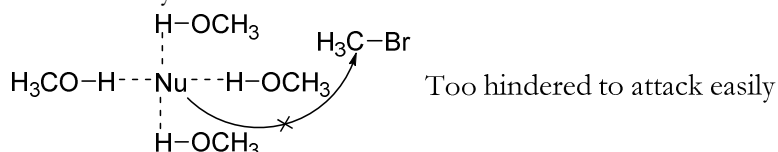
Base/Nu	$pK_a$	$S_N2$ rate
$\text{I}^-$	-10	$3.4 \times 10^{-3}$
$\text{Br}^-$	-8	$8.0 \times 10^{-5}$
$\text{Cl}^-$	-6	$3.0 \times 10^{-6}$
$\text{F}^-$	3.2	$5.0 \times 10^{-8}$

So iodide ( $\text{I}^-$ ) is a weak base but a really good nucleophile in protic solvents. Why is this? It has to do with hydrogen-bonding to protic solvents. Small atoms are the best at hydrogen bonds, especially when they're stronger bases. Unfortunately, this means

# Loudon Chapter 9 Review: Reactions of Alkyl Halides

Jacque Richardson, CU Boulder – Last updated 5/1/2016

they're so wrapped up in H-bonds to the solvent molecules that they're not able to attack the substrate as effectively.



However, switching to an aprotic solvent reverses this trend! In **aprotic solvents**:

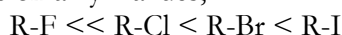
- More basic = more nucleophilic, for both directions in periodic table

Here are some rates again, for  $S_N2$  in two different solvents:  $\text{CH}_3\text{OH}$  (protic) and DMF (aprotic).

Base/Nu	pKa	$S_N2$ rate in $\text{CH}_3\text{OH}$	$S_N2$ rate in DMF
I <sup>-</sup>	-10	$3.4 \times 10^{-3}$	0.4
Br <sup>-</sup>	-8	$8.0 \times 10^{-5}$	1.3
Cl <sup>-</sup>	-6	$3.0 \times 10^{-6}$	2.5
F <sup>-</sup>	3.2	$5.0 \times 10^{-8}$	>3

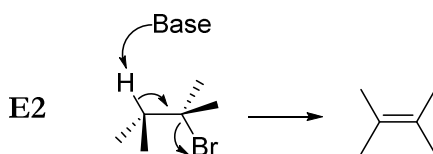
By taking away the option of H-bonding to solvent, not only are we speeding up the rates of all  $S_N2$  reactions, but we're also reversing the trend within a column of the periodic table. In general, aprotic solvents are the best choice for fast  $S_N2$  reactions, but for practical reasons (solubility, boiling point, etc). protic solvents are sometime used.

- Leaving group ability: since the C-LG bond breaks during the rate-determining step, it can really slow down the reaction if it's a difficult bond to break. This is based on bond strength for the C-LG bond, which is largely set by how stable the LG is with a negative charge after it leaves. Based on pKa values for HX acids, F<sup>-</sup> is the strongest base, so it's least stable with a negative charge, so it forms the strongest bond to C, so it's the worst leaving group. So for  $S_N2$  rates on alkyl halides,



## E2

This is another second-order reaction, but an elimination instead of a substitution. The base removes the H at the same time the LG dissociates.

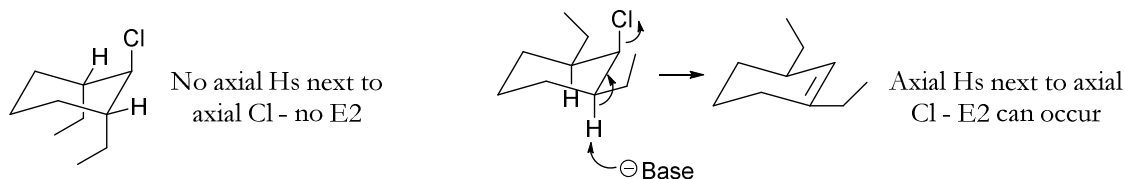


Like  $S_N2$ , this is a concerted reaction – everything happens at once.

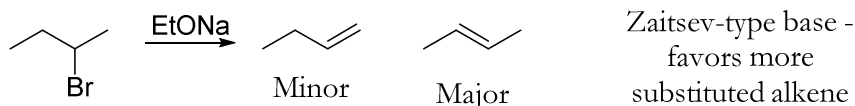
- Since everything is happening at once, geometry is important here just like it is for  $S_N2$ . You need antiplanar (also called antiperiplanar) geometry: the four atoms (H, C, C, and the leaving group) are all in the same plane, with the H and the leaving group pointing opposite directions. If you can't get antiplanar geometry, E2 can't happen. This comes up most often on rings, which are rotationally constrained more than linear chains. For E2 to happen on a cyclohexane, the leaving group and the H must be up axial or down axial on adjacent carbons.

# Loudon Chapter 9 Review: Reactions of Alkyl Halides

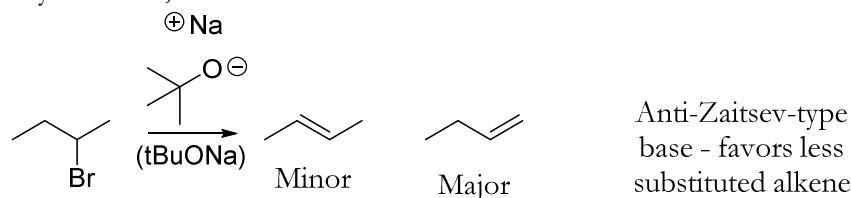
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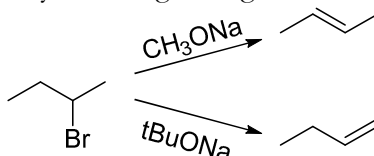
- Regiochemistry: often, there are multiple different protons that could be pulled off during an elimination, to form different alkenes. **Zaitsev's Rule** says that the more stable, substituted alkene will be formed as the major product.



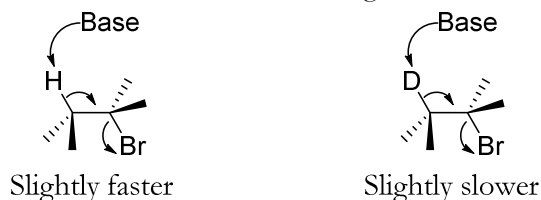
Almost all bases obey Zaitsev's Rule, with one major exception: bases which are large and sterically hindered, like *t*-butoxide.



This is because, being large and hindered, it takes too much energy to squeeze them up against the substrate to pick off the proton that would give the best product. Instead, they go for the short-term of a lower activation energy and take the easiest proton to access – the one that gives the less substituted alkene. For both these cases (Zaitsev and anti-Zaitsev bases) there's usually not an overwhelming majority in favor of one product or another. Product ratios are usually 2 or 3 to 1. However, this is still enough that we can target the desired product by choosing the right base.



- Leaving-groups effects: the same as for  $S_N2$ . RF is the slowest, RI is the fastest.
- Kinetic isotope effect (KIE): For reasons based on lowest-state vibrational energy, C-H bonds are just slightly weaker than C-D bonds. This means that if a C-H bond gets broken during the RDS of a reaction, the reaction will happen slightly slower if we replace the H with a D. This is called the "primary deuterium isotope effect", and can be used to prove that the E2 mechanism involves losing an H/D in the RDS.



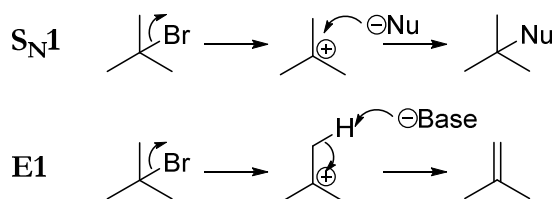
## $S_N1/E1$

These two reactions are covered together since they have so much in common. In both reactions, the leaving group dissociates first and leaves a carbocation behind, then the

# Loudon Chapter 9 Review: Reactions of Alkyl Halides

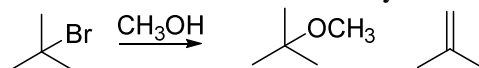
Jacque Richardson, CU Boulder – Last updated 5/1/2016

Base/Nu comes in to attack either C or H. Since the RDS involves only the alkyl halide, it's first-order.

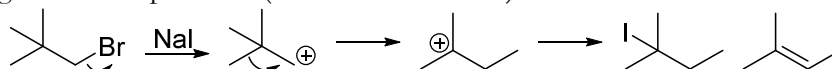


For both of these reactions, the overall arrows are exactly the same as for  $S_N2$  or  $E2$ , but they're broken into multiple steps instead of all simultaneous. This means it's a stepwise reaction, rather than concerted.

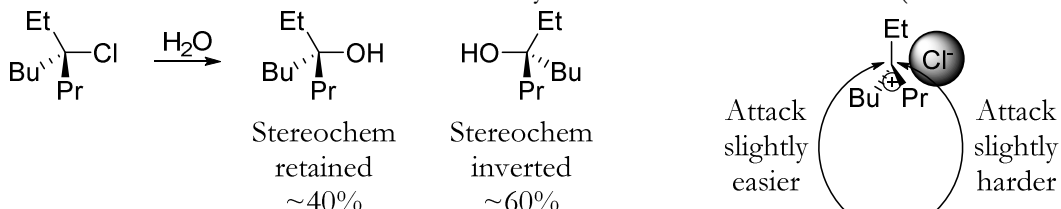
- Most of the behavior of these reactions is determined by the fact that they go through carbocations. More substituted carbocations are more stable, so the reaction rates are the opposite of  $S_N2$ :  $Me < 1^\circ < 2^\circ < 3^\circ$ .
- Leaving-groups effects: the same as for  $S_N2$ .  $RF$  is the slowest,  $RI$  is the fastest.
- $E1$  &  $S_N1$  have the same rate-determining step, but different product-determining steps. Anything that speeds up  $E1$  will also speed up  $S_N1$ , so these two reactions usually occur together and give a mixture of products.
- $E1$  &  $S_N1$  are fastest in polar protic solvents. This is because the carbocation benefits from being stabilized by the solvent. If there's nothing more nucleophilic around, the solvent itself can react with the substrate – this is **solvolysis**.



- $E1$  obeys Zaitsev's rule. However, like we've seen for carbocations previously, rearrangements are possible! (And for  $S_N1$  as well).



- $S_N1$ : The substrate goes through a carbocation intermediate, so you'd expect completely scrambled stereochemistry like for the carbocation reactions in Ch. 7. However, this is not quite accurate! The inverted product is favored by a slight margin. This is because the leaving group dissociates, but it is still nearby, partially blocking access to one face of the carbocation. If the carbocation existed for a long time this wouldn't happen, because the leaving group would have time to drift away. The fact that it still has an effect on the outcome means that the carbocation is only in existence for a short time ( $\sim 10^{-8}$  seconds).



## Predicting Reaction Outcomes


How can we predict which one of these four reactions will actually happen? We need to look at the three molecules involved: substrate, solvent, and Base/Nu.

1. Classify substrate as Me,  $1^\circ$ ,  $2^\circ$ , or  $3^\circ$ . Check for neopentyl effect ( $3^\circ \beta C$ ).

# Loudon Chapter 9 Review: Reactions of Alkyl Halides

Jacque Richardson, CU Boulder – Last updated 5/1/2016

- Classify solvent as protic or aprotic. Protic solvents are generally things like ROH, RCO<sub>2</sub>H, or H<sub>2</sub>O. Aprotic solvents are generally the ones that go by acronyms: DMSO, DMF, THF, DCM, chloroform, and acetone. In general, polar protic solvents favor E1 and S<sub>N</sub>1 reactions, while polar aprotic solvents favor E2 and S<sub>N</sub>2 reactions. Usually this preference is not strong enough to control the choice of reaction, but check for acid-base reactions with the Base/Nu.
- Classify base/nucleophile as strong or weak base, good or poor nucleophile.

	Strong Bases (usually in aprotic solvents)	Weak Bases (usually in protic solvents)
Good Nucleophiles	HO <sup>-</sup> , RO <sup>-</sup> (if R isn't bulky), RC≡C <sup>-</sup>	I <sup>-</sup> , Br <sup>-</sup> , HS <sup>-</sup> , RS <sup>-</sup> , CN <sup>-</sup> , N <sub>3</sub> <sup>-</sup>
Poor Nucleophiles	 (tBuO <sup>-</sup> )      (LDA)	Cl <sup>-</sup> , F <sup>-</sup> , RCO <sub>2</sub> <sup>-</sup> , H <sub>2</sub> O, ROH, RCO <sub>2</sub> H

**Strong bases** are technically anything with a pK<sub>a</sub> greater than about 15. In general, anything with a negative charge on C, N, or O is strong, unless there's additional stabilization coming from somewhere (resonance, etc.). If it's a strong base then it's assumed to be a good nucleophile, unless it's very bulky like tBuO<sup>-</sup>.

**Weak bases** are anything with a pK<sub>a</sub> below 15. Weak base/good nucleophiles fall into two categories: those at the stronger end of the weak base categories like N<sub>3</sub><sup>-</sup> (pK<sub>a</sub> of 9.4) and CN<sup>-</sup> (pK<sub>a</sub> of 4.7), and those with a minus charge on large atoms (I, Br or S). Weak base/poor nucleophiles are anything outside of this category, including molecules with no negative charge at all.

- Use this information to select which mechanism(s) will occur.

**If you have a strong base:** You must do S<sub>N</sub>2 or E2 only! Carbocations (from E1 or S<sub>N</sub>1) can't exist in the presence of strong bases. E2 is the default, unless both the substrate and the base/nucleophile are unhindered. However, if S<sub>N</sub>2 turns out to be the predicted mechanism, it can still be blocked by the neopentyl effect, giving NR.

- Strong base/good nucleophile:
  - S<sub>N</sub>2 on Me and 1°
  - S<sub>N</sub>2/E2 on 2°
  - E2 on 3°
- Strong base/poor nucleophile:
  - S<sub>N</sub>2 on Me
  - E2 on 1°, 2°, 3°

**If you have a weak base:** E1/S<sub>N</sub>1 mix is the default, but S<sub>N</sub>2 can happen under the right circumstances.

- Weak base/good nucleophile:
  - S<sub>N</sub>2 on Me, 1°, 2°
  - S<sub>N</sub>1/E1 on 3°
- Weak base/poor nucleophile:
  - S<sub>N</sub>2 on Me, 1°
  - S<sub>N</sub>1/E1 on 2°, 3°

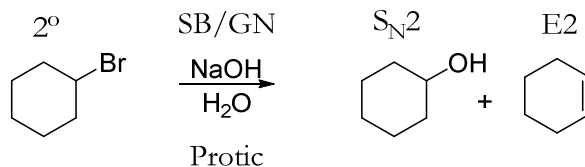
- Apply this mechanism to the substrate. In example below, the substrate is 2°, the solvent is protic, and the Base/Nu is a strong base/good nucleophile. This combination gives



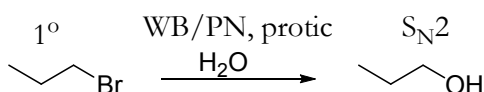
# Loudon Chapter 9 Review: Reactions of Alkyl Halides

Jacque Richardson, CU Boulder – Last updated 5/1/2016

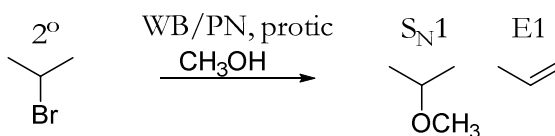
you a mixture of E2 and S<sub>N</sub>2 as the favored outcome. Using S<sub>N</sub>2 gives you the first product shown, and E2 gives you the second product.



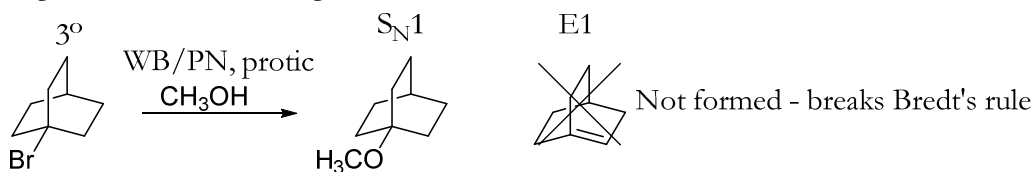
Here, the solvent is also working as the base/nucleophile. This is an example of solvolysis. You have a 1° substrate, protic solvent, and weak base/poor nucleophile, giving you an S<sub>N</sub>2 outcome.



Here, you have a 2° substrate, protic solvent, and weak base/poor nucleophile, giving you an S<sub>N</sub>1/E1 outcome.

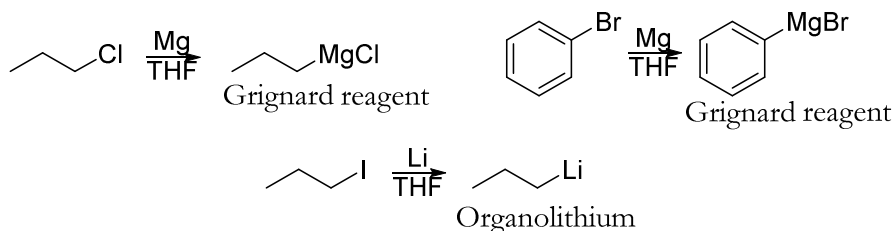


Sometimes a predicted outcome will be blocked by other reasons. Even though an S<sub>N</sub>1/E1 mix is predicted here, the E1 product isn't formed because it violates Bredt's rule.



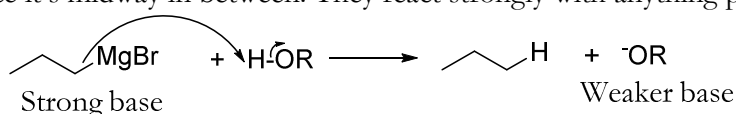
## Organometallics

Anything with a bond between a carbon atom and a metal atom is an organometallic compound. Two useful types are Grignard and organolithiums, which are both made from alkyl halides. The mechanism for this goes by a complicated single-electron-transfer mechanism that we won't cover.



For Grignards, you must have some kind of ether solvent (usually THF or diethyl ether). For organolithiums, ethers or alkane solvents like hexanes will work.

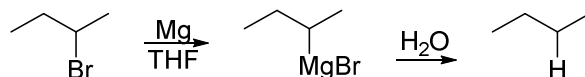
The organometallic that's formed has a big delta negative charge on carbon, which makes it act like a very, very strong base – in fact, it can be drawn as an ionic compound or a covalent compound, since it's midway in between. They react strongly with anything protic:



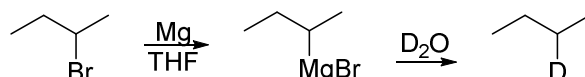
# Loudon Chapter 9 Review: Reactions of Alkyl Halides

Jacque Richardson, CU Boulder – Last updated 5/1/2016

This can be used as a way to turn alkyl halides into alkanes, in two steps. This is the first example we'll see of a multistep synthesis: using the product of one reaction as a starting material for the next.

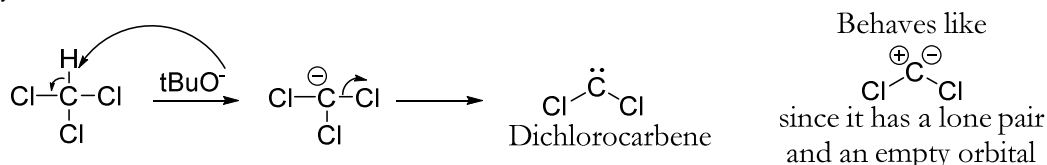


We can also use this to label molecules with deuterium in selected places, by using D<sub>2</sub>O instead of H<sub>2</sub>O.

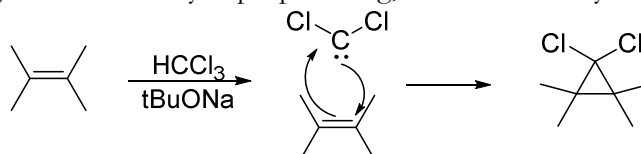


## Carbenes and Carbenoids

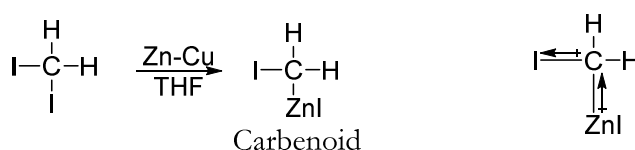
Both the eliminations we looked at were  $\beta$  eliminations- you lose an H and an LG from adjacent carbons. It's also possible to do an  $\alpha$  elimination, where you lose an H and an LG from the same carbon. These only happen under specific circumstances. To make this happen, you need a substrate that's good at stabilizing a minus charge, and a strong, bulky base. This creates a carbene, which has an unfilled octet. It behaves like a carbon with a negative charge and a positive charge at the same time, although you shouldn't draw it this way.



It's a neutral carbon with both an empty orbital (so it's a great electrophile) and a lone pair (so it's a great nucleophile). The one reaction that we'll see it doing involves both behaviors at the same time. This is the same mechanism as that simultaneous attack/back-attack thing we used to make bromonium ions, only the three-membered ring it makes is permanent. Since we're making an all-carbon cyclopropane ring, this is called a cyclopropanation.



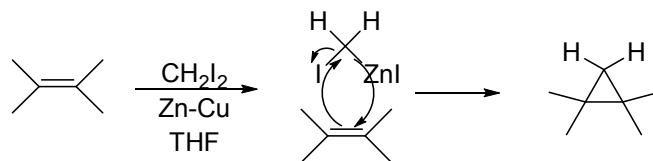
This particular reaction creates a ring with two halogens attached to one corner, but what if we don't want those halogens? In that case, we can use Simmons-Smith cyclopropanation instead. Combining diiodomethane with zinc-copper couple creates something that's very similar to a Grignard, but with Zn instead of Mg. It's not a true carbene - it doesn't have a full positive and negative charge, but it does have sizeable delta positive (due to the bond to iodine) and delta negative (due to the bond to zinc) charges. For this reason, it behaves like a milder carbene, and is called a carbenoid.



Again, it does the same attack and back-attack to make a three-membered ring.

# Loudon Chapter 9 Review: Reactions of Alkyl Halides

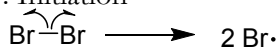
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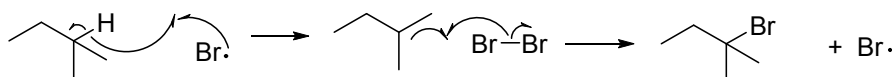
## Radical halogenations of alkanes

This is a way to create alkyl halides from alkanes (not from alkenes, which we saw in Ch. 4 & 5). Here, instead of adding an H and a Br to a double bond, we're pulling an H off the molecule and replacing it with a halogen. No radical initiator is needed – the dihalogen will split into radicals on its own, as long as you use UV light (written as  $h\nu$ ), or heat (written as  $\Delta$ ).

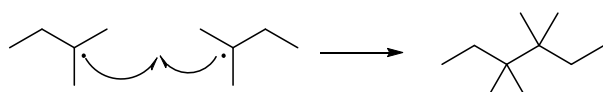
1. Initiation



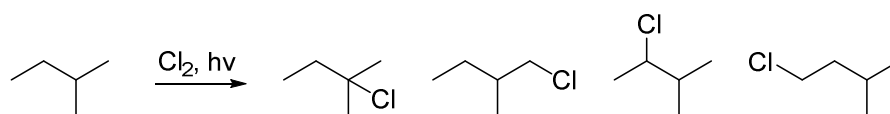
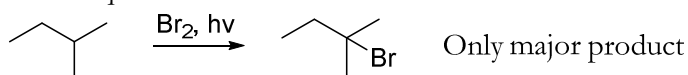
2. Propagation



3. Termination: any step that involves 2 radicals getting together, for example:

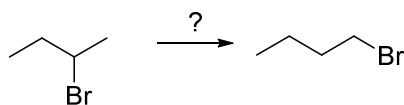


This works best for chlorine and bromine. For iodine it's too endothermic and reacts too slowly, and for fluorine it's too exothermic and goes out-of-control until most Hs are replaced. Bromine is significantly endothermic, so it's slow and energy-poor. For this reason, bromine will carefully select which H to pull off so that only the most stable radicals are formed. The net result is that radical halogenations with  $Br_2$  only adds a Br at the most substituted carbons. Chlorine, on the other hand, is much less endothermic and can afford to create radicals anywhere. It's a lot less predictable and basically useless unless every H on the molecule is equivalent.



## Using Elimination and Substitution in Synthesis

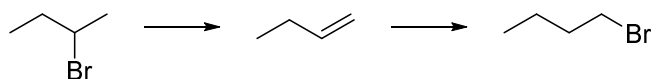
Now that we've covered reactions that create alkyl halides (in Ch. 4 & 5) and reactions that use them, we can start putting them together for synthesis. A common case is where we have a functional group on one carbon, and we want to end up with a functional group on a neighboring carbon instead.



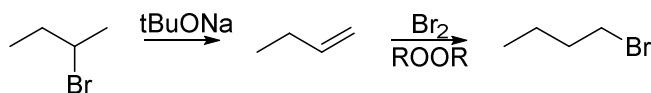
We know that at some point, we'll need to make an alkene between the two carbons by doing an elimination, and then adding things back to the alkene:

# Loudon Chapter 9 Review: Reactions of Alkyl Halides

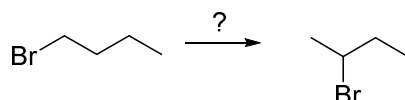
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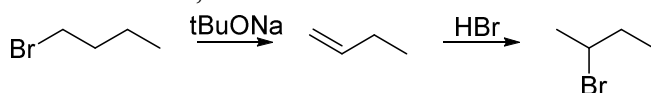
Now we can use Zaitsev/anti-Zaitsev eliminations, and Markovnikov/anti-Markovnikov additions, to control the regiochemistry of both reactions. The elimination needs to be anti-Zaitsev, and the addition needs to be anti-Markovnikov.



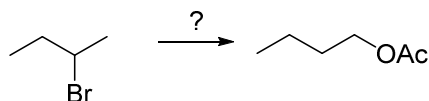
What about this synthesis?



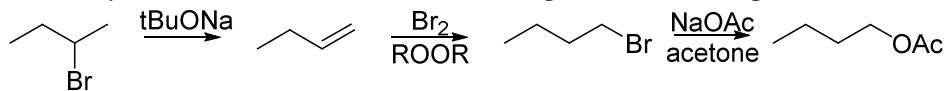
The elimination is neither Zaitsev nor anti-Zaitsev, since there's only one choice. However, we need to be careful – this is a 1° alkyl halide and will undergo S<sub>N</sub>2 if we use a strong base that's not hindered. For this reason, we still use tBuONa.



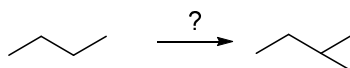
How about this one?



We need to add a group anti-Markovnikov as the last step, but we haven't covered any ways to add an OAc group. Instead, we can add a bromine in the correct location first, and then replace it later by an S<sub>N</sub>2 reaction. We can use some protic solvent to promote S<sub>N</sub>2.



One more synthesis:



We only know one reaction that can do anything with alkanes: radical halogenation. Our first step will be to add a bromine atom to the most substituted carbon. From there, we can eliminate to make an alkene, and then perform a Simmonds-Smith cyclopropanation.

