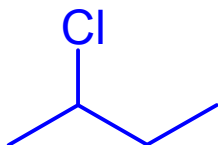


## 7. Haloalkanes (text 7.1 – 7.10)

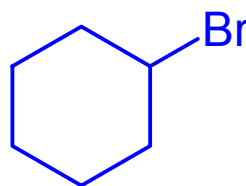
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### A. Structure and Nomenclature

- Like hydrogen, the halogens have a valence of one. Thus, a halogen atom can replace a hydrogen in a molecule.
- The general formula of a saturated mono-halo acyclic compound is  $C_nH_{2n+1}X$ . **So, treat X as an H when calculating unsaturation units.** e.g.  $C_3H_4Br_2$  = one unit of unsaturation
- Non-IUPAC, two-word names are commonly used for simple compounds. The first word identifies the alkyl group, the second identifies the halogen.



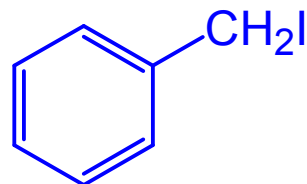
IUPAC: 2-chlorobutane  
Common: sec-butyl chloride



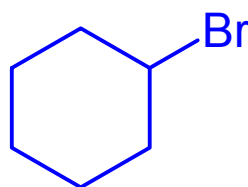
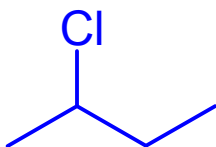
bromocyclohexane  
cyclohexyl bromide

- The reactions that alkyl halides undergo strongly depend on the nature of the alkyl position. It's essential that we recognize the “type” of alkyl halide.

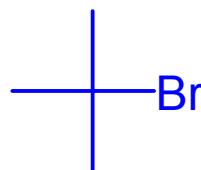
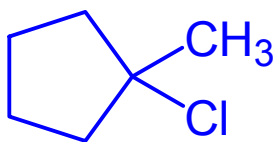
1. Primary halide ( $1^\circ$ ). The carbon bearing the halogen is bonded to one alkyl group and has two H.



2. Secondary halide ( $2^\circ$ ). The carbon bearing the halogen is bonded to two alkyl groups and one H.



3. Tertiary halide ( $3^\circ$ ). The carbon bearing the halogen is bonded to three alkyl groups (and no H).



- All the above have halogens bonded to  $sp^3$  carbon (alkyl). We need to know that there can be aryl or vinyl halides, which have rather different chemistry because the halogen is bonded to an  $sp^2$  carbon (covered later on).

## B. Physical Properties

- The halogens are more electronegative than carbon, so an  $sp^3$  C–X bond is polar. The polar bond does not cause alkyl halides to be H<sub>2</sub>O-soluble.  $\text{CH}_3\text{CH}_2\text{Br}$   $\delta^+ \delta^-$
- Halogenated organic compounds rarely occur in nature, and never in mammalian cells. This is why many organic halides are highly toxic and are very slowly destroyed, e.g. DDT.
- We study alkyl halides because they are very useful in laboratory syntheses. As well, they serve as excellent examples of natural reaction mechanisms.

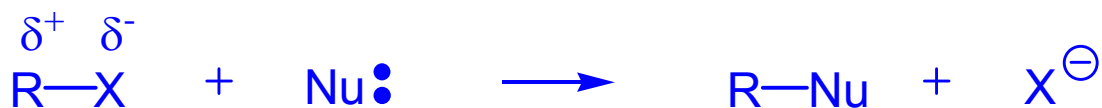
## C. Preparation of Alkyl Halides

- So far, we have only covered the addition to  $\pi$  bonds



## D. Substitution Reactions

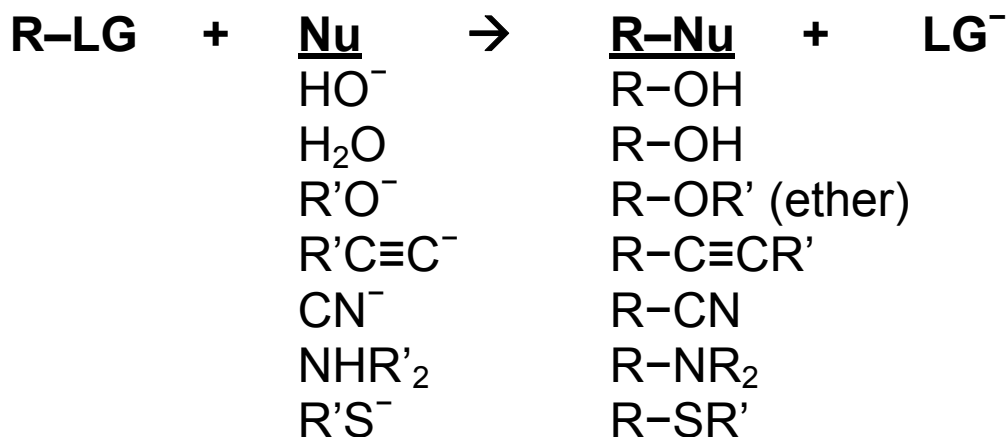
- The major reaction of haloalkanes was introduced in Chem 1050 and is **nucleophilic substitution**, where the halogen atom is replaced (substituted) by a nucleophile.



$\text{X} = \text{Cl}, \text{Br}, \text{I}$

$\text{Nu} = \text{nucleophile}$

- LG's are all electronegative groups that create a  $\delta^+$  charge on an  $sp^3$  carbon atom. All nucleophiles have an electron pair and can be neutrally or negatively charged.
- The halogen atom is just one representative of a whole range of groups that can be displaced by nucleophiles. These are generally called **leaving groups (LG)**.
- The above reaction is a template for a wide range of reactions differing in Nu and LG.

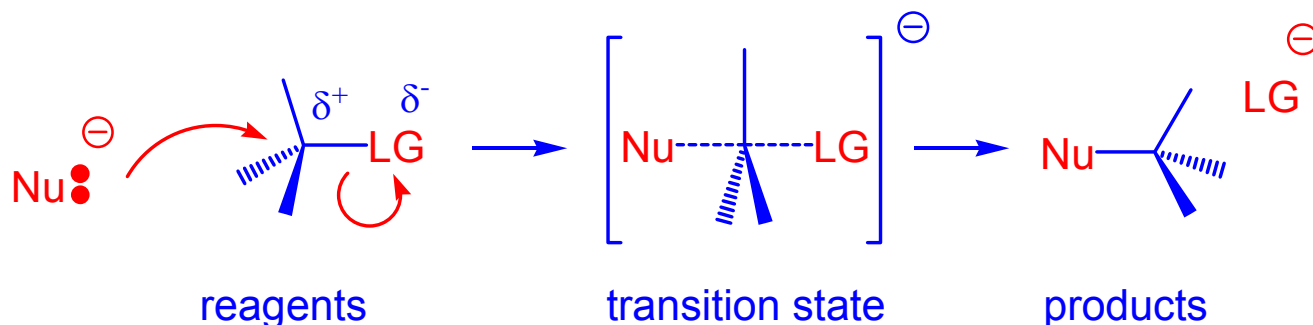


- If a neutrally charged nucleophile is used, there is usually a deprotonation step after the substitution reaction. (Compare to the addition of water to alkenes, where at the end, the oxonium ion is deprotonated.)

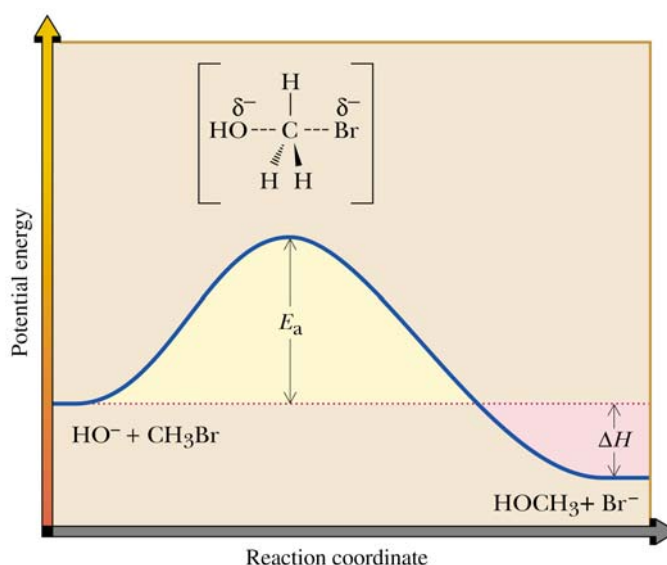
- How about the reaction mechanism? Think of X as a group attached to the  $sp^3$  carbon, and Nu wants to take its place. There are two ways this can occur:
  1. Nu waits until X departs *C on its own*, after which Nu comes and takes the empty spot; or
  2. Nu kicks X out through backside attack.
- With mechanism #1, the rate of the reaction is dependent entirely on how fast X decides to leave on its own. This would entail first-order kinetics.
- Whereas, the rate of mechanism #2 depends on how willing X is to allow itself to be kicked out, and also how good Nu is at kicking X out. This entails second-order kinetics.
- Respectively, these mechanisms are called:
  - $S_N1$  = unimolecular nucleophilic substitution**
  - $S_N2$  = bimolecular nucleophilic substitution**

## **$S_N2$ Reaction Mechanism**

- This is a **one-step mechanism** that involves the collision of the reagents to form a high-energy transition state that falls apart to give the products.



- This is a bimolecular reaction and everything happens at once (concerted). The nucleophile attacks as LG leaves.
- Useful reactions have  $\Delta H$  sufficiently exothermic so that products are formed in good yield.
- The stereochemical and energetic requirements of the mechanism allow us to predict various aspects.



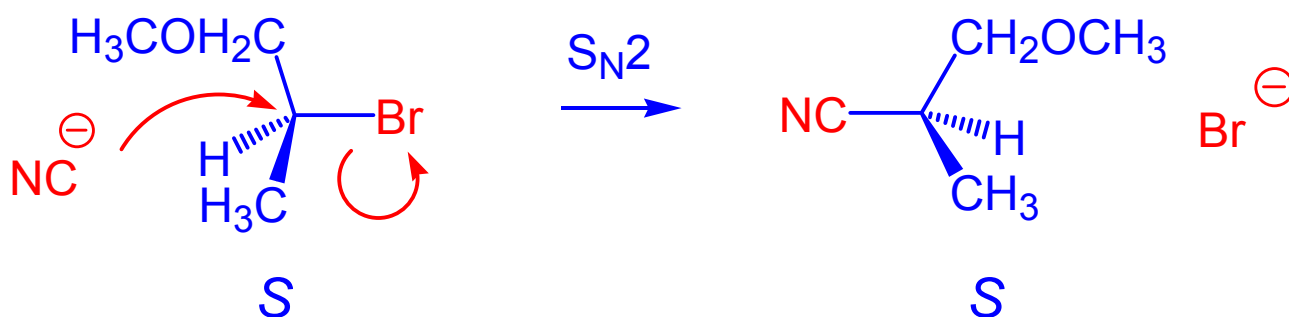
### 1. The mechanism is bimolecular

- Both the Nu and R-LG molecules must collide to form the transition state. This is the only step of reaction, so it is the rate-determining step. The rate law is second-order.

$$\text{Rate} = k [\text{Nu}] [\text{R-LG}]$$

## 2. Stereochemical inversion at the centre

- The Nu attacks R-LG directly opposite of the leaving group (backside attack), so the stereochemical configuration at that carbon is always inverted.
- Almost always, an *R* configuration becomes *S*, or an *S* becomes *R*. However, the label sometimes remains the same even though inversion has occurred, e.g.



- The reason for the retention of the *S* label in this example is due to the change in group priorities. In this case, the LG and the Nu don't have the same priority.

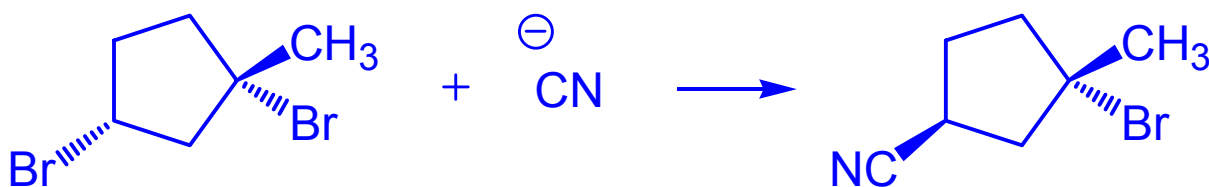
## 3. Steric bulk around the centre slows the reaction

- Nu needs to attack from the back. If something is in its way, the reaction will be slower.
- The reaction works best when groups on the carbon are small. Large groups block the incoming Nu.

- So, the rate of an  $S_N2$  reaction is in general



- In fact, tertiary alkyl halides DO NOT react by  $S_N2$  at all.
- In the example below, the only product formed is one where substitution has occurred at the secondary carbon.



#### 4. Aprotic solvents increase the reaction rate

- Aprotic (non-protic) solvents do not have an H atom with a  $\delta^+$  charge; *i.e.* they can't form hydrogen bonds.
- Normally, the lone pair on the Nu can be stabilized by hydrogen-bonding with the solvent. However this is NOT possible in aprotic solvents. *i.e.* Nu is not stabilized and is more reactive and better able to attack R-LG.
- Common aprotic solvents include diethyl ether, dichloromethane, acetone, etc. (textbook table 7.4).
- Note that this doesn't mean that an  $S_N2$  will not react in protic solvents... they just prefer aprotic solvents. (Protic solvents include water, alcohols, acids, etc.)



### 5. *The better the nucleophile, the better the reaction*

- Better nucleophiles are better at displacing LG.
- The strength of a Nu varies *inversely* with the stability of the non-bonded electron pair (text table 7.2). If the electrons are more available (less stable), Nu will be stronger.
- In general, all anions are better than neutral Nu



- The less electronegative it is, the more likely it will give away electrons and act as a nucleophile.
- HOWEVER.... with halogens, it is electronegativity order, not atomic size order (students in Chem 2273a learn why).

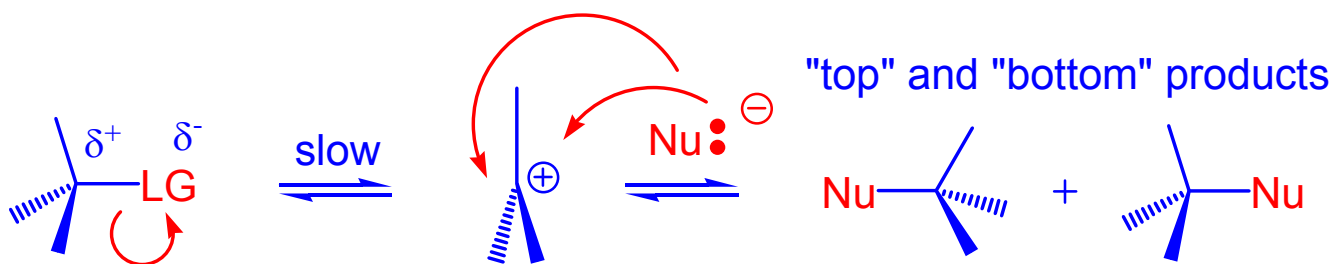


### 6. *The better the leaving group, the better the reaction*

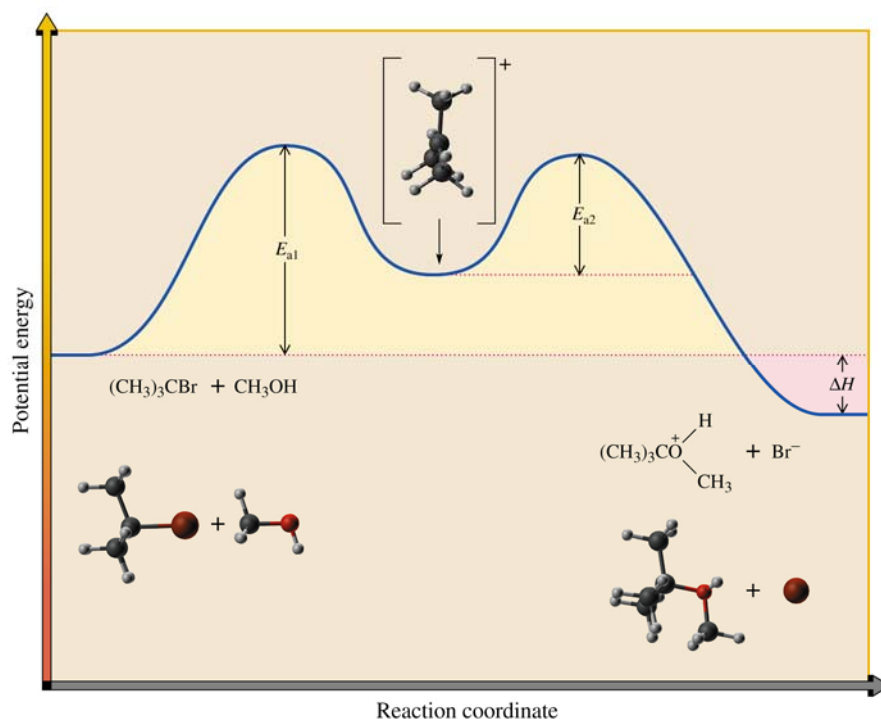
- The more stable the anion on the LG, the better it will be. We assess the stability of LG anion using the same criteria used to assess the stability of conjugate bases (Chapter 2).
- Order of stability = effectiveness as a leaving group



## $S_N1$ Reaction Mechanism



- This is a two-step mechanism, and both steps are reversible. The first, rate-determining step involves the ionization of the R-LG bond to form an intermediate carbocation. *i.e.* LG must come off on its own
- The second step is attack by Nu (neutral or anion) on both sides of the carbocation ( $sp^2$  = planar) to yield the products.
- The reaction coordinate diagram is just like the addition of HX to alkenes. An  $S_N1$  reaction also involves a carbocation.



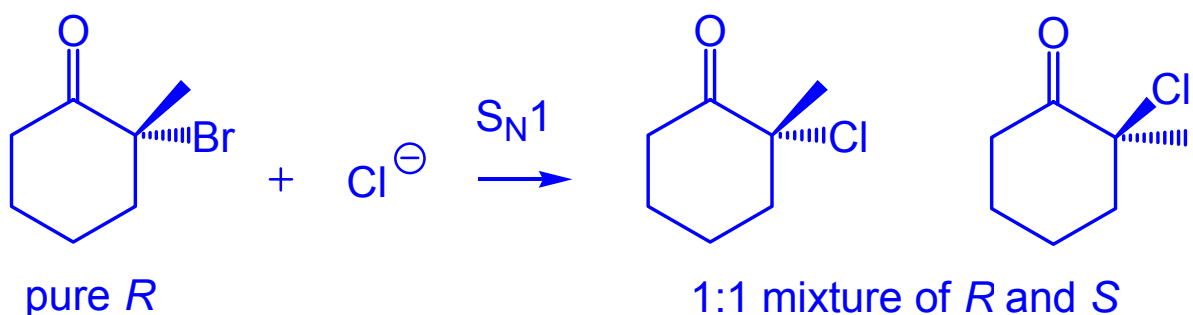
### 1. The first, rate-determining step is unimolecular

- In the ionization of R-LG to form the carbocation, LG must leave on its own and is the rate-determining step. The reaction rate only depends on the concentration of R-LG.

$$\text{Rate} = k [\text{R-LG}]$$

### 2. Racemic mixtures are formed

- If the reaction occurs at a stereocentre, an equal mixture of both enantiomers will be formed (a racemic mixture).
- Since the carbocation intermediate is  $sp^2$  (flat), the Nu can attack either face of the carbocation. If an enantiomerically pure starting material is used and the reaction occurs at the chiral centre, a racemic mixture is formed.
- An optically active reagent will give **optically inactive products** in an  $S_N1$  reaction.



### 3. Alkyl groups on substituted C increase reaction rates

- Just like how carbocation stability impacts the rate of addition of HCl, HBr, HI, etc. to alkenes.
- The rate of S<sub>N</sub>1 reactions is therefore ordered:

more-stable carbocation > less-stable carbocation

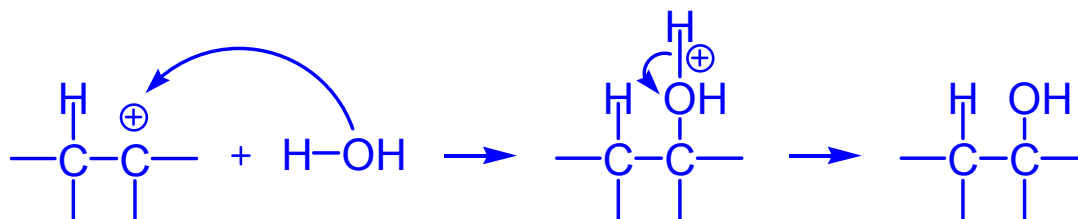
- Because 1° carbocations are so unstable in the absence of resonance, compounds with LG on primary carbons do not react S<sub>N</sub>1. Note that S<sub>N</sub>1 reactions proceed best for compounds that react poorly by S<sub>N</sub>2, and vice versa.

### 4. Protic solvents increase the reaction rate

- Protic solvents are those with an H that is  $\delta^+$  charged. They stabilize the ions formed in the first-step of the S<sub>N</sub>1 reaction, thus lowering the activation energy of the slow step and increasing the reaction rate.
- Common protic solvents are water; alcohols, R-OH; and small acids, R-COOH.

### 5. Poor nucleophiles can react in S<sub>N</sub>1 substitutions

- Because the Nu attacks a carbocation, which has a REAL positive charge (not a  $\delta^+$ ), even weak nucleophiles such as water will still work in S<sub>N</sub>1 reactions. In the case of water, a deprotonation step occurs after the substitution.



- Good Nu will tend to push mechanism towards  $S_N2$ , as a good Nu would not wait for the LG to depart on its own.

*6. The better the leaving group, the faster the reaction*

- Because the loss of the LG is an essential first step of the  $S_N1$  reaction, good leaving groups are still necessary for the reaction to proceed at an acceptable rate (just like  $S_N2$ ).
- Recall that better leaving groups are more stable.

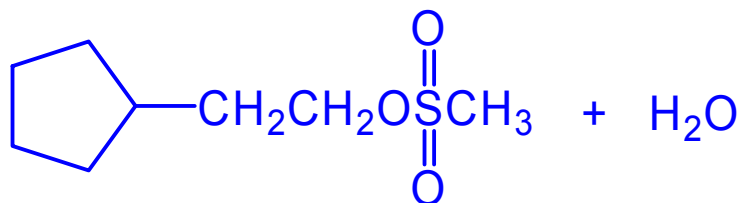
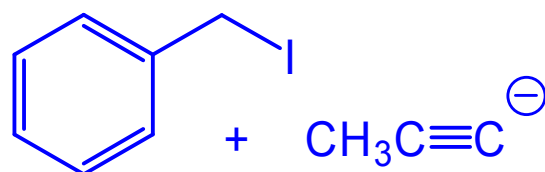
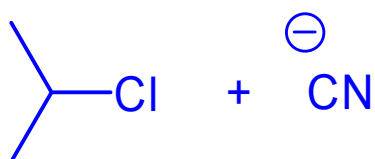
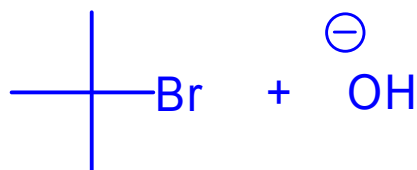
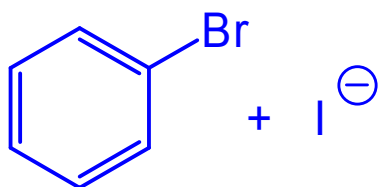
## Comparison between S<sub>N</sub>1 and S<sub>N</sub>2

- Since the two mechanisms are so different, we can predict which mechanism is favoured under the specified reaction conditions, as well as the stereochemical consequences.

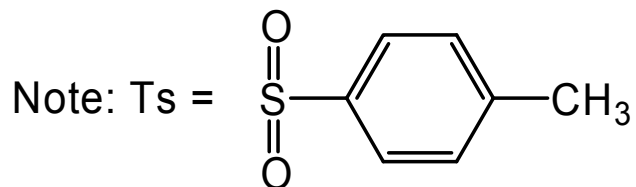
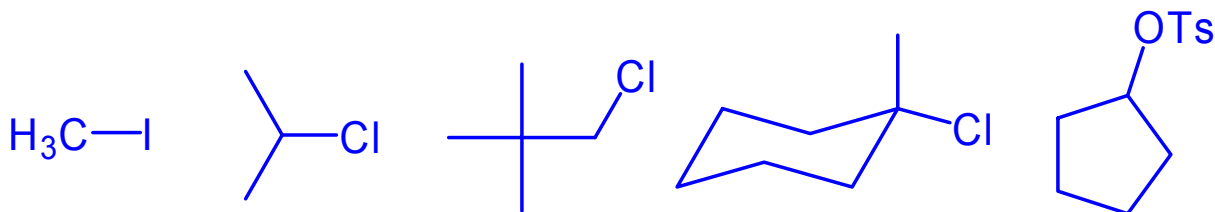
Reaction	Favoured by	Product
S <sub>N</sub> 2	Good LG Accessibility (low steric hindrance) Good Nu Aprotic solvents	Inversion
S <sub>N</sub> 1	Good LG Stable carbocation Not-so-good Nu Protic solvents	Racemization

- Pages covered: Chapter 7, p. 170-183
- Problems: 9, 12, 13, 18, 20, 22, 23, 24, 26, 29, 31, 32
- Dec 2005: 19, 20                      Dec 2006: 16, 18  
     Dec 2007: 17, 18, 20, 21        Dec 2008: 17, 18, 19

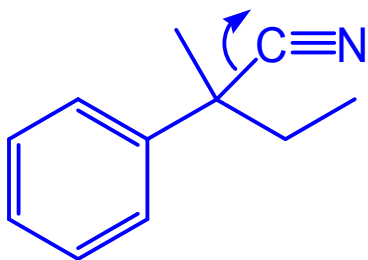
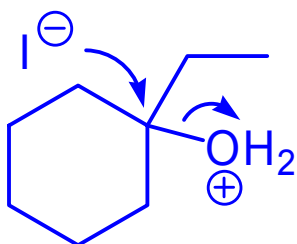
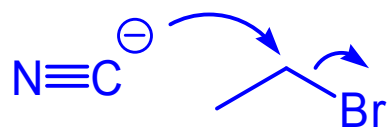
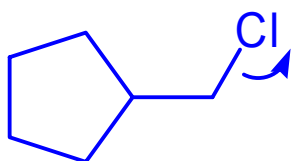
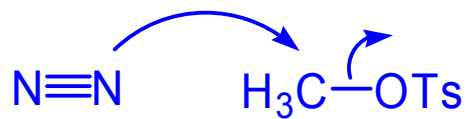
- Past test question: Which one of the following sets of reagents reacts the fastest in an  $S_N2$  reaction?



- Past test question: Which one of the following compounds reacts most rapidly when placed in water?



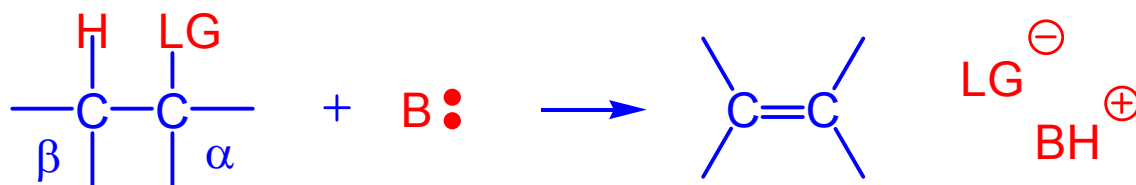
- Past test question: Which one of the following processes shown occurs fastest at room temperature?



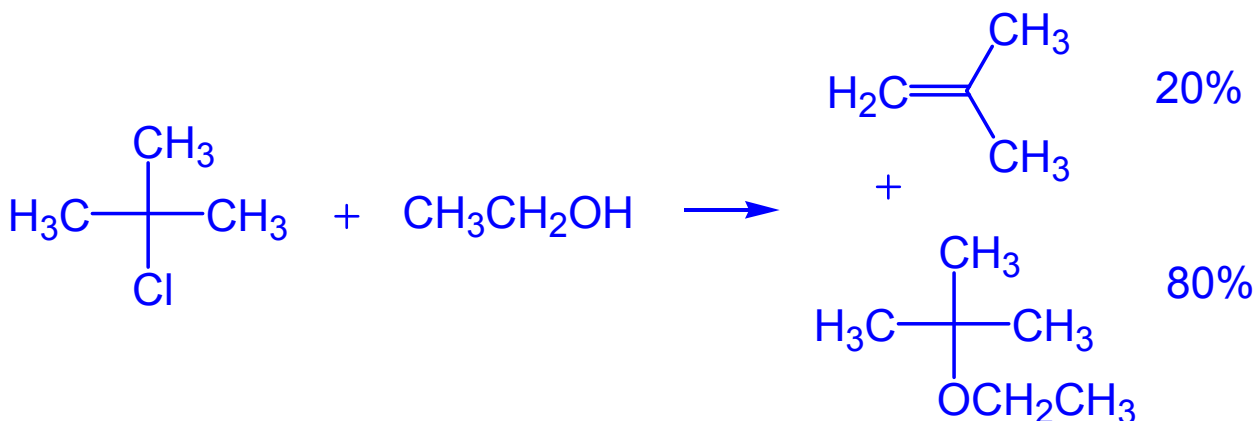


## E. Elimination Reactions

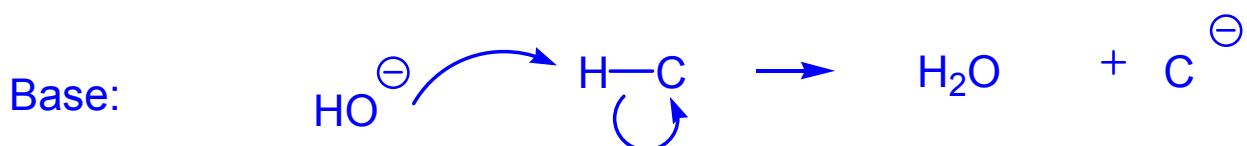
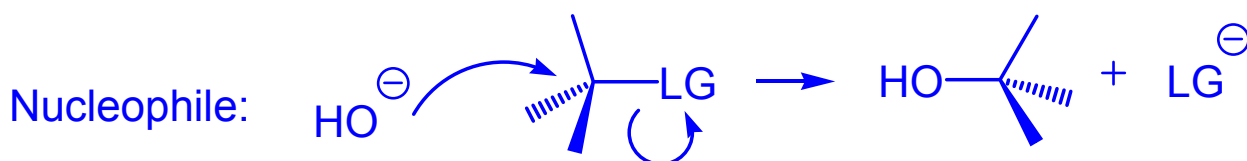
- In addition to substitution reactions, all molecules with a polar bond and a good LG can undergo **elimination**.
- In these reactions, the *nucleophile acts as a base* (B) and attacks H instead of attacking C as a nucleophile.
- At the molecular level, this difference in behaviour is a little more than the result of where the B/Nu bumps into the other reacting molecule.



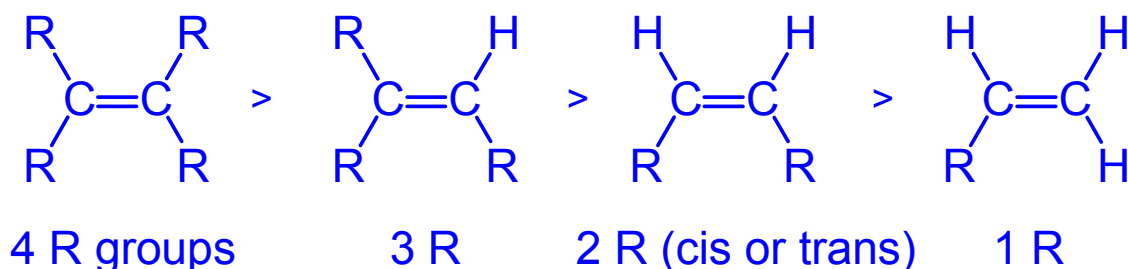
- Because the H atom (removed by the base) and the LG comes off C atoms that are adjacent (often labelled  $\alpha$  and  $\beta$ ), this reaction is called a  $\beta$  elimination.
- In many cases, elimination and substitution occur together.



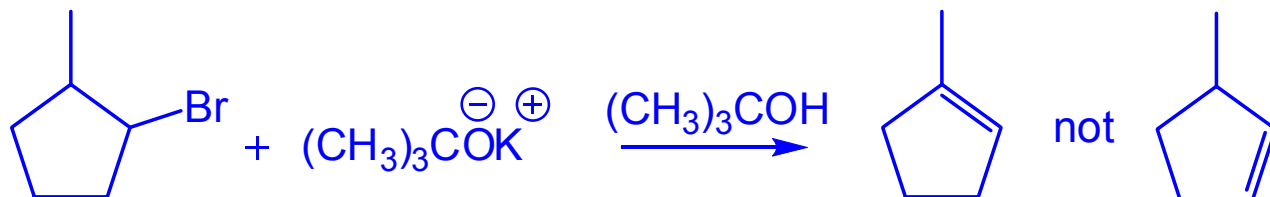
- A species bearing a lone pair (neutral or anionic) that we considered earlier as nucleophiles can also act as bases. The only difference is whether the species attacks a carbon or a H. We classify a group as a Nu or B depending on how it reacts, not on what its structure is, e.g.  $\text{HO}^-$



- Two molecular features act to increase the yield of elimination products at the expense of substitution products:
  1. A large anion, which can attack a more exposed H better than a sheltered C atom (sheltered by the groups around it). e.g. the *t*-butoxide anion  $(\text{CH}_3)_3\text{CO}^-$  normally gives more elimination than substitution.
  2. Stable alkene as a product. Alkyl groups stabilize alkenes, so the order of stability is:



- There is a simple rule for alkene formation when two or more alkene products are possible. **Zaitsev's Rule** says that the more substituted alkene (more R) will be preferred.



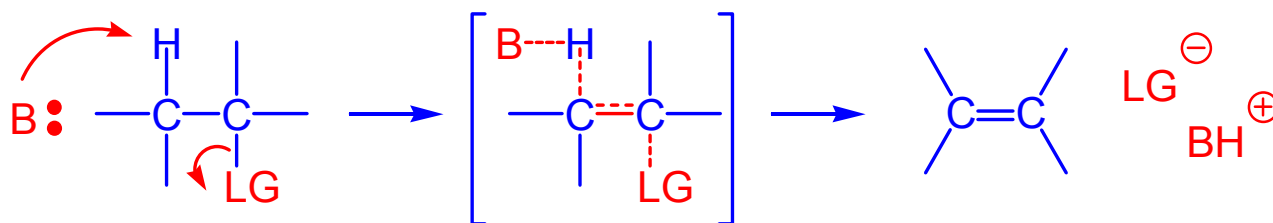
- Like substitution mechanisms, there are two for elimination.

**E1 = unimolecular elimination**

**E2 = bimolecular elimination**

## E2 Reaction Mechanism

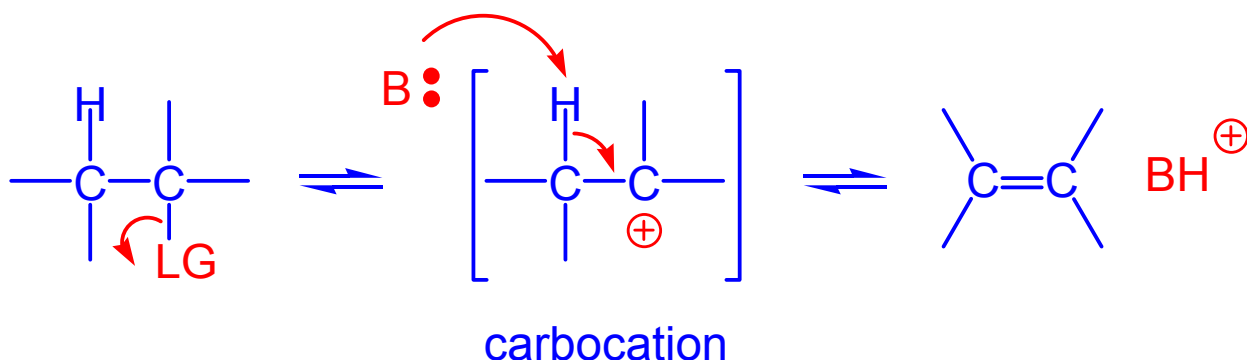
- This is a **one-step mechanism**, which is bimolecular and second-order. The rate is dependent on the concentration of both R-LG and B. (The B removes the proton and kicks off the LG at the same time). A strong base is needed!
- Elimination products by an E2 mechanism often accompany substitution products by an  $\text{S}_{\text{N}}2$  mechanism when large, bulky bases are used and/or stable alkenes can result.



- All halides can undergo E2, even tertiary, as long as a  $\beta$  H is present. In fact, tertiary results in stable alkenes!

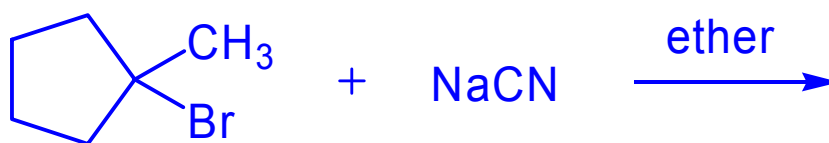
## E1 Reaction Mechanism

- This is similar to the  $S_N1$  and is a two-step reaction that has a slow unimolecular step. The reaction is first-order and the rate is depending only on the concentration of R-LG. (LG leaves on its own, after which B comes and removes  $H^+$ ). A weaker base is typical, but E1 needs a stable carbocation.
- Elimination products by an E1 mechanism often accompany substitution products by an  $S_N1$  mechanism when large, bulky bases are used and/or stable alkenes can result.

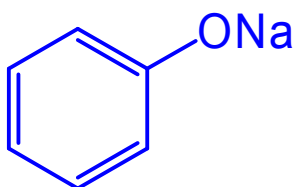
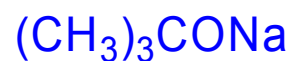


- Note: you're not expected to predict the relative amounts of substitution versus elimination products. However, if given which type of reaction is occurring, you should be able to predict the correct product and the mechanism.
- Textbook table 7.7 provides an excellent comparison.
- Pages covered: Chapter 7, p. 184-192
- Problems: 34, 36, 38, 40, 43, 45, 46
- Dec 2005: 21 – 23                      Dec 2006: 19, 20  
Dec 2007: 19, 23                      Dec 2008: 20, 21

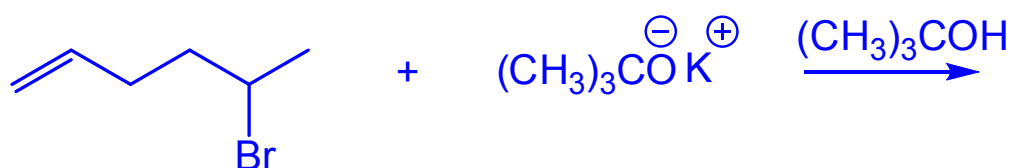
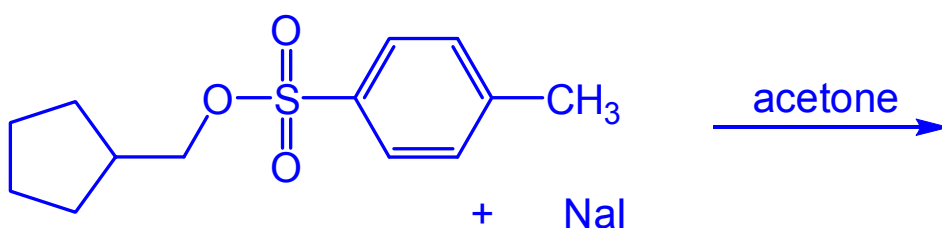
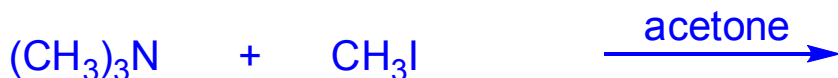
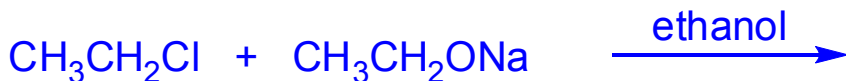
- Past test question: What is the major product of the following reaction?



- Past test question: Which one of the following gives the best yield of hexene products on reaction with 2-bromohexane?



- Past test question: For which one of the following reactions is  $S_N2$  not the major reaction pathway?



- MCAT Question: What is the product formed when NaBr is reacted with (S)-1-iodoethanol?

