

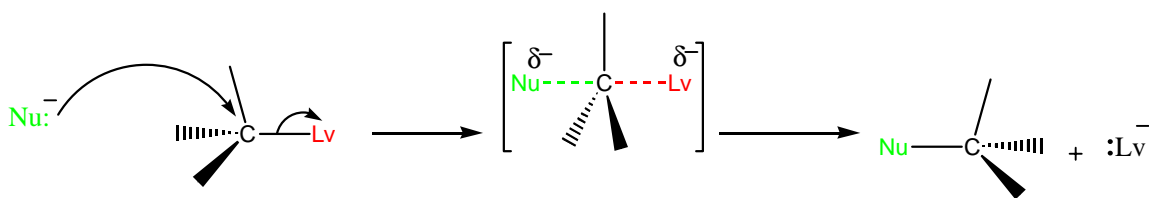
Nucleophilic Substitution and Elimination

Alkyl halides react with a nucleophile in one of two ways. Either they eliminate an HX to form an alkene, or they undergo a substitution with the nucleophile, Nu, taking the place of the X.

Substitution can occur by S_N2 or S_N1 mechanisms depending upon the conditions present.

S_N2 (Bimolecular Nucleophilic Substitution)

General Reaction:



Lv stands for leaving group, which is usually an X.

- S_N2 reactions take place in one step (concerted). The nucleophile forms a bond to the carbon at the same time that the leaving group leaves.
- Results in a complete inversion of configuration, which is similar to an umbrella being turned inside out.

Kinetics:

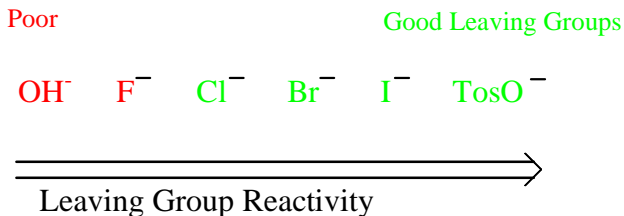
Since the nucleophile and alkyl halide are both involved in the Rate Determining Step (there is only one step in the reaction), the reaction is said to be bimolecular. The general rate law is:

$$\text{Rate} = k [\text{RX}] [\text{Nu}^-] \quad \text{where X = Cl, Br, I}$$

Variables affecting S_N2 Reactions:

Substrate: **Unhindered substrates work best.** Hindered substrates make the transition state more crowded, contributing steric strain. This makes the energy of activation higher, which means that the number of successful collisions per unit of time is much less than for unhindered substrates. Therefore, a 1° RX would be a better S_N2 substrate than a 2° or 3° RX.

Leaving Group: **A good leaving group is needed.** The leaving group leaves as the nucleophile forms a bond with the substrate. Most leaving groups end up with a negative charge once they are displaced by the incoming nucleophile. The best leaving groups are those that can stabilize the negative charge. The weakest bases are usually the best leaving groups.



Nucleophile: **A good nucleophile is needed.** Remember from chapter 5:

1. Nucleophilicity roughly parallels basicity when comparing nucleophiles that have the same “attacking” atom. e.g. OH⁻ is a stronger base and better nucleophile than HCO₃⁻
2. Nucleophilicity usually increases going down a column of the periodic table.
3. Negatively charged nucleophiles are usually more reactive than neutral ones.

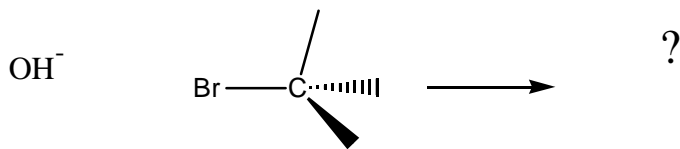
Solvent: **Polar aprotic solvents work best.** Polar Aprotic Solvents include DMF, DMSO, or HMPA.

Practice Problems

- 1) Rank the following compounds in order of their expected reactivity in S_N2 reactions:
- a) CH₃Cl b) (CH₃)₂CHCl c) (CH₃)₃CCl d) CH₃Br

Answer

- 2) Complete the following reaction (show stereochemistry):

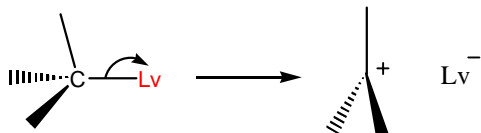


Answer

S_N1 (Unimolecular Nucleophilic Substitution)

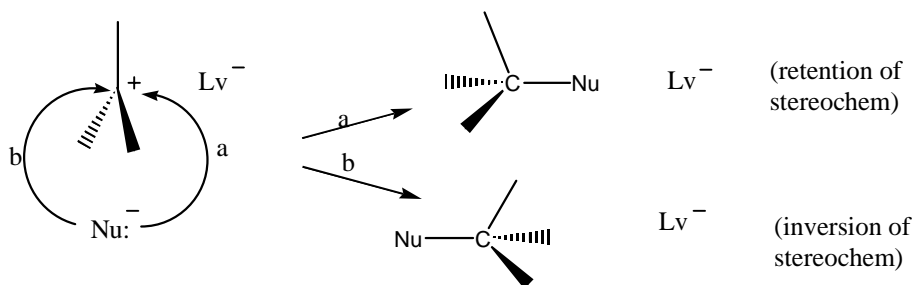
General Reaction:

step 1



In the first step, the leaving group leaves and a carbocation forms. This is the slow step, the rate determining step.

step 2



In the second step, the nucleophile attacks the positive charge, forming a bond with the carbon. It can attack from the left side (b) or the right side (a). Attacking from the left side results in a product with inverted configuration (as with S_N2 reactions). Attacking from the right side does not change the configuration. In cases where the leaving group "hangs around" the left side is usually easier for the nucleophile to reach.

- This results in mixture of products, with the inversion product being slightly favored.

Kinetics:

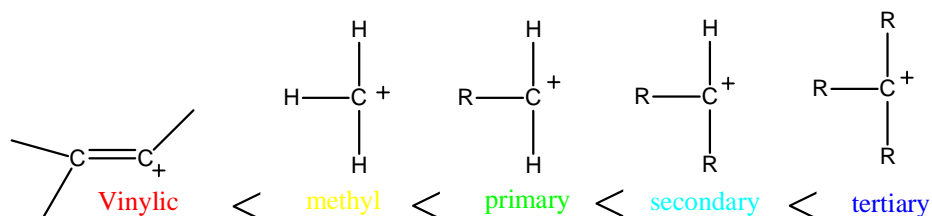
Only one molecule is involved in the Rate Determining Step. A reaction can only proceed as fast as the rate of its rate-determining step. The general rate law is therefore:

$$\text{Rate} = k [\text{RX}] \text{ where } X = \text{Cl, Br, I}$$

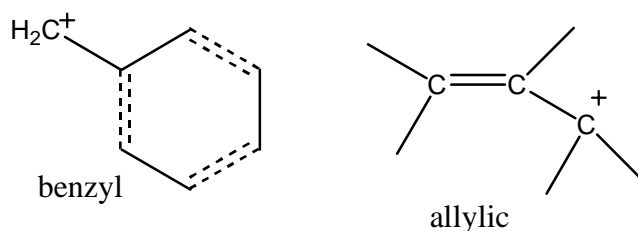
Variables affecting S_N1 Reactions:

Substrate: Substrates that stabilize the positive charge formed in the carbocation, lowering the energy of the transition state, are favored. This is because the more stable the carbocation intermediate, the faster the reaction occurs. Therefore, a 3° RX would be a better S_N1 substrate than a 2° or 1° RX.

Stability of Carbocations (revisited)



note: allylic and benzyl carbocations are particularly stable and reactive.



Leaving Group: Leaving group order for S_N1 follows the same order as S_N2 reactions. Note, however, that neutral molecules, such as water, can act as leaving groups in S_N1 reactions.

Nucleophile: Poor nucleophiles, such as water, work just as well good nucleophiles.

The nucleophile is not involved in the rate determining step. Thus, it does not affect the rate of the reaction.

Solvent: Polar protic solvents work best. Polar protic solvents include water and alcohols.

Substitution Summary:

- The S_N2 reaction is a concerted, one-step reaction. It causes inversion of configuration and is favored with unhindered reactants, such as methyl and primary alkyl halides, good leaving groups, strong nucleophiles, and polar aprotic solvents.
- The S_N1 reaction is a two-step reaction with a carbocation intermediate. It is favored with substrates that can stabilize the carbocation charge, $3^\circ > 2^\circ > 1^\circ$, and weak nucleophiles.

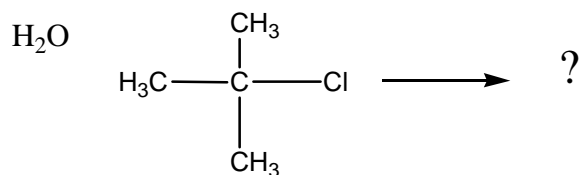
Practice Problems

3) Rank the following compounds in order of their expected reactivity in S_N1 reactions:



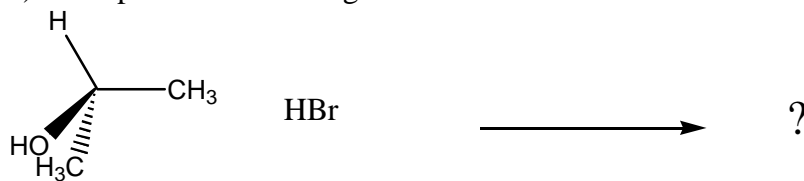
Answer

4) Complete the following reaction:



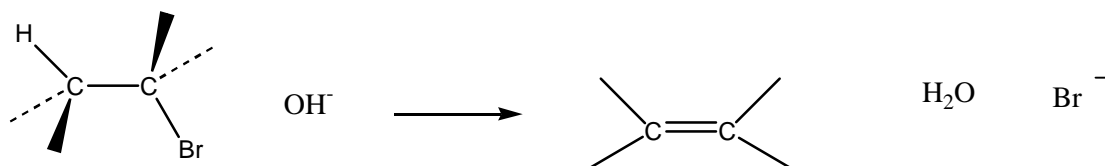
Answer

5) Complete the following reaction:



Answer

Elimination

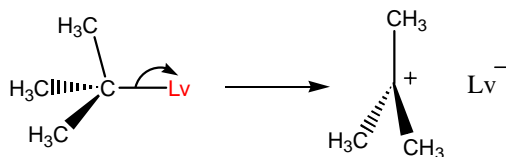


Elimination can occur by E1 or E2 reactions, depending on the conditions of the reaction.

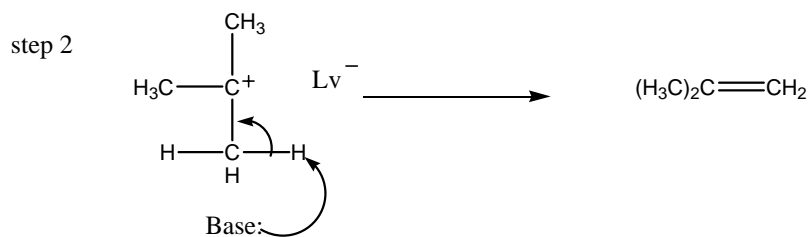
E1 Reaction

Mechanism:

step 1



The first step for an E1 reaction is identical to the first step in an $\text{S}_{\text{N}}1$ reaction. In the first step, the leaving group leaves and a carbocation forms. This is the slow step, the rate determining step.



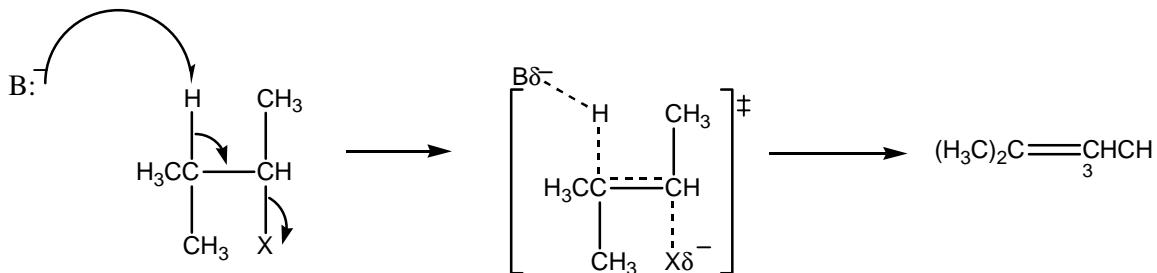
In the second step, a base removes an H^+ from a neighboring carbon. The electron pair from the C-H bond goes to form a pi bond, resulting in an alkene.

The conditions that favor E1 and $\text{S}_{\text{N}}1$ are similar. Both are good with weak nucleophiles and polar protic solvents. Both want a good leaving group and tertiary substrates. If $\text{S}_{\text{N}}1$ occurs, then E1 does too. E1 and $\text{S}_{\text{N}}1$ compete with each other.

E2 Reaction

Occurs when a strong base, such as RO^- , reacts with an alkyl halide

Mechanism:



- The H and X involved in the reaction must have **anti periplanar** geometry. This means that the hydrogen, both carbons and halogen involved in the reaction must all lie in the same plane. (Note: E2 elimination cannot occur in cyclohexanes if either the leaving group or the hydrogen is in an equatorial position).
- Most common elimination pathway
- Occurs in 1 step, like the $\text{S}_{\text{N}}2$ reaction

Kinetics:

$$\text{Rate} = k [\text{RX}] [\text{Base}]$$

Elimination Summary:

- The E2 reaction has a concerted, one-step mechanism involving a transition state in which the H and X being eliminated have antiperiplanar geometry.
- The E1 reaction has a two-step mechanism, involving a carbocation intermediate.

Deciding Whether Substitution or Elimination Occurs

Assume that elimination occurs EXCEPT when either of the following conditions is met:

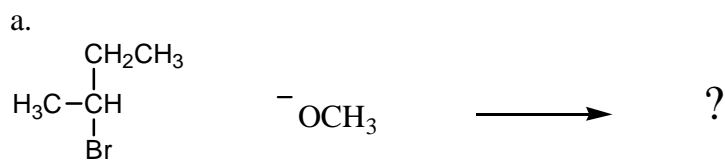
- 1) Unhindered substrate
- 2) Weak base

Case 1: Unhindered Substrate: In the case of an unhindered substrate, such as CH_3Cl , substitution via $\text{S}_{\text{N}}2$ will be most likely to occur. (Elimination cannot occur with a methyl halide because a double bond cannot form if there is only one carbon present in the molecule).

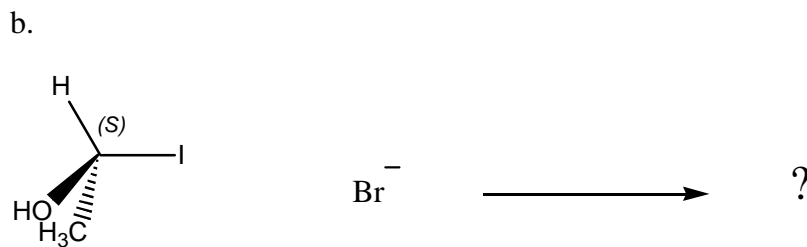
Case 2: Weak Base: Strong bases favor elimination. If the nucleophile is a weak base substitution is more likely to occur.

Practice Problems

6) Indicate the products and the most likely mechanisms involved in the following reactions:



Answer



Answer

Answer

- 1) Rank the following compounds in order of their expected reactivity in S_N2 reactions:

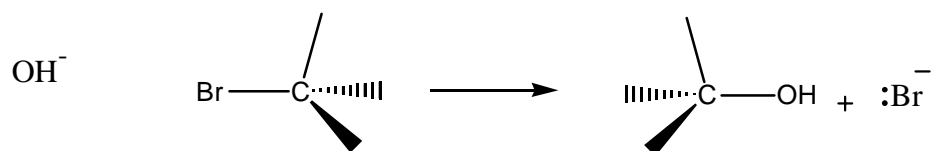
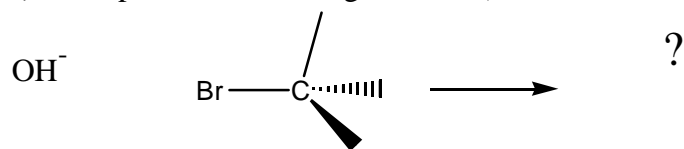
a) CH_3Cl b) $(\text{CH}_3)_2\text{CHCl}$ c) $(\text{CH}_3)_3\text{CCl}$ d) CH_3Br

$d > a > b > c$

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Answer

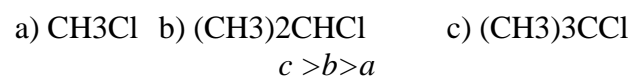
2) Complete the following reaction (show stereochemistry):



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Answer

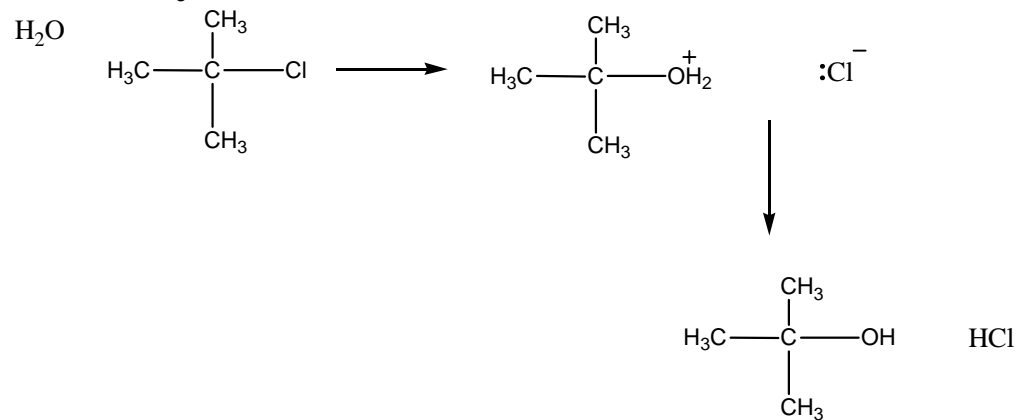
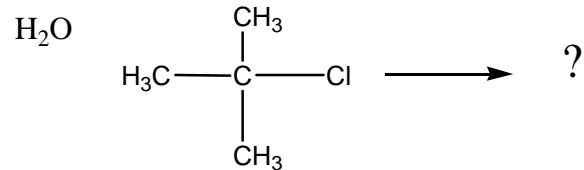
3) Rank the following compounds in order of their expected reactivity in S_N1 reactions:



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Answer

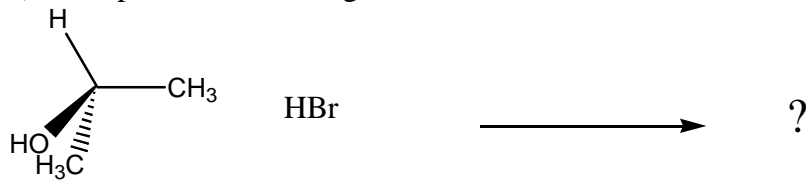
4) Complete the following reaction:



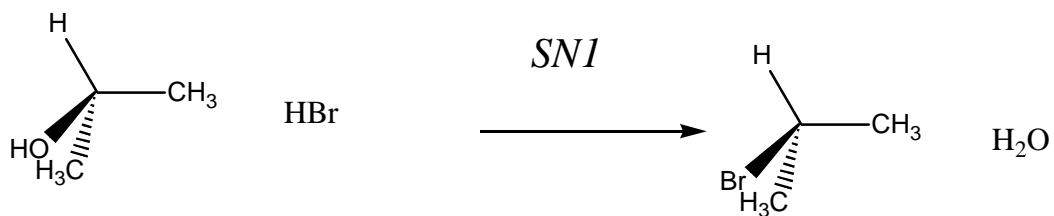
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Answer

5) Complete the following reaction:



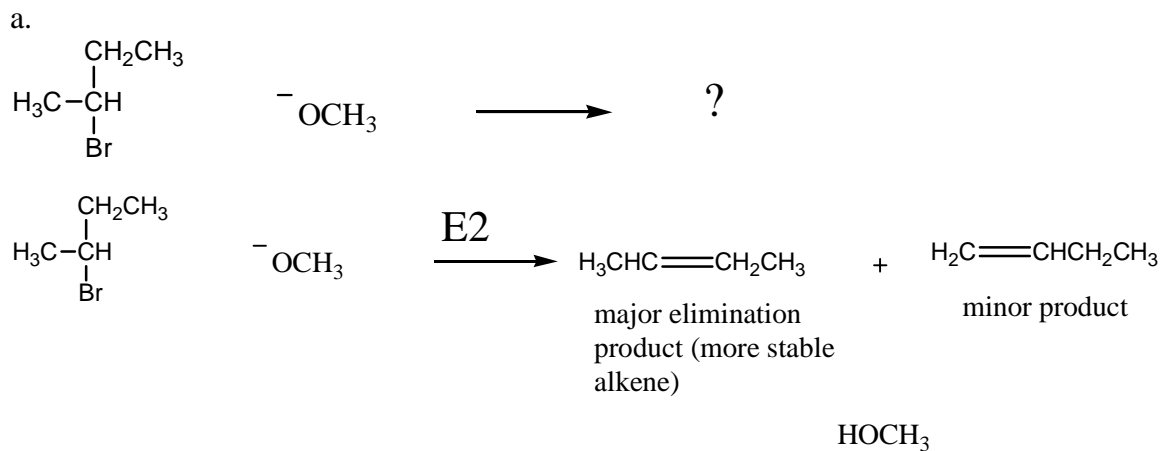
OH is a poor leaving group. It can be protonated to turn it into water, a better leaving group. Water leaves, forming a carbocation and Br⁻ adds to the carbon.



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Answer

6) Indicate the products and the most likely mechanisms involved in the following reactions:

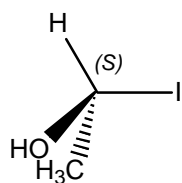


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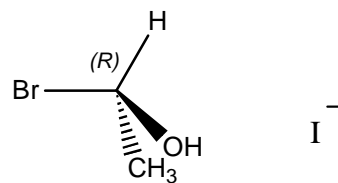
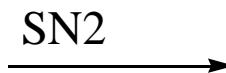
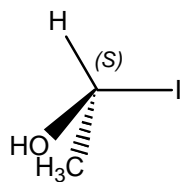
Answer

6) Indicate the products and the most likely mechanisms involved in the following reactions:

b.



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