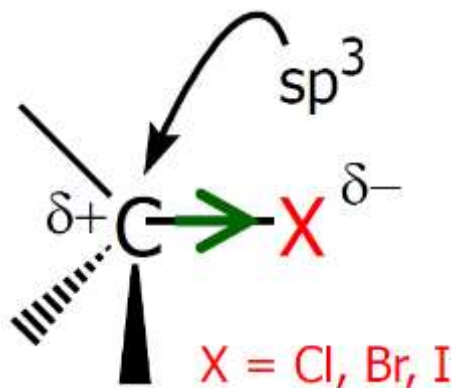# Alkyl Halides

- An **alkyl halide** has a halogen atom bonded to an sp^3-hybridized (tetrahedral) carbon atom.
- The carbon–halogen bond in an alkyl halide is polarized **because** the halogen is more electronegative than carbon.
  - Therefore, the carbon atom has a partial positive charge ($\delta+$) and the halogen has a partial negative charge ($\delta-$).
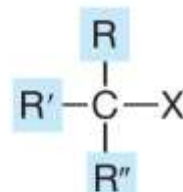

- Alkyl halides are classified as **primary** (1°), **secondary** (2°), or **tertiary** (3°) according to the number of carbon groups (R) directly bonded to the carbon bearing the halogen atom.
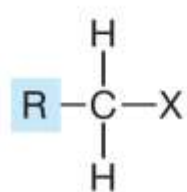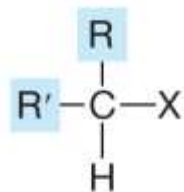
- Halogen atom size increases as we go down the periodic table:
  - Fluorine atoms are the *smallest* and iodine atoms the *largest*.
  - The carbon–halogen *bond length increases*
  - The carbon–halogen *bond strength decreases* as we go down the periodic table
- Fluoromethane is highly polar and has the shortest C−X bond length and the strongest C−X bond.
  - Iodomethane is much less polar and has the longest C−X bond length and the weakest C−X bond.

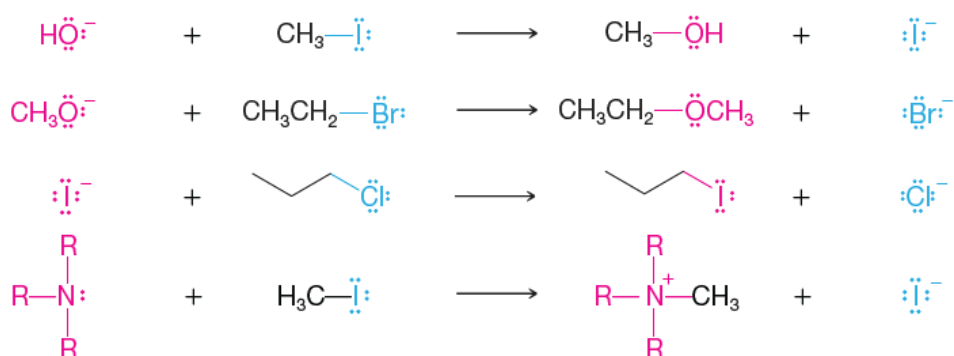| C—X Bond length (Å) | 1.39 | 1.78 | 1.93 | 2.14 |
| C—X Bond strength (kJ mol⁻¹) | 472 | 350 | 293 | 239 |

Note: bond strength units shown as $kJ\ mol^{-1}$

Nucleophilic Substitution Reactions

➢ In a **nucleophilic substitution reaction** a nucleophile (**Nu:**) displaces a leaving group (**LG**) in the molecule that undergoes the substitution (the substrate).

  ▪ The *nucleophile:* is a Lewis base (electron pair donor), and it may be negatively charged or neutral.

   • Has an unshared pair of e^-
   • **e.g.:** HO, CH_3O, H_2N (negative charge) - H_2O, NH_3 (neutral)

  ▪ The *leaving group***:** is always a species that takes a pair of electrons with it when it departs.

   • Must be able to leave as a relatively stable, weakly basic molecule or ion
   • **e.g.:** I^-, Br^-, Cl^-, TsO^-, MsO^-, H_2O, NH_3
  ▪ Often the **substrate** is an alkyl halide and the **leaving group** is a halide anion.

Examples:

$$HO^- \quad + \quad CH_3-I \quad \longrightarrow \quad CH_3-OH \quad + \quad I^-$$

$$CH_3O^- \quad + \quad CH_3CH_2-Br \quad \longrightarrow \quad CH_3CH_2-OCH_3 \quad + \quad Br^-$$

$$I^- \quad + \quad \text{(propyl)}Cl \quad \longrightarrow \quad \text{(propyl)}I \quad + \quad Cl^-$$

$$\begin{array}{c} R \\ | \\ R-N: \\ | \\ R \end{array} \quad + \quad H_3C-I \quad \longrightarrow \quad \begin{array}{c} R \\ | \\ R-\overset{+}{N}-CH_3 \\ | \\ R \end{array} \quad + \quad I^-$$
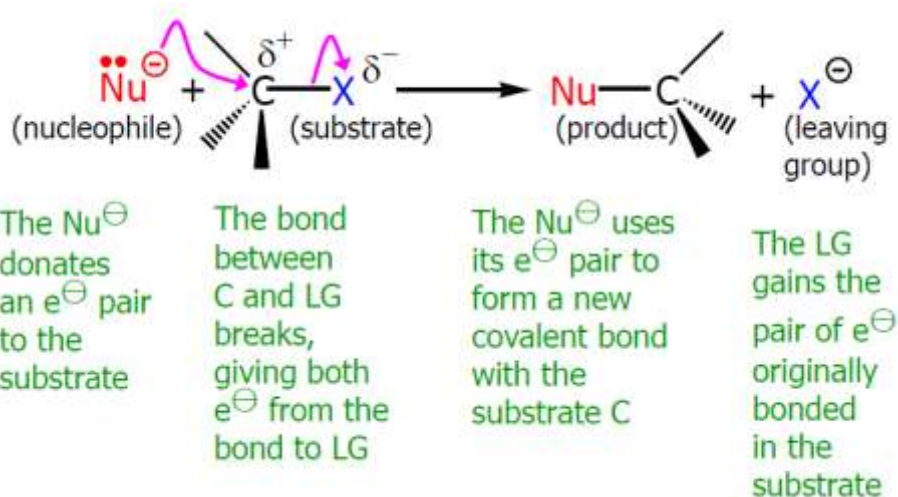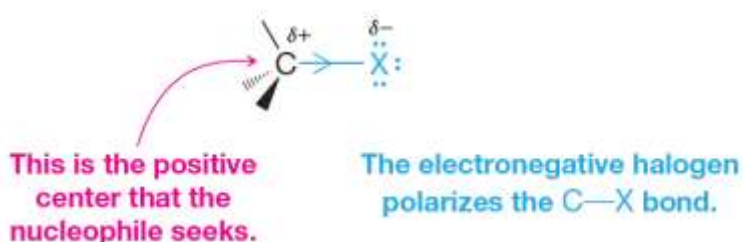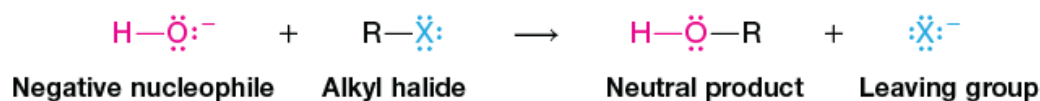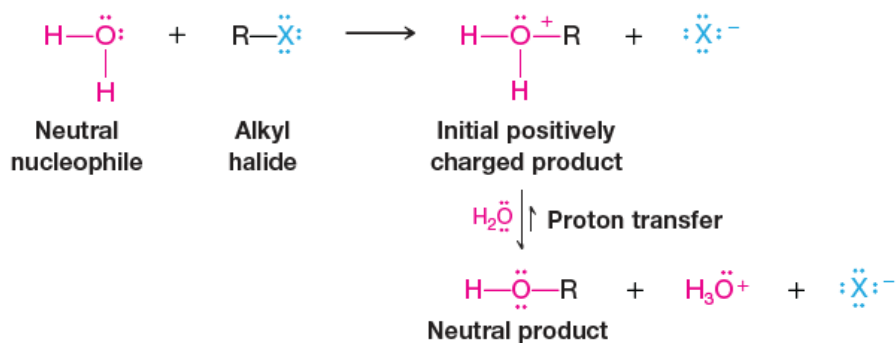
Nucleophiles

➢ A nucleophile is a reagent that seeks a positive center.

➢ Any **negative** ion or **uncharged molecule** with an unshared electron pair is a potential nucleophile.

➢ When a nucleophile reacts with an alkyl halide, the carbon atom bearing the halogen atom is the positive center that attracts the nucleophile. This carbon carries a partial positive charge **because** the electronegative halogen pulls the electrons of the carbon–halogen bond in its direction.
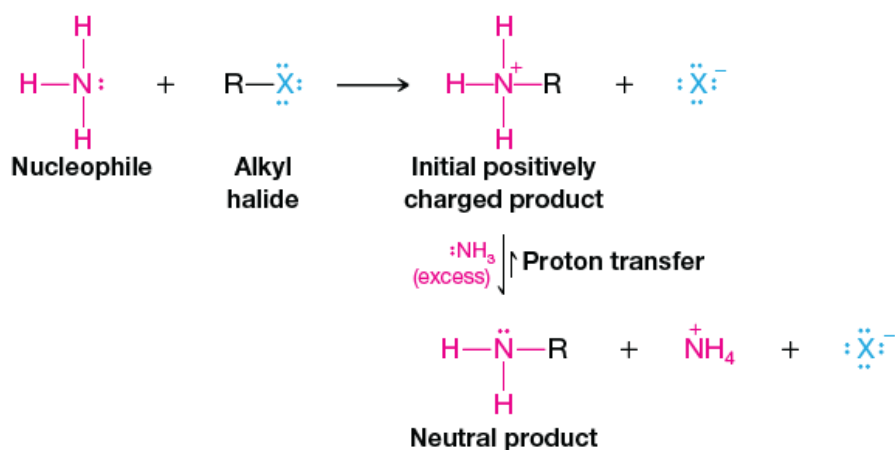

This is the positive center that the nucleophile seeks.

The electronegative halogen polarizes the C—X bond.

a- *Nucleophilic Substitution by a Negatively Charged Nucleophile Results Directly in a* **Neutral Product**

$$H-O^- \quad + \quad R-X \quad \longrightarrow \quad H-O-R \quad + \quad X^-$$

Negative nucleophile   Alkyl halide   Neutral product   Leaving group

b- *Nucleophilic Substitution by a Neutral Nucleophile Results Initially in a* **Positively Charged Product**

$$\begin{array}{c} H-O: \\ | \\ H \end{array} \quad + \quad R-X \quad \longrightarrow \quad \begin{array}{c} H-\overset{+}{O}-R \\ | \\ H \end{array} \quad + \quad X^-$$

Neutral nucleophile   Alkyl halide   Initial positively charged product

H_2O ↑ Proton transfer

$$H-O-R \quad + \quad H_3O^+ \quad + \quad X^-$$

Neutral product

3

$$H-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{N}}: \quad + \quad R-\ddot{X}: \quad \longrightarrow \quad H-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{\overset{+}{N}}}-R \quad + \quad :\ddot{X}:^{-}$$

| Nucleophile | Alkyl halide | Initial positively charged product | |

:NH₃ (excess) ↑↓ Proton transfer

$$H-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{N}}-R \quad + \quad \overset{+}{N}H_4 \quad + \quad :\ddot{X}:^{-}$$

Neutral product

Solved Problem

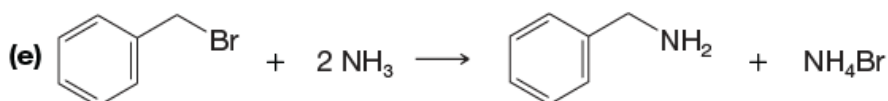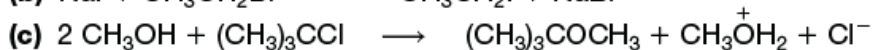**Write the following as net ionic equations and designate the nucleophile, substrate, and leaving group in each case.**

(a) $\diagup\!\!\diagdown\!\!\diagup\ddot{S}:^{-} Na^{+}$ + $CH_3-\ddot{I}:$ ⟶ $\diagup\!\!\diagdown\!\!\diagup\ddot{S}\diagdown_{CH_3}$ + $Na^{+} :\ddot{I}:^{-}$

(b) $\diagup\!\!\diagdown\!\!\equiv\!:^{-} Na^{+}$ + $CH_3-\ddot{I}:$ ⟶ $\diagup\!\!\diagdown\!\!\equiv\!-CH_3$ + $Na^{+} :\ddot{I}:^{-}$

(c) $H_3N:$ + (excess) $\diagup\!\!\diagdown\!\!\diagup\!\!\diagdown\ddot{B}r:$ ⟶ $\diagup\!\!\diagdown\!\!\diagup\!\!\diagdown\ddot{N}H_2$ + $\overset{+}{N}H_4$ + $:\ddot{B}r:^{-}$

Answers:

(a)

$\diagup\!\!\diagdown\!\!\diagup\ddot{S}:^{-}$ + $CH_3-\ddot{I}:$ ⟶ $\diagup\!\!\diagdown\!\!\diagup\ddot{S}\diagdown_{CH_3}$ + $:\ddot{I}:^{-}$

| Nucleophile | Substrate | | Leaving group |

(b)

$\diagup\!\!\diagdown\!\!\equiv\!:^{-}$ + $CH_3-\ddot{I}:$ ⟶ $\diagup\!\!\diagdown\!\!\equiv\!-CH_3$ + $:\ddot{I}:^{-}$

| Nucleophile | Substrate | | Leaving group |

(c)

$H_3N:$ + $\diagup\!\!\diagdown\!\!\diagup\!\!\diagdown\ddot{B}r:$ ⟶ $\diagup\!\!\diagdown\!\!\diagup\!\!\diagdown\ddot{N}H_2$ + $\overset{+}{N}H_4$ + $:\ddot{B}r:^{-}$
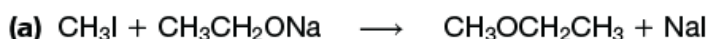
(excess)
Nucleophile | Substrate | | Leaving group |

4
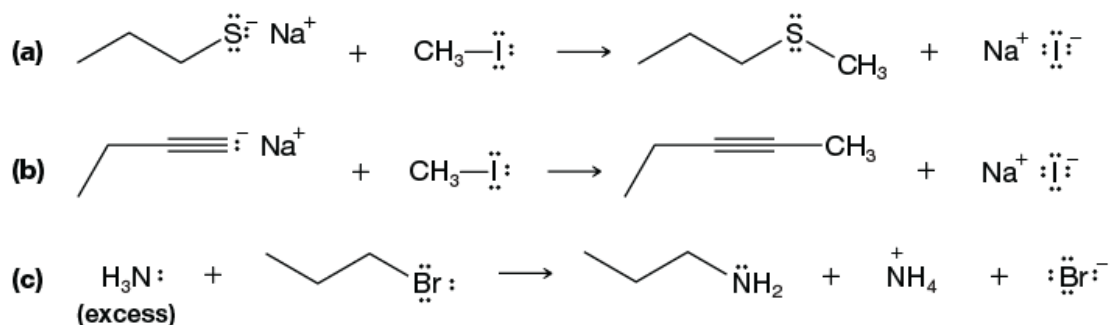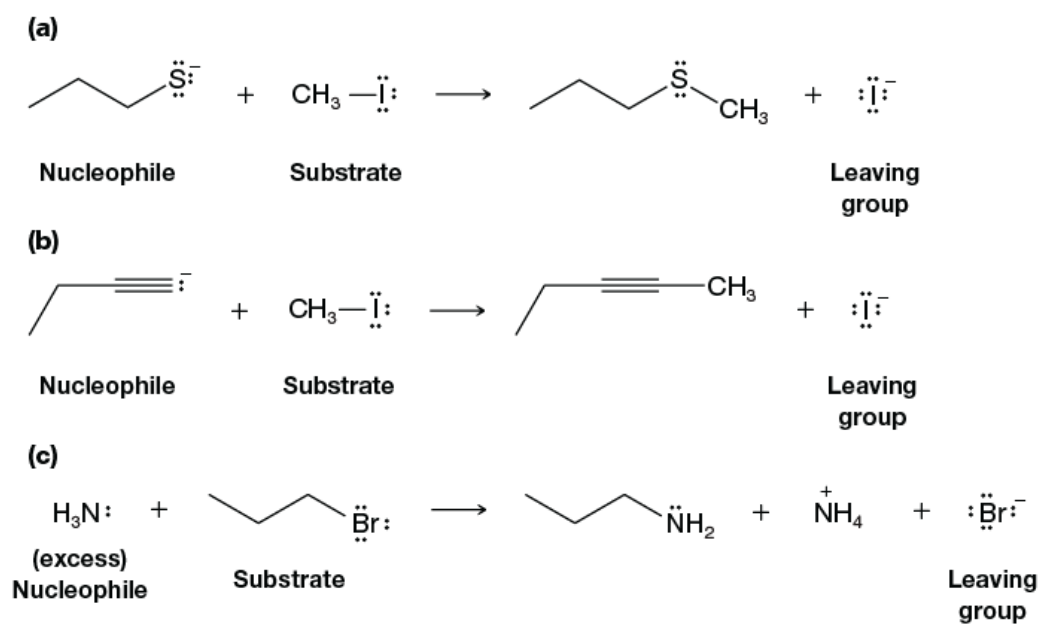
Practice Problem

Write the following as net ionic equations and designate the nucleophile, substrate, and leaving group in each reaction:

(a) $CH_3I + CH_3CH_2ONa \longrightarrow CH_3OCH_2CH_3 + NaI$

(b) $NaI + CH_3CH_2Br \longrightarrow CH_3CH_2I + NaBr$

(c) $2\ CH_3OH + (CH_3)_3CCl \longrightarrow (CH_3)_3COCH_3 + CH_3\overset{+}{O}H_2 + Cl^-$

(d) Br $+$ NaCN $\longrightarrow$ CN $+$ NaBr

(e) Br $+$ 2 NH$_3$ $\longrightarrow$ NH$_2$ $+$ NH$_4$Br

Leaving Groups

➢ To act as the substrate in a nucleophilic substitution reaction, a molecule must have a good leaving group.
  ▪ A good **leaving group** is a substituent that can leave as a relatively stable, weakly basic molecule or ion.
  ▪ Halide anions are weak bases, therefore they are good leaving groups.
  ▪ Some leaving groups depart as neutral molecules, such as a molecule of water or an alcohol.

The S$_N$2 Mechanism

Kinetics of a Nucleophilic Substitution Reaction: An S$_N$2 Reaction

How Do We Measure the Rate of This Reaction?

➢ **Consider an actual example:** the reaction that takes place between chloromethane and hydroxide ion in aqueous solution:
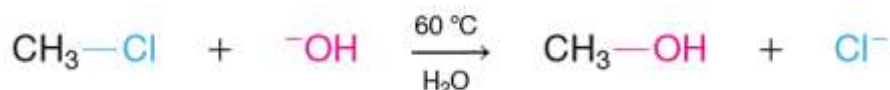
➢ The rate of the reaction can be determined experimentally by:
  ▪ The consumption of the reactants (HO$^-$ or CH$_3$Cl) or
  ▪ The appearance of the products (CH$_3$OH or Cl$^-$) over time

$$Rate = \frac{\Delta[CH_3Cl]}{\Delta t}$$

$$= -\left\{\frac{[CH_3Cl]_{t=t} - [CH_3Cl]_{t=0}}{Time\ in\ seconds}\right\}$$
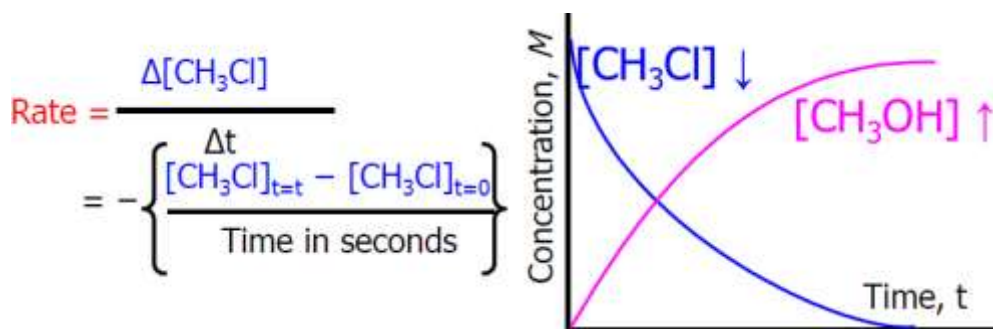
- ➤ The rate of reaction is directly proportional to the concentration of either reactant.
  - ▪ When the concentration of either reactant is doubled, the rate of reaction doubles.
- ➤ We can express these results as a proportionality,

Rate $\propto$ [CH$_3$Cl][HO$^-$]

Rate = k [CH$_3$Cl][HO$^-$]

- ➤ The reaction is said to be **second order overall**.
- ➤ The reaction is **bimolecular.**
  - ▪ **Biomolecular:** means the two species are involved in the step whose rate is being measured.
  - ▪ The number of species involved in a reaction step is called the **molecularity** of the reaction.
- ➤ The kind of reaction is **S$_N$2 reaction** (**substitution, nucleophilic, bimolecular**).

Mechanism for the S$_N$2 Reaction

a. The nucleophile approaches the carbon bearing the leaving group from the **back side**, that is, from the side directly opposite the leaving group.
b. As the nucleophile forms a bond and the leaving group departs, the substrate carbon atom undergoes **inversion** (its tetrahedral bonding configuration is turned inside out).
c. The S$_N$2 reaction proceeds in a single step (without any intermediates) through an unstable arrangement of atoms called the **transition state**.
  - ▪ This mechanism accounts for the **second-order reaction** kinetics **because** the transition state involves both the nucleophile (e.g., a hydroxide ion) and the substrate (e.g., a molecule of chloromethane),
d. The S$_N$2 reaction is said to be a **concerted reaction**, because bond forming and bond breaking occur in concert (*simultaneously*) through a single transition state.

Reaction

$$HO^- \quad + \quad CH_3Cl \quad \longrightarrow \quad CH_3OH \quad + \quad Cl^-$$
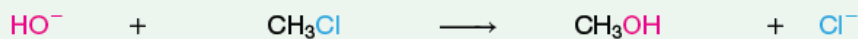
Mechanism
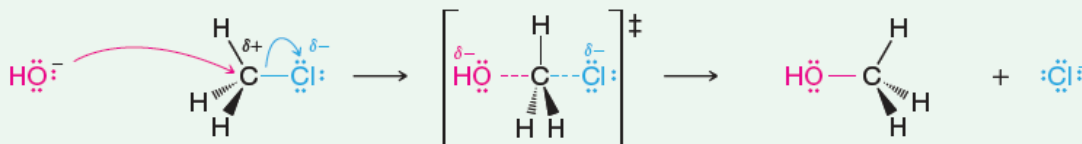
| The negative hydroxide ion brings a pair of electrons to the partially positive carbon from the back side with respect to the leaving group. The chlorine begins to move away with the pair of electrons that bonded it to the carbon. | In the transition state, a bond between oxygen and carbon is partially formed and the bond between carbon and chlorine is partially broken. The configuration of the carbon atom begins to invert. | Now the bond between the oxygen and carbon has formed and the chloride ion has departed. The configuration of the carbon has inverted. |

Transition State Theory: Free-Energy Diagrams

➢ **Exergonic:** is a reaction that proceeds with a negative free-energy change (releases energy to its surroundings).

➢ **Endergonic:** one that proceeds with a positive free-energy change (absorbs energy from its surroundings).

$$CH_3{-}Cl + {}^-OH \rightarrow CH_3{-}OH + Cl^- \quad \Delta G° = -100 \text{ kJ mol}^{-1}$$
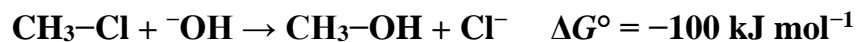
➢ The reaction between chloromethane and hydroxide ion in aqueous solution is:
  ▪ highly **exergonic**; at 60°C (333 K), $\Delta G° = -100$ kJ mol^{-1}.
  ▪ **exothermic**, $\Delta H° = -75$ kJ mol^{-1}.
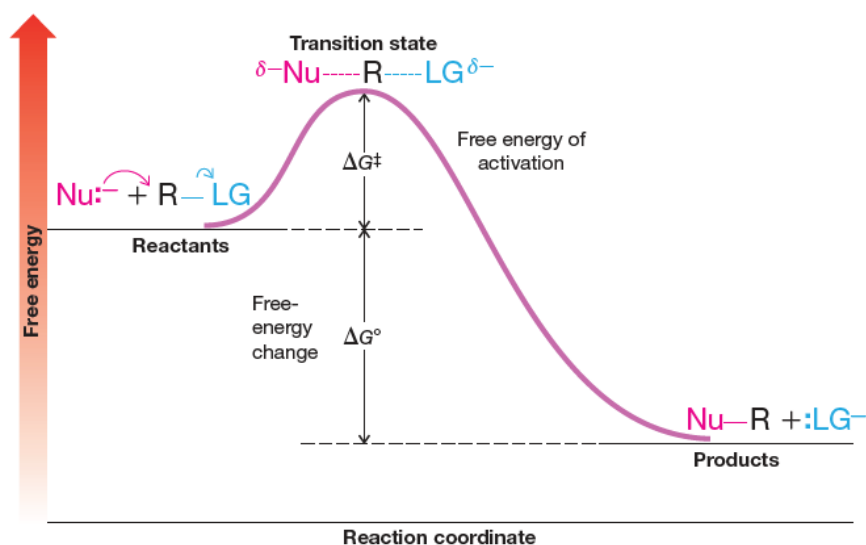
- The **reaction coordinate** indicates the progress of the reaction.
- The top of the energy curve corresponds to the **transition state** for the reaction.
- The **free energy of activation** ($\Delta G^{\ddagger}$) for the reaction is the difference in energy between the reactants and the transition state.
- The **free energy change for the reaction** ($\Delta G°$) is the difference in energy between the reactants and the products.
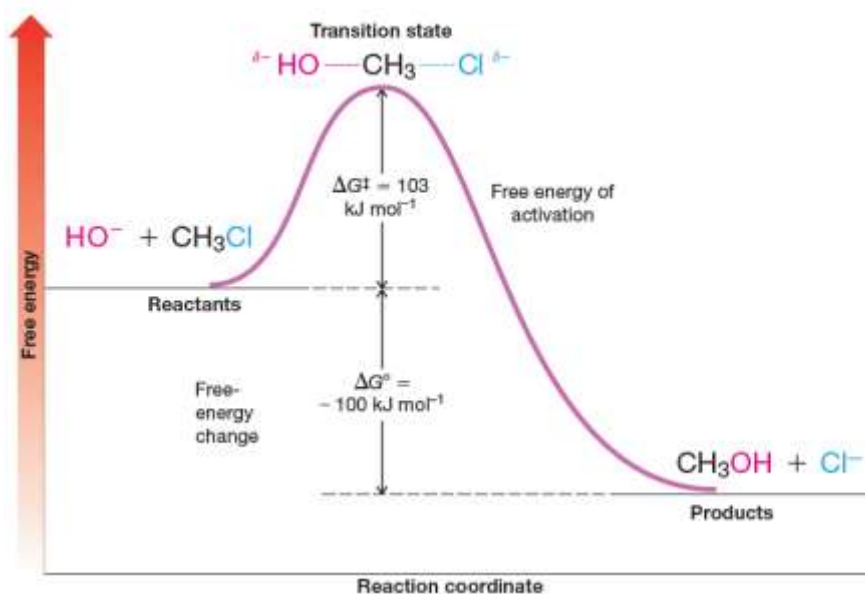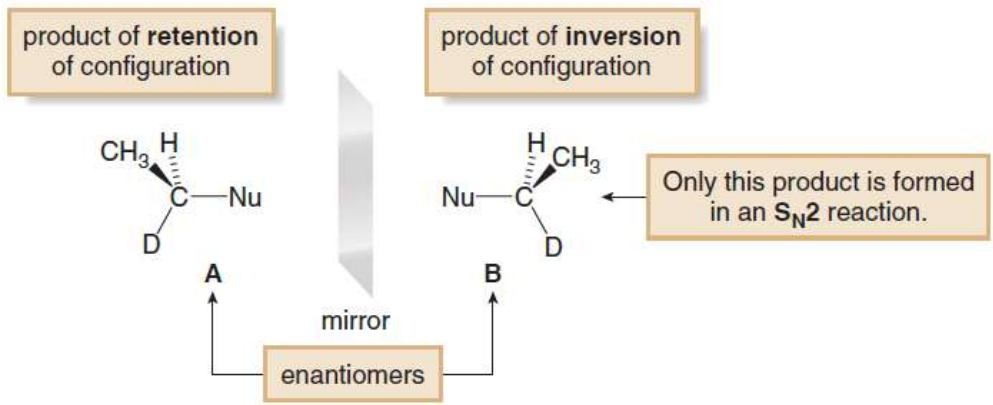

The Stereochemistry of S$_N$2 Reactions

➢ There are two possibilities for the attack of the nucleophile:

a. Frontside attack: The nucleophile approaches from the *same* side as the leaving group.

- Because the nucleophile and leaving group are in the same position relative to the other three groups on carbon, frontside attack results in **retention** of configuration around the stereogenic center.
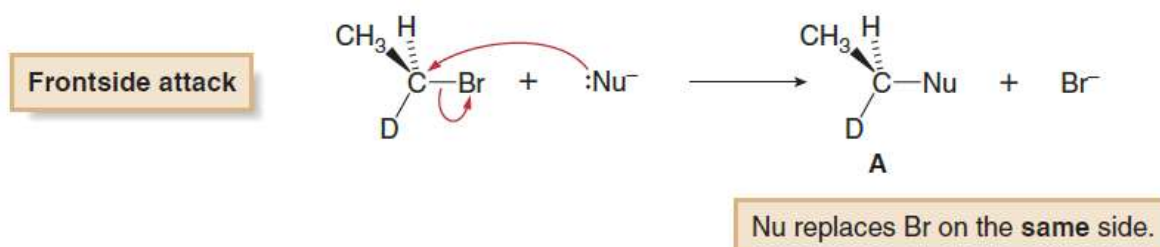
b. Backside attack: The nucleophile approaches from the side *opposite* the leaving group.

- Because the nucleophile and leaving group are in the opposite position relative to the other three groups on carbon, backside attack results in **inversion** of configuration around the stereogenic center.

8

Backside attack

Nu replaces Br on the **opposite** side.
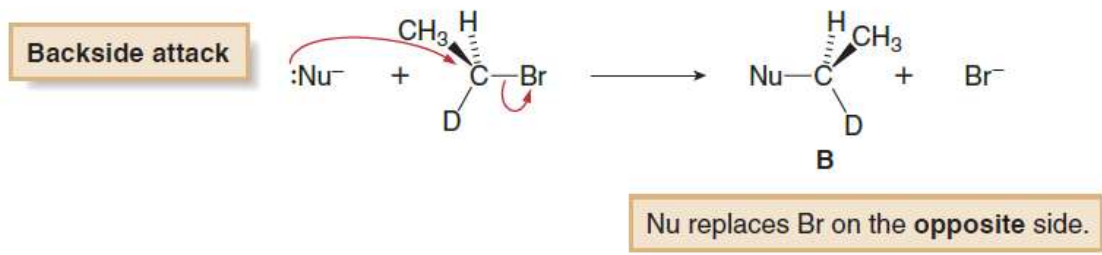
- The products of frontside and backside attack are *different* compounds.

product of **retention** of configuration

product of **inversion** of configuration

Only this product is formed in an S_N2 reaction.

mirror

enantiomers

- **A** and **B** are stereoisomers
- All S_N2 reactions proceed with backside attack of the nucleophile, resulting in *inversion* of confiuration at a stereogenic center.
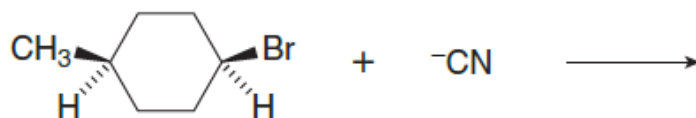
Examples:

An inversion of configuration
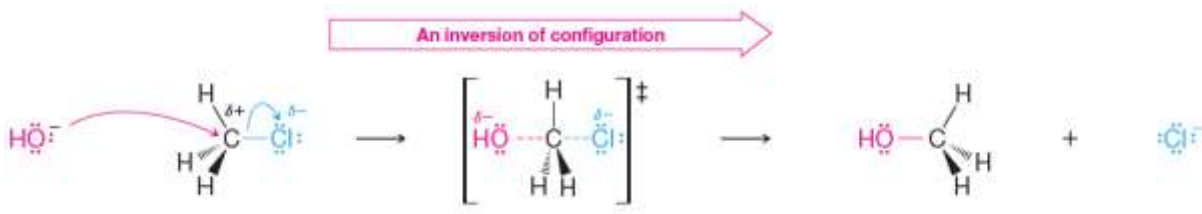
- Two examples of inversion of configuration in the S_N2 reaction

inversion of configuration

inversion of configuration
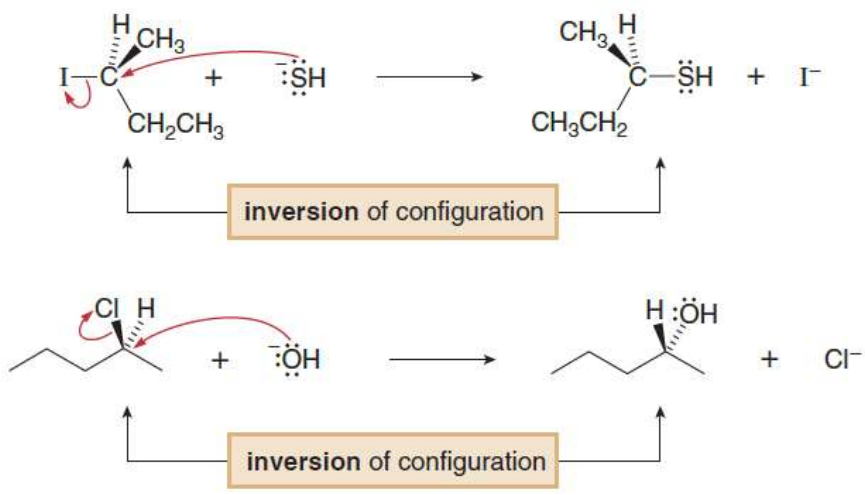
Sample Problem:
Draw the product (including stereochemistry) of the following S$_N$2 reaction.

CH$_3$ Br   + $^-$CN $\longrightarrow$
H   H

Solution

Br$^-$ is the leaving group and $^-$CN is the nucleophile. Because S$_N$2 reactions proceed with **inversion** of configuration and the leaving group is drawn above the ring (on a wedge), the nucleophile must come in from below.

The CH$_3$ group stays in its original orientation.

CH$_3$ Br   + $^-$CN $\longrightarrow$ CH$_3$ H   +   Br$^-$
H   H   H   CN

Inversion of configuration occurs at the C−Br bond.
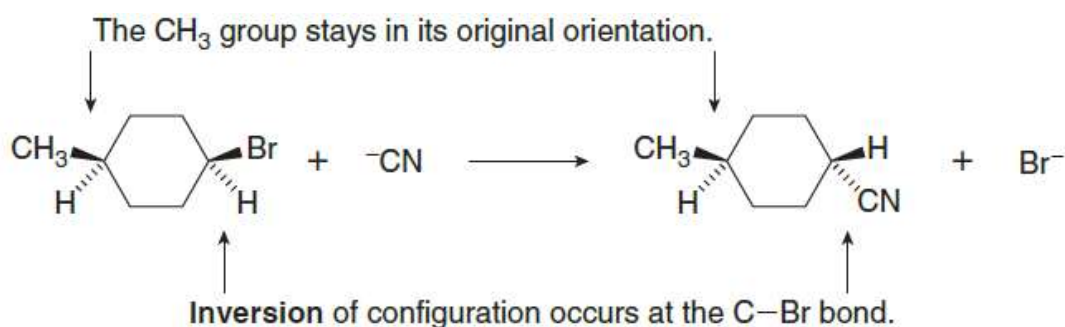
Backside attack converts the starting material, which has two groups **cis** to each other, to a product with two groups **trans** to each other because the nucleophile ($^-$CN) attacks from below the plane of the ring.

Problem: Draw the product of each S$_N$2 reaction and indicate stereochemistry.
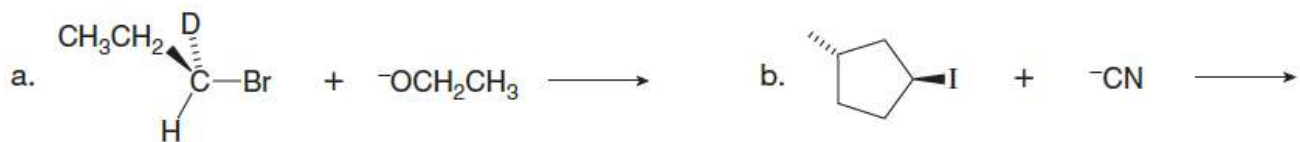
a.   CH$_3$CH$_2$ D
                 C−Br   + $^-$OCH$_2$CH$_3$ $\longrightarrow$
             H

b.   I   + $^-$CN $\longrightarrow$

The Identity of the R Group

➤ As the number of R groups on the carbon with the leaving group *increases,* the rate of an S$_N$2 reaction *decreases*.

CH$_3$−X	RCH$_2$−X	R$_2$CH−X	R$_3$C−X
methyl	1°	2°	3°

Increasing rate of an S$_N$2 reaction
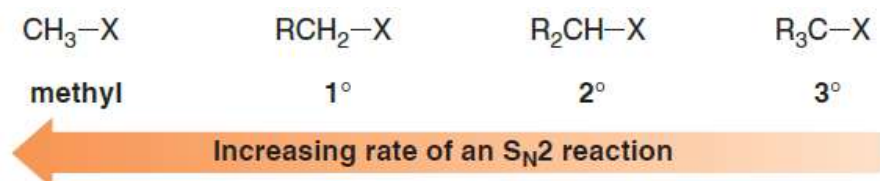
- Methyl and 1° alkyl halides undergo S$_N$2 reactions with ease.
- 2° Alkyl halides react more slowly.
- 3° Alkyl halides *do not* undergo S$_N$2 reactions.

➢ Increasing the number of R groups on the carbon with the leaving group *increases* crowding in the transition state, decreasing the rate of an S_N2 reaction.

➢ The S_N2 reaction is fastest with unhindered halides.

  ▪ As small H atoms are replaced by larger alkyl groups, steric hindrance caused by bulky R groups makes nucleophilic attack from the back side more difficult

Increasing steric hindrance

CH₃Br   CH₃CH₂Br   (CH₃)₂CHBr   (CH₃)₃CBr

Increasing reactivity in an S_N2 reaction
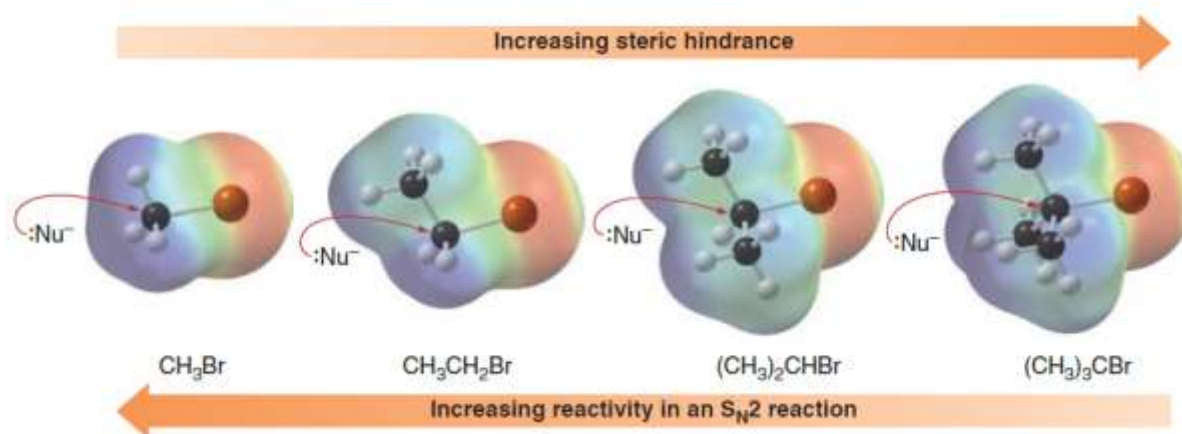
Problem: **Which compound in each pair undergoes a faster S_N2 reaction?**

a. CH_3CH_2-Cl or CH_3-Cl

b.   or

c.
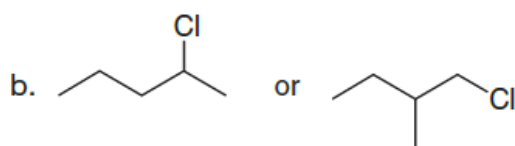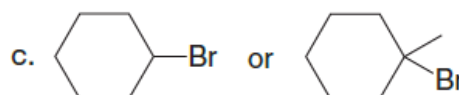
Characteristics of the S_N2 Mechanism

Characteristic	Result
Kinetics	Second-order kinetics; rate = $k[RX][:Nu-]$
Mechanism	One step
Stereochemistry	• Backside attack of the nucleophile • Inversion of confi guration at a stereogenic center
Identity of R	• Unhindered halides react fastest. • Rate: $CH_3X > RCH_2X > R_2CHX > R_3CX$

The S$_N$1 Mechanism

➢ An example of **S$_N$1 mechanism is** the reaction of $(CH_3)_3CBr$ with CH_3COO^-

| S$_N$1 reaction | $(CH_3)_3C-Br$ + | | | + Br$^-$ |

acetate
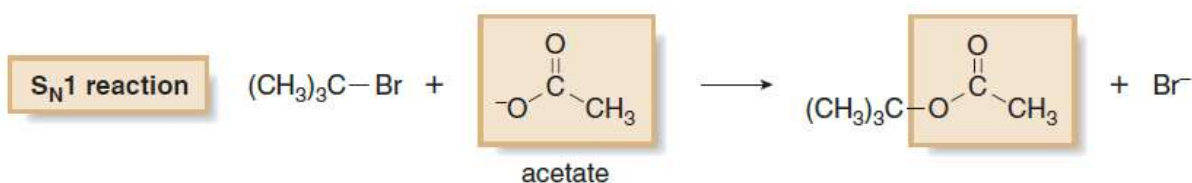
Kinetics

➢ S$_N$1 reaction (**substitution, nucleophilic, unimolecular**)
➢ The S$_N$1 reaction exhibits **first-order kinetics.**
➢ **Rate = k[(CH$_3$)$_3$CBr]**
➢ S$_N$1 mechanism involves **more than one step.**
  ▪ The slow step is **unimolecular,** involving *only* the alkyl halide.
➢ The identity and concentration of the nucleophile have no effect on the reaction rate.
  ▪ **For example:** doubling the concentration of $(CH_3)_3CBr$ doubles the rate, but doubling the concentration of the nucleophile has no effect.

Mechanism for the S$_N$1 Reaction

➢ The mechanism has two steps.
➢ Two distinct **intermediates** are formed.
➢ The first step is the slow step—it is the rate-determining step.

For example:
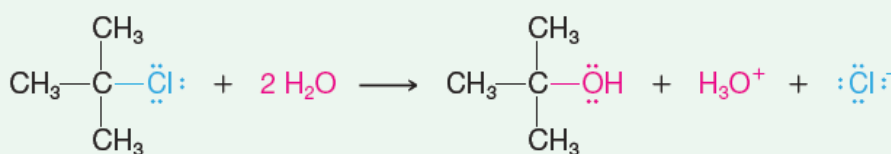
Mechanism

Step 1
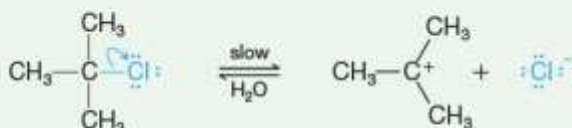
Aided by the polar solvent, a chlorine departs with the electron pair that bonded it to the carbon.
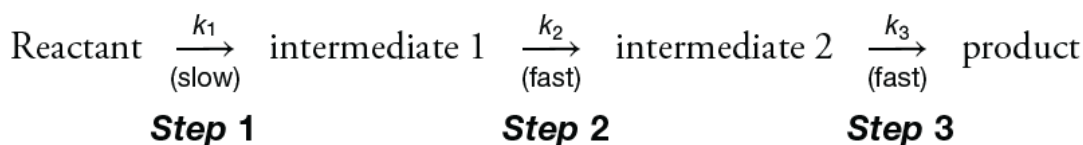
This slow step produces the 3° carbocation interme-diate and a chloride ion. Although not shown here, the ions are solvated (and stabilized) by water molecules.
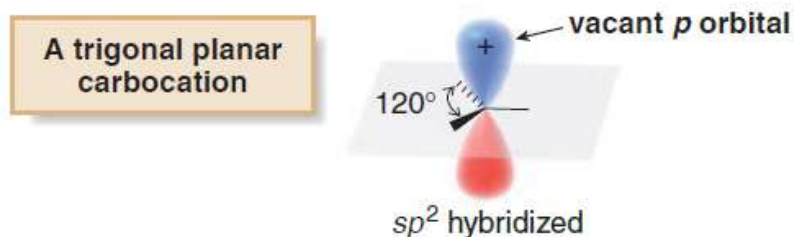
Step 1 $\Delta G^{\ddagger}_{(1)}$ is much larger than $\Delta G^{\ddagger}_{(2)}$ or $\Delta G^{\ddagger}_{(3)}$, hence this is the slowest step

Transition state 1

Free energy

Reaction coordinate

Step 2

A water molecule acting as a Lewis base donates an electron pair to the carbocation (a Lewis acid). This gives the cationic carbon eight electrons.

The product is a *tert*-butyloxonium ion (or protonated *tert*-butyl alcohol).

Step 2
Transition state 2
$\Delta G^{\ddagger}_{(2)}$

Step 3

A water molecule acting as a Brønsted base accepts a proton from the *tert*-butyloxonium ion.

The products are *tert*-butyl alcohol and a hydronium ion.

Step 3
Transition state 3
$\Delta G^{\circ \ddagger}$
$\Delta G^{\ddagger}_{(3)}$

Multistep Reactions and the Rate-Determining Step

➤ In a multistep reaction, the rate of the overall reaction is the same as the rate of the SLOWEST step, known as the rate-determining step (r.d.s)

$$\text{Reactant} \xrightarrow[\text{(slow)}]{k_1} \text{intermediate 1} \xrightarrow[\text{(fast)}]{k_2} \text{intermediate 2} \xrightarrow[\text{(fast)}]{k_3} \text{product}$$

Step 1   **Step 2**   **Step 3**

Narrow opening (rate determining)

Large openings

Sand

Sand

Reactant

Slow (rate determining)

Intermediate 1

Fast

Intermediate 2

Fast

Product

13
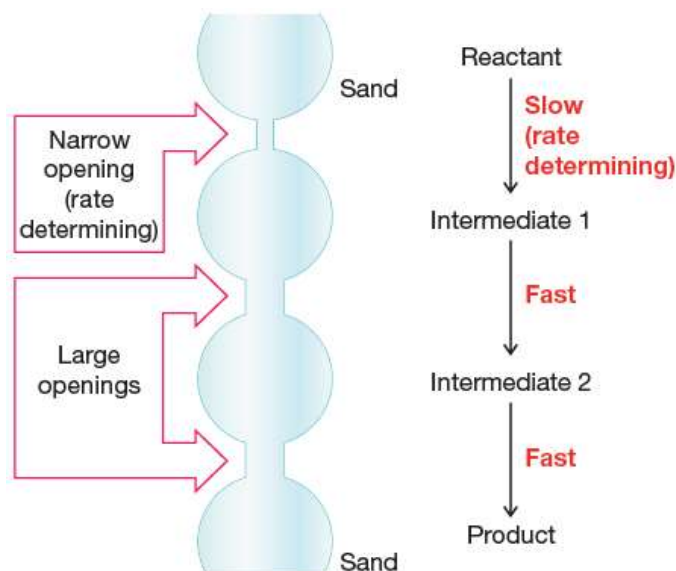
Stereochemistry of the S_N1 Reaction

A trigonal planar carbocation

vacant *p* orbital

120°

sp^2 hybridized

➢ A carbocation (with three groups around C) is sp^2 hybridized and trigonal planar, and contains a vacant *p* orbital extending above and below the plane.

➢ The energy diagram for the S_N1 reaction:

$$(CH_3)_3CBr + CH_3COO^- \rightarrow (CH_3)_3COCOCH_3 + Br^-$$
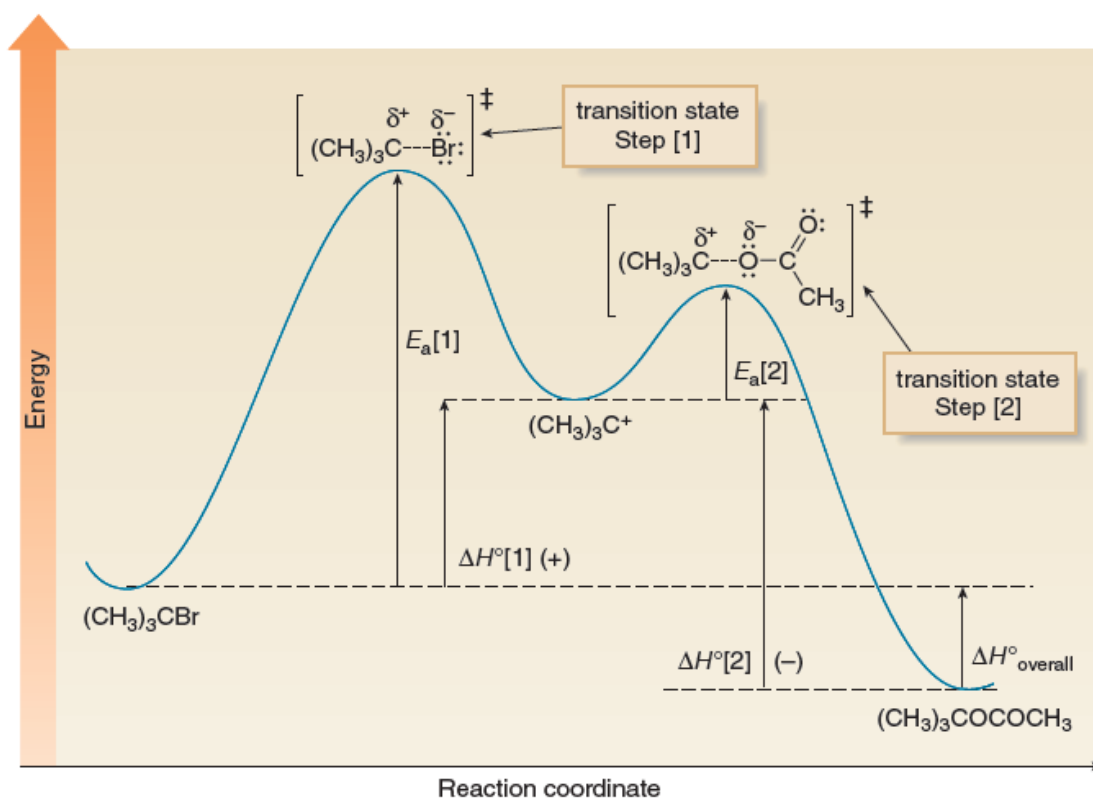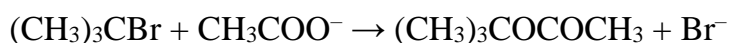
- Loss of the leaving group in Step [1] generates a planar carbocation that is now achiral.
- Attack of the nucleophile in Step [2] can occur from either side to afford *different* compounds containing one stereogenic center (stereoisomers).
- Because there is no preference for nucleophilic attack from either direction, an equal amount of the two enantiomers is formed a **racemic mixture.**
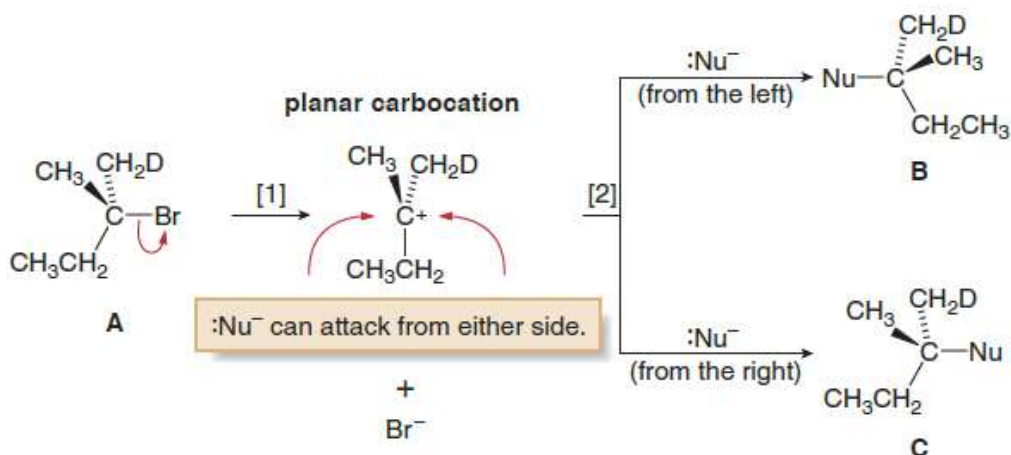
- **Racemization:** is the formation of equal amounts of two enantiomeric products from a single starting material.
- S$_N$1 reactions proceed with racemization at a single stereogenic center.

Sample Problem

Draw the products (including stereochemistry) of the following S$_N$1 reaction.
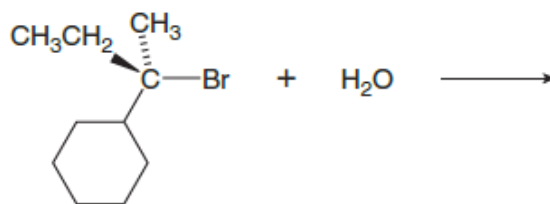
Solution

Br$^-$ is the leaving group and H$_2$O is the nucleophile. Loss of the leaving group generates a trigonal planar carbocation, which can react with the nucleophile from either direction to form two products.
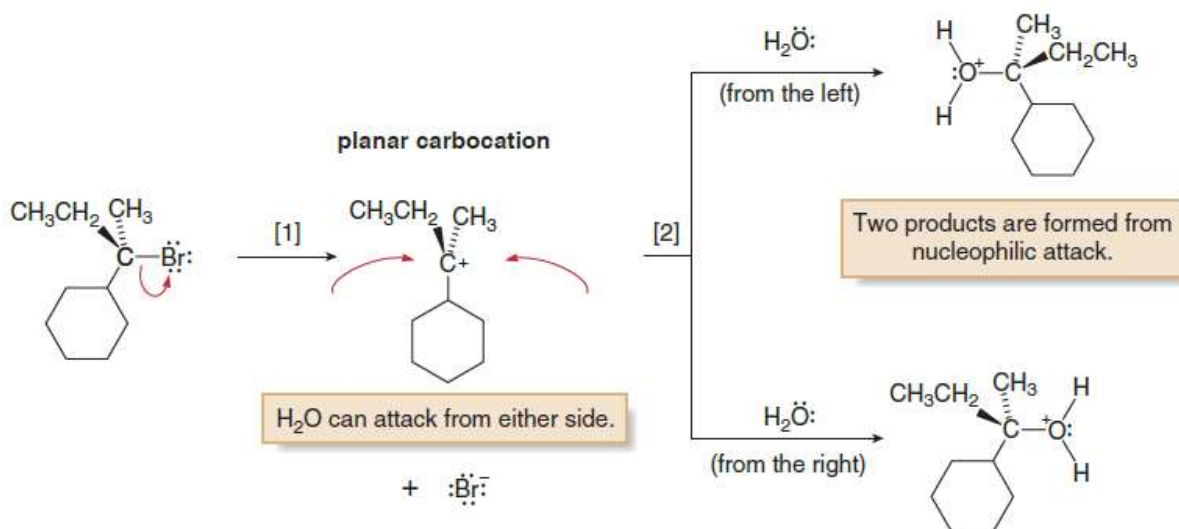
Examples:
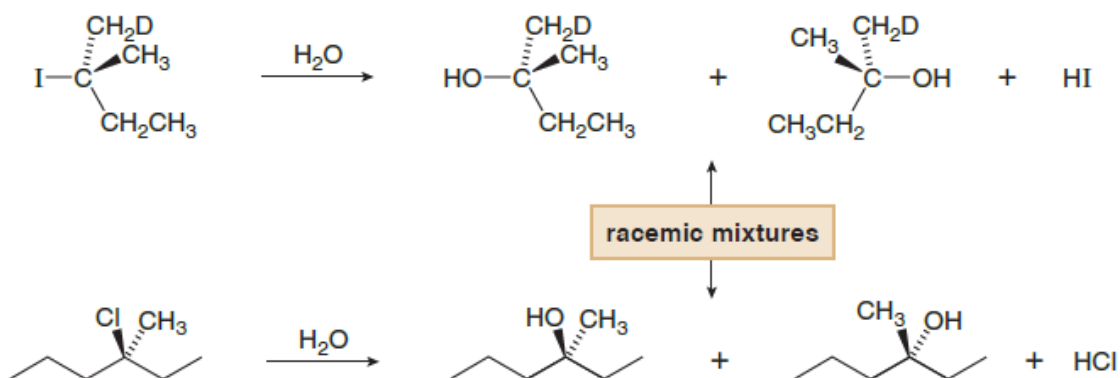
Problem: Draw the products of each S_N1 reaction and indicate the stereochemistry of any stereogenic centers.
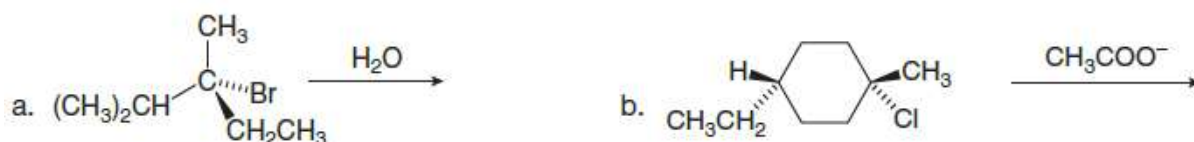
The Identity of the R Group

➤ As the number of R groups on the carbon with the leaving group *increases,* the rate of an S_N1 reaction *increases.*

- 3° Alkyl halides undergo S_N1 reactions rapidly.
- 2° Alkyl halides react more slowly.
- Methyl and 1° alkyl halides do *not* undergo S_N1 reactions.
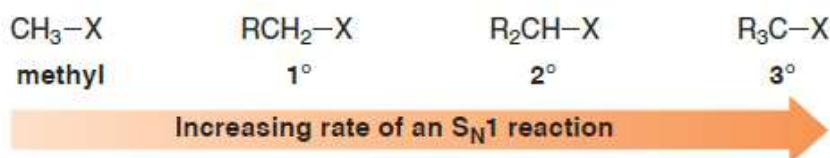
Characteristics of the S_N1 Mechanism

Characteristic	Result
Kinetics	First-order kinetics; rate = $k[RX]$
Mechanism	Two steps
Stereochemistry	• Trigonal planar carbocation intermediate • Racemization at a single stereogenic center
Identity of R	• More substituted halides react fastest. • Rate: $R_3CX > R_2CHX > RCH_2X > CH_3X$

Carbocations

The Structure of Carbocations

➢ Carbocations are **trigonal planar**.
➢ The central carbon atom in a carbocation is **electron deficient**; it has only six electrons in its valence shell.
➢ The p orbital of a carbocation contains **no electrons**.
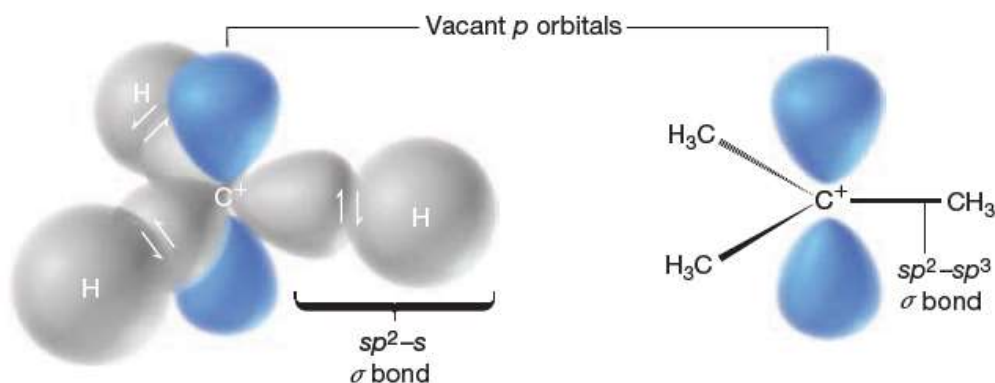

The Relative Stabilities of Carbocations

➢ **Carbocations** are classified as **primary (1°), secondary (2°), or tertiary (3°)** by the number of R groups bonded to the charged carbon atom.
➢ As the number of R groups on the positively charged carbon atom *increases*, the stability of the carbocation *increases*.
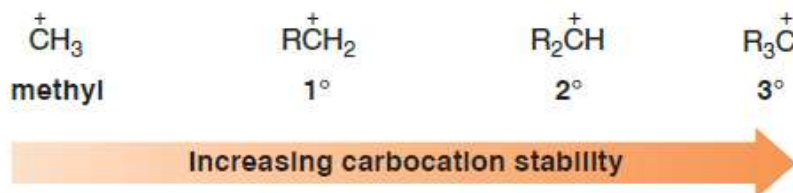
- Tertiary carbocations are the most stable, and the methyl carbocation is the least stable.
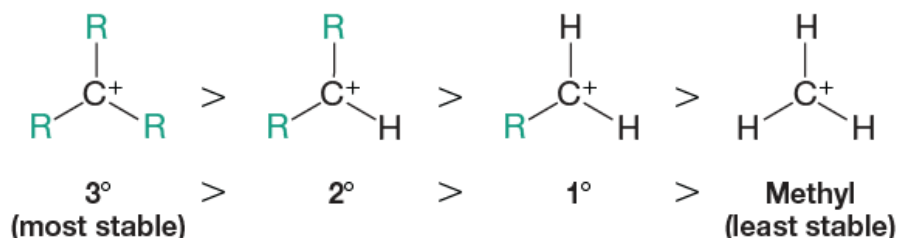
➢ To stabilize a positive charge, **electron-donating groups** are needed.
- Alkyl groups are electron donor groups that stabilize a positive charge.

- As R groups successively replace the H atoms in CH_3^+, the positive charge is more dispersed on the electron donor R groups, and the carbocation is **more stabilized**.

tert-Butyl cation (3°) (most stable)	Isopropyl cation (2°)	Ethyl cation (1°)	Methyl cation (least stable)
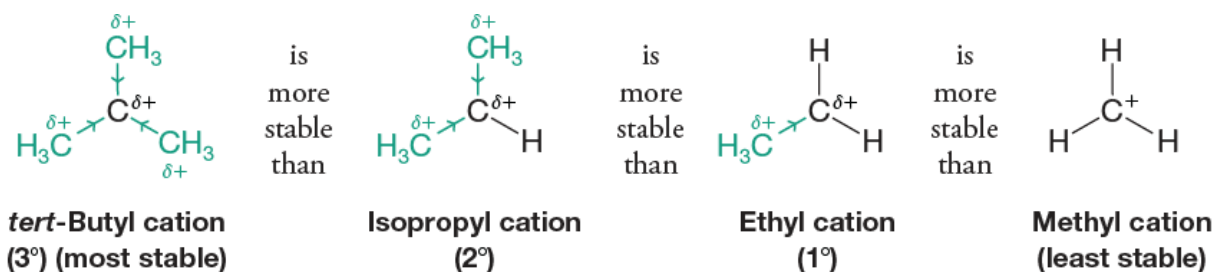
The Hammond Postulate

➢ The rate of an S_N1 reaction **increases** as the number of R groups on the carbon with the leaving group **increases**.

➢ The stability of a carbocation **increases** as the number of R groups on the positively charged carbon **increases**.

➢ Thus, the rate of an S_N1 reaction **increases** as the stability of the carbocation **increases**.
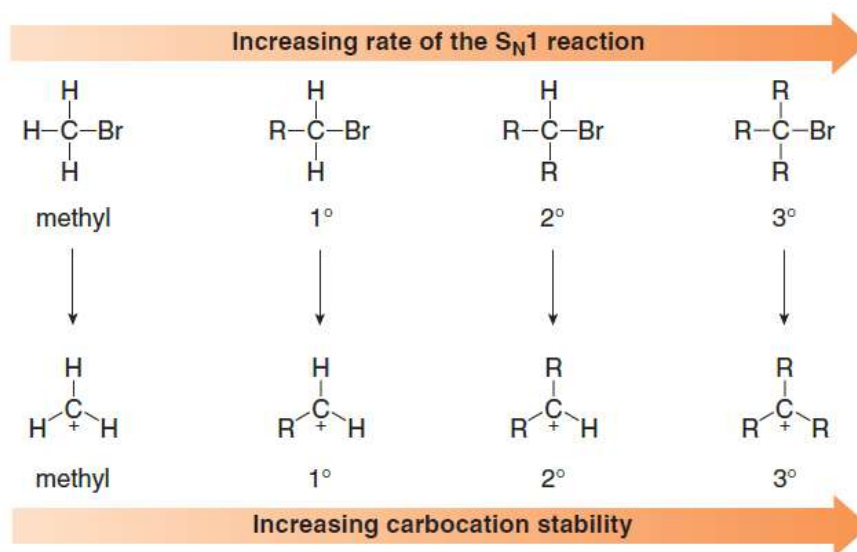
Factors Affecting the Rates of S$_N$1 and S$_N$2 Reactions

➢ A number of factors affect the relative rates of S$_N$1 and S$_N$2 reactions. The most important factors are:
1. The structure of the substrate
2. The concentration and reactivity of the nucleophile (for S$_N$2 reactions only)
3. The effect of the solvent
4. The nature of the leaving group

The Effect of the Structure of the Substrate

➢ The most important factor in determining whether a reaction follows the S$_N$1 or S$_N$2 mechanism is the *identity of the alkyl halide.*
   a. **Increasing** alkyl substitution favors **S$_N$1**.
   b. **Decreasing** alkyl substitution favors **S$_N$2**.
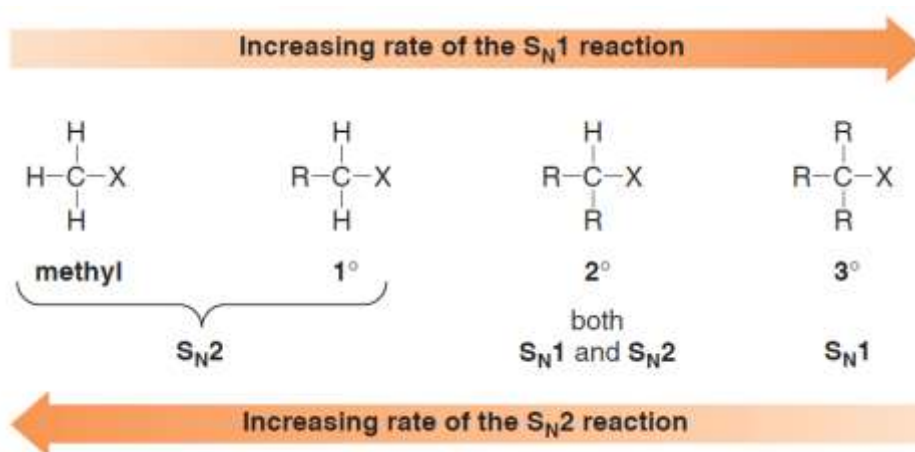
- Methyl and 1° halides (CH$_3$X and RCH$_2$X) undergo S$_N$2 reactions only.
- 3° Alkyl halides (R$_3$CX) undergo S$_N$1 reactions only.
- 2° Alkyl halides (R$_2$CHX) undergo both S$_N$1 and S$_N$2 reactions.
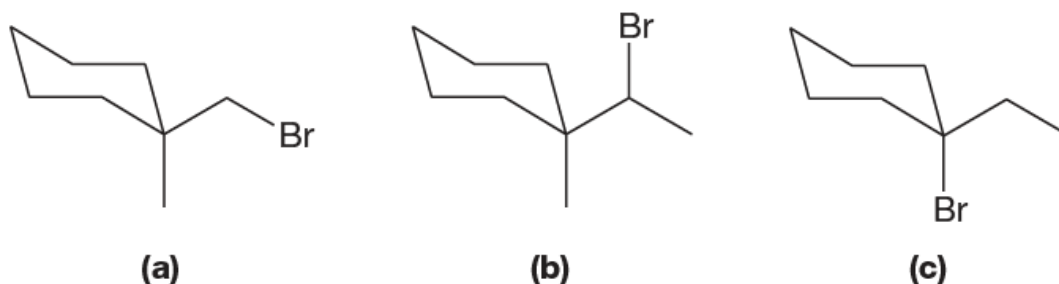
Problem:

1. **What is the likely mechanism of nucleophilic substitution for each alkyl halide?**
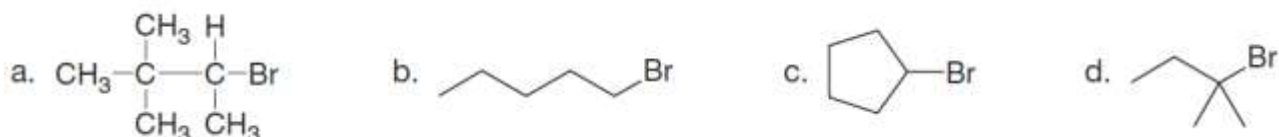
2. **Rank the following alkyl bromides in order of decreasing reactivity (from fastest to slowest) as a substrate in an S$_N$2 reaction.**

A   B   C   D
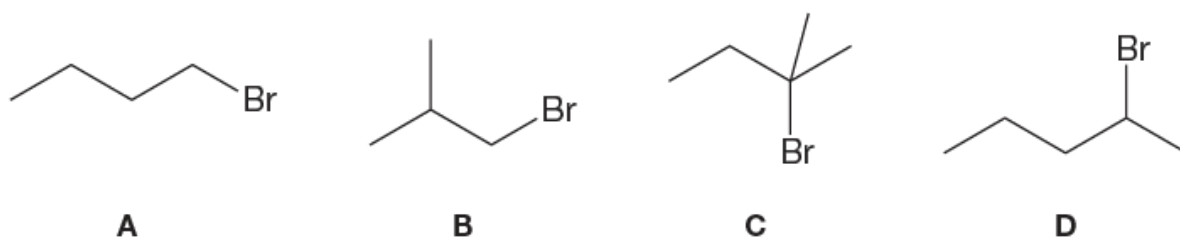
3. **Which of the following alkyl halides is most likely to undergo substitution by an S$_N$1 mechanism?**

(a)   (b)   (c)

The Effect of the Concentration and Strength of the Nucleophile

For S$_N$1 reaction

➤ The rate of an S$_N$1 reaction is unaffected by either the concentration or the identity of the nucleophile **because** the nucleophile does not participate in the rate-determining step of an S$_N$1 reaction.

▪ Rate = k[RX]

For S$_N$2 reaction

➤ The rate of an S$_N$2 reaction depends on *both* the **concentration** *and* the **identity** of the attacking nucleophile.

▪ Rate = k[RX][:Nu$^-$]

Identity of the Nucleophile

➤ The relative strength of a nucleophile (its **nucleophilicity**) is measured in terms of the relative rate of its S$_N$2 reaction with a given substrate.

   a- A **good nucleophile** is one that reacts rapidly in an S$_N$2 reaction with a given substrate.

      • **For example:** methoxide anion is a good nucleophile for a substitution reaction with iodomethane. It reacts rapidly by an S$_N$2 mechanism to form dimethyl ether:

$$CH_3O^- + CH_3I \xrightarrow{\text{rapid}} CH_3OCH_3 + I^-$$

20
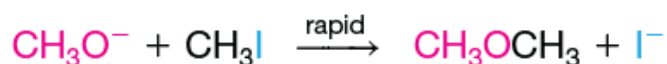
b- A **poor nucleophile** is one that reacts slowly in an S_N2 reaction with the same substrate under comparable reaction conditions.

- **For example:** Methanol is a poor nucleophile for reaction with iodomethane.

$$CH_3OH + CH_3I \xrightarrow{\text{very slow}} CH_3\overset{+}{\underset{H}{O}}CH_3 + I^-$$
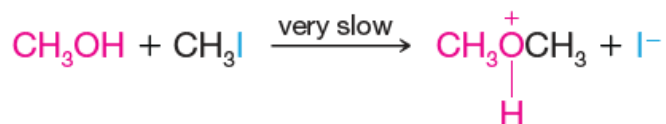
The Relative Strengths of Nucleophiles

➢ The relative strengths of nucleophiles can be correlated with three structural features:

a- **A negatively charged nucleophile is always a more reactive nucleophile than its conjugate acid**.

- HO^- is a better nucleophile than H_2O
- RO^- is better than ROH.

b- **In a group of nucleophiles in which the nucleophilic atom is the same, nucleophilicities parallel basicities**.

- **For example:** oxygen compounds show the following order of reactivity:
$$RO^- > HO^- >> RCO_2^- > ROH > H_2O$$

c- **When the nucleophilic atoms are different, nucleophilicities may not parallel basicities**.

- **For example:** in protic solvents HS^-, $N{\equiv}C^-$, and I^- are all weaker bases than HO^-, yet they are **stronger nucleophiles** than HO^-.
$$HS^- > N{\equiv}C^- > I^- > HO^-$$

N.B

☞ Strong nucleophiles present in high concentration favor S_N2 reactions.

☞ Weak nucleophiles favor S_N1 reactions by decreasing the rate of any competing S_N2 reaction.

☞ The most common nucleophiles in S_N2 reactions bear a **net negative charge**.

☞ The most common nucleophiles in S_N1 reactions are **weak nucleophiles** such as H_2O and ROH.

Problem:

1. **For each alkyl halide and nucleophile: [1] Draw the product of nucleophilic substitution; [2] determine the likely mechanism (S_N1 or S_N2) for each reaction.**

a. + CH₃OH → CH_3OH

c. + $CH_3CH_2O^-$

b. + ⁻SH

d. + CH_3OH
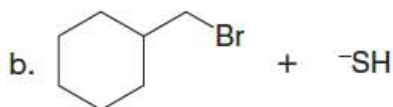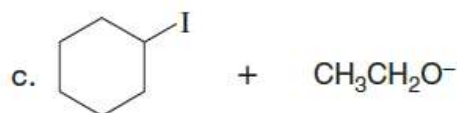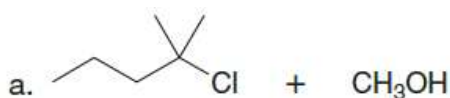
2. Draw the products (including stereochemistry) for each reaction.

a. + H_2O ⟶

b. + ⁻:C≡C–H ⟶
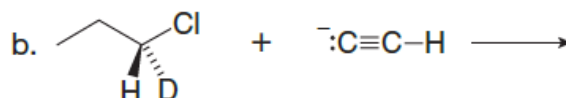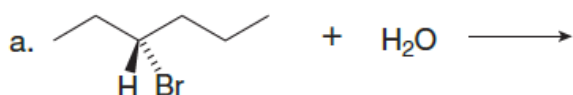
# Solvent Effects in S_N2 and S_N1 Reactions

> **S_N2** reactions are favored by **polar aprotic solvents** (e.g., acetone, DMF, DMSO).
> **S_N1** reactions are favored by **polar protic solvents** (e.g., EtOH, MeOH, H₂O).

➤ Important reasons for these **solvent effects** have to do with:
  (a) minimizing the solvent's interaction with the nucleophile in S_N2 reactions,
  (b) facilitating ionization of the leaving group and stabilizing ionic intermediates by solvents in S_N1 reactions.
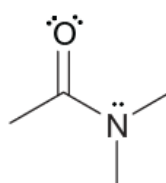
Polar Aprotic Solvents Favor S_N2 Reactions

➤ An aprotic solvent does not have hydrogen atoms that are capable of hydrogen bonding.
➤ They are often used alone or as co-solvents for S_N2 reactions.
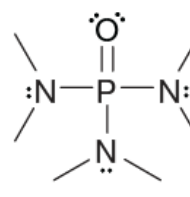➤ **Examples:** acetone, DMF, DMSO, and HMPA
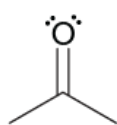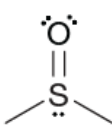

Acetone   **DMSO**   **DMF**   **HMPA**
             (Dimethylsulfoxide)   (N,N-Dimethyl-   (Hexamethyl
                                     formamide)   phosphoramide)

➤ The rates of S_N2 reactions are increased when they are carried out in polar aprotic solvents.
➤ Polar aprotic solvents solubilize cations well using their unshared electron pairs, but do not interact as strongly with anions **because**
  a. they cannot hydrogen bond with them and
 **b.** the positive regions of the solvent are shielded by steric effects from the anion.

- **For example:** sodium ions of sodium iodide can be solvated by DMSO leaving the iodide anion more free to act as a nucleophile.

Sodium iodide showing the sodium cation solvated by dimethylsulfoxide molecules.
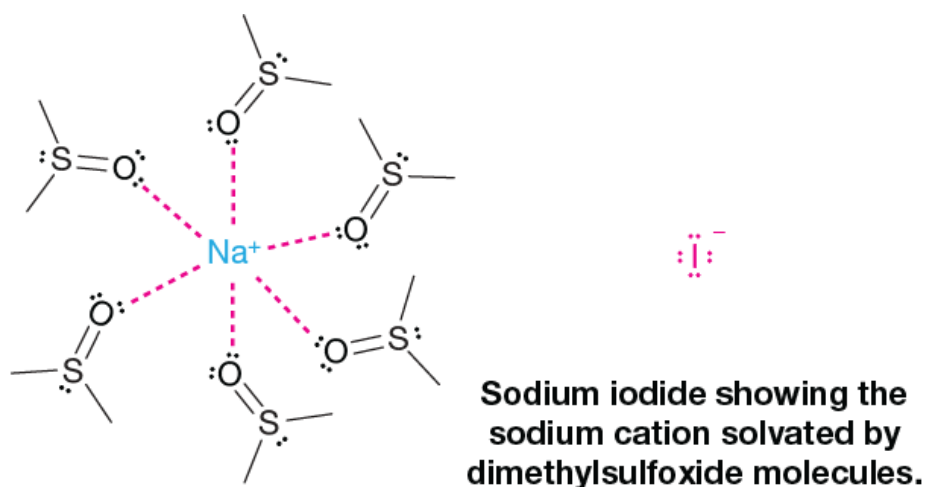
➤ Halide basicity is opposite to nucleophilicity in protic solvents.

$$F^- > Cl^- > Br^- > I^-$$
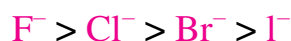
Halide nucleophilicity in aprotic solvents

(strongly solvated)   (weakly solvated)
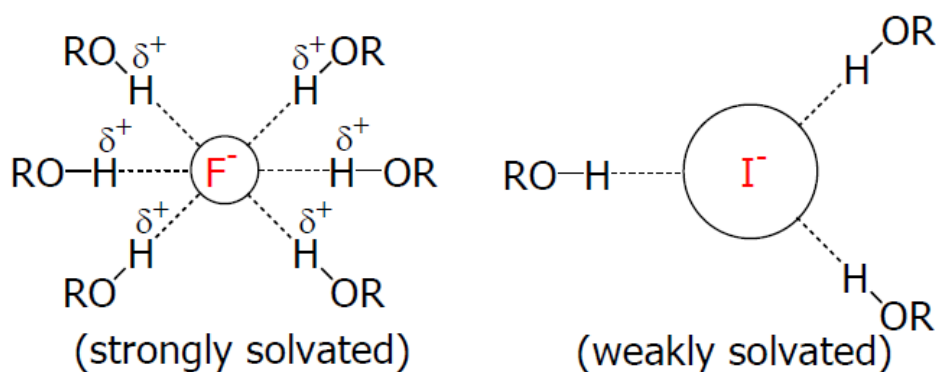
## Polar Protic Solvents Favor S_N1 Reactions

➤ A protic solvent has at least one hydrogen atom capable of participating in a hydrogen bond.
➤ Protic solvents facilitate formation of a carbocation by forming hydrogen bonds with the leaving group as it departs, thereby lowering the energy of the transition state leading to a carbocation.
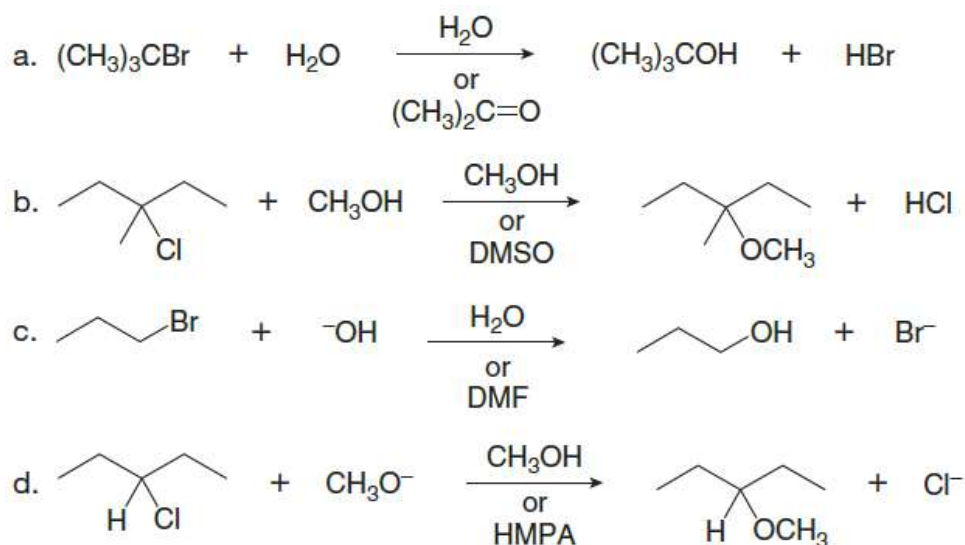➤ **Examples:** H_2O, EtOH, and MeOH,

| Hydrogen bonding with the substrate | Departure of the leaving group is assisted by hydrogen bonding in the transition state | Carbocation intermediate | Solvated leaving group |
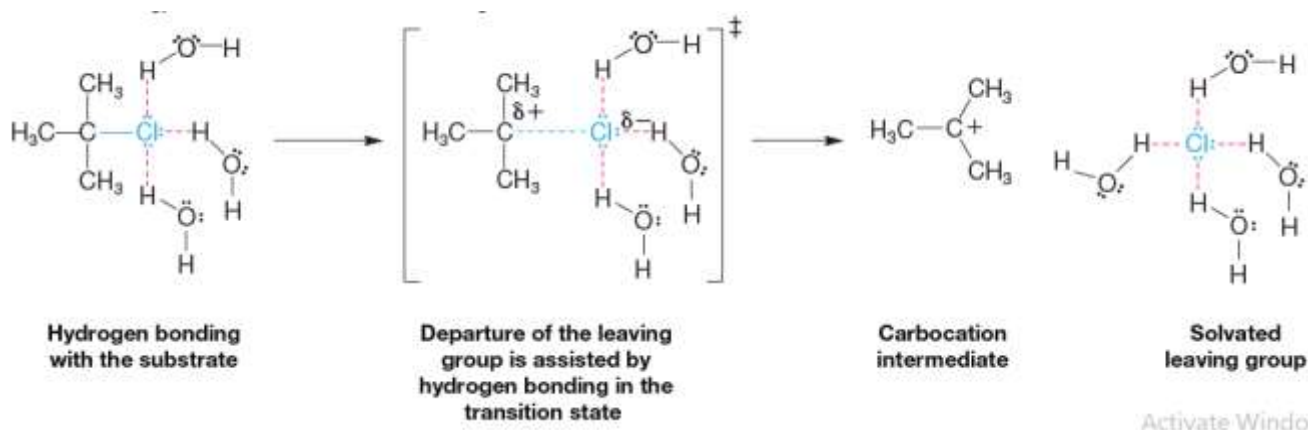
➢ The general trend in nucleophilicity among the halide anions is as follows:

$$I^- > Br^- > Cl^- > F^-$$
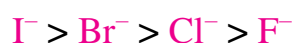
Halide nucleophilicity in protic solvents
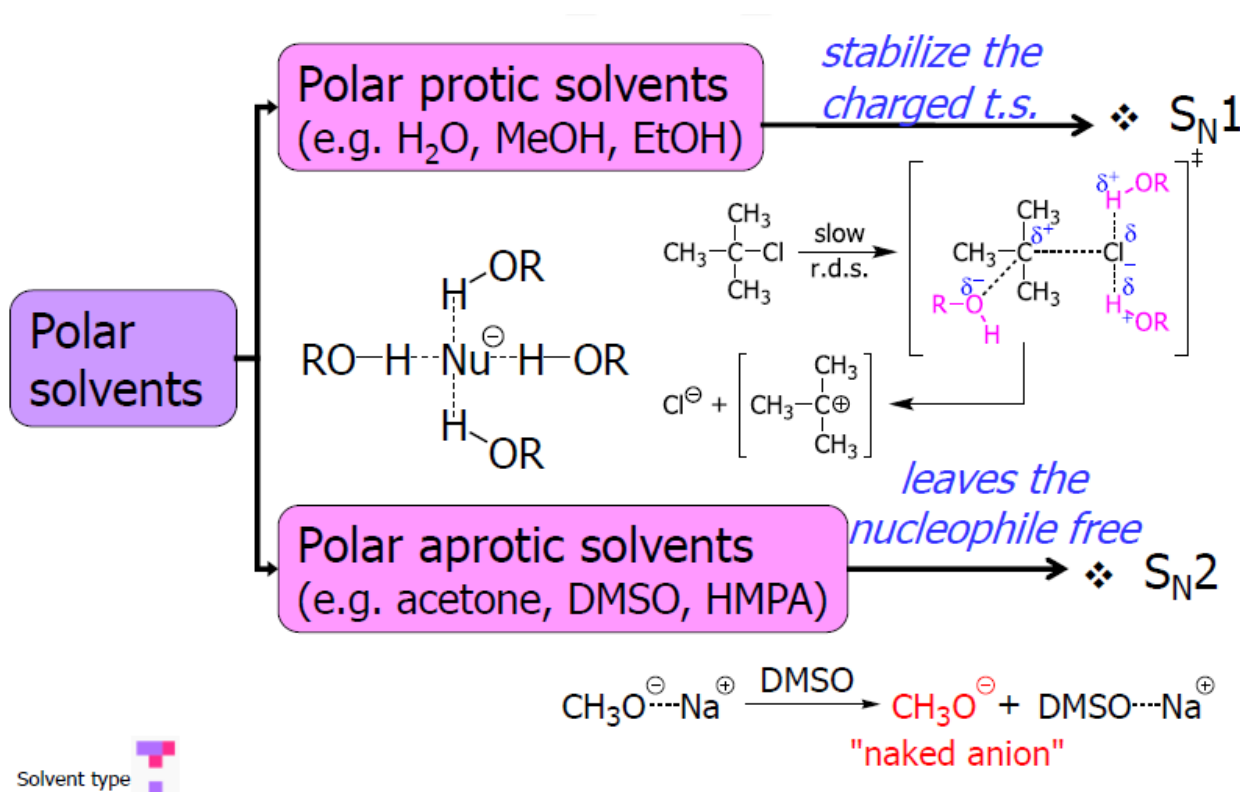
Problem: For each reaction, use the identity of the alkyl halide and nucleophile to determine which substitution mechanism occurs. Then determine which solvent affords the faster reaction.

a. $(CH_3)_3CBr$ + H_2O $\xrightarrow[\substack{\text{or} \\ (CH_3)_2C=O}]{H_2O}$ $(CH_3)_3COH$ + HBr

b. [structure with Cl] + CH_3OH $\xrightarrow[\substack{\text{or} \\ DMSO}]{CH_3OH}$ [structure with OCH_3] + HCl

c. [structure with Br] + ^-OH $\xrightarrow[\substack{\text{or} \\ DMF}]{H_2O}$ [structure with OH] + Br^-

d. [structure with H Cl] + CH_3O^- $\xrightarrow[\substack{\text{or} \\ HMPA}]{CH_3OH}$ [structure with H OCH_3] + Cl^-

The Nature of the Leaving Group

A better leaving group increases the rate of both **S$_N$1** and **S$_N$2** reactions.

➢ Leaving groups depart with the electron pair that was used to bond them to the substrate.
➢ The best leaving groups are those that become a relatively stable anion or a neutral molecule when they depart.
➢ Leaving groups that become weak bases are good leaving groups **because** weak bases stabilize a negative charge effectively.
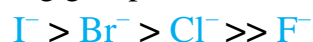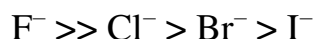
S$_N$1 Reaction (Rate-Limiting Step)

Transition state

S$_N$2 Reaction

Transition state
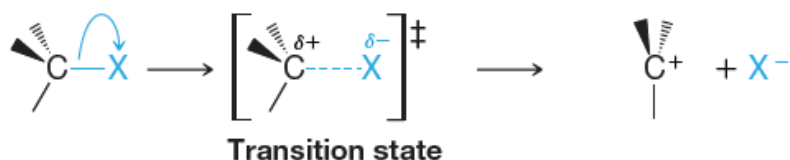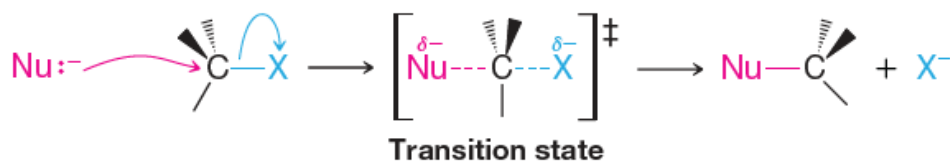
➤ An iodide ion is the best leaving group and a fluoride ion is the poorest:
$$I^- > Br^- > Cl^- \gg F^-$$
▪ The order is the opposite of the basicity in an aprotic solvent:
$$F^- \gg Cl^- > Br^- > I^-$$
➤ **Strongly basic ions** rarely act as leaving groups.
▪ Reactions like the following do **not** take place because hydroxide ion is a strong base.

This reaction does not take place because the leaving group is a strongly basic hydroxide ion.

▪ When an alcohol is dissolved in a strong acid, it can undergo substitution by a nucleophile.
  • **Because** the acid protonates the $^-$OH group of the alcohol, the leaving group no longer needs to be a hydroxide ion; it is now a molecule of water—a much weaker base than a hydroxide ion and a good leaving group:
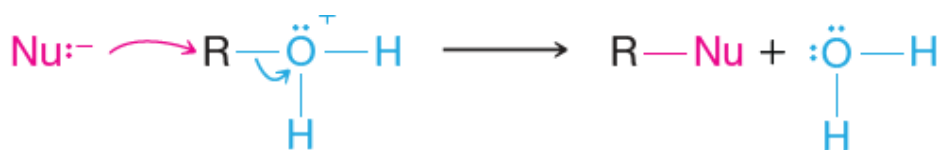
This reaction takes place because the leaving group is a weak base.

➤ **Very powerful bases** never act as leaving groups.
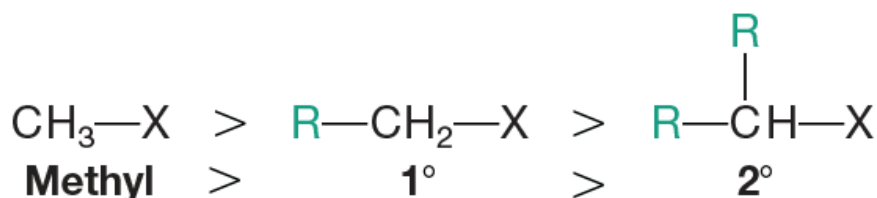▪ **For example:** hydride ions (H:$^-$) and alkanide ions (R:$^-$)

These are not leaving groups.
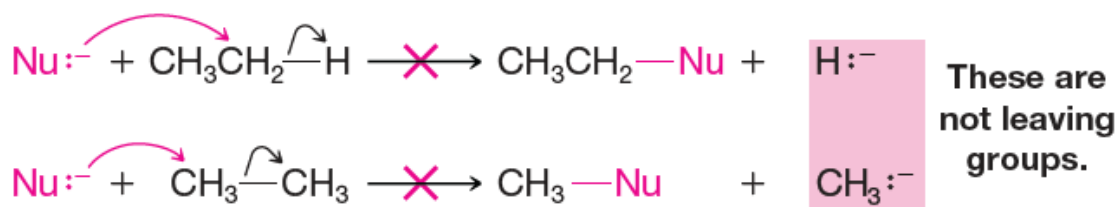
Summary of S$_N$1 versus S$_N$2 Reactions

S$_N$1: The Following Conditions Favor an S$_N$1 Reaction

1. A substrate that can form a relatively stable carbocation (such as a substrate with a leaving group at a tertiary position)
2. A relatively weak nucleophile
3. A polar, protic solvent such as EtOH, MeOH, or H$_2$O

S$_N$2: The Following Conditions Favor an S$_N$2 Reaction

1. A substrate with a relatively unhindered leaving group (such as a methyl, primary, or secondary alkyl halide).
   - The order of reactivity is

$$CH_3\text{—}X \quad > \quad R\text{—}CH_2\text{—}X \quad > \quad R\text{—}\overset{\displaystyle R}{\underset{|}{C}}H\text{—}X$$
$$\textbf{Methyl} \quad > \qquad\qquad \textbf{1°} \qquad > \qquad\quad \textbf{2°}$$

2. A strong nucleophile (usually negatively charged)
3. High concentration of the nucleophile
4. A polar, aprotic solvent

Factors Favoring S$_N$1 versus S$_N$2 Reactions

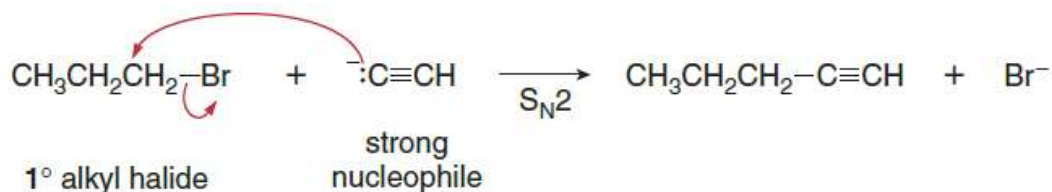| Factor	S$_N$1	S$_N$2
Substrate	3° (requires formation of a relatively stable carbocation)	Methyl > 1° > 2° (requires unhindered substrate)
Nucleophile	Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolysis)	Strong Lewis base, rate increased by high concentration of nucleophile
Solvent	Polar protic (e.g., alcohols, water)	Polar aprotic (e.g., DMF, DMSO)
Leaving group	I > Br > Cl > F for both SN1 and SN2 (the weaker the base after the group departs, the better the leaving group)	

Sample Problem 1

Determine the mechanism of nucleophilic substitution for each reaction and draw the products.

a. $CH_3CH_2CH_2-Br$ + $^-:C\equiv CH$ $\longrightarrow$ b. [cyclopentyl]$-Br$ + ^-CN $\longrightarrow$
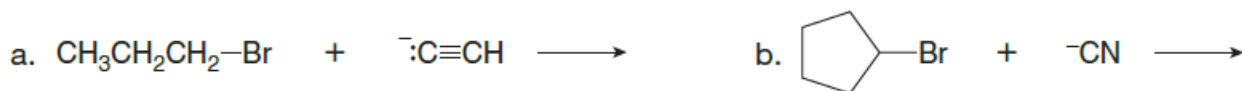
Solution

a. The alkyl halide is 1°, so it must react by an S_N2 mechanism with the nucleophile $^-:C\equiv CH$.

$$CH_3CH_2CH_2-Br \quad + \quad ^-:C\equiv CH \quad \xrightarrow{S_N2} \quad CH_3CH_2CH_2-C\equiv CH \quad + \quad Br^-$$
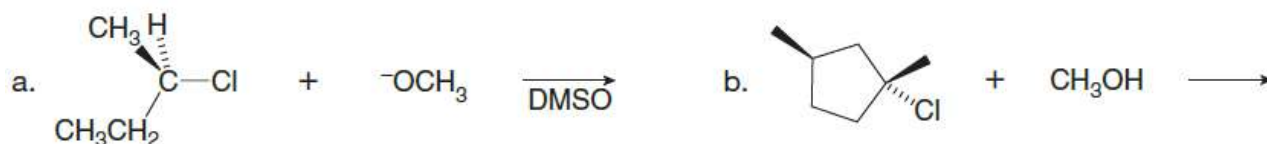
1° alkyl halide   strong nucleophile

b. The alkyl halide is 2°, so it can react by either the S_N1 or S_N2 mechanism. The strong nucleophile (^-CN) favors the S_N2 mechanism.

[cyclopentyl]$-Br$ + $^-:CN$ $\xrightarrow{S_N2}$ [cyclopentyl]$-CN$ + Br^-
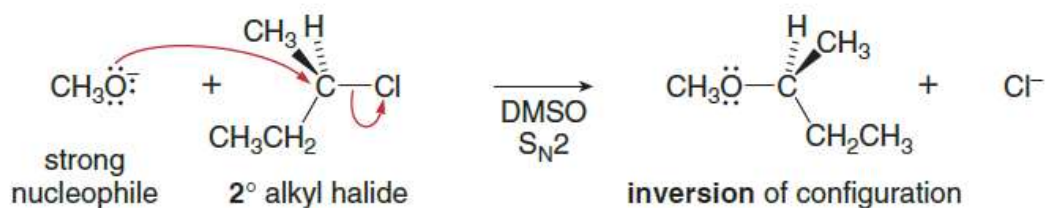
2° alkyl halide   strong nucleophile
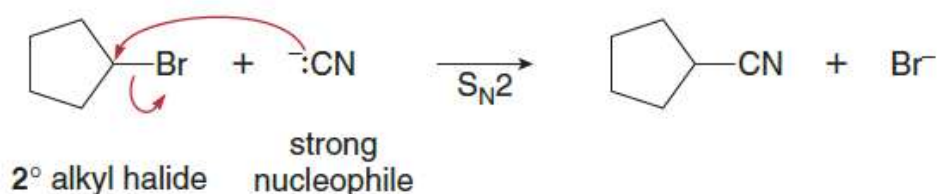
Sample Problem 2

Determine the mechanism of nucleophilic substitution for each reaction and draw the products, including stereochemistry.

a. $\underset{CH_3CH_2}{\overset{CH_3\ H}{C}}-Cl$ + $^-OCH_3$ $\xrightarrow{DMSO}$ b. [structure]$_{CI}$ + CH_3OH $\longrightarrow$

Solution

a. The 2° alkyl halide can react by either the S_N1 or S_N2 mechanism. The strong nucleophile ($^-OCH_3$) favors the S_N2 mechanism, as does the polar aprotic solvent (DMSO). S_N2 reactions proceed with inversion of configuration.

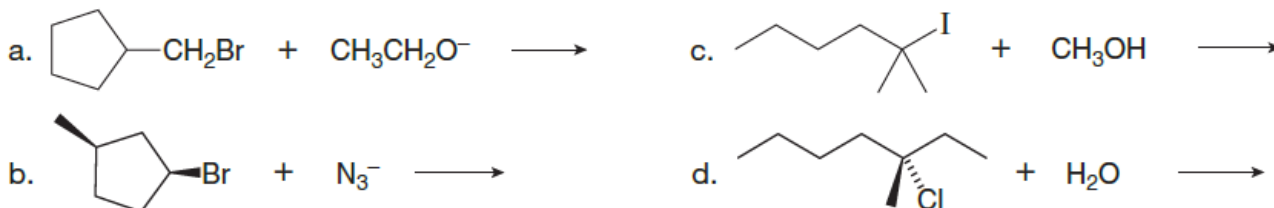$$CH_3\ddot{O}: \quad + \quad \underset{CH_3CH_2}{\overset{CH_3\ H}{C}}-Cl \quad \xrightarrow[S_N2]{DMSO} \quad CH_3\ddot{O}-\underset{CH_2CH_3}{\overset{H\ CH_3}{C}} \quad + \quad Cl^-$$

strong nucleophile   2° alkyl halide   **inversion** of configuration

b. The alkyl halide is 3°, so it reacts by an S_N1 mechanism with the weak nucleophile CH_3OH. S_N1 reactions proceed with racemization at a single stereogenic center, so two products are formed.
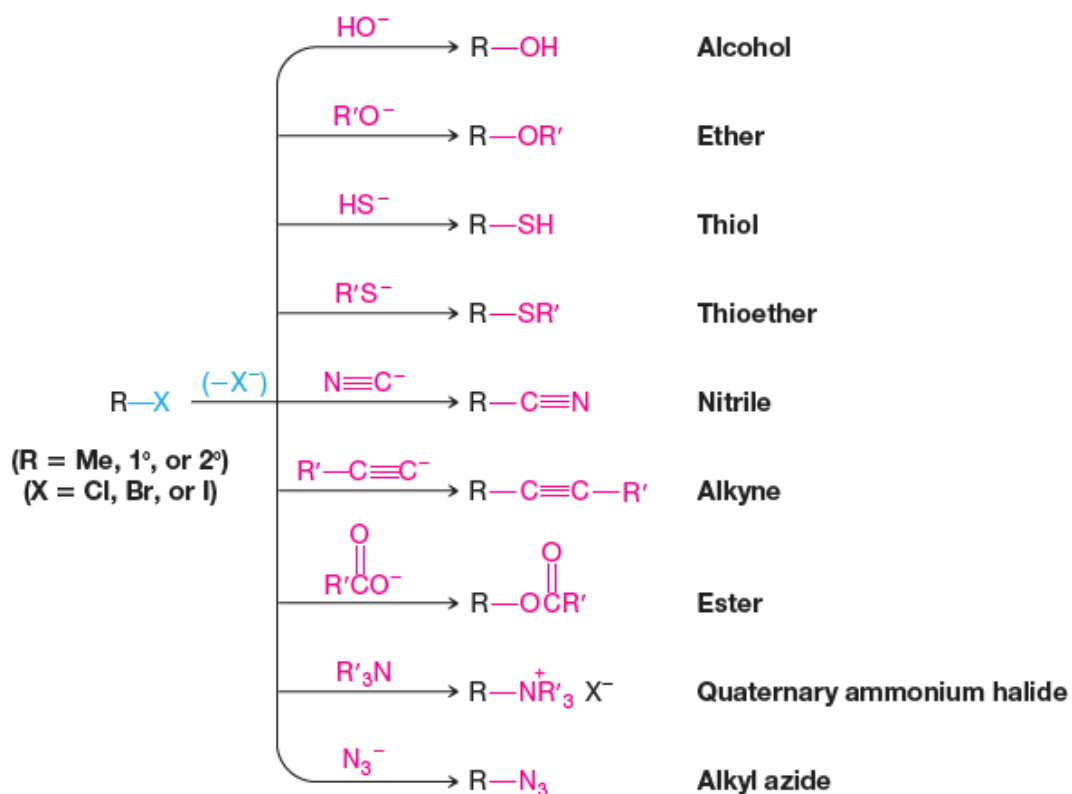
3° alkyl halide   weak nucleophile   two products of nucleophilic substitution
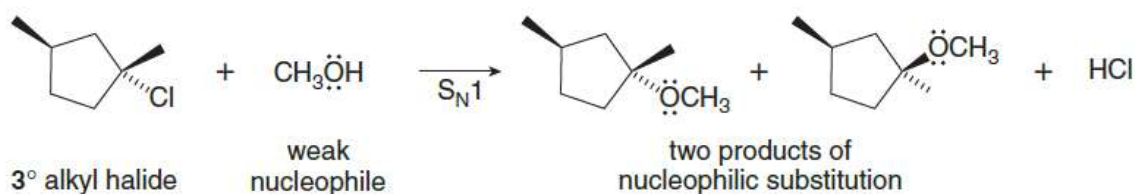
Problem

Determine the mechanism and draw the products of each reaction. Include the stereochemistry at all stereogenic centers.

a. ⬠—CH$_2$Br + CH$_3$CH$_2$O$^-$ ⟶

c. (structure) I + CH$_3$OH ⟶

b. (structure) Br + N$_3^-$ ⟶

d. (structure) Cl + H$_2$O ⟶

Organic Synthesis:
Functional Group Transformations Using S$_N$2 Reactions

➤ S$_N$2 reactions are highly useful in organic synthesis **because** they enable us to convert one functional group into another—a process that is called a **functional group transformation** or a **functional group interconversion**.
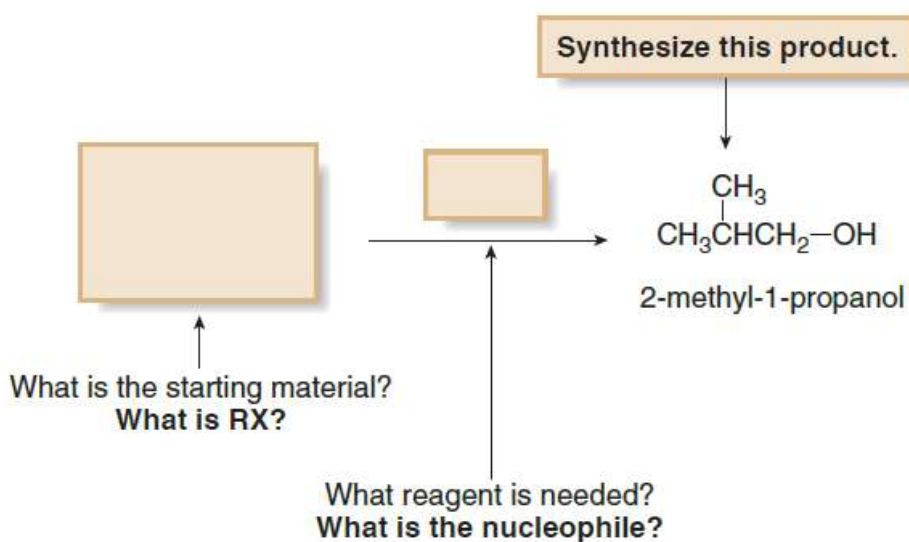

Nucleophile	Product	Name
HO$^-$	R—OH	Alcohol
R'O$^-$	R—OR'	Ether
HS$^-$	R—SH	Thiol
R'S$^-$	R—SR'	Thioether
N≡C$^-$	R—C≡N	Nitrile
R'—C≡C$^-$	R—C≡C—R'	Alkyne
R'CO$_2^-$	R—OCR' (ester)	Ester
R'$_3$N	R—NR'$_3$ X$^-$	Quaternary ammonium halide
N$_3^-$	R—N$_3$	Alkyl azide

R—X (R = Me, 1°, or 2°) (X = Cl, Br, or I) ──(−X$^-$)→

- Alkyl chlorides and bromides are also easily converted to alkyl iodides by nucleophilic substitution reactions.

$$R-Cl \text{ or } R-Br \xrightarrow{I^-} R-I \, (+ \, Cl^- \text{ or } Br^-)$$
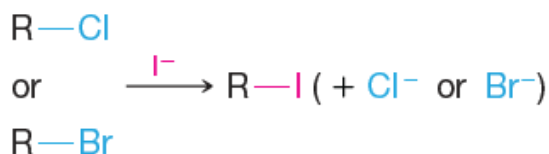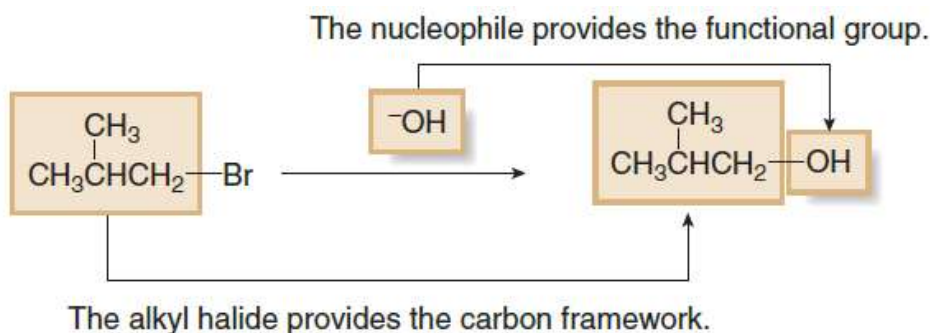
Nucleophilic Substitution and Organic Synthesis

- ➢ If we are using nucleophilic substitution, we must determine what alkyl halide and what nucleophile can be used to form a specific product.
- ➢ **For example:** that we are asked to prepare $(CH_3)_2CHCH_2OH$ (2-methyl-1-propanol) from an alkyl halide and any required reagents.

Synthesize this product.

$$CH_3CHCH_2-OH$$
2-methyl-1-propanol

What is the starting material?
What is RX?

What reagent is needed?
What is the nucleophile?

- To determine the two components needed for the synthesis
  - The carbon atoms come from the organic starting material, in this case a 1° alkyl halide [$(CH_3)_2CHCH_2Br$].
  - The functional group comes from the nucleophile, ⁻OH in this case. With these two components, we can "fill in the boxes" to complete the synthesis.

The nucleophile provides the functional group.

$$CH_3CHCH_2-Br \quad \xrightarrow{^-OH} \quad CH_3CHCH_2-OH$$

The alkyl halide provides the carbon framework.

Elimination Reactions of Alkyl Halides

➢ **Elimination reactions** introduce π bonds into organic compounds, so they can be used to synthesize **alkenes** and **alkynes**.

➢ Alkyl halides undergo elimination reactions with Brønsted–Lowry bases.

- ▪ The elements of HX are lost and an alkene is formed.
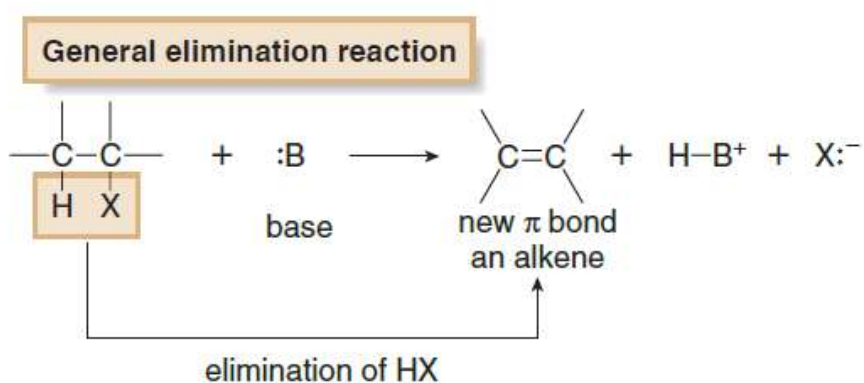
- ▪ Removal of the elements of HX, called **dehydrohalogenation**.
- ▪ Dehydrohalogenation is an example of **β elimination,** because it involves loss of elements from two adjacent atoms: the **α carbon** bonded to the leaving group X, and the **β carbon** adjacent to it.
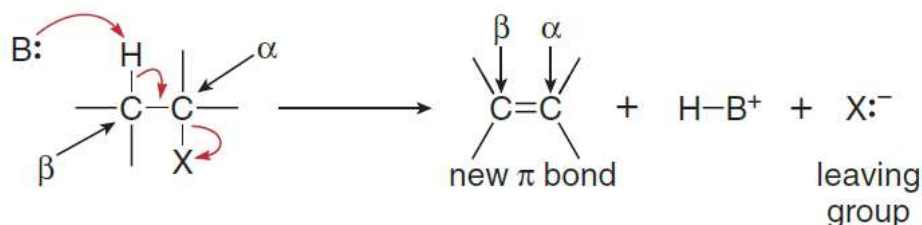
- • The base (**B:**) removes a proton on the **β** carbon, thus forming H –B$^+$.
- • The electron pair in the **β** C – H bond forms the new π bond between the **α** and **β** carbons.
- • The electron pair in the C – X bond ends up on halogen, forming the leaving group :X$^-$.
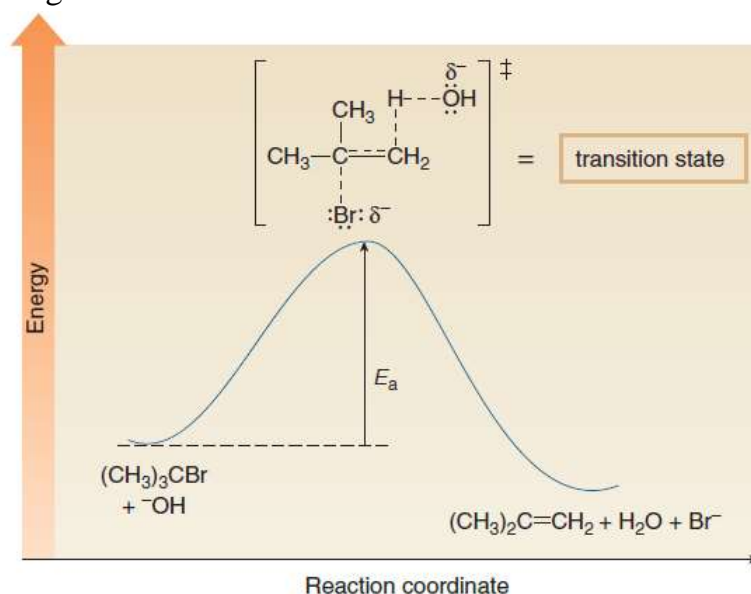

The Mechanisms of Elimination

The E2 Mechanism

➢ The most common mechanism for dehydrohalogenation is the E2 mechanism.

E2 reaction

$$CH_3-\underset{\underset{Br}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_3 \xrightarrow{\ ^-OH\ } \underset{CH_3}{\overset{CH_3}{\diagup}}C=CH_2 \ + \ H_2O \ + \ Br^-$$
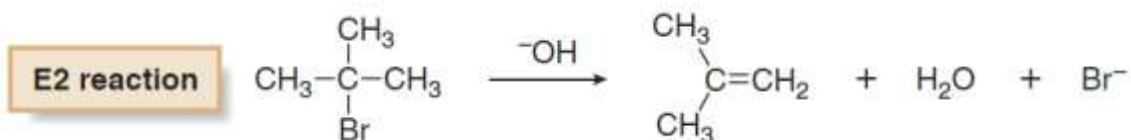
Kinetics

➢ An E2 reaction exhibits **second-order kinetics**.

➢ The reaction is **bimolecular**.

➢ **Rate = k[(CH₃)₃CBr][⁻OH]**

➢ Free Energy Diagram of E2 Reaction

A One-Step Mechanism

Reaction

$$C_2H_5O^- \ + \ CH_3CHBrCH_3 \ \longrightarrow \ CH_2{=}CHCH_3 \ + \ C_2H_5OH \ + \ Br^-$$

Mechanism
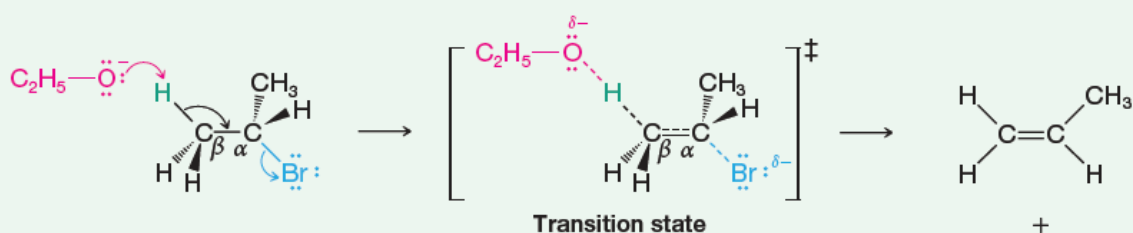
|		
The basic ethoxide ion begins to remove a proton from the β carbon using its electron pair to form a bond to it. At the same time, the electron pair of the β C—H bond begins to move in to become the π bond of a double bond, and the bromine begins to depart with the electrons that bonded it to the α carbon.	Partial bonds in the transition state extend from the oxygen atom that is removing the β hydrogen, through the carbon skeleton of the developing double bond, to the departing leaving group. The flow of electron density is from the base toward the leaving group as an electron pair fills the π bonding orbital of the alkene.	At completion of the reaction, the double bond is fully formed and the alkene has a trigonal planar geometry at each carbon atom. The other products are a molecule of ethanol and a bromide ion.

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The Base

➢ The base appears in the rate equation, so the rate of the E2 reaction increases as the strength of the base increases.

Two useful bases for E2 reactions
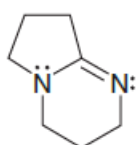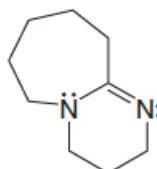
DBN   DBU

The Leaving Group

➢ Because the bond to the leaving group is partially broken in the transition state, the better the leaving group the faster the E2 reaction.

Order of reactivity of RX:

R—F   R—Cl   R—Br   R—I

Increasing leaving group ability
Increasing rate of the E2 reaction

The Solvent

➢ Polar aprotic solvents increase the rate of E2 reactions.
➢ Because **polar aprotic solvents** like $(CH_3)_2C=O$ do not solvate anions well, a negatively charged base is not "hidden" by strong interactions with the solvent, and the base is stronger.
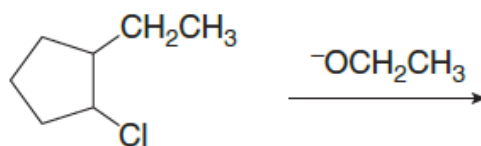➢ A stronger base increases the reaction rate.

The Identity of the Alkyl Halide

➢ The S_N2 and E2 mechanisms differ in how the R group affects the reaction rate.
➢ As the number of R groups on the carbon with the leaving group increases, the rate of the E2 reaction increases.
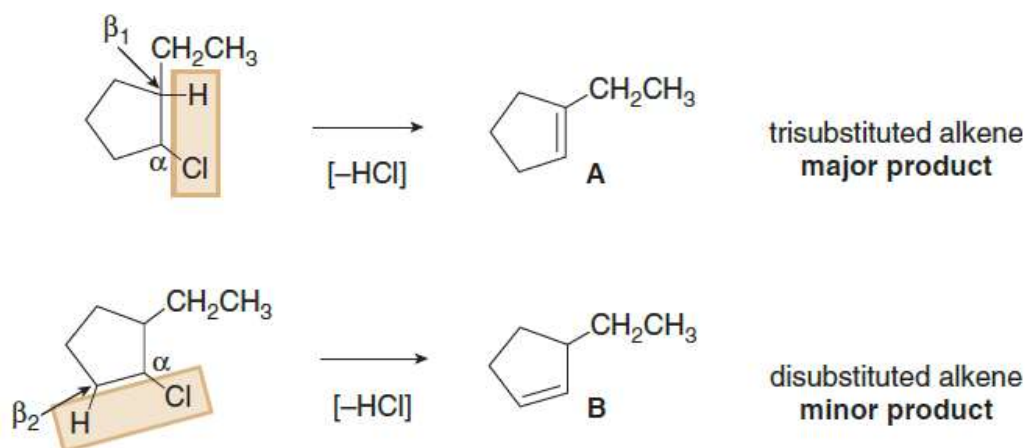

Increasing rate of an S_N2 reaction

$RCH_2—X$ $R_2CH—X$ $R_3C—X$

1°   2°   3°

Increasing rate of an E2 reaction
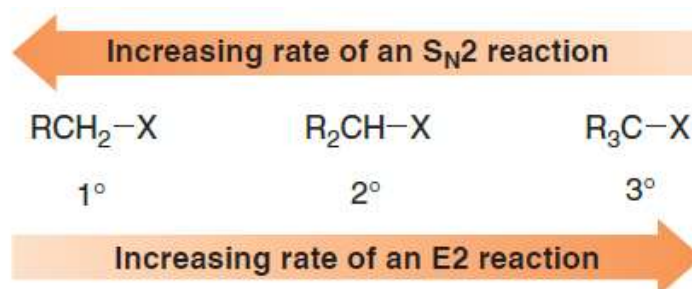
➤ Increasing the number of R groups on the carbon with the leaving group forms more highly substituted, more stable alkenes in E2 reactions.

■ **For example:** the E2 reaction of a 1° alkyl halide (1-bromobutane) forms a monosubstituted alkene, whereas the E2 reaction of a 3° alkyl halide (2-bromo-2-methylpropane) forms a disubstituted alkene.

1-bromobutane → monosubstituted alkene less stable

2-bromo-2-methylpropane → disubstituted alkene more stable
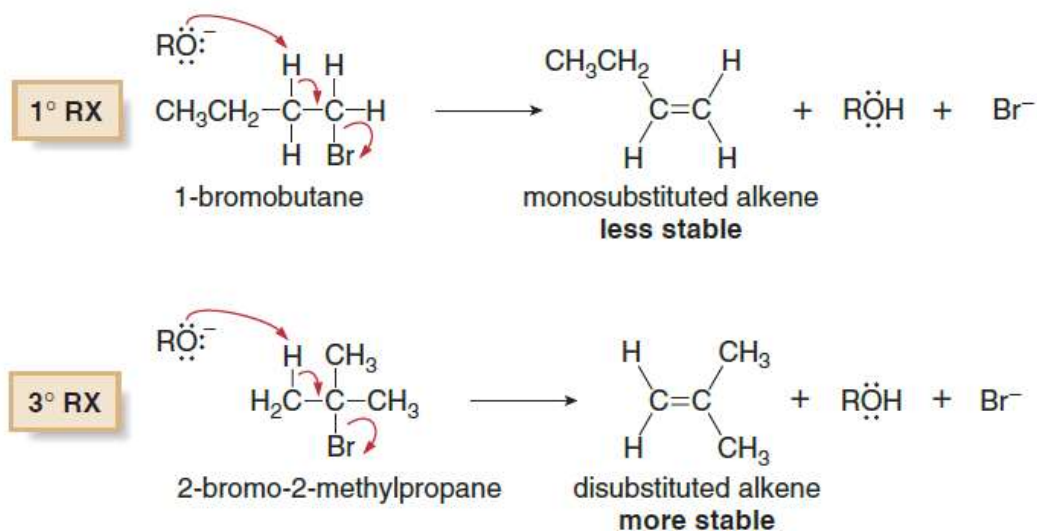
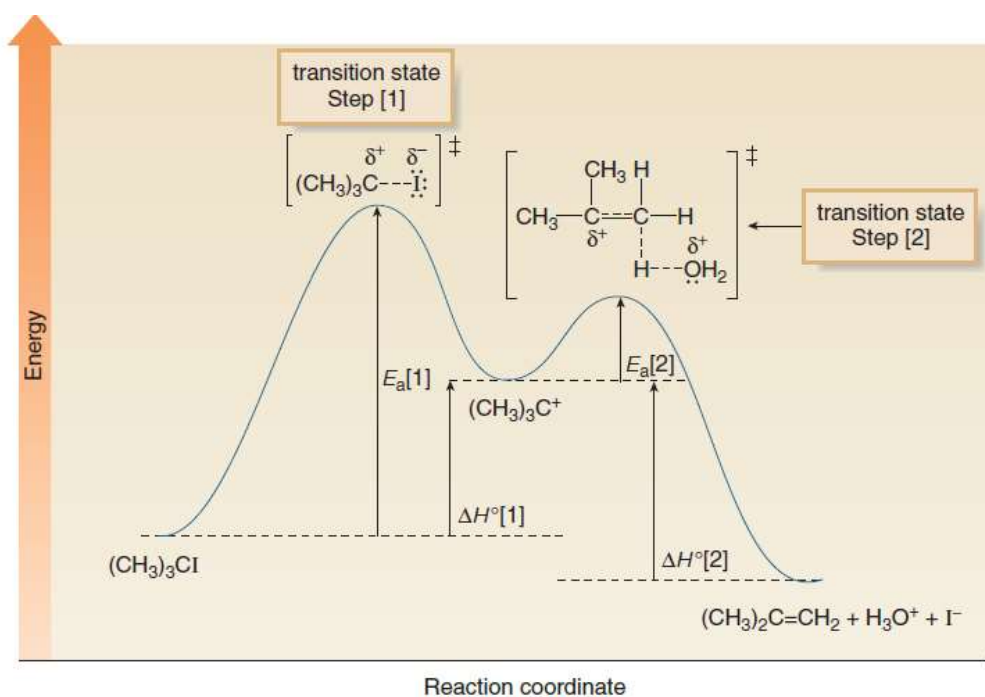**Sample Problem** Predict the major product in the following E2 reaction.

Solution

A — trisubstituted alkene major product

B — disubstituted alkene minor product

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The E1 Mechanism

E1 reaction

$$CH_3-\underset{\underset{I}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_3 \xrightarrow{H_2O} \underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}=CH_2 \quad + \quad H_3O^+ \quad + \quad I^-$$
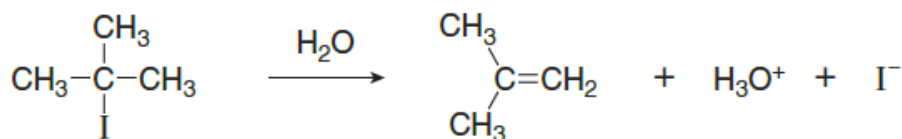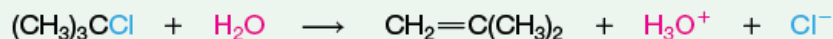
Kinetics

➢ An E1 reaction exhibits **second-order kinetics**.
➢ The reaction is **unimolecular**.
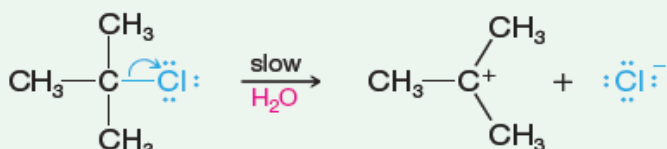➢ **Rate = k[(CH₃)₃CI]**
➢ Free Energy Diagram of E1 Reaction

A Two-Step Mechanism

Reaction

$$(CH_3)_3CCl \quad + \quad H_2O \quad \longrightarrow \quad CH_2{=}C(CH_3)_2 \quad + \quad H_3O^+ \quad + \quad Cl^-$$
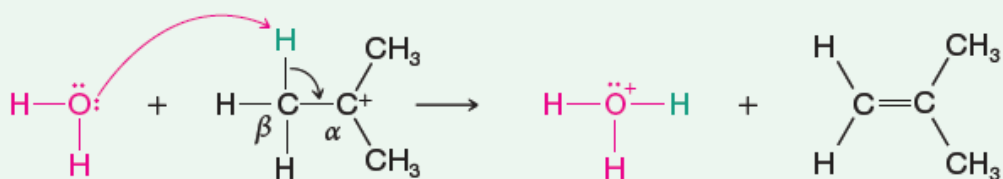
Mechanism

Step 1

Aided by the polar solvent, a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the relatively stable 3° carbocation and a chloride ion. The ions are solvated (and stabilized) by surrounding water molecules.

Step 2

A molecule of water removes one of the hydrogens from the β carbon of the carbocation. These hydrogens are acidic due to the adjacent positive charge. At the same time an electron pair moves in to form a double bond between the α and β carbon atoms.
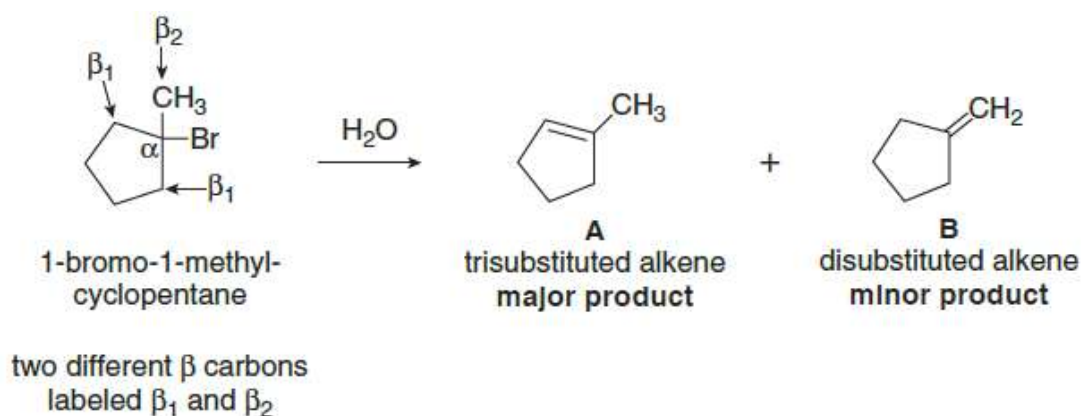
This step produces the alkene and a hydronium ion.

➢ In an E1 reaction, the leaving group comes off *before* the a proton is removed, and the reaction occurs in two steps.
➢ In an E2 reaction, the leaving group comes off *as* the a proton is removed, and the reaction occurs in one step.

Characteristics of E1 Reactions

1. The rate of an E1 reaction increases as the number of R groups on the carbon with the leaving group increases.
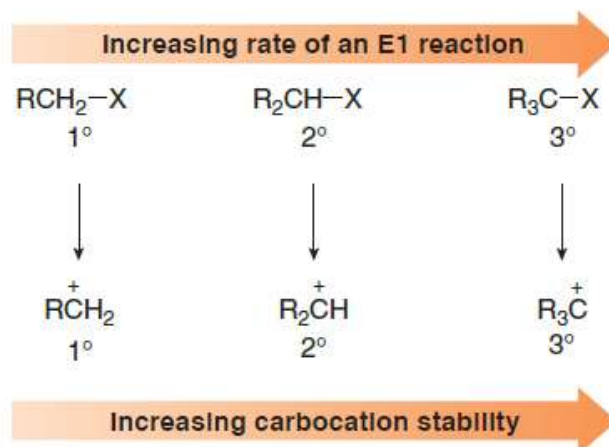
2. Weak bases favor E1 reactions **because** the base does not appear in the rate equation.
   - Strong bases like ^-OH and ^-OR favor E2 reactions, whereas weaker bases like H_2O and ROH favor E1 reactions.

3. E1 reactions are regioselective, favoring formation of the more substituted, more stable alkene.
   - **For example:** E1 elimination of HBr from 1-bromo-1-methylcyclopentane yields alkenes **A** and **B**. **A**, having the more substituted double bond, is the major product.

Characteristic	E2	E1
Kinetics	Second order	First order
Mechanism	One step	Two steps
Identity of R	More substituted halides react fastest. **Rate:** $R_3CX > R_2CHX > RCH_2X$	More substituted halides react fastest. Rate: $R_3CX > R_2CHX > RCH_2X$
Base	Favored by strong bases	Favored by weaker bases such as H_2O and ROH
Leaving group	Better leaving group → faster reaction	A better leaving group makes the reaction faster because the bond to the leaving group is partially broken in the rate-determining step.
Solvent	Favored by polar aprotic solvents	Polar protic solvents that solvate the ionic intermediates are needed.

Elimination and Substitution Reactions Compete With Each Other

➢ All nucleophiles are potential bases and all bases are potential nucleophiles **because** the reactive part of both nucleophiles and bases is an unshared electron pair.

➢ Substitution reactions are always in competition with elimination reactions.

➢ Different factors can affect which type of reaction is favoured.

S$_N$2 versus E2

➢ S$_N$2 and E2 reactions are both favored by a high concentration of a strong nucleophile or base.

- When the nucleophile (base) attacks a β hydrogen atom, elimination occurs.
- When the nucleophile attacks the carbon atom bearing the leaving group, substitution results
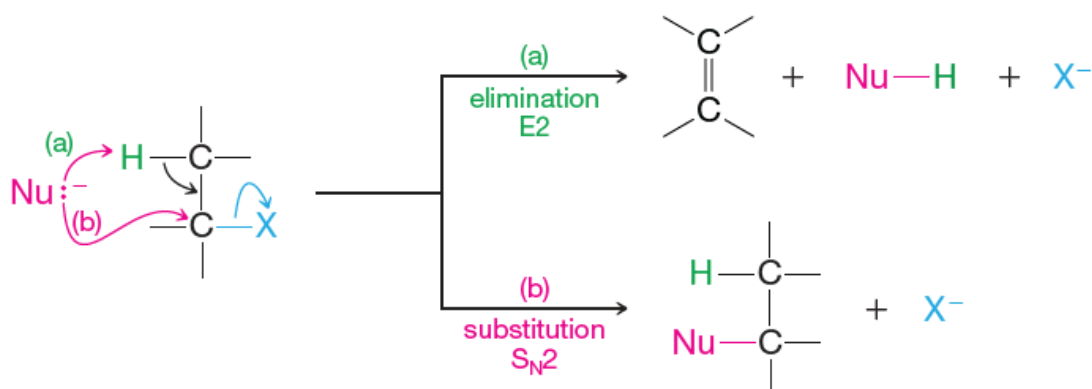
# Parameters affecting on Substitution and Elimination

Primary Substrate

➢ When the substrate is a primary halide and the base is strong and unhindered, substitution is highly favored **because** the base can easily approach the carbon bearing the leaving group:

Primary

S$_N$2 Major (90%)

+

E2 Minor (10%)
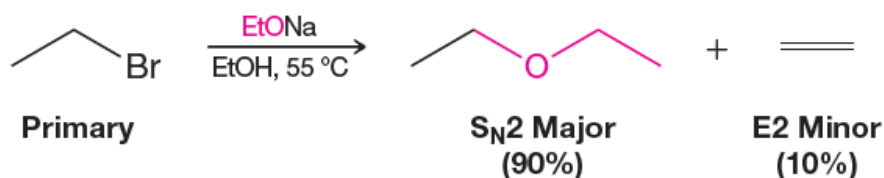
Secondary Substrate

➢ With *secondary* halides, a strong base favors elimination **because** steric hindrance in the substrate makes substitution more difficult:


Secondary

E2 Major (79%)

+

S$_N$2 Minor (21%)
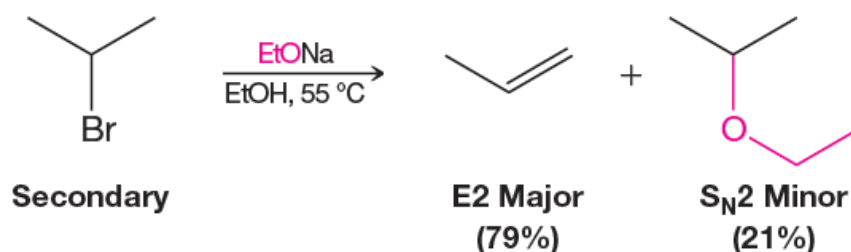
Tertiary Substrate

➢ With *tertiary* halides, steric hindrance in the substrate is severe and an S$_N$2 reaction cannot take place.
➢ Elimination is highly *favored*, especially when the reaction is carried out at higher temperatures.
➢ Any substitution that occurs must take place through an S$_N$1 mechanism:

Without Heating

Tertiary

E2 Major (91%)

+

S$_N$1 Minor (9%)

With Heating

Tertiary

E2 + E1 Only (100%)

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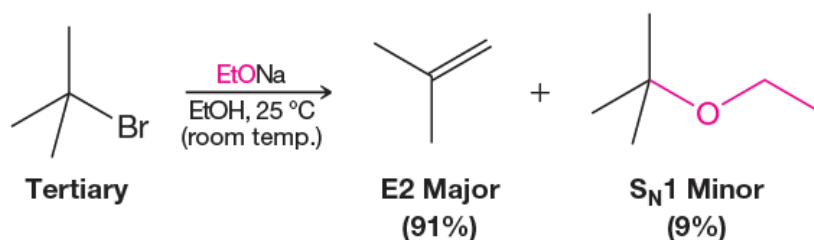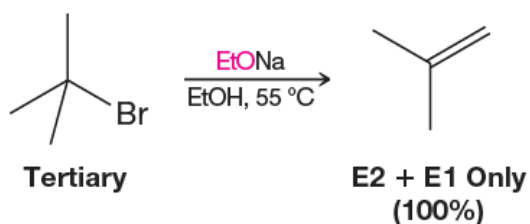
Temperature

➢ Increasing the reaction temperature favors elimination (E1 and E2) over substitution.

Size of the Base/Nucleophile

➢ The bulky methyl groups of the *tert-* butoxide ion inhibit its reaction by substitution, allowing elimination reactions to take precedence.

➢ **For example:** The relatively unhindered methoxide ion reacts with octadecyl bromide primarily by *substitution*, whereas the bulky *tert*-butoxide ion gives mainly *elimination*.

### Unhindered (Small) Base/Nucleophile
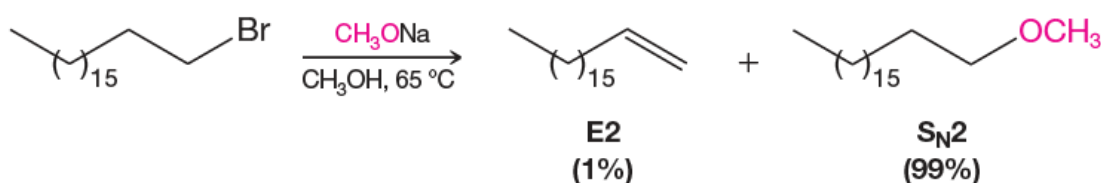
Hindered Base/Nucleophile
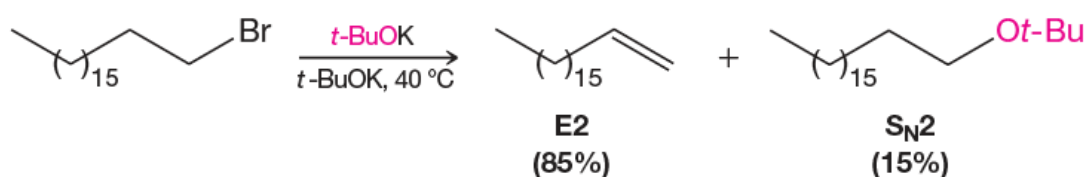
Basicity and Polarizability

➢ Use of a strong, slightly polarizable base such as hydroxide ion, amide ion (NH_2-), or alkoxide ion (especially a hindered one) tends to increase the likelihood of elimination (E2).

➢ Use of a weakly basic ion such as a chloride ion (Cl^-) or an acetate ion ($CH_3CO_2^-$) or a weakly basic and highly polarizable one such as Br^-, I^-, or RS^- increases the likelihood of substitution (S_N2).
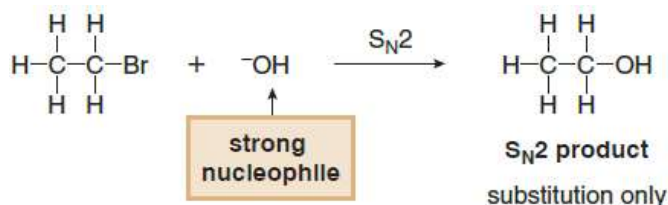
CH$_3$-C-O$^{\ominus}$
(weak base)

S$_N$2: 100%   E2: 0%

EtO$^{\ominus}$
(strong base)

S$_N$2: 20%   E2: 80%
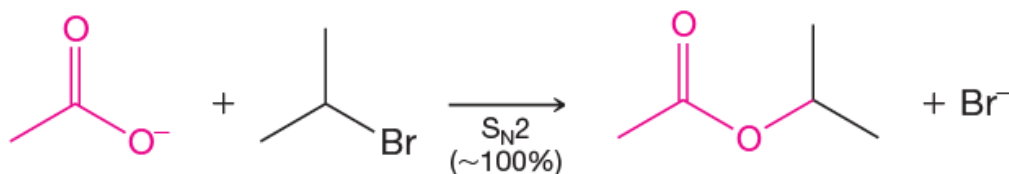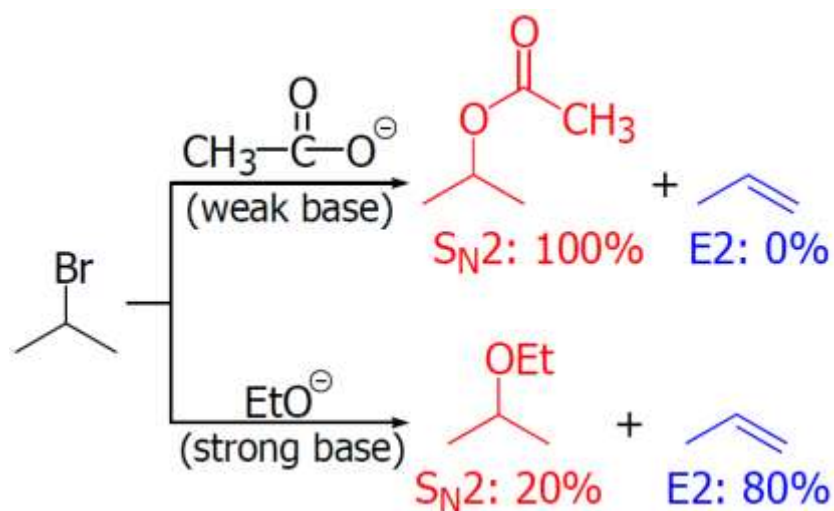
Determining whether an alkyl halide reacts by an S$_N$1, S$_N$2, E1, or E2 mechanism

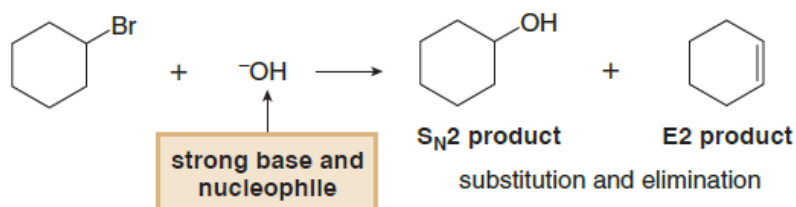| [1] 1° Alkyl halides (RCH$_2$X react by S$_N$2 and E2 mechanisms.)	
▪ **With strong nucleophiles**	• **Substitution occurs by an S$_N$2 mechanism.** • **Rationale:** A strong base or nucleophile favors S$_N$2 or E2, but 1° halides are the least reactive halide type in elimination; therefore, only an S$_N$2 reaction occurs. • **Example:**
▪ **With strong, sterically hindered bases**	• **Elimination occurs by an E2 mechanism.** • **Rationale:** A strong, sterically hindered base cannot act as a nucleophile, so elimination occurs and the mechanism is E2. • **Example:**
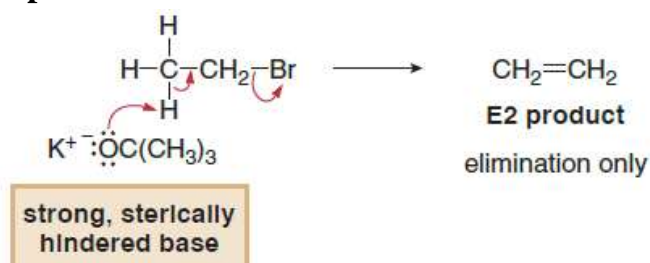
[1] 2° Alkyl halides (R₂CHX react by all mechanisms.)
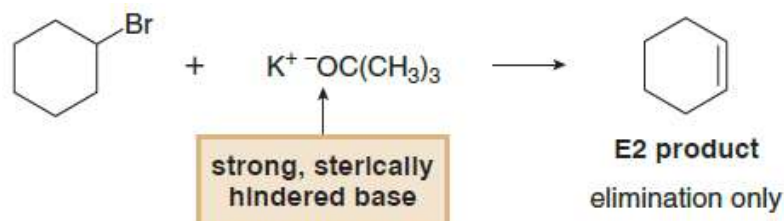
|	
▪ **With strong bases and nucleophiles**	• **A mixture of S$_N$2 and E2 products results.** • **Rationale:** A strong base that is also a strong nucleophile gives a mixture of S$_N$2 and E2 products. • **Example:**
▪ **With strong, sterically hindered bases**	• **Elimination occurs by an E2 mechanism.** • **Rationale:** A strong, sterically hindered base cannot act as a nucleophile, so elimination occurs and the mechanism is E2. • **Example:**
▪ **With weak nucleophiles or bases**	• **A mixture of S$_N$1 and E1 products results.** • **Rationale:** A weak base or nucleophile favors S$_N$1 and E1 mechanisms, and both occur. • **Example:**
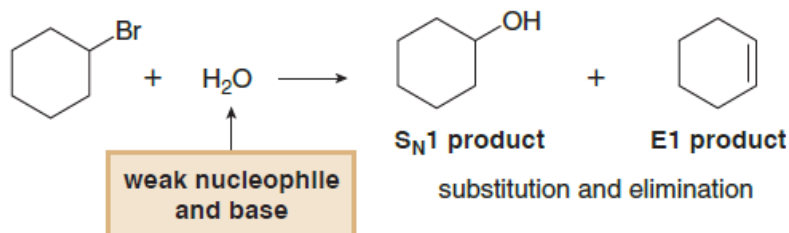
[1] 1° Alkyl halides (RCH₂X react by S$_N$2 and E2 mechanisms.)

▪ **With strong bases**	• **Elimination occurs by an E2 mechanism.** • **Rationale:** A strong base or nucleophile favors an S$_N$2 or E2 mechanism, but 3° halides are too sterically hindered to undergo an S$_N$2 reaction, so only E2 elimination occurs. • **Example:**

	E2 product elimination only
▪ **With weak nucleophiles or bases**	• **A mixture of S_N1 and E1 products results.** • **Rationale:** A weak base or nucleophile favors S_N1 and E1 mechanisms, and both occur. • **Example:**