

Chapter 6

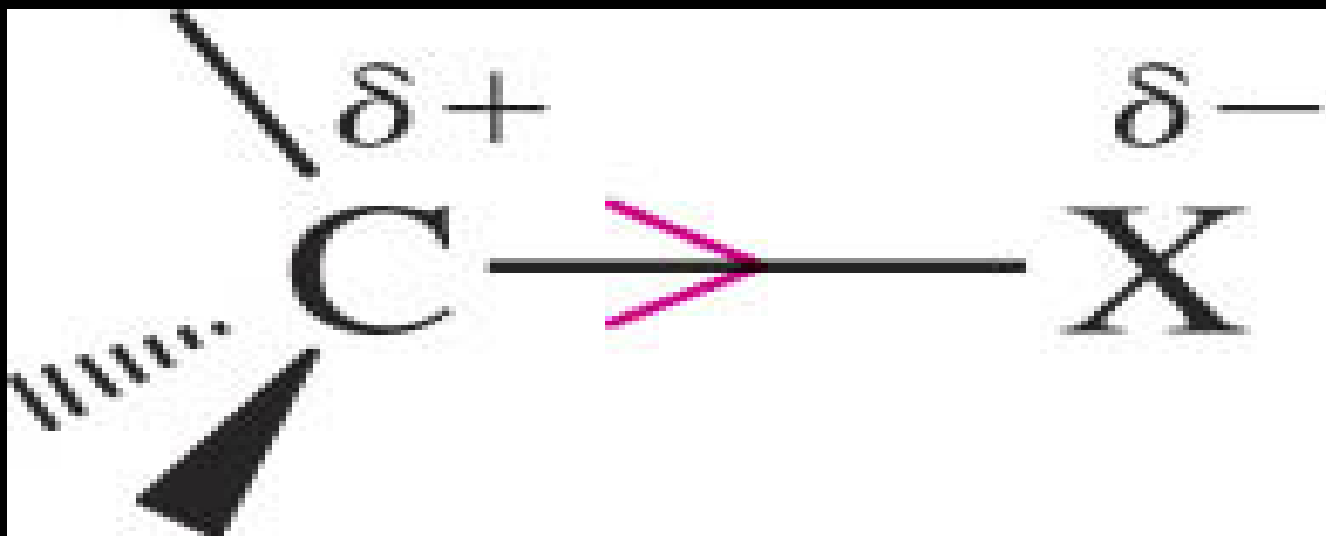
Alkyl Halides

NEPHAR 109 Organic Chemistry

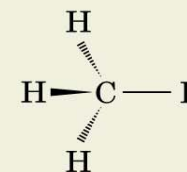
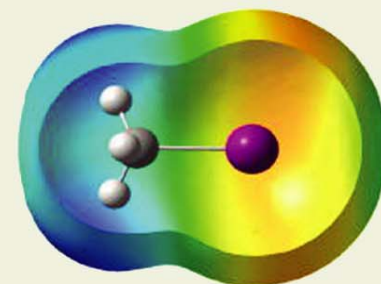
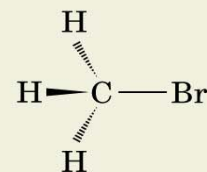
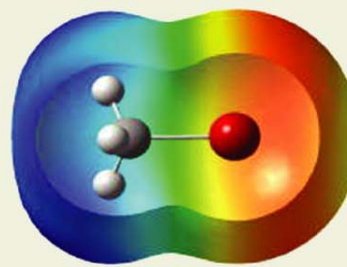
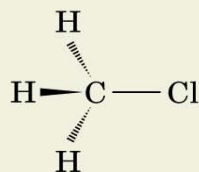
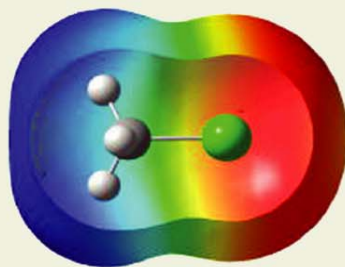
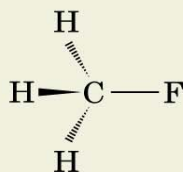
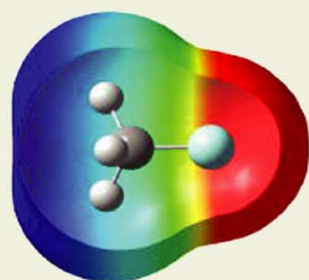
Assist.Prof. Banu Keşanlı

6.1 Alkyl Halides

- The polarity of a carbon-halogen bond leads to the carbon having a partial positive charge
- In alkyl halides this polarity causes the carbon to become activated to substitution reactions with nucleophiles



- Carbon-halogen bonds get less polar, longer and weaker in going from fluorine to iodine



C—X Bond
length (Å)
C—X Bond
strength
(kJ mol⁻¹)

1.39

472

1.78

350

1.93

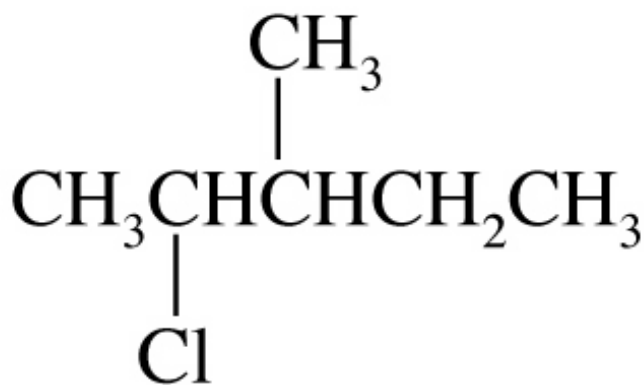
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2.14

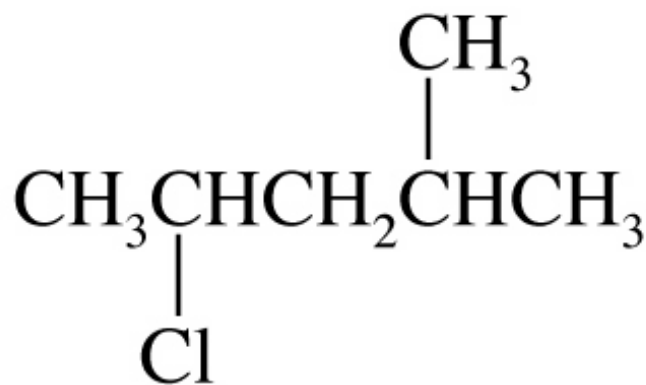
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4.3E Nomenclature of Alkyl Halides (RX)

- In IUPAC nomenclature halides are named as substituents on the parent chain
- Halo and alkyl substituents are considered to be of equal ranking



2-Chloro-3-methylpentane



2-Chloro-4-methylpentane

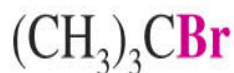
- Common nomenclature of simple alkyl halides is accepted by IUPAC and still used



Ethyl
chloride



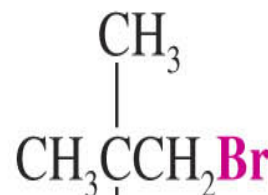
Isopropyl
bromide



tert-Butyl
bromide

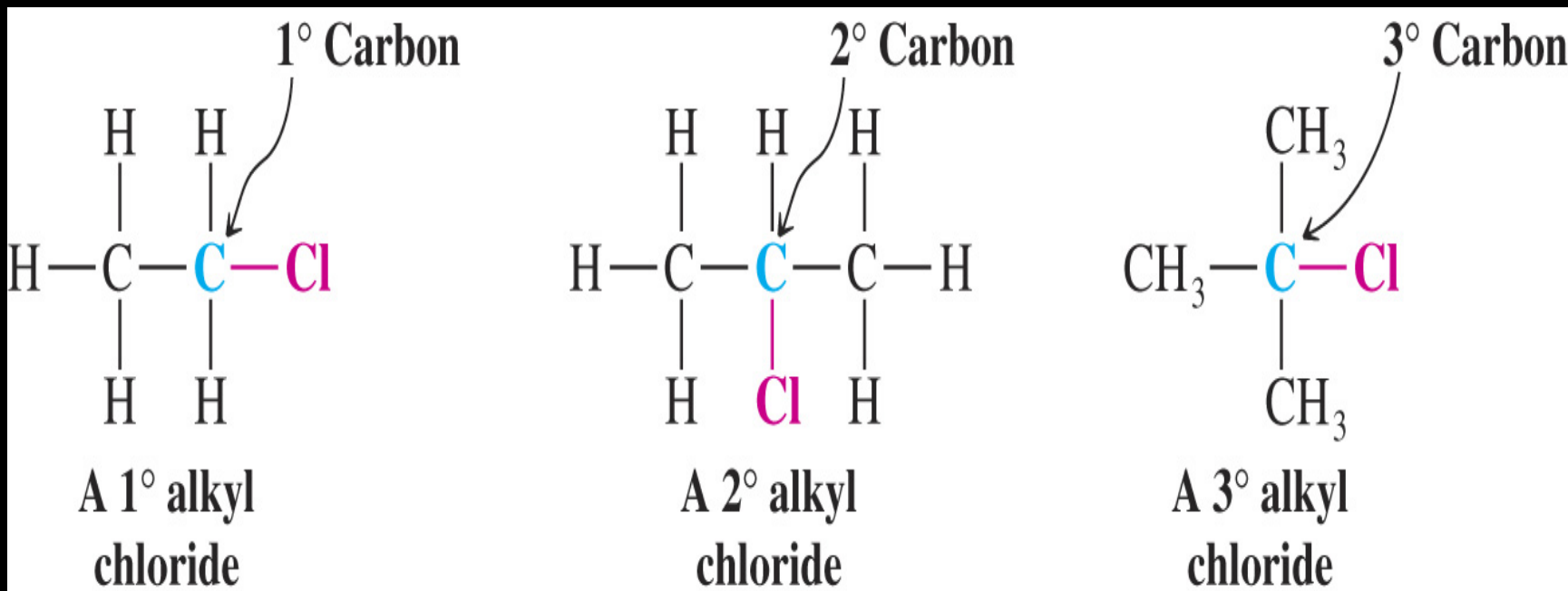


Isobutyl
chloride



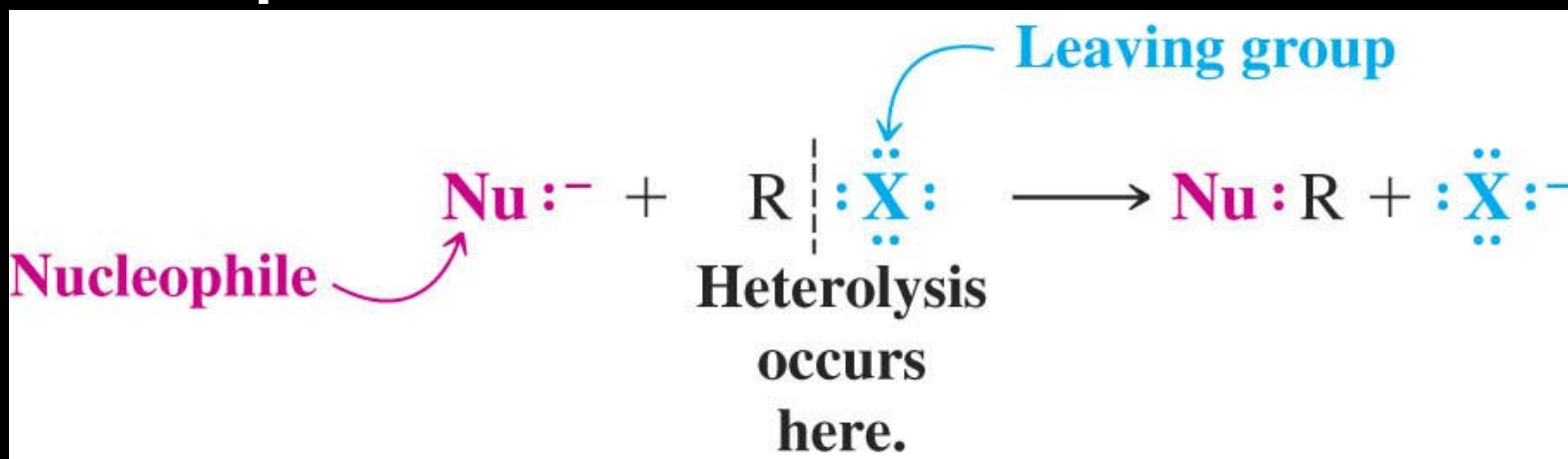
Neopentyl
bromide

- If the carbon is attached to one other carbon that carbon is **primary (1°)** and the alkyl halide is also 1°
- If the carbon is attached to two other carbons, that carbon is **secondary (2°)** and the alkyl halide is 2°
- If the carbon is attached to three other carbons, the carbon is **tertiary (3°)** and the alkyl halide is 3°

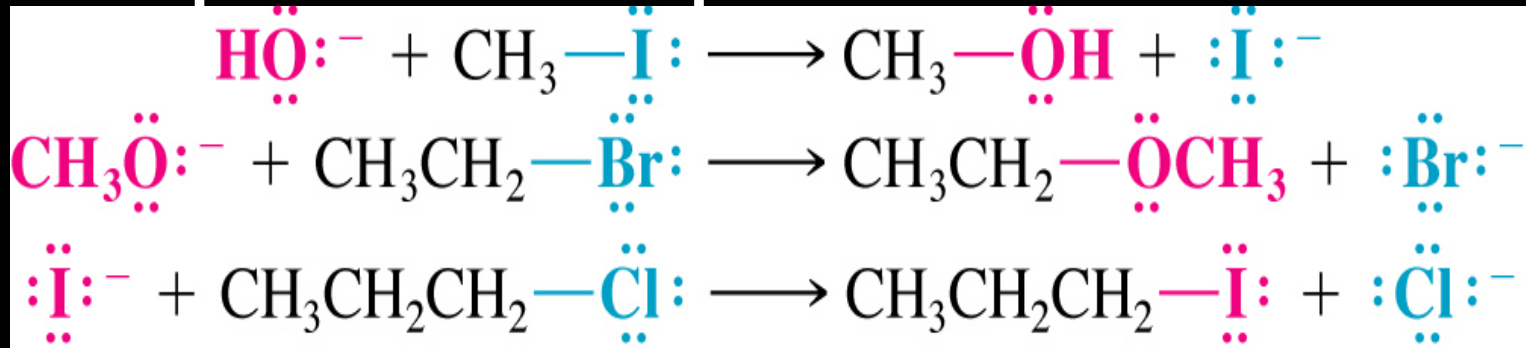


6.3 Nucleophilic Substitution Reactions (S_N)

- In this reaction a nucleophile is species with an unshared electron pair which reacts with an electron deficient carbon
- A leaving group is substituted by a nucleophile

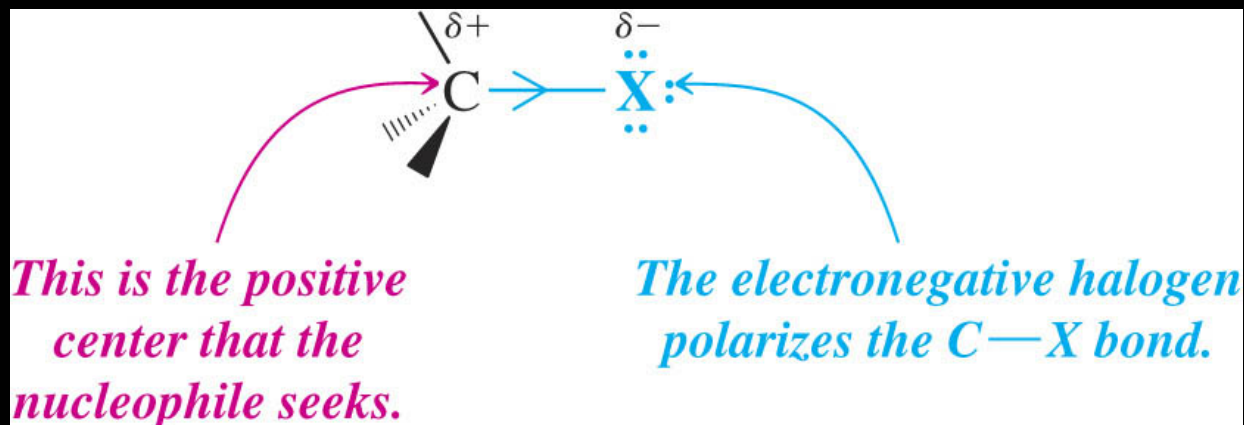


- Examples of nucleophilic substitution

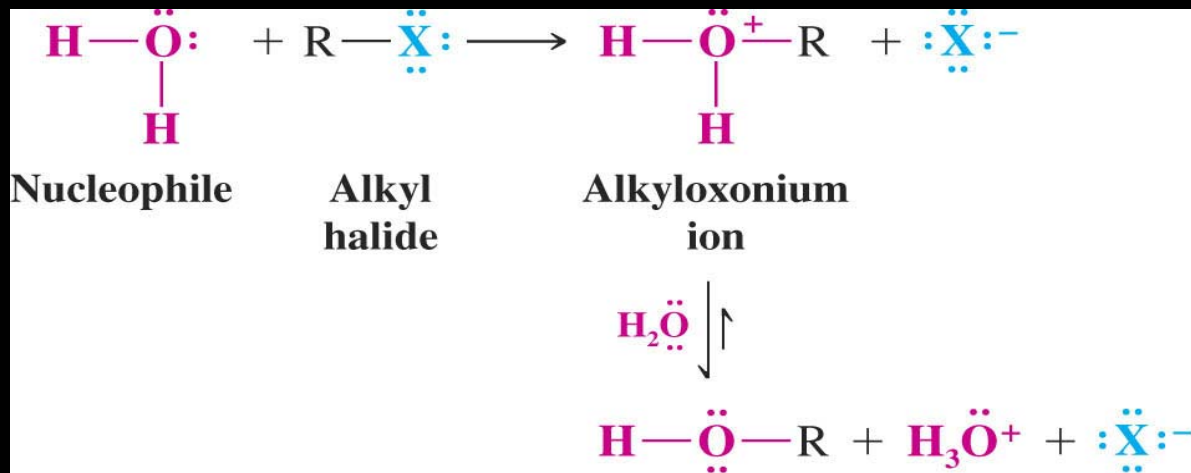


6.4 Nucleophile

→ The nucleophile reacts at the electron deficient carbon

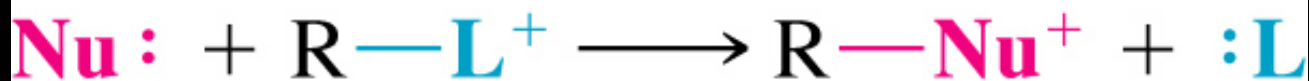
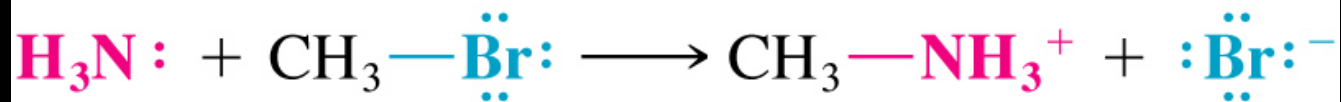
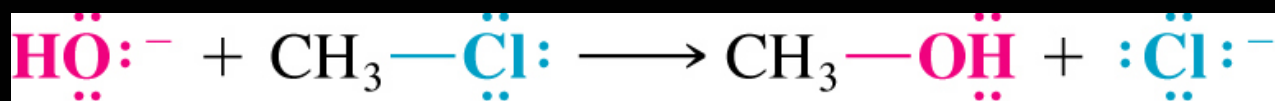
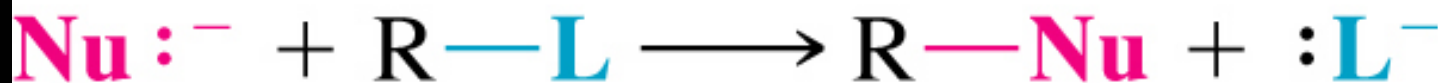


→ A nucleophile may be any molecule with an unshared electron pair

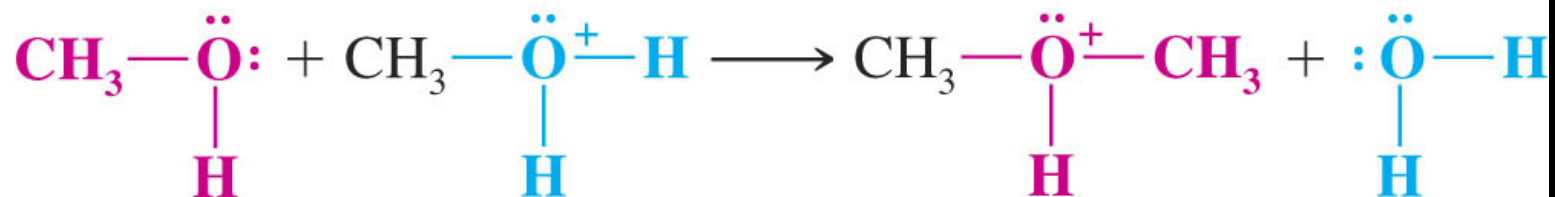


6.5 Leaving Group

- A leaving group is a substituent that can leave as a relatively stable entity
- It can leave as an anion or a neutral species

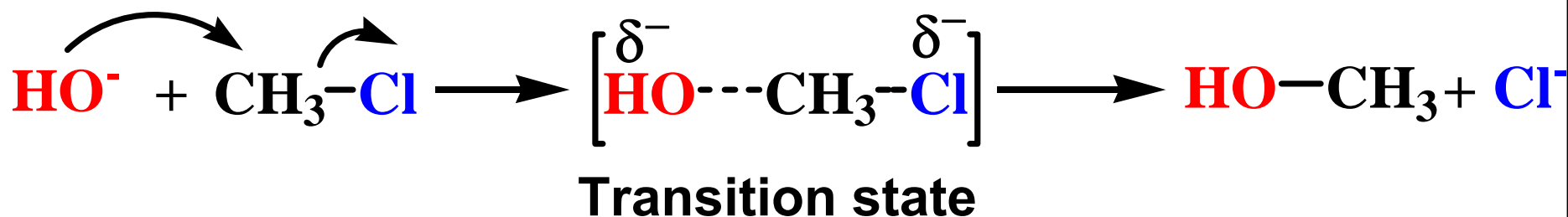


Specific Example



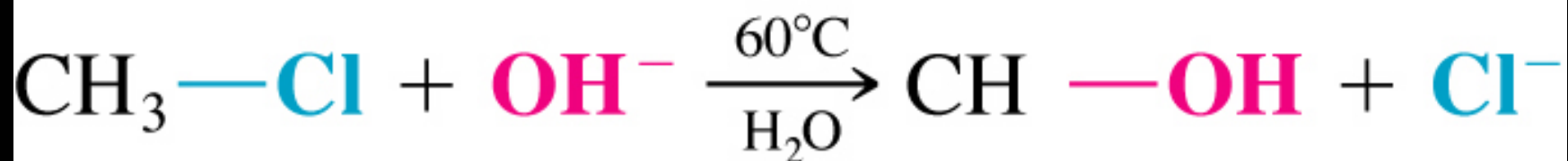
S_N2 Reactions

- Rate determining step is bimolecular
- Methyl and 1° alkyl halides undergo S_N2 type nucleophilic substitutions



6.6 Kinetics of a Nucleophilic Substitution Reaction: An S_N2 Reaction

- The rate equation reflects this dependence
- S_N2 reaction: substitution, nucleophilic, 2nd order (bimolecular)



$$\text{Rate} = k[\text{CH}_3\text{Cl}][\text{OH}^-]$$

A Mechanism for the S_N2 Reaction

→ A *transition state* is the high energy state of the reaction

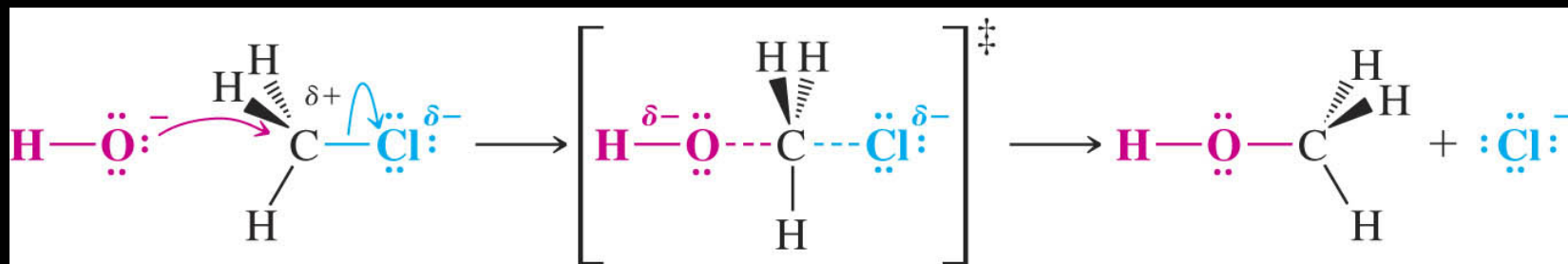
- It is an unstable entity with a very brief existence (10^{-12} s)

→ In the transition state of this reaction bonds are partially formed and broken

- Both chloromethane and hydroxide are involved in the transition state and this explains why the reaction is second order

A Mechanism for the S_N2 Reaction

Mechanism of a Reaction: The events that are postulated to take place at the molecular level as reactants become products



Transition state

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.

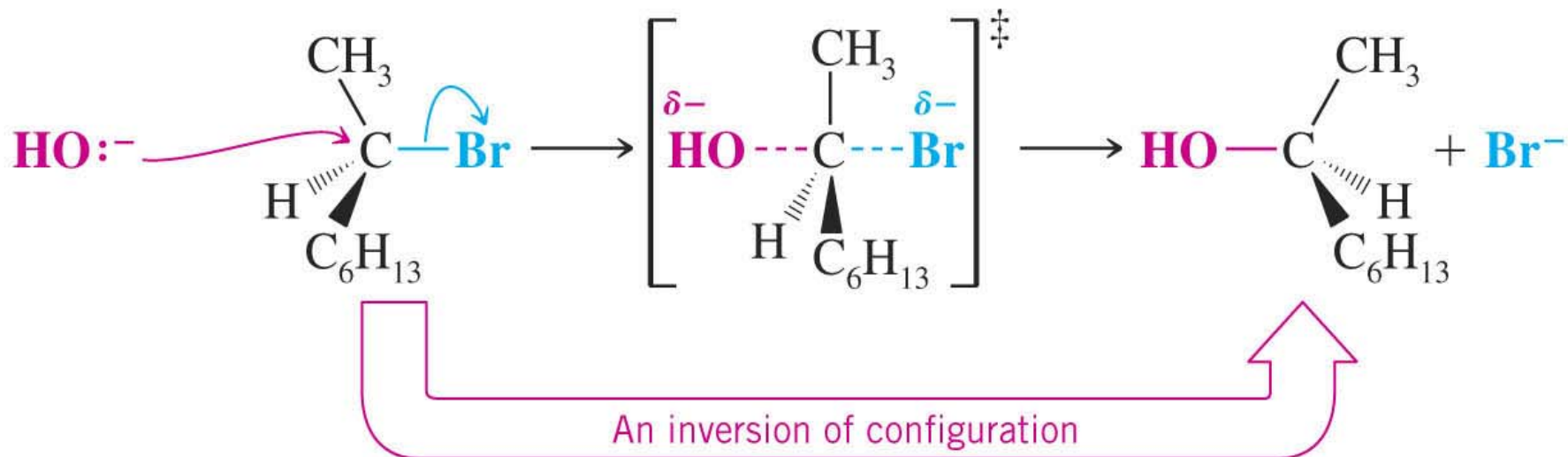
In the transition state, a bond between oxygen and carbon is partially formed and the bond between carbon and chlorine is partially broken. The configuration of the carbon atom begins to invert.

Now the bond between the oxygen and carbon has formed and the chloride ion has departed. The configuration of the carbon has inverted.

6.9 The Stereochemistry of S_N2 Reactions

→ Stereochemistry can be controlled in S_N2 reactions

- Backside attack of nucleophile results in an inversion of configuration



(*R*)-(-)-2-Bromooctane

$[\alpha]_{\text{D}}^{25} = -34.25^{\circ}$

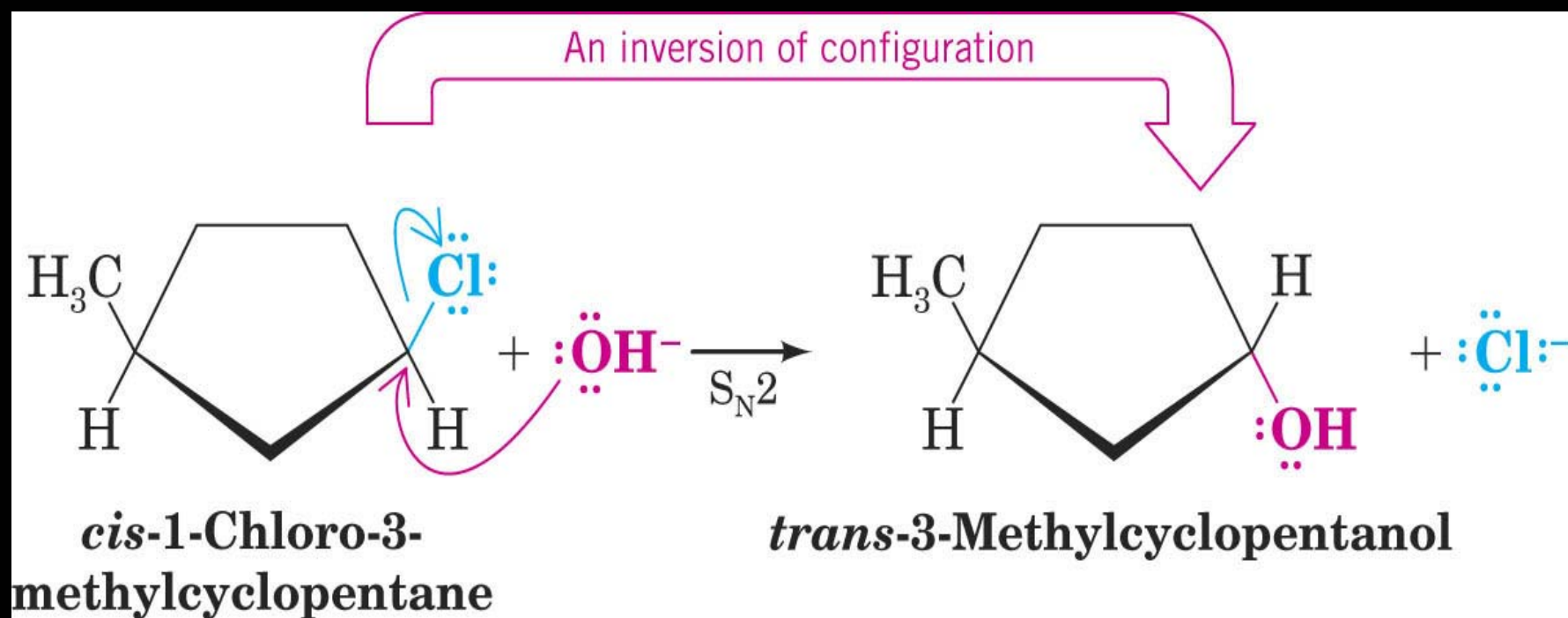
Enantiomeric purity = 100%

(*S*)-(+)-2-Octanol

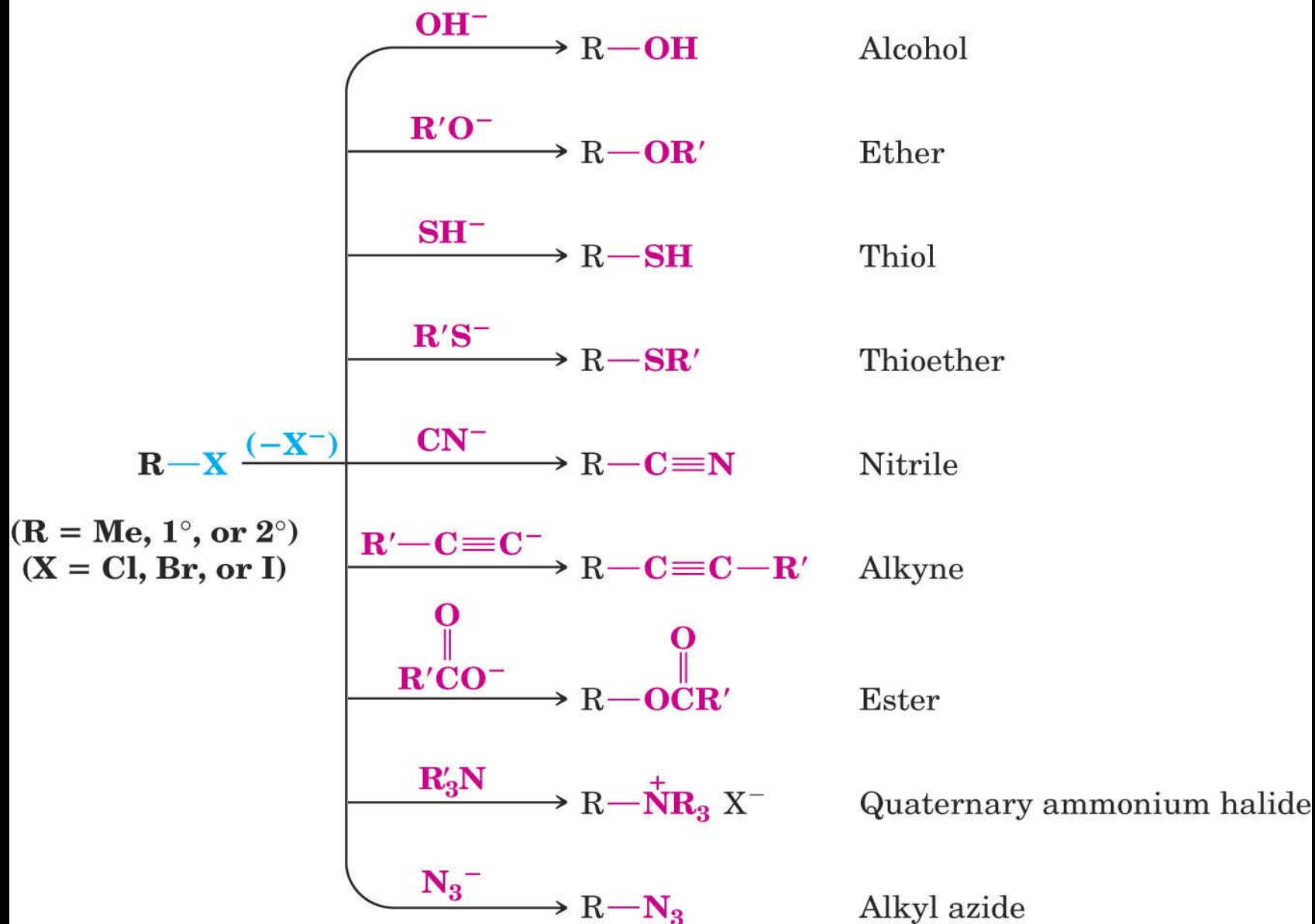
$[\alpha]_{\text{D}}^{25} = +9.90^{\circ}$

Enantiomeric purity = 100%

- In cyclic systems a cis compound can react and become trans product

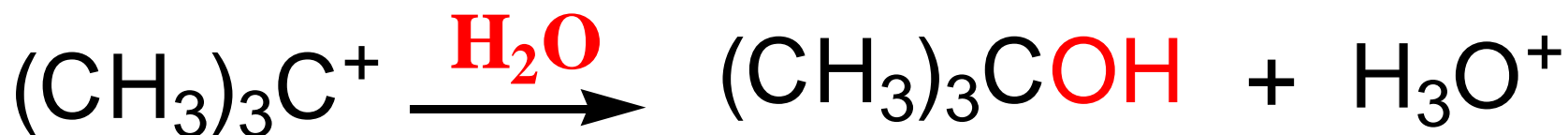
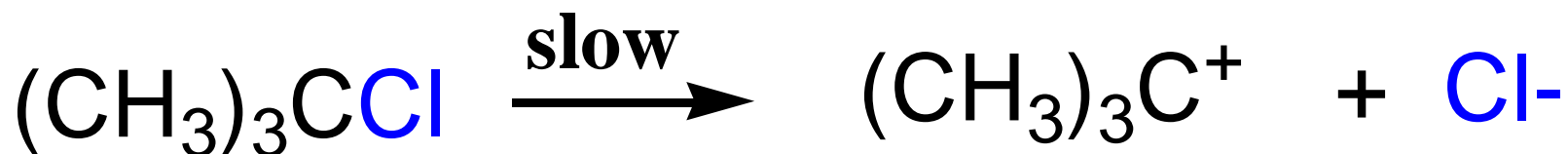


Transformations Using S_N2 Reactions



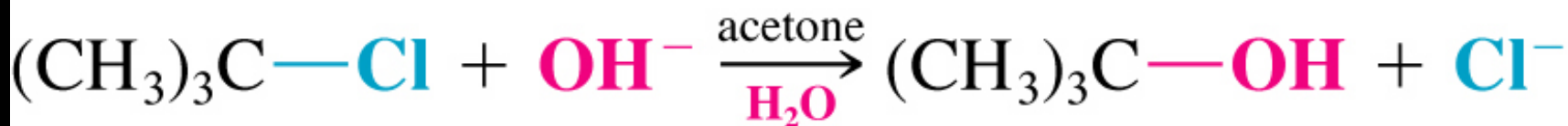
6.10 S_N1 Reactions

- Rate determining step is unimolecular
- Tertiary halides show S_N1 type nucleophilic substitution reactions



6.10 The Reaction of *tert*-Butyl Chloride with Hydroxide Ion: An S_N1 Reaction

- *tert*-Butyl chloride undergoes substitution with hydroxide
- The rate is independent of hydroxide concentration and depends only on concentration of *tert*-butyl chloride



$$\text{Rate} \propto [(\text{CH}_3)_3\text{CCl}]$$

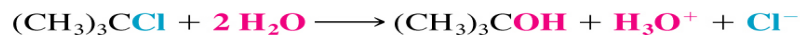
$$\text{Rate} = k[(\text{CH}_3)_3\text{CCl}]$$

- **S_N1 reaction:** Substitution, nucleophilic, 1st order (unimolecular)
- The rate depends only on the concentration of the alkyl halide
- Only the alkyl halide (and not the nucleophile) is involved in the transition state of the step that controls the rate

6.11 A Mechanism for the S_N1 Reaction

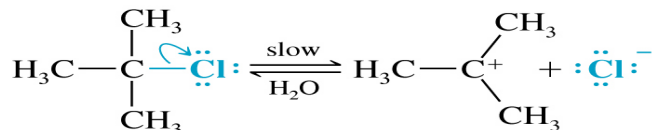
- Step 1 is rate determining (slow) because it requires the formation of unstable ionic products
- In step 1 water molecules help stabilize the ionic products

Reaction:



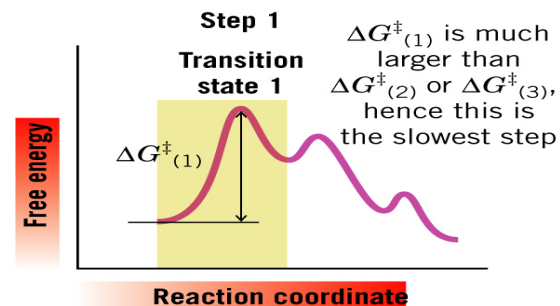
Mechanism:

Step 1

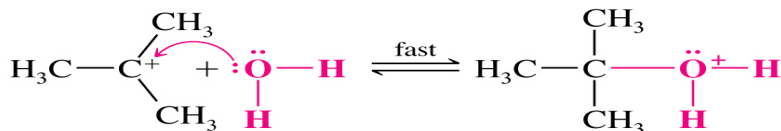


Aided by the polar solvent a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the relatively stable 3° carbocation and a chloride ion. Although not shown here, the ions are solvated (and stabilized) by water molecules.

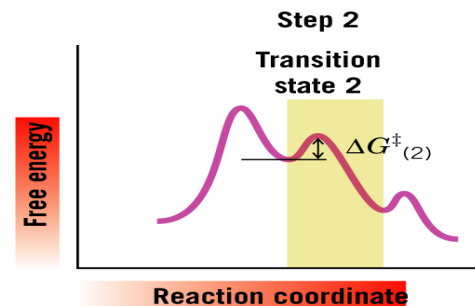


Step 2

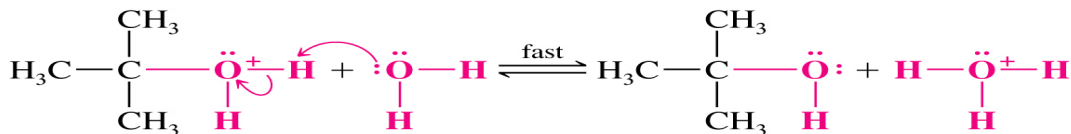


A water molecule acting as a Lewis base donates an electron pair to the carbocation (a Lewis acid). This gives the cationic carbon eight electrons.

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

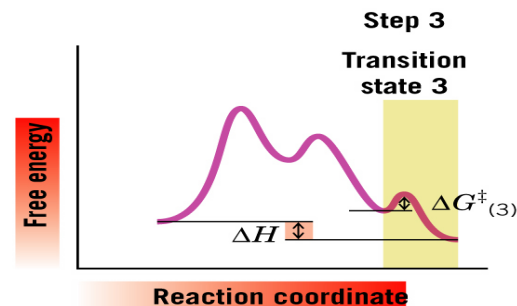


Step 3



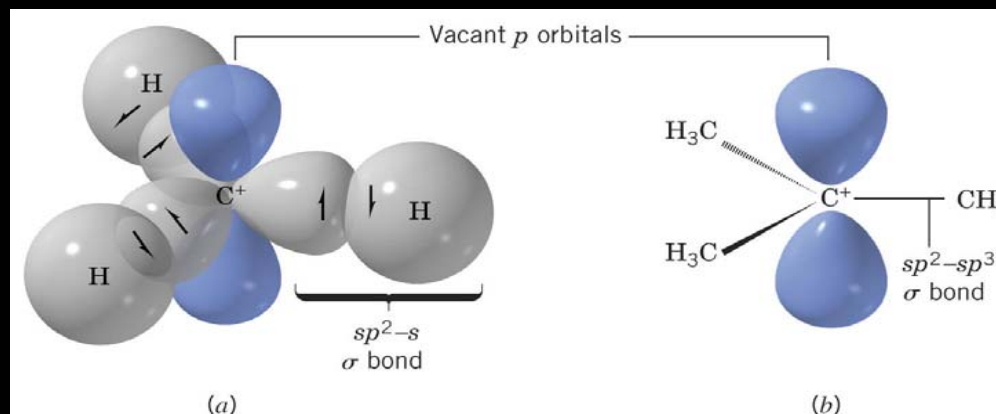
A water molecule acting as a Brønsted base accepts a proton from the *tert*-butyloxonium ion.

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

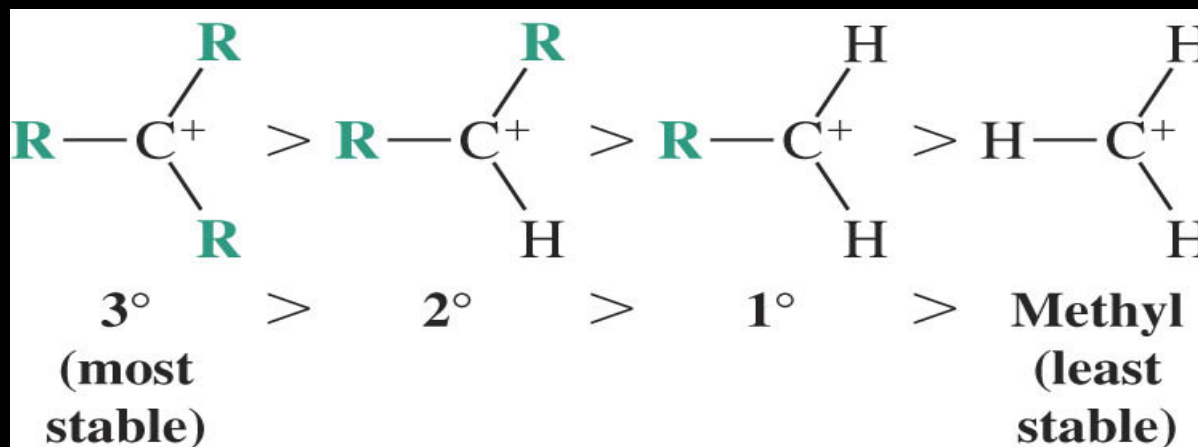


6.12 Carbocations

➔ A carbocation has only 6 electrons, is sp^2 hybridized and has an empty p orbital

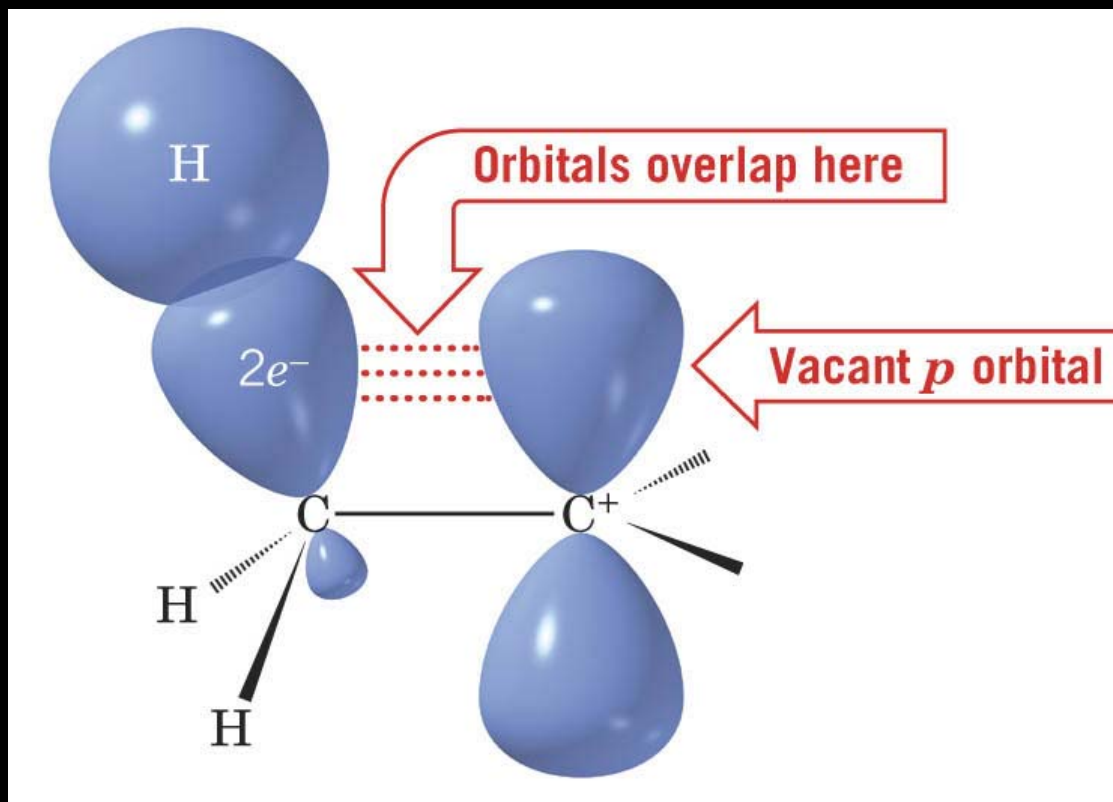


➔ The more highly substituted a carbocation is, the more stable it is and the easier it is to form



→ **Hyperconjugation** stabilizes the carbocation by donation of electrons from an adjacent carbon-hydrogen or carbon-carbon σ bond into the empty p orbital

- More substitution provides more opportunity for hyperconjugation

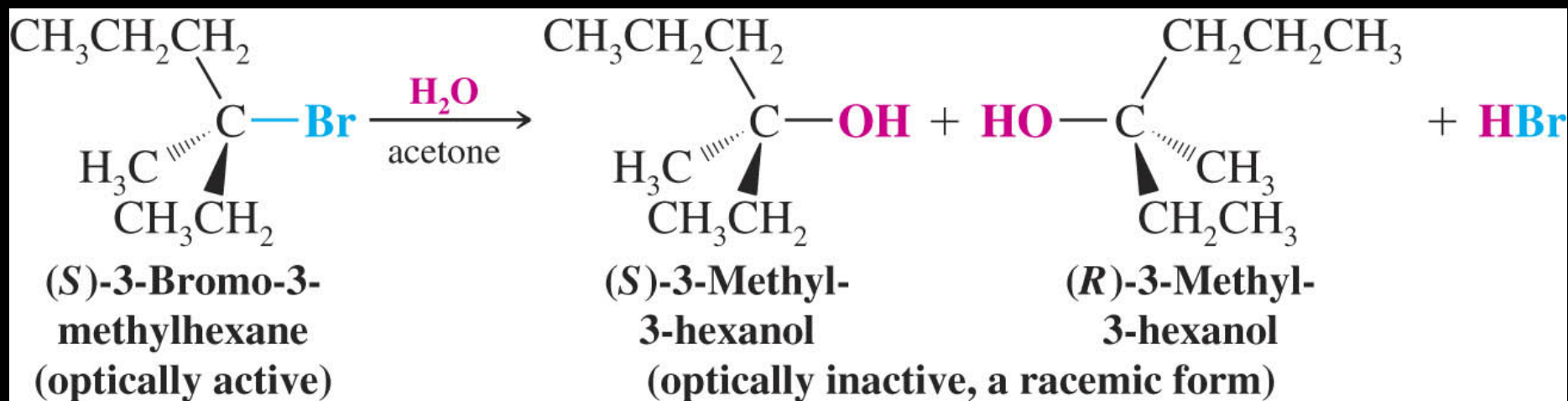


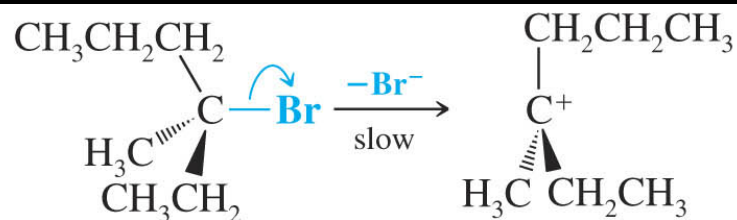
6.13 The Stereochemistry of S_N1 Reactions

→ When the leaving group leaves from a stereogenic center of an optically active compound in an S_N1 reaction, racemization will occur

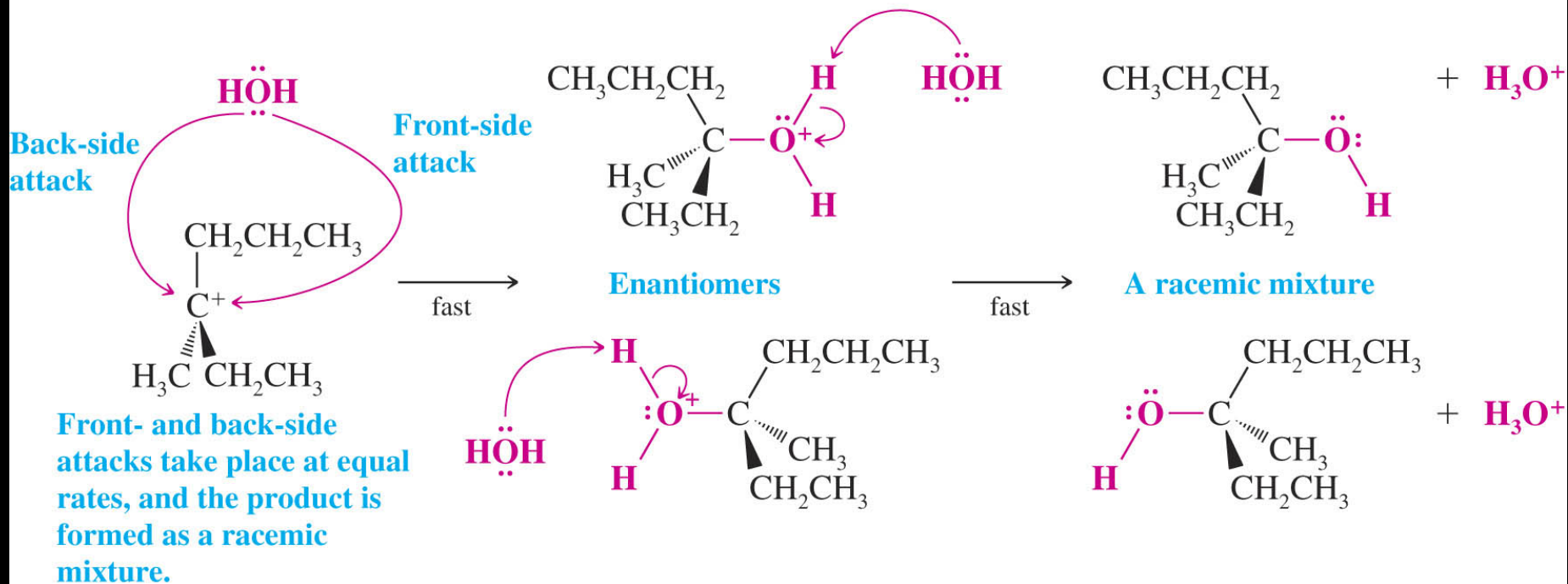
- This is because an achiral carbocation intermediate is formed

Racemization: transformation of an optically active compound to a racemic mixture



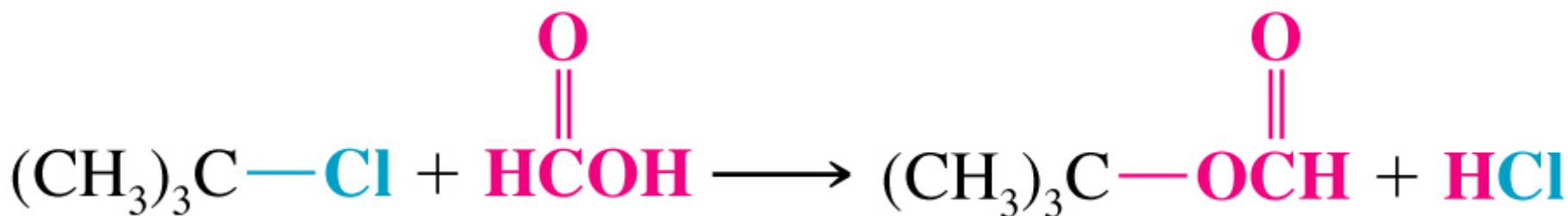
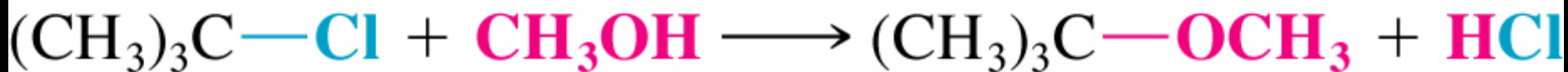
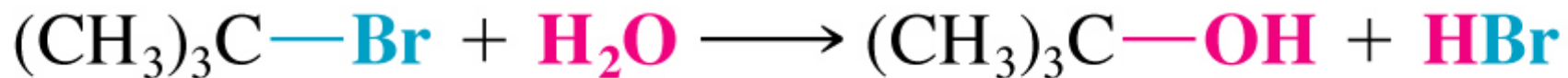


The carbocation has a trigonal planar structure and is achiral.



Solvolysis

- A molecule of the solvent is the nucleophile in a substitution reaction
- If the solvent is water the reaction is a hydrolysis



6.14 Factors Affecting the Rate of S_N1 and S_N2 Reactions

- The Effects of the Structure of the Substrate

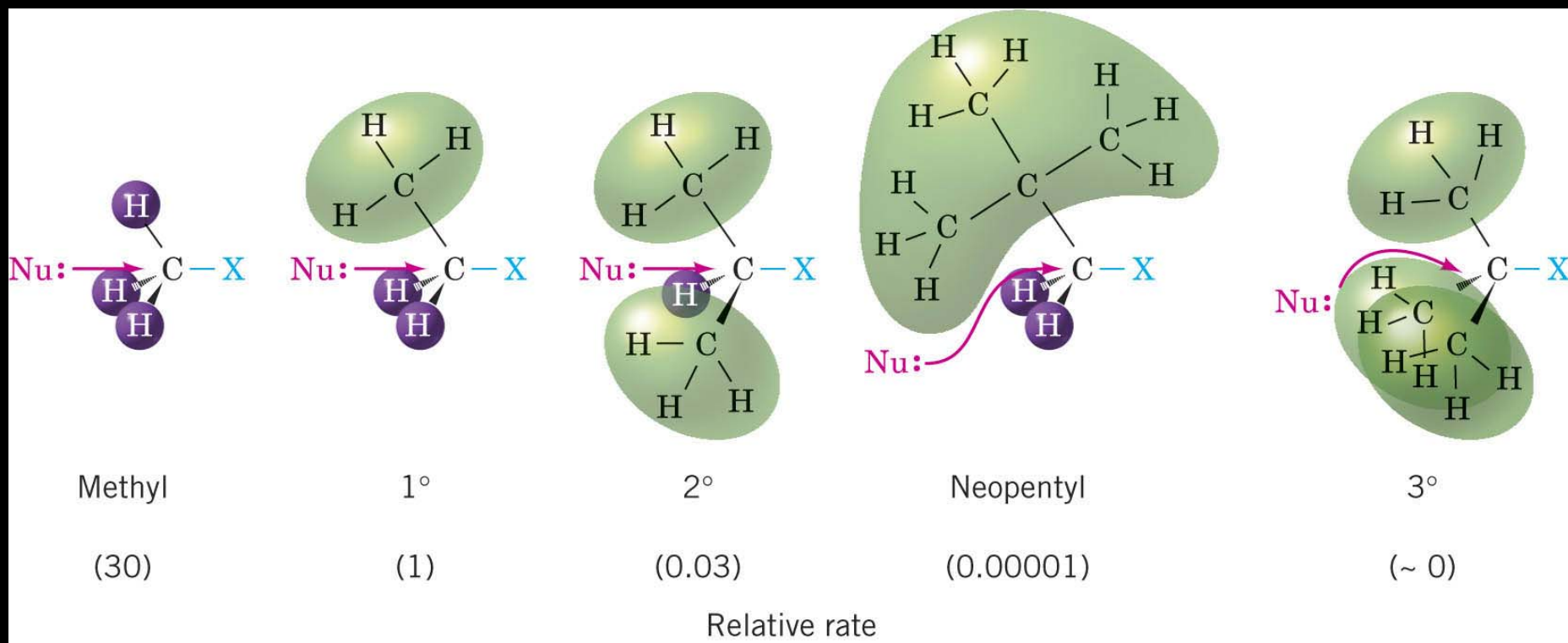
- S_N2 Reactions

→ In S_N2 reactions alkyl halides show the following general order of reactivity

Methyl > primary > secondary >> (tertiary — unreactive)

➔ **Steric hindrance: the spatial arrangement of the atoms or groups at or near a reacting site hinders or retards a reaction**

- In tertiary and neopentyl halides, the reacting carbon is too sterically hindered to react



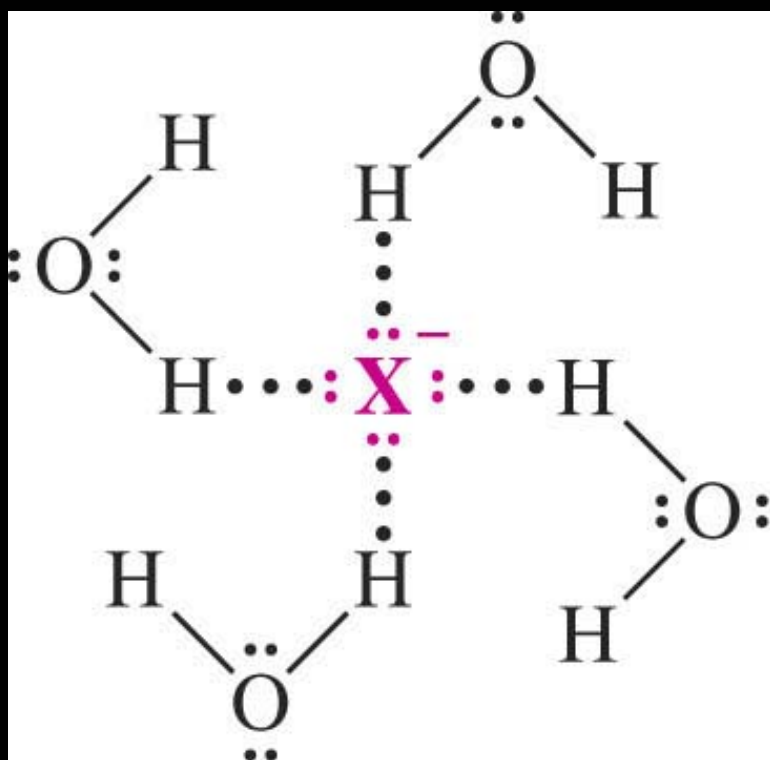
- ***S_N1 reactions***

- ➔ Generally only tertiary halides undergo S_N1 reactions because only they can form relatively stabilized carbocations

Solvent Effects on S_N2 Reactions: Polar Protic and Aprotic Solvents

Polar Protic Solvents

- Polar solvents have a hydrogen atom attached to strongly electronegative atoms
- They solvate nucleophiles and make them less reactive



Molecules of the protic solvent, water, solvate a halide ion by forming hydrogen bonds to it.

➤ Larger nucleophilic atoms are less solvated and therefore more reactive in polar protic solvents



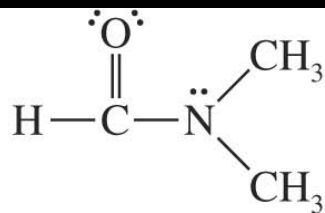
➤ Larger nucleophiles are also more polarizable and can donate more electron density

*Relative nucleophilicity in polar solvents:

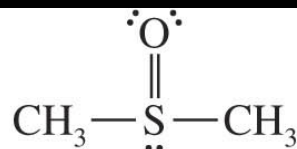


→ Polar Aprotic Solvents

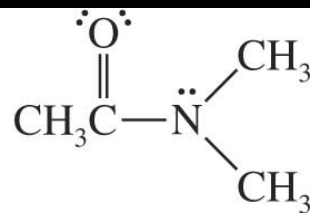
- Polar aprotic solvents do not have a hydrogen attached to an electronegative atom



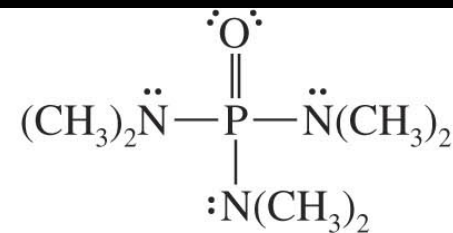
N,N-Dimethylformamide
(DMF)



Dimethyl sulfoxide
(DMSO)

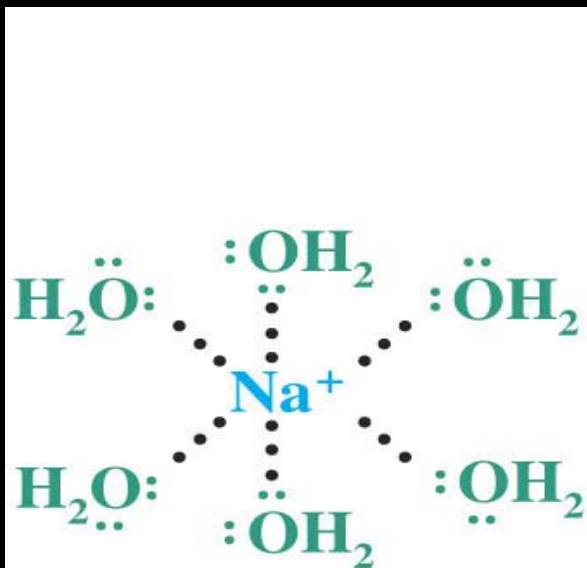


Dimethylacetamide
(DMA)

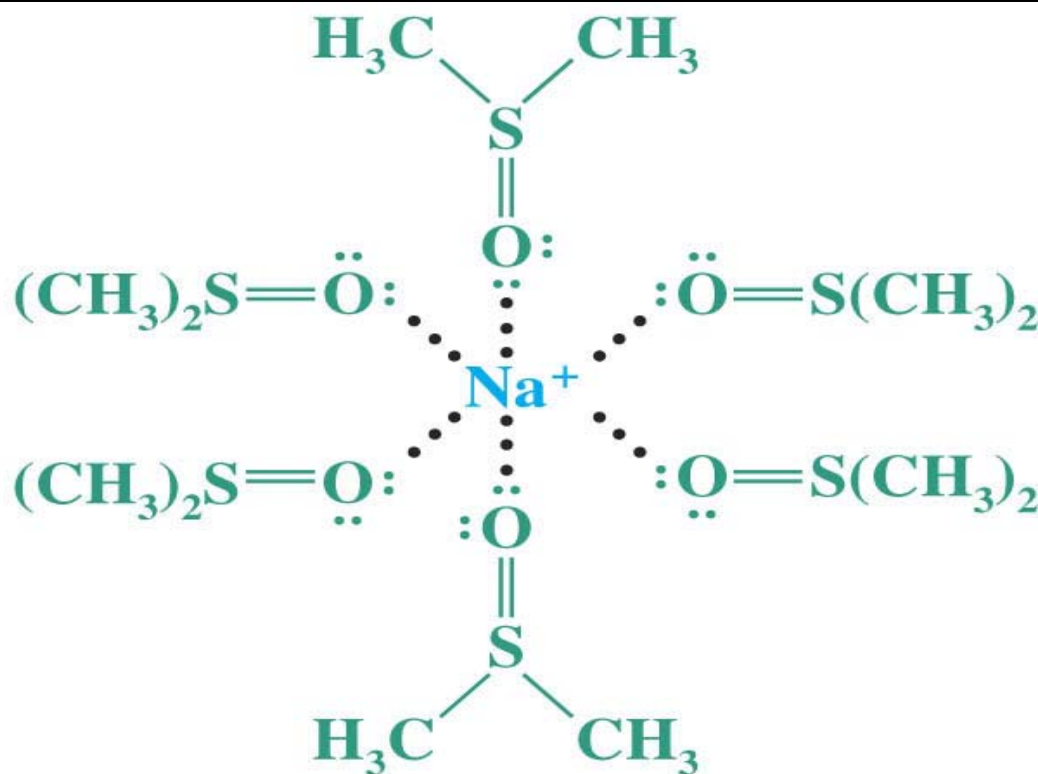


Hexamethylphosphoramide
(HMPA)

- Polar aprotic solvents solvate cations well but leave anions unsolvated because positive centers in the solvent are sterically hindered



A sodium ion solvated
by molecules of the
protic solvent water

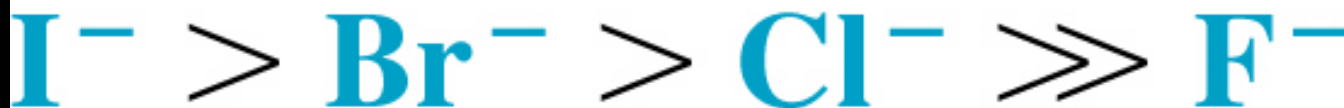


A sodium ion solvated by
molecules of the aprotic
solvent DMSO

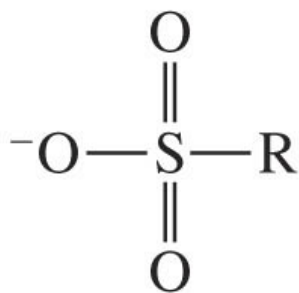
- Polar aprotic solvents lead to generation of “naked” and very reactive nucleophiles
- Trends for nucleophilicity are the same as for basicity
- They are excellent solvents for S_N2 reactions

• The Nature of the Leaving Group

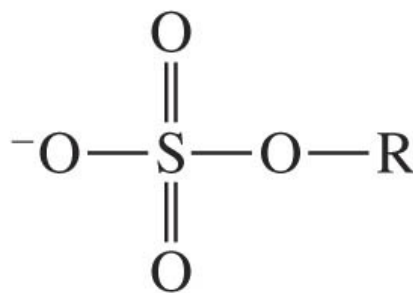
- The best leaving groups are weak bases which are relatively stable
 - The leaving group can be an anion or a neutral molecule
- Leaving group ability of halides:



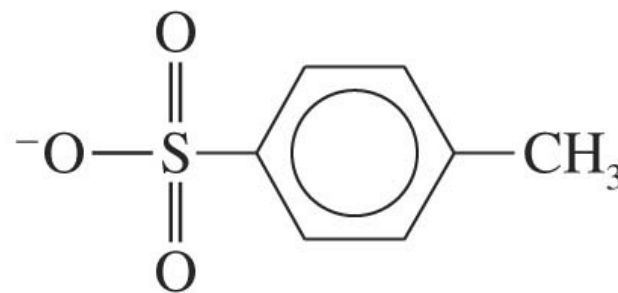
- Other very weak bases which are good leaving groups:



An alkanesulfonate ion

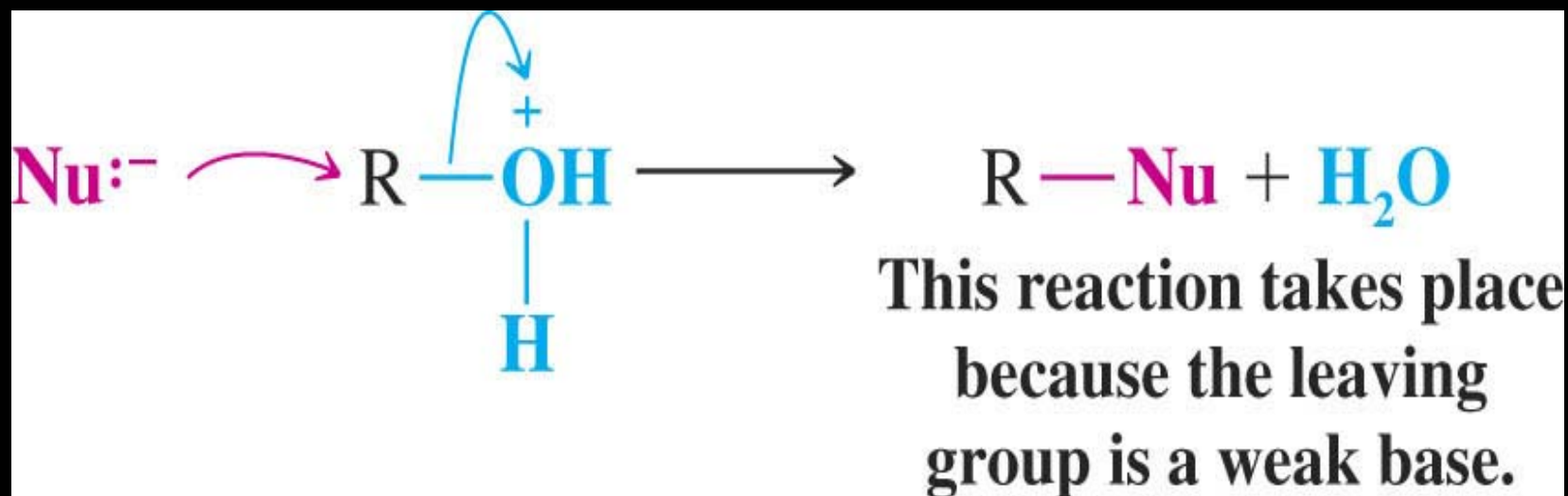
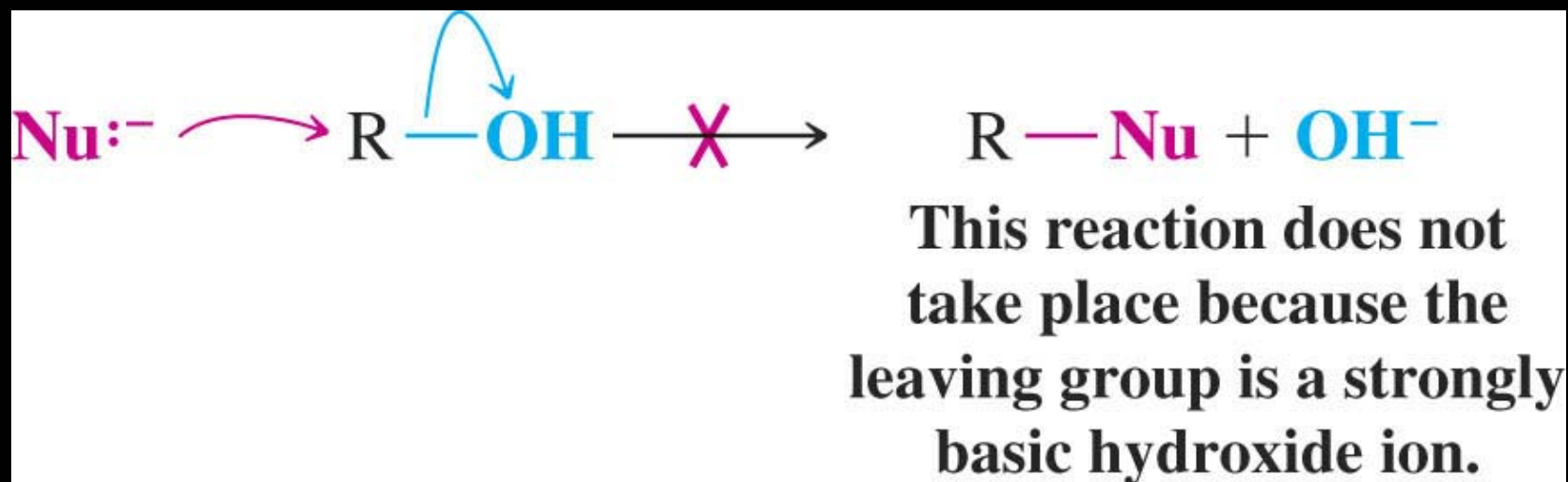


An alkyl sulfate ion



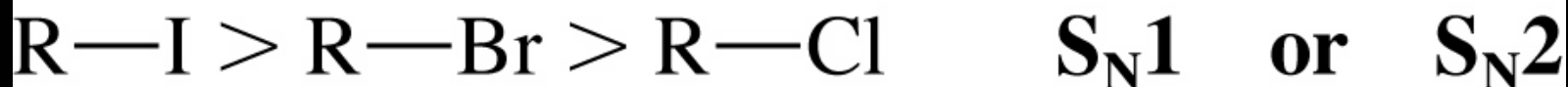
p-Toluenesulfonate ion

➔ The poor leaving group hydroxide can be changed into the good leaving group water by protonation



Summary S_N1 vs. S_N2

→ In both types of reaction alkyl iodides react the fastest because of superior leaving group ability



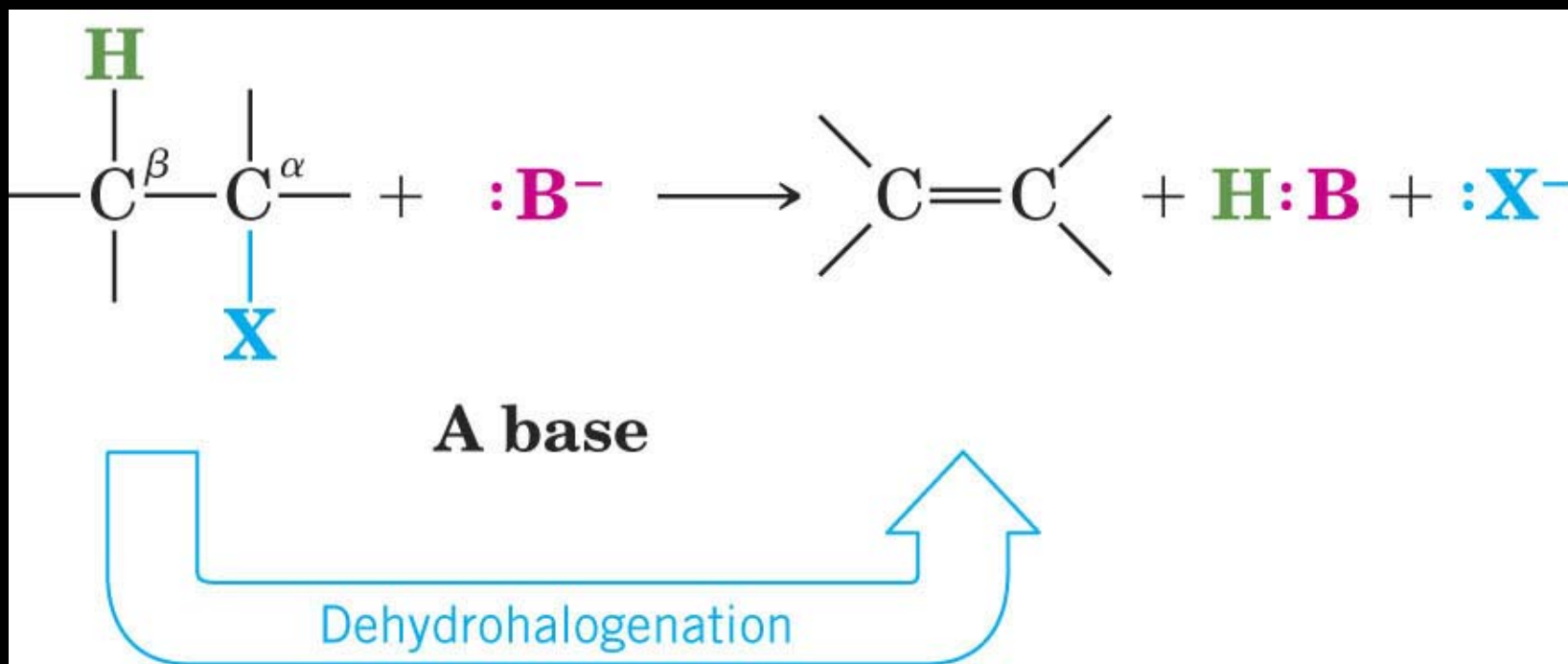
Factor	S _N 1	S _N 2
Substrate	3° (requires formation of a relatively stable carbocation)	Methyl > 1° > 2° (requires unhindered substrate)
Nucleophile	Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolysis)	Strong Lewis base, rate favored by high concentration of nucleophile
Solvent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

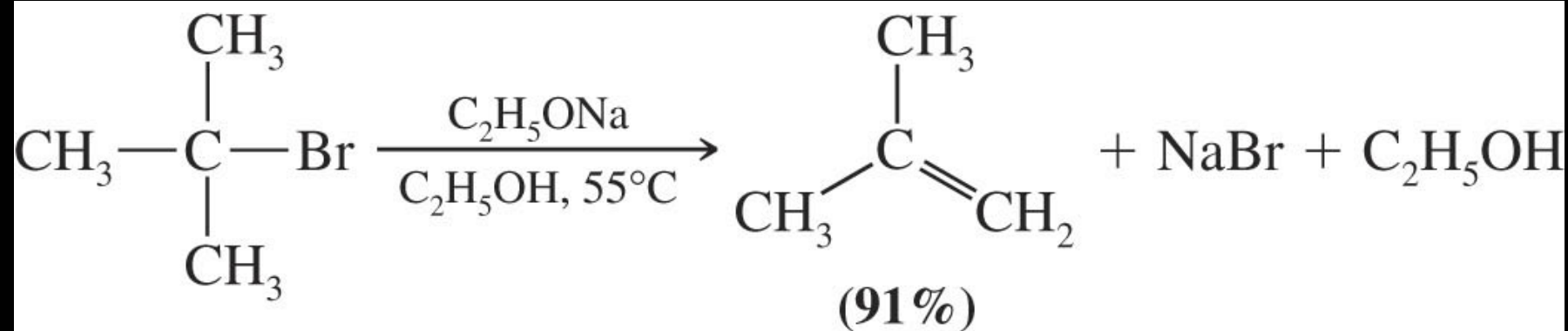
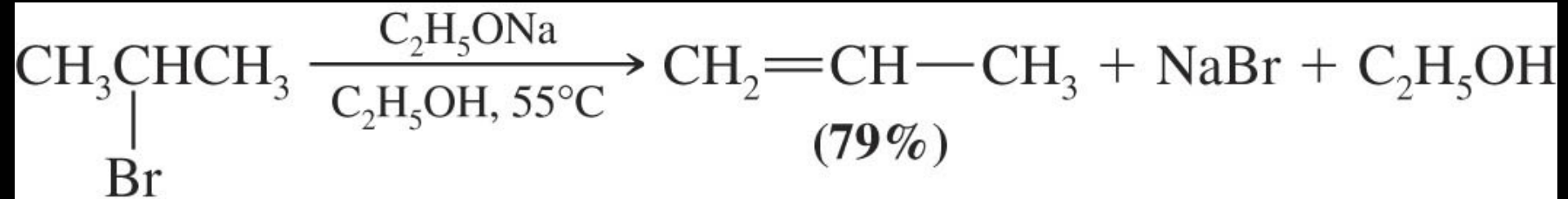
6.16 Elimination Reactions of Alkyl Halides

Dehydrohalogenation

→ Used for the synthesis of alkenes

- Elimination competes with substitution reaction
- Strong bases such as alkoxides favor elimination





6.17 The E2 Reaction

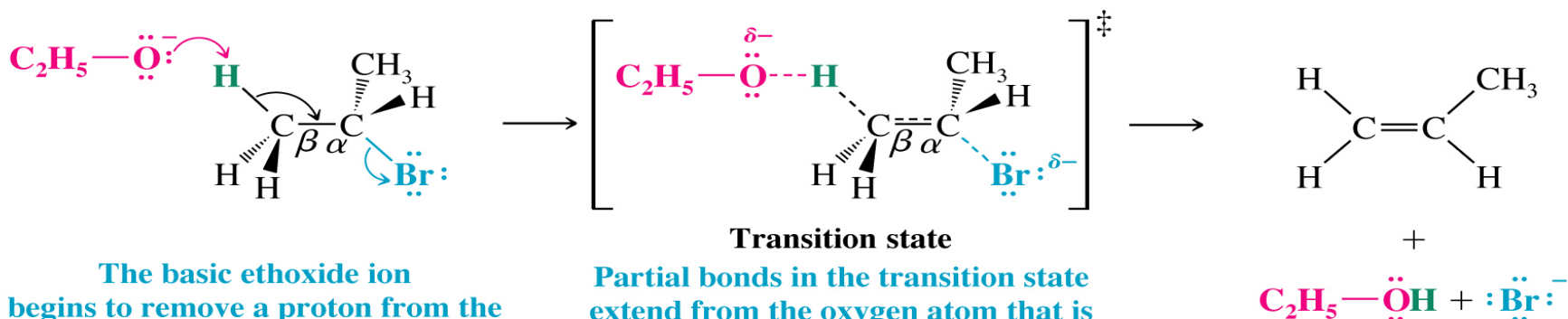
- E2 reaction involves concerted removal of the proton, formation of the double bond, and departure of the leaving group
- Both alkyl halide and base concentrations affect rate and therefore the reaction is 2nd order

E2 Reaction Mechanism

Reaction:



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.

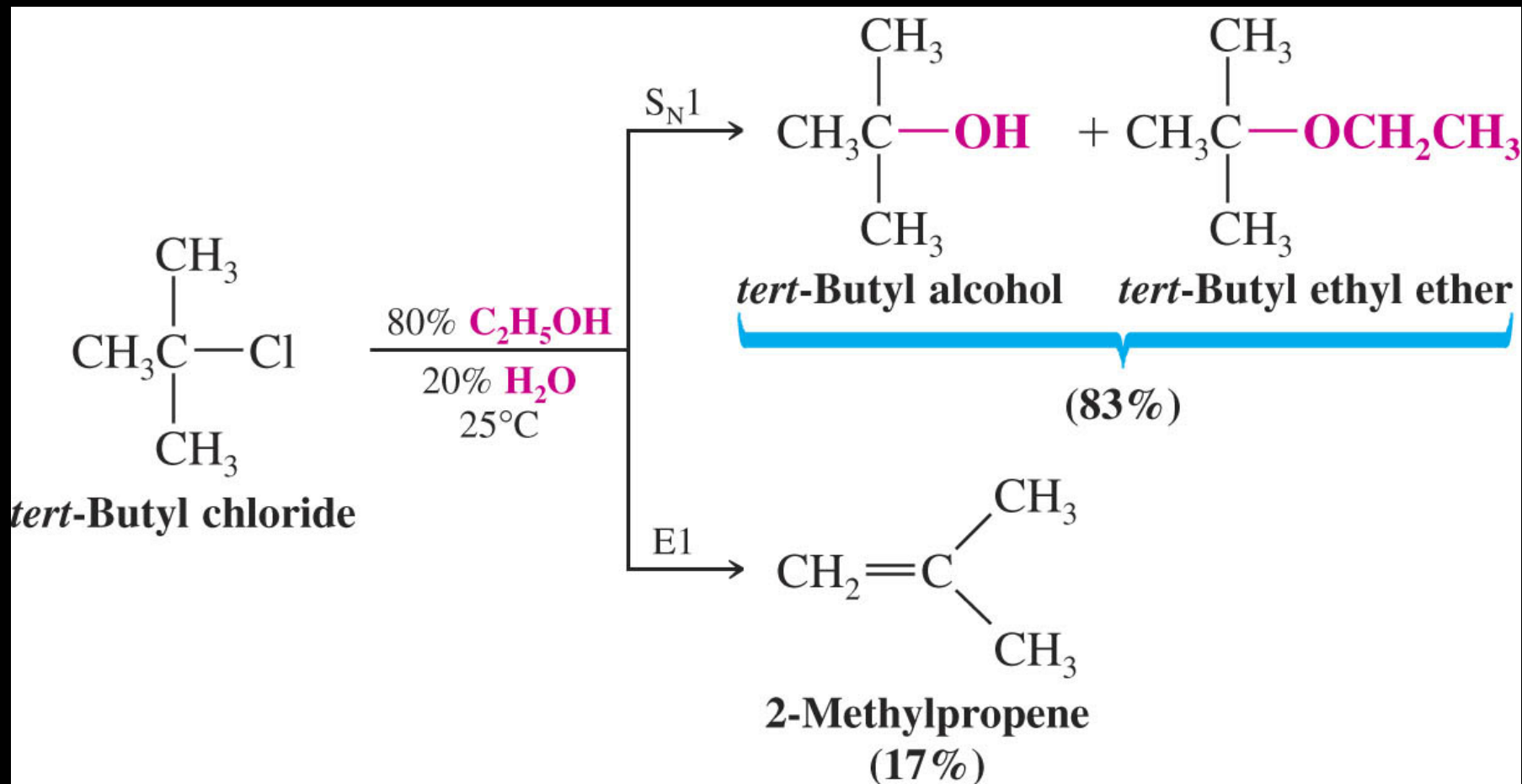
At completion of the reaction, the double bond is fully formed and the alkene has a trigonal planar geometry at each carbon atom. The other products are a molecule of ethanol and a bromide ion.

$$\text{Rate} \propto [\text{CH}_3\text{CHBrCH}_3][\text{C}_2\text{H}_5\text{O}^-]$$

$$\text{Rate} = k[\text{CH}_3\text{CHBrCH}_3][\text{C}_2\text{H}_5\text{O}^-]$$

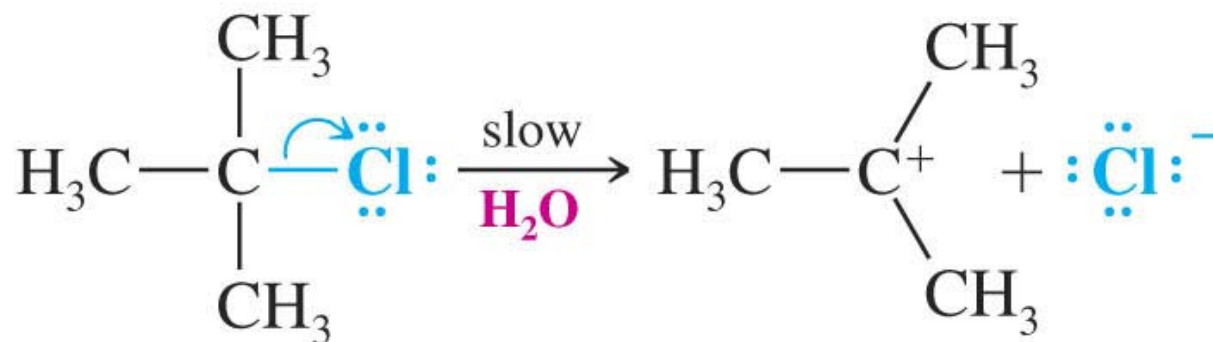
6.18 The E1 Reaction

→ The E1 reaction competes with the S_N1 reaction and likewise goes through a carbocation intermediate



E1 Reaction Mechanism

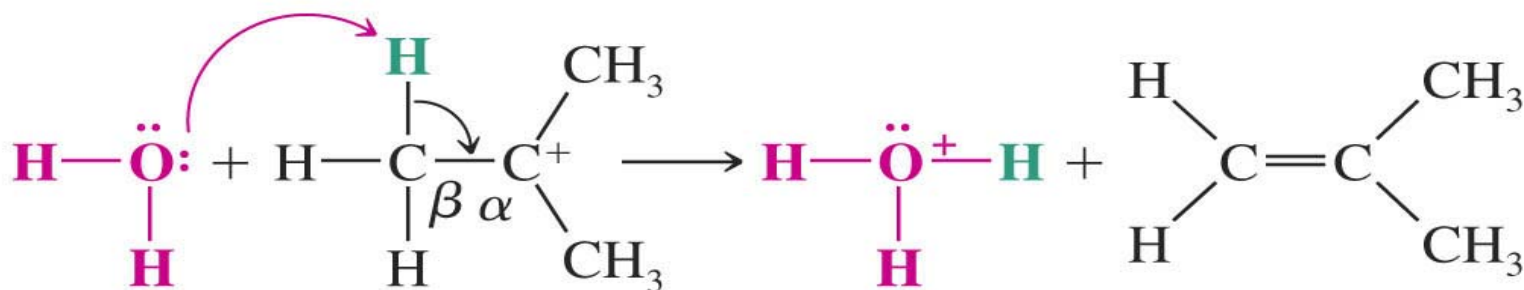
Step 1



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.

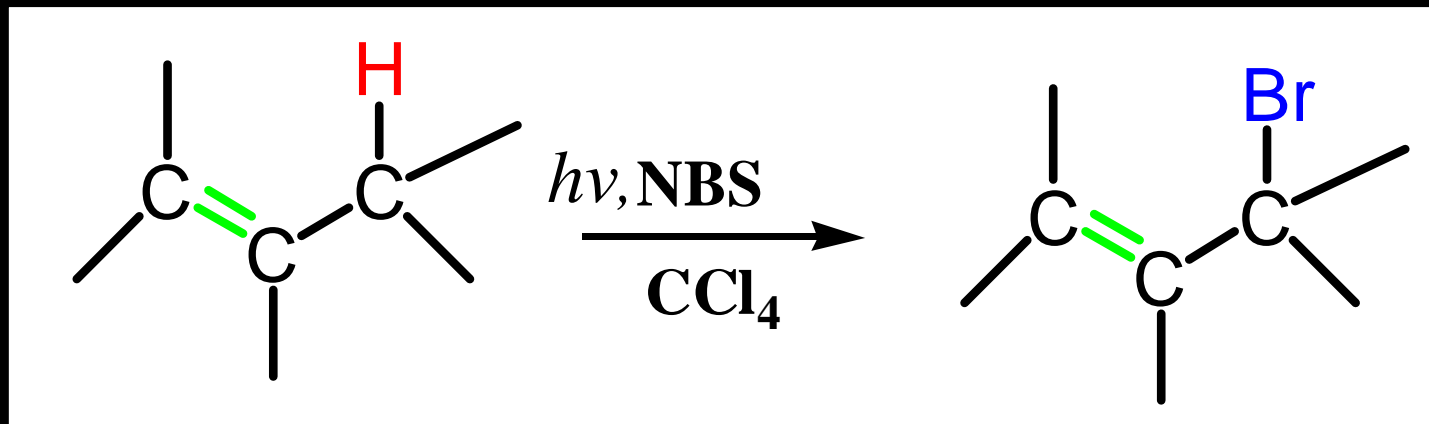
6.20 Reaction Types of Alkyl Halides

A Summary of Substitution and Elimination Reactions

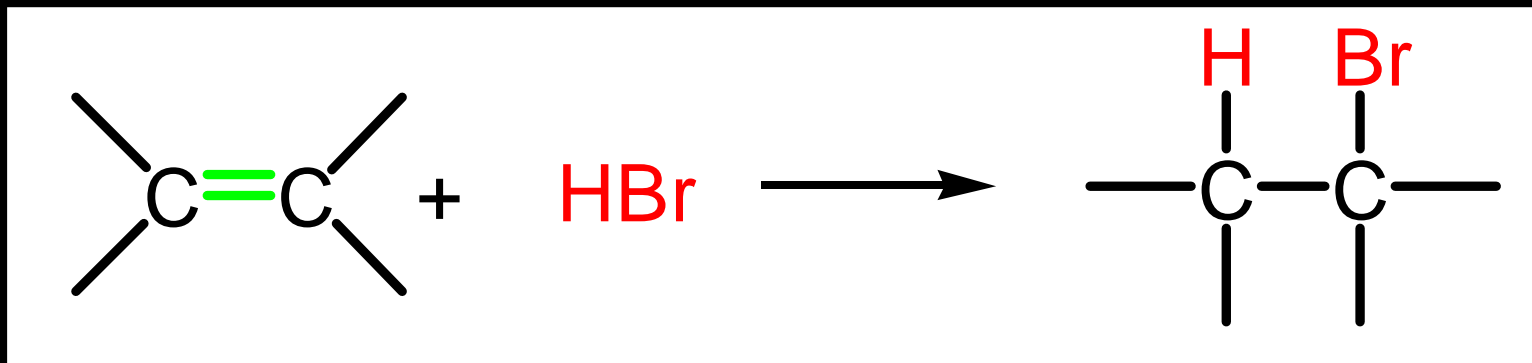
Halide Type	S _N 1	S _N 2	E1	E2
RCH₂X (primary)	Does not occur	Highly favored	Does not occur	Occurs when strong bases are used
R₂CHX (secondary)	Can occur with benzylic allylic halides	Occurs in competition with E2 reaction	Can occur with benzylic and allylic halides	Favored when strong bases are used
R₃CX (tertiary)	Favored in hydroxylic solvents	Does not occur	Occurs in competition with S _N 1 reaction	Favored when bases are used

Preparation of Alkyl Halides

- **From radical halogenation of alkenes**
e.g. allylic bromination with N-bromosuccinimide (NBS) and light



- **From alkenes by addition of HBr and HCl**

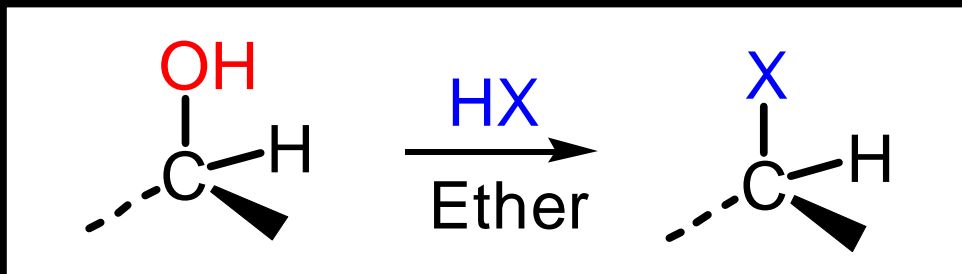


11.12 Conversion of Alcohols into Alkyl Halides

- Hydroxyl groups are poor leaving groups, and as such, are often converted to alkyl halides when a good leaving group is needed
- Three general methods exist for conversion of alcohols to alkyl halides, depending on the classification of the alcohol and the halogen desired
- Reaction can occur with phosphorus tribromide, thionyl chloride or hydrogen halides

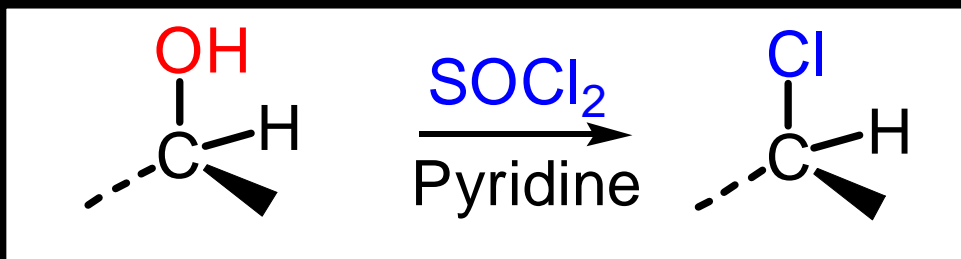
➤ From alcohols

- Reaction with HX, where X=Cl, Br, I

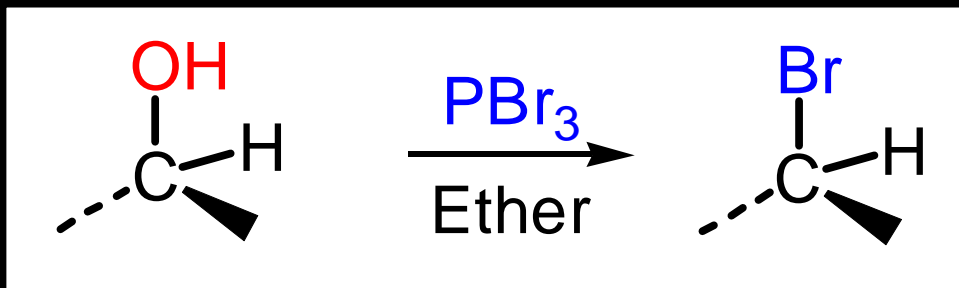


Reactivity order $3^\circ > 2^\circ > 1^\circ$

- Reaction of 1° and 2° alcohols with SOCl_2

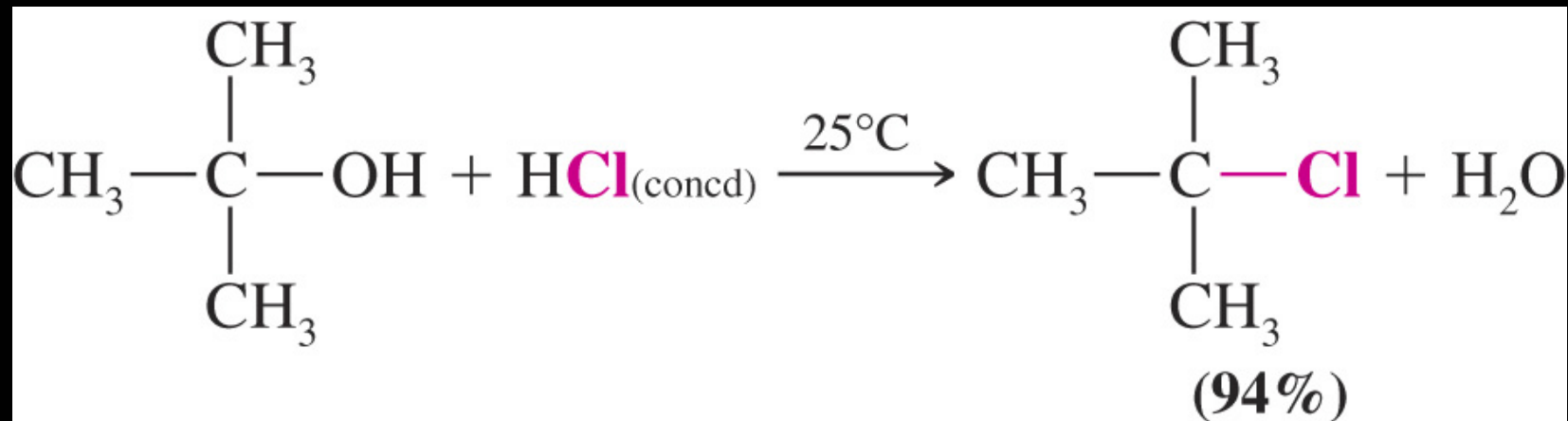


- Reaction of 1° and 2° alcohols with PBr_3

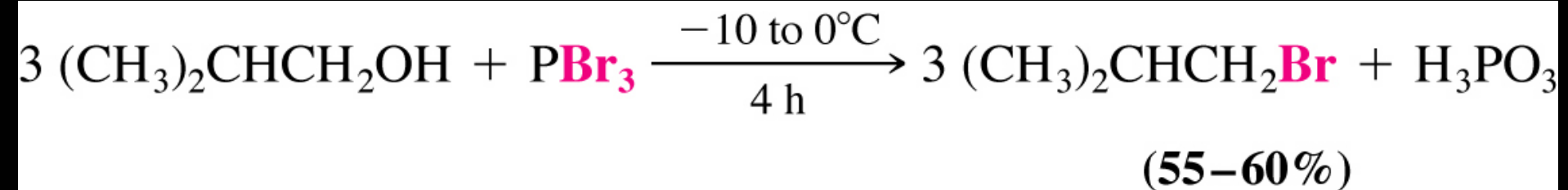


Examples

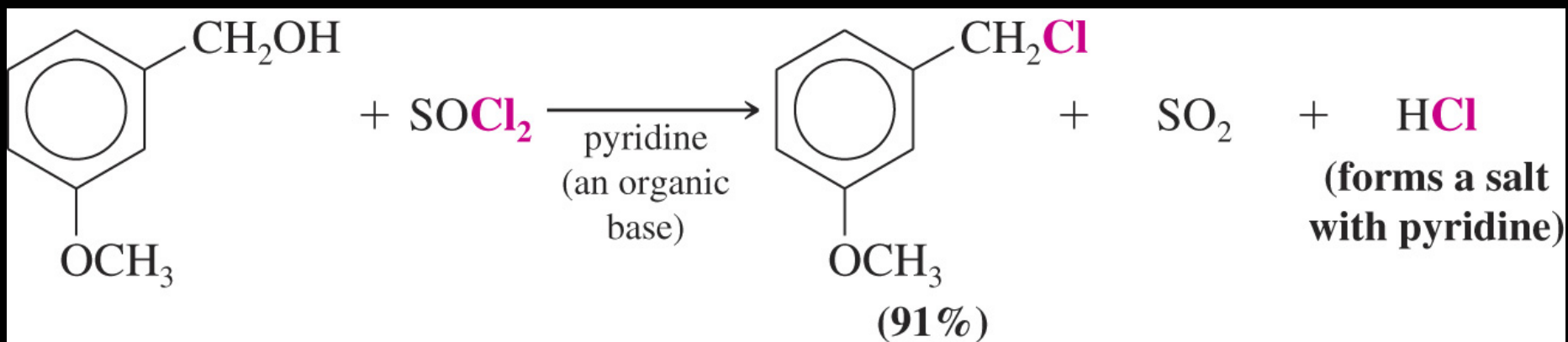
- By using hydrogen halides, HX



- By using PBr_3



- By using SOCl_2



12.7 Reactions of Organolithium and Organo-magnesium Compounds

● Reactions with Compounds Containing Acidic Hydrogen Atoms

➔ Organolithium and Grignard reagents behave as if they were carbanions and they are therefore very strong bases

