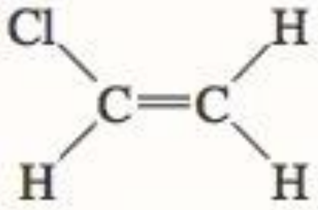
ALKYL HALIDES

Alkyl halides are alkanes bearing halogen substituents. There are three major classes of halogenated organic compounds: the alkyl halides, the vinyl halides, and the aryl halides. An **alkyl halide** simply has a halogen atom bonded to one of the sp3 hybrid carbon atoms of an alkyl group. A **vinyl halide** has a halogen atom bonded to one of the sp2 hybrid carbon atoms of an alkene. An **aryl halide** has a halogen atom bonded to one of the sp2 hybrid carbon atoms of an aromatic ring

Alkyl halides

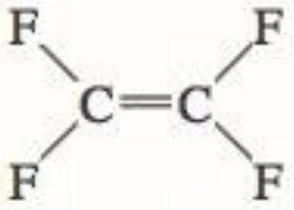
$CHCl_3$	$CHClF_2$	$CCl_3{-}CH_3$	$CF_3{-}CHClBr$
chloroform	Freon-22®	1,1,1-trichloroethane	Halothane
solvent	refrigerant	cleaning fluid	nonflammable anesthetic

Vinyl halides



vinyl chloride

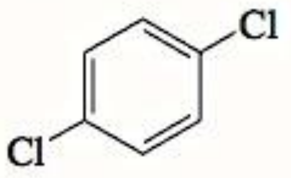
monomer for poly(vinyl chloride)



tetrafluoroethylene (TFE)

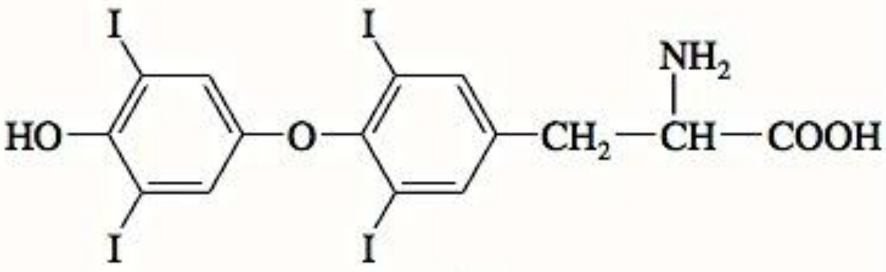
monomer for Teflon®

Aryl halides



para-dichlorobenzene

mothballs

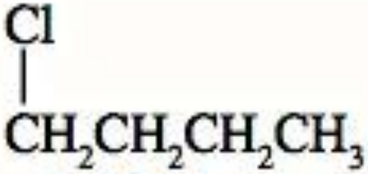
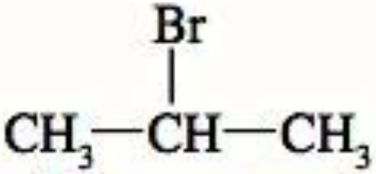


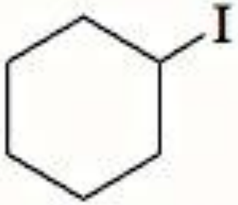
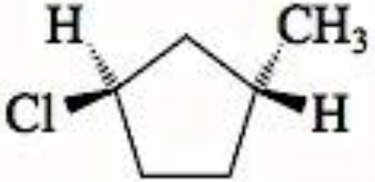
thyroxine

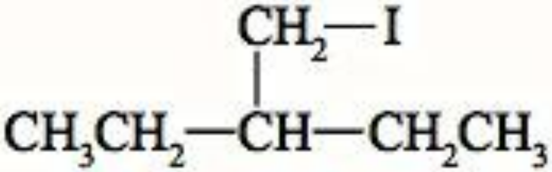
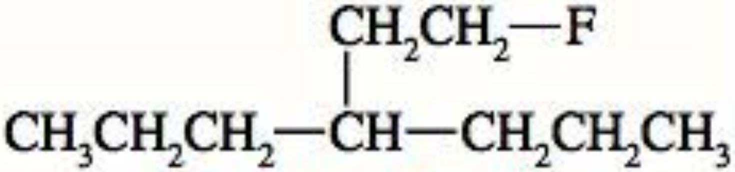
thyroid hormone

Nomenclature

There are two ways of naming alkyl halides. **The systematic (IUPAC) nomenclature** treats an alkyl halide as an alkane with a *halo*- substituent: Fluorine is *fluoro*-, chlorine is *chloro*-, bromine is *bromo*-, and iodine is *iodo*-. The result is a systematic **haloalkane** name, as in 1-chlorobutane or 2-bromopropane. **Common or "trivial"** names are constructed by naming the alkyl group and then the halide, as in "isopropyl bromide." This is the origin of the term *alkyl halide*

	$CH_3CH_2{-}F$	 $\begin{array}{l} Cl \\ \vert \\ CH_2CH_2CH_2CH_3 \end{array}$	 $\begin{array}{c} \quad\; Br \\ \quad\; \vert \\ CH_3{-}CH{-}CH_3 \end{array}$
IUPAC name:	fluoroethane	1-chlorobutane	2-bromopropane
common name:	ethyl fluoride	*n*-butyl chloride	isopropyl bromide

		
IUPAC name:	iodocyclohexane	*trans*-1-chloro-3-methylcyclopentane
common name:	cyclohexyl iodide	(none)

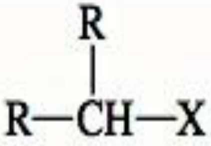
	 $\begin{array}{c} \qquad CH_2{-}I \\ \vert \\ CH_3CH_2{-}CH{-}CH_2CH_3 \end{array}$	 $\begin{array}{c} \qquad\quad CH_2CH_2{-}F \\ \vert \\ CH_3CH_2CH_2{-}CH{-}CH_2CH_2CH_3 \end{array}$
IUPAC name:	3-(iodomethyl)pentane	4-(2-fluoroethyl)heptane

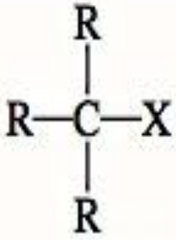
Classification

Alkyl halides are classified according to the nature of the carbon atom bonded to the halogen. If the halogen-bearing carbon is bonded to one carbon atom, it is primary (1°) and the alkyl halide is a **primary halide.** If two carbon atoms are bonded to the halogen-bearing carbon, it is secondary (2°) and the compound is a **secondary halide.** A **tertiary halide** (3°) has three other carbon atoms bonded to the halogen-bearing carbon atom. If the halogen-bearing carbon atom is a methyl group (bonded to no other carbon atoms), the compound is a *methyl halide*.

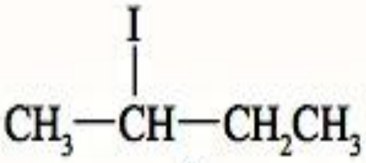
$CH_3{-}X$
methyl halide

$R{-}CH_2{-}X$
primary (1°) halide

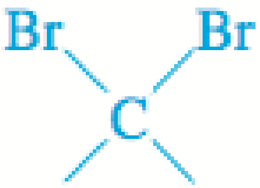

$R-\overset{\overset{R}{|}}{C}H-X$
secondary (2°) halide


$R-\underset{\underset{R}{|}}{\overset{\overset{R}{|}}{C}}-X$
tertiary (3°) halide

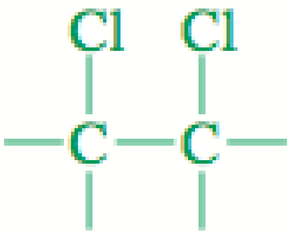
Examples

	$CH_3{-}Br$	$CH_3CH_2CH_2{-}F$ 1°	 $CH_3-\overset{\overset{I}{|}}{C}H-CH_2CH_3$ 2°	$(CH_3)_3C{-}Cl$ 3°
IUPAC name:	bromomethane	1-fluoropropane	2-iodobutane	2-chloro-2-methylpropane
common name:	methyl bromide	*n*-propyl fluoride	*sec*-butyl iodide	*tert*-butyl chloride

A **geminal dihalide** (Latin, *geminus*, “twin”) has the two halogen atoms bonded to the same carbon atom. A **vicinal dihalide** (Latin, *vicinus*, “neighboring”) has the two halo- gens bonded to adjacent carbon atoms.



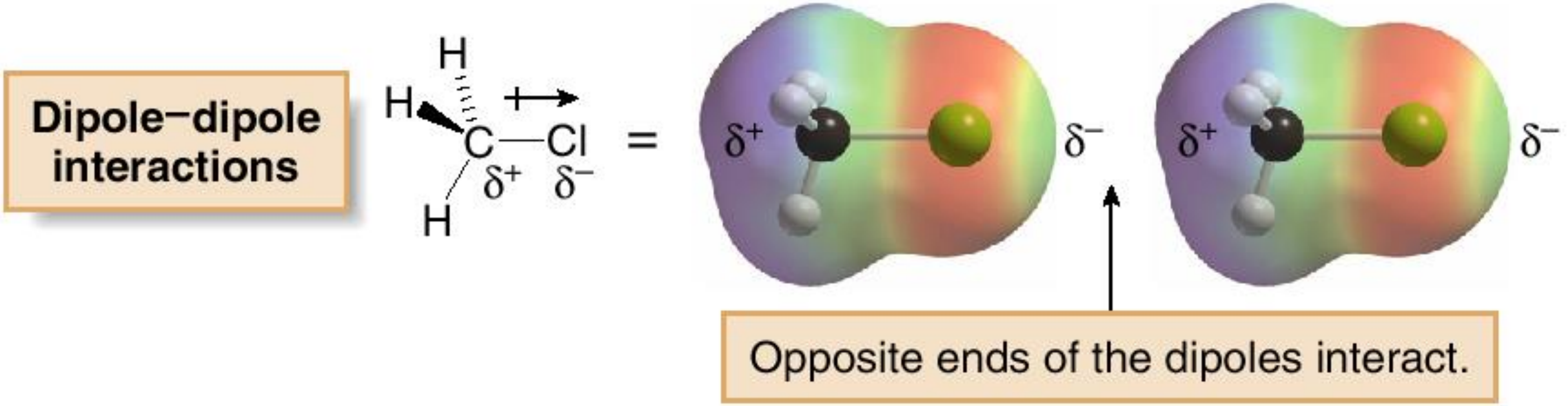
a geminal dibromide



a vicinal dichloride

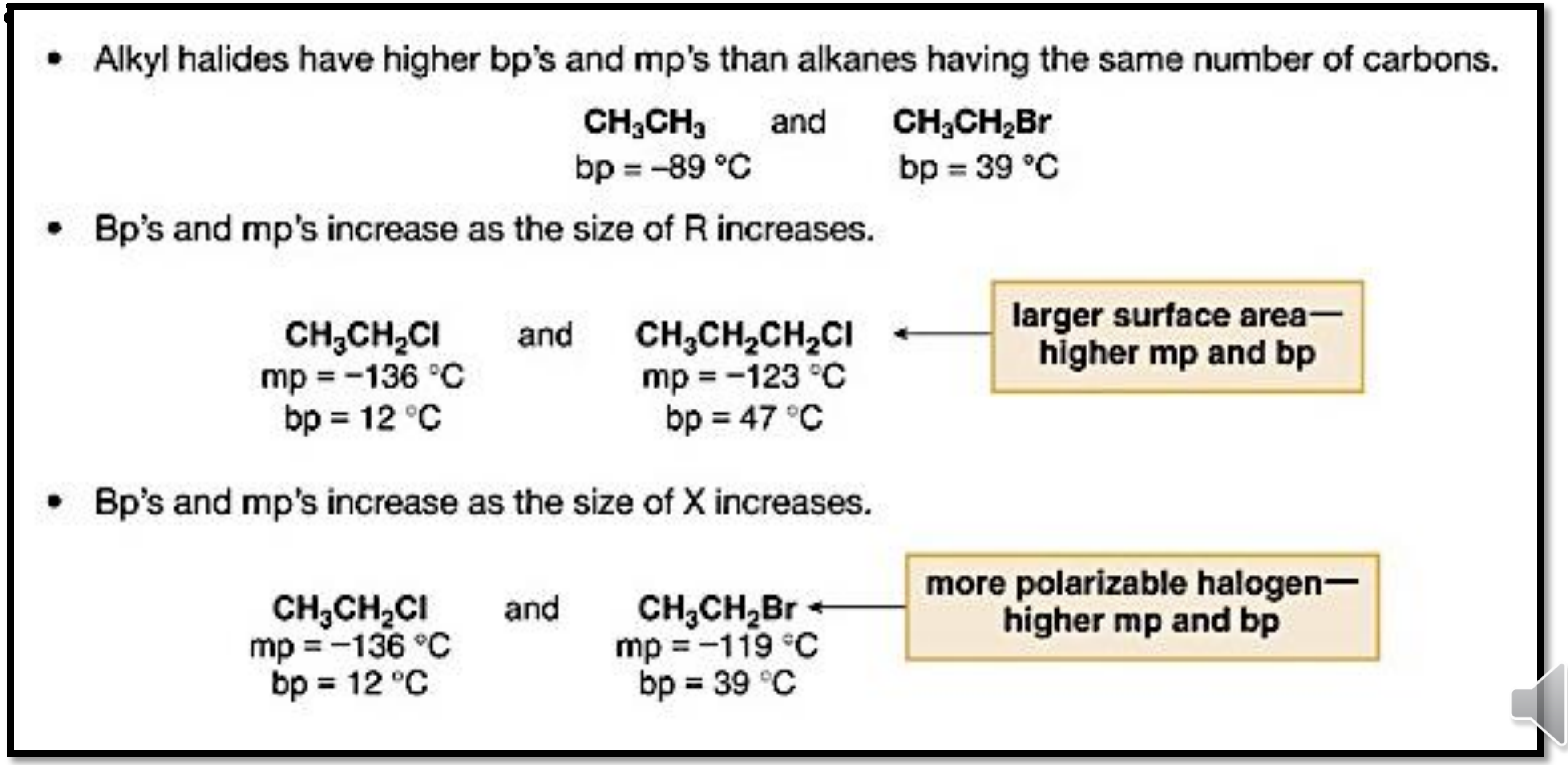
Physical properties

Because halogen atoms are more electronegative than carbon, the carbon-halogen bond of alkyl halides is polarized; the carbon atom bears a partial positive charge, the halogen atom a partial negative charge.



<u>Boiling Point</u>: Two types of intermolecular forces influence the boiling points of alkyl halides. **<u>The London force</u>** is the strongest intermolecular attraction in alkyl halides. London forces are *surface* attractions, resulting from coordinated temporary dipoles. Molecules with larger surface areas have larger London attractions, resulting in higher boiling points. **<u>Dipole–dipole attractions</u>** (arising from the polar C ¬ X bond) also affect the boiling points, but to a smaller extent.

Molecules with higher molecular weights generally have higher boiling points because they are heavier (and therefore slower moving), and they have greater surface



- Alkyl halides have higher bp's and mp's than alkanes having the same number of carbons.

CH_3CH_3 and CH_3CH_2Br

bp = –89 °C and bp = 39 °C

- Bp's and mp's increase as the size of R increases.

CH_3CH_2Cl mp = −136 °C, bp = 12 °C and $CH_3CH_2CH_2Cl$ mp = −123 °C, bp = 47 °C ← larger surface area— higher mp and bp

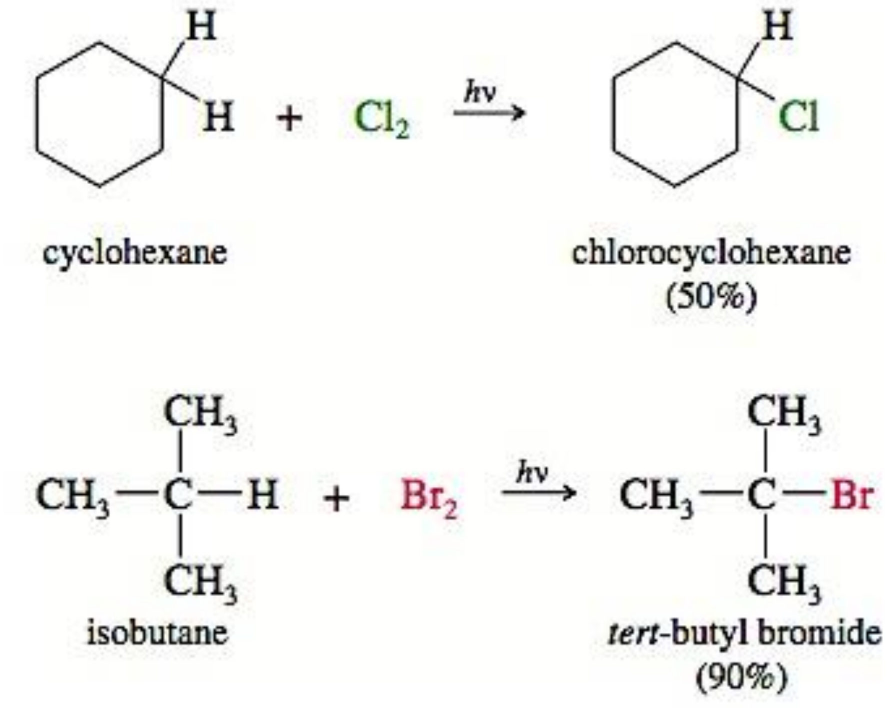
- Bp's and mp's increase as the size of X increases.

CH_3CH_2Cl mp = −136 °C, bp = 12 °C and CH_3CH_2Br mp = −119 °C, bp = 39 °C ← more polarizable halogen— higher mp and bp

Synthesis

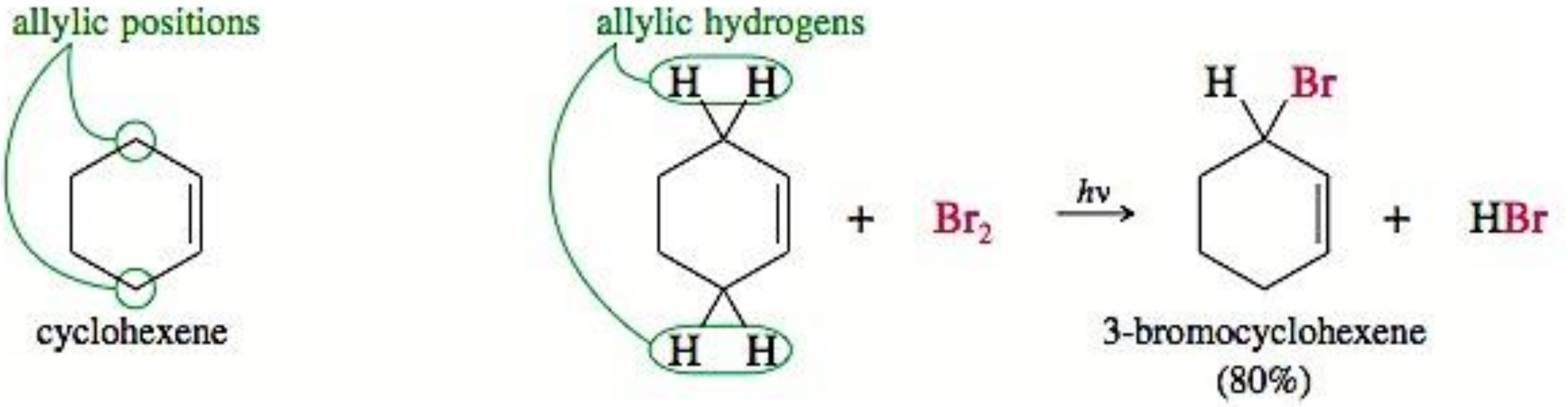
Free-Radical Halogenation

Free-radical halogenation is rarely an effective method for the synthesis of alkyl halides. It usually produces mixtures of products because there are different kinds of hydrogen atoms that can be abstracted. Laboratory syntheses using free-radical halogenation are generally limited to specialized compounds that give a single major product, such as the following examples.



Allylic bromination

An **allylic** position is a carbon atom next to a carbon–carbon double bond. Allylic intermediates (cations, radicals, and anions) are stabilized by resonance with the double bond, allowing the charge or radical to be delocalized. Under the right conditions, free-radical bromination of cyclohexene can give a good yield of 3-bromocyclohexene, where bromine has substituted for an allylic hydrogen on the carbon atom next to the double bond.

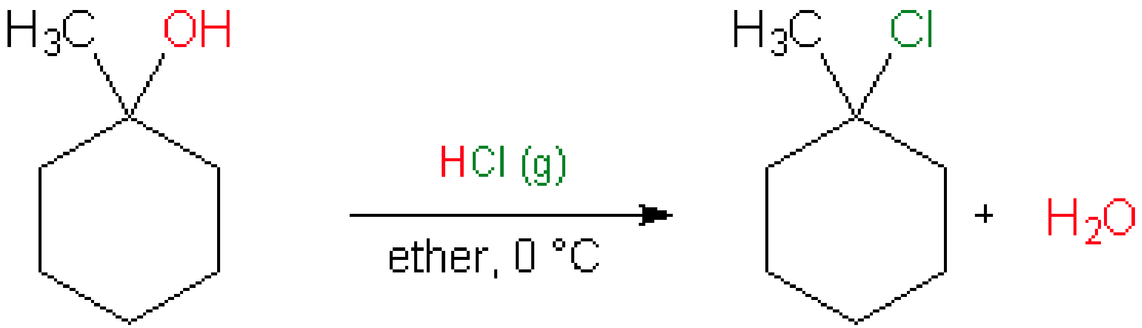


From alcohol

The hydroxyl group of an alcohol can be replaced by a halide group via a nucleophilic substitution reaction.

$$ROH + HX \longrightarrow RX + H_2O \qquad (X = Cl, Br \text{ or } I)$$

Fig.4 | **Alkyl halide synthesis by treatment of alcohols with HX**

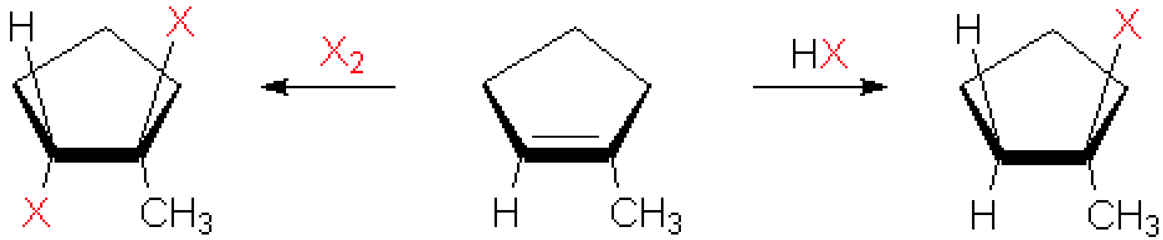


1-methylcyclohexanol

1-chloro-1-methylcyclohexane
(90%)

From alkene

Adding a halogen or hydrogen halide to an alkene will yeild an alkyl halide.

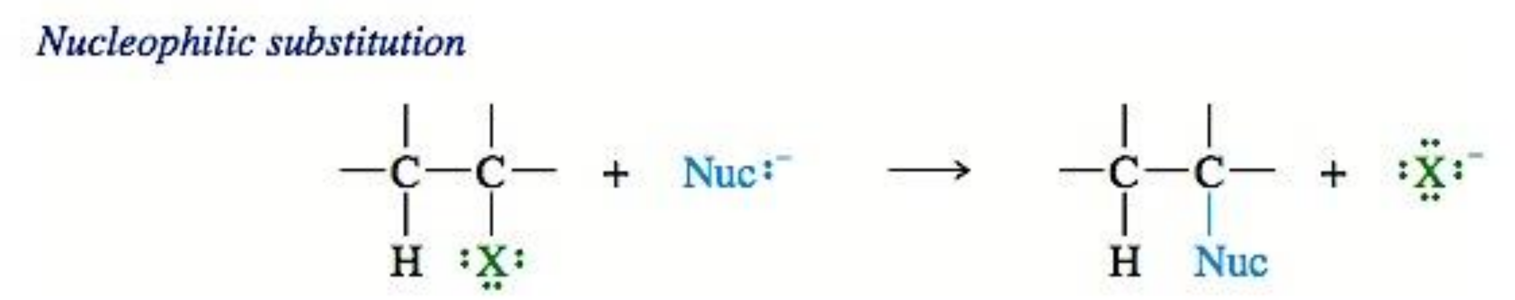


Reactions of Alkyl Halides: Substitution and Elimination

Alkyl halides are easily converted to many other functional groups. The halogen atom can leave with its bonding pair of electrons to form a stable halide ion; we say that a halide is a good **leaving group.** When another atom replaces the halide ion, the reaction is a **substitution.** When the halide ion leaves with another atom or ion (often H+) and forms a new pi bond, the reaction is elimination**.** In many eliminations, a molecule of H ¬ X is lost from the alkyl halide to give an alkene. These eliminations are called **dehydrohalogenations** because a hydrogen halide has been removed from the alkyl halide. Substitution and elimination reactions often compete with each other.

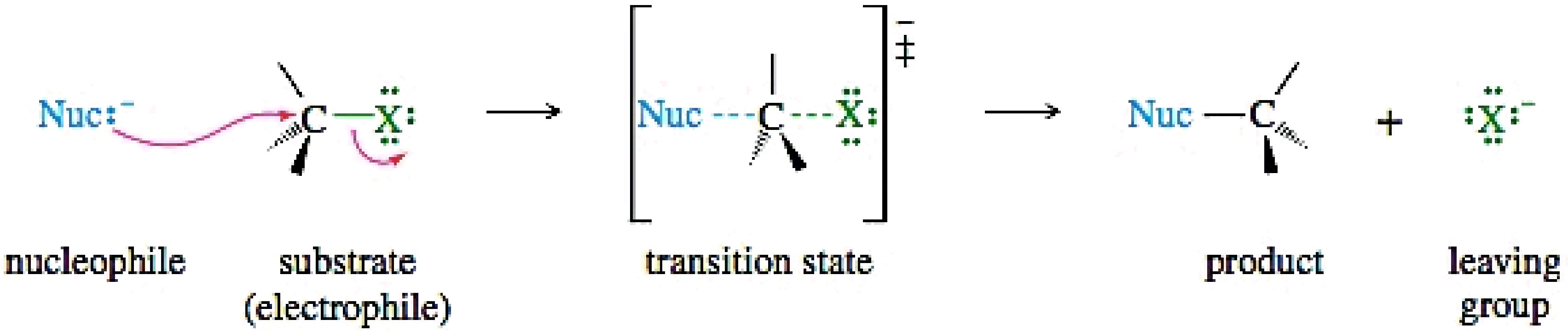
Nucleophilic substitution reactions:

In a **nucleophilic substitution,** a nucleophile (Nuc:$^-$) replaces a leaving group (X$^-$) from a carbon atom, using its lone pair of electrons to form a new bond to the carbon atom.



I) Bimolecular nucleophilic substitution reaction mechanism (S_N2 reaction mechanism):

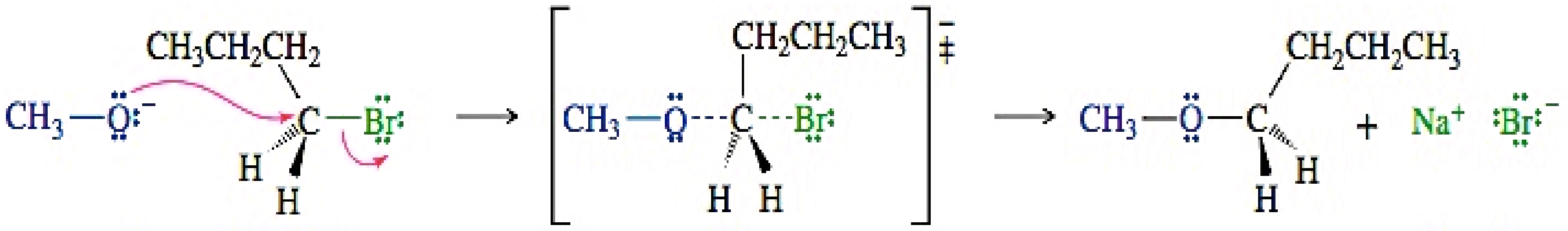
The SN 2 reaction takes place in a single (concerted) step. A strong nucleophile attacks the electrophilic carbon forcing the leaving group to leave.



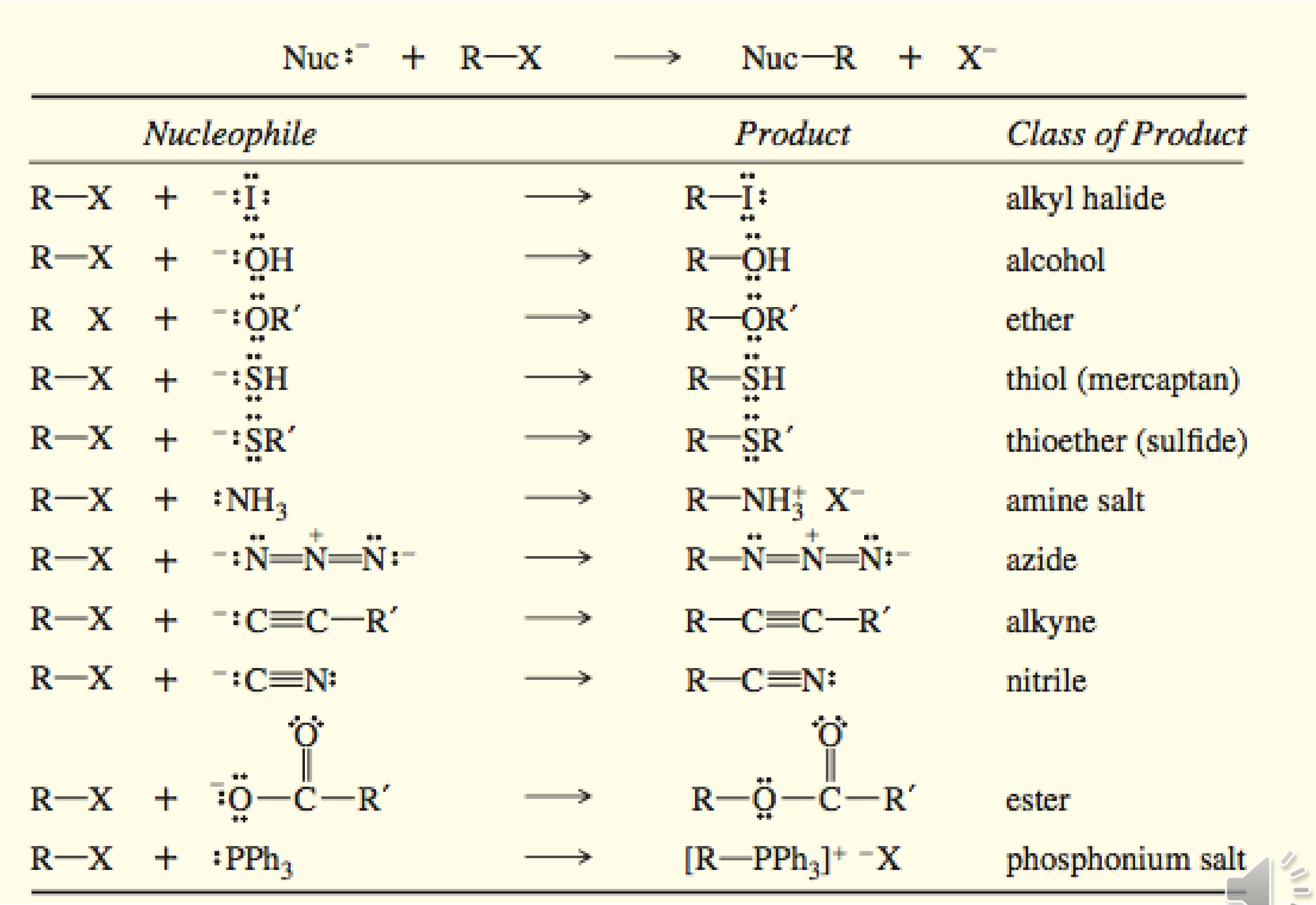
This one-step nucleophilic substitution is an example of the **SN2 mechanism.** The abbreviation SN2 stands for *Substitution, Nucleophilic, bimolecular*. The term *bimolecular* means that the transition state of the rate-limiting step (the only step in this reaction) involves the collision of *two* molecules. Bimolecular reactions usually have rate equations that are second order overall.

EXAMPLE: Reaction of 1-bromobutane with sodium methoxide gives 1-methoxybutane.

$$\underset{\text{sodium methoxide}}{NaOCH_3} + \underset{\text{1-bromobutane}}{CH_3CH_2CH_2CH_2Br} \longrightarrow \underset{\text{1-methoxybutane}}{CH_3CH_2CH_2CH_2OCH_3} + NaBr$$



Many useful reactions take place by the SN2 mechanism. The reaction of an alkyl halide, such as methyl iodide, with hydroxide ion gives an alcohol. Other nucleophiles convert alkyl halides to a wide variety of functional groups. The following table summarizes some of the types of compounds that can be formed by nucleophilic displacement of alkyl halides.



$$\text{Nuc}{:}^{-} + \text{R—X} \longrightarrow \text{Nuc—R} + \text{X}^{-}$$

		Nucleophile		*Product*	*Class of Product*
R—X	+	$^{-}{:}\ddot{\underset{..}{\text{I}}}{:}$	$\longrightarrow$	$\text{R—}\ddot{\underset{..}{\text{I}}}{:}$	alkyl halide
R—X	+	$^{-}{:}\ddot{\underset{..}{\text{O}}}\text{H}$	$\longrightarrow$	$\text{R—}\ddot{\underset{..}{\text{O}}}\text{H}$	alcohol
R X	+	$^{-}{:}\ddot{\underset{..}{\text{O}}}\text{R}'$	$\longrightarrow$	$\text{R—}\ddot{\underset{..}{\text{O}}}\text{R}'$	ether
R—X	+	$^{-}{:}\ddot{\underset{..}{\text{S}}}\text{H}$	$\longrightarrow$	$\text{R—}\ddot{\underset{..}{\text{S}}}\text{H}$	thiol (mercaptan)
R—X	+	$^{-}{:}\ddot{\underset{..}{\text{S}}}\text{R}'$	$\longrightarrow$	$\text{R—}\ddot{\underset{..}{\text{S}}}\text{R}'$	thioether (sulfide)
R—X	+	$:\text{NH}_3$	$\longrightarrow$	$\text{R—NH}_3^{+}\ \text{X}^{-}$	amine salt
R—X	+	$^{-}{:}\ddot{\text{N}}{=}\overset{+}{\text{N}}{=}\ddot{\text{N}}{:}^{-}$	$\longrightarrow$	$\text{R—}\ddot{\text{N}}{=}\overset{+}{\text{N}}{=}\ddot{\text{N}}{:}^{-}$	azide
R—X	+	$^{-}{:}\text{C}{\equiv}\text{C—R}'$	$\longrightarrow$	$\text{R—C}{\equiv}\text{C—R}'$	alkyne
R—X	+	$^{-}{:}\text{C}{\equiv}\text{N}{:}$	$\longrightarrow$	$\text{R—C}{\equiv}\text{N}{:}$	nitrile
R—X	+	$^{-}{:}\ddot{\underset{..}{\text{O}}}\text{—}\overset{\overset{\displaystyle :\ddot{\text{O}}:}{\Vert}}{\text{C}}\text{—R}'$	$\longrightarrow$	$\text{R—}\ddot{\underset{..}{\text{O}}}\text{—}\overset{\overset{\displaystyle :\ddot{\text{O}}:}{\Vert}}{\text{C}}\text{—R}'$	ester
R—X	+	$:\text{PPh}_3$	$\longrightarrow$	$[\text{R—PPh}_3]^{+}\ {}^{-}\text{X}$	phosphonium salt

Halogen Exchange Reactions

The SN2 reaction provides a useful method for synthesizing alkyl iodides and fluorides, which are more difficult to make than alkyl chlorides and bromides. Halides can be converted to other halides by **halogen exchange reactions,** in which one halide displaces another.

$$R{-}X + I^- \longrightarrow R{-}I + X^-$$

$$R{-}X + KF \xrightarrow[CH_3CN]{\text{18-crown-6}} R{-}F + KX$$

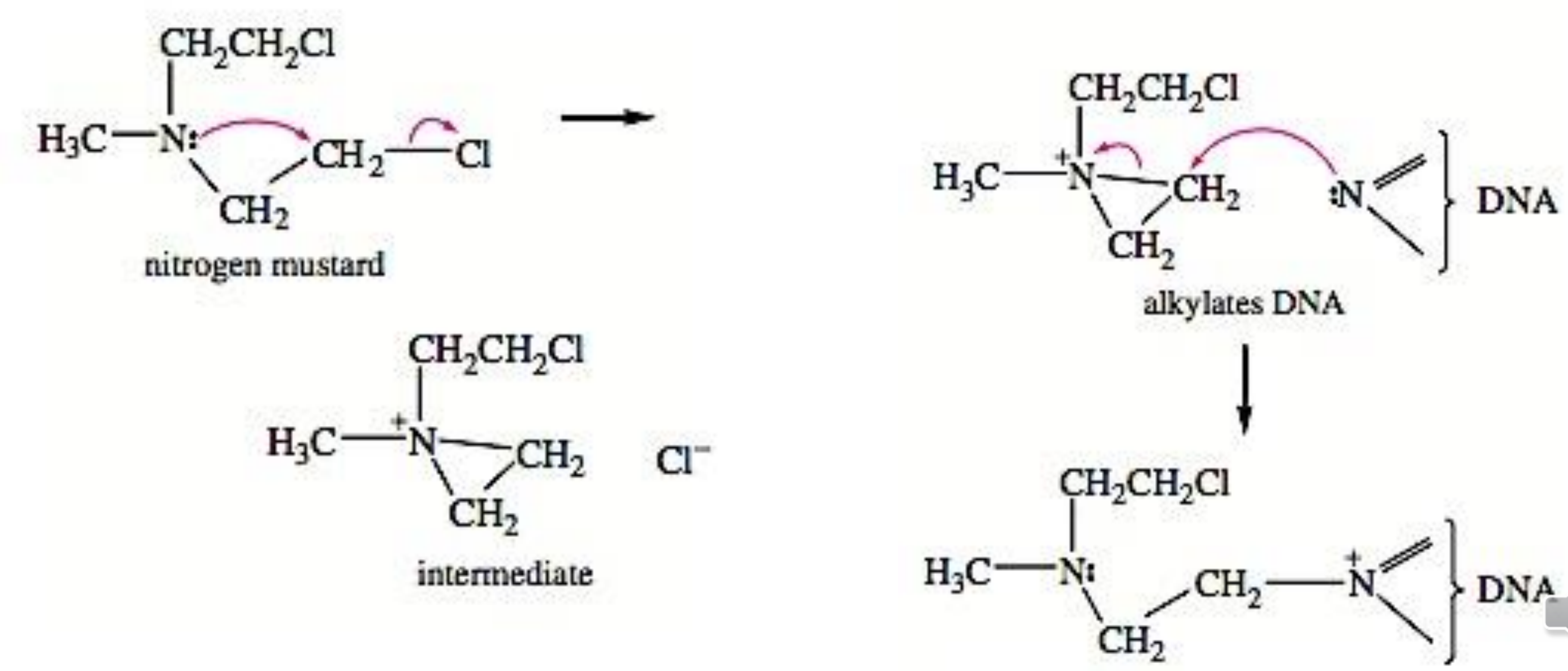
Examples

$$\underset{\text{allyl chloride}}{H_2C{=}CH{-}CH_2Cl} + NaI \longrightarrow \underset{\text{allyl iodide}}{H_2C{=}CH{-}CH_2I} + NaCl$$

$$\underset{\text{ethyl chloride}}{CH_3CH_2Cl} + KF \xrightarrow[CH_3CN]{\text{18-crown-6}} \underset{\text{ethyl fluoride}}{CH_3CH_2F} + KCl$$

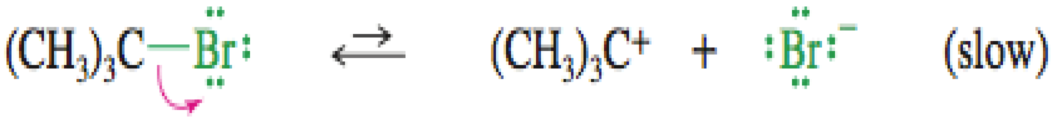
Application:

The “**nitrogen mustard**” anticancer drugs are believed to alkylate DNA using two S_N2 reactions. First, the nitrogen nucleophile displaces chloride on the primary alkyl chloride portion to generate a reactive intermediate that alkylates a nitrogen atom of DNA. The process is repeated, linking the two strands of the double-helix DNA, and thereby preventing replication of the DNA.



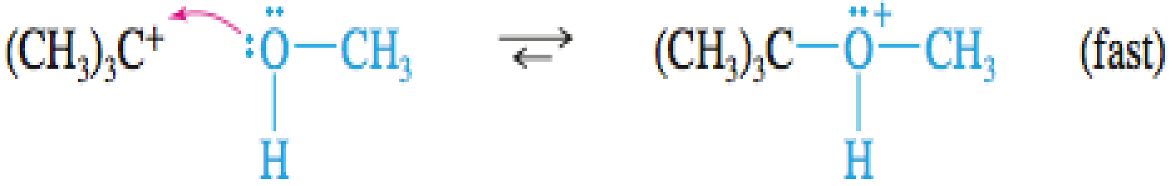
1st order Nucleophilic substitution
S_N1

Step 1: Formation of carbocation (rate limiting)



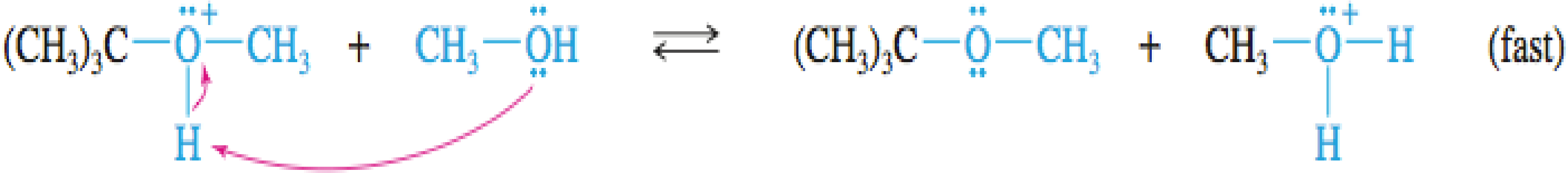
$$(CH_3)_3C-\ddot{\underset{\cdot\cdot}{Br}}: \rightleftharpoons (CH_3)_3C^+ + :\ddot{\underset{\cdot\cdot}{Br}}:^- \quad \text{(slow)}$$

Step 2: Nucleophilic attack on the carbocation



$$(CH_3)_3C^+ \quad :\underset{\displaystyle H}{\overset{\cdot\cdot}{O}}-CH_3 \rightleftharpoons (CH_3)_3C-\underset{\displaystyle H}{\overset{\cdot\cdot\,+}{O}}-CH_3 \quad \text{(fast)}$$

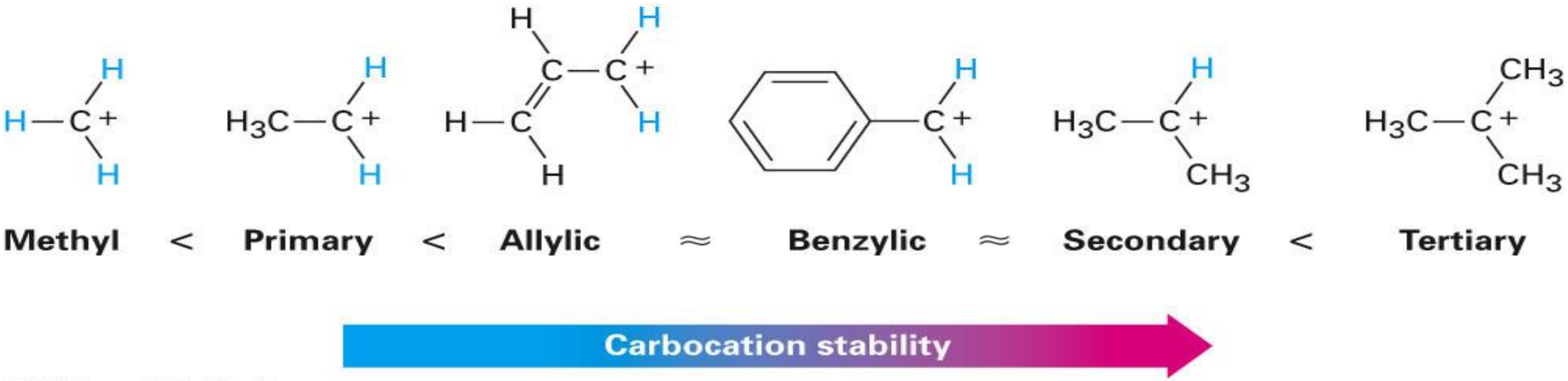
Final Step: Loss of proton to solvent



$$(CH_3)_3C-\underset{\displaystyle H}{\overset{\cdot\cdot\,+}{O}}-CH_3 + CH_3-\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}H \rightleftharpoons (CH_3)_3C-\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}-CH_3 + CH_3-\underset{\displaystyle H}{\overset{\cdot\cdot\,+}{O}}-H \quad \text{(fast)}$$

Substrate

- Tertiary alkyl halide is most reactive by this mechanism
  - Controlled by stability of carbocation



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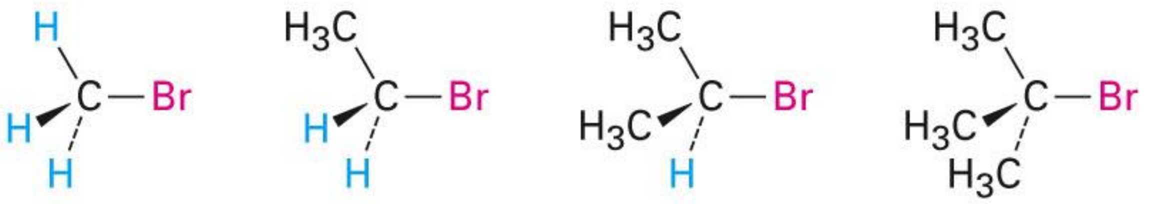
- Allylic and benzylic intermediates stabilized by delocalization of charge
  - Primary, allylic and benzylic are also more reactive in the S_N**2** mechanism

$R-Br + H_2O \dashrightarrow R-OH + HBr$



	Methyl	**Primary**	**Secondary**	**Tertiary**
Relative reactivity	< 1	1	12	1,200,000

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# of carbons attached to carbocation:	3	2	1	0
	"tertiary"	*"secondary"*	*"primary"*	*"methyl"*

Most stable → Least stable