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Pravara Rural Education Society

Arts, Science & Commerce College Kolhar

Organic Chemistry

Class- T.Y.B.Sc.

Nucleophilic Substitution Reactions : The SN1 and SN2 Mechanisms

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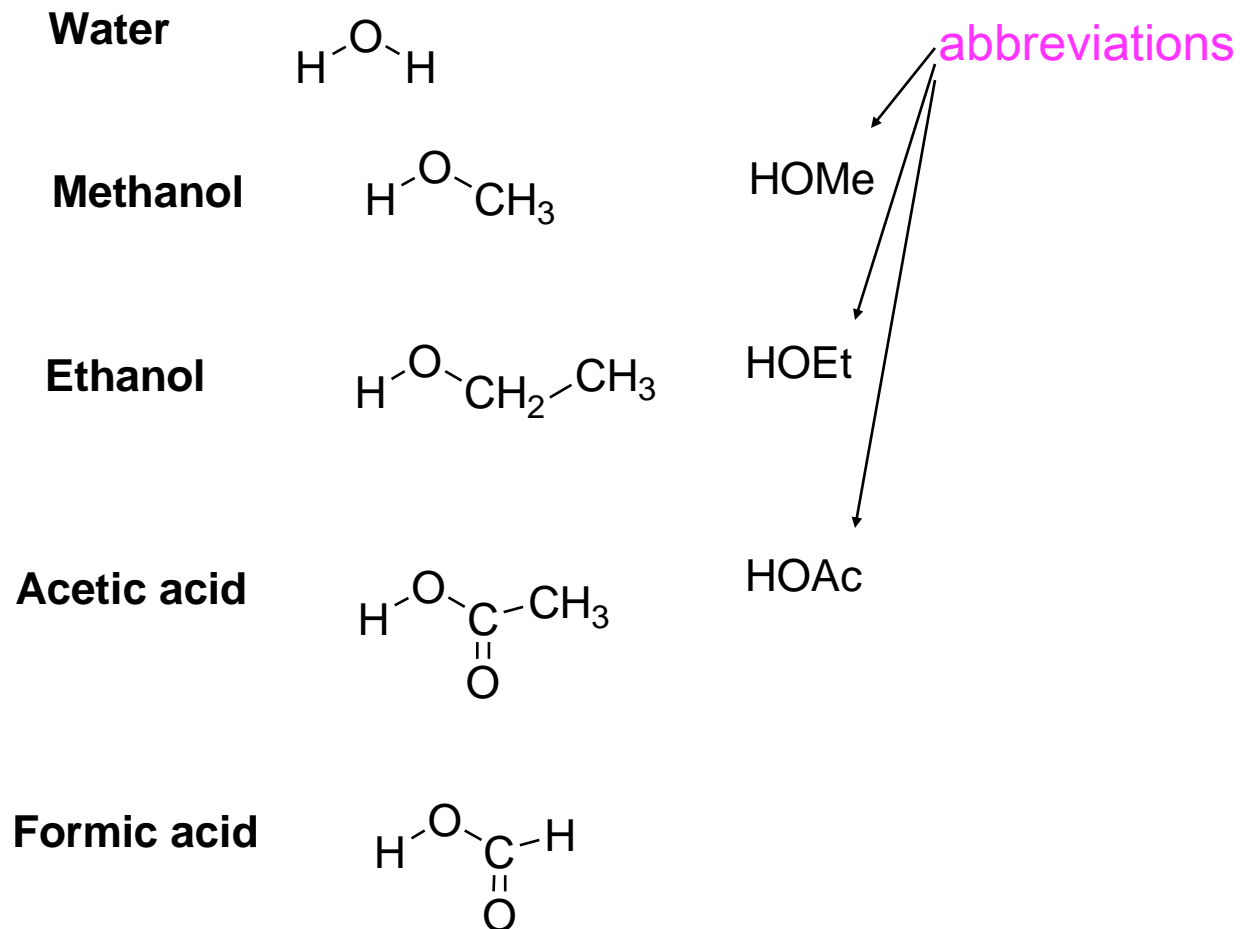
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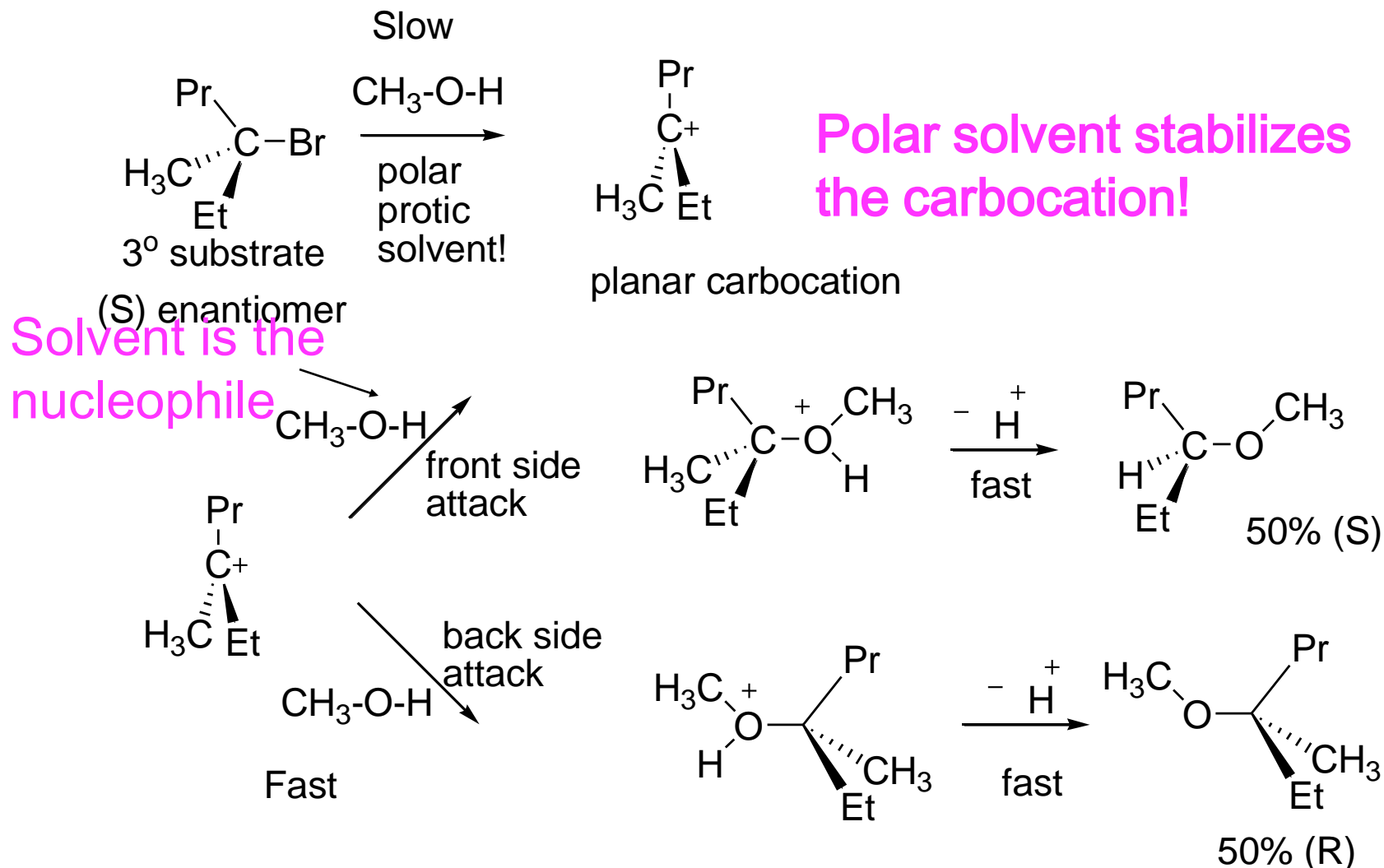
# Nucleophiles

- Usually  $S_N1$  reactions are run in polar protic solvents; compounds with O-H groups.
- The polar protic solvent acts as ***BOTH*** nucleophile as well as the solvent.
- Common solvent/nucleophiles include: water, ethanol, methanol, acetic acid, and formic acid.

# A protic solvent acts as both a solvent and nucleophile in $S_N1$ reactions - solvolysis:



# Typical solvolysis reaction



# Leaving groups

- Leaving groups are the same as in  $S_N2$  reactions:
- Cl, Br, I, OTs are the usual ones.

# $S_N1$ Reaction: solvent polarity

- $S_N1$  solvolysis reactions go much faster in trifluoroacetic acid and water (high ionizing power).
- $S_N1$  solvolysis reactions go slower in ethanol and acetic acid (lower ionizing power).
- See table 10-9.

# $S_N2$ versus $S_N1$ Reactions

- A *primary* alkyl halide or a methyl halide should react by an  $S_N2$  process. Look for a good nucleophile, such as hydroxide, methoxide, etc. in an polar ***aprotic*** solvent.
- A *tertiary* alkyl halide should react by an  $S_N1$  mechanism. Make sure to run the reaction under ***solvolysis*** (polar protic solvent) conditions! Don't use strong base conditions -- it will give you nothing but E2 elimination!
- A *secondary* alkyl halide can go by *either* mechanism. Look at the solvent/nucleophile conditions!!

# $S_N2$ versus $S_N1$ Reactions (continued)

- If the reaction medium is KI or NaI in acetone, this *demand*s an  $S_N2$  mechanism.
- If the reaction medium is  $AgNO_3$  in ethanol, this *demand*s an  $S_N1$  mechanism.
- If the medium is basic, look for  $S_N2$ .
- If the medium is acidic or neutral, expect  $S_N1$ .



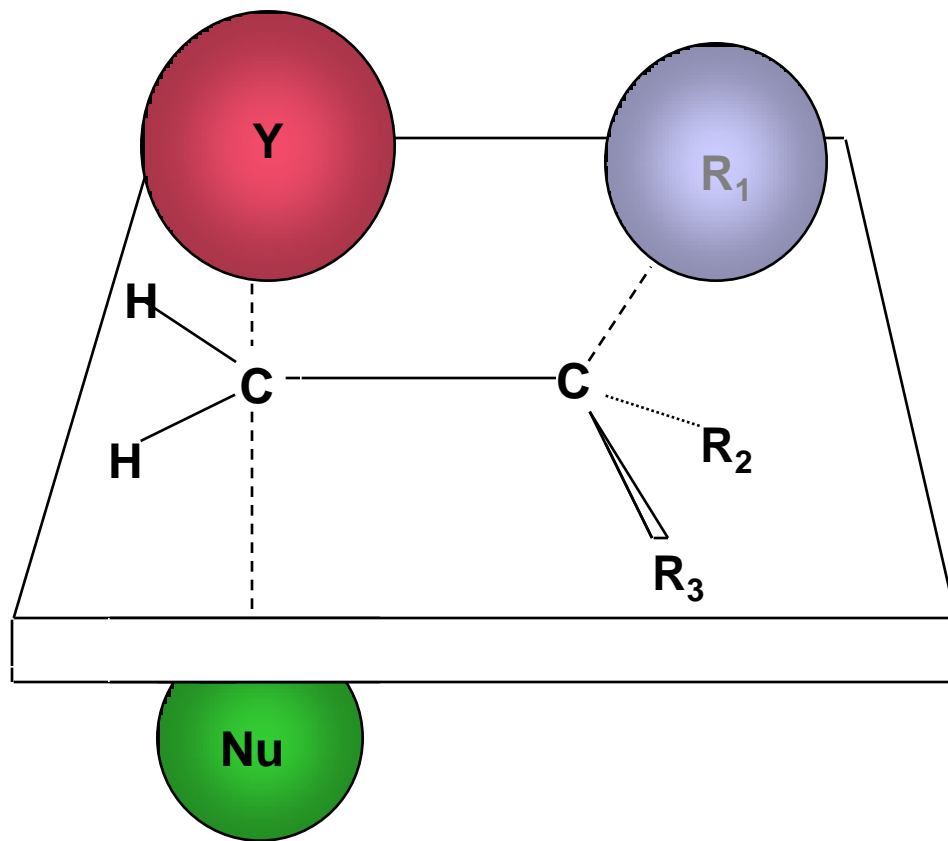
# classification tests

- Sodium iodide and potassium iodide in acetone are typical  $S_N2$  reagents!!
- Silver nitrate in ethanol is a typical  $S_N1$  reagent!!

# Effect of $\beta$ -substitution on $S_N2$ reactivity

	<u><math>k_{rel}</math></u>
$\text{H}-\overset{\beta}{\text{CH}_2}-\text{CH}_2-\text{Br}$	1.0
$\text{CH}_3-\overset{\beta}{\text{CH}_2}-\text{CH}_2-\text{Br}$	0.65
$\begin{array}{c} \text{CH}_3 \\   \\ \text{CH}_3-\text{CH}-\text{CH}_2-\text{Br} \\ \beta \end{array}$	0.15
$\begin{array}{c} \text{CH}_3 \\   \\ \text{CH}_3-\text{C}-\text{CH}_2-\text{Br} \\   \\ \text{CH}_3 \\ \beta \end{array}$ Neopentyl bromide	0.000026

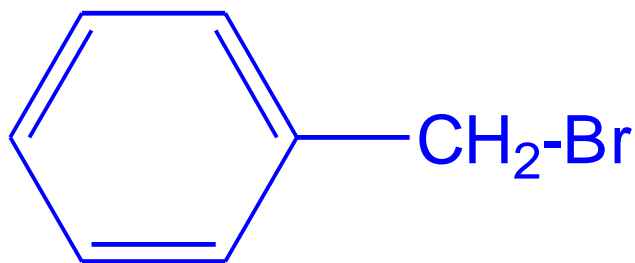
# Neopentyl Transition State



# Allylic and Benzylic compounds

Allylic and benzylic compounds are especially reactive in  $S_N1$  reactions.

Even though they are primary substrates, they are more reactive most other halides! They form resonance stabilized carbocations.



benzyl bromide



allyl bromide

# Solvolysis Rates: S<sub>N</sub>1

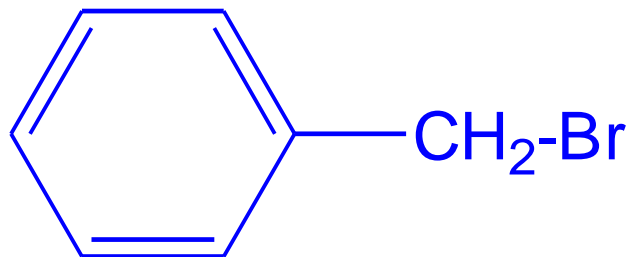
	$k_{rel}$
Ethyl chloride	very small
Isopropyl chloride	1
Allyl chloride	74
Benzyl chloride	140
tert-Butyl chloride	12,000

**80% Ethanol-water at 50°**

# Allylic and Benzylic compounds

Allylic and benzylic compounds are especially reactive in  $S_N2$  reactions.

They are more reactive than typical primary compounds!



benzyl bromide



allyl bromide

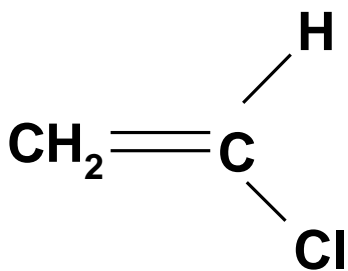
# Reaction with KI in Acetone: $S_N2$

	$k_{rel}$
Ethyl chloride	1
Allyl chloride	33
Methyl chloride	93
Benzyl chloride	93

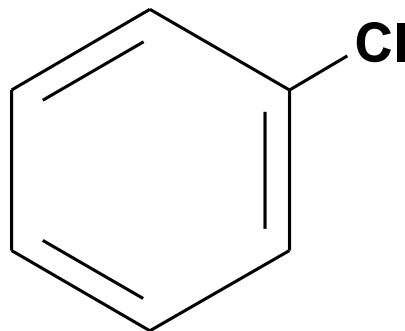
60° C

# Vinyl and Phenyl Compounds

Vinyl and Phenyl compounds are completely inert in both  $S_N1$  and  $S_N2$  reactions!!



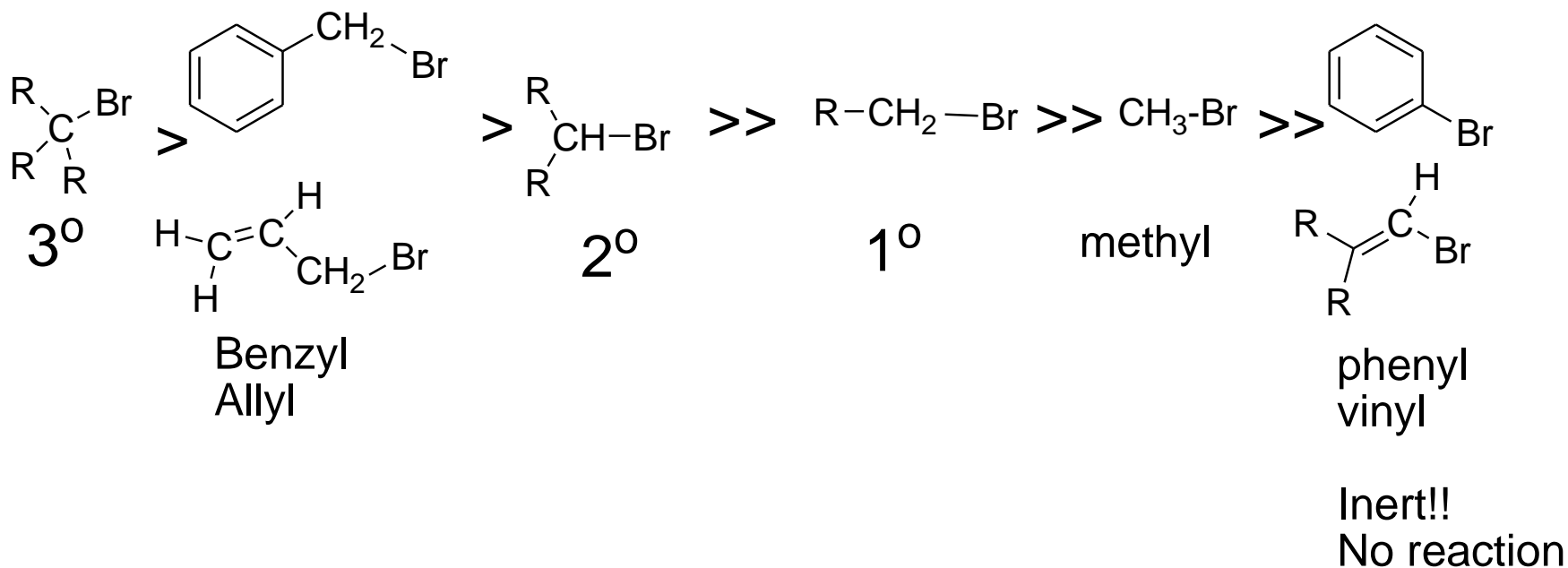
vinyl



phenyl

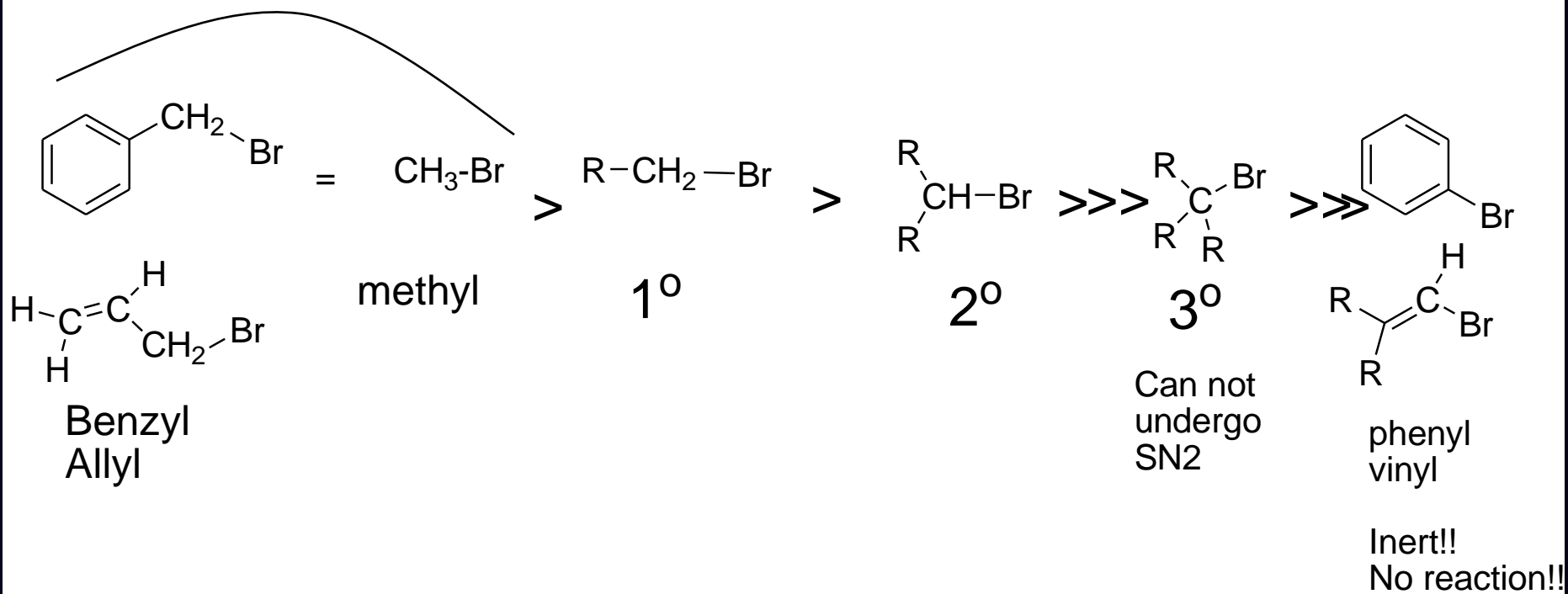


# Reactivity order for S<sub>N</sub>1



# Reactivity order for S<sub>N</sub>2

About same reactivity



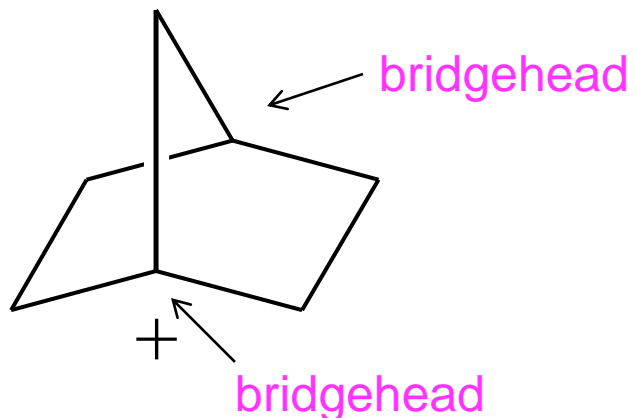
# Cyclic Systems

- Cyclopropyl and cyclobutyl halides are very unreactive in both  $S_N1$  and  $S_N2$  reactions
- Cyclopentyl halides are more reactive than cyclohexyl halides in  $S_N1$  and  $S_N2$  reactions.

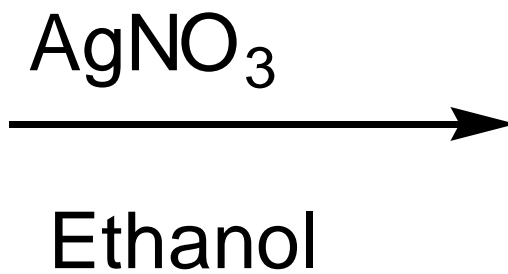
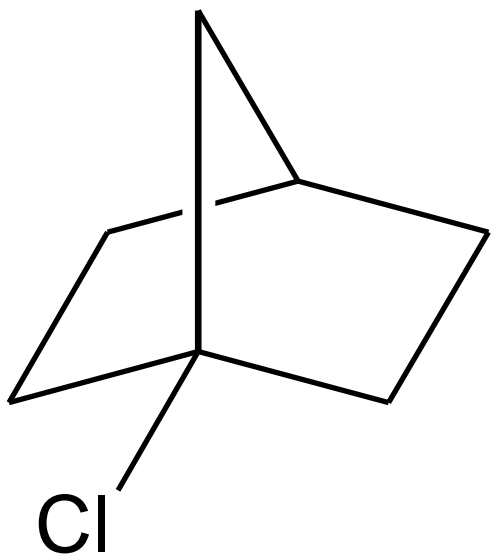
# Bicyclic systems: Bredt's Rule

You can't have  $p$  orbitals on a bridgehead position in a rigid bicyclic molecule.

-- You cannot form a carbocation at a bridgehead position.

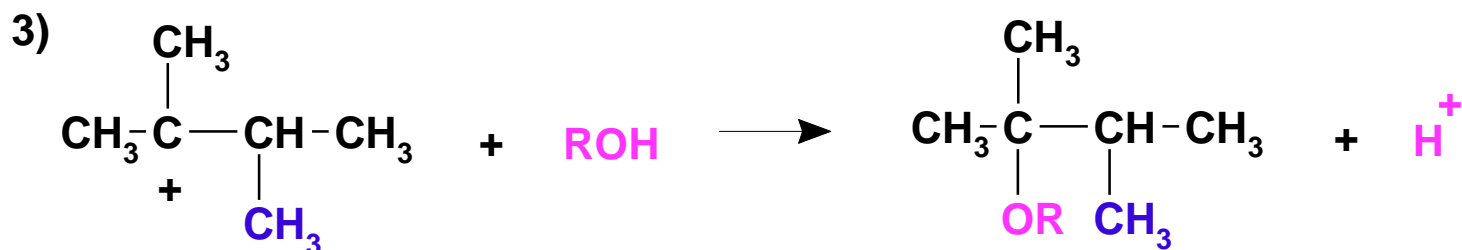
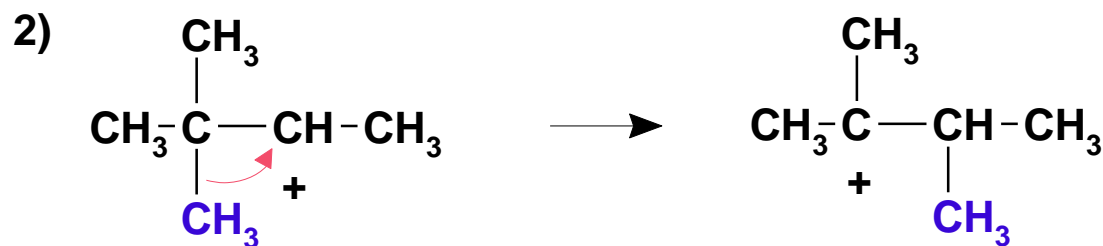
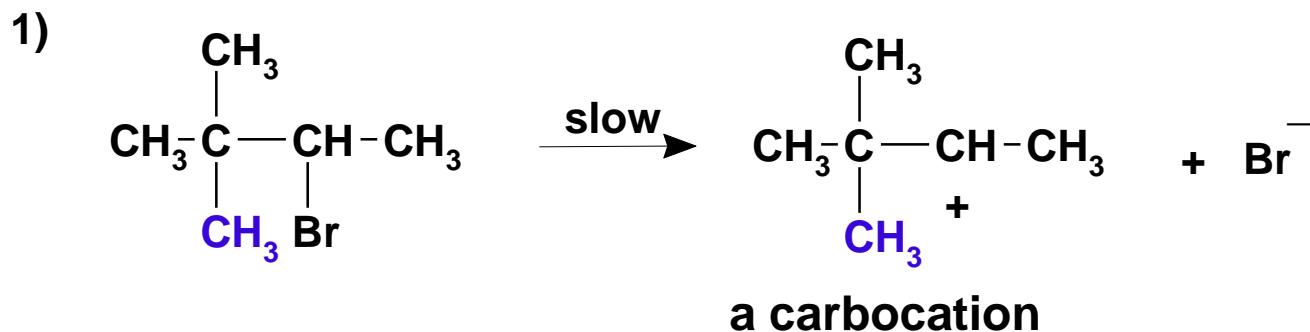


-- You cannot have a double bond at a bridgehead position.

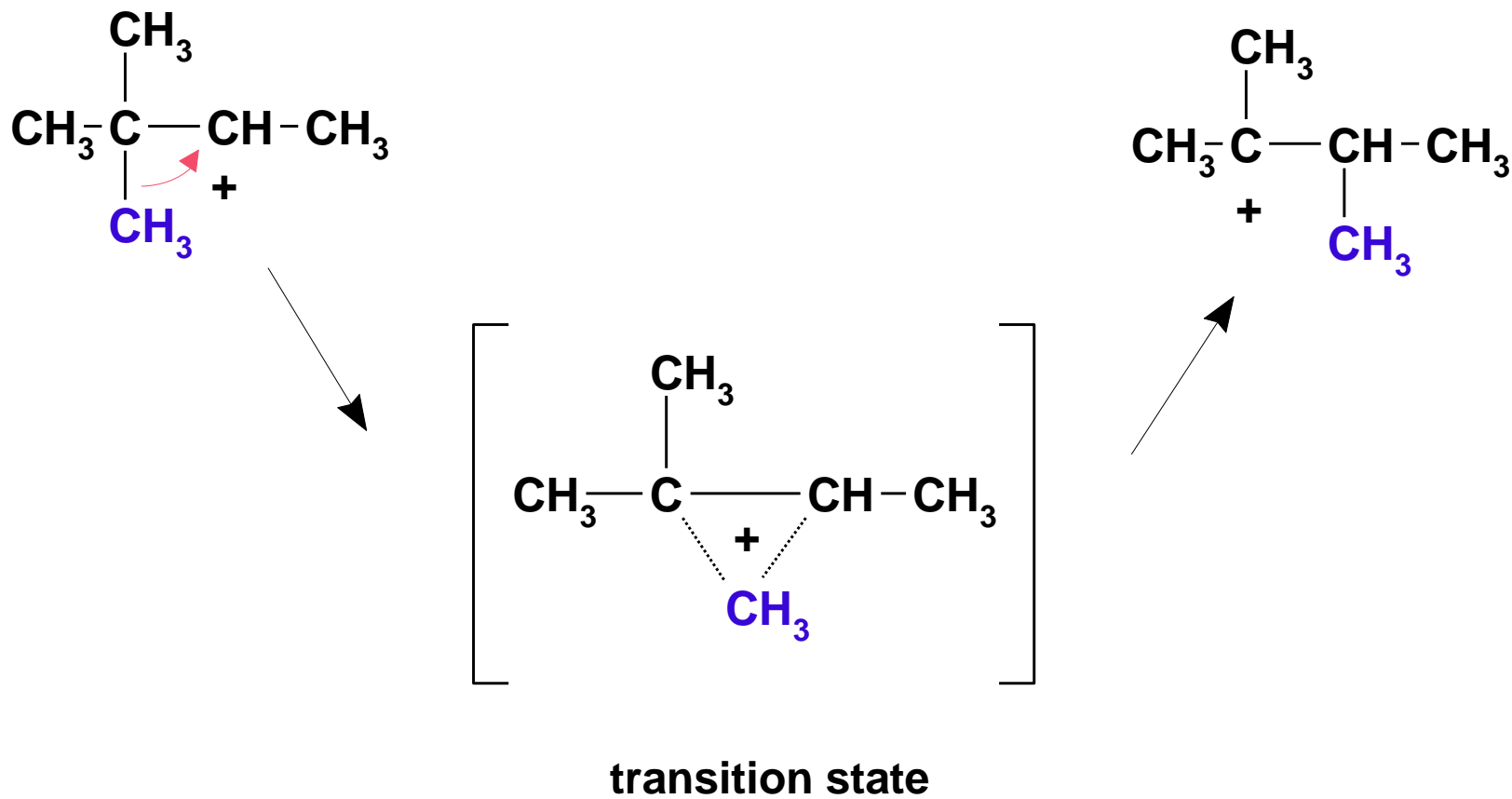


No reaction!

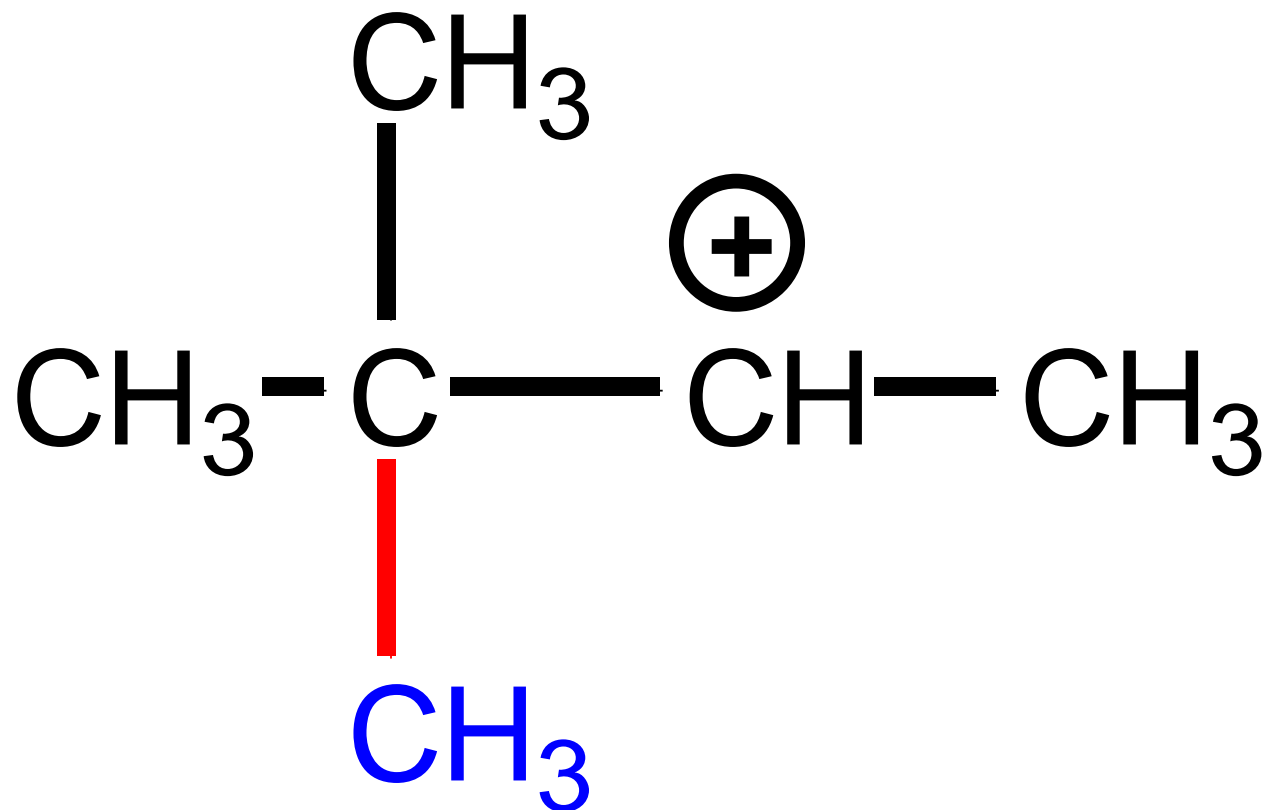
# Carbocation Rearrangement



# A Closer Look...

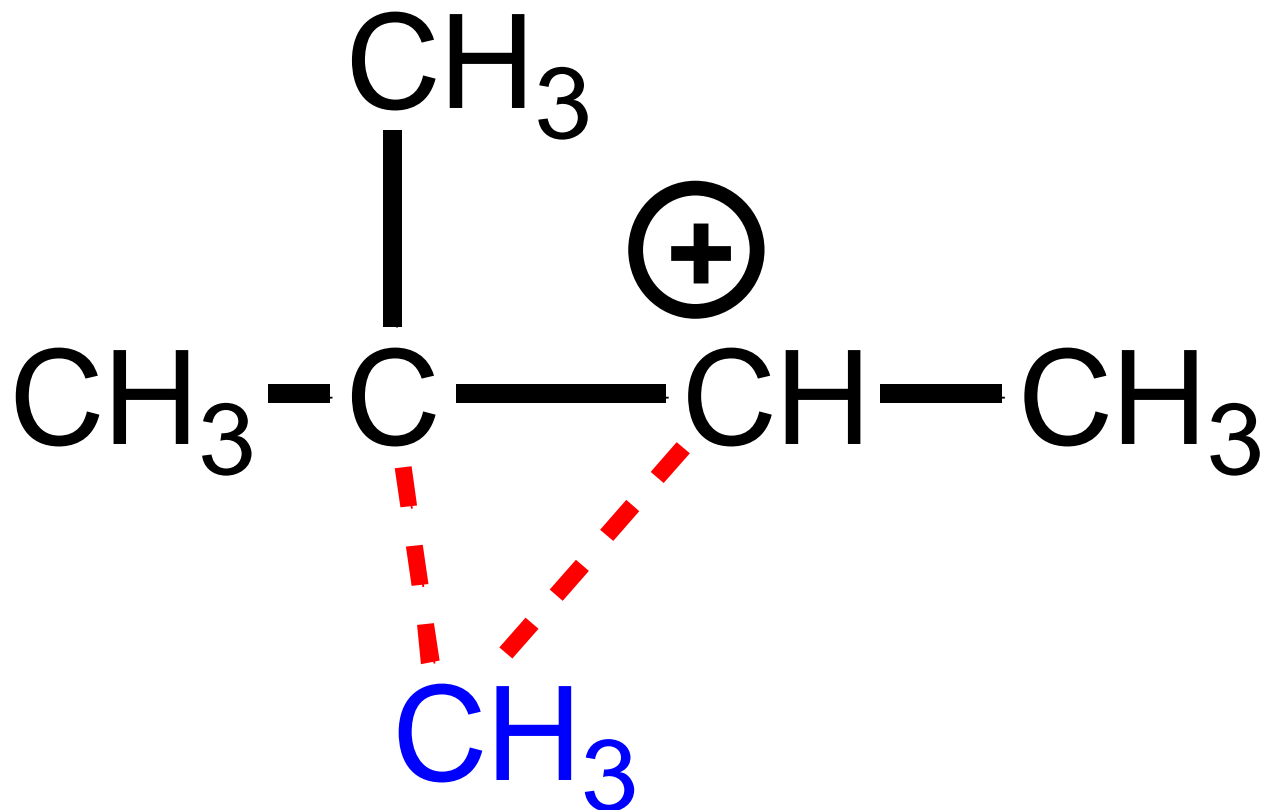


# Carbocation Rearrangement

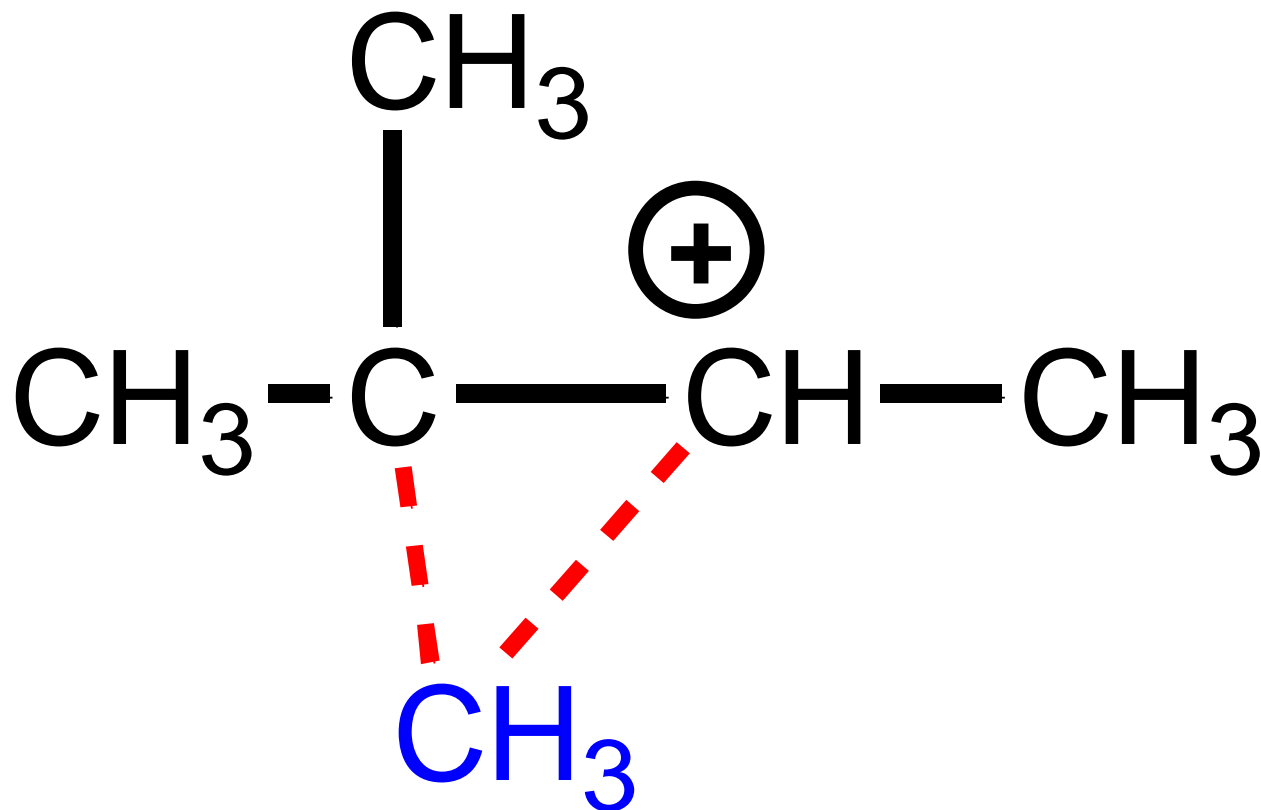




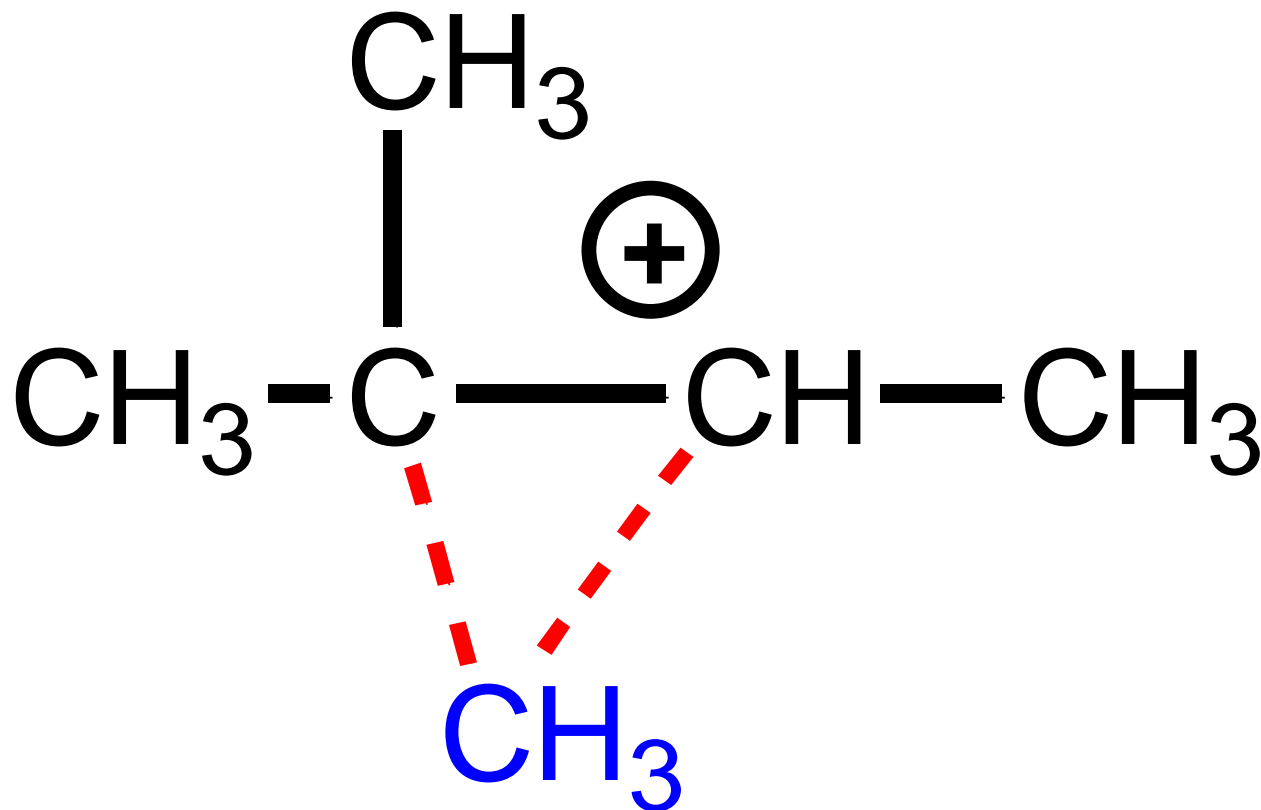
# Carbocation Rearrangement



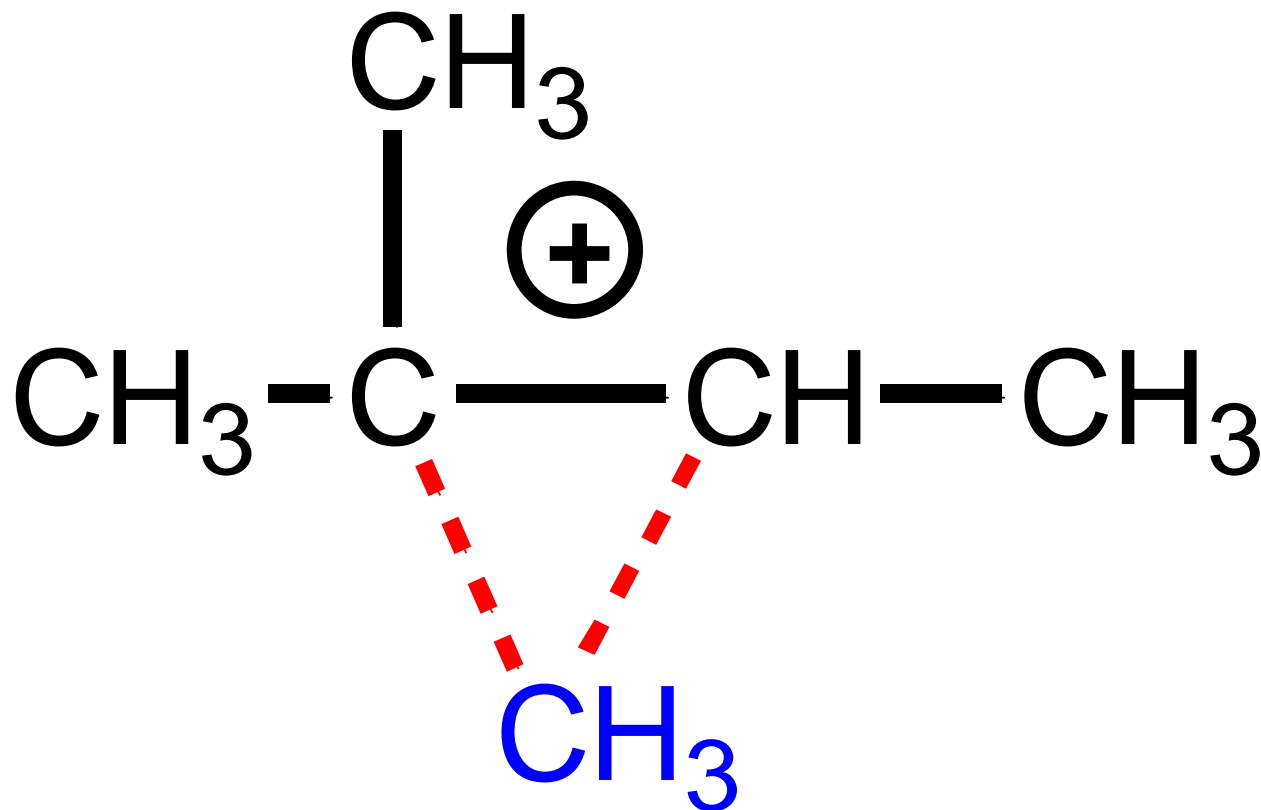
# Carbocation Rearrangement



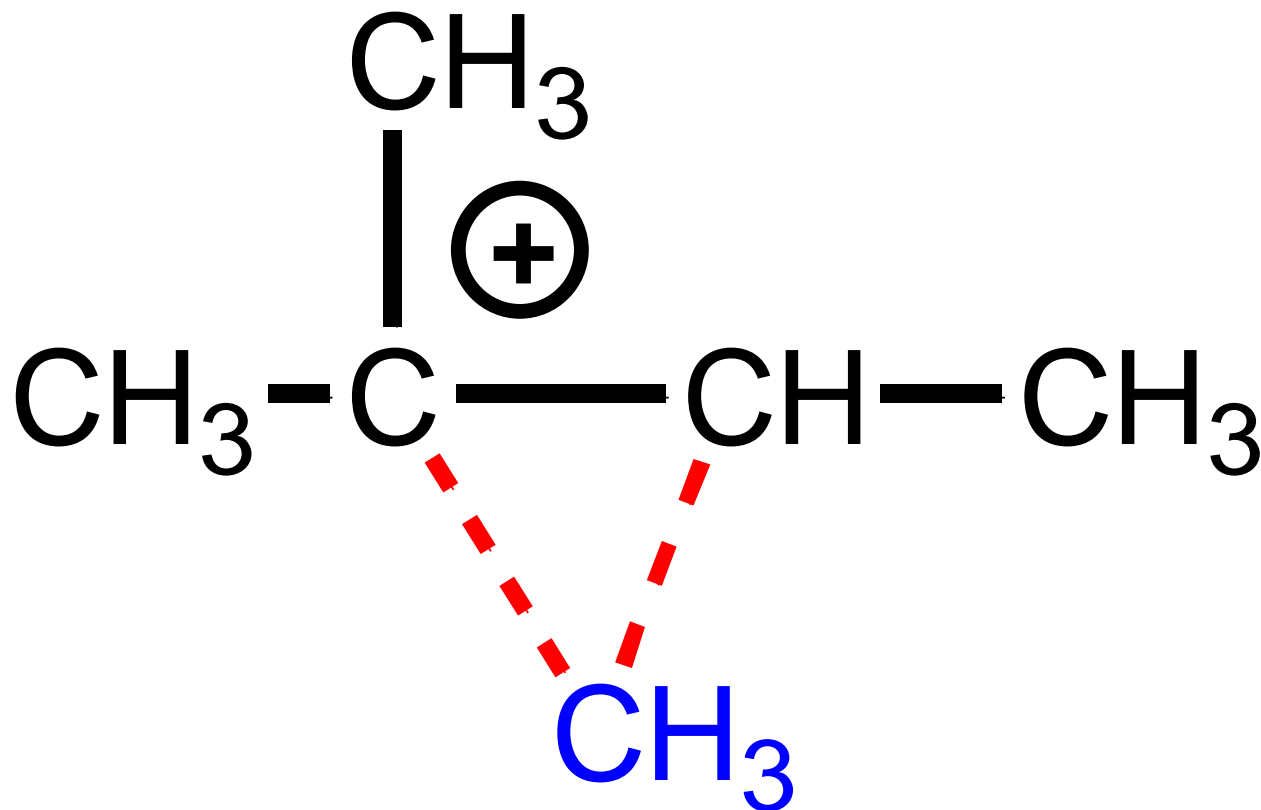
# Carbocation Rearrangement



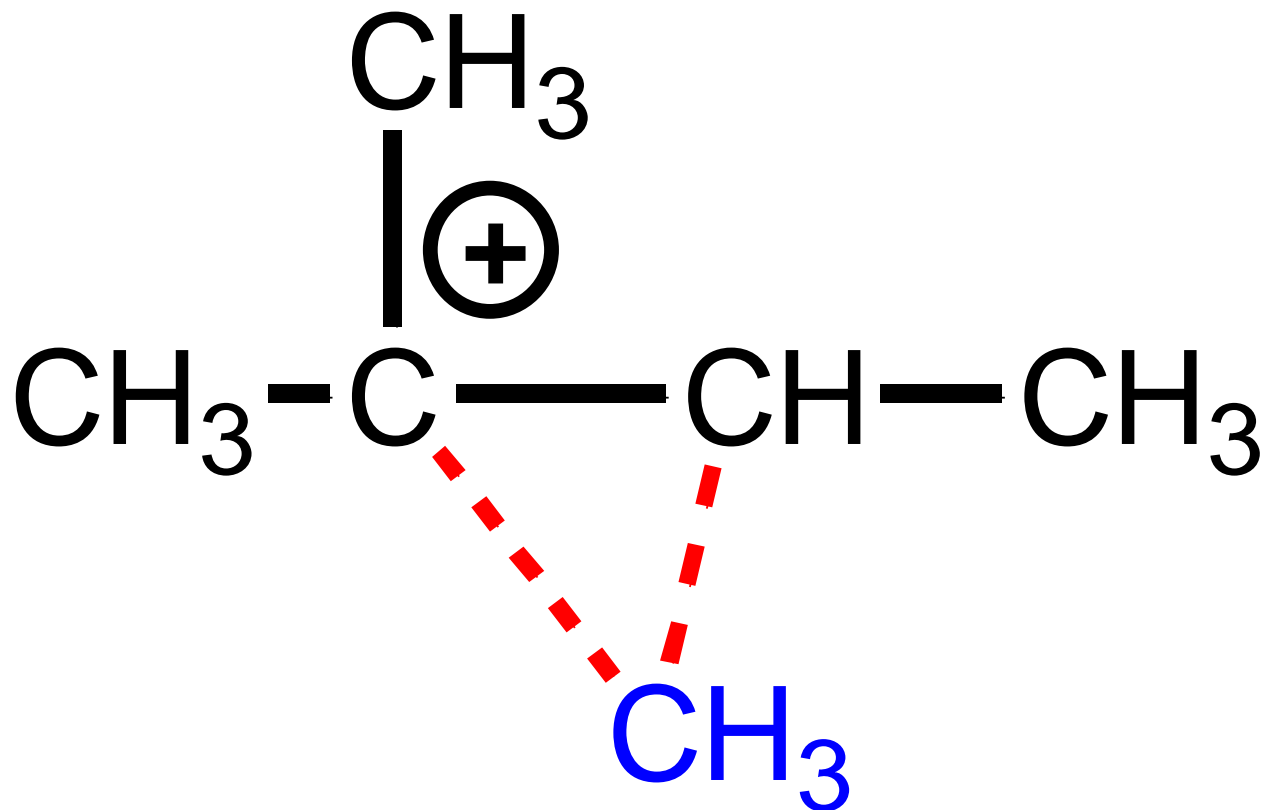
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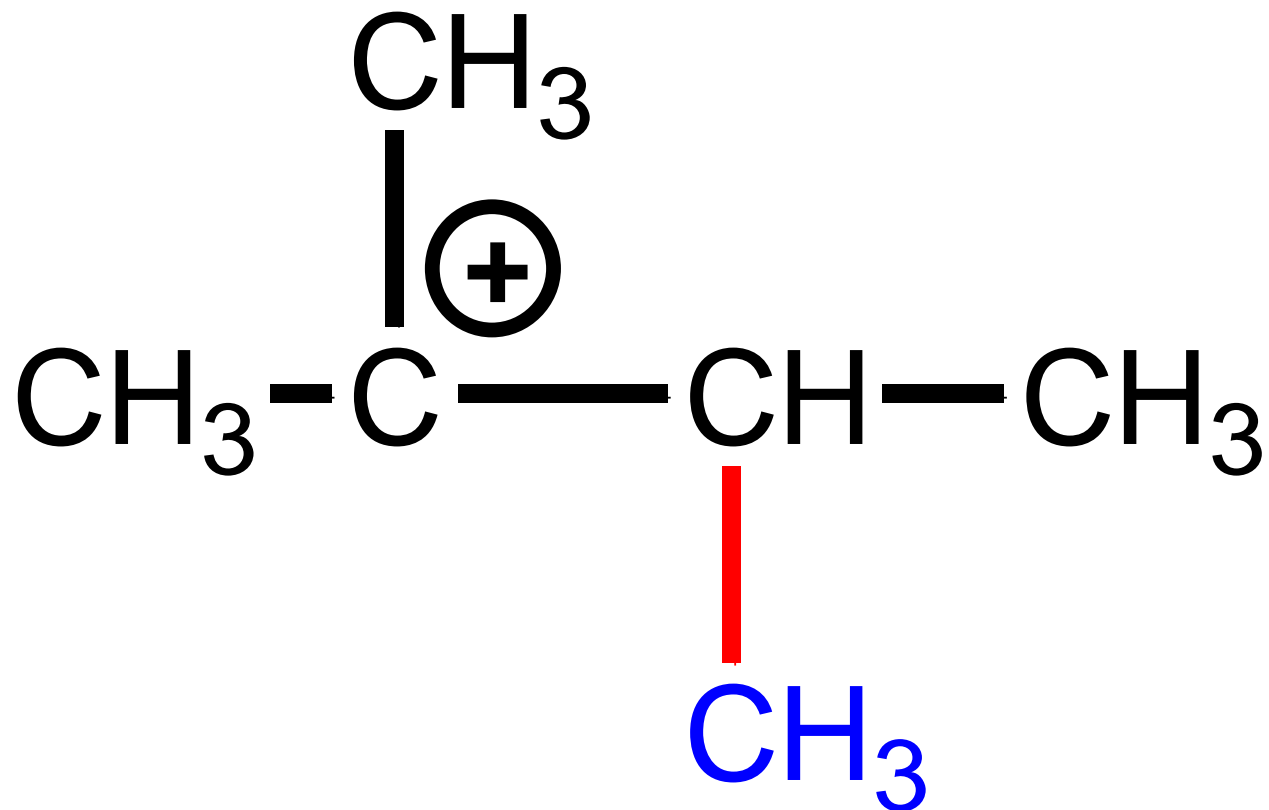
# Carbocation Rearrangement



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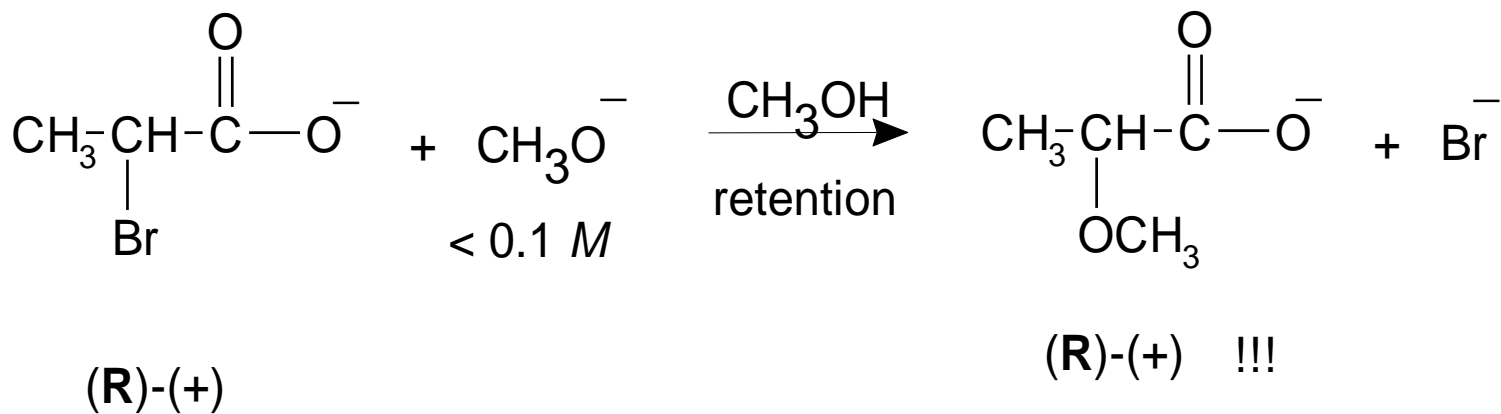
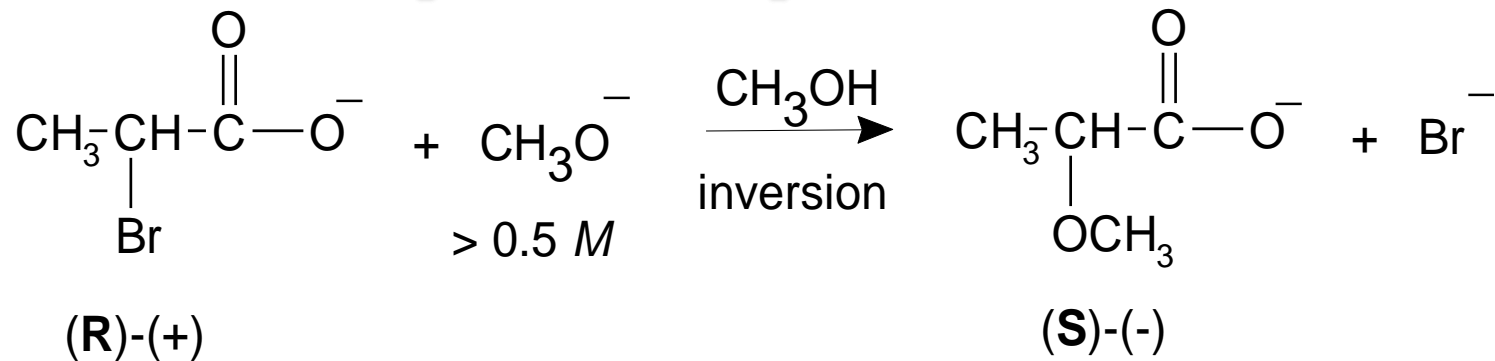


# Competing Reactions: Elimination

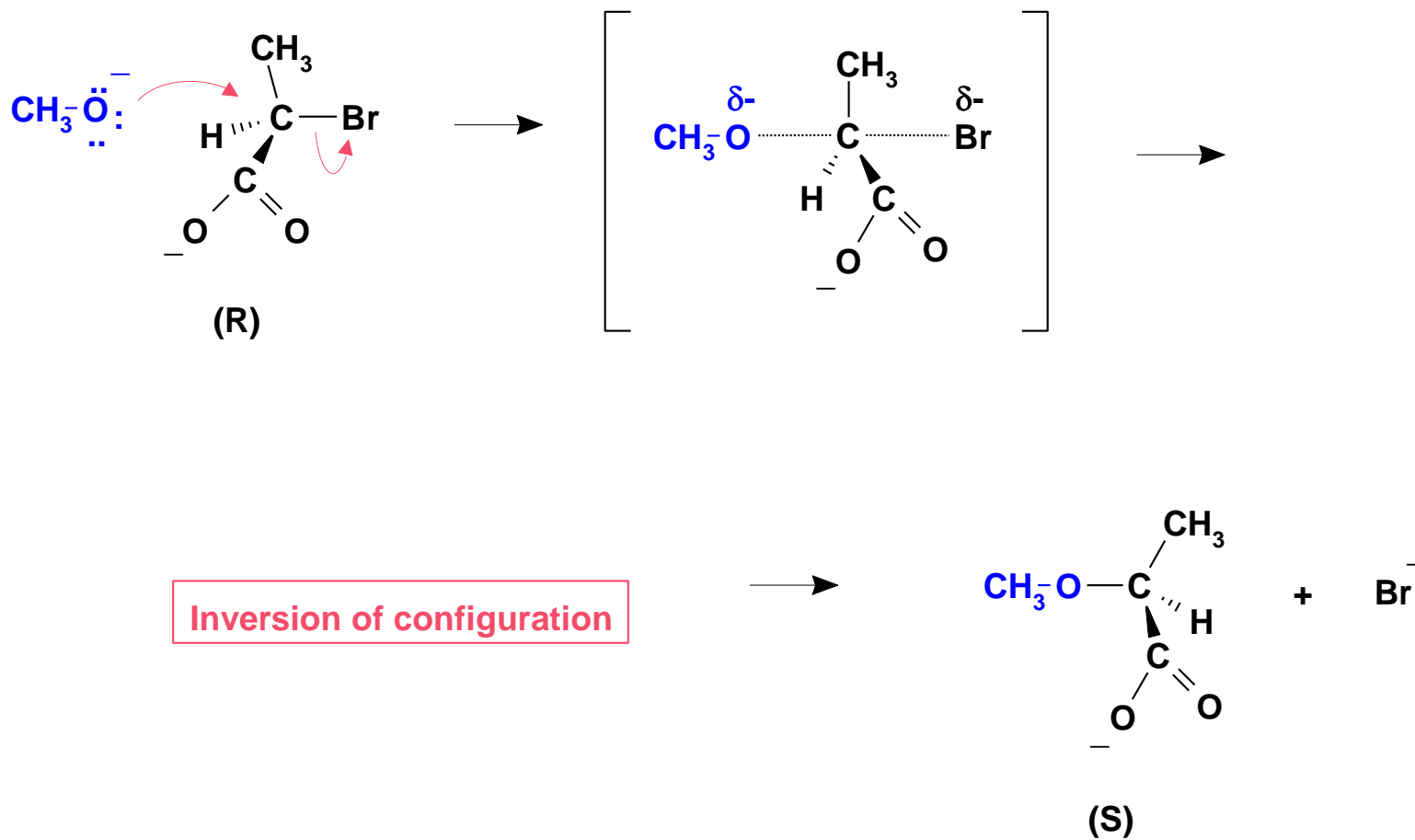
- Lower temperatures favor substitution; higher temperatures give more elimination.
- Highly branched compounds (secondary and tertiary compounds) give mostly elimination with strong bases. Weaker bases give more substitution. A basic medium favors E2; a more nucleophilic medium favors S<sub>N</sub>2.
- Primary compounds give mostly substitution with non-bulky nucleophiles. A bulky base (tert-butoxide) gives elimination.
- Tertiary compounds should be reacted under solvolysis conditions to give substitution!!!



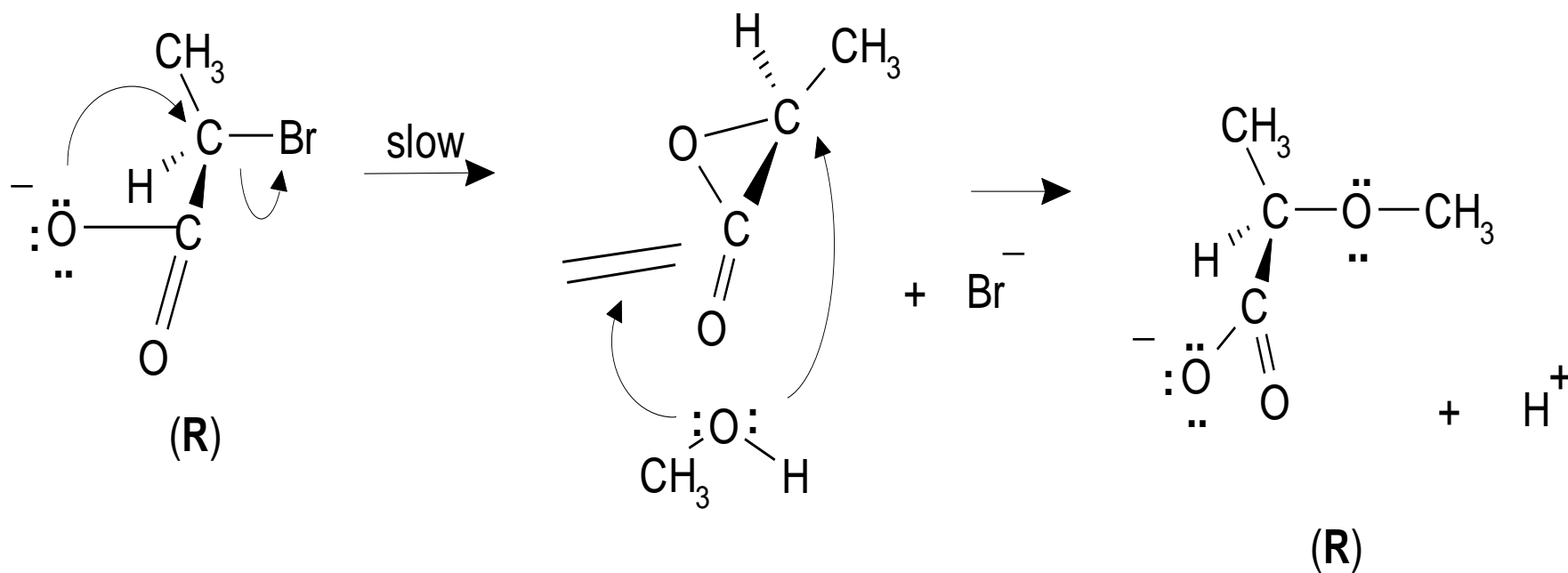
# Neighboring group participation



# Under S<sub>N</sub>2 Conditions

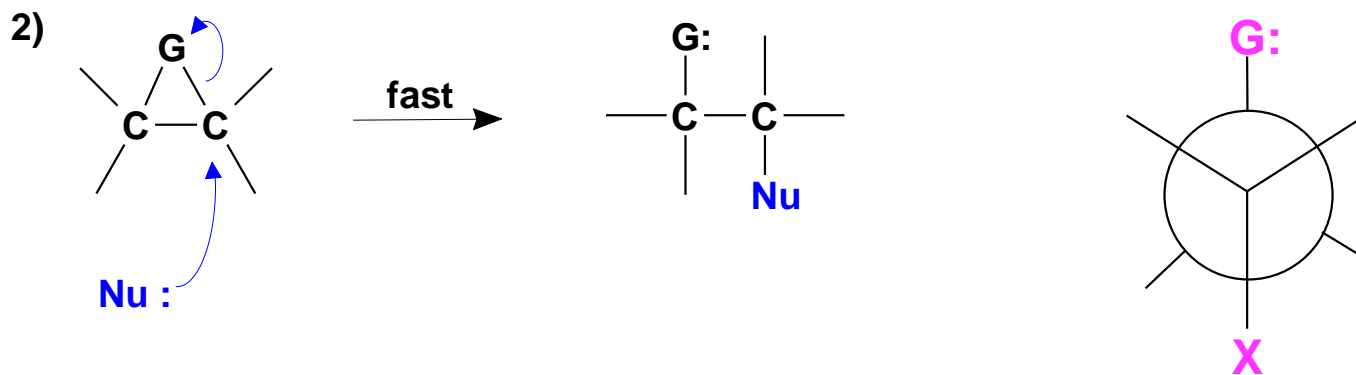
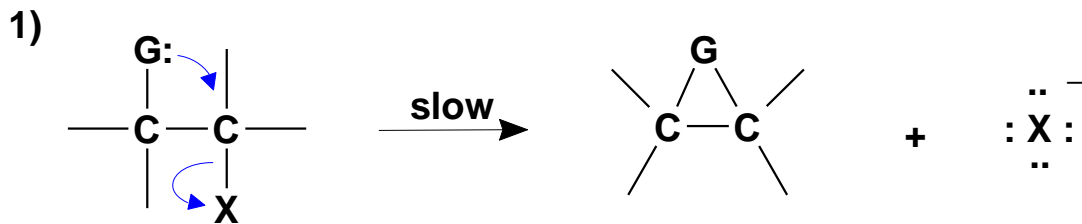


# Internal S<sub>N</sub>2 reaction followed by an external S<sub>N</sub>2 reaction



Retention of Configuration

# Neighboring Group Participation

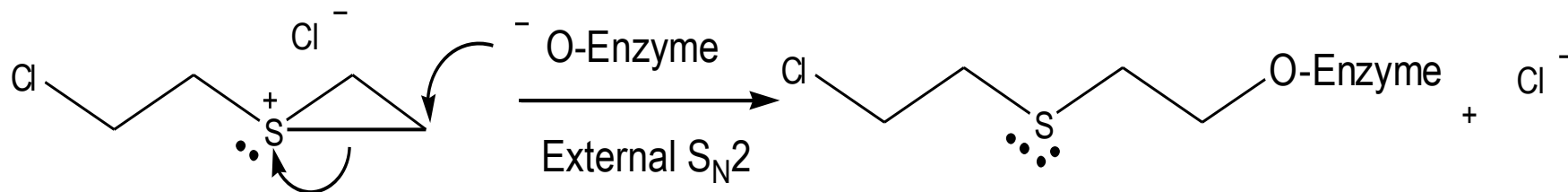
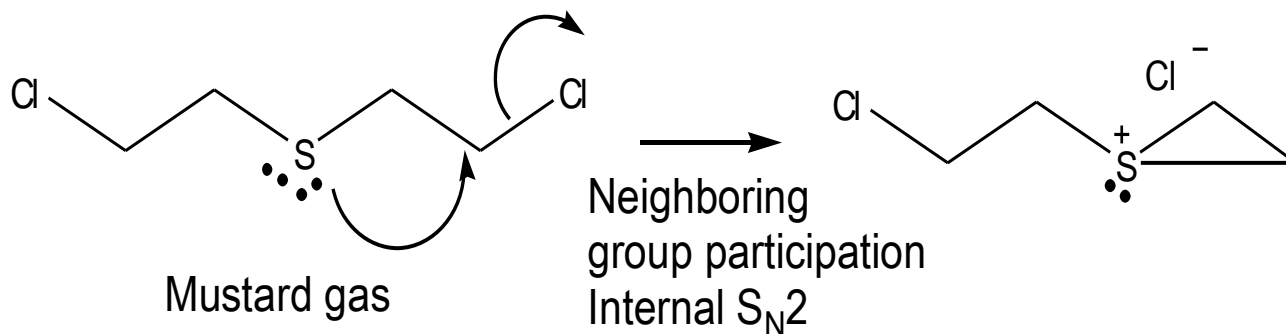


# Neighboring group participation: Summary

- Retention of configuration
- Enhanced rate of reaction

# Mustard gas

- Mustard gas is a substance that causes tissue blistering (a vesicant). It is highly reactive compound that combines with proteins and DNA and results in cellular changes immediately after exposure. Mustard gas was used as a chemical warfare agent in World War I by both sides.

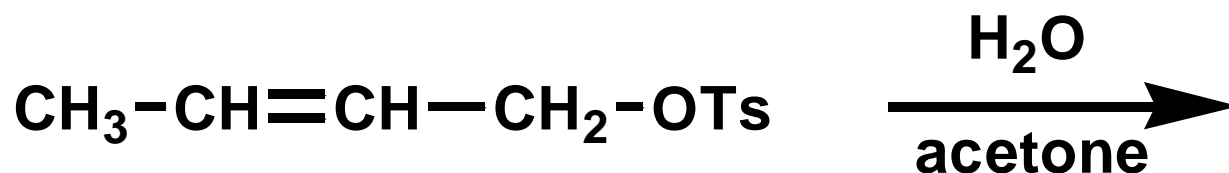


# Ion-pair mechanisms

- $S_N1$  reactions are “expected” to give a 50-50 (racemic) mixture of the two enantiomers!!
- But, if the leaving group doesn't get out of the way, you will get more inversion than retention, which makes it “look like”  $S_N2$ .
- In the extreme, you could have a carbocation give only inversion of configuration by an  $S_N1$  mechanism!!

# In-Class Problem

For the following reaction,



- A) Identify the mechanism of this reaction.
- B) Predict the product(s) of this reaction, and identify them as *major* or *minor*, if appropriate.



# Substitution *versus* Elimination

	<b>S<sub>N</sub>1</b>	<b>S<sub>N</sub>2</b>	<b>E1</b>	<b>E2</b>
<b>Substrate</b>	Strong effect; reaction favored by tertiary halide	Strong effect; reaction favored by methyl or primary halide	Strong effect; reaction favored by tertiary halide	Strong effect; reaction favored by tertiary halide
<b>Reactivity – primary</b>	Does not occur	Highly favored	Does not occur	Occurs with strong base!
<b>Reactivity – tertiary</b>	Favored when nucleophile is the solvent – solvolysis	Does not occur	Occurs under solvolysis conditions or with strong acids	Highly favored when strong bases (OH <sup>-</sup> , OR <sup>-</sup> ) are used
<b>Reactivity – secondary</b>	Can occur in polar, protic solvents	Favored by good nucleophile in polar, aprotic solvents	Can occur in polar, protic solvents	Favored when strong bases are used
<b>Solvent</b>	Very strong effect; reaction favored by polar, protic solvents	Strong effect; reaction favored by polar, aprotic solvents	Very strong effect; reaction favored by polar, protic solvents	Strong effect; reaction favored by polar, aprotic solvent
<b>Nucleophile/Base</b>	Weak effect; reaction favored by good nucleophile/weak base	Strong effect; reaction favored by good nucleophile/weak base	Weak effect; reaction favored by weak base	Strong effect; reaction favored by strong base
<b>Leaving Group</b>	Strong effect; reaction favored by good leaving group	Strong effect; reaction favored by good leaving group	Strong effect; reaction favored by good leaving group	Strong effect; reaction favored by good leaving group