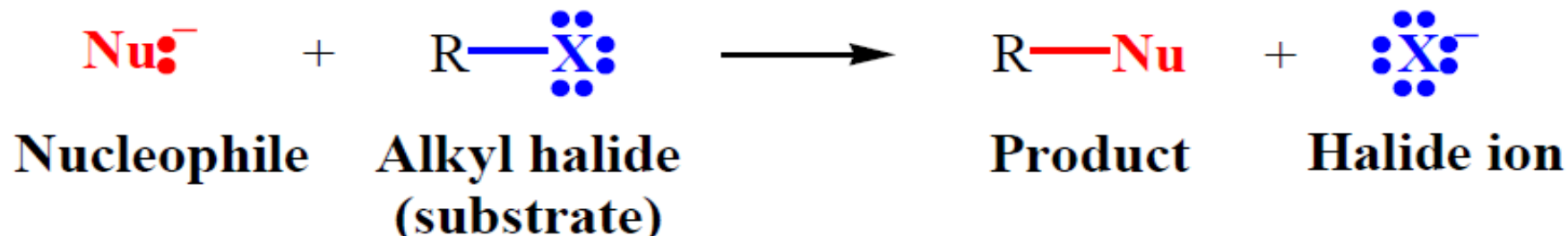


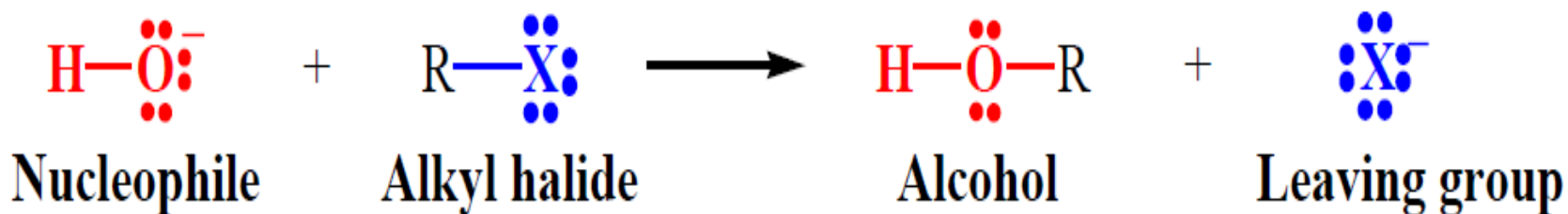
# Nucleophilic Substitution Reactions

$S_N1$  and  $S_N2$



- **A nucleophile, a species with an unshared electron pair (lone-pair electrons), reacts with an alkyl halide (substrate) by replacing the halogen substituent (leaving group).**
- **In nucleophilic substitution reactions, the C–X bond of the substrate undergoes *heterolysis*, and the lone-pair electrons of the nucleophile is used to form a new bond to the carbon atom.**

A nucleophile is any negative ion or any neutral molecule that has at least one unshared electron pair-*General Reaction for Nucleophilic Substitution of an Alkyl Halide by Hydroxide Ion.*



- *To be a good leaving group the substituent must be able to leave as a relatively stable, weakly basic molecule or ion.*
- **In alkyl halides the leaving group is the halogen substituent — it leaves as a halide ion.**
- **Because halide ions are relatively stable and very weak bases, they are good leaving groups.**

# NUCLEOPHILIC SUBSTITUTION REACTION AN S<sub>N</sub>2 REACTION

- The rate of the reaction depends on the concentration of methyl chloride and the concentration of hydroxide ion
- The reaction is second order overall.
- The reaction is first order with respect to methyl chloride and first order with respect to hydroxide ion

**Rate equation:**  $\text{Rate} \propto [\text{CH}_3\text{Cl}] [\text{OH}^-] \Rightarrow \text{Rate} = k [\text{CH}_3\text{Cl}] [\text{OH}^-]$

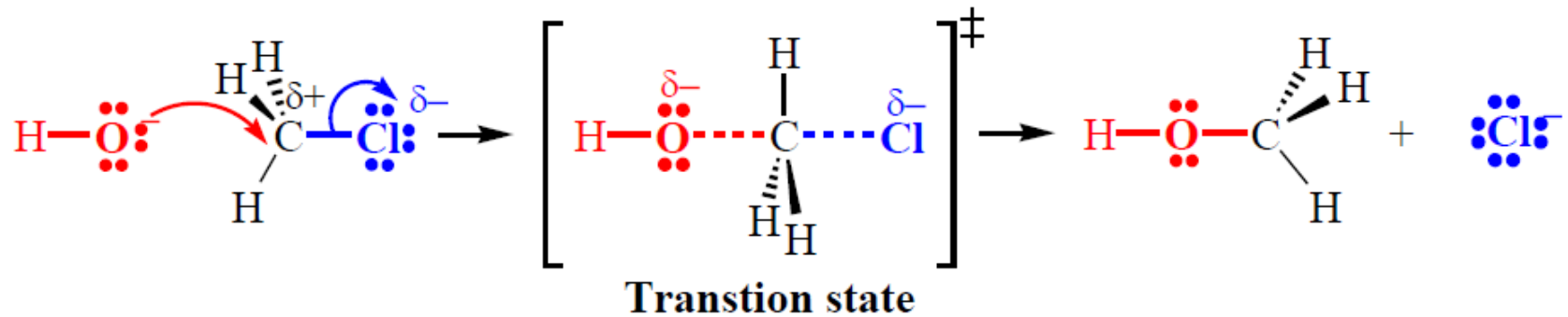
$k$  is the rate constant.

# MECHANISM FOR THE S<sub>N</sub>2 REACTION

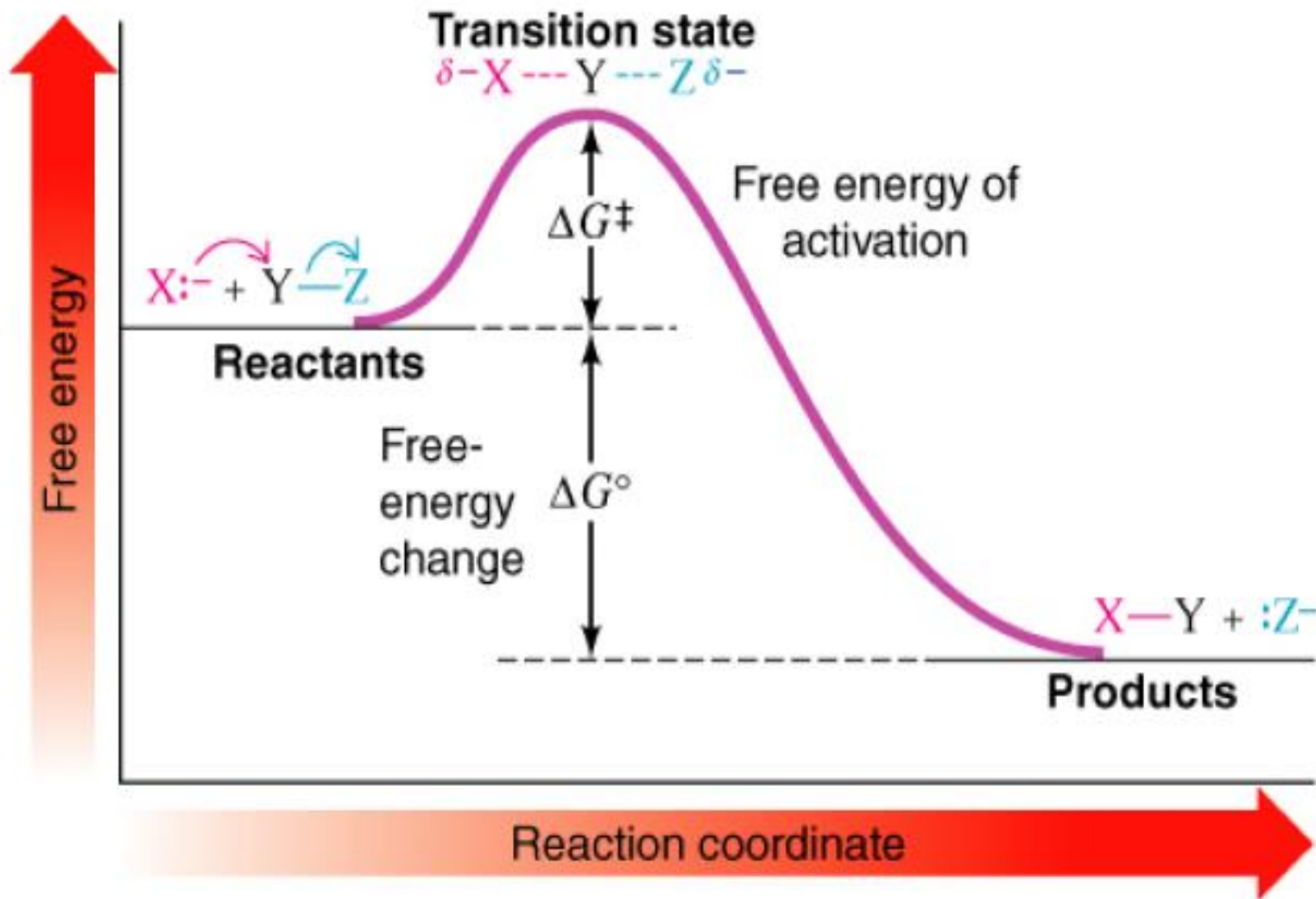
- The nucleophile attacks the carbon bearing the leaving group from the back side.
- The bond between the nucleophile and the carbon atom is forming, and the bond between the carbon atom and the leaving group is breaking.
- The configuration of the carbon atom becomes inverted during S<sub>N</sub>2 reaction.
- Because bond formation and bond breaking occur simultaneously in a single transition state, the S<sub>N</sub>2 reaction is a *concerted reaction*.

# Mechanism

**Mechanism:**

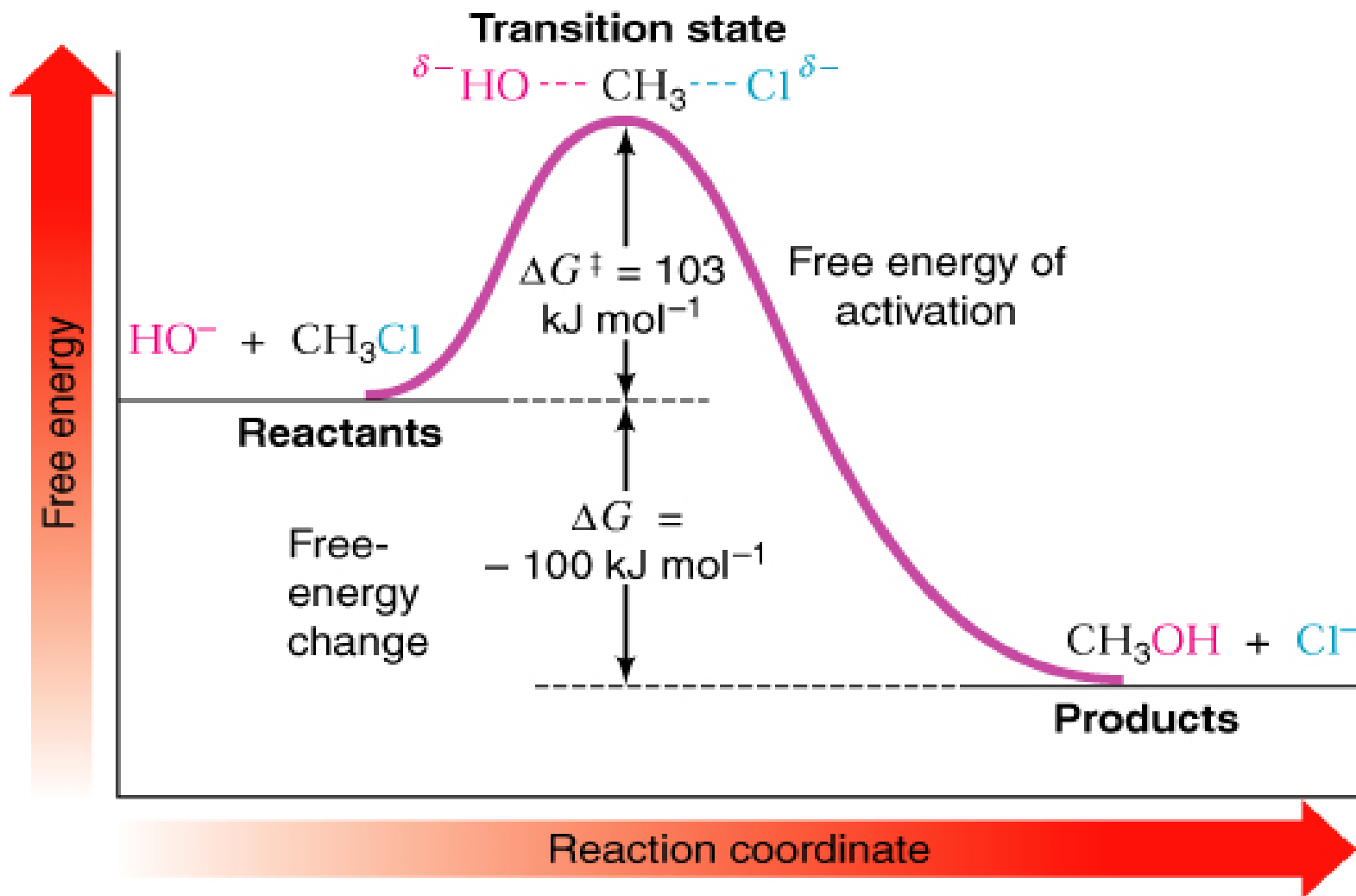


# Free Energy Diagram

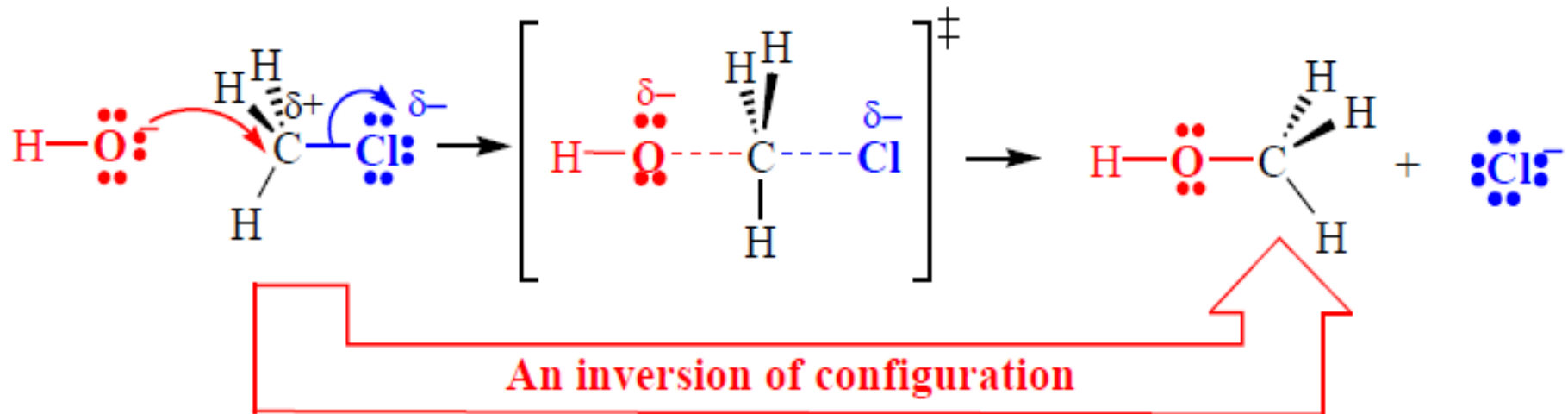




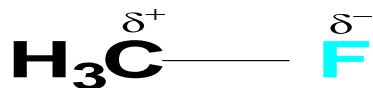
# For Methanol



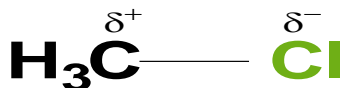
# Stereo Chemistry



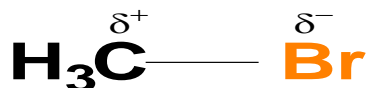
# Reactions of Alkyl Halides (R-X): [SN1, SN2 reactions]



$$\Delta\text{EN (F-C)} = (4.0 - 2.5) = 1.5$$



$$\Delta\text{EN (Cl-C)} = (3.0 - 2.5) = 0.5$$



$$\Delta\text{EN (Br-C)} = (2.8 - 2.5) = 0.3$$



$$\Delta\text{EN (I-C)} = (2.5 - 2.5) = 0.0$$

The  $\alpha$ -carbon in an alkyl halide is electrophilic (electron accepting) for either or both of two reasons...

a) the C to X (F, Cl, Br) bond is polar making carbon  $\delta^+$

b) X (Cl, Br, I) is a leaving group

decreasing basicity, increasing stability

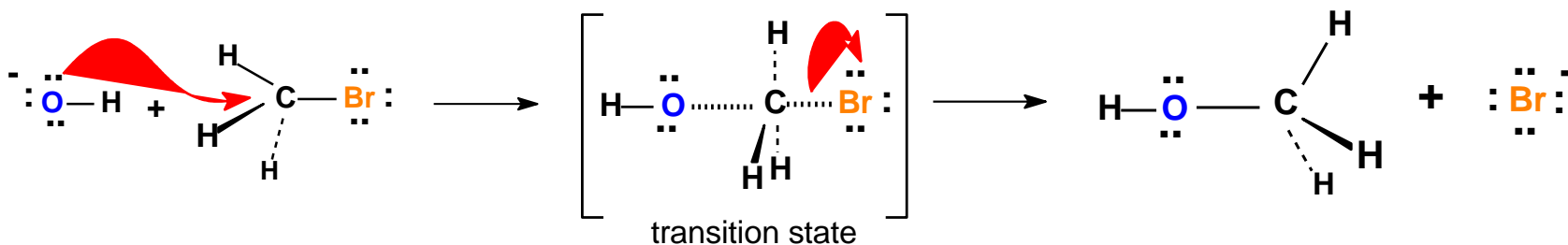
The best leaving groups are the weakest bases.

pKb = 23	pKb = 22	pKb = 21	pKb = 11	pKb = -1.7
I <sup>-</sup>	Br <sup>-</sup>	Cl <sup>-</sup>	F <sup>-</sup>	HO <sup>-</sup>
30,000	10,000	200	1	0

The poorest leaving groups are the strongest bases.

increasing leaving ability

# 2nd Order Nucleophilic Substitution Reactions, i.e., $S_N2$ reactions



The rate of an  $S_N2$  reaction depends upon 4 factors:

1. The nature of the substrate (the alkyl halide)
2. The power of the nucleophile
3. The ability of the leaving group to leave
4. The nature of the solvent

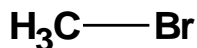
## 1. Consider the nature of the substrate:

- Unhindered alkyl halides, those in which the back side of the  $\alpha$ -carbon is not blocked, will react fastest in  $S_N2$  reactions, that is:



- While a methyl halides reacts quickly in  $S_N2$  reactions, a  $3^\circ$  does not react. The back side of an  $\alpha$ -carbon in a  $3^\circ$  alkyl halide is completely blocked.

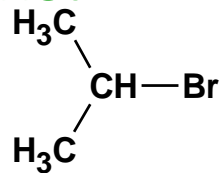
# Effect of nature of substrate on rate of $S_N2$ reactions:



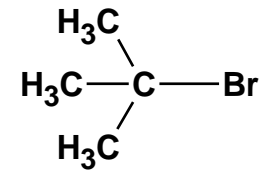
methyl bromide



ethyl bromide

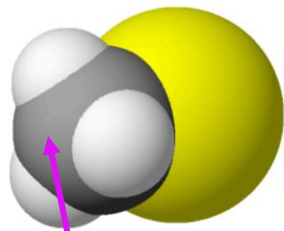


isopropyl bromide

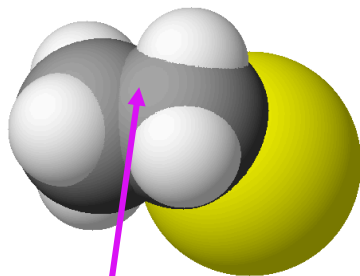


t-butyl bromide

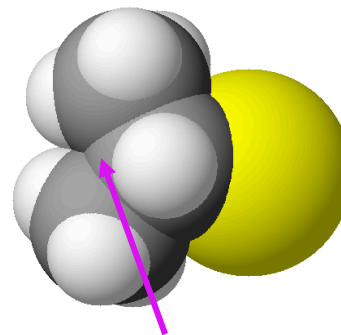
SPACE FILLING MODELS SHOW ACTUAL SHAPES AND RELATIVE SIZES



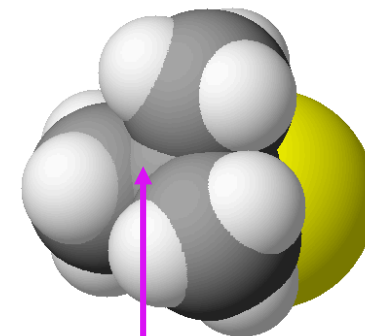
Back side of  $\alpha$ -C of a methyl halide is unhindered.



Back side of  $\alpha$ -C of a  $1^\circ$  alkyl halide is slightly hindered.



Back side of  $\alpha$ -C of a  $2^\circ$  alkyl halide is mostly hindered.



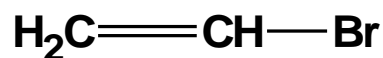
Back side of  $\alpha$ -C of a  $3^\circ$  alkyl halide is completely blocked.



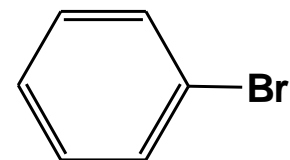
decreasing rate of  $S_N2$  reactions

## Effect of the nucleophile on rate of $S_N2$ reactions:

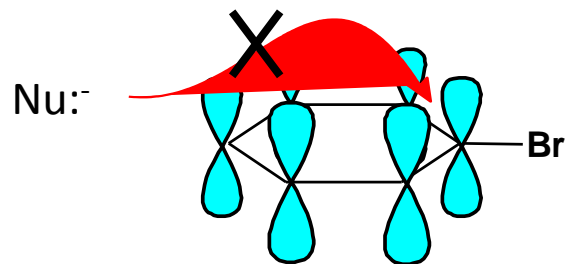
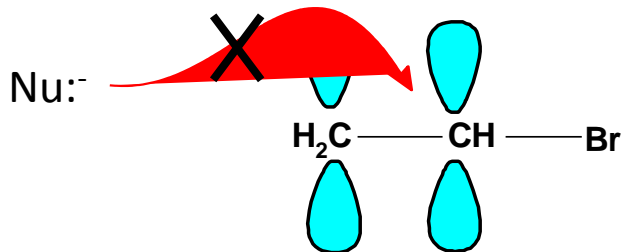
- The  $\alpha$ -carbon in vinyl and aryl halides, as in  $3^\circ$  carbocations, is completely hindered and these alkyl halides do not undergo  $S_N2$  reactions.



vinyl bromide



bromobenzene



The overlapping p-orbitals that form the  $\pi$ -bonds in vinyl and aryl halides completely block the access of a nucleophile to the back side of the  $\alpha$ -carbon.

## Effect of nature substrate on rate of S<sub>N</sub>2 reactions:

### Consider the power of the nucleophile:

- The better the nucleophile, the faster the rate of S<sub>N</sub>2 reactions.
- The table below show the relative power or various nucleophiles.
- The best nucleophiles are the best electron donors.

Reactivity	Nu: <sup>-</sup>	Relative Reactivity
very weak	HSO <sub>4</sub> <sup>-</sup> , H <sub>2</sub> PO <sub>4</sub> <sup>-</sup> , RCOOH	< 0.01
weak	ROH	1
	HOH, NO <sub>3</sub> <sup>-</sup>	100
fair	F <sup>-</sup>	500
	Cl <sup>-</sup> , RCOO <sup>-</sup>	20 × 10 <sup>3</sup>
	NH <sub>3</sub> , CH <sub>3</sub> SCH <sub>3</sub>	300 × 10 <sup>3</sup>
good	N <sub>3</sub> <sup>-</sup> , Br <sup>-</sup>	600 × 10 <sup>3</sup>
	OH <sup>-</sup> , CH <sub>3</sub> O <sup>-</sup>	2 × 10 <sup>6</sup>
very good	CN <sup>-</sup> , HS <sup>-</sup> , RS <sup>-</sup> , (CH <sub>3</sub> ) <sub>3</sub> P:, NH <sub>2</sub> <sup>-</sup> , RMgX, I <sup>-</sup> , H <sup>-</sup>	> 100 × 10 <sup>6</sup>

increasing

Effect of nature of the leaving group on rate of  $S_N2$  reactions:

### • 3. Consider the nature of the leaving group:

- The leaving group usually has a negative charge
- ❑ Groups which best stabilize a negative charge are the best leaving groups, i.e., the weakest bases are stable as anions and are the best leaving groups.
- ❑ Weak bases are readily identified. They have high pK<sub>b</sub> values.

pK <sub>b</sub> = 23	pK <sub>b</sub> = 22	pK <sub>b</sub> = 21	pK <sub>b</sub> = 11	pK <sub>b</sub> = -1.7	pK <sub>b</sub> = -2	pK <sub>b</sub> = -21
I <sup>-</sup>	Br <sup>-</sup>	Cl <sup>-</sup>	F <sup>-</sup>	HO <sup>-</sup>	RO <sup>-</sup>	H <sub>2</sub> N <sup>-</sup>
30,000	10,000	200	1	0	0	0



Increasing leaving ability

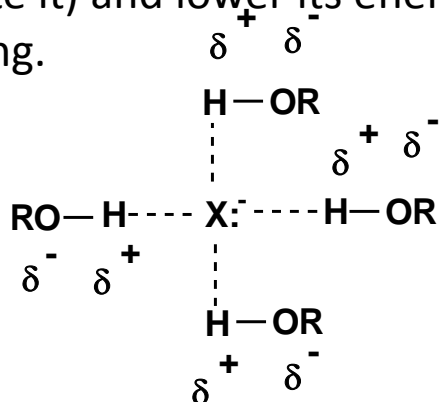
- ❑ Iodine (-I) is a good leaving group because iodide (I<sup>-</sup>) is non basic.
- ❑ The hydroxyl group (-OH) is a poor leaving group because hydroxide (OH<sup>-</sup>) is a strong base.



# Effect of the solvent on rate of $S_N2$ reactions:

- **4. Consider the nature of the solvent:**
- There are 3 classes of organic solvents:
  - ☐ **Protic solvents**, which contain  $-OH$  or  $-NH_2$  groups. Protic solvents slow down  $S_N2$  reactions.
  - ☐ **Polar aprotic solvents** like acetone, which contain strong dipoles but no  $-OH$  or  $-NH_2$  groups. Polar aprotic solvents speed up  $S_N2$  reactions.
  - ☐ **Non polar solvents**, e.g., hydrocarbons.  $S_N2$  reactions are relatively slow in non polar solvents.

Protic solvents (e.g.,  $H_2O$ ,  $MeOH$ ,  $EtOH$ ,  $CH_3COOH$ , etc.) cluster around the  $Nu:-$  (solvate it) and lower its energy (stabilize it) and reduce its reactivity via H-bonding.

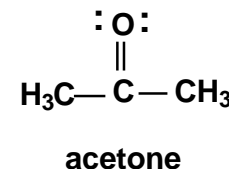


**A solvated anion ( $Nu:-$ ) has reduced nucleophilicity, reduced reactivity and increased stability**

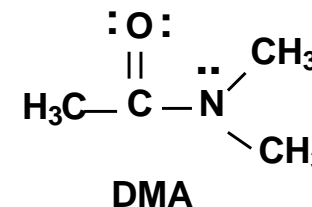
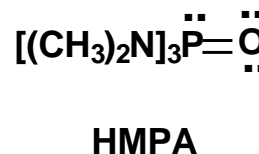
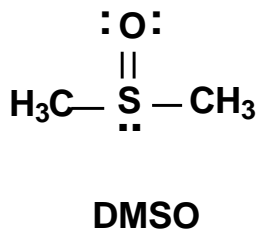
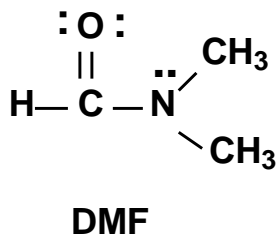
A solvated nucleophile has difficulty hitting the  $\alpha$ -carbon.

CH<sub>3</sub>—C≡N :  
acetonitrile

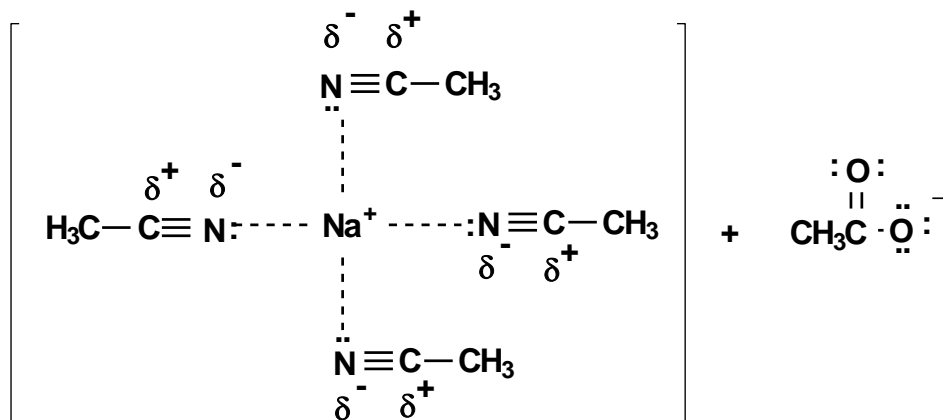
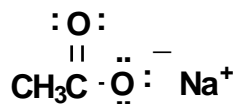
## Effect of the solvent on rate of S<sub>N</sub>2 reactions:



- ❑ Polar Aprotic Solvents solvate the cation counterion of the nucleophile but not the nucleophile.
- ❑ Examples include acetonitrile (CH<sub>3</sub>CN), acetone (CH<sub>3</sub>COCH<sub>3</sub>), dimethylformamide (DMF) [(CH<sub>3</sub>)<sub>2</sub>NC=O], dimethyl sulfoxide, DMSO [(CH<sub>3</sub>)<sub>2</sub>SO], hexamethylphosphoramide, HMPA {[(CH<sub>3</sub>)<sub>2</sub>N]<sub>3</sub>PO} and dimethylacetamide (DMA).



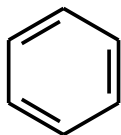
Polar aprotic solvents solvate metal cations leaving the anion counterion (Nu: <sup>-</sup>) bare and thus more reactive



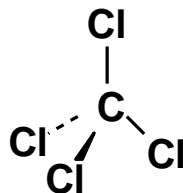
## Effect of the solvent on rate of $S_N2$ reactions:

• Non polar solvents (benzene, carbon tetrachloride, hexane, etc.) do not solvate or stabilize nucleophiles.

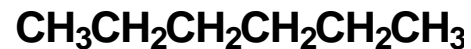
- $S_N2$  reactions are relatively slow in non polar solvents similar to that in protic solvents.



benzene



carbon  
tetrachloride

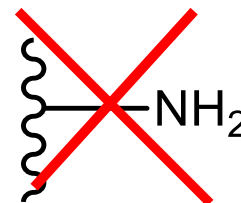
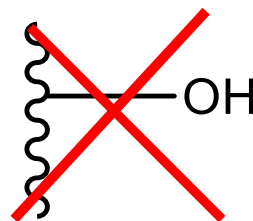


n-hexane

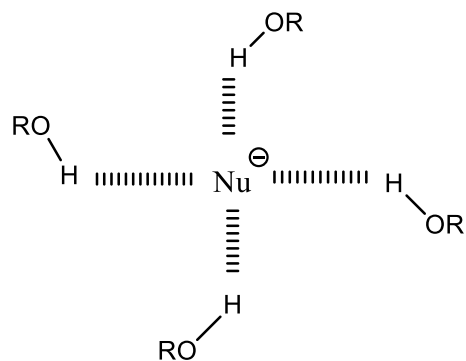
# Solvent Effect for S<sub>N</sub>2 reactions

- Requires a polar, aprotic solvent...

- NO alcohols or amines

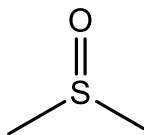


Why...because hydrogen bonding with the nucleophile can occur...slowing down the reaction



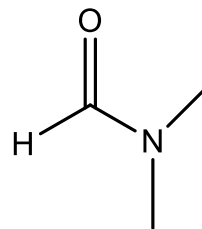
# Polar, Aprotic Solvents

DMSO

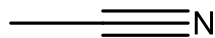


dimethyl sulfoxide

DMF

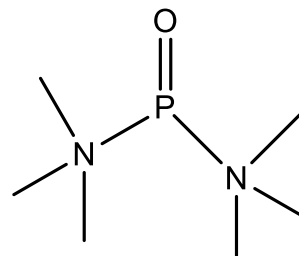


dimethyl formamide



acetonitrile

HMPA



hexamethyl phosphamide

# $S_N2$ Conditions Summary

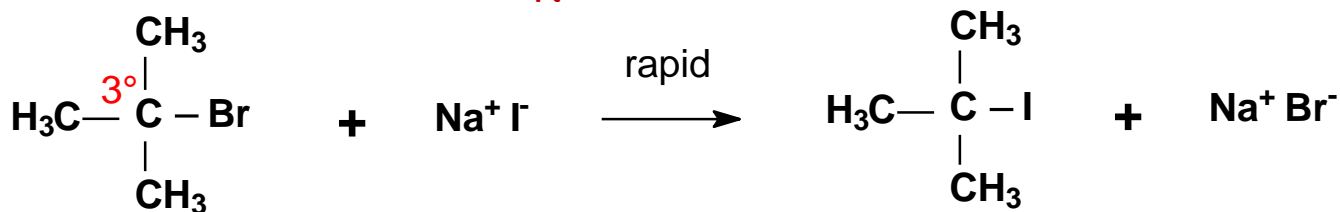
- 1) Substrate (methyl > primary > secondary >> tertiary)
- 2) Nucleophile (negative charge > neutral)
- 3) leaving group (Y) (Y stabilizes a negative charge)
- 4) solvent (needs to be polar and aprotic)

# AN S<sub>N</sub>1 REACTION

- THE REACTION OF *TERT-BUTYL CHLORIDE* WITH HYDROXIDE ION



# 1st Order Nucleophilic Substitution Reactions, i.e., S<sub>N</sub>1 reactions

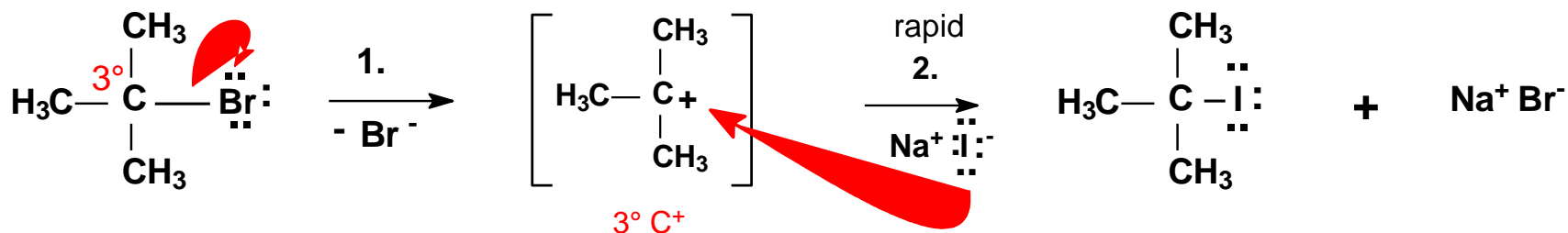


- ❑ 3° alkyl halides are essentially inert to substitution by the S<sub>N</sub>2 mechanism because of steric hindrance at the back side of the α-carbon.
- ❑ Despite this, 3° alkyl halides do undergo nucleophilic substitution reactions quite rapidly, but by a different mechanism, i.e., the S<sub>N</sub>1 mechanism.
- ❑ S<sub>N</sub>1 = Substitution, Nucleophilic, 1st order (unimolecular).
- ❑ S<sub>N</sub>1 reactions obey 1st order kinetics, i.e., Rate = k·[RX].
- ❑ The rate depends upon the concentration of only 1 reactant, the alkyl halide-not the nucleophile
- ❑ The order of reactivity of substrates for S<sub>N</sub>1 reactions is the reverse of S<sub>N</sub>2
  - 3° > 2° > 1° > vinyl > phenyl > Me°
  - R<sub>3</sub>C-Br   R<sub>2</sub>HC-Br   RH<sub>2</sub>C-Br                      CH<sub>2</sub>=CH-Br   φ-Br   H<sub>3</sub>C-Br

←—————  
increasing rate of S<sub>N</sub>1 reactions

# Mechanism of S<sub>N</sub>1 reactions

- The mechanism of an S<sub>N</sub>1 reaction occurs in 2 steps:



- Reaction Steps ...
  - the slower, rate-limiting dissociation of the alkyl halide forming a C<sup>+</sup> intermediate
  - a rapid nucleophilic attack on the C<sup>+</sup>

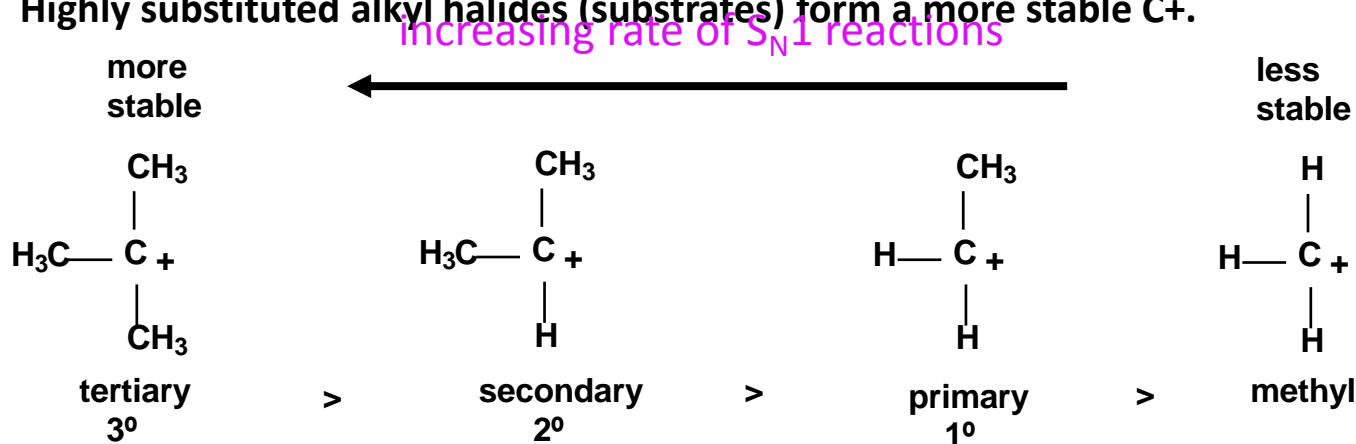
Note that the nucleophile is not involved in the slower, rate-limiting step.

# The Rate of S<sub>N</sub>1 reactions

- The rate of an S<sub>N</sub>1 reaction depends upon 3 factors:
  1. The nature of the substrate (the alkyl halide)
  2. The ability of the leaving group to leave
  3. The nature of the solvent
- The rate is independent of the power of the nucleophile.

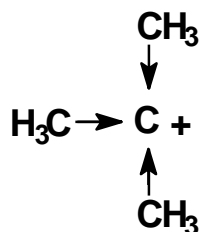
## • 1. Consider the nature of the substrate:

Highly substituted alkyl halides (substrates) form a more stable C<sup>+</sup>.



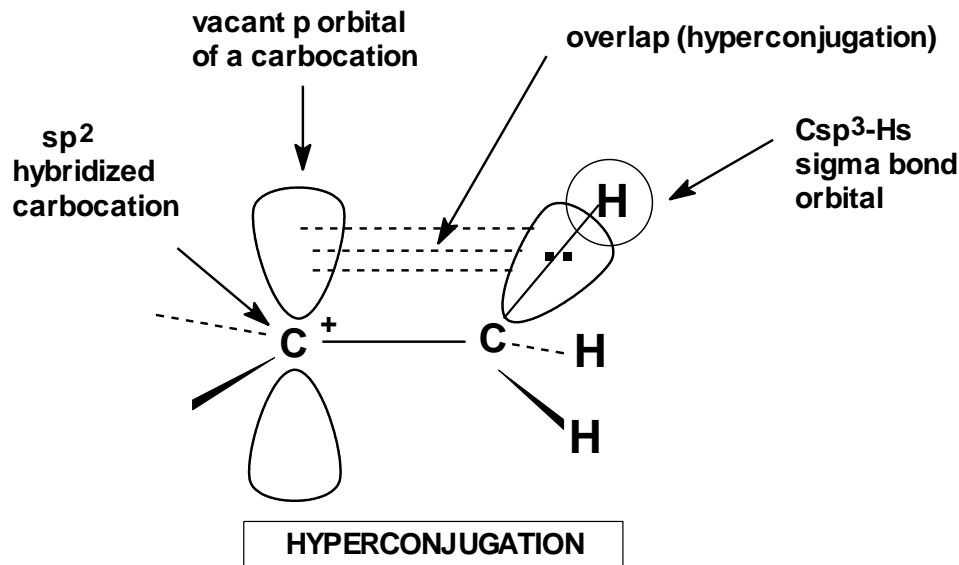
# Stability of Carbocations

- Alkyl groups are weak electron donors.
- They stabilize carbocations by donating electron density by induction (through  $\sigma$  bonds)



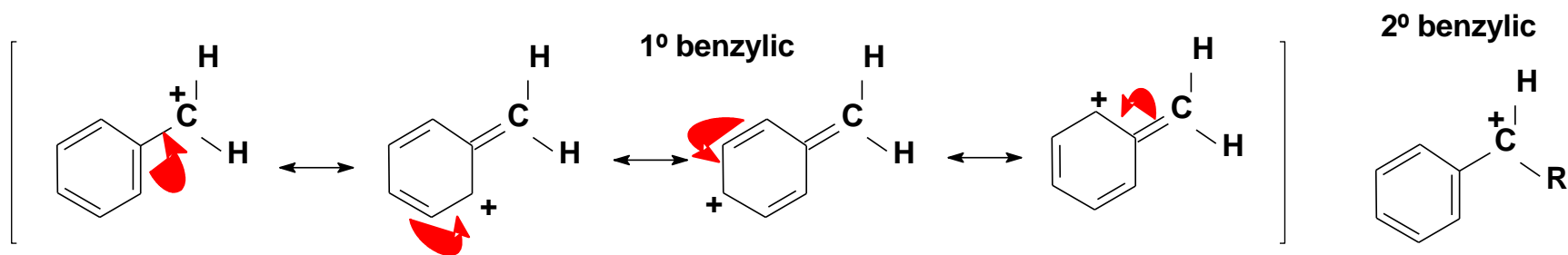
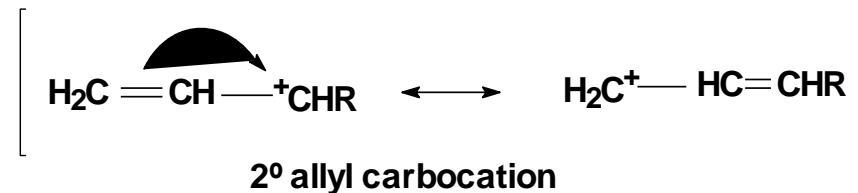
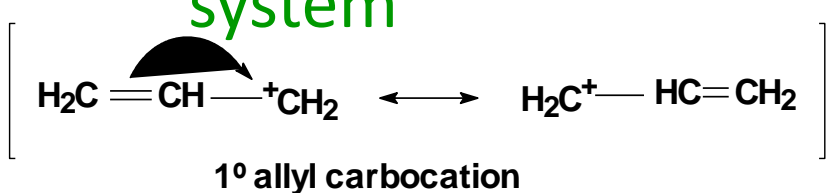
Inductive effects:  
Alkyl groups donate (shift) electron density through sigma bonds to electron deficient atoms.  
This stabilizes the carbocation.

- They stabilize carbocations by hyperconjugation (by partial overlap of the alkyl C-to-H bonds with the empty p-orbital of the carbocation).



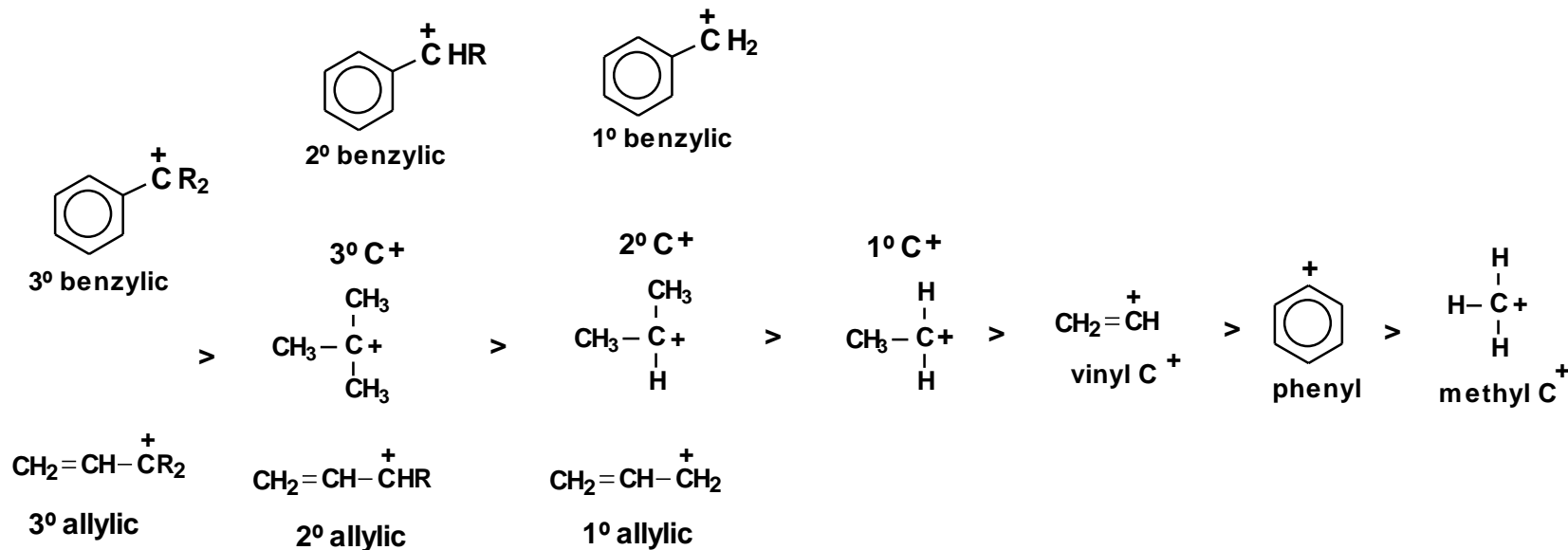
# Stability of Carbocations

□ Allyl and benzyl halides also react quickly by  $S_N1$  reactions because their carbocations are unusually stable due to their resonance forms which delocalize charge over an extended  $\pi$  system



# Relative Stability of All Types of Carbocations

Increasing C<sup>+</sup> stability and rate of S<sub>N</sub>1 reaction



Note that 1° allylic and 1° benzylic C<sup>+</sup>'s are about as stable as 2° alkyl C<sup>+</sup>'s.

Note that 2° allylic and 2° benzylic C<sup>+</sup>'s are about as stable as 3° alkyl C<sup>+</sup>'s.

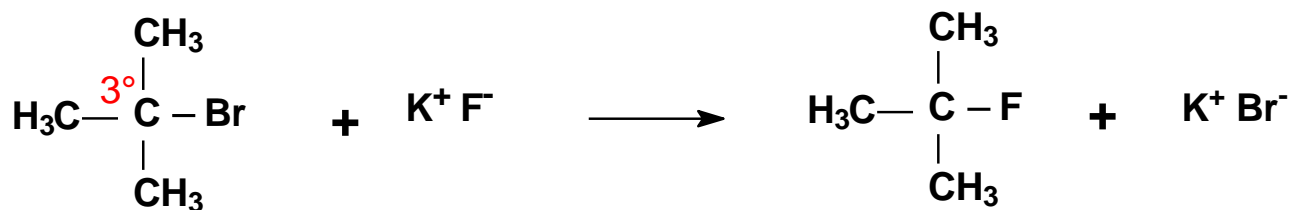
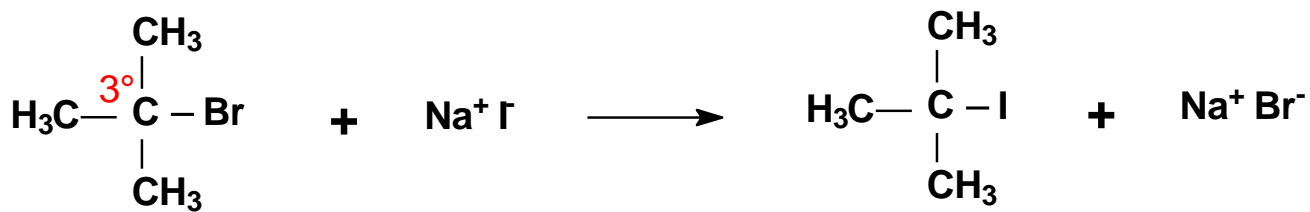
Note that 3° allylic and 3° benzylic C<sup>+</sup>'s are more stable than 3° alkyl C<sup>+</sup>'s

Note that phenyl and vinyl C<sup>+</sup>'s are unstable. Phenyl and vinyl halides do not usually react by S<sub>N</sub>1 or S<sub>N</sub>2 reactions

## Effect of the nucleophile on rate of S<sub>N</sub>1 reactions:

- Consider the nature of the Nucleophile:

- ❑ Recall again that the nature of the nucleophile has no effect on the rate of S<sub>N</sub>1 reactions because the slowest (rate-determining) step of an S<sub>N</sub>1 reaction is the dissociation of the leaving group and formation of the carbocation.
- ❑ All carbocations are very good electrophiles (electron acceptors) and even weak nucleophiles, like H<sub>2</sub>O and methanol, will react quickly with them.
- ❑ The two S<sub>N</sub>1 reactions will proceed at essentially the same rate since the only difference is the nucleophile.



# Effect of nature of the leaving group on rate of $S_N1$ reactions:

- **2. Consider the nature of the leaving group:**
- The nature of the leaving group has the same effect on both  $S_N1$  and  $S_N2$  reactions.
- The better the leaving group, the faster a  $C^+$  can form and hence the faster will be the  $S_N1$  reaction.
- The leaving group usually has a negative charge
- ❑ Groups which best stabilize a negative charge are the best leaving groups, i.e., the weakest bases are stable as anions and are the best leaving groups.
- ❑ Weak bases are readily identified. They have high  $pK_b$  values.

<b>pK<sub>b</sub> = 23</b>	<b>pK<sub>b</sub> = 22</b>	<b>pK<sub>b</sub> = 21</b>	<b>pK<sub>b</sub> = 11</b>	<b>pK<sub>b</sub> = -1.7</b>	<b>pK<sub>b</sub> = -2</b>	<b>pK<sub>b</sub> = -21</b>
<b>I<sup>-</sup></b>	<b>Br<sup>-</sup></b>	<b>Cl<sup>-</sup></b>	<b>F<sup>-</sup></b>	<b>HO<sup>-</sup></b>	<b>RO<sup>-</sup></b>	<b>H<sub>2</sub>N<sup>-</sup></b>
<b>30,000</b>	<b>10,000</b>	<b>200</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>

←  
Increasing leaving ability

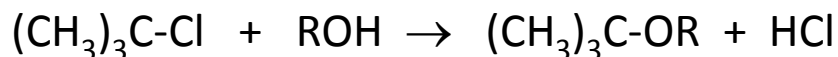
- ❑ Iodine (-I) is a good leaving group because iodide (I<sup>-</sup>) is non basic.
- ❑ The hydroxyl group (-OH) is a poor leaving group because hydroxide (OH<sup>-</sup>) is a strong base.



## Effect of the solvent on rate of $S_N1$ reactions:

- 3. Consider the nature of the solvent:
  - ❑ For  $S_N1$  reactions, the solvent affects the rate only if it influences the stability of the charged transition state, i.e., the  $C^+$ . The  $Nu^-$  is not involved in the rate determining step so solvent effects on the  $Nu^-$  do not affect the rate of  $S_N1$  reactions.
  - ❑ Polar solvents, both protic and aprotic, will solvate and stabilize the charged transition state ( $C^+$  intermediate), lowering the activation energy and accelerating  $S_N1$  reactions.
  - ❑ Nonpolar solvents do not lower the activation energy and thus make  $S_N1$  reactions relatively slower

The relative rates of an  $S_N1$  reaction due to solvent effects are given



$H_2O$	20% EtOH (aq)	40% EtOH (aq)	EtOH
100,000	14,000	100	1

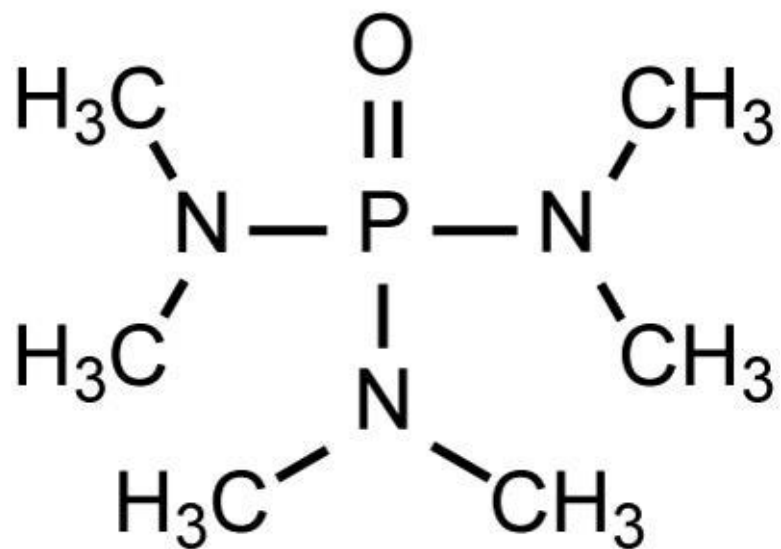
reaction rate increases with polarity of solvent

## Effect of the solvent on rate of S<sub>N</sub>1 reactions:

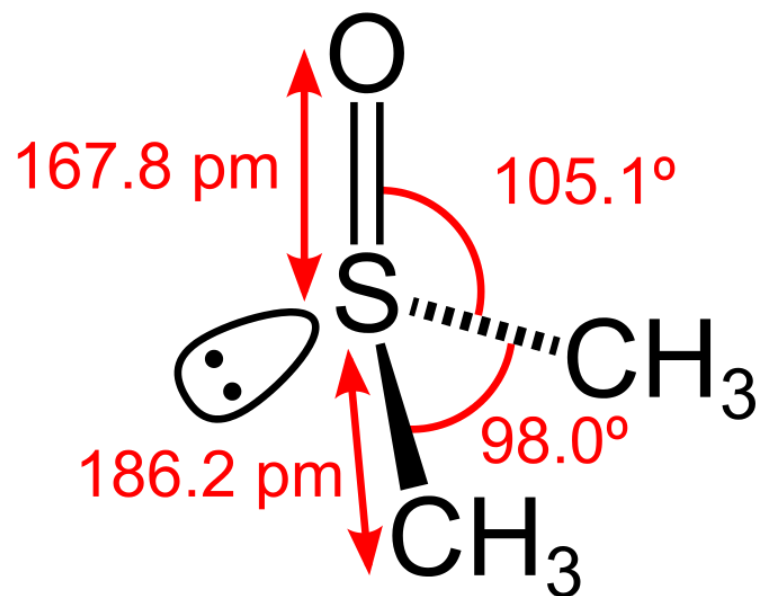
- ❑ Solvent polarity is usually expressed by the “dielectric constant”,  $\epsilon$ , which is a measure of the ability of a solvent to act as an electric insulator.
- ❑ Polar solvents are good electric insulators because their dipoles surround and associate with charged species.
- ❑ Dielectric constants of some common solvents are given in the following table

name	dielectric constant	name	dielectric constant
<b>aprotic solvents</b>		<b>protic solvents</b>	
hexane	1.9	acetic acid	6.2
benzene	2.3	acetone	20.7
diethyl ether	4.3	ethanol	24.3
chloroform	4.8	methanol	33.6
HMPA	30	formic acid	58.0
DMF	38	<b>water</b>	<b>80.4</b>
DMSO	48		

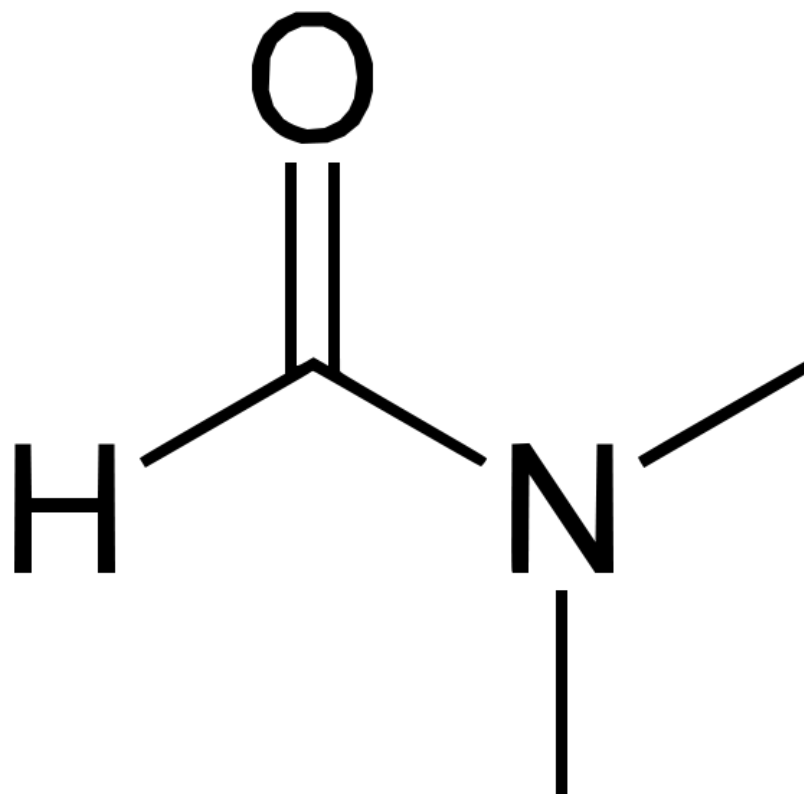
# HMPA



# DMSO



DMF



# Reactivity of alkyl halides toward substitution and elimination

<i>Halide type</i>	<i>S<sub>N</sub>1</i>	<i>S<sub>N</sub>2</i>	<i>E1</i>	<i>E2</i>
<b>Primary halide</b>	Does not occur	<b>Highly favored</b>	Does not occur	Occurs when strong, hindered bases are used
<b>Secondary halide</b>	Can occur under solvolysis conditions in polar solvents	<b>Favored by good nucleophiles in polar aprotic solvents</b>	Can occur under solvolysis conditions in polar solvents	<b>Favored when strong bases are used</b>
<b>Tertiary halide</b>	<b>Favored by nonbasic nucleophiles in polar solvents</b>	Does not occur	Occurs under solvolysis conditions	<b>Highly favored when bases are used</b>

# Effects of reaction variables on substitution and elimination reactions

<i>Reaction</i>	<i>Solvent</i>	<i>Nucleophile/base</i>	<i>Leaving group</i>	<i>Substrate structure</i>
<b>S<sub>N</sub>1</b>	<b>Very strong effect;</b> reaction favored by polar solvents	<b>Weak effect;</b> reaction favored by good nucleophile/weak base	<b>Strong effect;</b> reaction favored by good leaving group	<b>Strong effect;</b> reaction favored by 3°, allylic, and benzylic substrates
<b>S<sub>N</sub>2</b>	<b>Strong effect;</b> reaction favored by polar aprotic solvents	<b>Strong effect;</b> reaction favored by good nucleophile/weak base	<b>Strong effect;</b> reaction favored by good leaving group	<b>Strong effect;</b> reaction favored by 1°, allylic, and benzylic substrates
<b>E1</b>	<b>Very strong effect;</b> reaction favored by polar solvents	<b>Weak effect;</b> reaction favored by weak base	<b>Strong effect;</b> reaction favored by good leaving group	<b>Strong effect;</b> reaction favored by 3°, allylic, and benzylic substrates
<b>E2</b>	<b>Strong effect;</b> reaction favored by polar aprotic solvents	<b>Strong effect;</b> reaction favored by poor nucleophile/strong base	<b>Strong effect;</b> reaction favored by good leaving group	<b>Strong effect;</b> reaction favored by 3° substrates

## Overall Summary of S<sub>N</sub>1, S<sub>N</sub>2, E1 and E2 Reactions

CH <sub>3</sub> X Methyl	RCH <sub>2</sub> X 1°	RR'CHX 2°	RR'R''CX 3°
	<b>Bimolecular reactions only</b>		<b>S<sub>N</sub>1/E1 or E2</b>
Gives S <sub>N</sub> 2 reactions	Gives mainly S <sub>N</sub> 2 except with a hindered strong base [e.g., (CH <sub>3</sub> ) <sub>3</sub> CO <sup>-</sup> ] and then gives mainly E2	Gives mainly S <sub>N</sub> 2 with weak bases (e.g., I <sup>-</sup> , CN <sup>-</sup> , RCO <sub>2</sub> <sup>-</sup> ) and mainly E2 with strong bases (e.g., RO <sup>-</sup> )	No S <sub>N</sub> 2 reaction. In solvolysis gives S <sub>N</sub> 1/E1, and at lower temperatures S <sub>N</sub> 1 is favored. When a strong base (e.g., RO <sup>-</sup> ) is used E2 predominates