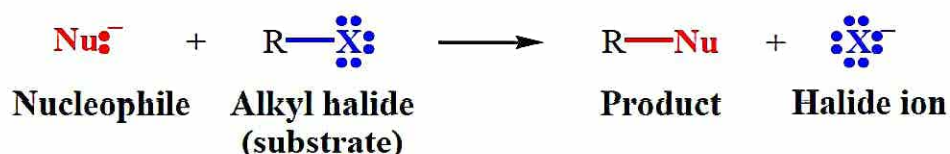


# Nucleophilic Substitution Reactions

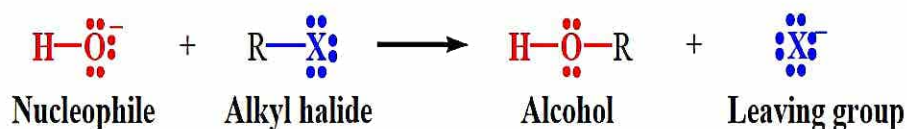
**$S_N1$  and  $S_N2$**



- **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.**

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

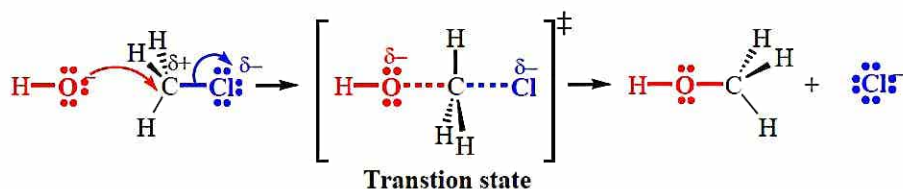
$k$  is the rate constant.

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

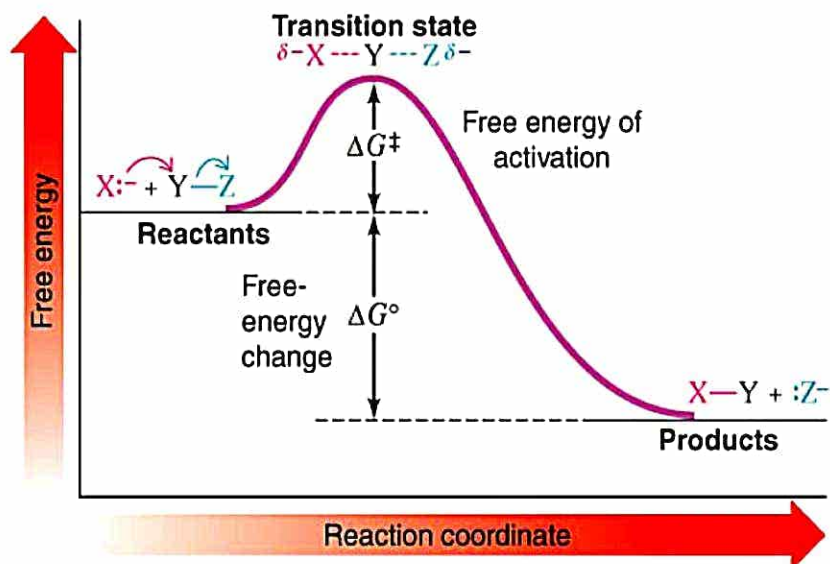
- The nucleophile attacks the carbon bearing the leaving group from the back side.
- The bond between the nucleophile and the carbon atom is forming, and the bond between the carbon atom and the leaving group is breaking.
- The configuration of the carbon atom becomes inverted during S<sub>N</sub>2 reaction.
- 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

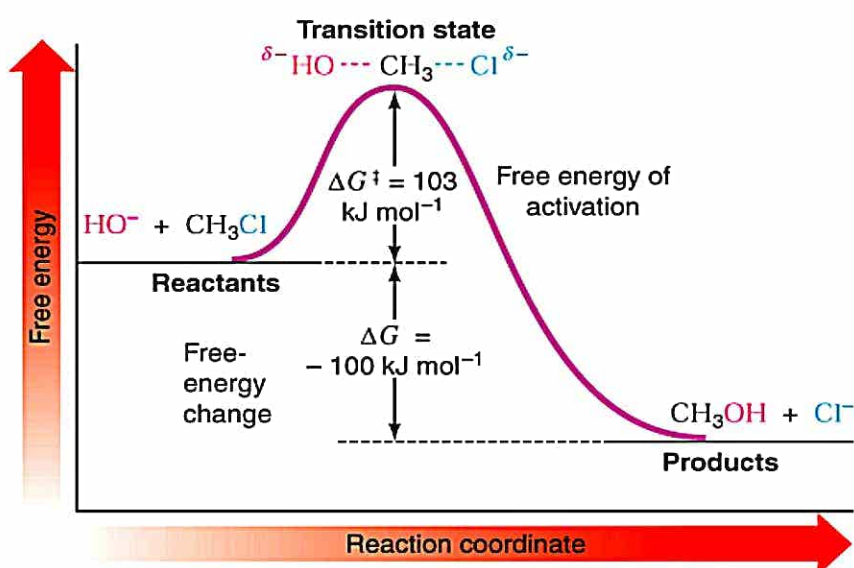
Mechanism:



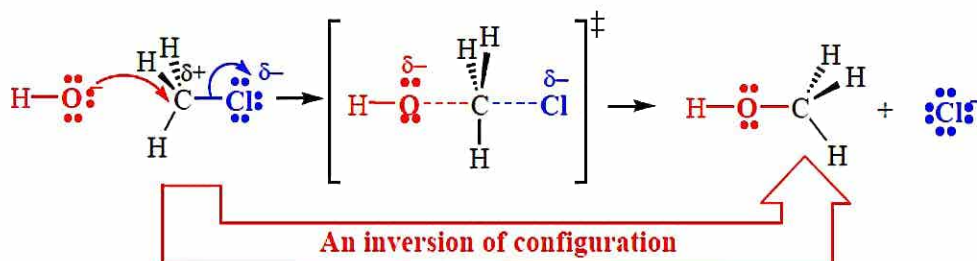
## Free Energy Diagram



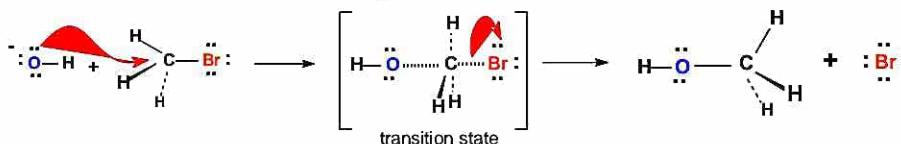
## For Methanol



## Stereo Chemistry



## 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:

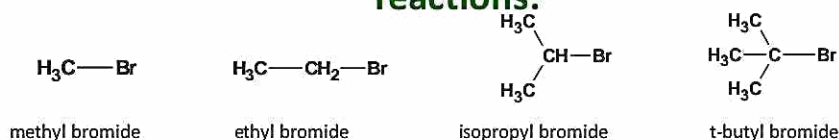
- Unhindered alkyl halides, those in which the back side of the  $\alpha$ -carbon is not blocked, will react fastest in  $S_N2$  reactions, that is:



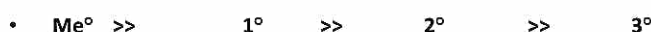
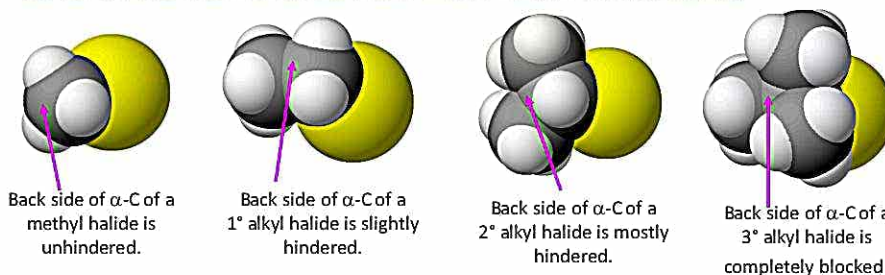
- While a methyl halides reacts quickly in  $S_N2$  reactions, a  $3^\circ$  does not react. The back side of an  $\alpha$ -carbon in a  $3^\circ$  alkyl halide is completely blocked.

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



SPACE FILLING MODELS SHOW ACTUAL SHAPES AND RELATIVE SIZES

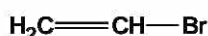


decreasing rate of  $S_N2$  reactions

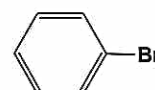
13

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

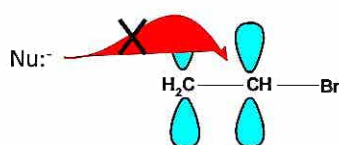
•The  $\alpha$ -carbon in vinyl and aryl halides, as in  $3^\circ$  carbocations, is completely hindered and these alkyl halides do not undergo  $S_N2$  reactions.



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.

### Consider the power of the nucleophile:

- The better the nucleophile, the faster the rate of  $S_N2$  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	$\text{HSO}_4^-$ , $\text{H}_2\text{PO}_4^-$ , $\text{RCOOH}$	< 0.01
weak	ROH	1
	$\text{HOH}$ , $\text{NO}_3^-$	100
fair	$\text{F}^-$	500
	$\text{Cl}^-$ , $\text{RCOO}^-$	$20 \times 10^3$
	$\text{NH}_3$ , $\text{CH}_3\text{SCH}_3$	$300 \times 10^3$
good	$\text{N}_3^-$ , $\text{Br}^-$	$600 \times 10^3$
	$\text{OH}^-$ , $\text{CH}_3\text{O}^-$	$2 \times 10^6$
very good	$\text{CN}^-$ , $\text{HS}^-$ , $\text{RS}^-$ , $(\text{CH}_3)_3\text{P}^-$ , $\text{NH}_2^-$ , $\text{RMgX}$ , $\text{I}^-$ , $\text{H}^-$	$> 100 \times 10^6$

↑ increasing

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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  $\text{pK}_b$  values.

$\text{pK}_b = 23$	$\text{pK}_b = 22$	$\text{pK}_b = 21$	$\text{pK}_b = 11$	$\text{pK}_b = -1.7$	$\text{pK}_b = -2$	$\text{pK}_b = -21$
$\text{I}^-$	$\text{Br}^-$	$\text{Cl}^-$	$\text{F}^-$	$\text{HO}^-$	$\text{RO}^-$	$\text{H}_2\text{N}^-$
30,000	10,000	200	1	0	0	0

← Increasing leaving ability

- Iodine ( $\text{I}^-$ ) is a good leaving group because iodide ( $\text{I}^-$ ) is non basic.
- The hydroxyl group ( $-\text{OH}$ ) is a poor leaving group because hydroxide ( $\text{OH}^-$ ) is a strong base.

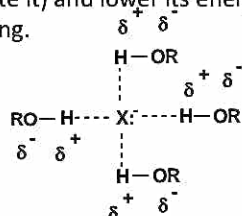
16

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  $-\text{OH}$  or  $-\text{NH}_2$  groups. Protic solvents slow down  $S_N2$  reactions.
- **Polar aprotic solvents** like acetone, which contain strong dipoles but no  $-\text{OH}$  or  $-\text{NH}_2$  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.,  $\text{H}_2\text{O}$ ,  $\text{MeOH}$ ,  $\text{EtOH}$ ,  $\text{CH}_3\text{COOH}$ , etc.) cluster around the  $\text{Nu}^-$  (solvate it) and lower its energy (stabilize it) and reduce its reactivity via H-bonding.

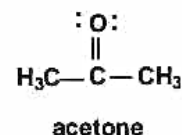


A solvated anion ( $\text{Nu}^-$ ) has reduced nucleophilicity, reduced reactivity and increased stability

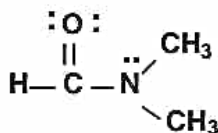
A solvated nucleophile has difficulty hitting the  $\alpha$ -carbon.

$\text{CH}_3\text{—C}\equiv\text{N}:$  **Effect of the solvent on rate of  $\text{S}_{\text{N}}2$  reactions:**

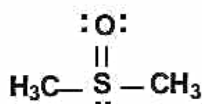
acetonitrile



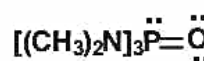
- Polar Aprotic Solvents solvate the cation counterion of the nucleophile but not the nucleophile.
- Examples include acetonitrile ( $\text{CH}_3\text{CN}$ ), acetone ( $\text{CH}_3\text{COCH}_3$ ), dimethylformamide (DMF) [ $(\text{CH}_3)_2\text{NC=O}$ ], dimethyl sulfoxide, DMSO [ $(\text{CH}_3)_2\text{SO}$ ], hexamethylphosphoramide, HMPA [ $(\text{CH}_3)_2\text{N}_3\text{PO}$ ] and dimethylacetamide (DMA).



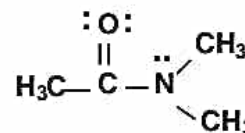
DMF



DMSO

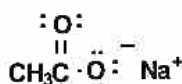


HMPA

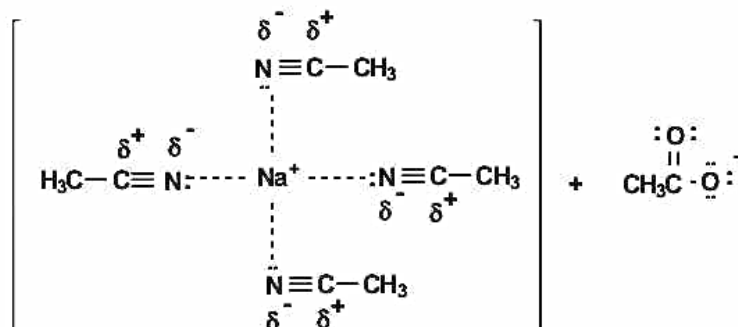


DMA

Polar aprotic solvents solvate metal cations leaving the anion counterion ( $\text{Nu}^-$ ) bare and thus more reactive



$\xrightarrow{\text{CH}_3\text{CN:}}$



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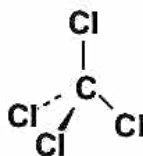
**Effect of the solvent on rate of  $\text{S}_{\text{N}}2$  reactions:**

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

- $\text{S}_{\text{N}}2$  reactions are relatively slow in non polar solvents similar to that in protic solvents.



benzene



carbon tetrachloride



n-hexane

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# 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

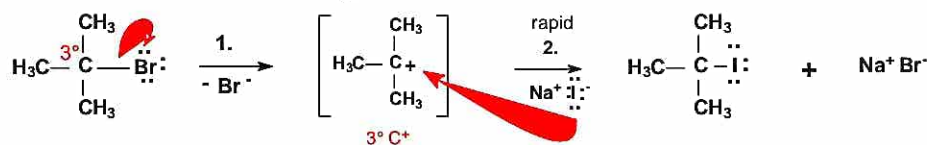


- 3° alkyl halides are essentially inert to substitution by the S<sub>N</sub>2 mechanism because of steric hindrance at the back side of the α-carbon.
- Despite this, 3° alkyl halides do undergo nucleophilic substitution reactions quite rapidly, but by a different mechanism, i.e., the S<sub>N</sub>1 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:

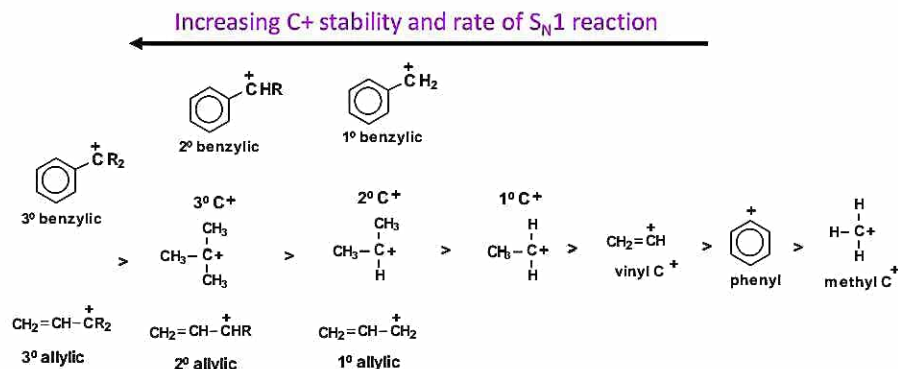


- Reaction Steps ...
  1. the slower, rate-limiting dissociation of the alkyl halide forming a C<sup>+</sup> intermediate
  2. a rapid nucleophilic attack on the C<sup>+</sup>

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



# Relative Stability of All Types of Carbocations



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

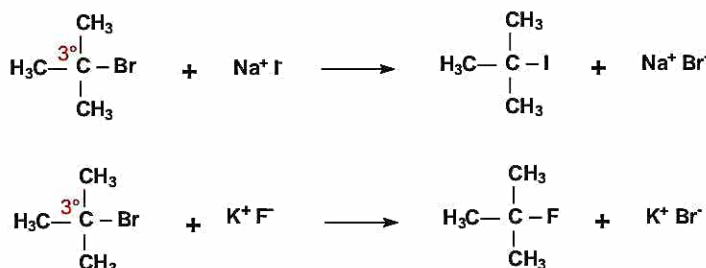
Note that phenyl and vinyl C<sup>+</sup>'s are unstable. Phenyl and vinyl halides do not usually react by S<sub>N</sub>1 or S<sub>N</sub>2 reactions

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## 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.



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## Effect of nature of the leaving group on rate of S<sub>N</sub>1 reactions:

- **2. Consider the nature of the leaving group:**

- The nature of the leaving group has the same effect on both S<sub>N</sub>1 and S<sub>N</sub>2 reactions.
- The better the leaving group, the faster a C<sup>+</sup> can form and hence the faster will be the S<sub>N</sub>1 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<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

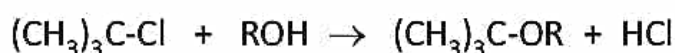
← Increasing leaving ability

- 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 $S_N1$ 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

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

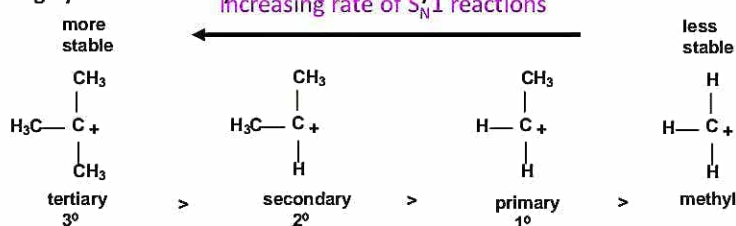
name	dielectric constant	name	dielectric constant
<b>aprotic solvents</b>		<b>protic solvents</b>	
hexane	1.9	acetic acid	6.2
benzene	2.3	acetone	20.7
diethyl ether	4.3	ethanol	24.3
chloroform	4.8	methanol	33.6
HMPA	30	formic acid	58.0
DMF	38	<b>water</b>	<b>80.4</b>
DMSO	48		

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

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

## 1. Consider the nature of the substrate:

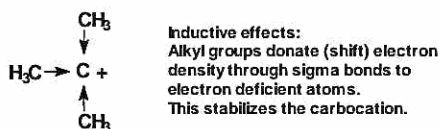
Highly substituted alkyl halides (substrates) form a more stable C<sup>+</sup>.



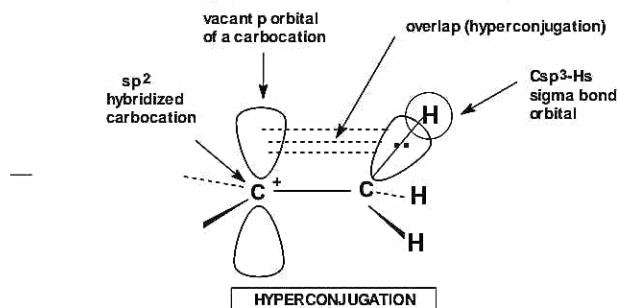
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## Stability of Carbocations

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



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



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## Stability of Carbocations

- Allyl and benzyl halides also react quickly by S<sub>N</sub>1 reactions because their carbocations are unusually stable due to their resonance forms which delocalize charge over an extended  $\pi$  system

