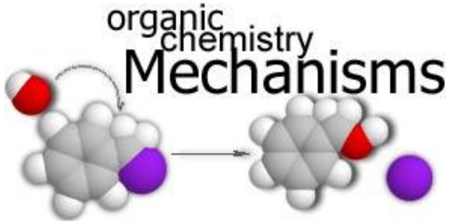


CHEM 344

ORGANIC REACTION MECHANISM

FOR CHEMISTRY’ STUDENTS, COLLEGE OF SCIENCE

PRE-REQUISITES COURSE; CHEM 241

CREDIT HOURS; 2 (2+0+0)

Prof. Mohamed El-Newehy **Prof. Zainab Almarhoon**

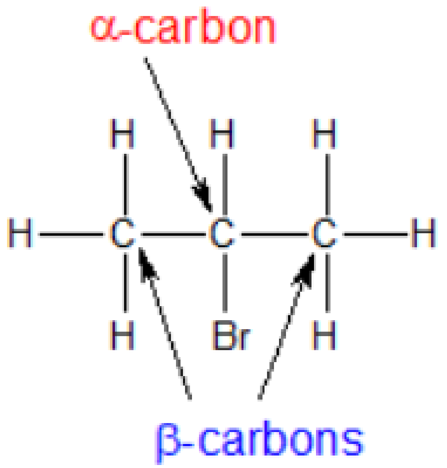
http://fac.ksu.edu.sa/melnewehy https://fac.ksu.edu.sa/zalmarhoon

Chemistry Department, College of Science, King Saud University

Nucleophilic Substitution Reactions

ALKYL HALIDE STRUCTURE

- The carbon bonded to a halide is called the alpha-carbon.
- The carbons bonded to the alpha-carbon are called beta-carbons.

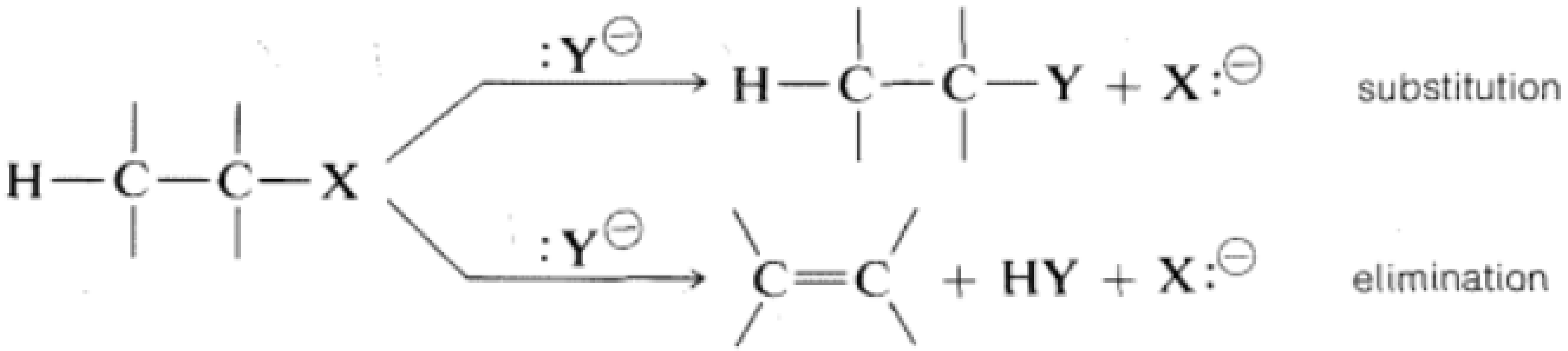


Note: The hydrogens bonded to the β-carbons are called β-hydrogens.

- ***Alkyl halides*** are polarized at the *carbon-halide bond*, making the *carbon electrophilic.*

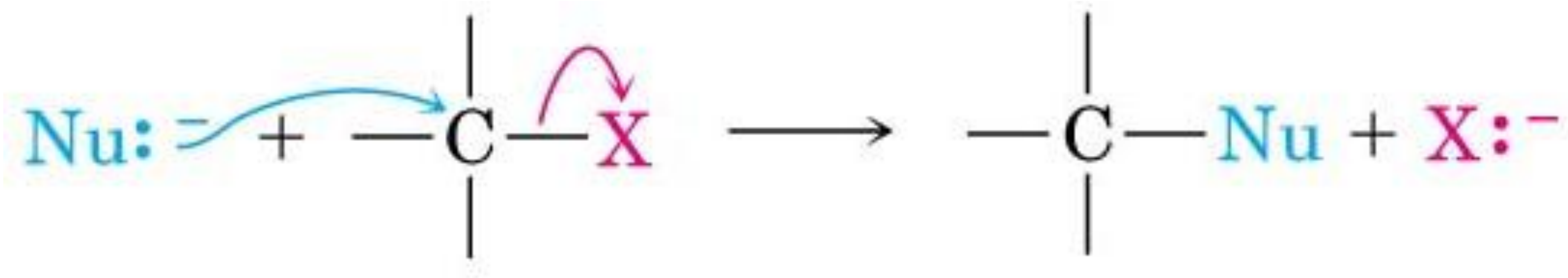
ALKYL HALIDE STRUCTURE

- ***Alkyl halides*** can undergo two major types of reactions:
  - *Substitution reactions and/or*
  - *Elimination reactions*



- *Nucleophiles will replace the halide in C-X bonds of many alkyl halides (reaction as Lewis base).*
- *Nucleophiles that are Brønsted bases produce elimination.*

SUBSTITUTION REACTIONS



- **Nu** is called the **attacking group** or a **nucleophile**
- **X** is called the **leaving group** or **nucleofuge**.
- In the process forms a new compound R -Nu
- The ***solvent*** can play the dual role of functioning as *a medium* or *a reactant*.
- When the solvent acts as one of the reactants the process is called ***solvolysis***.
  - *Many other alkyl derivatives such as alcohols, ethers, esters, and "onium ions" also can undergo S_N reactions if conditions are appropriate.*

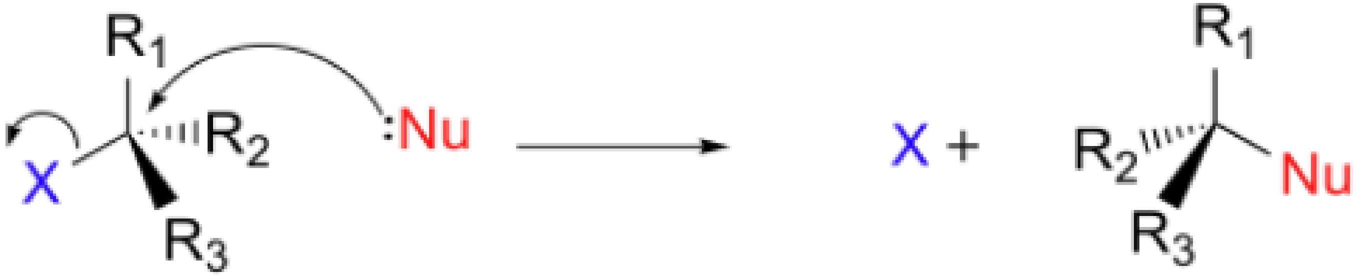
TYPES OF NUCLEOPHILIC SUBSTITUTION MECHANISMS

- **S_N1** (*Nucleophilic Substitution Reaction Unimolecular*).
  - Two steps with carbocation intermediate
  - Occurs in 3º, allyl, benzyl
- **S_N2** (*Nucleophilic Substitution Reaction Bimolecular*).
  - One step without intermediate
  - Occurs in 1º, 2º

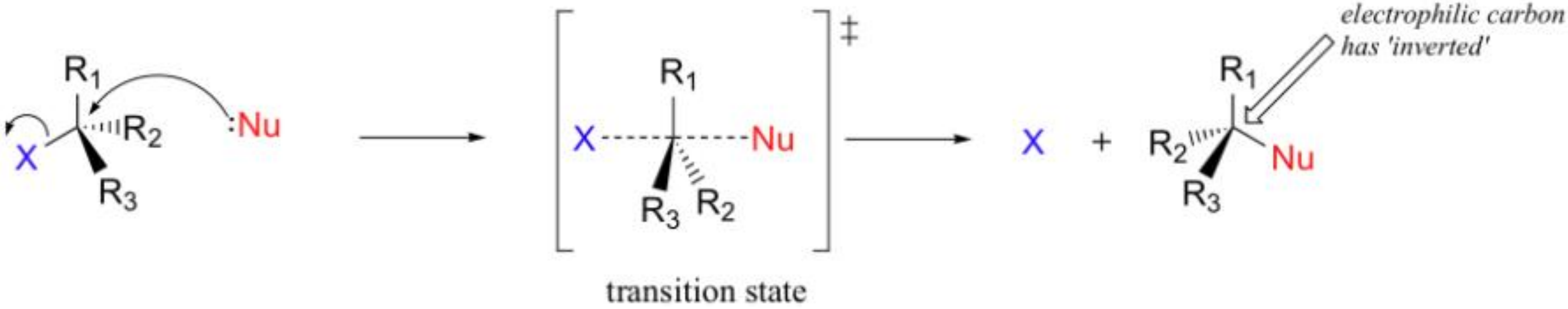
- The mechanism of substitution reaction and the reactivity of a given alkyl compound RX toward a nucleophile Nu depend upon
  - The nature of R, X, and Nu, and
  - The nature of the solvent;

    It is very important to select a solvent that will dissolve both the alkyl compound and the nucleophilic reagent.

REACTION PROCESS

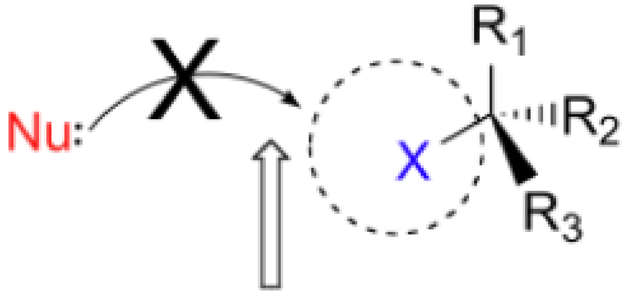


- The reaction takes place in a single step; *bond-forming and bond-breaking occur simultaneously*.
- The reaction involves a *transition state (TS)* .

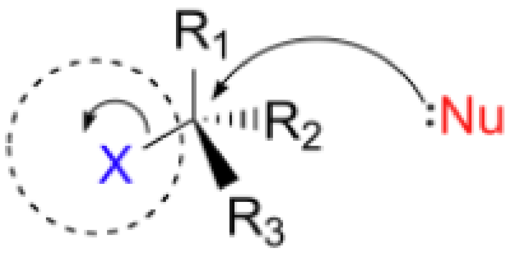


REACTION PROCESS

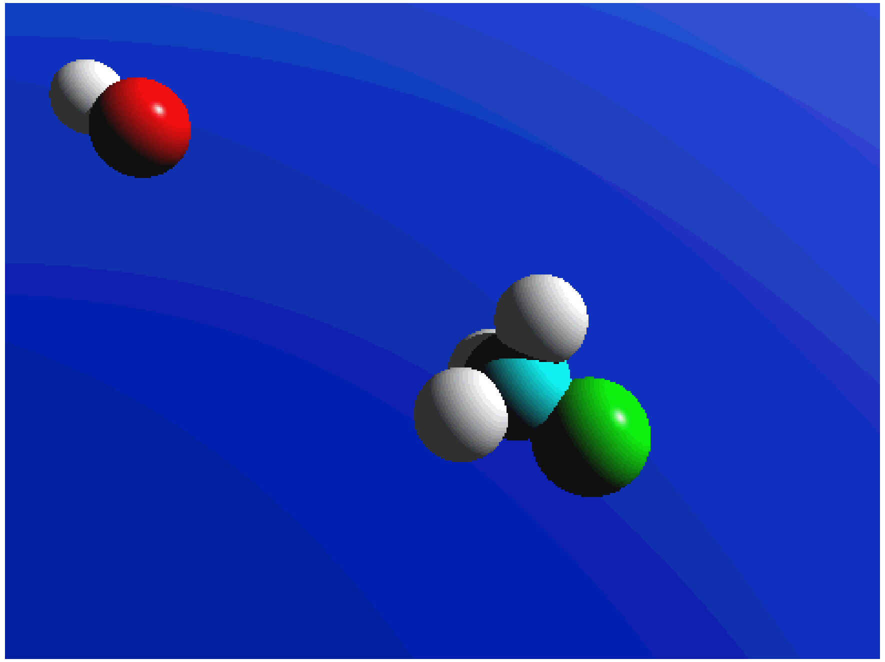
- The nucleophile, being an electron-rich species, *must attack the electrophilic carbon from the backside relative to the location of the leaving group.*
- Approach from the front side simply doesn't work: *the leaving group - which is also an electron-rich group - blocks the way.*



nucleophilic attack is blocked from the front side . . .



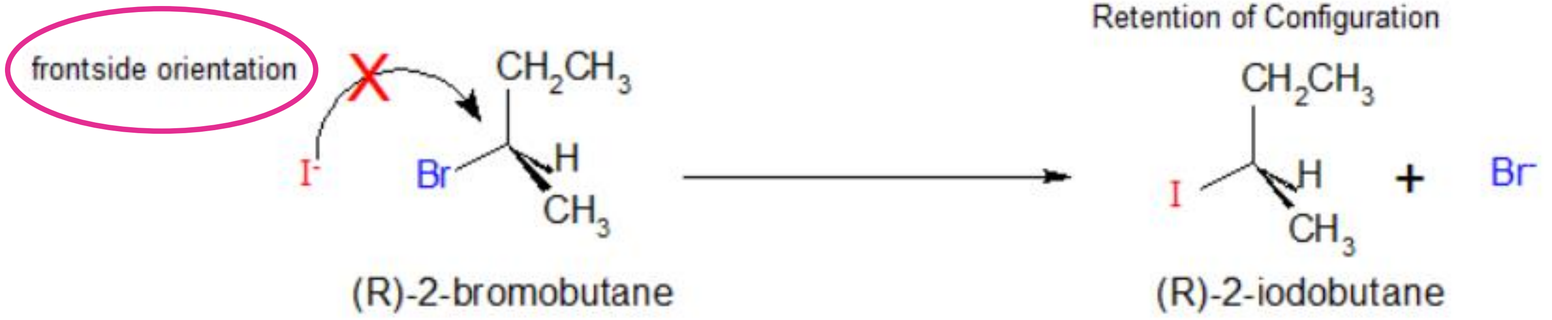
. . .so attack occurs from the back side



STEREOCHEMISTRY OF S_N2 REACTIONS

Frontside Orientation:

- *The nucleophile approaches the electrophilic center on the same side as the leaving group.*
- The stereochemistry of the product remains the same; **retention of configuration**.

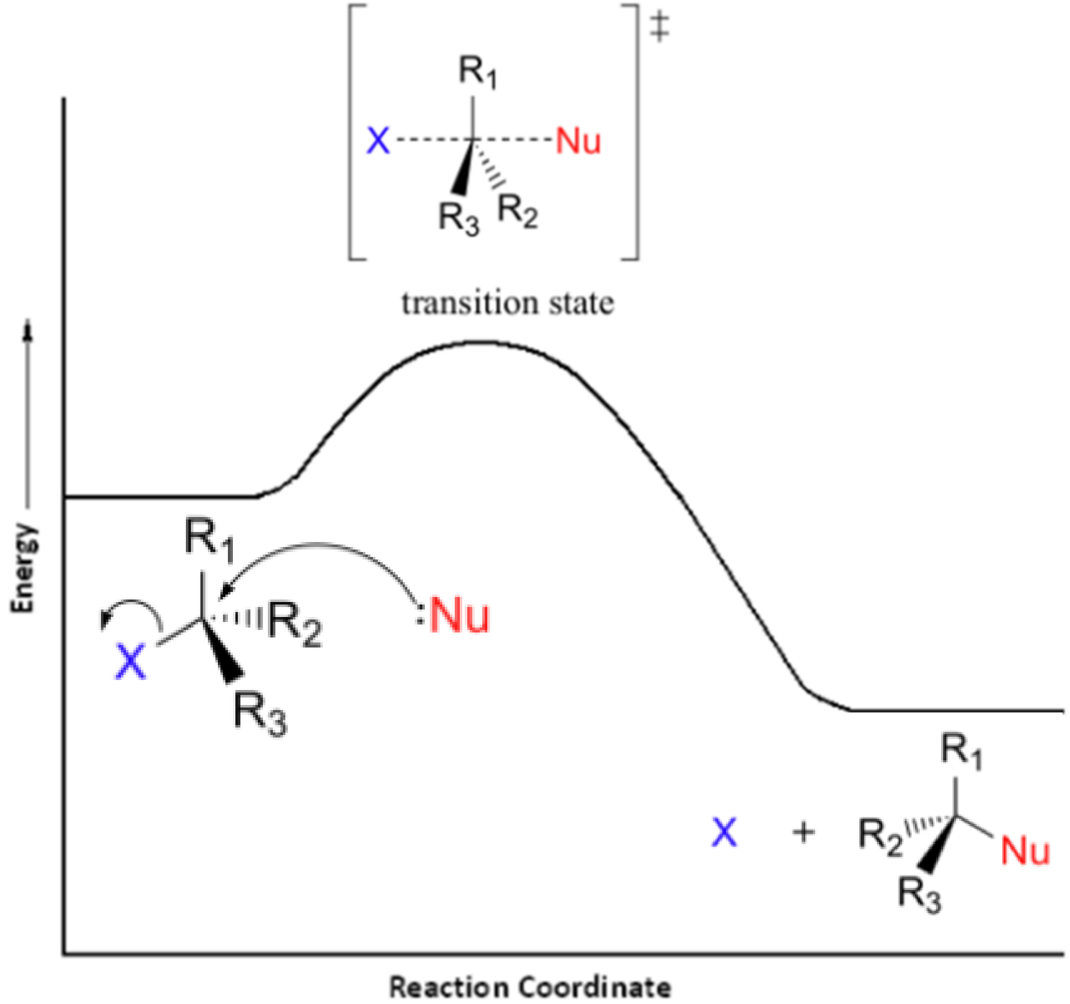


Backside Orientation

- *The nucleophile approaches the electrophilic center on the opposite side to the leaving group.*
- The stereochemistry of the product remains the same; **inversion of configuration**.

ENERGY PROFILE DIAGRAM

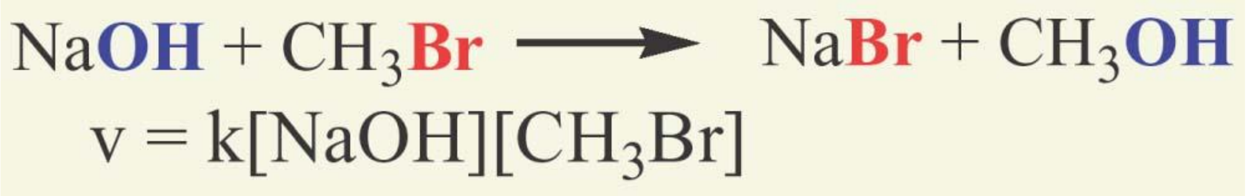
- A potential energy diagram for this reaction shows the transition state (TS) as the highest point on the pathway from reactants to products.
- Upon nucleophilic attack, a single transition state is formed.
- A transition state, unlike a reaction intermediate, is a very short-lived species that cannot be isolated or directly observed.
- Again, this is a single-step, concerted process with the occurrence of a single transition state.



REACTION KINETICS

- **Bimolecular;** there are *two molecules* involved in the *rate determining step*.
- The rate of reactions depends on the concentration of both the *haloalkane* and the *nucleophile*.

R



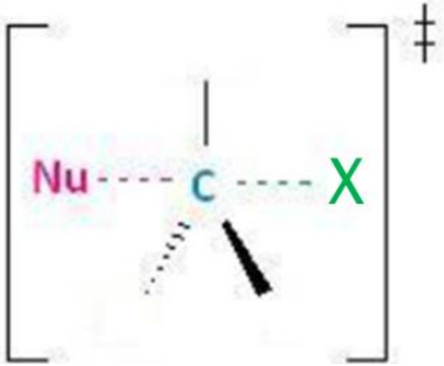
$$NaOH + CH_3Br \longrightarrow NaBr + CH_3OH$$

$$v = k[NaOH][CH_3Br]$$

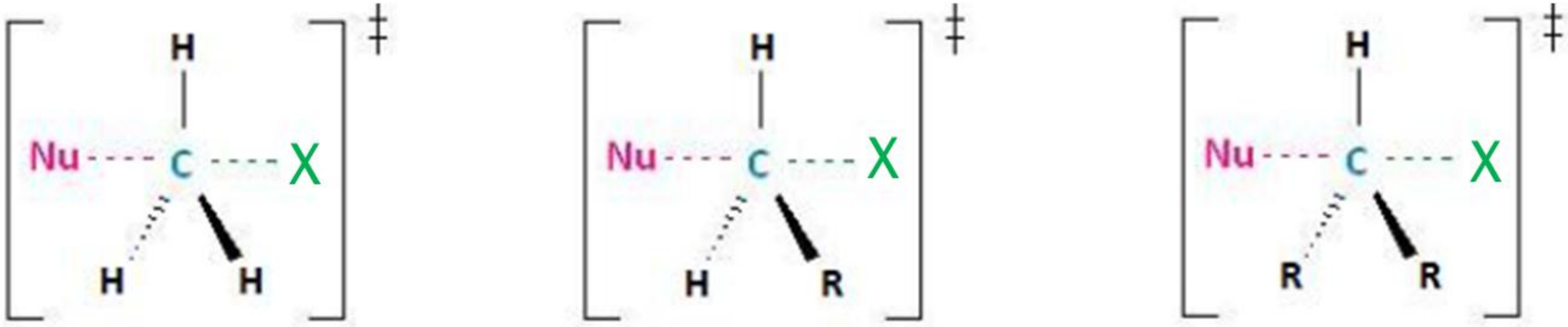
- Rates decrease as concentrations decrease but the rate constant does not
- **Rate units:** [concentration]/time such as L/(mol x s)
- The order of a reaction is sum of the exponents of the concentrations in the rate law – the example is second order
- *In the presence of large excess of nucleophile, the kinetics tends to follow first order even though the mechanism is bimolecular.*

STERIC HINDRANCE EFFECT ON THE S_N2 REACTION RATE

- **Transition state;** there are a total of five groups around the electrophilic center; *the nucleophile*, *the* *leaving group* and *three substituents*.



- *If the hydrogens were replaced by R groups*, there would be an increase in steric repulsion with the incoming nucleophile.

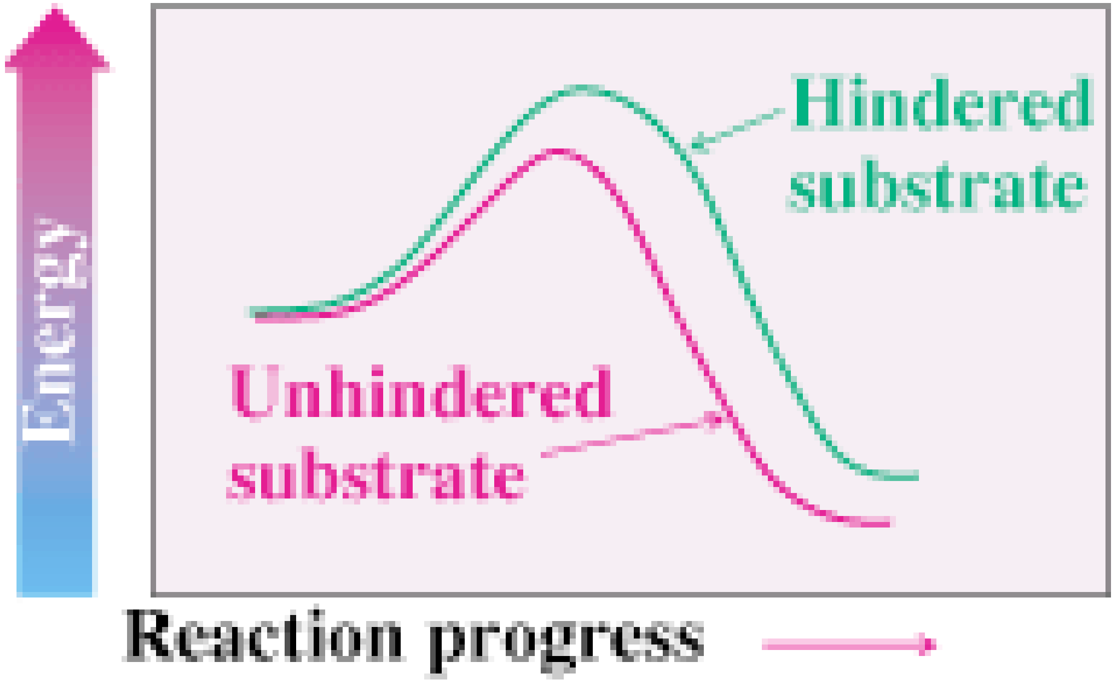


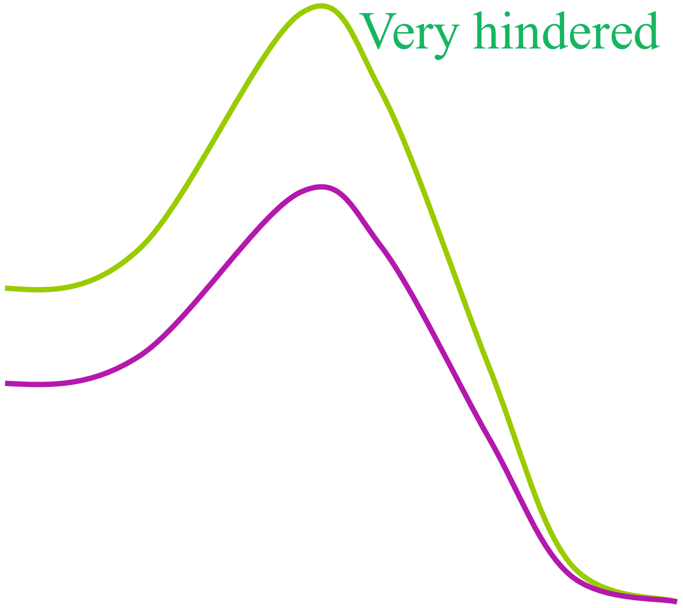
Least Steric Repulsion

Greater Steric Repulsion

STERIC HINDRANCE EFFECT ON THE S_N2 REACTION RATE

- Steric Hindrance raises Transition State Energy



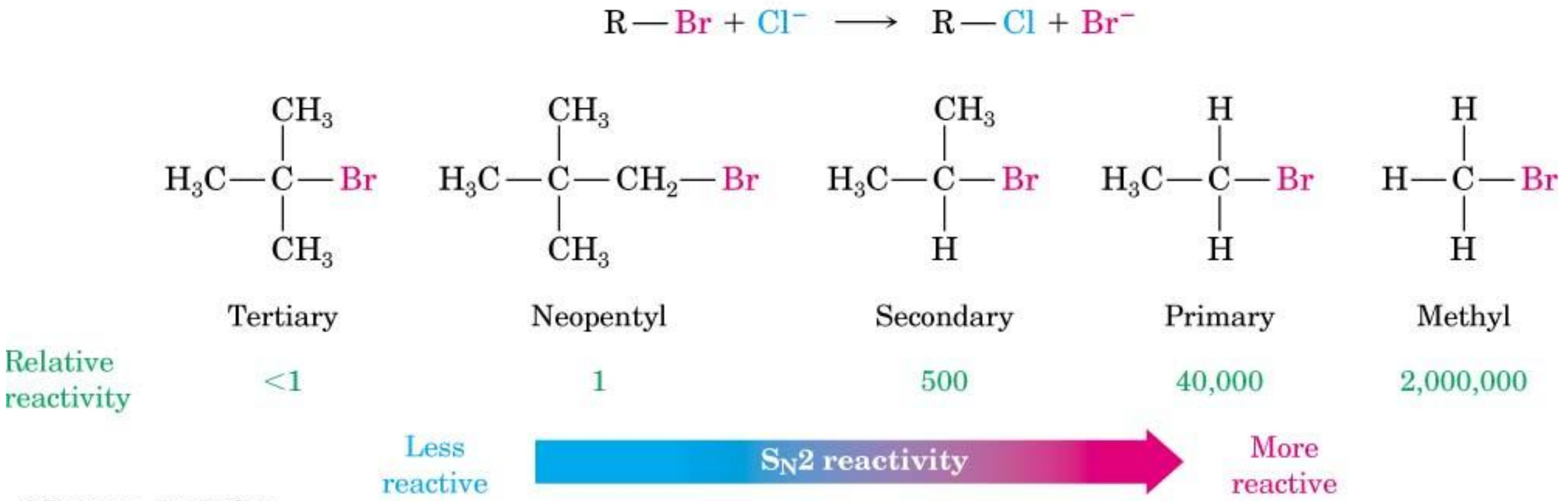


- Steric effects destabilize transition states
- Severe steric effects can also destabilize ground state

FACTORS AFFECTING THE S_N2 REACTION

- **The Electrophile:** *Structure of the alkyl group*
  - *If the groups attached to the carbon are larger,* though, like methyl groups; *the transition state energy increases*, *the activation energy increases*, and *the reaction becomes much slower*.
  - This means that the **reactivity order for alkyl halides in S_N2 reactions** is:

$$R{-}Br + Cl^- \longrightarrow R{-}Cl + Br^-$$



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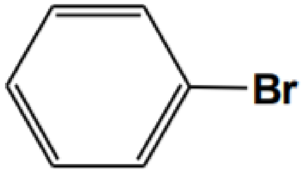
FACTORS AFFECTING THE S_N2 REACTION

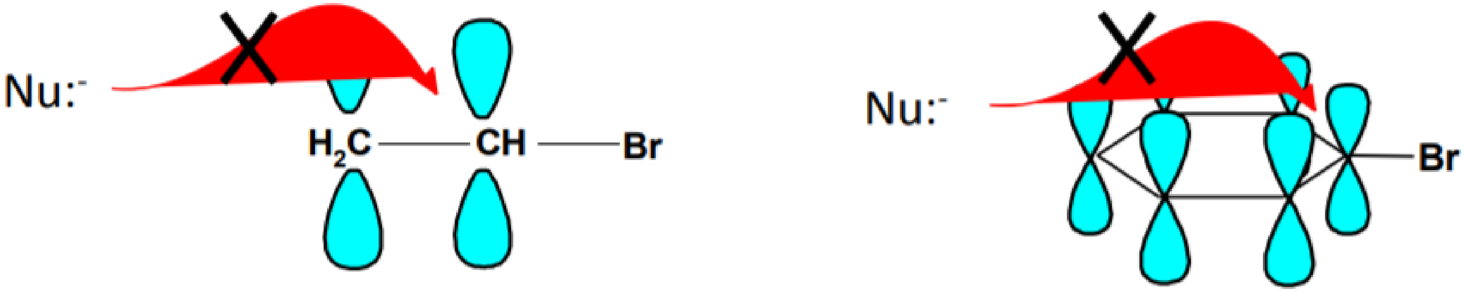
- **The Electrophile:** *Structure of the alkyl group*
  - The α-carbon in vinyl and aryl halides, as in 3° carbocation, is completely hidered and these alkyl halides do not undergo S_N2 reactions.

$H_2C{=}CH{-}Br$

vinyl bromide



bromobenzene



The overlapping p-orbitals that form the π-bonds in vinyl and aryl halides completely block the access of a nucleophile to the back side of the α-carbon

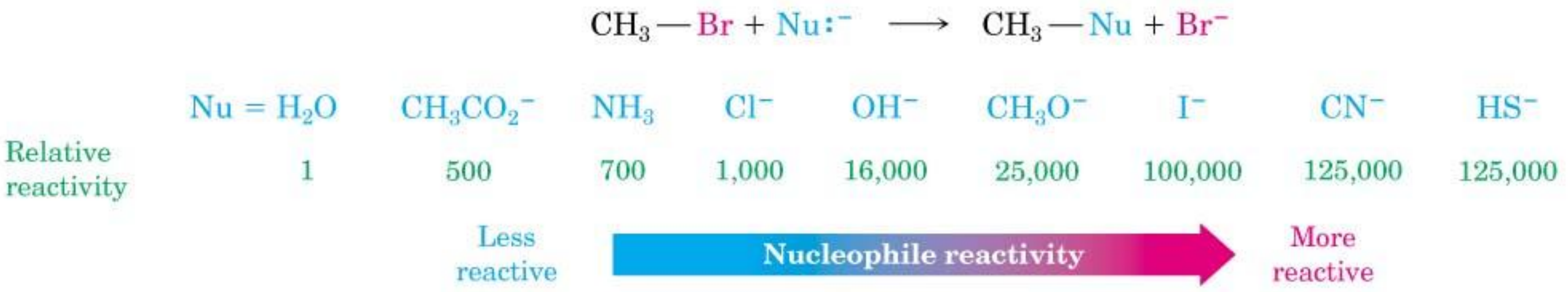
FACTORS AFFECTING THE S_N2 REACTION

- **The Nucleophile:** ***Structure Function Correlation with Nucleophile***
  - In S_N2 reaction, *stronger the nucleophile faster would be the reaction*.
  - **Strength of a nucleophile** can be determined by the following general guidelines:

(1) A nucleophile with negative charge is more powerful than its conjugate acid.

(2) Nucleophilicity generally follows similar order as basicity

(3) Going down in a group, nucleophilicity increase while basicity decrease.



$$CH_3-Br + Nu:^- \longrightarrow CH_3-Nu + Br^-$$

	Nu = H_2O	$CH_3CO_2^-$	NH_3	Cl^-	OH^-	CH_3O^-	I^-	CN^-	HS^-
Relative reactivity	1	500	700	1,000	16,000	25,000	100,000	125,000	125,000

Less reactive → Nucleophile reactivity → More reactive

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FACTORS AFFECTING THE S_N2 REACTION

- **The Nucleophile:** *Structure Function Correlation with Nucleophile*

(4) More free nucleophile, more nucleophilicity

$NaOH_{DMSO} > NaOH_{water}$ (basicity)

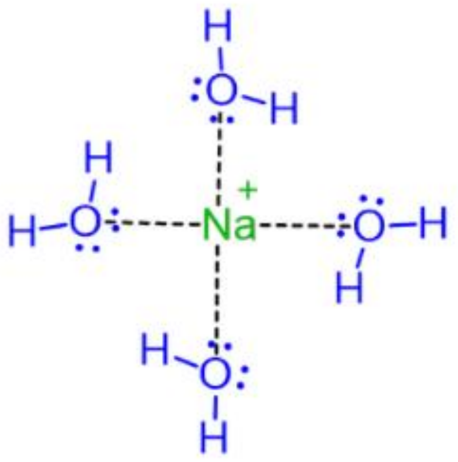
- In water Na^+ and HO^- both are solvated
- while in DMSO, Na^+ is solvated preferably than HO^- leaving HO^- as free nucleophile.

FACTORS AFFECTING THE S_N2 REACTION

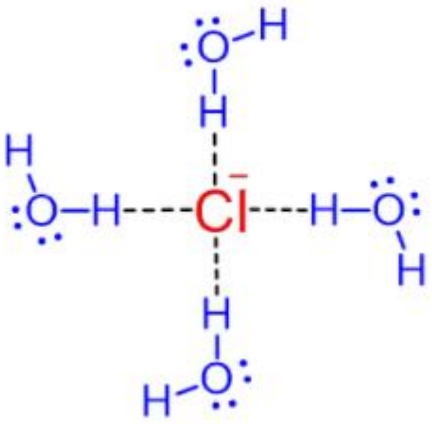
- **The Solvent:** ***The Role of Solvent in S_N2 Reactions***
  - There are two types of polar solvents; ***polar protic*** and ***polar aprotic***.
    - **Polar protic** solvents; *contain a hydrogen connected to an electronegative atom*
      - *They can make **intermolecular hydrogen bonding** and **dipole-dipole interactions***
      - *Examples:* ***water and alcohols.***

- Protic solvent puts the **nucleophile** in a cage, thus **making it weaker**,

Polar protic solvents solvate both cations and anions



Dipole interactions



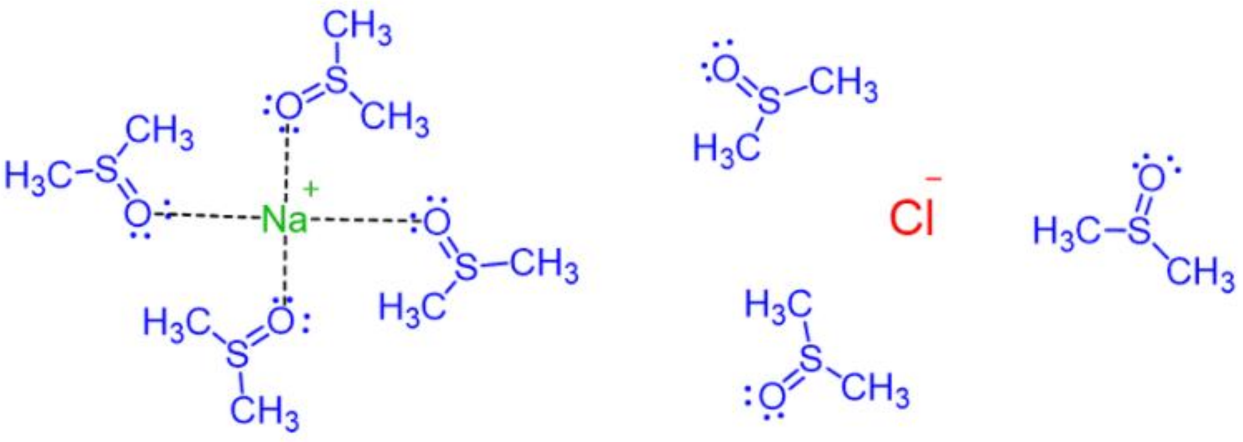
Hydrogen bonding

FACTORS AFFECTING THE S_N2 REACTION

- **The Solvent:** ***The Role of Solvent in S_N2 Reactions***
  - There are two types of polar solvents; ***polar protic*** and ***polar aprotic***.
    - **Polar aprotic** solvents; *are the ones without a hydrogen*
      - ***lack of intermolecular hydrogen bonding.***
      - *can make* ***dipole-dipole interactions***
      - *Examples:* ***acetone, acetonitrile, DMF, DMSO, HMPA.***

- **Polar aprotic solvent** solvates the cation leaving the nucleophile free.
- As a result, **in the polar aprotic solvent**, it becomes a **stronger nucleophile** since the countering does reduce its reactivity.

Polar aprotic solvents solvate only cations leaving the anions naked

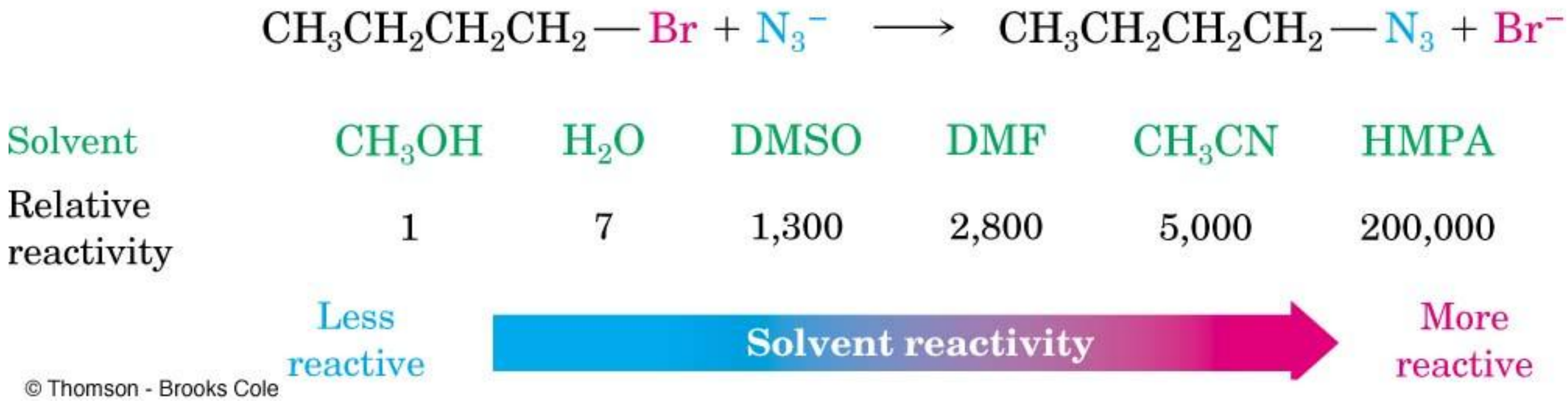


Dipole interactions

No hydrogen bonding, no interaction

FACTORS AFFECTING THE S_N2 REACTION

- **The Solvent:** ***The Role of Solvent in S_N2 Reactions***
  - **Polar protic solvents** that can donate hydrogen bonds (-OH or –NH) *slow S_N2 reactions* by associating with reactants.
  - Energy is required to break interactions between reactant and solvent
  - **Polar aprotic solvents** (no NH, OH, SH) form weaker interactions with substrate and permit faster reaction.



$$CH_3CH_2CH_2CH_2{-}Br + N_3^- \longrightarrow CH_3CH_2CH_2CH_2{-}N_3 + Br^-$$

Solvent	CH_3OH	H_2O	DMSO	DMF	CH_3CN	HMPA
Relative reactivity	1	7	1,300	2,800	5,000	200,000

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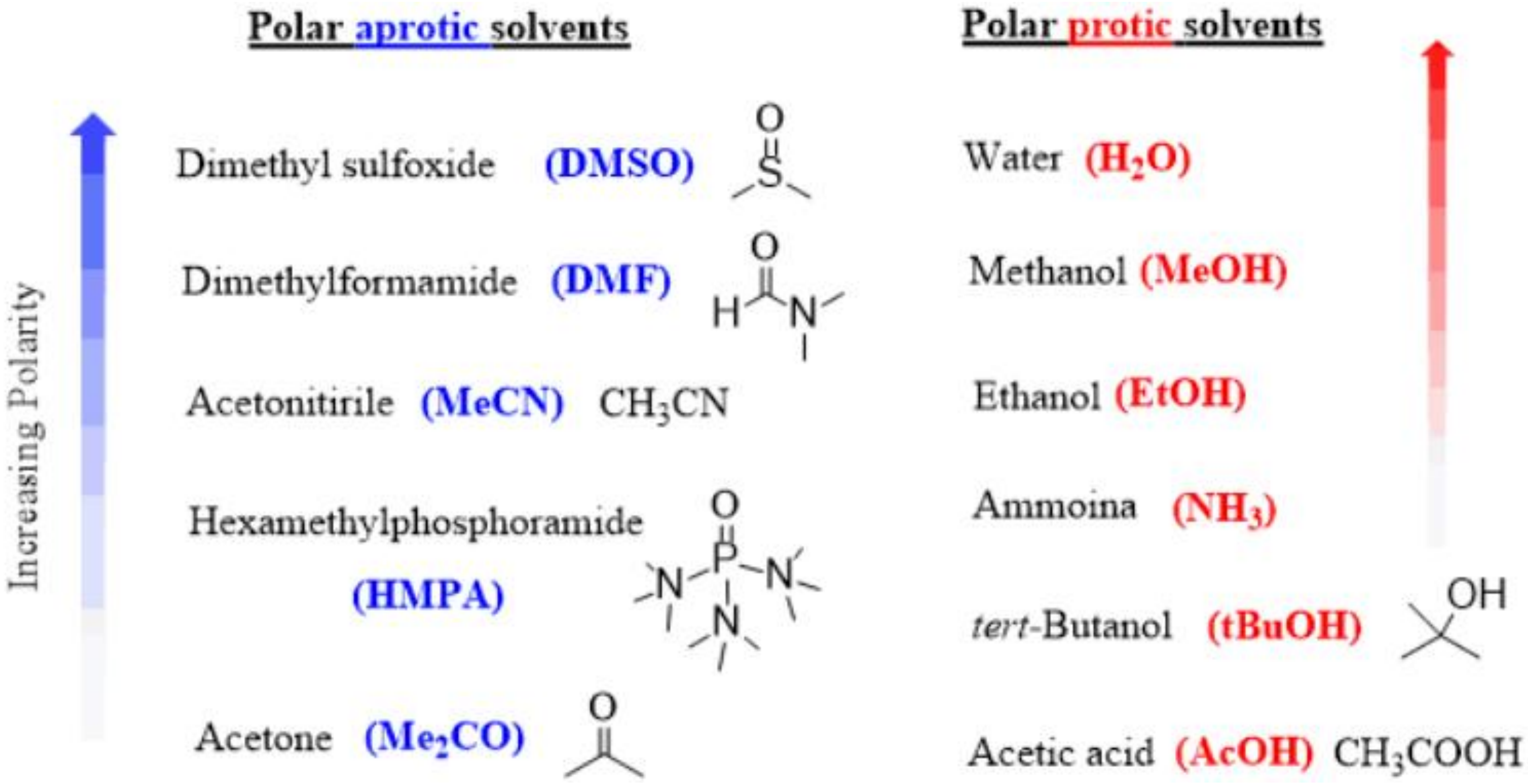
FACTORS AFFECTING THE S_N2 REACTION

The Solvent: *The Role of Solvent in S_N2 Reactions*

- Polar aprotic solvents favor bimolecular S_N2 and E2 mechanisms.
- Polar protic solvents favor bimolecular S_N1 and E1 mechanisms.



Polar aprotic solvents

Increasing Polarity

Dimethyl sulfoxide **(DMSO)**

Dimethylformamide **(DMF)**

Acetonitirile **(MeCN)** CH_3CN

Hexamethylphosphoramide **(HMPA)**

Acetone **(Me_2CO)**

Polar protic solvents

Water **(H_2O)**

Methanol **(MeOH)**

Ethanol **(EtOH)**

Ammoina **(NH_3)**

tert-Butanol **(tBuOH)**

Acetic acid **(AcOH)** CH_3COOH

FACTORS AFFECTING THE S_N^2 REACTION

- **The Leaving Group:** *Structure function correlation with leaving group*

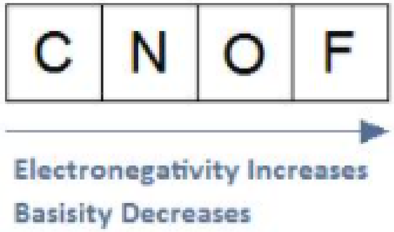
Weak bases make the best leaving groups.

For a leaving group to leave, it must be able to accept electrons.
A strong bases wants to donate electrons; therefore, the leaving group must be a weak base.

- As Electronegativity Increases

Basicity Decreases:

- *Species will be less likely to act as base; the species will be less likely to share its electrons.*



The ability of the leaving group to leave increases:

- *This is because an increase in electronegativity results in a species that wants to hold onto its electrons rather than donate them.*

$^-CH_3 < {}^-NH_2 < {}^-OH < {}^-F$

Worst   Best

FACTORS AFFECTING THE S_N2 REACTION

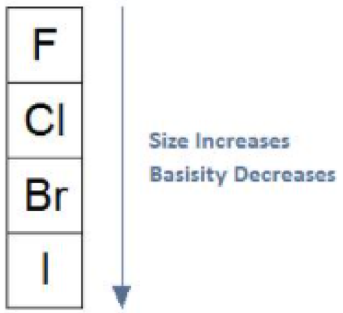
- **The Leaving Group:** *Structure function correlation with leaving group*

  Weak bases make the best leaving groups.

- As Size Increases

Basicity Decreases:

- *Species will be less likely to act as a base; the species will be less likely to share its electrons.*



The ability of the leaving group to leave increases:

- *With an increase in size, basicity decreases, and the ability of the leaving group to leave increases.*

F	<	Cl	<	Br	<	I
Worst		Fair		Good		Excellent

FACTORS AFFECTING THE S_N2 REACTION

- **The Leaving Group:** *Structure function correlation with leaving group*

  Weak bases make the best leaving groups.

- Resonance

Decreases Basicity:

- *Resonance stabilized structures are weak bases.*
- *Since strong bases, by definition, want to share their electrons,.*

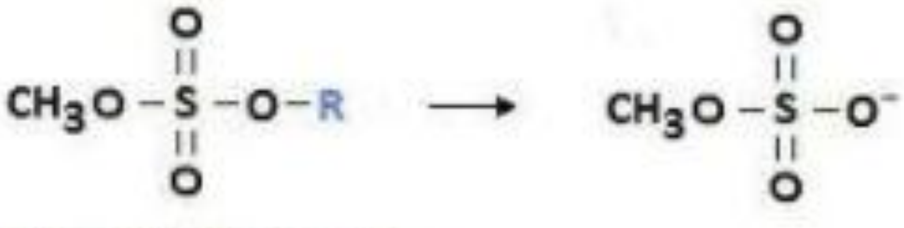
Increases the Ability of the Leaving Group to Leave:

- *Resonance stabilized structures are weak bases.*
- *Therefore, leaving groups that form resonance structures upon leaving are considered to be excellent leaving groups.*

FACTORS AFFECTING THE $S_N{}^2$ REACTION

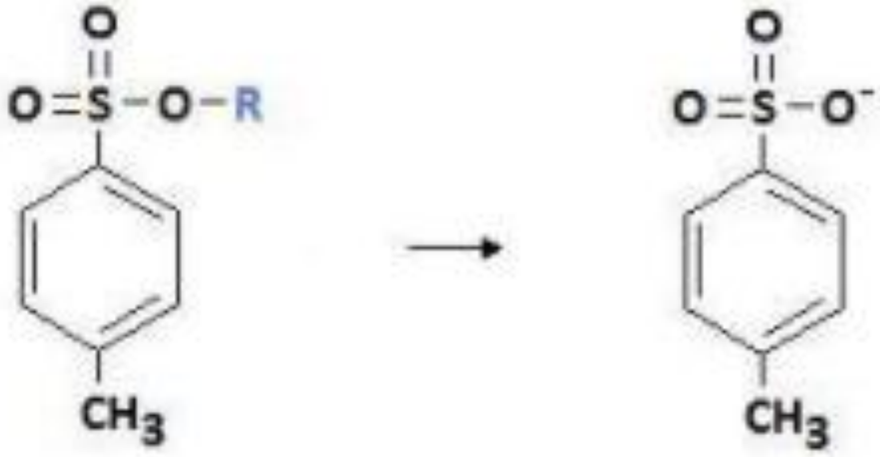
- **The Leaving Group:** *Structure function correlation with leaving group*
  - Weak bases make the best leaving groups.

- Resonance Increases the Ability of the Leaving Group to Leave.



Methyl Sulfate Ion

Methanesulfonate Ion (Mesylate)

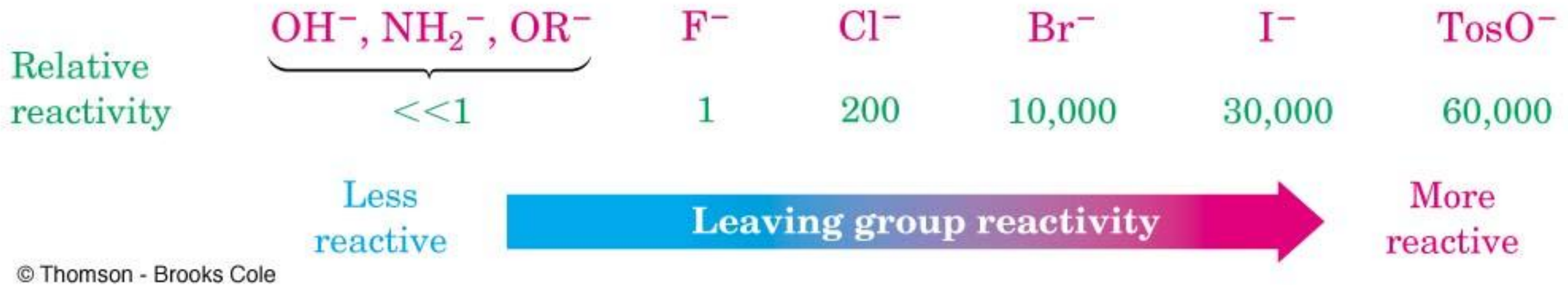


4-Methylbenzenesulfonate Ion (Tosylate)

FACTORS AFFECTING THE S_N2 REACTION

The Leaving Group: *Structure function correlation with leaving group*

- Better the leaving group, faster is the reaction.
- In general good leaving groups are:
  - large,
  - of low electronegativity and
  - of low nucleophilicity.



	$\underbrace{OH^-, NH_2^-, OR^-}$	F^-	Cl^-	Br^-	I^-	$TosO^-$
Relative reactivity	<<1	1	200	10,000	30,000	60,000

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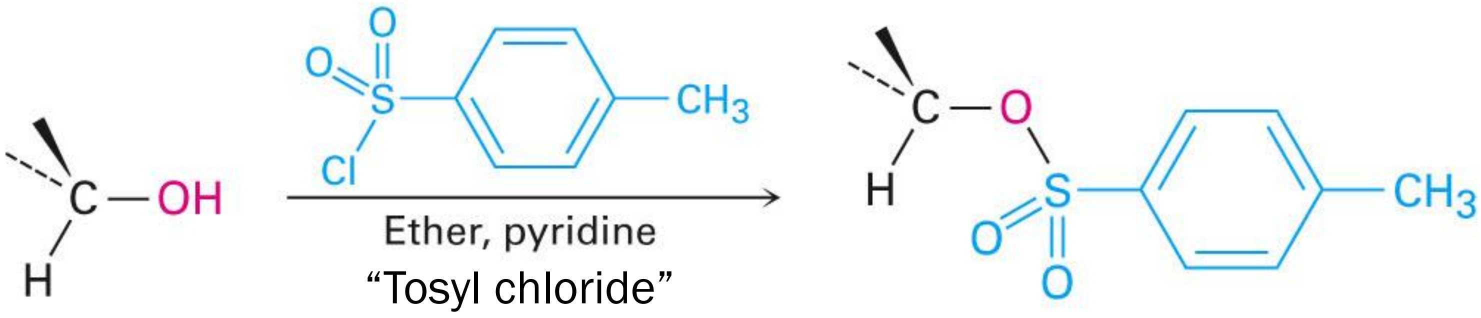
The iodide ion (I^-) is larger in size, thus has high polarizability, and is better solvated by the solvent, therefore, it is better leaving group than fluoride ion.

FACTORS AFFECTING THE S_N2 REACTION

- **The Leaving Group:** *Structure function correlation with leaving group*
  - **Poor Leaving Groups**; Alkyl fluorides, alcohols, ethers, and amines do not typically undergo S_N2 reactions.

$$\underbrace{R-F \qquad R-OH \qquad R-OR' \qquad R-NH_2}_{\text{These compounds do not undergo } S_N2 \text{ reactions.}}$$

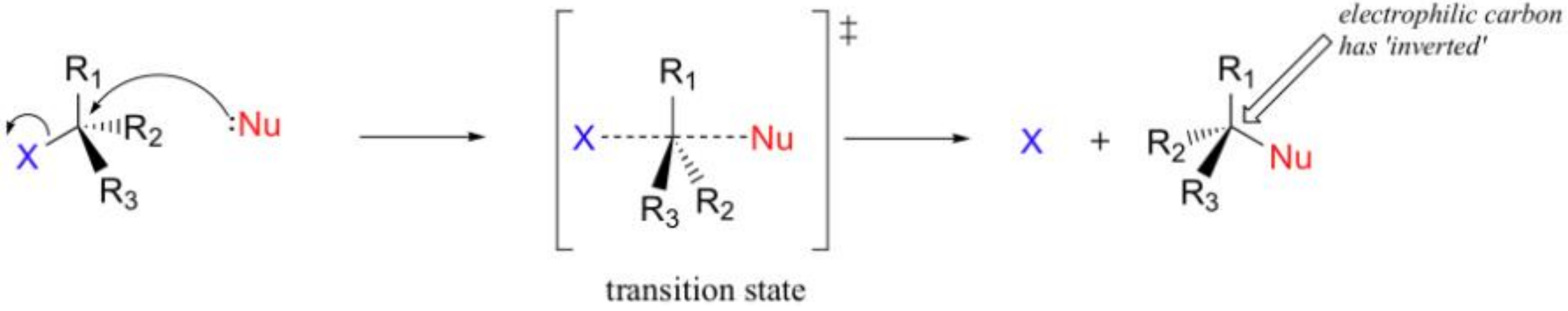
  - **Poor Leaving groups** can be made into good leaving groups.



A 1° or 2° alcohol

A tosylate

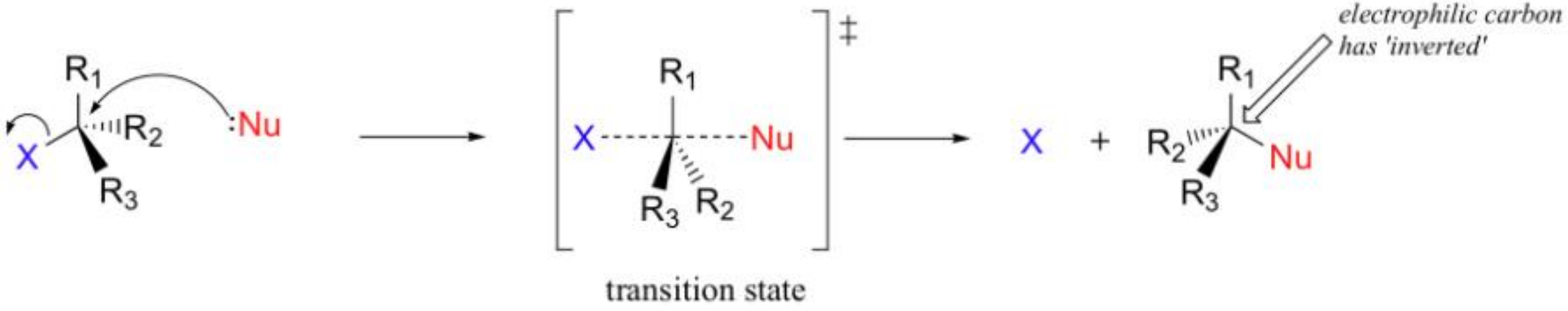
SUMMARY



transition state

- **Reaction is:**
  - Stereospecific (*Walden Inversion of configuration*)
  - Concerted - *all bonds form and break at same time*
  - Bimolecular - *rate depends on concentration of both nucleophile and substrate*
- **Substrate:**
  - Best if *primary* (one substituent on carbon bearing leaving group)
  - *works if secondary*, *fails if tertiary*
- **Nucleophile:** Best if more reactive *(i.e. more anionic or more basic*)

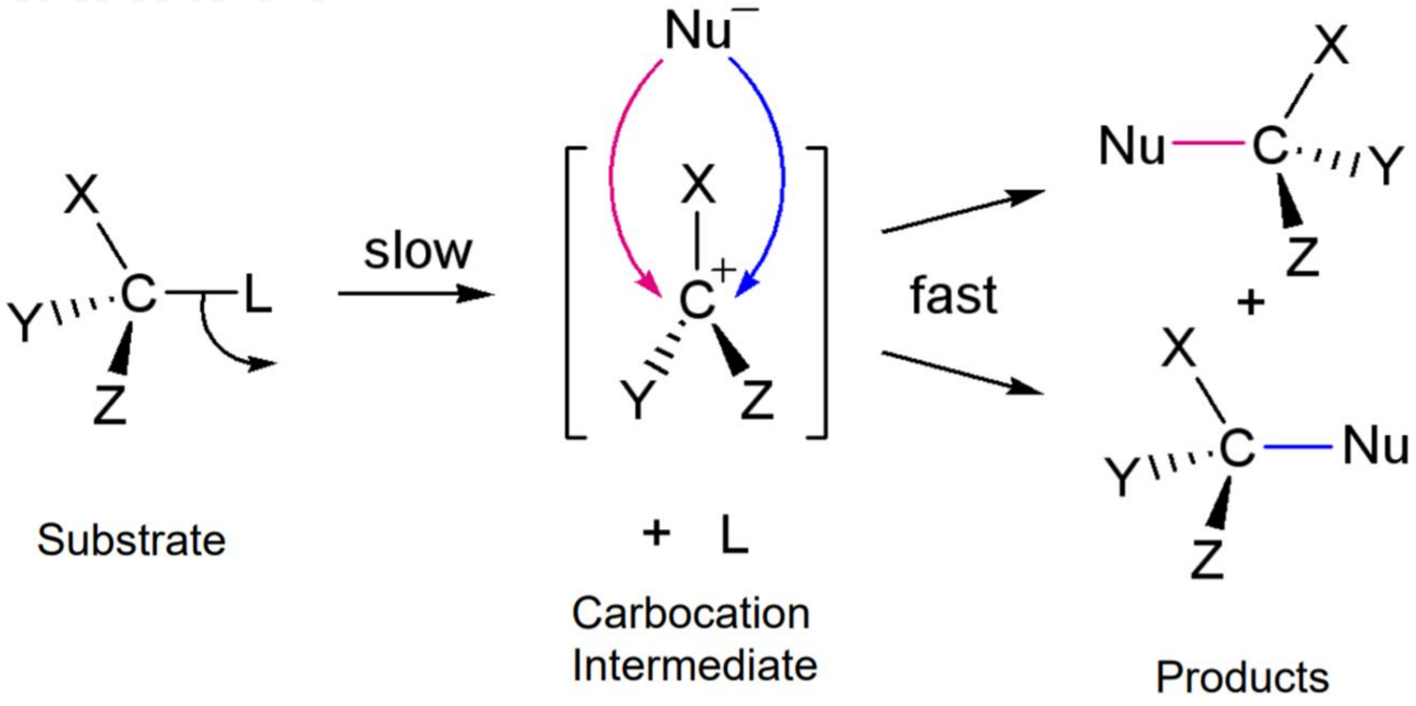
SUMMARY



transition state

- **Leaving Group:** Best if more stable (i.e. can support negative charge well):
  - TsO- (very good) > I- > Br- > Cl- > F- (poor)
  - RF , ROH , ROR , RNH_2 are NEVER Substrates for S_N2 reactions
  - Leaving Groups on double-bonded carbons are never replaced by S_N2 reactions
- **Solvent:**
  - Polar Aprotic (i.e. no OH) is best
  - Protic solvents (e.g. H_2O or ROH) deactivate nucleophile by hydrogen bonding but can be used in some case

REACTION PROCESS

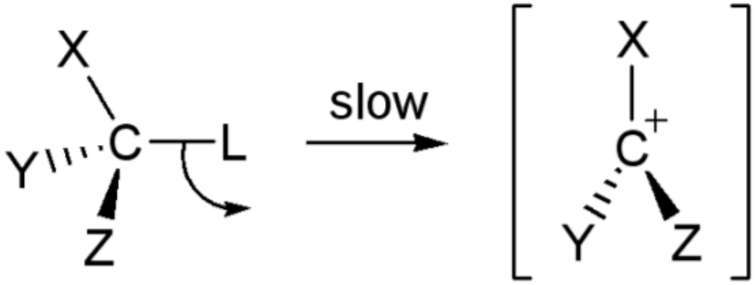


- **$S_N{}^1$ reactions:** involve replacing of a leaving group by a nucleophile
- **$S_N{}^1$ reactions** are unimolecular: the rate of this reaction depends only on the concentration of one reactant (substrate).
- **$S_N{}^1$ reactions** happen in two steps:

REACTION PROCESS

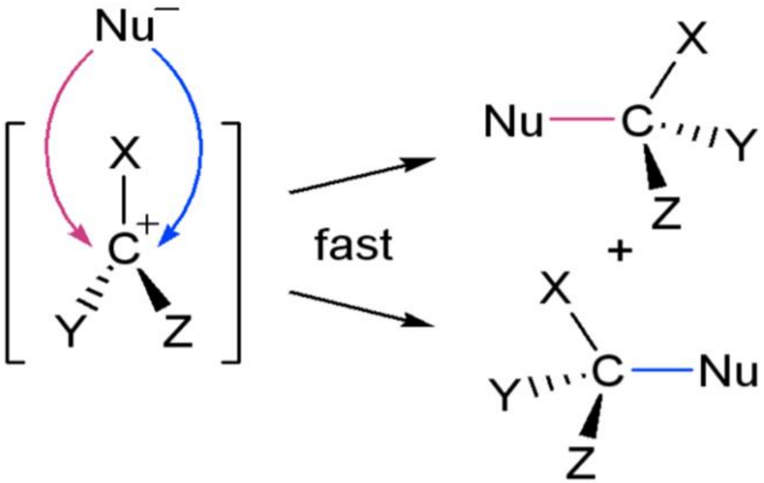
S_N1 Reactions happen in Two Steps:

(1) The Slow Step:



- The leaving group leaves, and the substrate forms a *carbocation intermediate*.
- The rate-Limiting Step
- Carbocation stability: 3º > 2º >> 1º

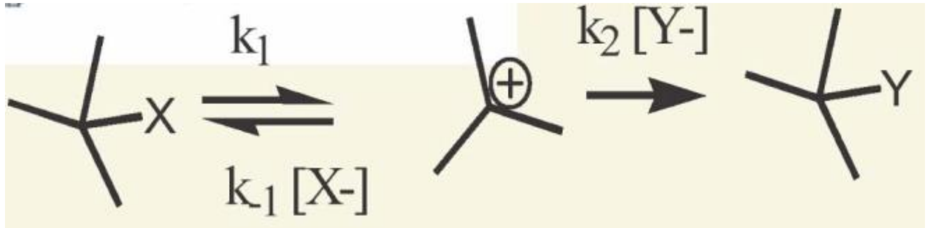
(2) The Fast Step:



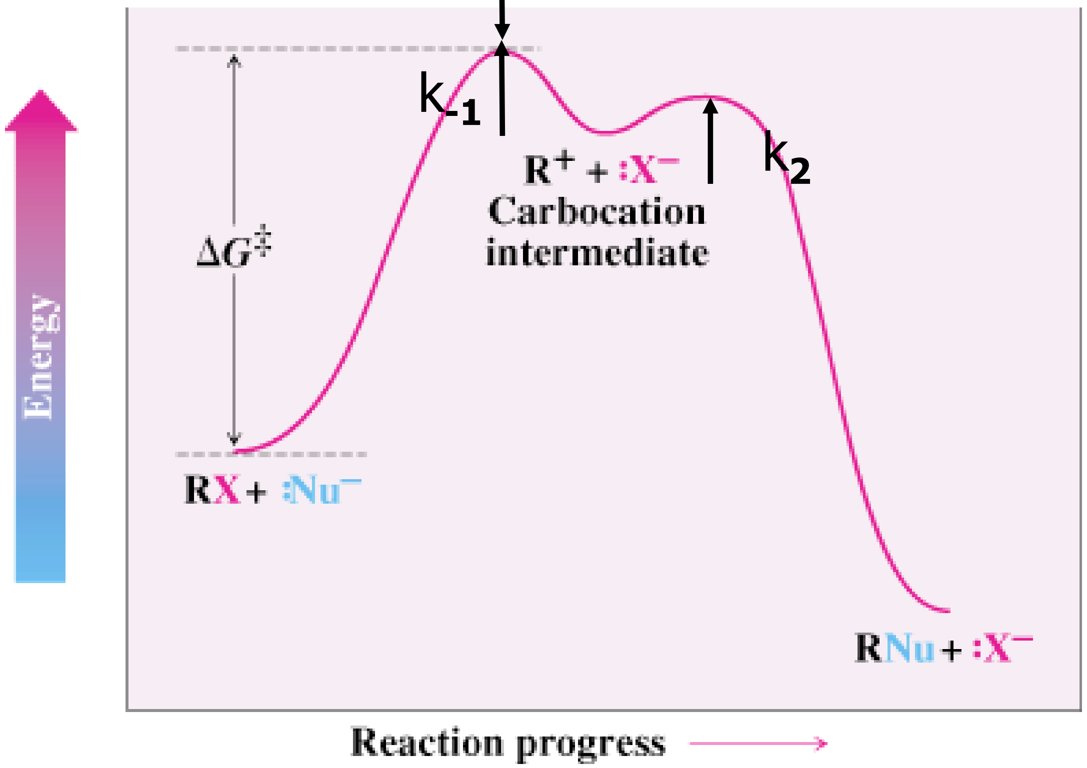
- The nucleophile attacks the carbocation, forming the product.
- The substrate loses any stereospecificity during the carbocation intermediate

ENERGY PROFILE DIAGRAM

- The overall rate of a reaction is controlled by the rate of the slowest step



Step through highest energy point is rate-limiting (k_1 in forward direction)



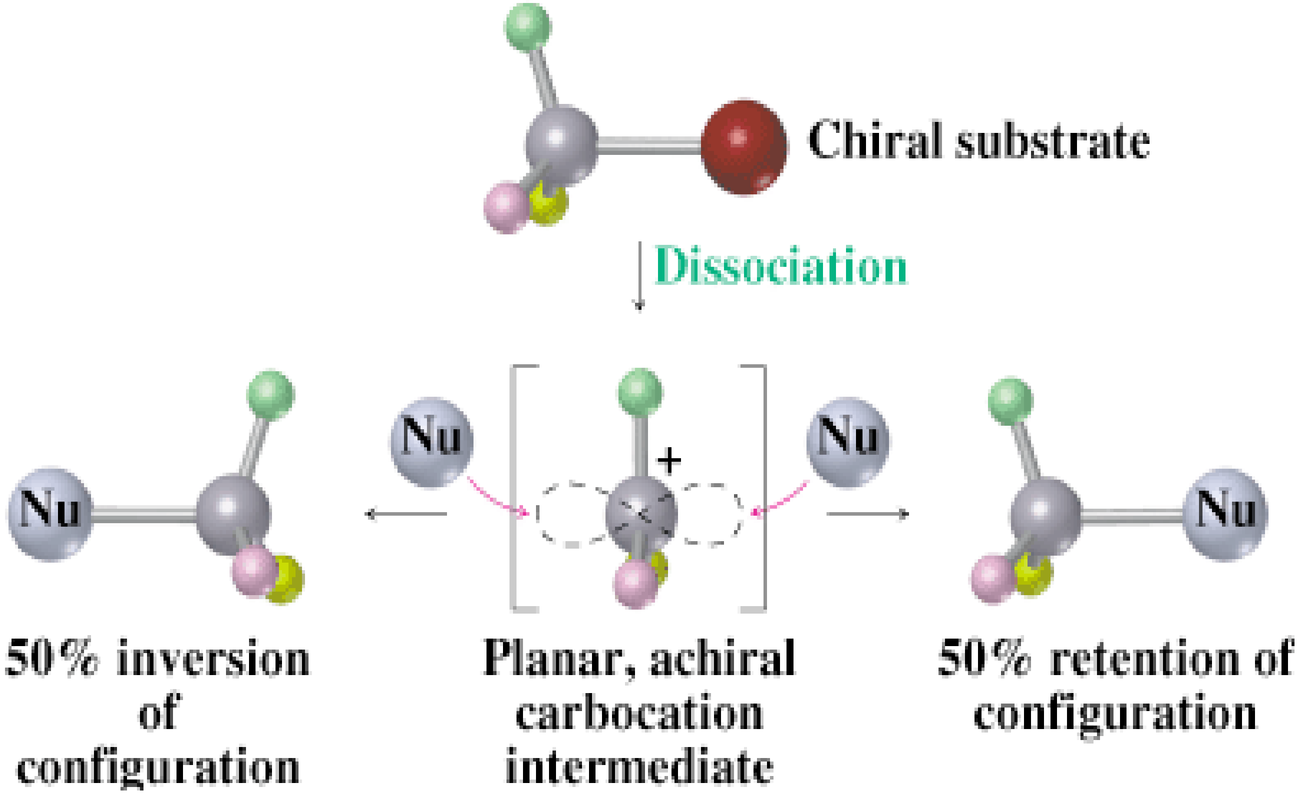
REACTION KINETICS

- **Unimolecular;** there are *one molecule* involved in the *rate-determining step*.
- The nucleophile does not appear in the rate expression changing the nucleophile concentration does not affect
- The rate depends on the concentration of the haloalkane and the rate constant of the step.
- Must be a two-step reaction
- The overall rate of a reaction is dependent upon the slowest
- step: rate-determining step

$$V = k[RX]$$

STEREOCHEMISTRY OF S_N1 REACTIONS

- The carbocation intermediate is in *trigonal planar shape*, with the empty *2p* orbital particular to the plane.
- The central carbon is *sp*^{2} hybridized and has the incomplete octet, *so carbocation is the highly reactive intermediate*.
- There is the same possibility for the nucleophile to attack from either side of the plane, (*racemic mixture*).



S_N1 REACTION

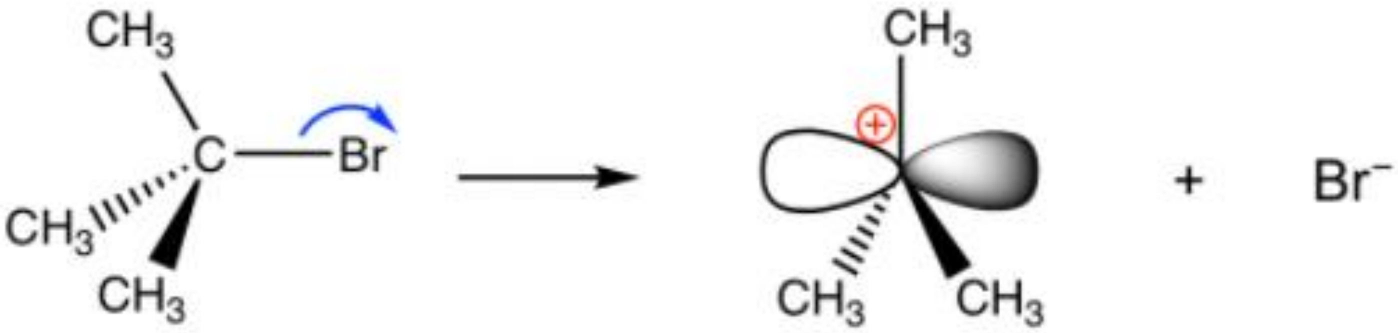
EXAMPLE: REACTION BETWEEN $(CH_3)_3CBr$ AND H_2O

Reaction:

$$(CH_3)_3CBr + H_2O \longrightarrow (CH_3)_3COH + HBr$$

Mechanism:

Step 1: Cleavage of C - Br bond **slowly** to form the carbocation intermediate. It is the **rate-determining step**.



carbocation intermediate
trigonal planar shape

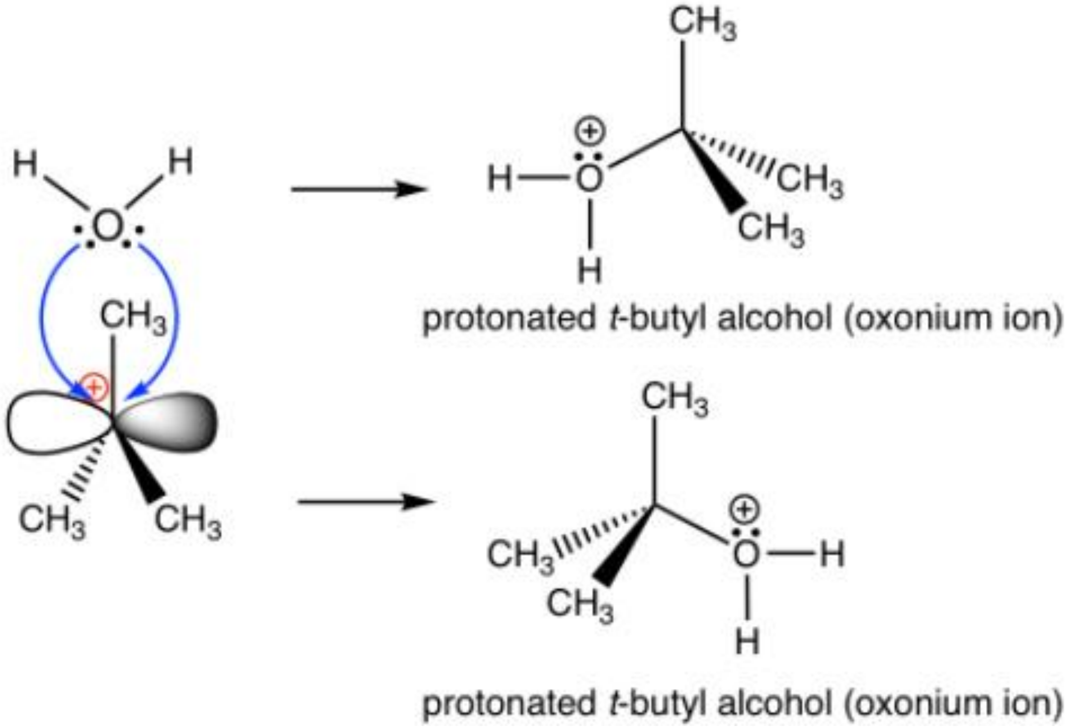
EXAMPLE: REACTION BETWEEN $(CH_3)_3CBr$ AND H_2O

Reaction:

$$(CH_3)_3CBr \quad + \quad H_2O \longrightarrow (CH_3)_3COH \quad + \quad HBr$$

Mechanism:

Step 2: Rapid reaction between carbocation intermediate and nucleophile H_2O; H_2O attacks from both sides of the planar carbocation.



S_N1 REACTION

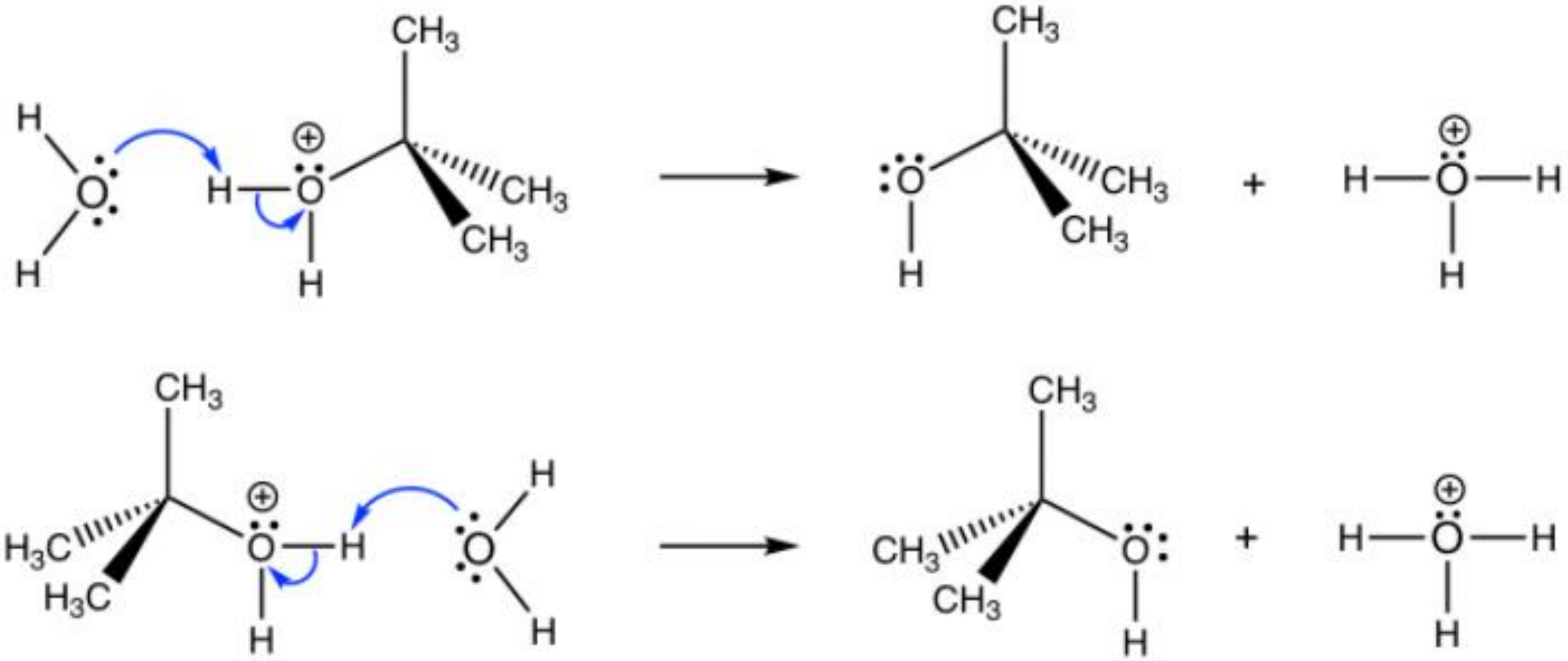
EXAMPLE: REACTION BETWEEN $(CH_3)_3CBr$ AND H_2O

Reaction:

$$(CH_3)_3CBr + H_2O \longrightarrow (CH_3)_3COH + HBr$$

Mechanism:

Step 3: Rapid deprotonation to produce neutral final product *t*-butyl alcohol (very fast step, and sometimes can be combined with step 2 together as one step.

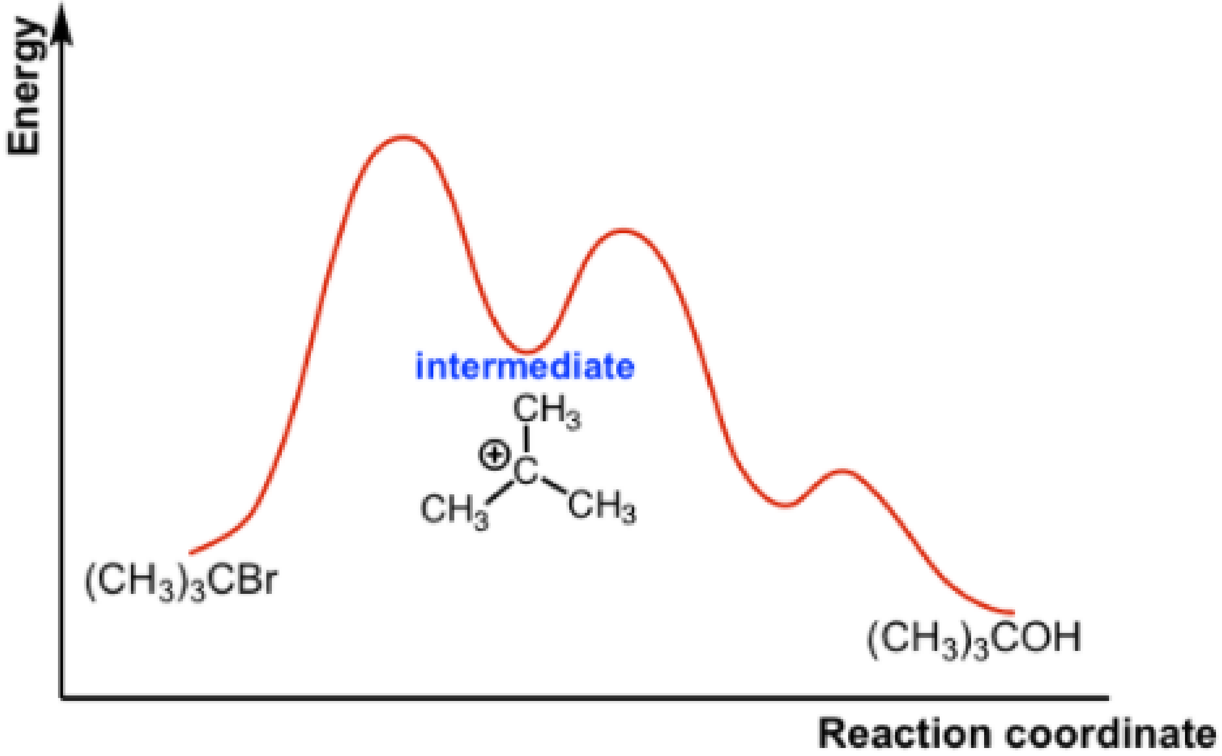


EXAMPLE: REACTION BETWEEN $(CH_3)_3CBr$ AND H_2O

Reaction:

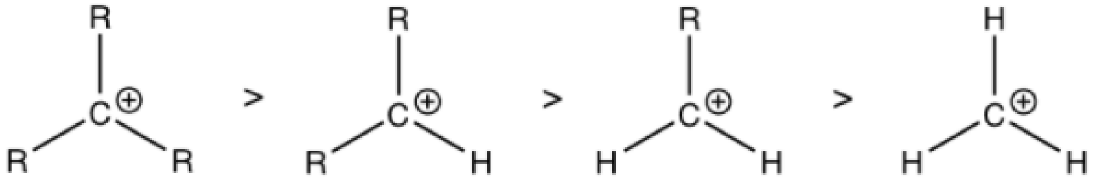
$$(CH_3)_3CBr + H_2O \longrightarrow (CH_3)_3COH + HBr$$

Energy diagram of $S_N{}^1$ mechanism:



FACTORS AFFECTING THE $S_N{}^1$ REACTION

- **The Substrate:** ***Stability of Carbocation***
  - *Highly substituted alkyl halides (substrates) form a more stable carbocation.*
  - The more stable the carbocation intermediate is, the faster the rate of a reaction.

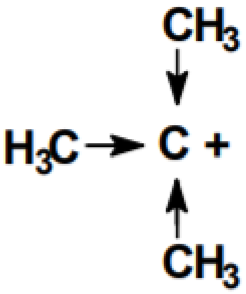


tertiary, 3°, most stable

methyl, least stable

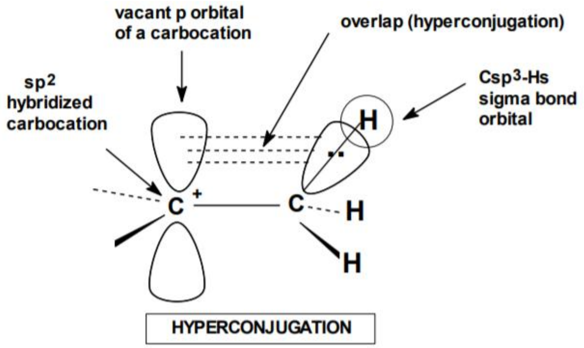
too unreactive to undergo S_N1 reaction

- **Inductive effect;** Alkyl groups donate electron and stabilize the carbocation.



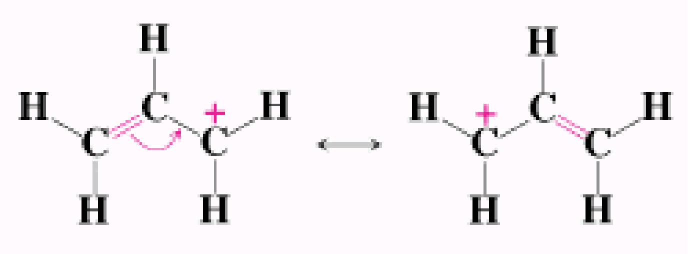
- Alkyl groups stabilize carbocations by hyperconjugation

  (*by partial overlap of the alkyl C-to-H bonds with the empty p-orbital of the carbocation*).

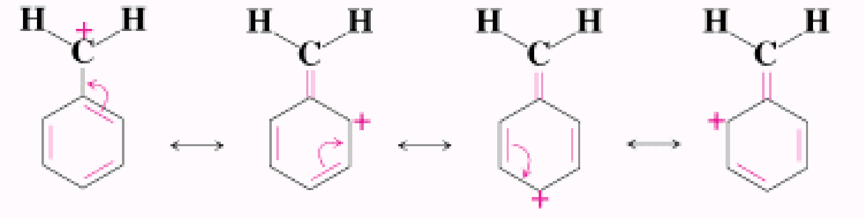


FACTORS AFFECTING THE S_N1 REACTION

- **The Substrate:** ***Delocalized Carbocation***
  - *Allyl and benzyl halides; their carbocations stabilize due to their resonance forms which delocalize charge over an extended π-system*

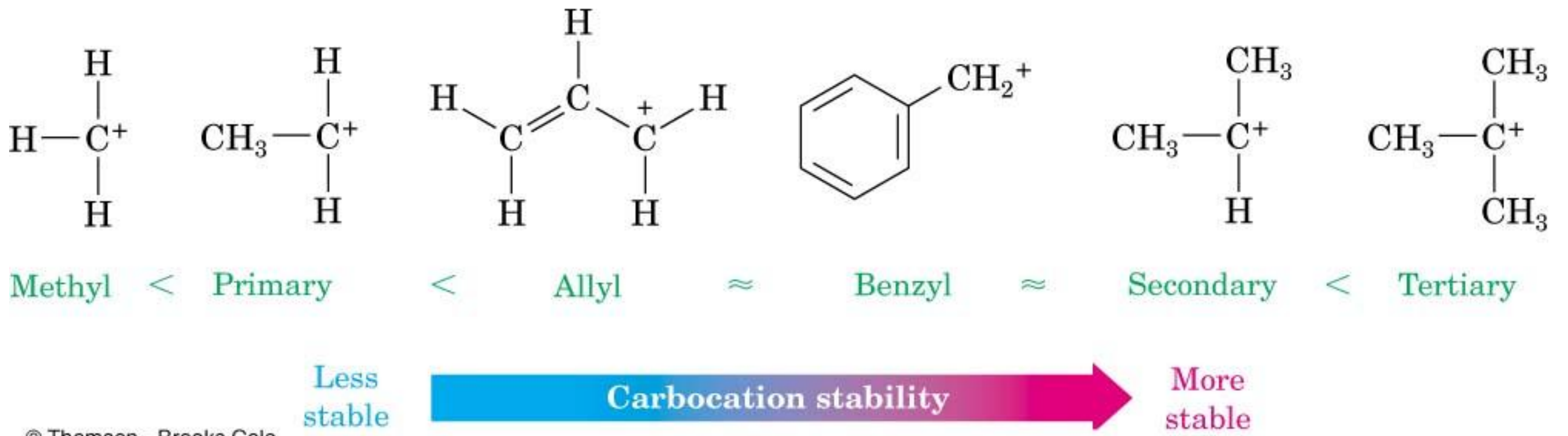


Allyl carbocation



Benzyl carbocation

  - *Relative Stability of All Types of Carbocations*



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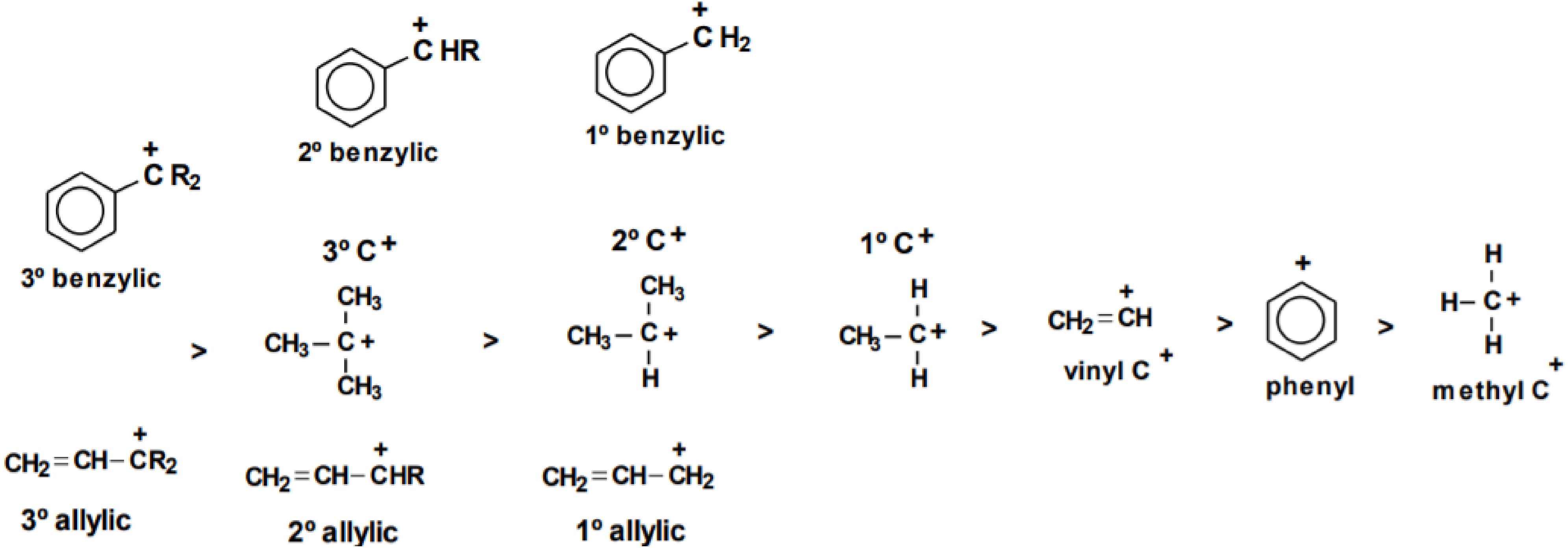
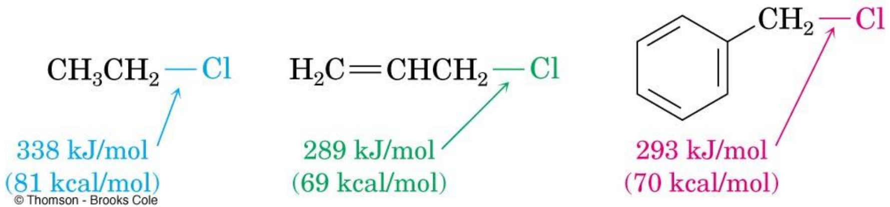
FACTORS AFFECTING THE S_N1 REACTION

- The Substrate: ***Delocalized Carbocation***
  - *Relative Stability of All Types of Carbocations*



  - Primary allylic and benzylic are also more reactive in the S_N2 mechanism



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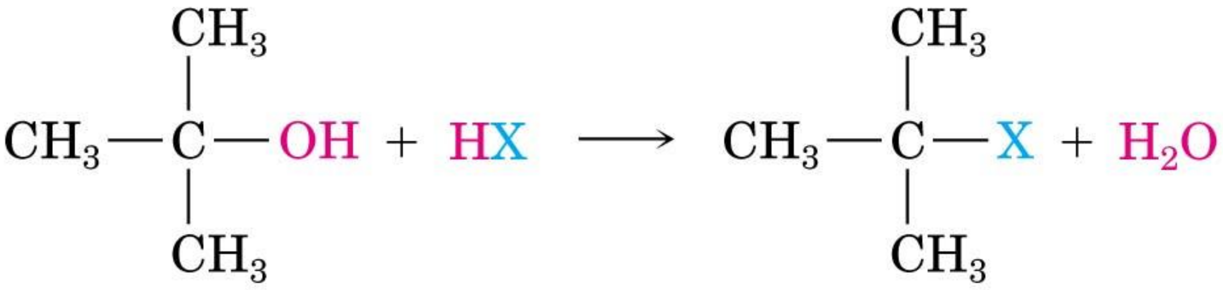
FACTORS AFFECTING THE S_N1 REACTION

- **The Nucleophile:**
  - The rate-determining step of S_N1 reaction does not include nucleophile, *so theoretically the strength of nucleophile has no effect on S_N1 reaction.*
  - A strong nucleophile has high tendency to go with S_N2 reaction instead of S_N1, *A weaker nucleophile is a better choice for S_N1.*
  - In practice, neutral substances such as H_2O, ROH, RCOOH are usually used as nucleophiles in S_N1 reaction and they also serve as solvents.
  - So, when substances are used as *both* nucleophiles and solvents for S_N1 reaction, and such reaction is also called the solvolysis reaction.



$$CH_3-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-OH + HX \longrightarrow CH_3-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-X + H_2O$$

2-Methyl-2-propanol

(Same rate for X = Cl, Br, I)

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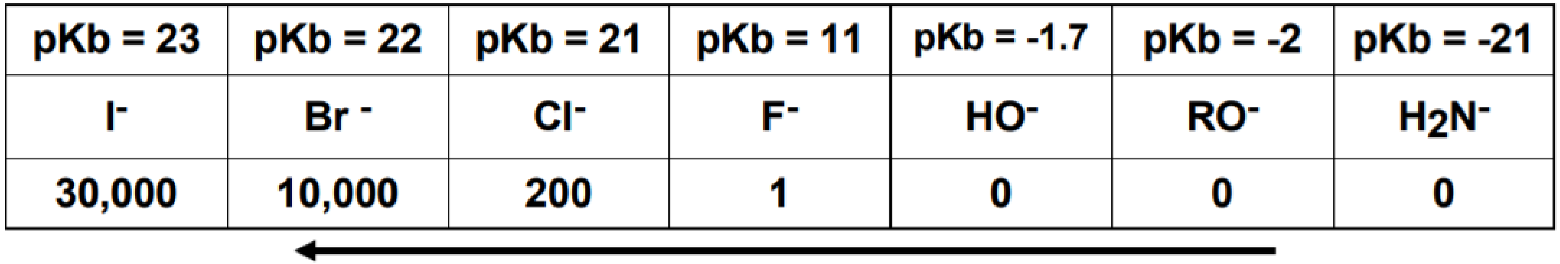
FACTORS AFFECTING THE S_N1 REACTION

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



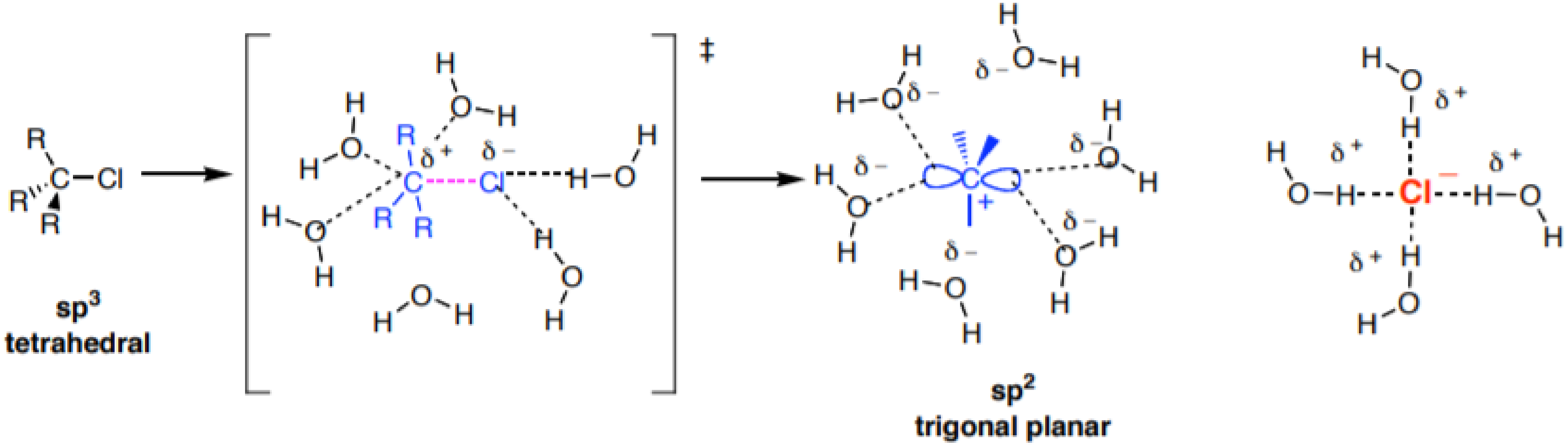
pKb = 23	pKb = 22	pKb = 21	pKb = 11	pKb = -1.7	pKb = -2	pKb = -21
I^-	Br^-	Cl^-	F^-	HO^-	RO^-	H_2N^-
30,000	10,000	200	1	0	0	0

Increasing leaving ability

FACTORS AFFECTING THE S_N1 REACTION

The Solvent:

- Polar protic solvents, such as water and alcohols, organic acids and inorganic acids (H_2SO_4, H_3PO_4), stabilize the transition state by solvating the carbocation intermediate and therefore increase the reaction rate even more.
- In general, polar protic solvents are able to solvate both cations and anions through hydrogen bonds.



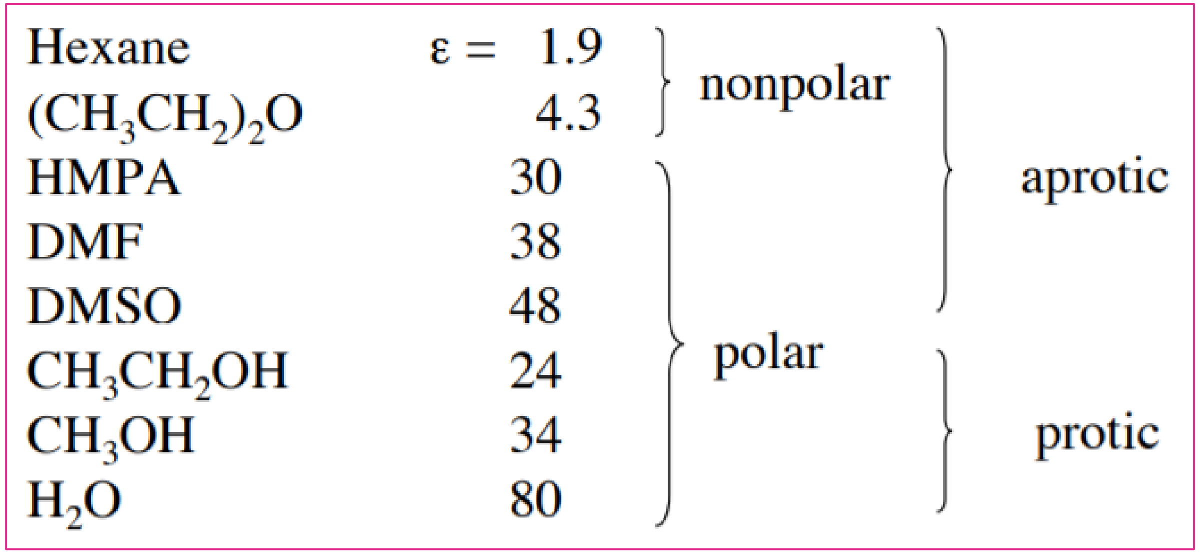
Solvent stablization of the transition state

Solvent stablization of the intermediates

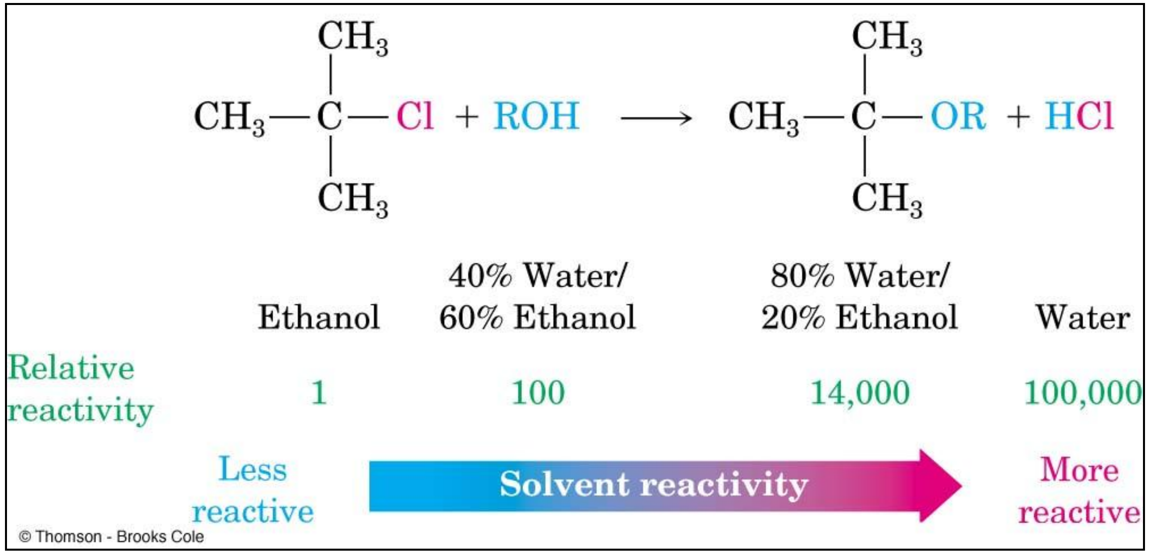
FACTORS AFFECTING THE S_N1 REACTION

The Solvent:

- Polar solvents are favored over non-polar for the S_N1 reaction
- Protic solvents are favored over aprotic for the S_N1 reaction
- Solvent polarity is measured by dielectric constant (ε)



	ε =		
Hexane	1.9	nonpolar	aprotic
$(CH_3CH_2)_2O$	4.3		
HMPA	30	polar	
DMF	38		
DMSO	48		
CH_3CH_2OH	24		protic
CH_3OH	34		
H_2O	80		



$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-Cl + ROH \longrightarrow CH_3-\overset{CH_3}{\underset{CH_3}{C}}-OR + HCl$$

	Ethanol	40% Water/ 60% Ethanol	80% Water/ 20% Ethanol	Water
Relative reactivity	1	100	14,000	100,000

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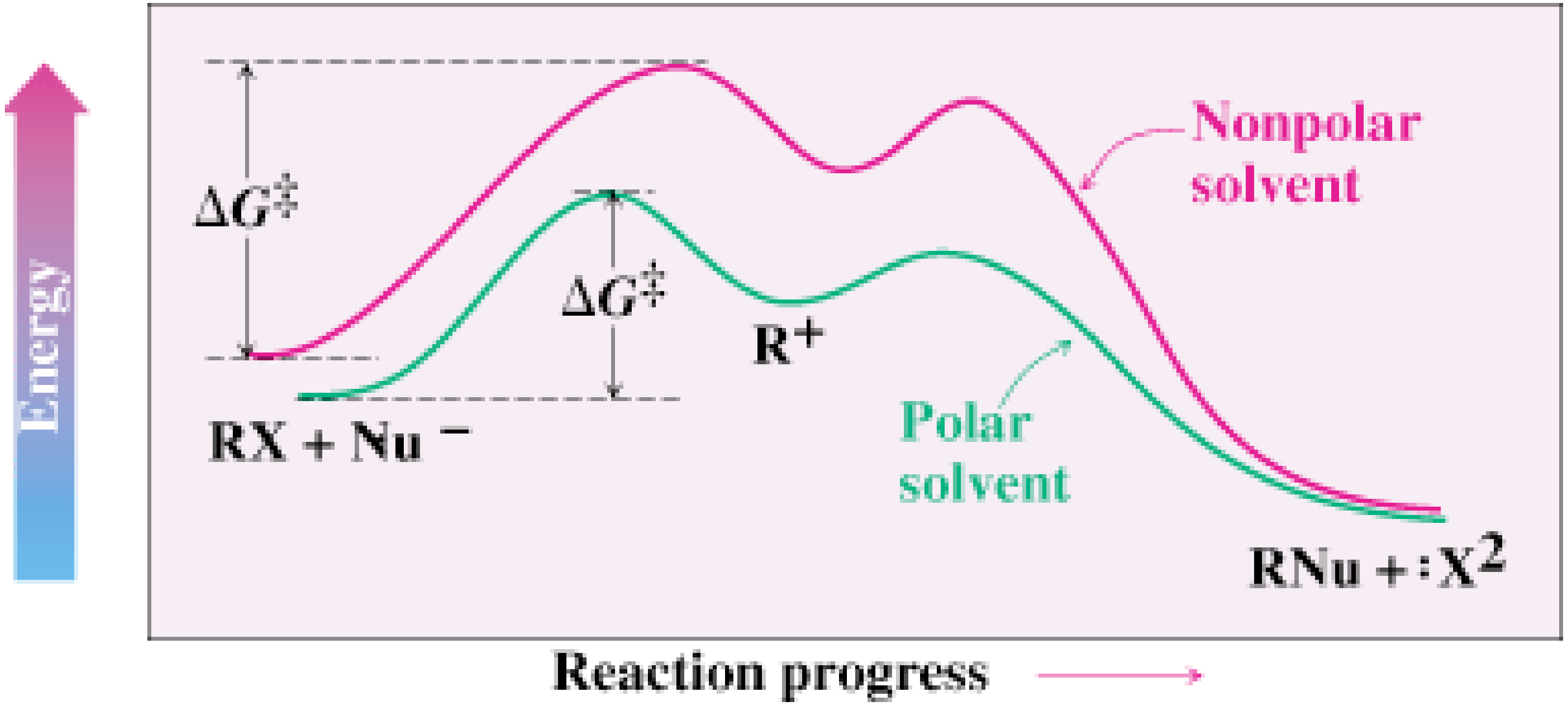
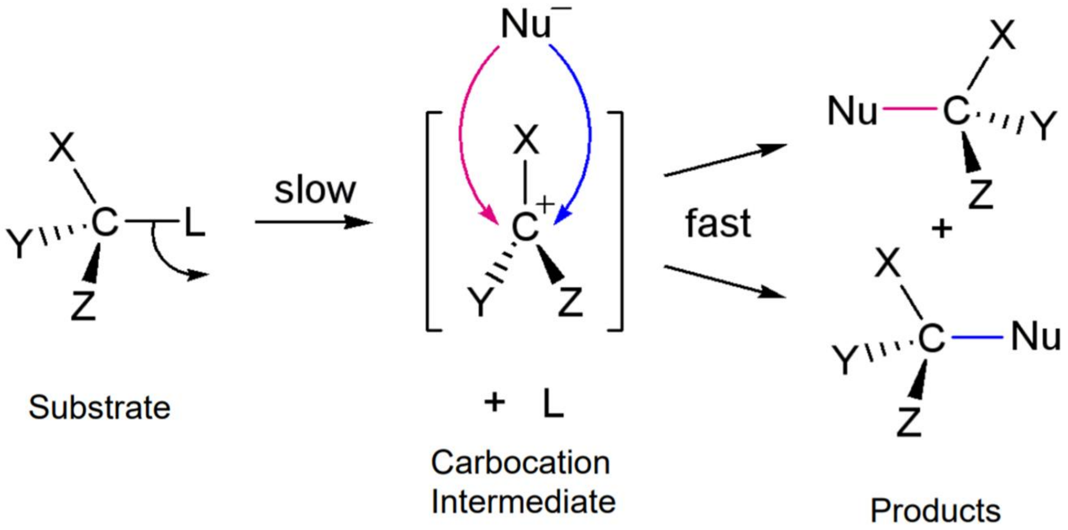
FACTORS AFFECTING THE S_N1 REACTION

- **The Solvent:**
  - Stabilization of the intermediate carbocation and the transition state by polar protic solvents in the S_N1 reaction

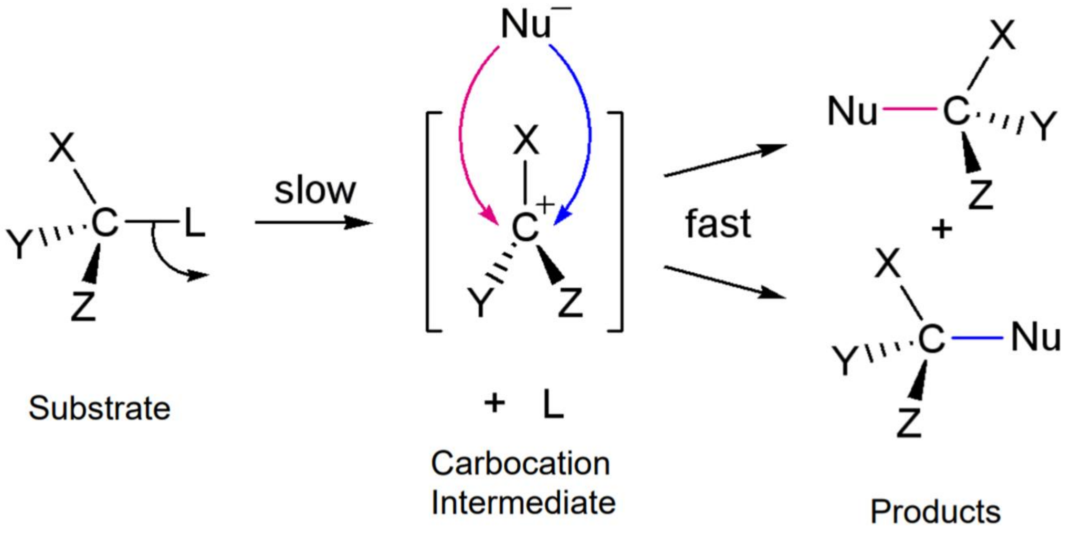


SUMMARY



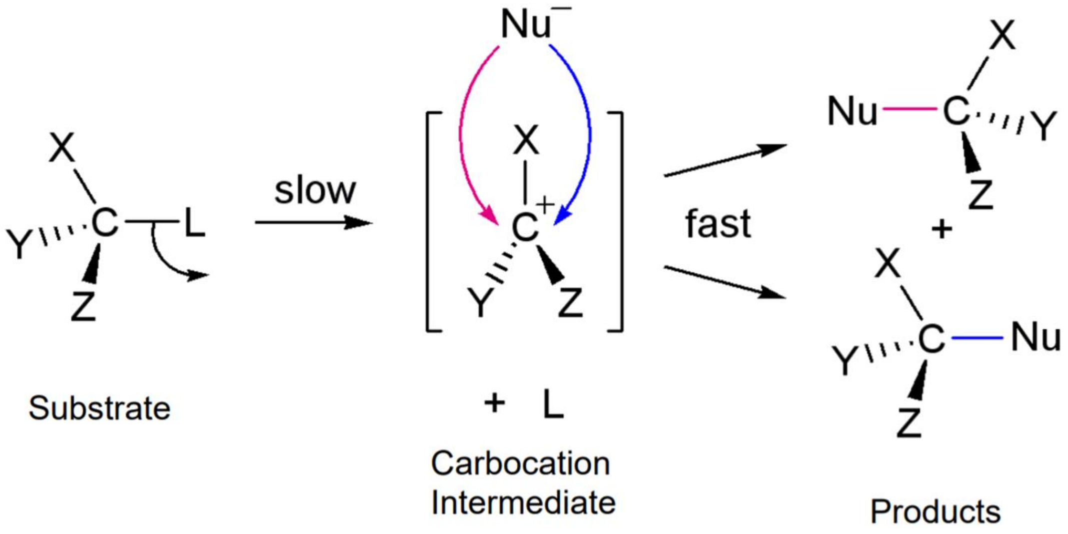
- **Reaction is:**
  - Non-stereospecific (*attack by nucleophile occurs from both sides*)
  - Non-concerted - *has carbocation intermediate*
  - Unimolecular - *rate depends on concentration of only the substrate*
- **Substrate:**
  - Best if *tertiary or conjugated* (benzylic or allylic) carbocation can be formed as
  - leaving group departs
  - *never primary*

SUMMARY



- **Nucleophile:** Best if more reactive (i.e. more anionic or more basic)
- **Leaving Group:** Best if more stable (i.e. can support negative charge well):
  - Same as S_N2
  - best if more stable (i.e. can support negative charge well)
  - Examples: TsO^- (very good) > I^- > Br^- > Cl^- > F^- (poor)
  - However, tertiary or allylic ROH or ROR' can be reactive under strongly acidic conditions to replace OH or OR

SUMMARY



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  - Protic solvents are favored over aprotic for the S_N1 reaction