

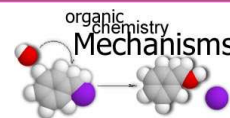
CHEM 344

ORGANIC REACTION MECHANISM

FOR CHEMISTRY' STUDENTS, COLLEGE OF SCIENCE

PRE-REQUISITES COURSE; CHEM 241

CREDIT HOURS; 2 (2+0+0)



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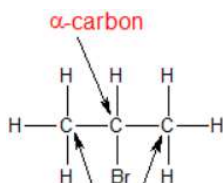
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Nucleophilic Substitution Reactions

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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.



β -carbons

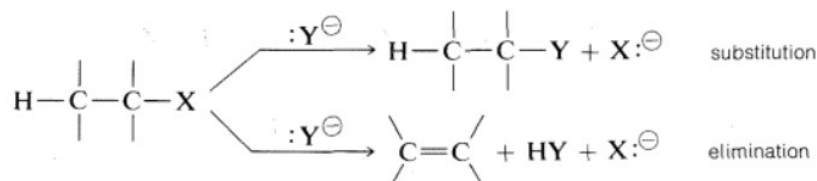
Note: The hydrogens bonded to the β -carbons are called β -hydrogens.

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

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ALKYL HALIDE STRUCTURE

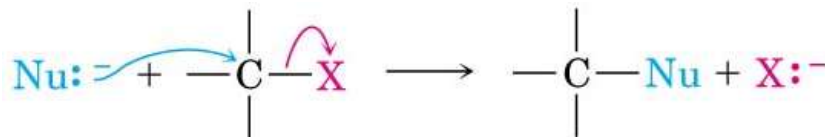
- **Alkyl halides** can undergo two major types of reactions:
 - *Substitution reactions and/or*
 - *Elimination reactions*



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

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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.

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SUBSTITUTION REACTIONS

TYPES OF NUCLEOPHILIC SUBSTITUTION MECHANISMS

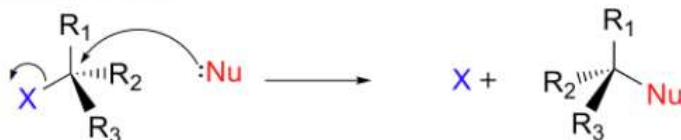
- S_N^1 (*Nucleophilic Substitution Reaction Unimolecular*).
 - Two steps with carbocation intermediate
 - Occurs in 3°, allyl, benzyl
- S_N^2 (*Nucleophilic Substitution Reaction Bimolecular*).
 - One step without intermediate
 - Occurs in 1°, 2°
- The mechanism of substitution reaction and the reactivity 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.

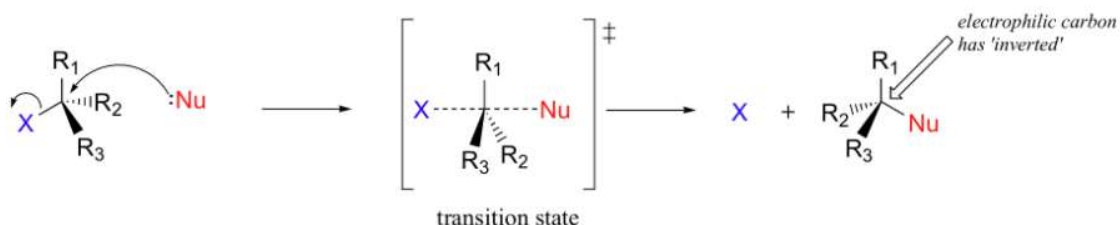
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S_N^2 REACTION

REACTION PROCESS



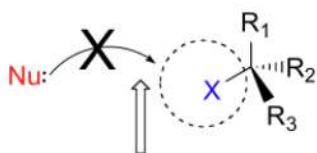
- The reaction takes place in a single step; *bond-forming and bond-breaking occur simultaneously*.
- The reaction involves a *transition state (TS)*.



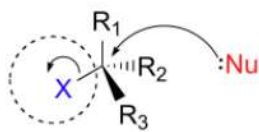
S_N^2 REACTION

REACTION PROCESS

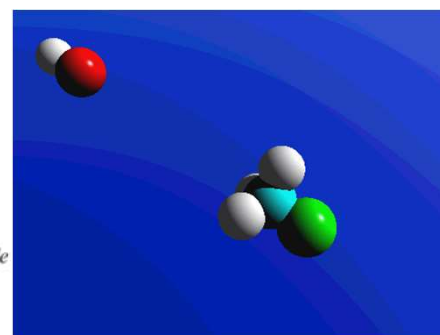
- The nucleophile, being an electron-rich species, *must attack the electrophilic carbon from the backside relative to the location of the leaving group*.
- Approach from the front side simply doesn't work: *the leaving group - which is also an electron-rich group - blocks the way*.



nucleophilic attack is blocked from the front side . . .



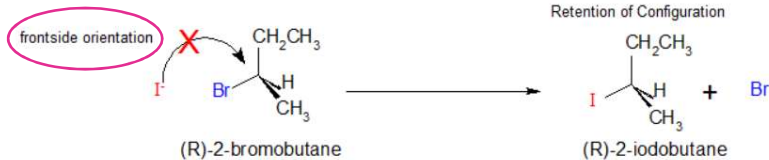
. . .so attack occurs from the back side



S_N² REACTIONSTEREOCHEMISTRY 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.

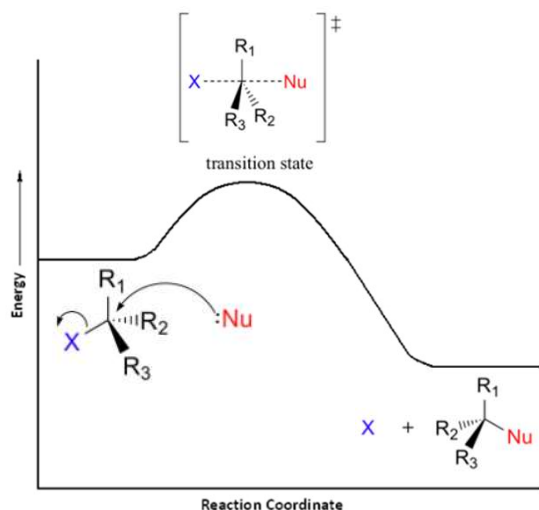


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S_N² REACTION

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.



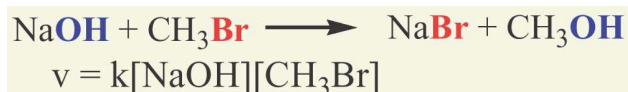
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S_N² REACTION

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

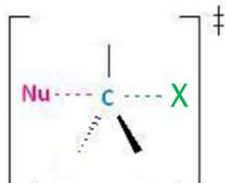


- Rates decrease as concentrations decrease but the rate constant does not
- **Rate units**: [concentration]/time such as L/(mol x s)
- The order of a reaction is sum of the exponents of the concentrations in the rate law – the example is second order
- *In the presence of large excess of nucleophile,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

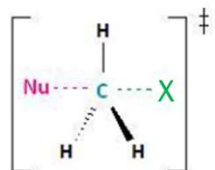
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S_N² REACTIONSTERIC HINDRANCE EFFECT ON THE S_N² REACTION RATE

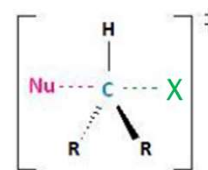
- **Transition state**; there are a total of five groups around the electrophilic center; *the nucleophile, the leaving group* and *three substituents*.



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



Least Steric Repulsion

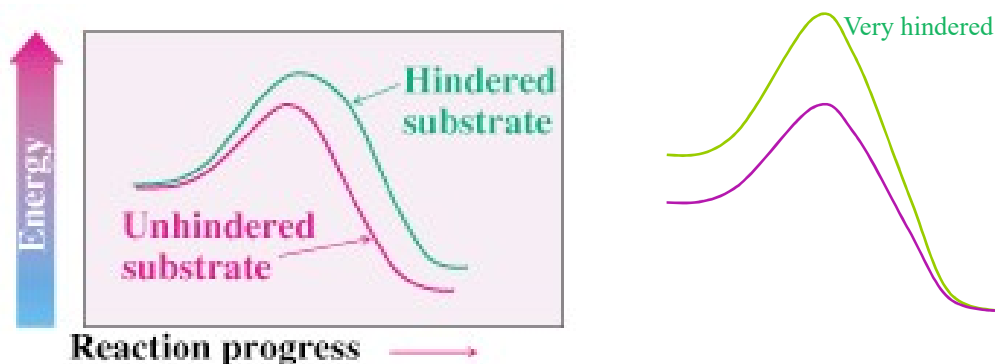


Greater Steric Repulsion

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S_N² REACTION**STERIC HINDRANCE EFFECT ON THE S_N² REACTION RATE**

- Steric Hindrance raises Transition State Energy



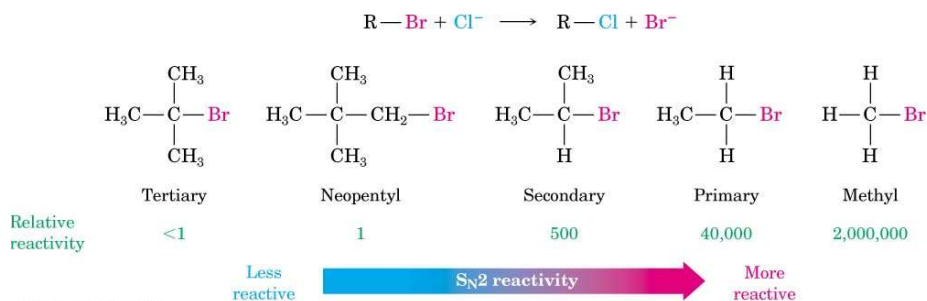
- Steric effects destabilize transition states
- Severe steric effects can also destabilize ground state

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S_N² REACTION**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:



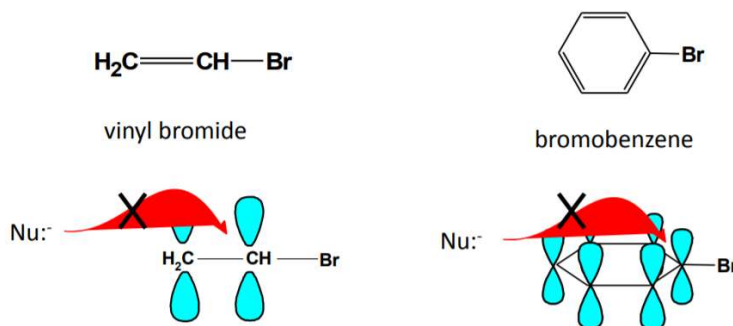
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S_N² REACTIONFACTORS AFFECTING THE S_N² REACTION

○ The Electrophile: Structure of the alkyl group

- The α-carbon in vinyl and aryl halides, as in 3° carbocation, is completely hindered and these alkyl halides do not undergo S_N² reactions.



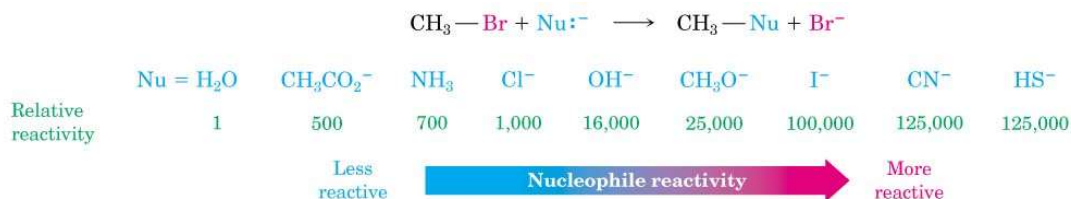
The overlapping p-orbitals that form the π-bonds in vinyl and aryl halides completely block the access of a nucleophile to the back side of the α-carbon

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S_N² REACTIONFACTORS 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.



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S_N² REACTIONFACTORS AFFECTING THE S_N² REACTION○ The Nucleophile: *Structure Function Correlation with Nucleophile*

(4) More free nucleophile, more nucleophilicity



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

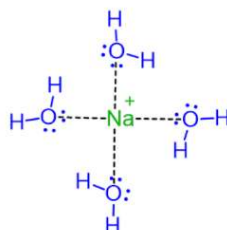
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S_N² REACTIONFACTORS AFFECTING THE S_N² REACTION○ The Solvent: *The Role of Solvent in S_N² Reactions*

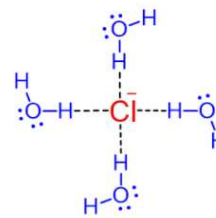
- There are two types of polar solvents; **polar protic** and **polar aprotic**.
 - **Polar protic solvents**; contain a hydrogen connected to an electronegative atom
 - They can make **intermolecular hydrogen bonding** and **dipole-dipole interactions**
 - Examples: **water and alcohols**.

Polar protic solvents solvate both cations and anions

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



Dipole interactions



Hydrogen bonding

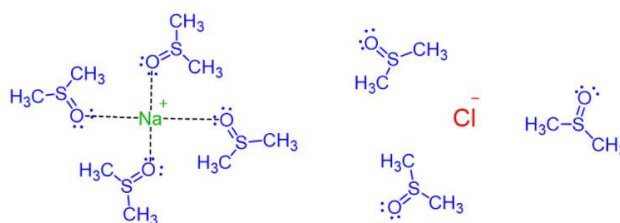
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S_N² REACTION**FACTORS AFFECTING THE S_N² REACTION**○ **The Solvent: The Role of Solvent in S_N² Reactions**

- 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 solvents solvate only cations leaving the anions naked

- **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 counterion does reduce its reactivity.



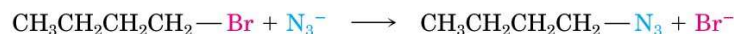
Dipole interactions

No hydrogen bonding, no interaction

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S_N² REACTION**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.



Solvent	CH ₃ OH	H ₂ O	DMSO	DMF	CH ₃ CN	HMPA
Relative reactivity	1	7	1,300	2,800	5,000	200,000

Less reactive

More reactive

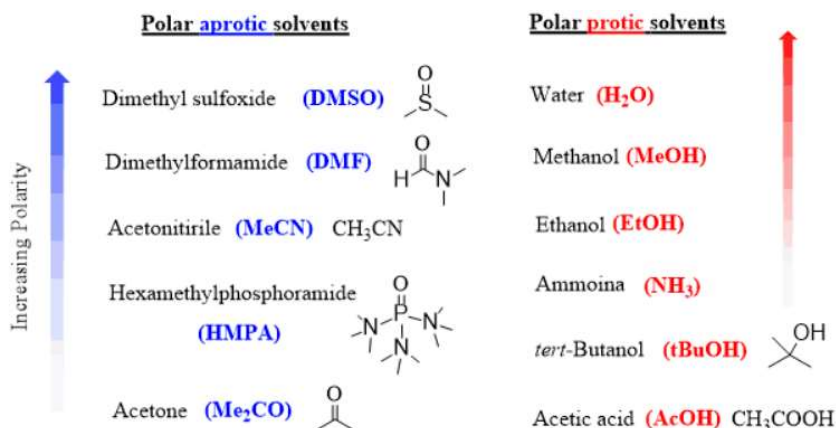
Solvent reactivity

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S_N² REACTIONFACTORS 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.



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S_N² REACTIONFACTORS AFFECTING THE S_N² REACTION○ The Leaving Group: *Structure function correlation with leaving group*

Weak bases make the best leaving groups.

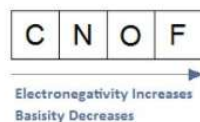
For a leaving group to leave, it must be able to accept electrons.

A strong base wants to donate electrons; therefore, the leaving group must be a weak base.

• As Electronegativity Increases

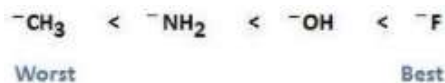
Basicity Decreases:

- 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.



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S_N² REACTION**FACTORS AFFECTING THE S_N² REACTION**

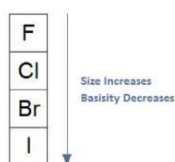
- **The Leaving Group:** Structure function correlation with leaving group

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.



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S_N² REACTION**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:

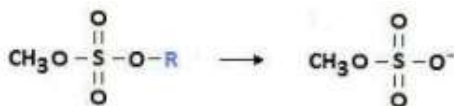
- Resonance stabilized structures are weak bases.
- Therefore, leaving groups that form resonance structures upon leaving are considered to be excellent leaving groups.

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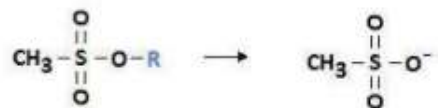
S_N² REACTIONFACTORS AFFECTING THE S_N² REACTION

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

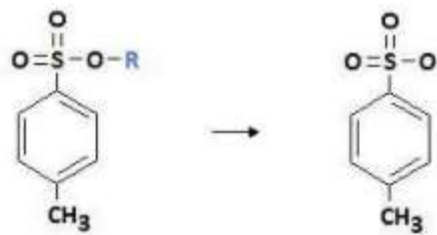
- Resonance Increases the Ability of the Leaving Group to Leave.



Methyl Sulfate Ion



Methanesulfonate Ion (Mesylate)



4-Methylbenzenesulfonate Ion (Tosylate)

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S_N² REACTIONFACTORS 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.

Relative reactivity	$\text{OH}^-, \text{NH}_2^-, \text{OR}^-$	F^-	Cl^-	Br^-	I^-	TosO^-
	<<1	1	200	10,000	30,000	60,000
	Less reactive	Leaving group reactivity				More reactive

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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.

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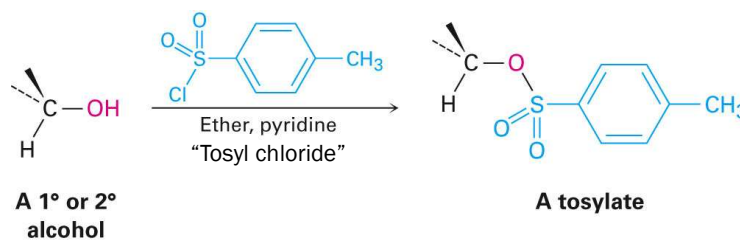
S_N² REACTIONFACTORS AFFECTING THE S_N² REACTION

○ 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.



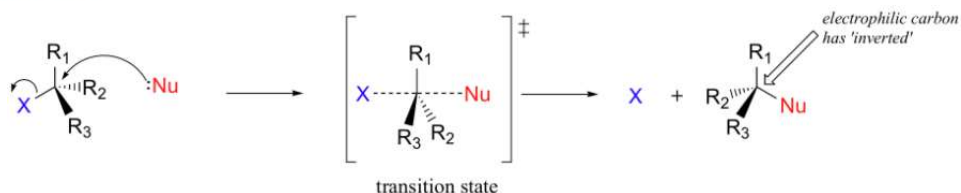
- **Poor Leaving groups** can be made into good leaving groups.



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S_N² REACTION

SUMMARY



○ Reaction is:

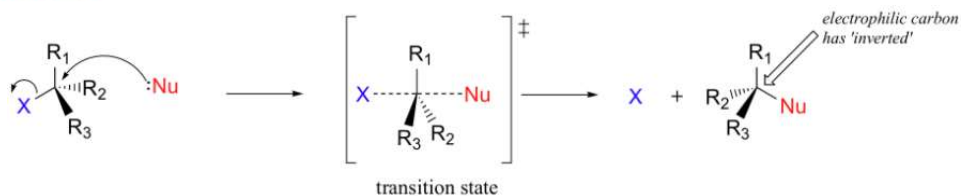
- Stereospecific (*Walden Inversion of configuration*)
- Concerted - *all bonds form and break at same time*
- Bimolecular - *rate depends on concentration of both nucleophile and substrate*

○ Substrate:

- Best if *primary* (one substituent on carbon bearing leaving group)
- *works if secondary, fails if tertiary*

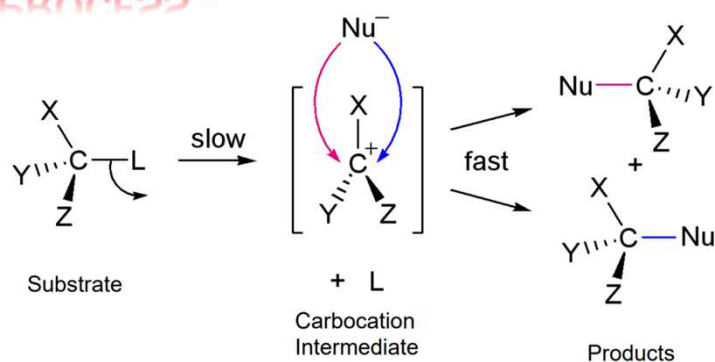
○ Nucleophile: Best if more reactive (*i.e. more anionic or more basic*)

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S_N² REACTION**SUMMARY**

- **Leaving Group:** Best if more stable (i.e. can support negative charge well):
 - TsO⁻ (very good) > I⁻ > Br⁻ > Cl⁻ > F⁻ (poor)
 - RF, ROH, ROR, RNH₂ 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. H₂O or ROH) deactivate nucleophile by hydrogen bonding but can be used in some case

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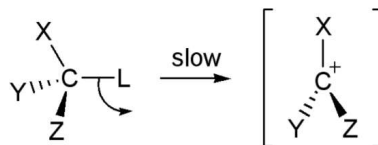
S_N¹ REACTION**REACTION PROCESS**

- **S_N¹ reactions:** involve replacing of a leaving group by a nucleophile
- **S_N¹ reactions** are unimolecular: the rate of this reaction depends only on the concentration of one reactant (substrate).
- **S_N¹ reactions** happen in two steps:

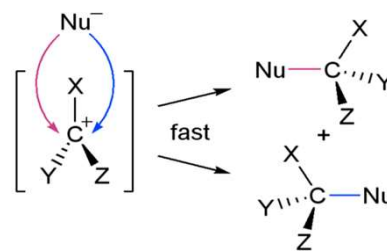
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S_N¹ REACTION**REACTION PROCESS****S_N¹ Reactions happen in Two Steps:****(1) The Slow Step:**

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

**(2) The Fast Step:**

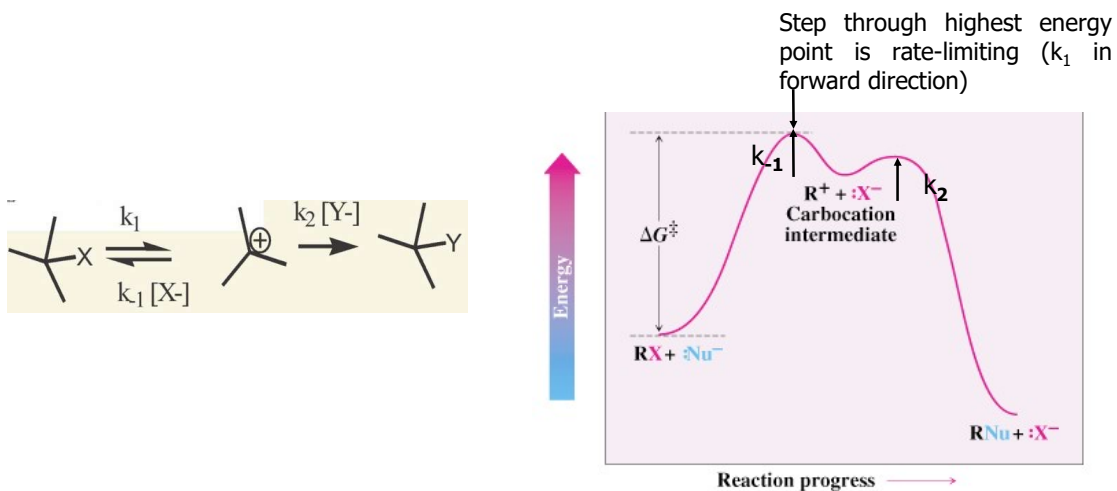
- The nucleophile attacks the carbocation, forming the product.
- The substrate loses any stereospecificity during the carbocation intermediate



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S_N¹ REACTION**ENERGY PROFILE DIAGRAM**

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



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S_N¹ REACTION

REACTION KINETICS

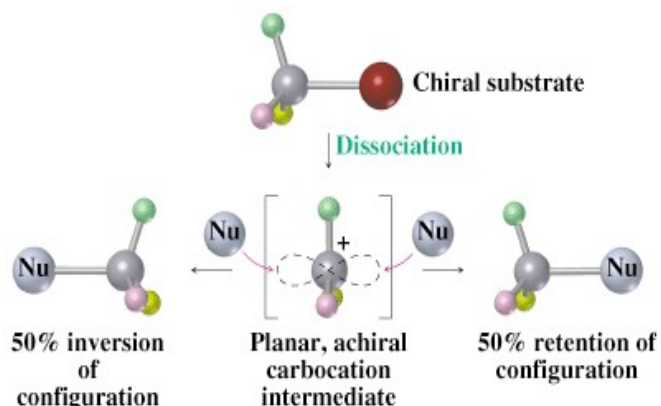
- **Unimolecular**; there are *one molecule* involved in the *rate-determining step*.
- The nucleophile does not appear in the rate expression changing the nucleophile concentration does not affect
- The *rate depends on the concentration of the haloalkane* and the rate constant of the step.
- Must be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

$$V = k[RX]$$

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S_N¹ REACTIONSTEREOCHEMISTRY OF S_N¹ REACTIONS

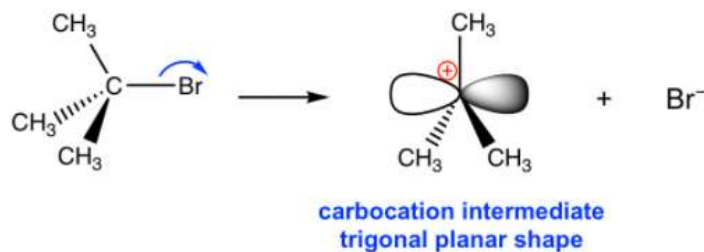
- The carbocation intermediate is in *trigonal planar shape*, with the empty 2p orbital particular to the plane.
- The central carbon is sp² hybridized and has the incomplete octet, *so carbocation is the highly reactive intermediate*.
- There is the same possibility for the nucleophile to attack from either side of the plane, (*racemic mixture*).



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S_N¹ REACTION**EXAMPLE: REACTION BETWEEN (CH₃)₃CBr AND H₂O****Reaction:****Mechanism:**

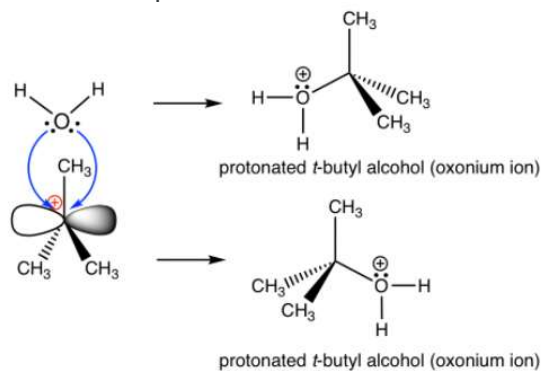
Step 1: Cleavage of C - Br bond **slowly** to form the carbocation intermediate. It is the **rate-determining step**.



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S_N¹ REACTION**EXAMPLE: REACTION BETWEEN (CH₃)₃CBr AND H₂O****Reaction:****Mechanism:**

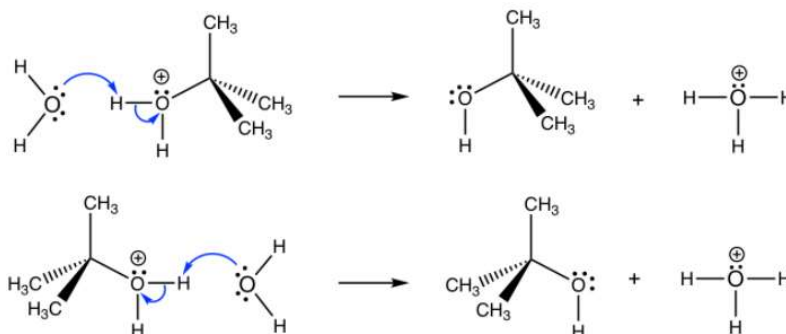
Step 2: Rapid reaction between carbocation intermediate and nucleophile H₂O; H₂O attacks from both sides of the planar carbocation.



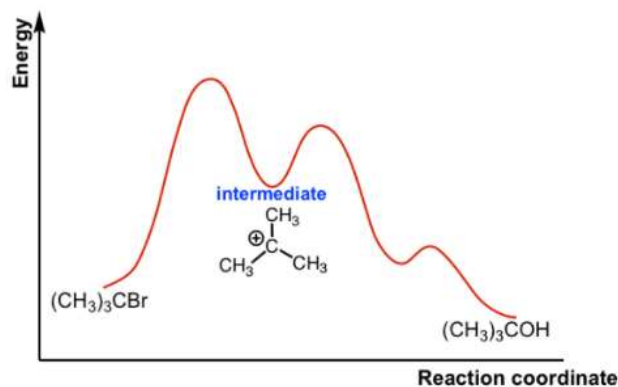
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S_N¹ REACTION**EXAMPLE: REACTION BETWEEN (CH₃)₃CBr AND H₂O****Reaction:****Mechanism:**

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).



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S_N¹ REACTION**EXAMPLE: REACTION BETWEEN (CH₃)₃CBr AND H₂O****Reaction:****Energy diagram of S_N¹ mechanism:**

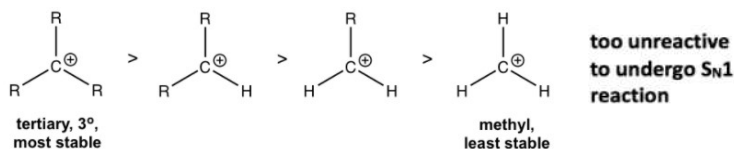
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S_N¹ REACTION

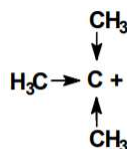
FACTORS AFFECTING THE S_N¹ REACTION

○ The Substrate: Stability of Carbocation

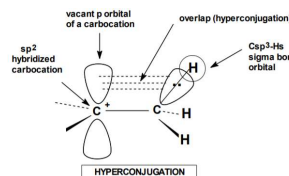
- Highly substituted alkyl halides (substrates) form a more stable carbocation.
- The more stable the carbocation intermediate is, the faster the rate of a reaction.



- 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).



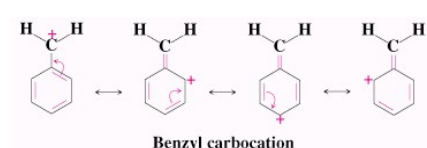
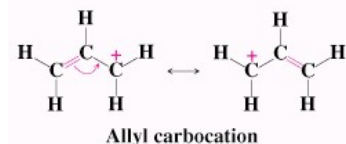
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S_N¹ REACTION

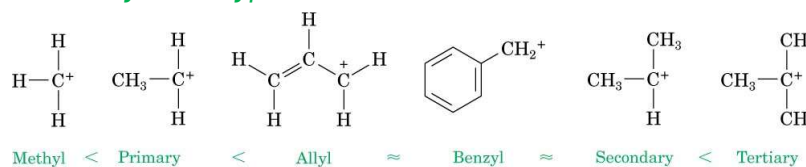
FACTORS AFFECTING THE S_N¹ REACTION

○ The Substrate: Delocalized Carbocation

- Allyl and benzyl halides; their carbocations stabilize due to their resonance forms which delocalize charge over an extended π-system



- Relative Stability of All Types of Carbocations



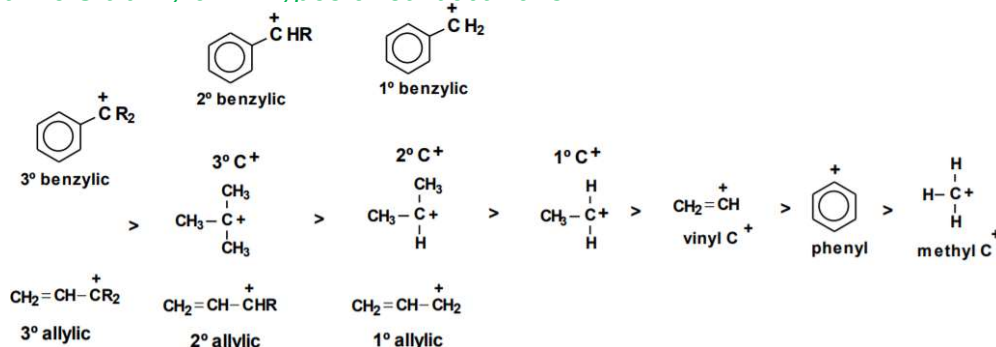
Less stable → Carbocation stability → More stable

© Thomson - Brooks Cole

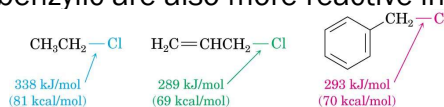
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S_N¹ REACTION**FACTORS AFFECTING THE S_N¹ REACTION**○ **The Substrate: Delocalized Carbocation**

- Relative Stability of All Types of Carbocations



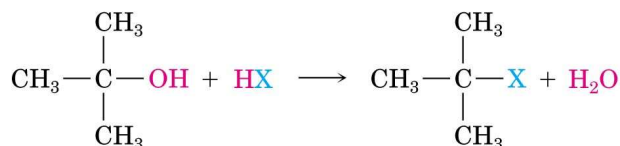
- Primary allylic and benzylic are also more reactive in the S_N² mechanism



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S_N¹ REACTION**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 H₂O, 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**.



2-Methyl-2-propanol

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

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S_N¹ REACTION**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.

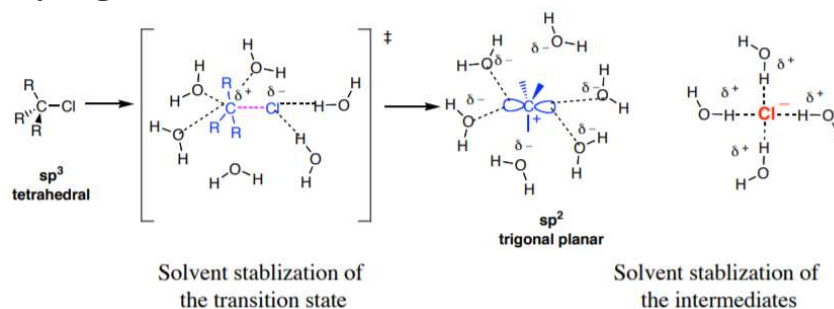
pK _b = 23	pK _b = 22	pK _b = 21	pK _b = 11	pK _b = -1.7	pK _b = -2	pK _b = -21
I ⁻	Br ⁻	Cl ⁻	F ⁻	HO ⁻	RO ⁻	H ₂ N ⁻
30,000	10,000	200	1	0	0	0

← Increasing leaving ability

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S_N¹ REACTION**FACTORS AFFECTING THE S_N¹ REACTION**○ **The Solvent:**

- **Polar protic solvents**, such as water and alcohols, organic acids and inorganic acids (H₂SO₄, H₃PO₄), 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.

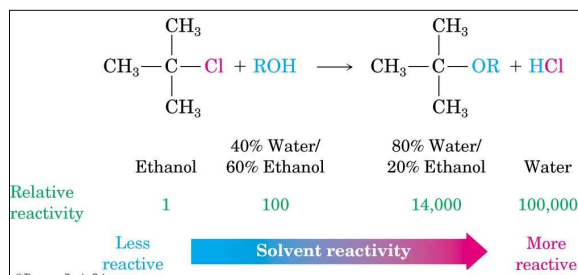


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S_N¹ REACTION**FACTORS AFFECTING THE S_N¹ REACTION**○ **The Solvent:**

- 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)

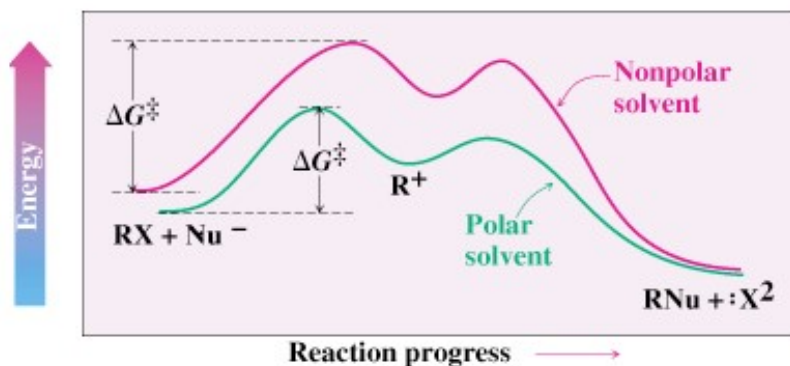
Hexane	ε = 1.9	} nonpolar	} aprotic	
(CH ₃ CH ₂) ₂ O	4.3			
HMPA	30	} polar		} protic
DMF	38			
DMSO	48			
CH ₃ CH ₂ OH	24			
CH ₃ OH	34			
H ₂ O	80			



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S_N¹ REACTION**FACTORS AFFECTING THE S_N¹ REACTION**○ **The Solvent:**

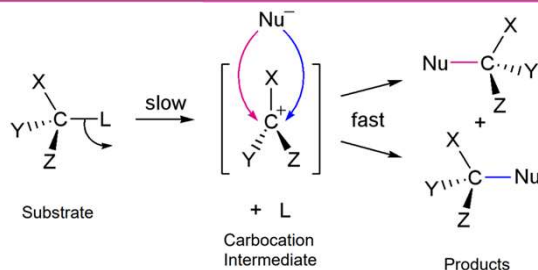
- Stabilization of the intermediate carbocation and the transition state by polar protic solvents in the S_N¹ reaction



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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*

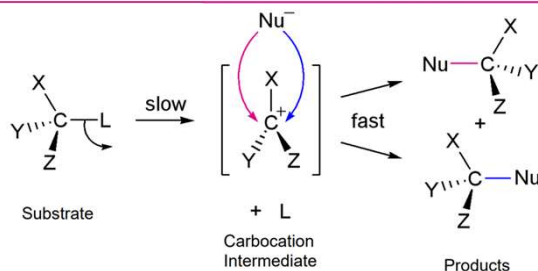
○ Substrate:

- Best if *tertiary or conjugated* (benzylic or allylic) carbocation can be formed as leaving group departs
- *never primary*

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S_N¹ REACTION

SUMMARY

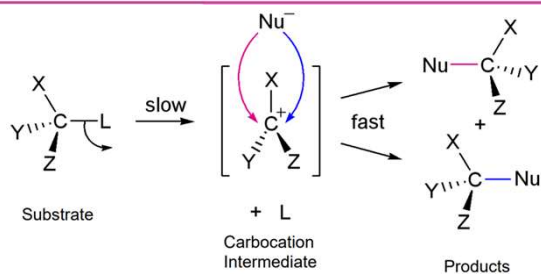


○ Nucleophile: Best if more reactive (i.e. more anionic or more basic)

○ 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

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S_N¹ REACTION**SUMMARY**○ **Solvent:**

- Polar protic solvents, such as water and alcohols, organic acids and inorganic acids (H₂SO₄, H₃PO₄), stabilize the transition state.
- Polar solvents are favored over non-polar for the S_N¹ reaction.
- Protic solvents are favored over aprotic for the S_N¹ reaction