

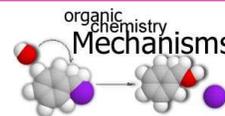
**CHEM 344**

**ORGANIC REACTION MECHANISM**

FOR CHEMISTRY' STUDENTS, COLLEGE OF SCIENCE

PRE-REQUISITES COURSE; CHEM 241

CREDIT HOURS; 2 (2+0+0)



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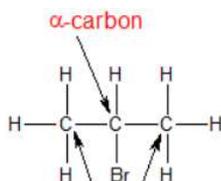
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**Nucleophilic Substitution Reactions**

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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.



$\beta$ -carbons

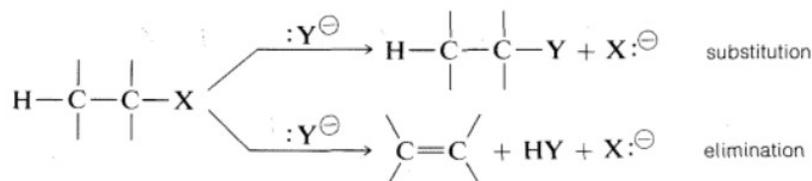
Note: The hydrogens bonded to the  $\beta$ -carbons are called  $\beta$ -hydrogens.

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

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## ALKYL HALIDE STRUCTURE

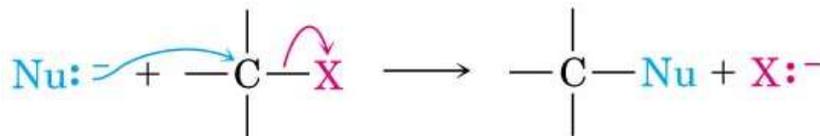
- **Alkyl halides** can undergo two major types of reactions:
  - *Substitution reactions and/or*
  - *Elimination reactions*



- *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

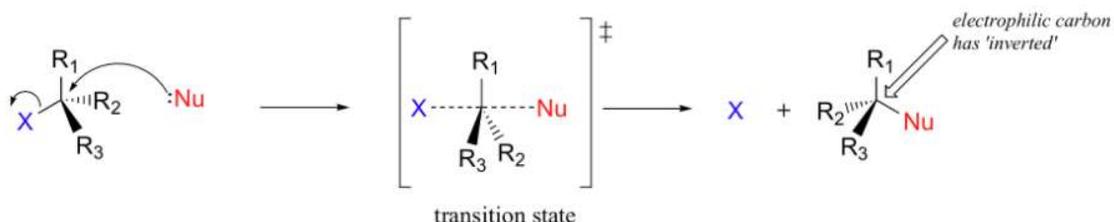
- $S_N^1$  (*Nucleophilic Substitution Reaction Unimolecular*).
  - Two steps with carbocation intermediate
  - Occurs in 3°, allyl, benzyl
- $S_N^2$  (*Nucleophilic Substitution Reaction Bimolecular*).
  - One step without intermediate
  - Occurs in 1°, 2°
- The mechanism of substitution reaction and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

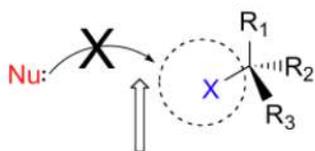
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**S<sub>N</sub><sup>2</sup> REACTION****REACTION PROCESS**

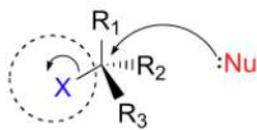
- The reaction takes place in a single step; *bond-forming and bond-breaking occur simultaneously*.
- The reaction involves a *transition state (TS)*.

**S<sub>N</sub><sup>2</sup> REACTION****REACTION PROCESS**

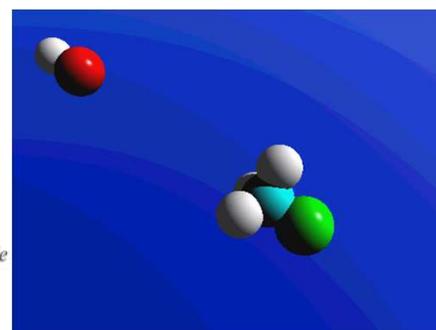
- The nucleophile, being an electron-rich species, *must attack the electrophilic carbon from the backside relative to the location of the leaving group*.
- Approach from the front side simply doesn't work: *the leaving group - which is also an electron-rich group - blocks the way*.



*nucleophilic attack is blocked from the front side . . .*

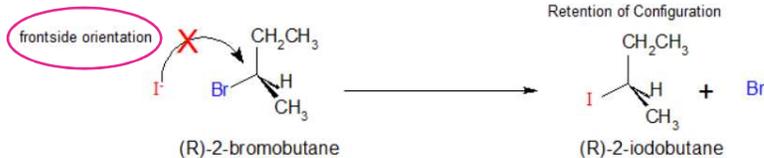


*. . .so attack occurs from the back side*

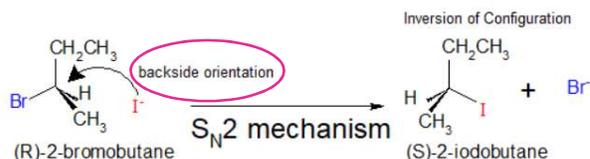


**S<sub>N</sub><sup>2</sup> REACTION****STEREOCHEMISTRY OF S<sub>N</sub><sup>2</sup> REACTIONS****Frontside Orientation:**

- 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**

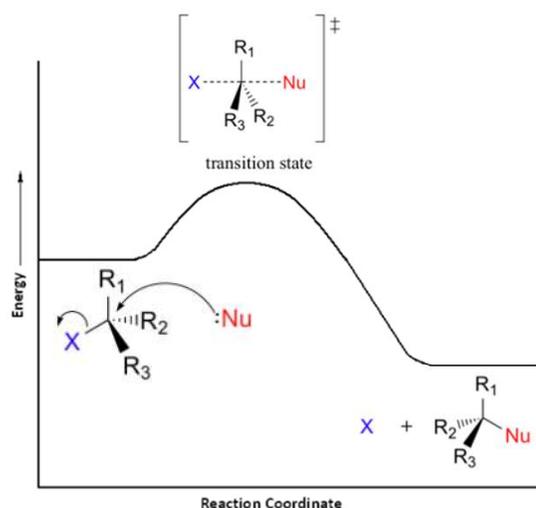
- The nucleophile approaches the electrophilic center on the opposite side to the leaving group.
- The stereochemistry of the product remains the same; **inversion of configuration**.



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**S<sub>N</sub><sup>2</sup> 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<sub>N</sub><sup>2</sup> 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*.

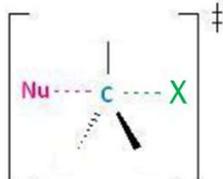


- Rates decrease as concentrations decrease but the rate constant does not
- **Rate units**: [concentration]/time such as L/(mol x s)
- The order of a reaction is sum of the exponents of the concentrations in the rate law – the example is second order
- *In the presence of large excess of nucleophile,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

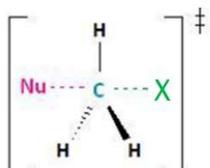
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S<sub>N</sub><sup>2</sup> REACTIONSTERIC HINDRANCE EFFECT ON THE S<sub>N</sub><sup>2</sup> REACTION RATE

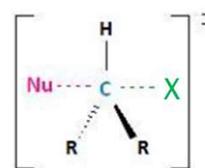
- **Transition state**; there are a total of five groups around the electrophilic center; *the nucleophile, the leaving group* and *three substituents*.



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



Least Steric Repulsion



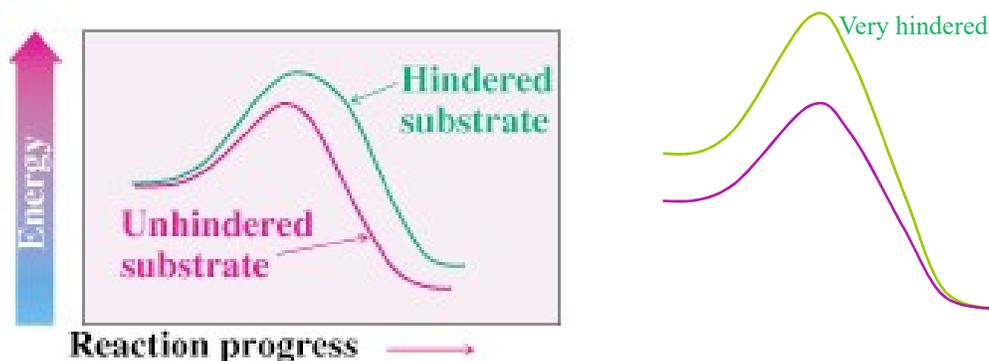
Greater Steric Repulsion

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## S<sub>N</sub><sup>2</sup> REACTION

# STERIC HINDRANCE EFFECT ON THE S<sub>N</sub><sup>2</sup> REACTION RATE

- Steric Hindrance raises Transition State Energy



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

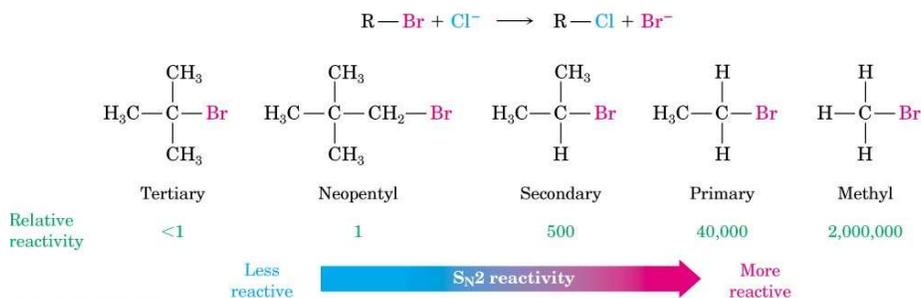
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## S<sub>N</sub><sup>2</sup> REACTION

# FACTORS AFFECTING THE S<sub>N</sub><sup>2</sup> 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<sub>N</sub><sup>2</sup> reactions is:

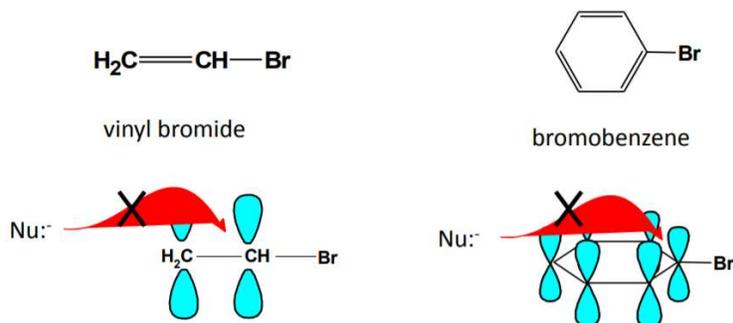


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**S<sub>N</sub><sup>2</sup> REACTION****FACTORS AFFECTING THE S<sub>N</sub><sup>2</sup> REACTION**○ **The Electrophile: Structure of the alkyl group**

- The α-carbon in vinyl and aryl halides, as in 3° carbocation, is completely hindered and these alkyl halides do not undergo S<sub>N</sub><sup>2</sup> reactions.

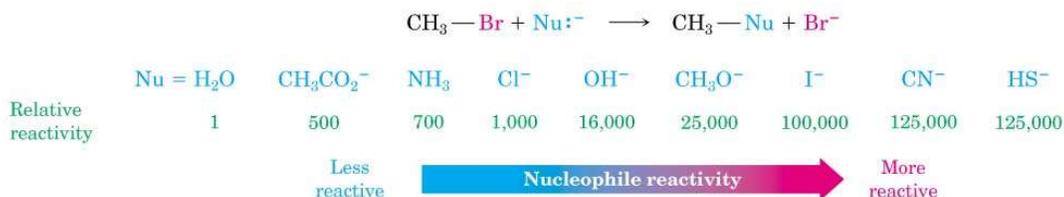


The overlapping p-orbitals that form the π-bonds in vinyl and aryl halides completely block the access of a nucleophile to the back side of the α-carbon

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**S<sub>N</sub><sup>2</sup> REACTION****FACTORS AFFECTING THE S<sub>N</sub><sup>2</sup> REACTION**○ **The Nucleophile: Structure Function Correlation with Nucleophile**

- In S<sub>N</sub><sup>2</sup> 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<sub>N</sub><sup>2</sup> REACTIONFACTORS AFFECTING THE S<sub>N</sub><sup>2</sup> REACTION○ The Nucleophile: *Structure Function Correlation with Nucleophile*

(4) More free nucleophile, more nucleophilicity



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

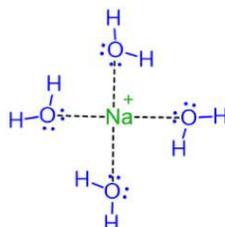
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S<sub>N</sub><sup>2</sup> REACTIONFACTORS AFFECTING THE S<sub>N</sub><sup>2</sup> REACTION○ The Solvent: *The Role of Solvent in S<sub>N</sub><sup>2</sup> Reactions*

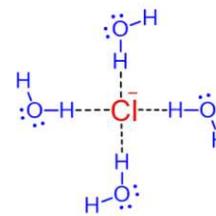
- There are two types of polar solvents; **polar protic** and **polar aprotic**.
  - **Polar protic solvents**; contain a hydrogen connected to an electronegative atom
    - They can make **intermolecular hydrogen bonding** and **dipole-dipole interactions**
    - Examples: **water and alcohols**.

Polar protic solvents solvate both cations and anions

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



Dipole interactions



Hydrogen bonding

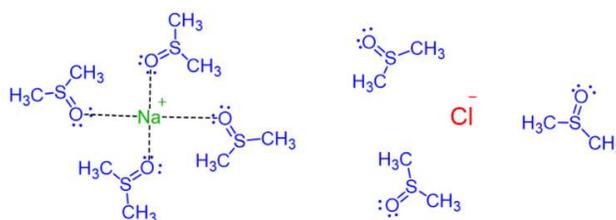
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S<sub>N</sub><sup>2</sup> REACTIONFACTORS AFFECTING THE S<sub>N</sub><sup>2</sup> REACTION○ The Solvent: The Role of Solvent in S<sub>N</sub><sup>2</sup> Reactions

- 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<sub>N</sub><sup>2</sup> REACTIONFACTORS AFFECTING THE S<sub>N</sub><sup>2</sup> REACTION○ The Solvent: The Role of Solvent in S<sub>N</sub><sup>2</sup> Reactions

- **Polar protic solvents** that can donate hydrogen bonds (-OH or -NH) *slow S<sub>N</sub><sup>2</sup> 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 <sub>3</sub> OH	H <sub>2</sub> O	DMSO	DMF	CH <sub>3</sub> 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<sub>N</sub><sup>2</sup> REACTION****FACTORS AFFECTING THE S<sub>N</sub><sup>2</sup> REACTION**

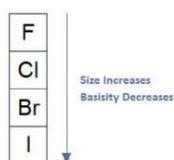
- **The Leaving Group:** Structure function correlation with leaving group

*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<sub>N</sub><sup>2</sup> REACTION****FACTORS AFFECTING THE S<sub>N</sub><sup>2</sup> 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:**

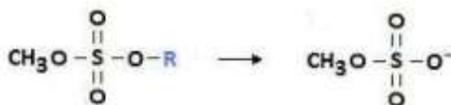
- Resonance stabilized structures are weak bases.
- Therefore, leaving groups that form resonance structures upon leaving are considered to be excellent leaving groups.

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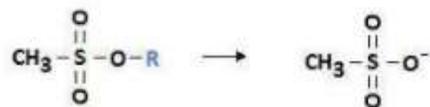
S<sub>N</sub><sup>2</sup> REACTIONFACTORS AFFECTING THE S<sub>N</sub><sup>2</sup> REACTION

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

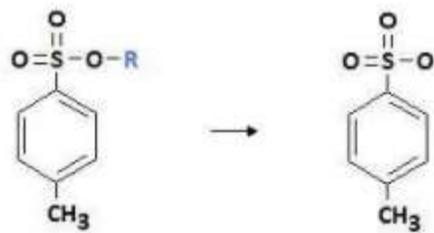
- Resonance Increases the Ability of the Leaving Group to Leave.



Methyl Sulfate Ion



Methanesulfonate Ion (Mesylate)



4-Methylbenzenesulfonate Ion (Tosylate)

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S<sub>N</sub><sup>2</sup> REACTIONFACTORS AFFECTING THE S<sub>N</sub><sup>2</sup> 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	$\text{OH}^-, \text{NH}_2^-, \text{OR}^-$	$\text{F}^-$	$\text{Cl}^-$	$\text{Br}^-$	$\text{I}^-$	$\text{TosO}^-$
	<<1	1	200	10,000	30,000	60,000
	Less reactive	Leaving group reactivity				More reactive

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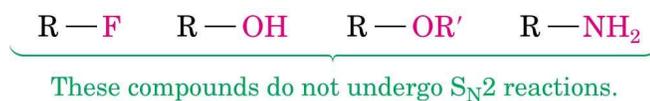
The iodide ion (I<sup>-</sup>) is larger in size, thus has high polarizability, and is better solvated by the solvent, therefore, it is better leaving group than fluoride ion.

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S<sub>N</sub><sup>2</sup> REACTIONFACTORS AFFECTING THE S<sub>N</sub><sup>2</sup> REACTION

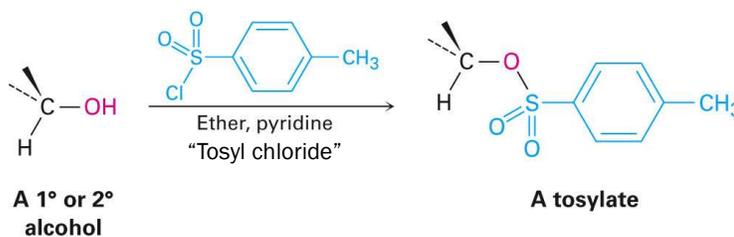
## ○ The Leaving Group: Structure function correlation with leaving group

- **Poor Leaving Groups;** Alkyl fluorides, alcohols, ethers, and amines do not typically undergo S<sub>N</sub><sup>2</sup> reactions.



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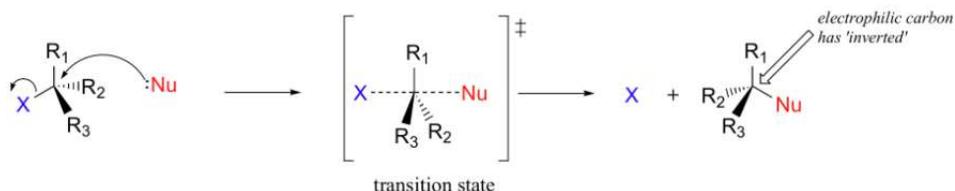
- **Poor Leaving groups** can be made into good leaving groups.



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S<sub>N</sub><sup>2</sup> REACTION

## SUMMARY



## ○ Reaction is:

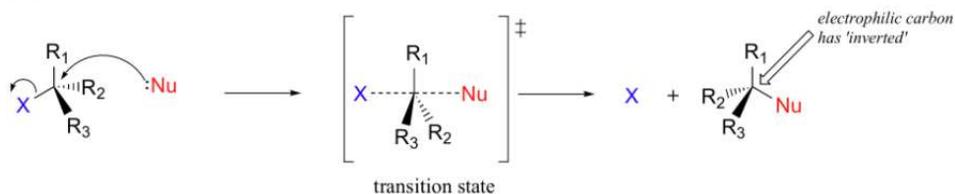
- Stereospecific (*Walden Inversion of configuration*)
- Concerted - *all bonds form and break at same time*
- Bimolecular - *rate depends on concentration of both nucleophile and substrate*

## ○ Substrate:

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

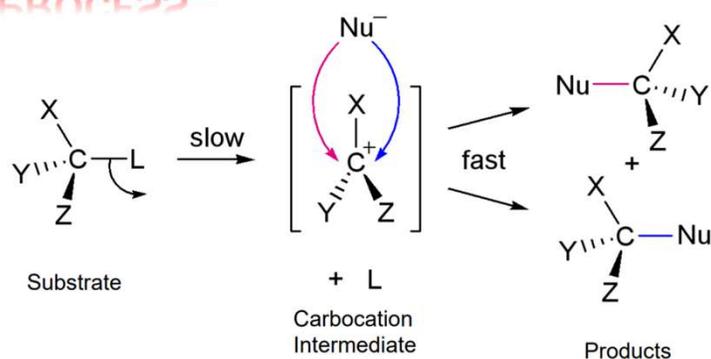
○ Nucleophile: Best if more reactive (*i.e. more anionic or more basic*)

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**S<sub>N</sub><sup>2</sup> REACTION****SUMMARY**

- **Leaving Group:** Best if more stable (i.e. can support negative charge well):
  - TsO<sup>-</sup> (very good) > I<sup>-</sup> > Br<sup>-</sup> > Cl<sup>-</sup> > F<sup>-</sup> (poor)
  - RF, ROH, ROR, RNH<sub>2</sub> are NEVER Substrates for S<sub>N</sub><sup>2</sup> reactions
  - Leaving Groups on double-bonded carbons are never replaced by S<sub>N</sub><sup>2</sup> reactions
- **Solvent:**
  - **Polar Aprotic** (i.e. no OH) is best
  - **Protic solvents** (e.g. H<sub>2</sub>O or ROH) deactivate nucleophile by hydrogen bonding but can be used in some case

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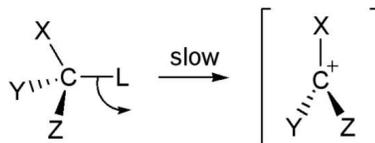
**S<sub>N</sub><sup>1</sup> REACTION****REACTION PROCESS**

- **S<sub>N</sub><sup>1</sup> reactions:** involve replacing of a leaving group by a nucleophile
- **S<sub>N</sub><sup>1</sup> reactions** are unimolecular: the rate of this reaction depends only on the concentration of one reactant (substrate).
- **S<sub>N</sub><sup>1</sup> reactions** happen in two steps:

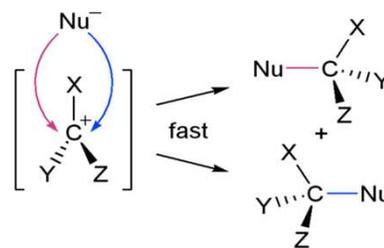
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**S<sub>N</sub><sup>1</sup> REACTION****REACTION PROCESS****S<sub>N</sub><sup>1</sup> Reactions happen in Two Steps:****(1) The Slow Step:**

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

**(2) The Fast Step:**

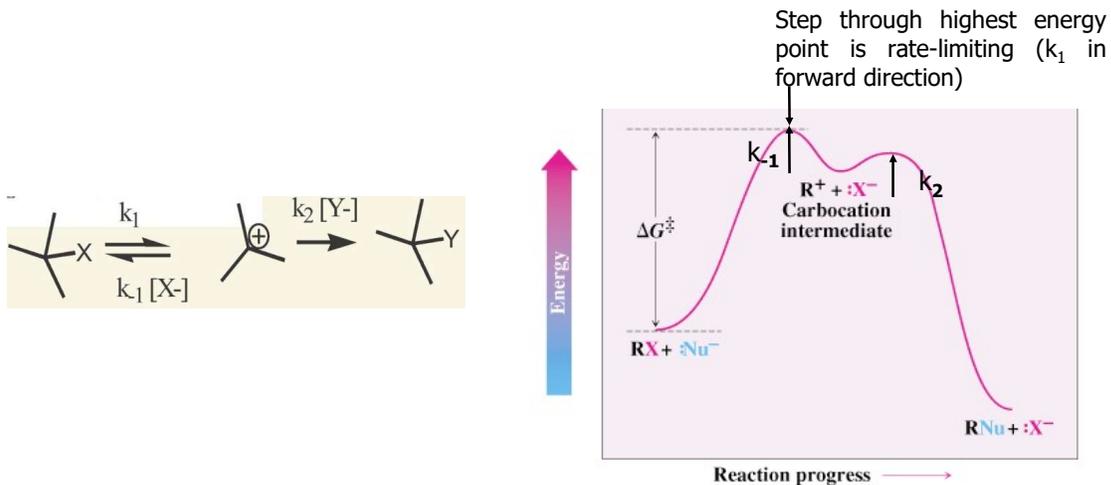
- The nucleophile attacks the carbocation, forming the product.
- The substrate loses any stereospecificity during the carbocation intermediate



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**S<sub>N</sub><sup>1</sup> REACTION****ENERGY PROFILE DIAGRAM**

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



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S<sub>N</sub><sup>1</sup> 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<sub>N</sub><sup>1</sup> REACTIONSTEREOCHEMISTRY OF S<sub>N</sub><sup>1</sup> REACTIONS

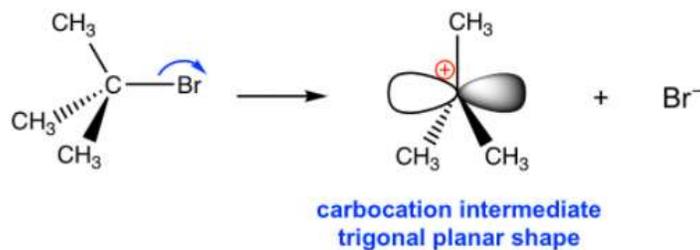
- The carbocation intermediate is in *trigonal planar shape*, with the empty 2p orbital particular to the plane.
- The central carbon is sp<sup>2</sup> hybridized and has the incomplete octet, *so carbocation is the highly reactive intermediate*.
- There is the same possibility for the nucleophile to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



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**S<sub>N</sub><sup>1</sup> REACTION****EXAMPLE: REACTION BETWEEN (CH<sub>3</sub>)<sub>3</sub>CBr AND H<sub>2</sub>O****Reaction:****Mechanism:**

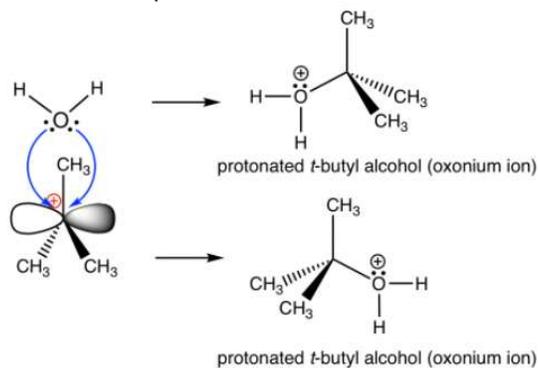
**Step 1:** Cleavage of C - Br bond **slowly** to form the carbocation intermediate. It is the **rate-determining step**.



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**S<sub>N</sub><sup>1</sup> REACTION****EXAMPLE: REACTION BETWEEN (CH<sub>3</sub>)<sub>3</sub>CBr AND H<sub>2</sub>O****Reaction:****Mechanism:**

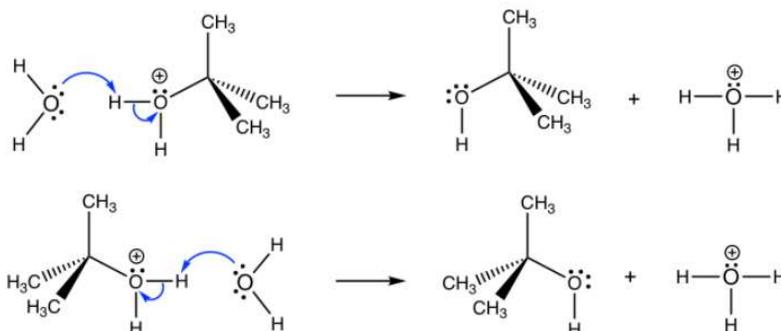
**Step 2:** Rapid reaction between carbocation intermediate and nucleophile H<sub>2</sub>O; H<sub>2</sub>O attacks from both sides of the planar carbocation.



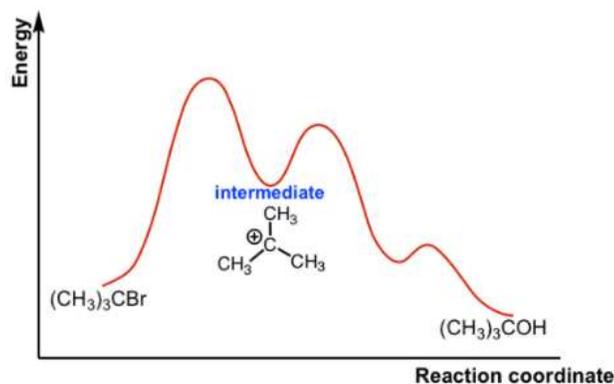
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**S<sub>N</sub><sup>1</sup> REACTION****EXAMPLE: REACTION BETWEEN (CH<sub>3</sub>)<sub>3</sub>CBr AND H<sub>2</sub>O****Reaction:****Mechanism:**

**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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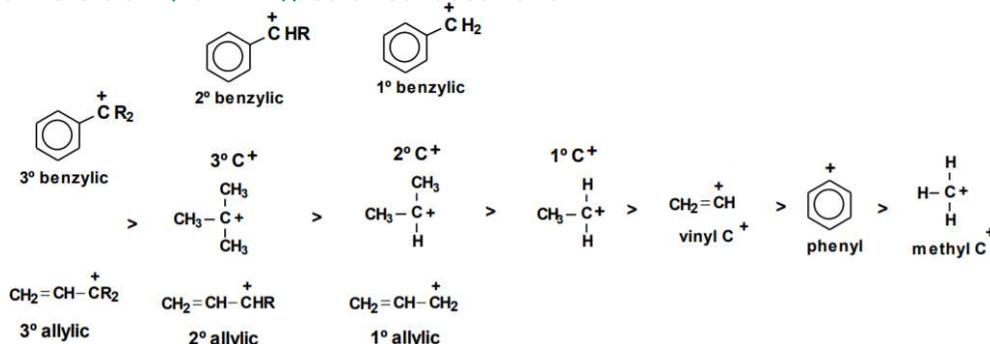
**S<sub>N</sub><sup>1</sup> REACTION****EXAMPLE: REACTION BETWEEN (CH<sub>3</sub>)<sub>3</sub>CBr AND H<sub>2</sub>O****Reaction:****Energy diagram of S<sub>N</sub><sup>1</sup> mechanism:**

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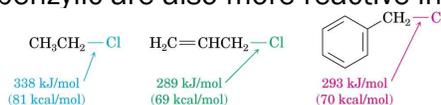


**S<sub>N</sub><sup>1</sup> REACTION****FACTORS AFFECTING THE S<sub>N</sub><sup>1</sup> REACTION**○ **The Substrate: Delocalized Carbocation**

- Relative Stability of All Types of Carbocations



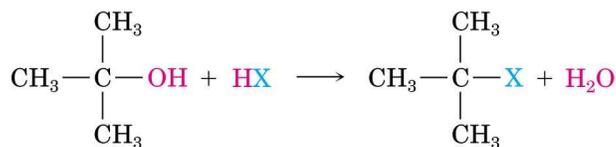
- Primary allylic and benzylic are also more reactive in the S<sub>N</sub><sup>2</sup> mechanism



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**S<sub>N</sub><sup>1</sup> REACTION****FACTORS AFFECTING THE S<sub>N</sub><sup>1</sup> REACTION**○ **The Nucleophile:**

- The rate-determining step of S<sub>N</sub><sup>1</sup> reaction does not include nucleophile, *so theoretically the strength of nucleophile has no effect on S<sub>N</sub><sup>1</sup> reaction.*
- A strong nucleophile has high tendency to go with S<sub>N</sub><sup>2</sup> reaction instead of S<sub>N</sub><sup>1</sup>, *A weaker nucleophile is a better choice for S<sub>N</sub><sup>1</sup>.*
- In practice, neutral substances such as H<sub>2</sub>O, ROH, RCOOH are usually used as nucleophiles in S<sub>N</sub><sup>1</sup> reaction and they also serve as solvents.
- So, when substances are used as *both* nucleophiles and solvents for S<sub>N</sub><sup>1</sup> 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<sub>N</sub><sup>1</sup> REACTION****FACTORS AFFECTING THE S<sub>N</sub><sup>1</sup> REACTION**○ **The Leaving Group:**

- The nature of the leaving group has the same effect on both S<sub>N</sub><sup>1</sup> and S<sub>N</sub><sup>2</sup> 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><sup>1</sup> 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.
  - 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.

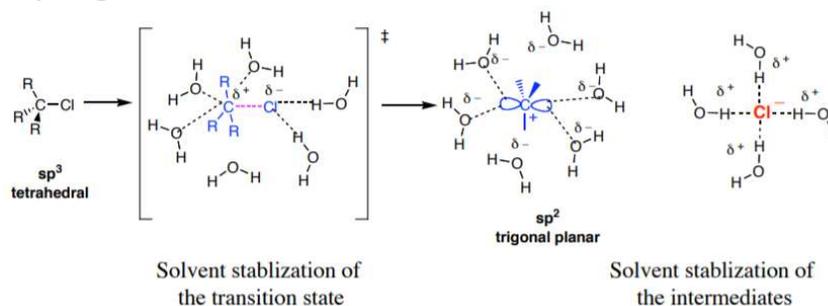
pK <sub>b</sub> = 23	pK <sub>b</sub> = 22	pK <sub>b</sub> = 21	pK <sub>b</sub> = 11	pK <sub>b</sub> = -1.7	pK <sub>b</sub> = -2	pK <sub>b</sub> = -21
I <sup>-</sup>	Br <sup>-</sup>	Cl <sup>-</sup>	F <sup>-</sup>	HO <sup>-</sup>	RO <sup>-</sup>	H <sub>2</sub> N <sup>-</sup>
30,000	10,000	200	1	0	0	0

← Increasing leaving ability

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**S<sub>N</sub><sup>1</sup> REACTION****FACTORS AFFECTING THE S<sub>N</sub><sup>1</sup> REACTION**○ **The Solvent:**

- **Polar protic solvents**, such as water and alcohols, organic acids and inorganic acids (H<sub>2</sub>SO<sub>4</sub>, H<sub>3</sub>PO<sub>4</sub>), 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.

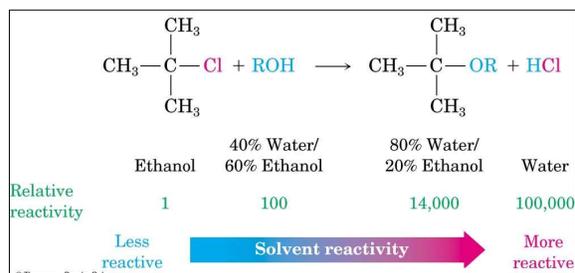


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**S<sub>N</sub><sup>1</sup> REACTION****FACTORS AFFECTING THE S<sub>N</sub><sup>1</sup> REACTION**○ **The Solvent:**

- Polar solvents are favored over non-polar for the S<sub>N</sub><sup>1</sup> reaction
- Protic solvents are favored over aprotic for the S<sub>N</sub><sup>1</sup> reaction
- Solvent polarity is measured by dielectric constant (ε)

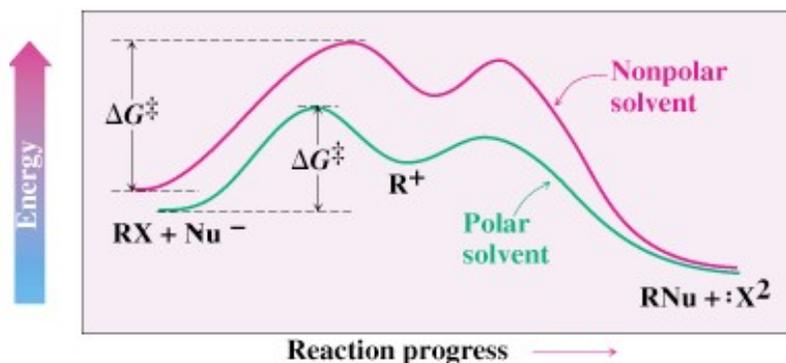
Hexane	ε = 1.9	} nonpolar	} aprotic	
(CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> O	4.3			
HMPA	30	} polar		} protic
DMF	38			
DMSO	48			
CH <sub>3</sub> CH <sub>2</sub> OH	24			
CH <sub>3</sub> OH	34			
H <sub>2</sub> O	80			



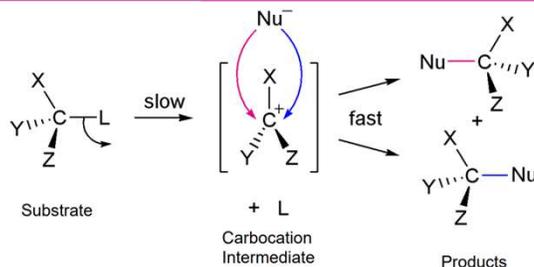
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**S<sub>N</sub><sup>1</sup> REACTION****FACTORS AFFECTING THE S<sub>N</sub><sup>1</sup> REACTION**○ **The Solvent:**

- Stabilization of the intermediate carbocation and the transition state by polar protic solvents in the S<sub>N</sub><sup>1</sup> reaction



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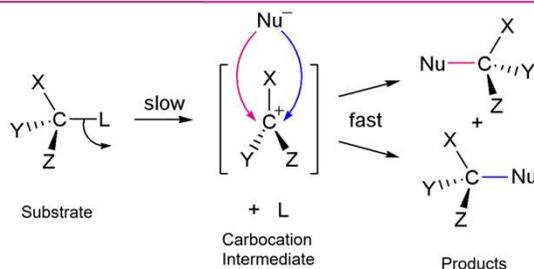
**S<sub>N</sub><sup>1</sup> REACTION****SUMMARY**○ **Reaction is:**

- Non-stereospecific (*attack by nucleophile occurs from both sides*)
- Non-concerted - *has carbocation intermediate*
- Unimolecular - *rate depends on concentration of only the substrate*

○ **Substrate:**

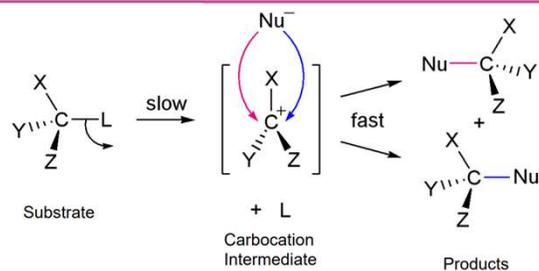
- Best if *tertiary or conjugated* (benzylic or allylic) carbocation can be formed as leaving group departs
- *never primary*

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**S<sub>N</sub><sup>1</sup> 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<sub>N</sub><sup>2</sup>
- best if more stable (i.e. can support negative charge well)
- Examples: TsO<sup>-</sup> (very good) > I<sup>-</sup> > Br<sup>-</sup> > Cl<sup>-</sup> > F<sup>-</sup> (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<sub>N</sub><sup>1</sup> REACTION****SUMMARY**○ **Solvent:**

- Polar protic solvents, such as water and alcohols, organic acids and inorganic acids (H<sub>2</sub>SO<sub>4</sub>, H<sub>3</sub>PO<sub>4</sub>), stabilize the transition state.
- Polar solvents are favored over non-polar for the S<sub>N</sub><sup>1</sup> reaction.
- Protic solvents are favored over aprotic for the S<sub>N</sub><sup>1</sup> reaction