



B.Sc SEM-II Chemistry (Honours); PAPER-CC-4

Nucleophilic Substitution Reactions

Presented by

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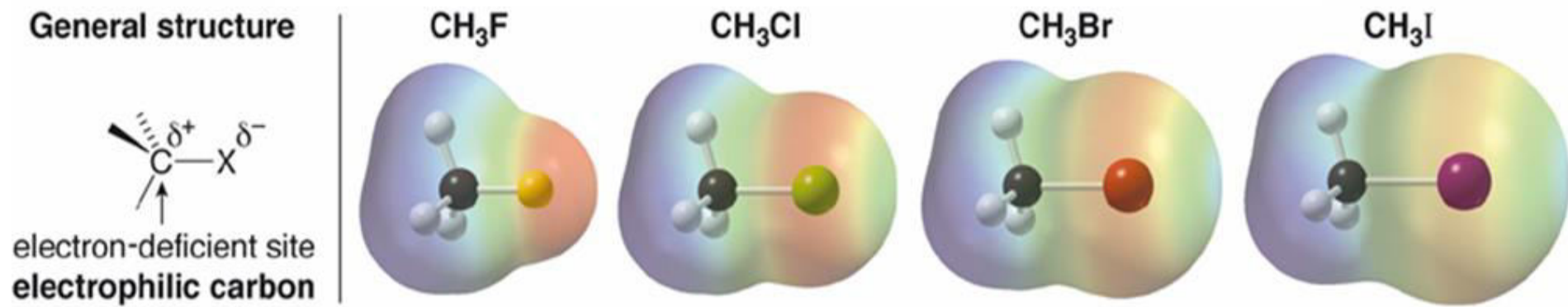
We are familiar with this picture.....



The Polar Carbon-Halogen Bond

- The electronegative halogen atom in alkyl halides creates a polar C—X bond, making the carbon atom electron deficient. Electrostatic potential maps of four simple alkyl halides illustrate this point.

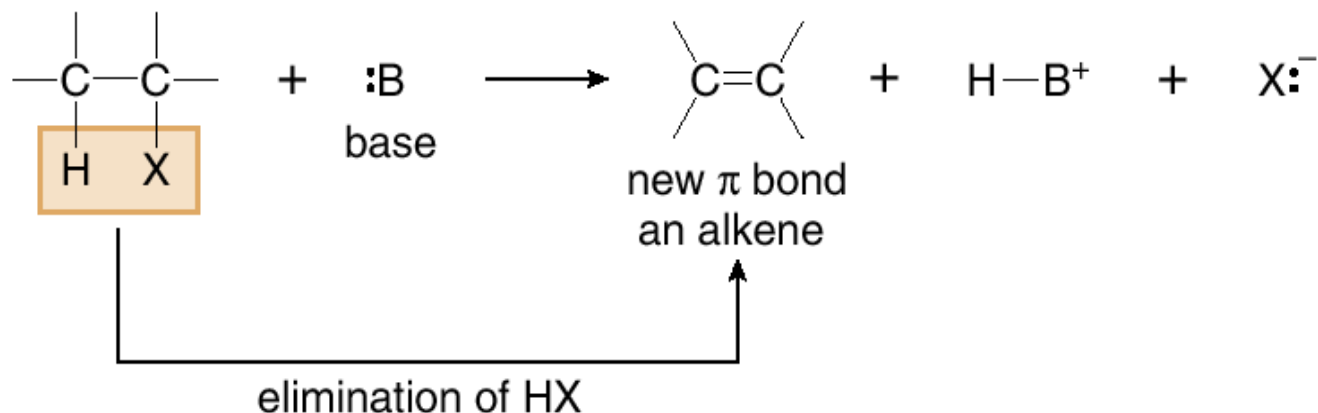
Figure Electrostatic potential maps of four halomethanes (CH_3X)



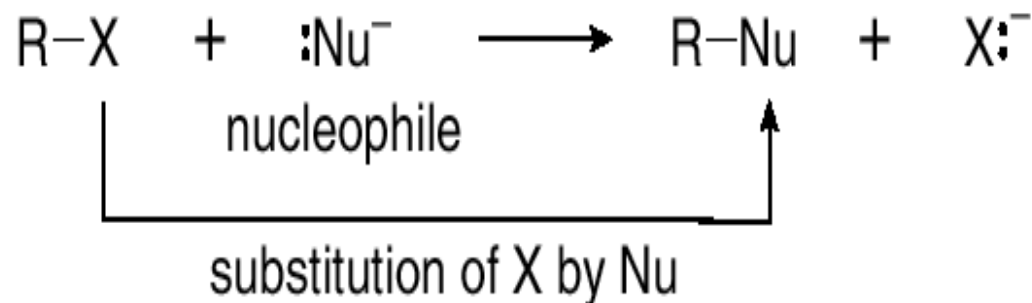
- The polar C—X bond makes the carbon atom *electron deficient* in each CH_3X molecule.

The Polar Carbon-Halogen Bond

- Alkyl halides undergo elimination reactions with Brønsted–Lowry bases.

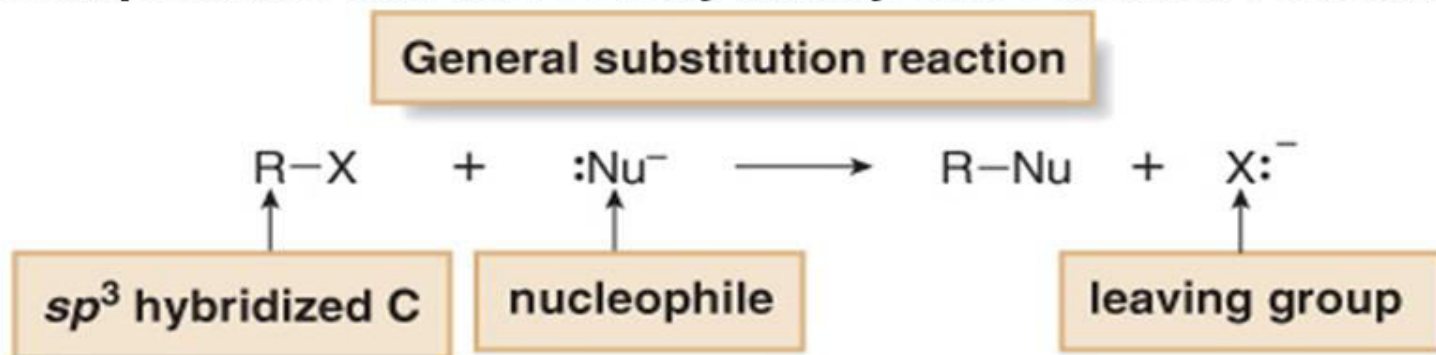


- Alkyl halides undergo substitution reactions with nucleophiles.

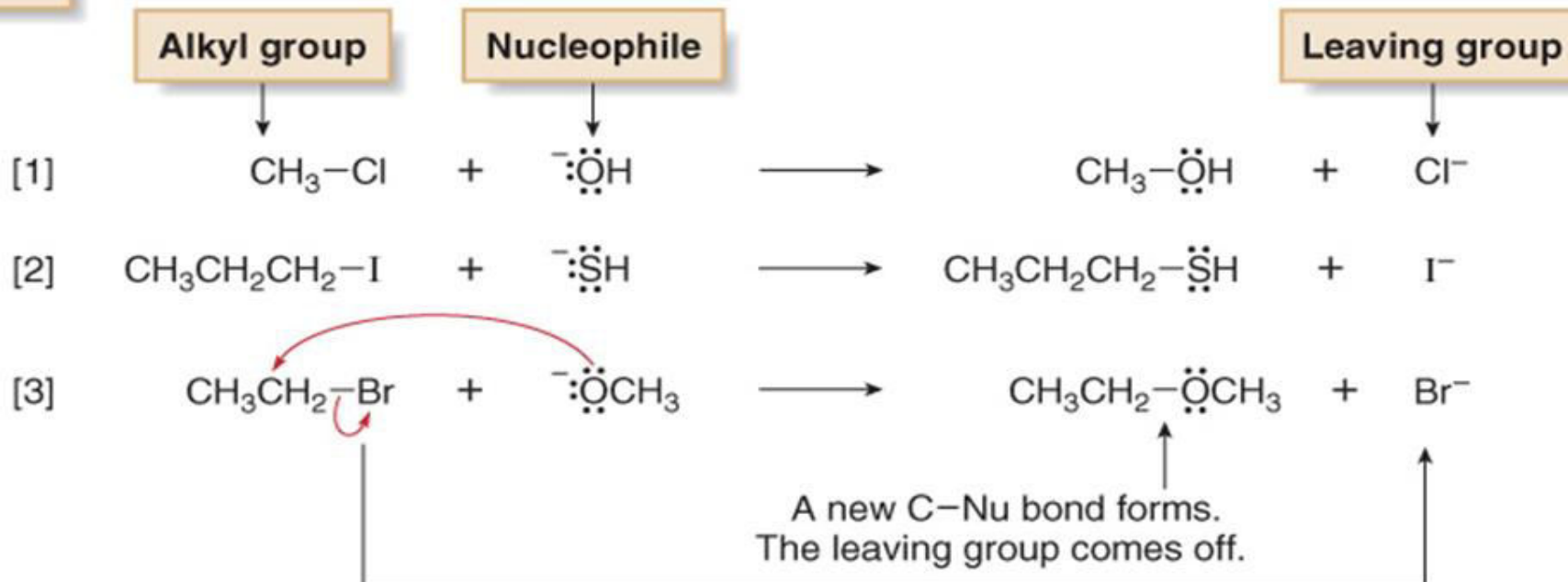


General Features of Nucleophilic Substitution

- Three components are necessary in any substitution reaction.

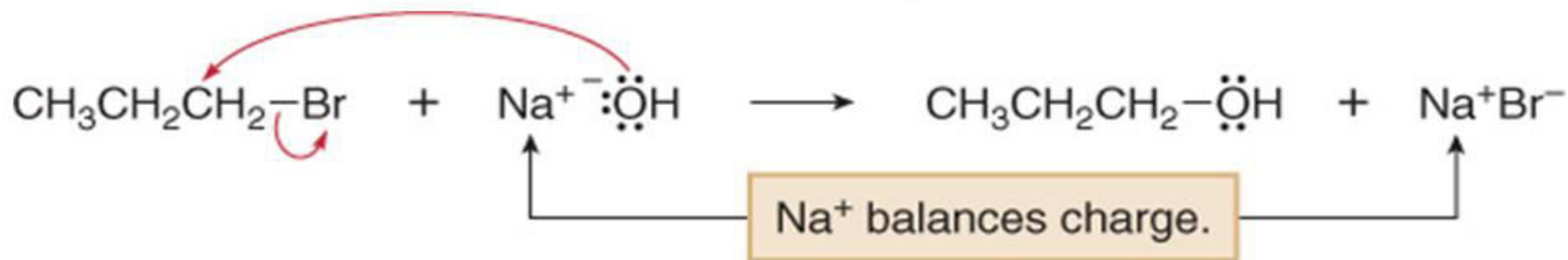


Examples

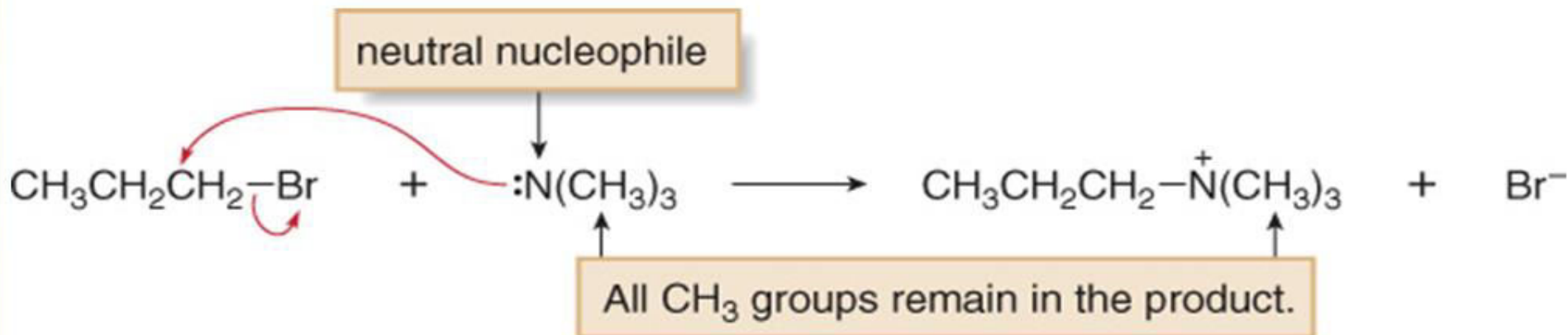


General Features of Nucleophilic Substitution

- Negatively charged nucleophiles like HO^- and HS^- are used as salts with Li^+ , Na^+ , or K^+ counterions to balance the charge. Since the identity of the counterion is usually inconsequential, it is often omitted from the chemical equation.

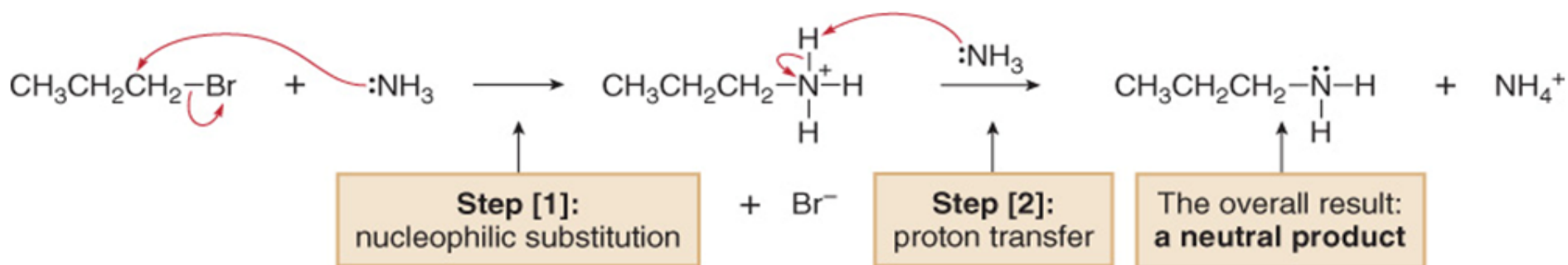


- When a neutral nucleophile is used, the substitution product bears a positive charge.



General Features of Nucleophilic Substitution

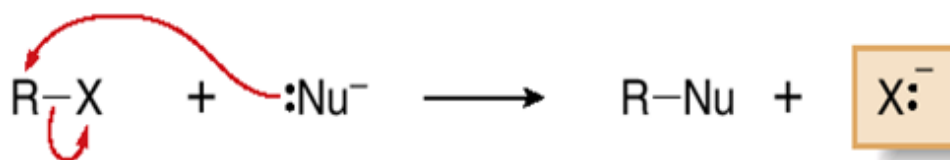
- Furthermore, when the substitution product bears a positive charge and also contains a proton bonded to O or N, the initially formed substitution product readily loses a proton in a Brønsted-Lowry acid-base reaction, forming a neutral product.



- To draw any nucleophilic substitution product:
 - Find the sp^3 hybridized carbon with the leaving group.
 - Identify the nucleophile, the species with a lone pair or π bond.
 - Substitute the nucleophile for the leaving group and assign charges (if necessary) to any atom that is involved in bond breaking or bond formation.

The Leaving Group

- In a nucleophilic substitution reaction of $R-X$, the $C-X$ bond is heterolytically cleaved, and the leaving group departs with the electron pair in that bond, forming $X:^-$. The more stable the leaving group $X:^-$, the better able it is to accept an electron pair.
- In comparing two leaving groups, the better leaving group is the weaker base.



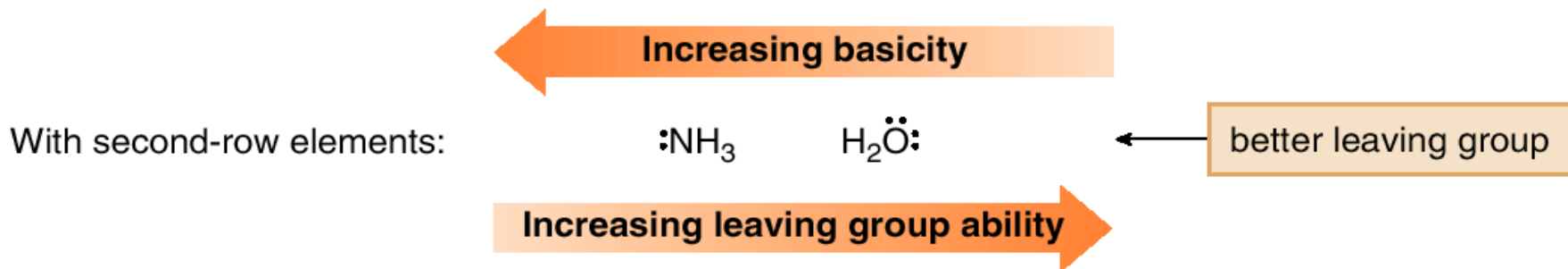
Nucleophilic substitution occurs with leaving groups that are weak bases.

- For example, H_2O is a better leaving group than HO^- because H_2O is a weaker base.

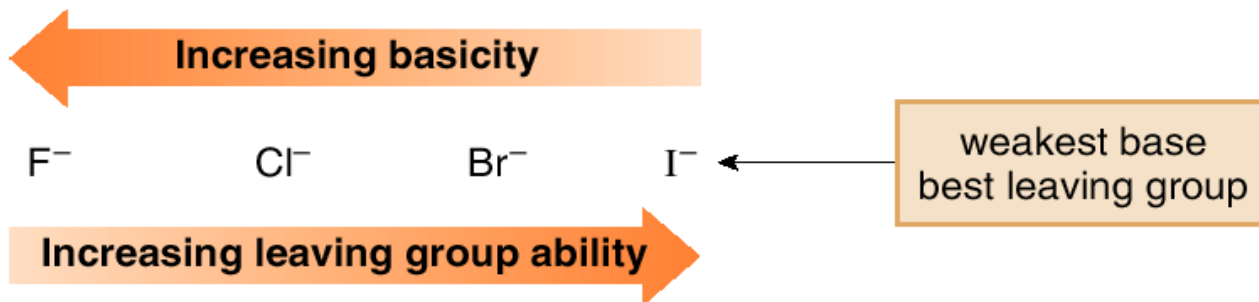
The Leaving Group

- There are periodic trends in leaving group ability:

- Left-to-right across a row of the periodic table, basicity *decreases* so leaving group ability *increases*.



- Down a column of the periodic table, basicity *decreases* so leaving group ability *increases*.



The Leaving Group

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Table -1

Good Leaving Groups for Nucleophilic Substitution

Starting material	Leaving group	Conjugate acid	pK _a
R-Cl	Cl ⁻	HCl	-7
R-Br	Br ⁻	HBr	-9
R-I	I ⁻	HI	-10
R-OH ₂ ⁺	H ₂ O	H ₃ O ⁺	-1.7

These molecules undergo nucleophilic substitution.

good leaving groups

The Leaving Group

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Table -2

Poor Leaving Groups for Nucleophilic Substitution

Starting material	Leaving group	Conjugate acid	pK _a
R-F	F ⁻	HF	3.2
R-OH	⁻ OH	H ₂ O	15.7
R-NH ₂	⁻ NH ₂	NH ₃	38
R-H	H ⁻	H ₂	35
R-R	R ⁻	RH	50

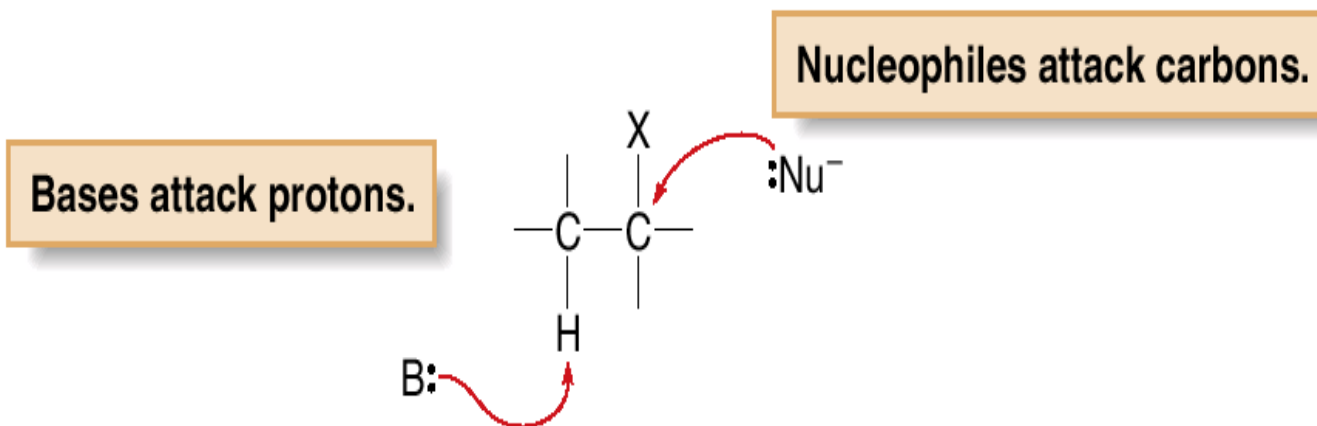
These molecules do *not* undergo nucleophilic substitution.

poor leaving groups

The Nucleophile

- Nucleophiles and bases are structurally similar: both have a lone pair or a π bond. They differ in what they attack.

- Bases attack protons. Nucleophiles attack other electron-deficient atoms (usually carbons).



The Nucleophile

- Although nucleophilicity and basicity are interrelated, they are fundamentally different.
 - ➔ Basicity is a measure of how readily an atom donates its electron pair to a proton. It is characterized by an equilibrium constant, K_a in an acid-base reaction, making it a thermodynamic property.
 - ➔ Nucleophilicity is a measure of how readily an atom donates its electron pair to other atoms. It is characterized by a rate constant, k , making it a kinetic property.

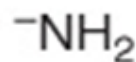
The Nucleophile

- Nucleophilicity parallels basicity in three instances:
 1. For two nucleophiles with the same nucleophilic atom, the stronger base is the stronger nucleophile.

The relative nucleophilicity of HO^- and CH_3COO^- , two oxygen nucleophiles, is determined by comparing the $\text{p}K_a$ values of their conjugate acids ($\text{H}_2\text{O} = 15.7$, and $\text{CH}_3\text{COOH} = 4.8$). HO^- is a stronger base and stronger nucleophile than CH_3COO^- .
 2. A negatively charged nucleophile is always a stronger nucleophile than its conjugate acid.

HO^- is a stronger base and stronger nucleophile than H_2O .
 3. Right-to-left-across a row of the periodic table, nucleophilicity increases as basicity increases:

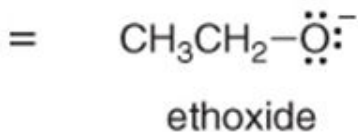
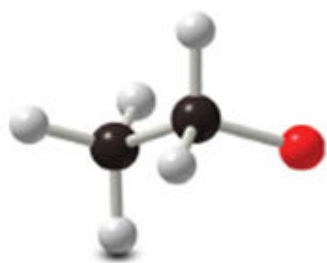
For second-row elements with the same charge:



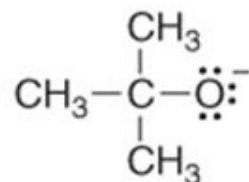
←
Increasing basicity
Increasing nucleophilicity

The Nucleophile

- Nucleophilicity does not parallel basicity when steric hindrance becomes important.
- **Steric hindrance** is a decrease in reactivity resulting from the presence of bulky groups at the site of a reaction.
- Steric hindrance decreases nucleophilicity but not basicity.
- Sterically hindered bases that are poor nucleophiles are called **nonnucleophilic bases**.

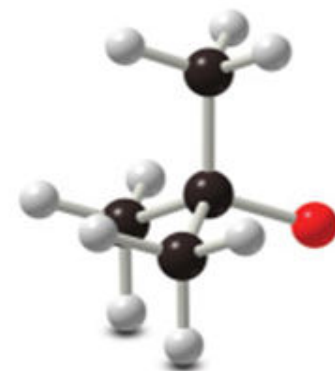


stronger nucleophile



tert-butoxide

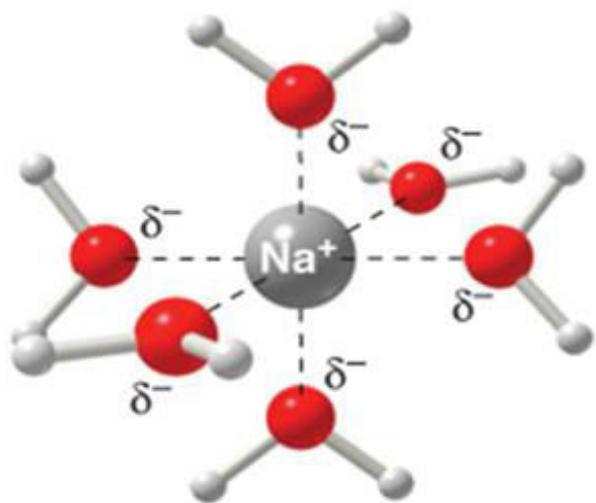
stronger base



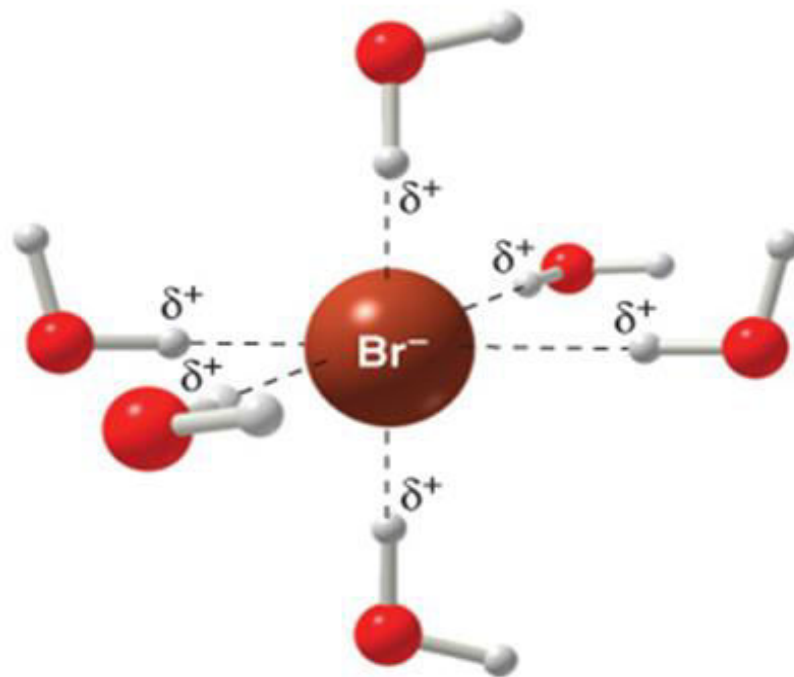
Three CH_3 groups sterically hinder the O atom, making it a **weaker nucleophile**.

The Nucleophile

- If the salt NaBr is used as a source of the nucleophile Br^- in H_2O , the Na^+ cations are solvated by ion-dipole interactions with H_2O molecules, and the Br^- anions are solvated by strong hydrogen bonding interactions.



Na^+ is solvated by ion-dipole interactions with H_2O .



Br^- is solvated by hydrogen bonding with H_2O .

The Nucleophile

- In **polar protic solvents**, nucleophilicity increases down a column of the periodic table as the size of the anion increases. This is the opposite of basicity.

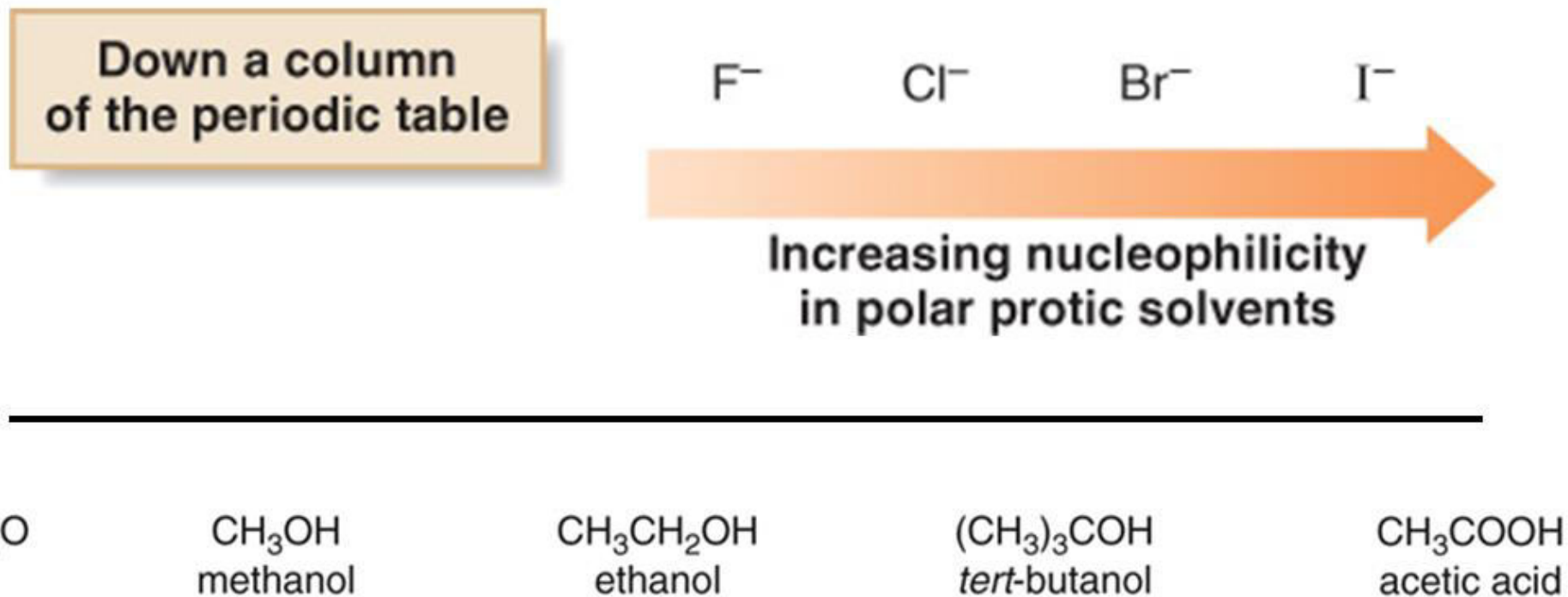
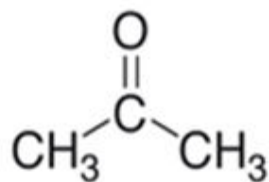


Figure Example of polar protic solvents

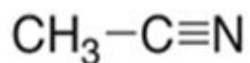
The Nucleophile

- **Polar aprotic solvents** also exhibit dipole—dipole interactions, but they have no O—H or N—H bonds. Thus, they are incapable of hydrogen bonding.

Figure Examples of polar aprotic solvents



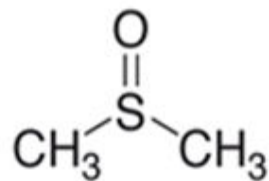
acetone



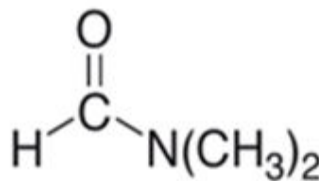
acetonitrile



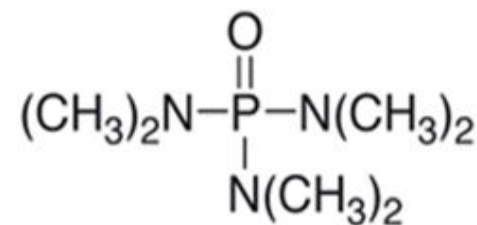
tetrahydrofuran
THF



dimethyl sulfoxide
DMSO



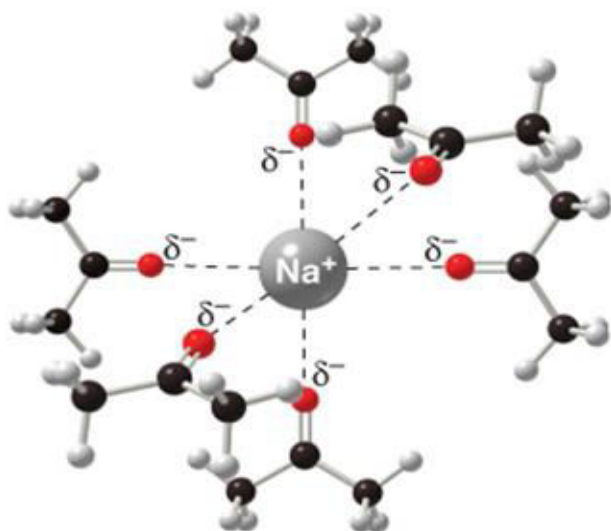
dimethylformamide
DMF



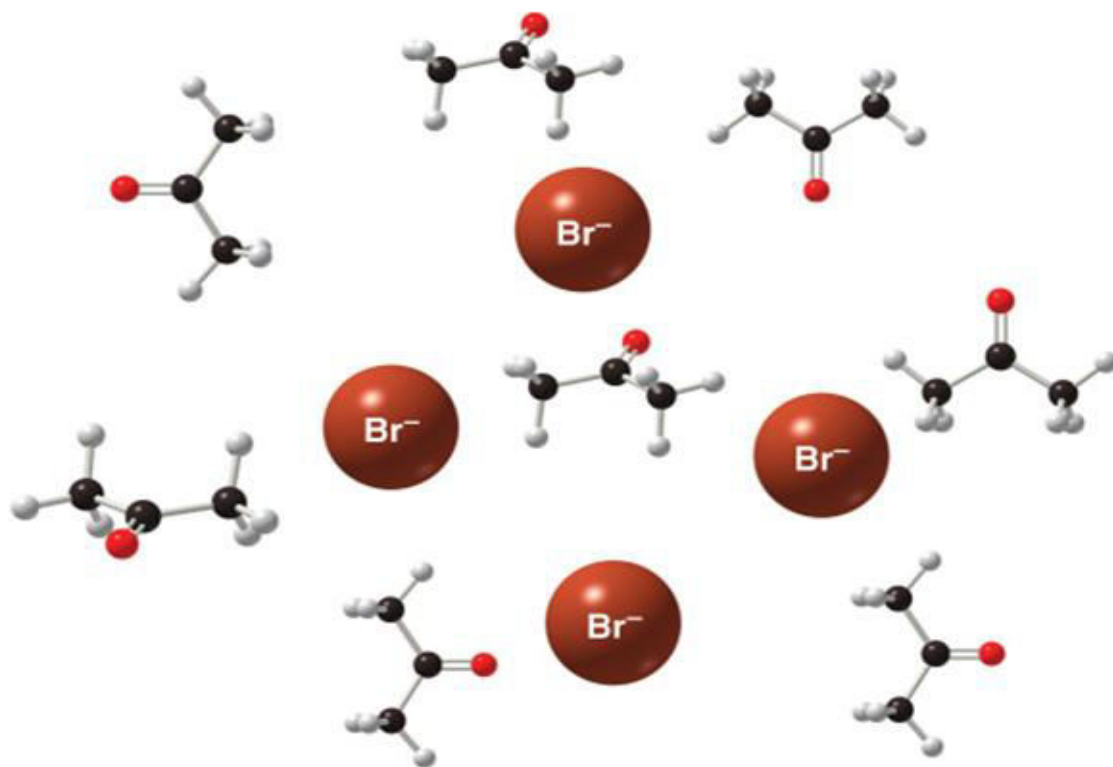
hexamethylphosphoramide
HMPA

The Nucleophile

- Polar aprotic solvents solvate cations by ion—dipole interactions.
- Anions are not well solvated because the solvent. These anions are said to be “naked”.



$(\text{CH}_3)_2\text{C}=\text{O}$ solvates Na^+ well by ion—dipole interactions.



Br^- anions are surrounded by solvent but not well solvated by the $(\text{CH}_3)_2\text{C}=\text{O}$ molecules.

The Nucleophile

- In polar aprotic solvents, nucleophilicity parallels basicity, and the stronger base is the stronger nucleophile.
- Because basicity decreases as size increases down a column, nucleophilicity decreases as well.

Down a column
of the periodic table



←
Increasing nucleophilicity
in polar aprotic solvents

The Nucleophile

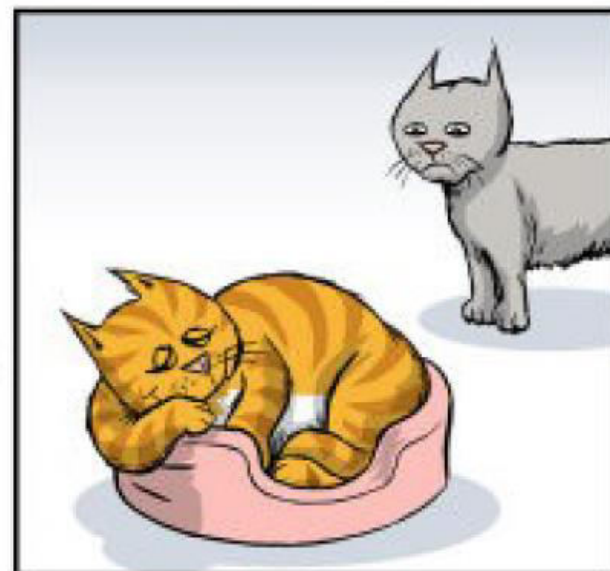
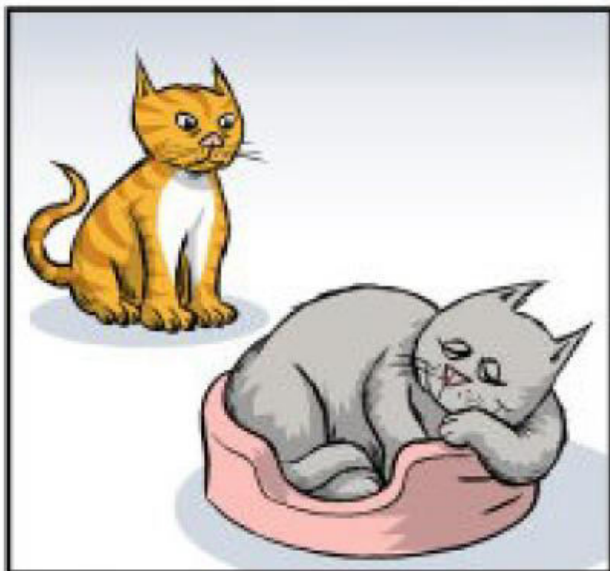
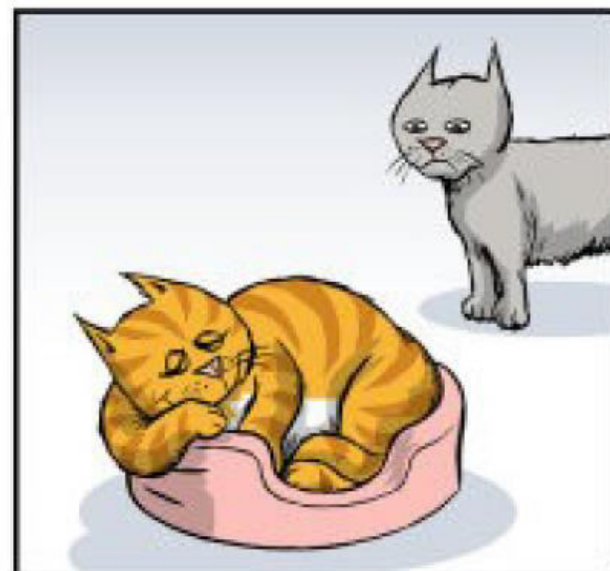
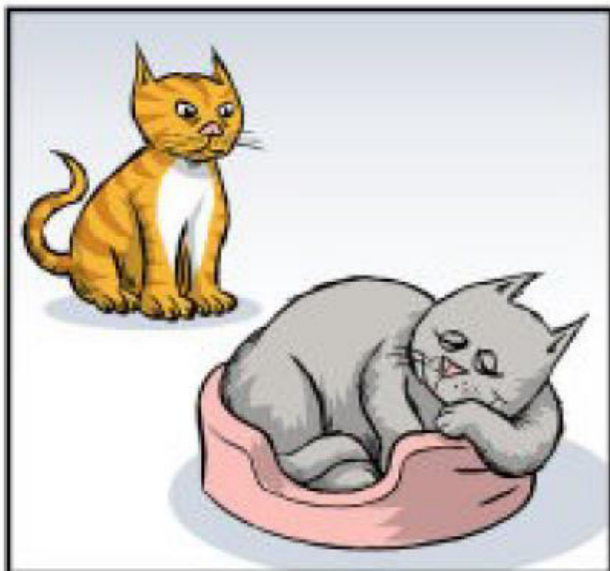
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Table -3

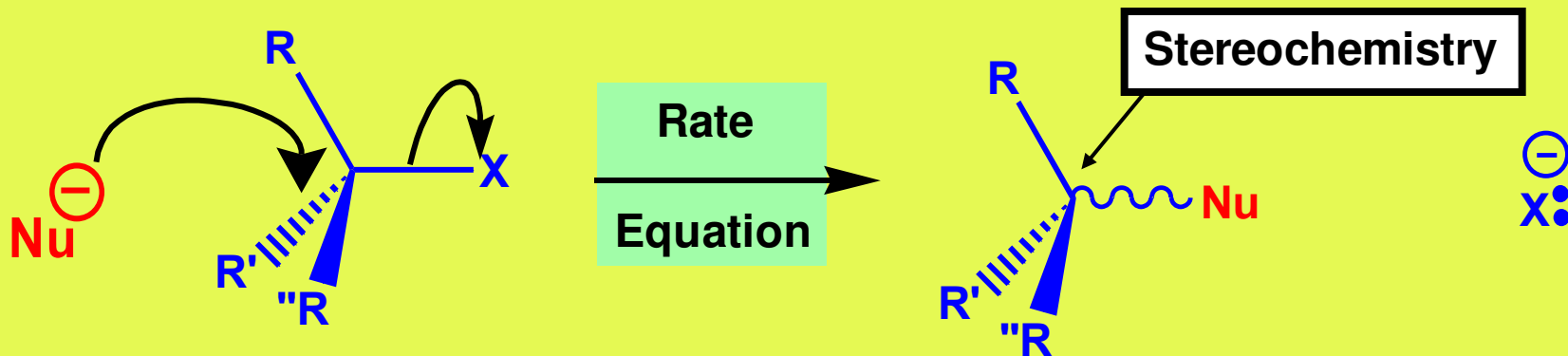
Common Nucleophiles in Organic Chemistry

	Negatively charged nucleophiles			Neutral nucleophiles	
Oxygen	^-OH	^-OR	CH_3COO^-	H_2O	ROH
Nitrogen	N_3^-			NH_3	RNH_2
Carbon	^-CN	$\text{HC}\equiv\text{C}^-$			
Halogen	Cl^-	Br^-	I^-		
Sulfur	HS^-	RS^-		H_2S	RSH

Substitution Reaction



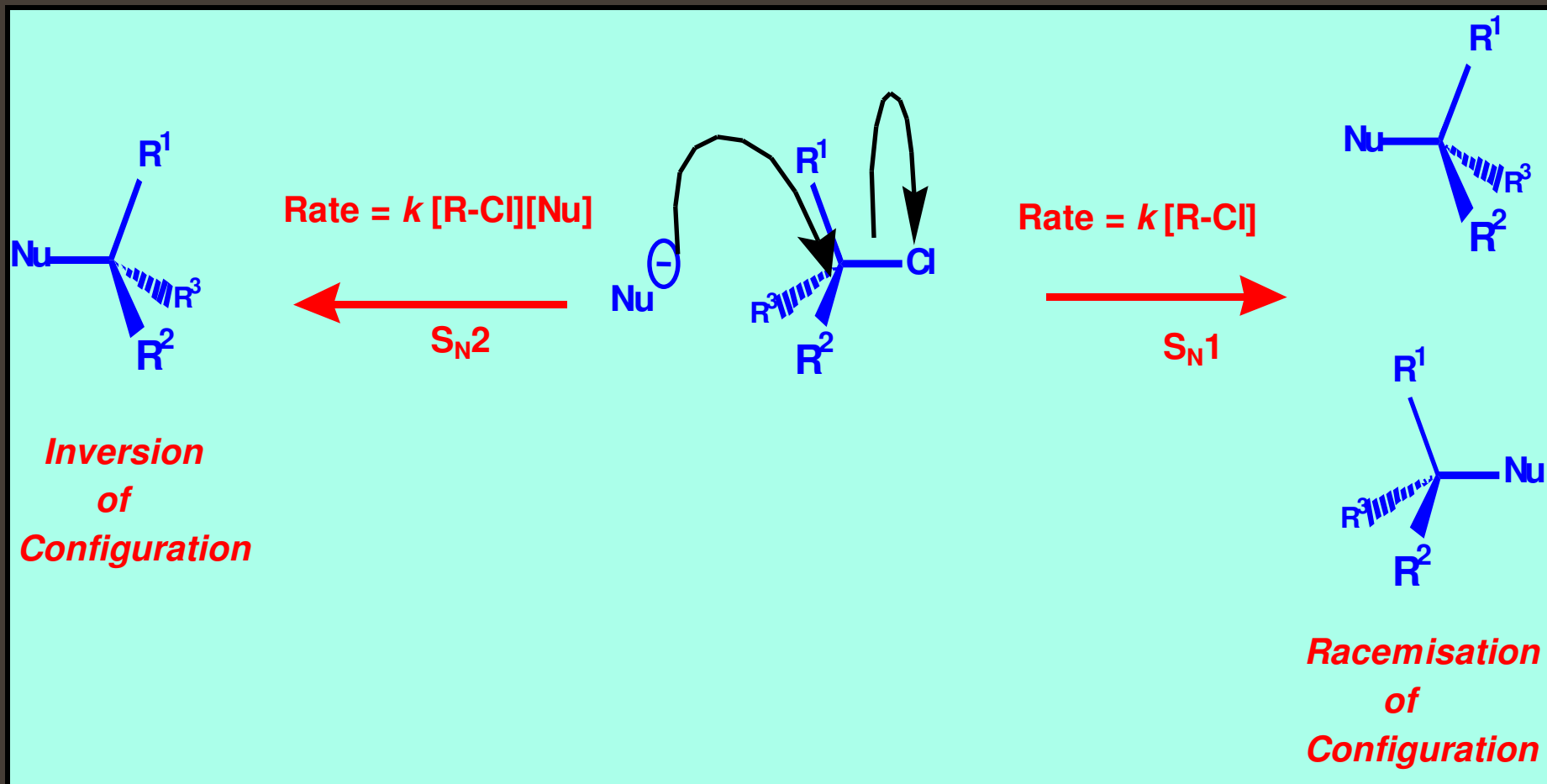
Nucleophilic Substitution Reactions at sp^3 Carbons



It is found that there are two possible stereochemical outcomes, each described by a different rate equation, and different stereochemical outcomes.

Descriptor	Rate Equation	Stereochemical Outcome
S_N2	$\text{rate} = k[\text{R-Hal}][\text{Nu}]$	Inversion
S_N1	$\text{rate} = k[\text{R-Hal}]$	Racemisation

Substitution Reaction

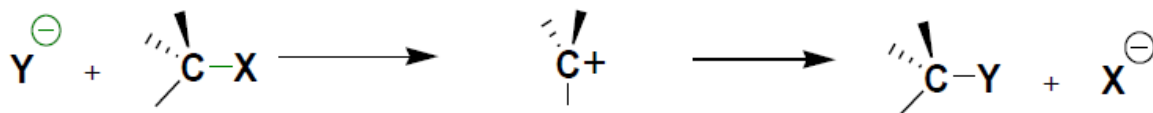


Nucleophilic Substitution Reaction

S_N1

S: Substitution
N: Nucleophilic
1: unimolecular

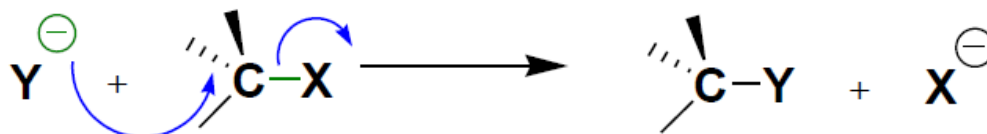
leaving group goes first and nucleophile comes later




S_N2

S: Substitution
N: Nucleophilic
2: Bimolecular

nucleophile attacks and leaving group goes simultaneously

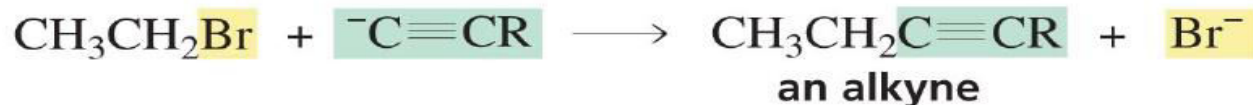
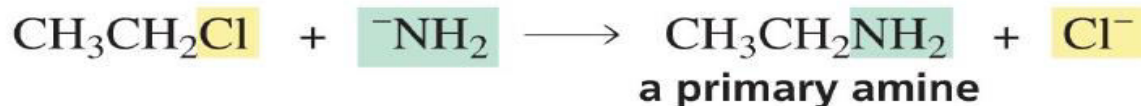
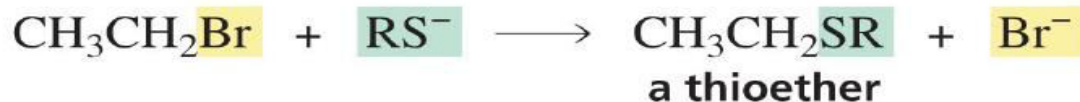
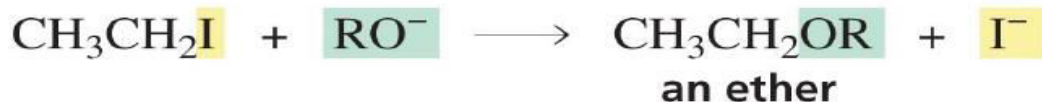
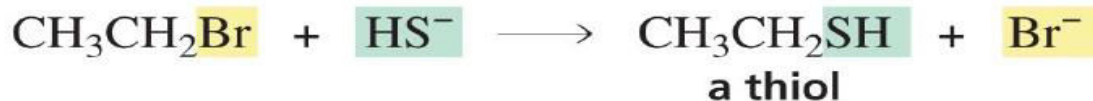
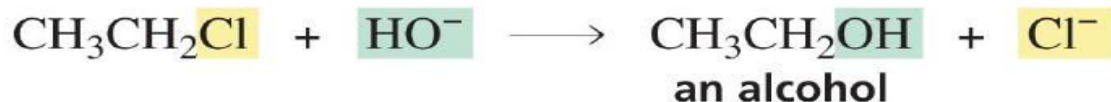




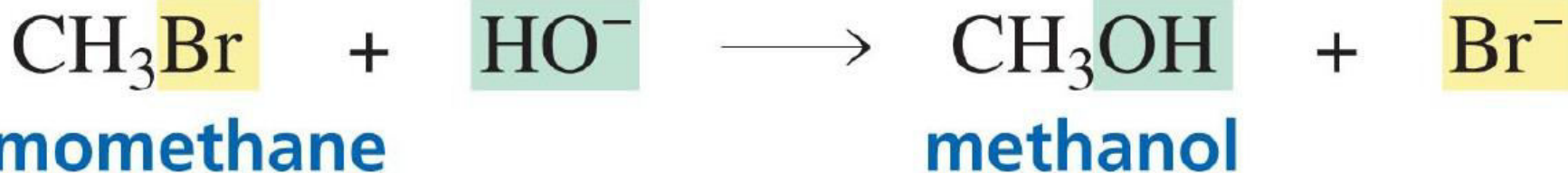
S_{N_2}

Synthetic Utility of the S_N2 Reaction

A variety of functional groups can be prepared employing a good nucleophile and an electrophile with a good leaving group:



S_N2 Reaction : Kinetics



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Obtained experimentally:

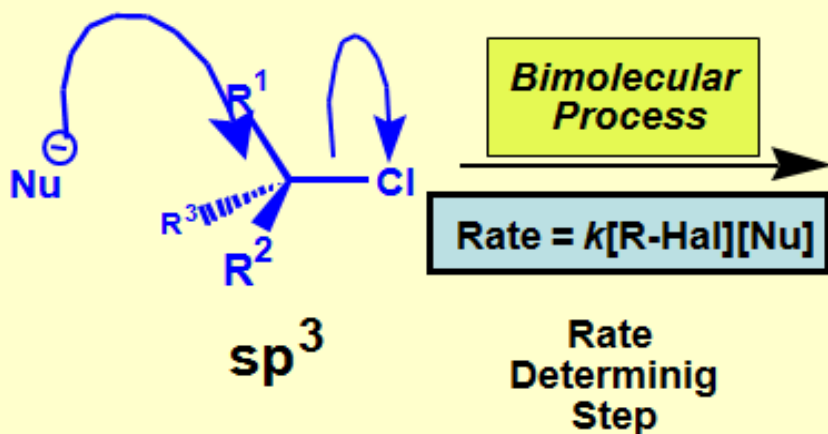
$$\text{rate} = k [\text{alkyl halide}][\text{nucleophile}]$$

the rate constant

Rate law includes both the alkyl halide and the nucleophile, a second-order process

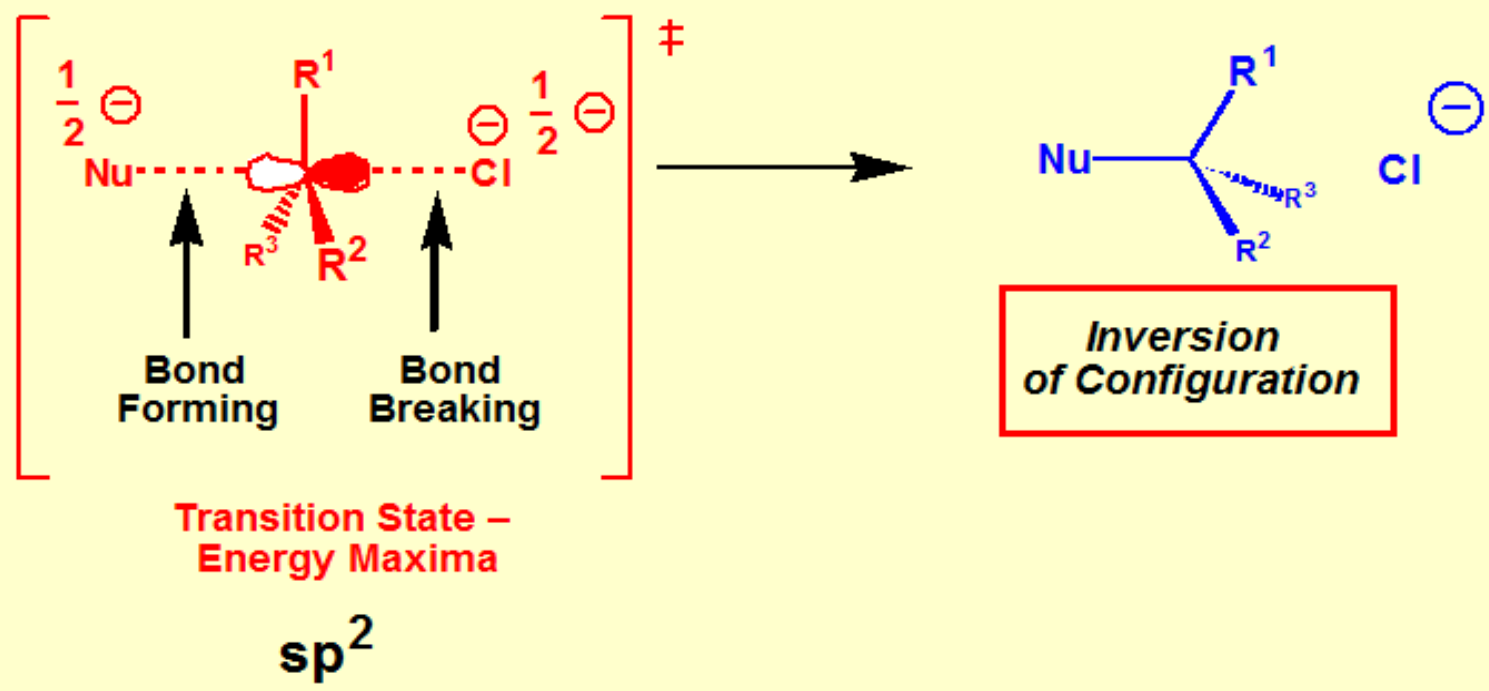
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The S_N2 Reaction Mechanism

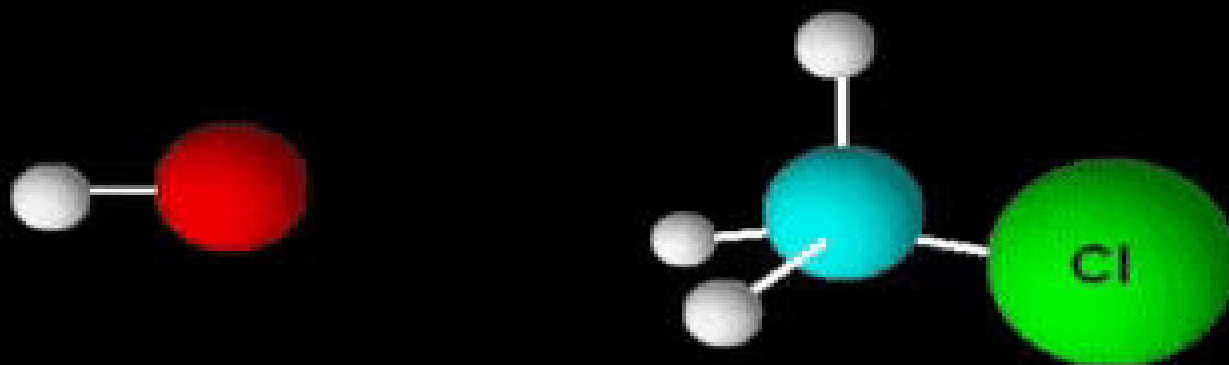


Nucleophile attacks from behind the C-Cl σ -bond.

This is where the σ^* -antibonding orbital of the C-Cl bond is situated.



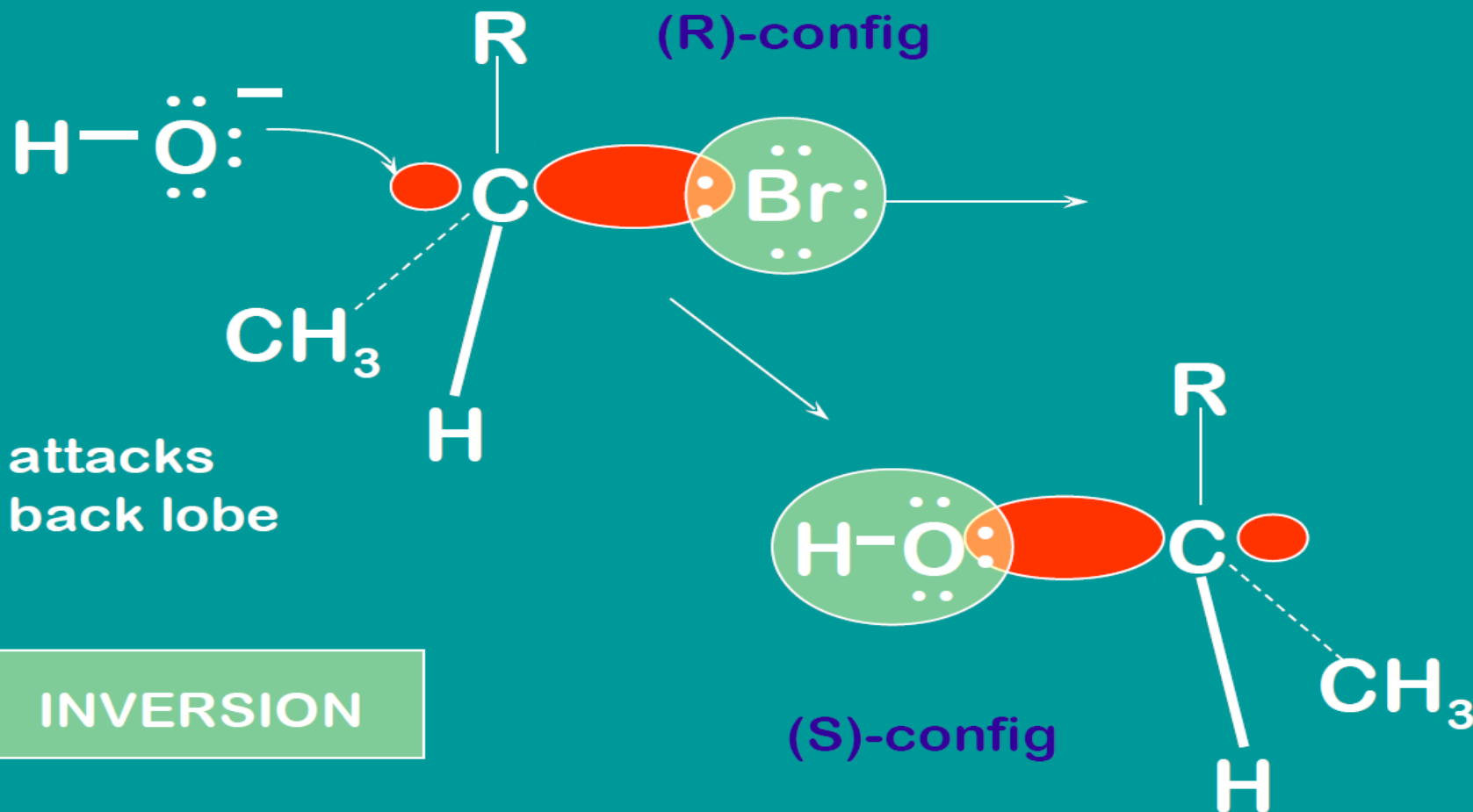
The S_N2 Reaction Mechanism



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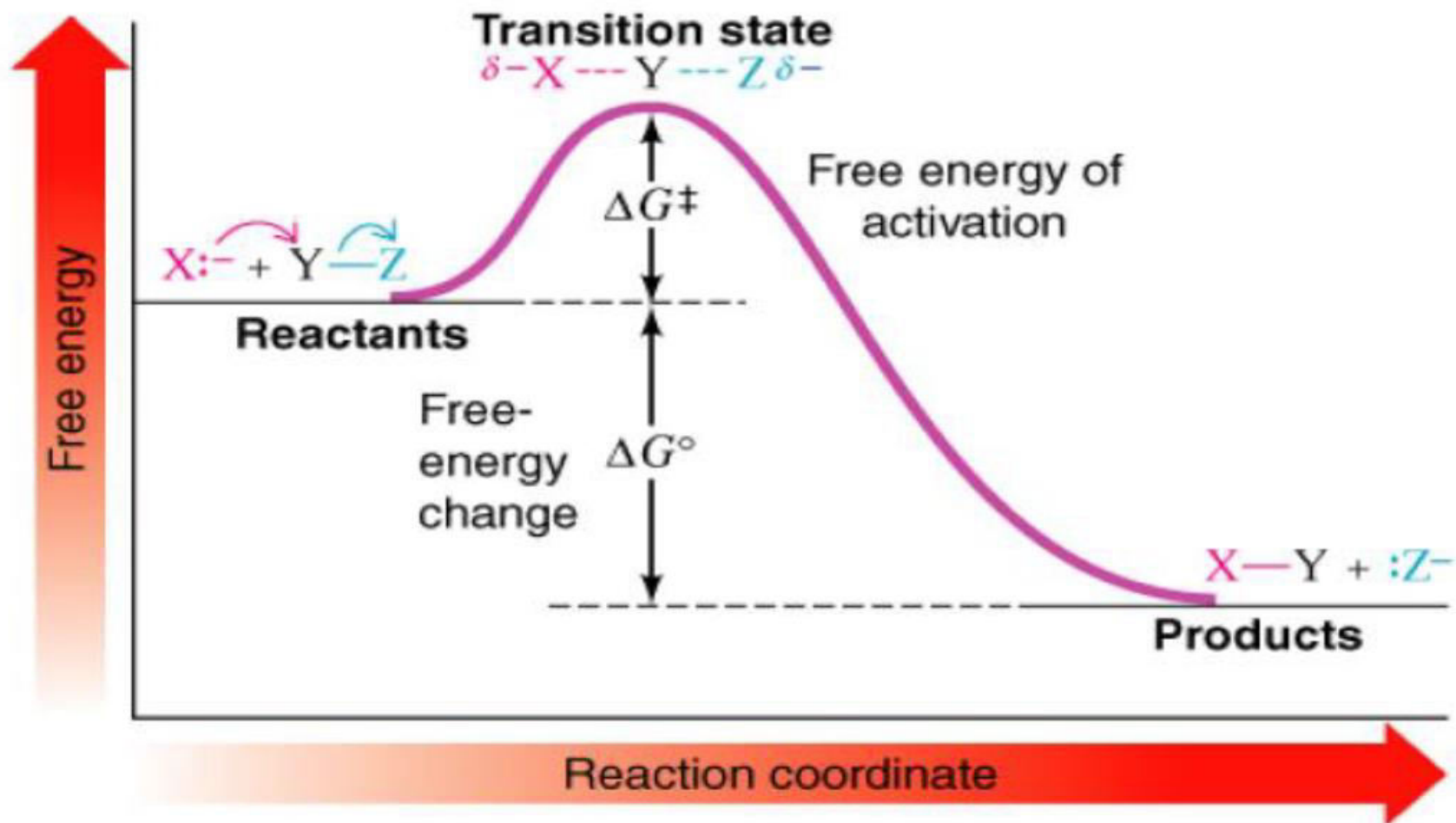
The S_N2 Reaction Mechanism

S_N2 MECHANISM nucleophilic attack

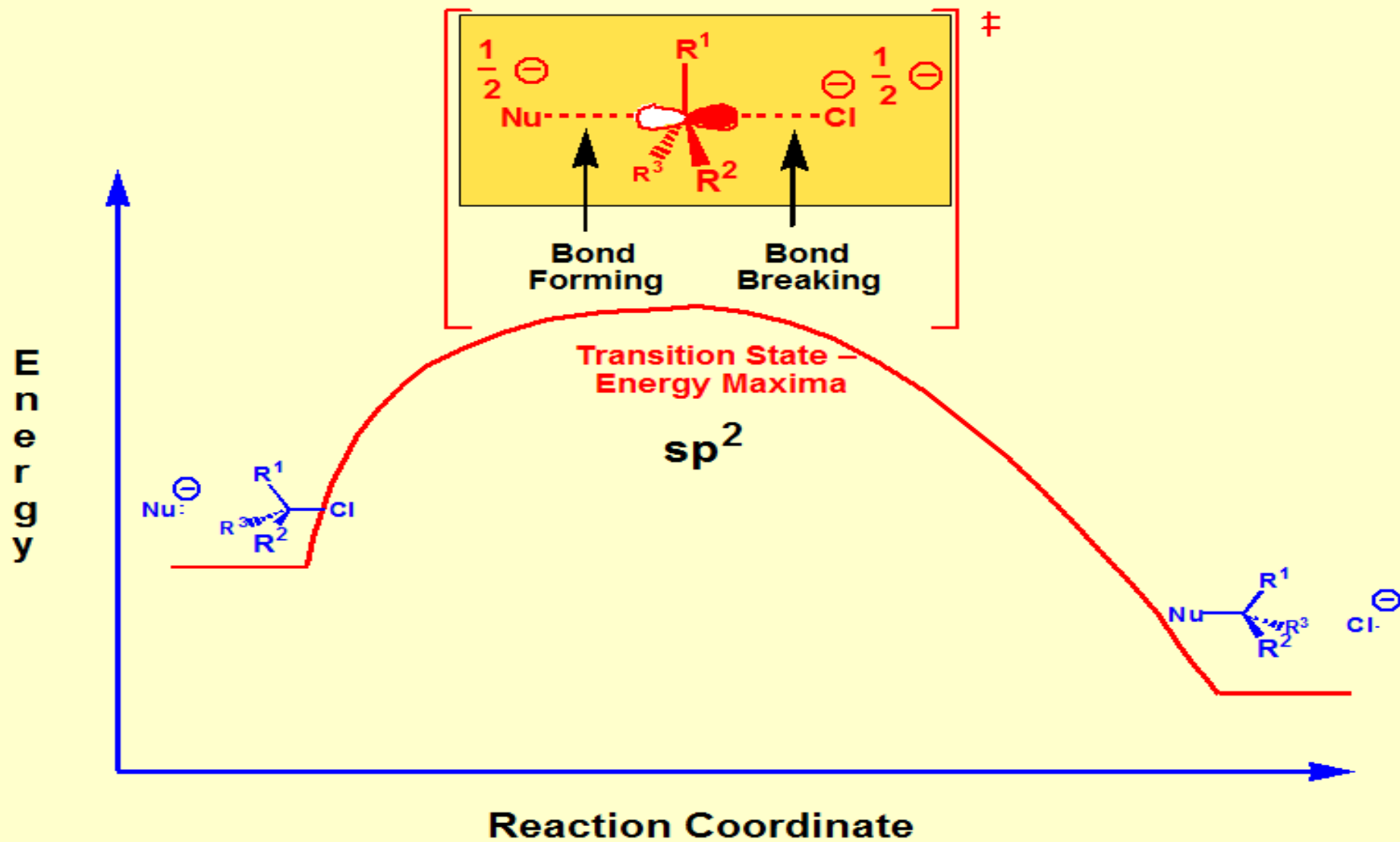


Transition States

Free Energy Diagram



Transition States

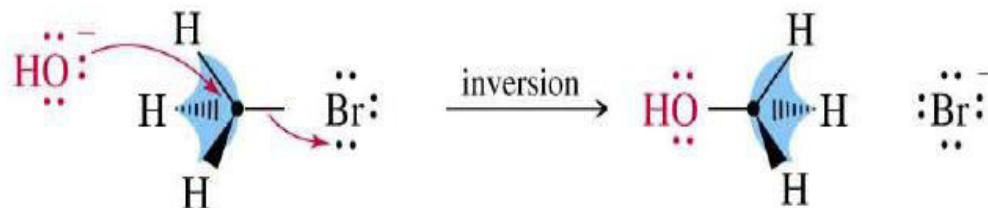
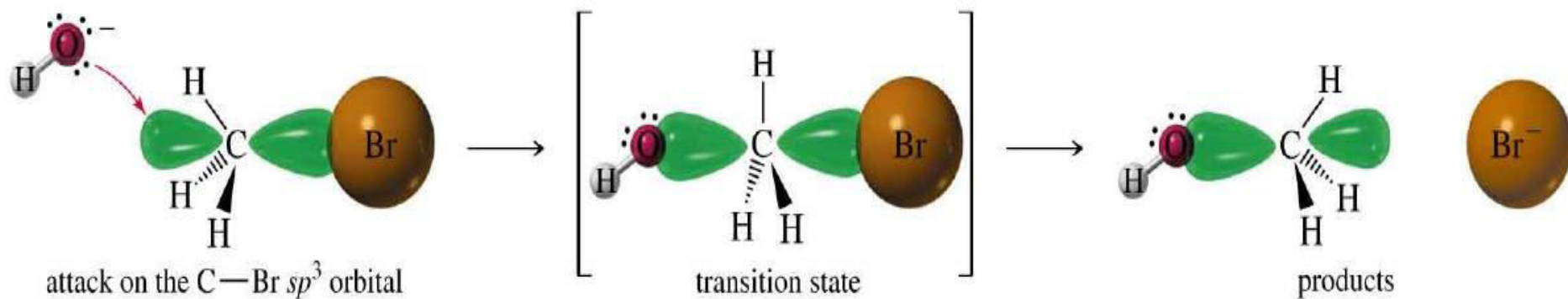


Transition States: Video Clip



Stereochemistry of S_N2

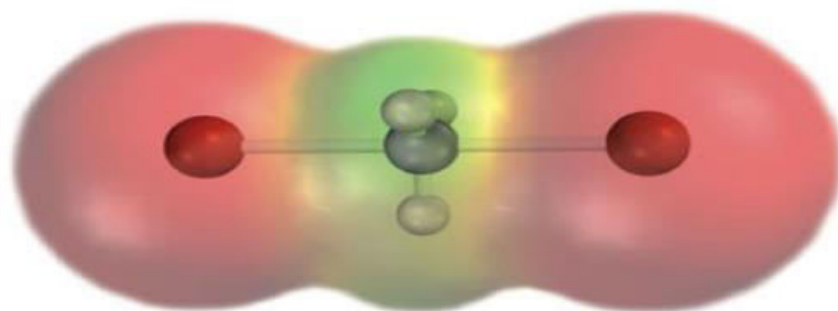
Walden inversion



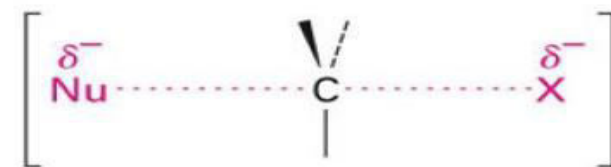
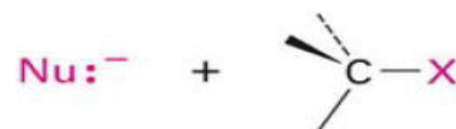
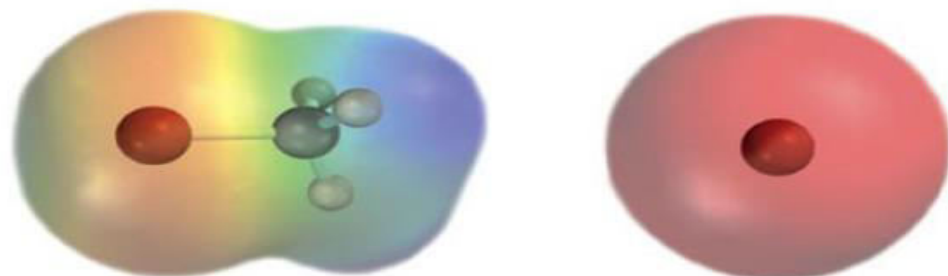
Stereochemistry of S_N2



Tetrahedral

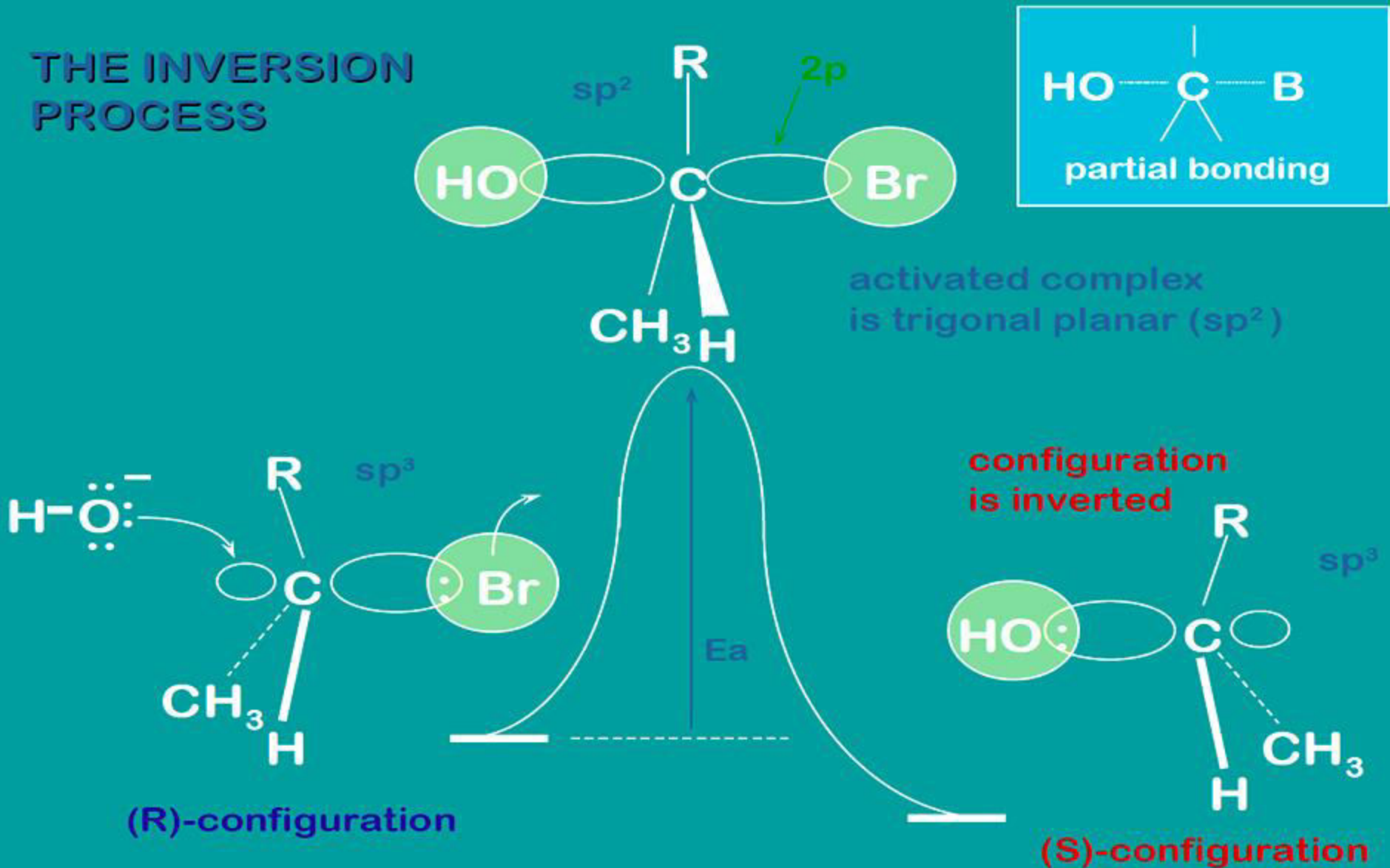


Planar



Stereochemistry of S_N2

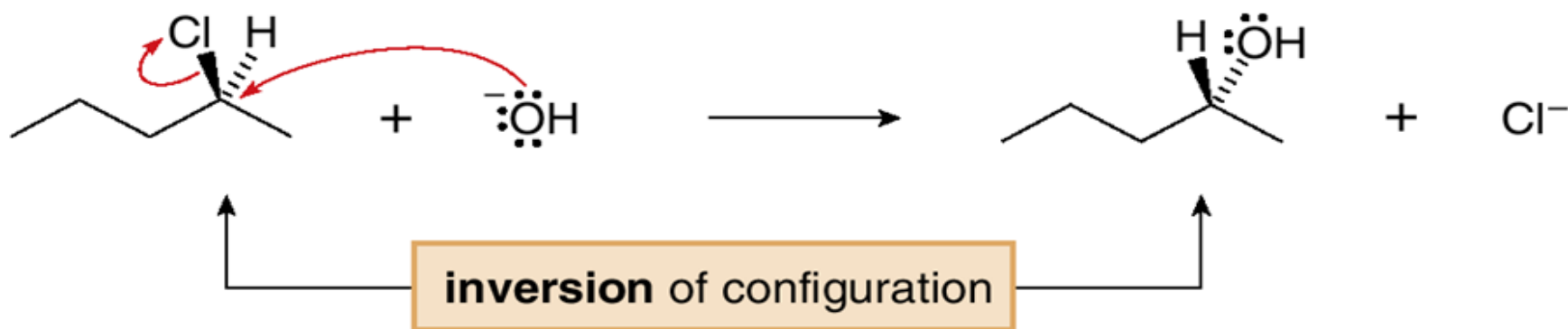
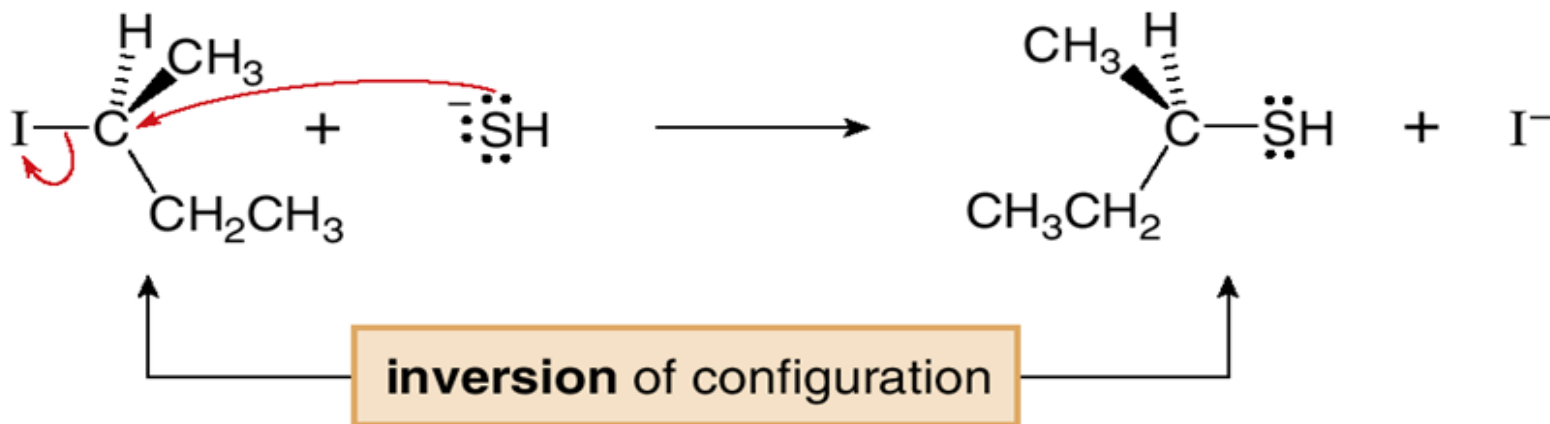
THE INVERSION PROCESS



Stereochemistry of S_N2: Example

Figure:
Two examples of inversion of configuration in the S_N2 reaction

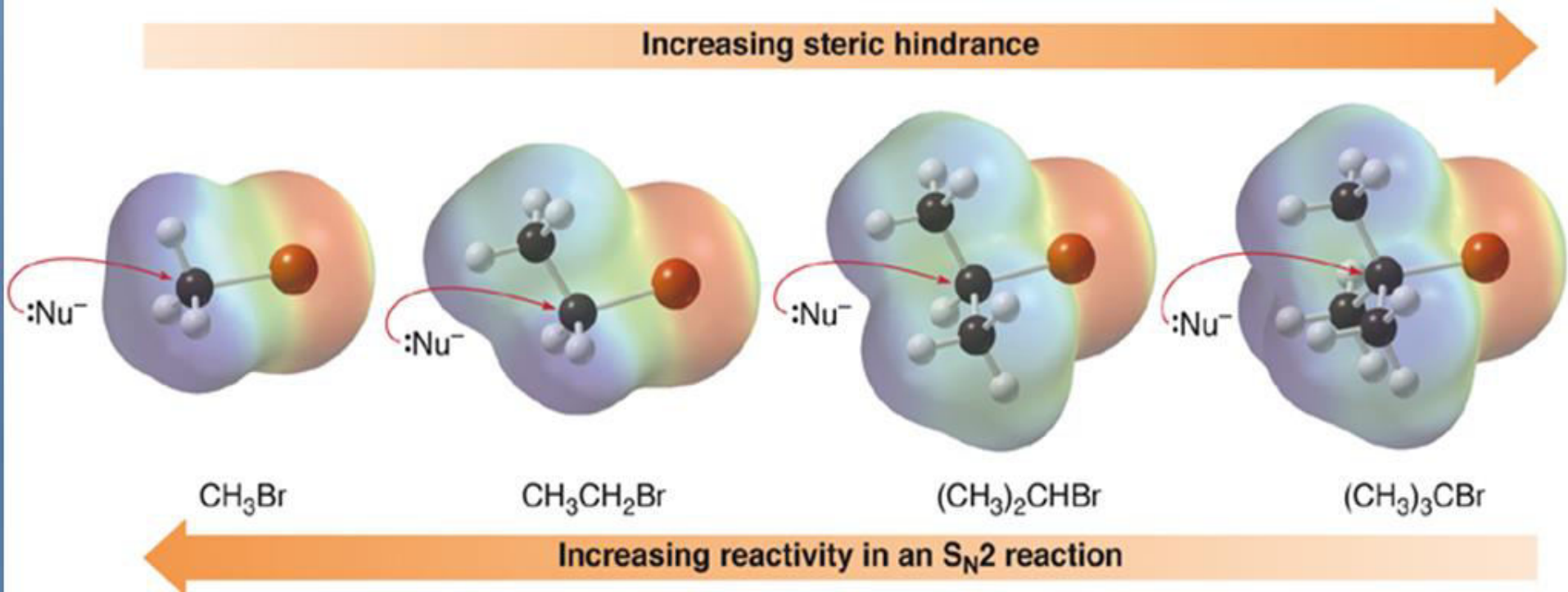
- The bond to the nucleophile in the product is always on the **opposite side** relative to the bond to the leaving group in the starting material.



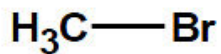
S_N2 : Effect of Nature of Substrate

Electrostatic potential maps illustrate the effects of steric hindrance around the carbon bearing the leaving group in a series of alkyl halides.

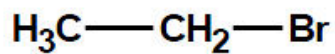
Figure: Steric effects in the S_N2 reaction



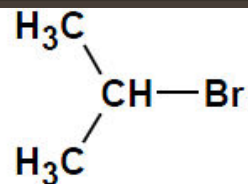
S_N2 : Effect of Nature of Substrate



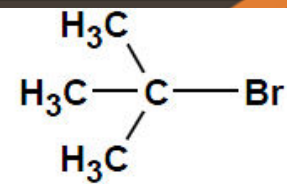
methyl bromide



ethyl bromide

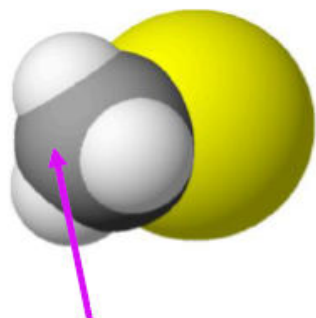


isopropyl bromide

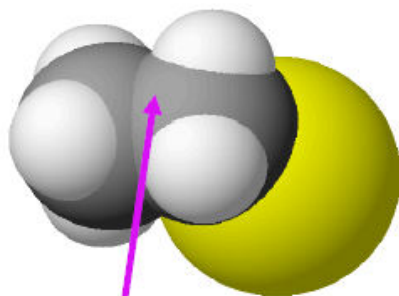


t-butyl bromide

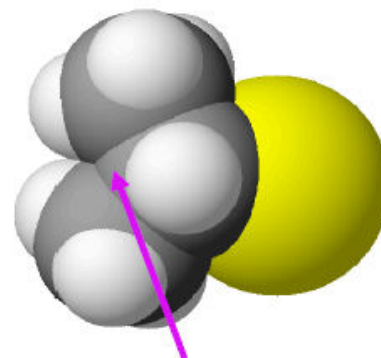
SPACE FILLING MODELS SHOW ACTUAL SHAPES AND RELATIVE SIZES



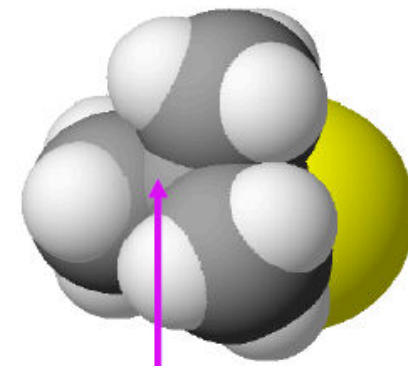
Back side of α -C of a methyl halide is unhindered.



Back side of α -C of a 1° alkyl halide is slightly hindered.



Back side of α -C of a 2° alkyl halide is mostly hindered.



Back side of α -C of a 3° alkyl halide is completely blocked.



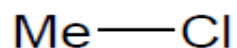
decreasing rate of S_N2 reactions

S_N2 : Effect of Nature of Substrate

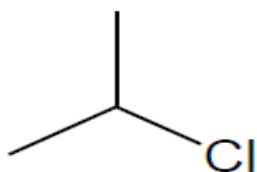
The rates are given with respect to n-BuCl

Alkyl chloride

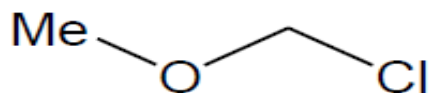
relative rate



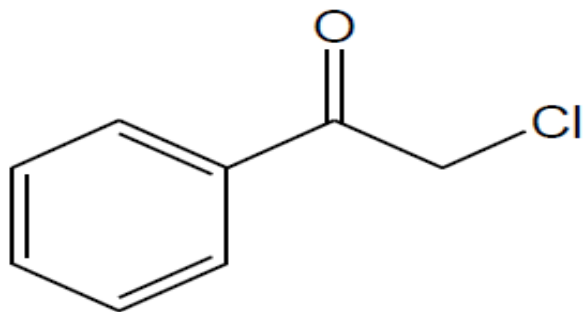
200



0.02

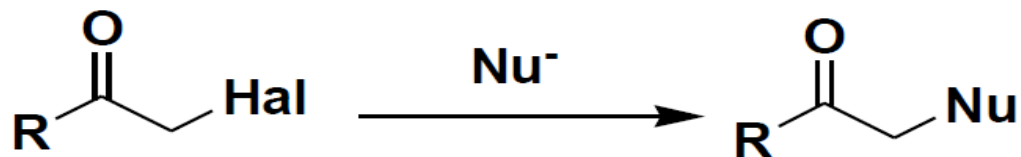


920



1,00,000

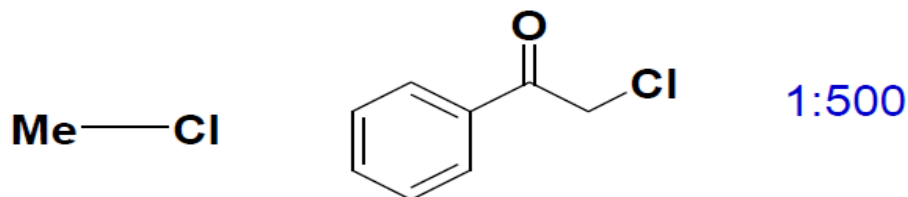
S_N2 : Effect of Nature of Substrate



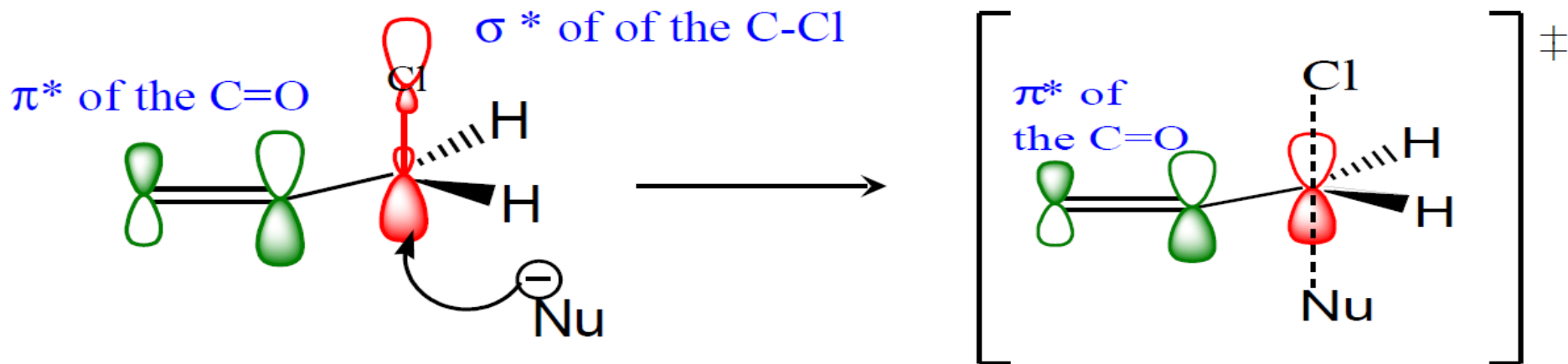
only S_N2 , no S_N1

R = alkyl, aryl, OR'

Relative rates of S_N2 reactions with iodide ion



C=O group stabilizes the T.S. by Overlap of its π^* orbital with full P-orbital of the C-atom under attack



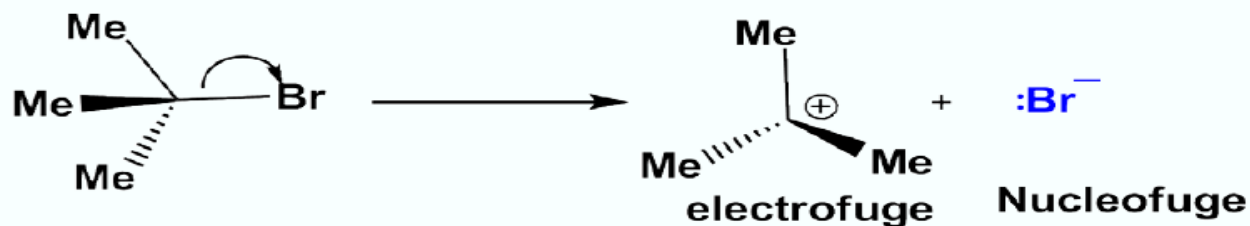
S_N2 : Effect of Nucleophile

Additional terminologies: Nucleophile and Nucleofuge

- Nucleophile is a species that would combine with a positive charge (nucleus) to which it can donate its electron.
- Usually nucleophiles are electron rich species.
- They have higher energy HOMO



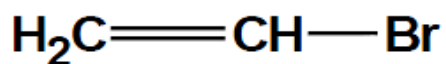
- A Nucleofuge is nucleophile that departs from a molecule (leaving group)



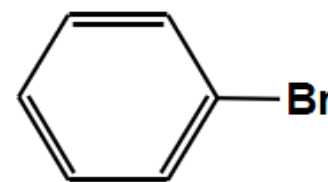
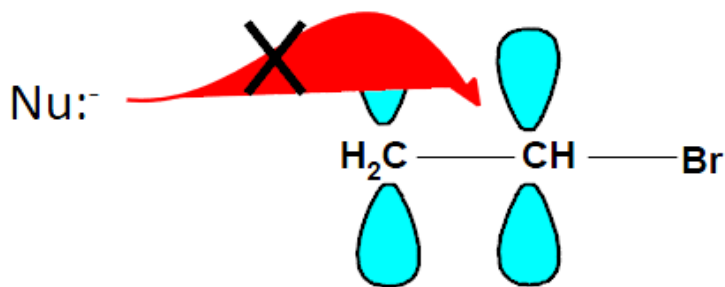
- The terms Nucleophile and Nucleofuge are generally used in the discussion of reactivity and kinetics.

S_N2 : Effect of Nucleophile

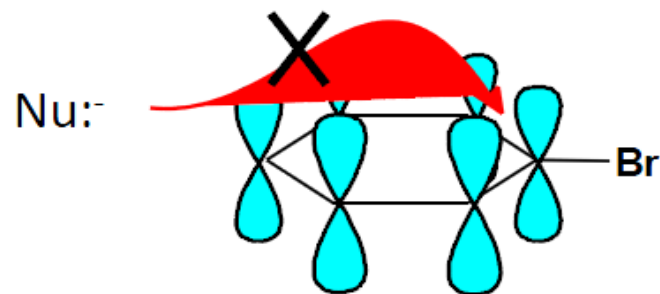
•The α -carbon in vinyl and aryl halides, as in 3° carbocations, is completely hindered and these alkyl halides do not undergo S_N2 reactions.



vinyl bromide



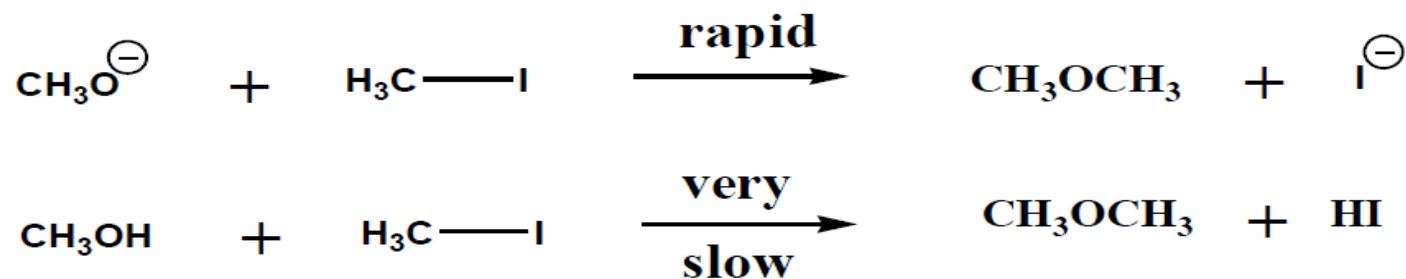
bromobenzene



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.

S_N2 : Effect of Nucleophile

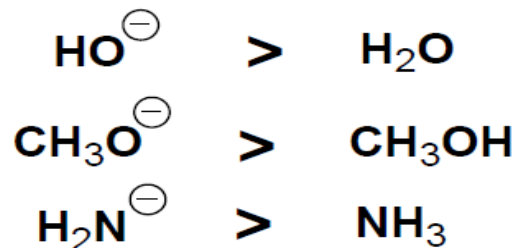
The nucleophilicity may be correlated to its basicity as both involve the availability of the electron pairs and the ease with which it is donated



Nucleophilicity of $\text{CH}_3\text{O}^- > \text{CH}_3\text{OH}$ **A negatively charged nucleophile is always stronger than its conjugate acid.**

Stronger base
better nucleophile

weaker base
poorer nucleophile



The direct relationship between basicity and nucleophilicity is maintained if the reaction occurs in the gas phase

S_N2 : Effect of Nucleophile

Consider the power of the nucleophile:

- The better the nucleophile, the faster the rate of S_N2 reactions.
- The table below shows the relative power of various nucleophiles.
- The best nucleophiles are the best electron donors.

Reactivity	Nu: ⁻	Relative Reactivity
very weak	HSO_4^- , H_2PO_4^- , RCOOH	< 0.01
weak	ROH	1
	HOH, NO_3^-	100
fair	F^-	500
	Cl^- , RCOO^-	20×10^3
	NH_3 , CH_3SCH_3	300×10^3
good	N_3^- , Br^-	600×10^3
	OH^- , CH_3O^-	2×10^6
very good	CN^- , HS^- , RS^- , $(\text{CH}_3)_3\text{P}^-$, NH_2^- , RMgX , I^- , H^-	$> 100 \times 10^6$

increasing

S_N2 : Effect of Leaving Group

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

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



Increasing leaving ability

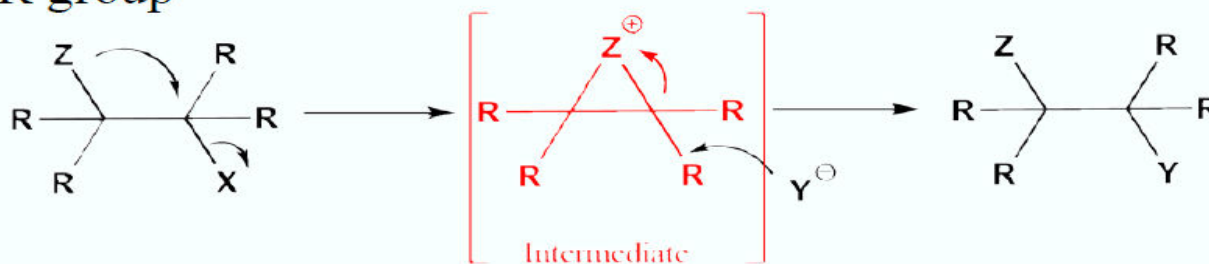
- ❑ Iodine (-I) is a good leaving group because iodide (I^-) is non basic.
- ❑ The hydroxyl group (-OH) is a poor leaving group because hydroxide (OH^-) is a strong base.

S_N2 : Effect of Leaving Group

Neighboring Group Participation (NGP)

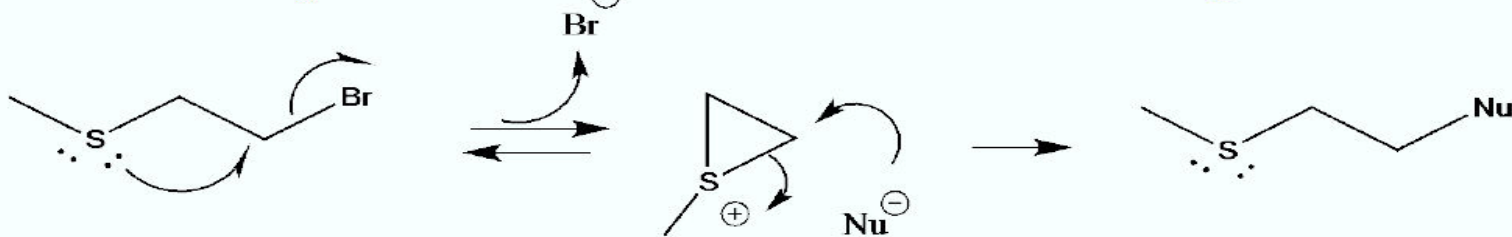
➤ In the presence of an electron donating neighboring group, the reaction proceeds faster than expected. In addition, either inversion nor racemisation is observed in such cases.

➤ In the following generalized representation, a neighboring group participation is illustrated. The lone-pair bearing atom/group such as Z would help in the removal of the leaving group by the mechanism shown below. (please note that the incoming nucleophile "Y" attacks the carbon atom of the three membered ring, not on the R group)



➤ Two consecutive S_N2 substitution, leads to retention of configuration.

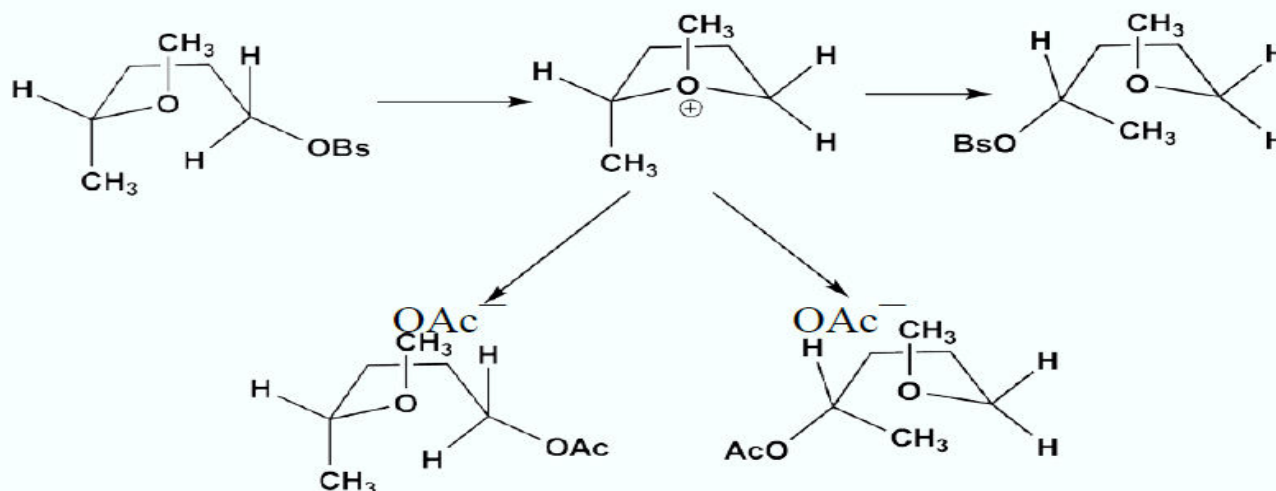
Example 1



S_N2 : Effect of Leaving Group

Neighboring Group Participation

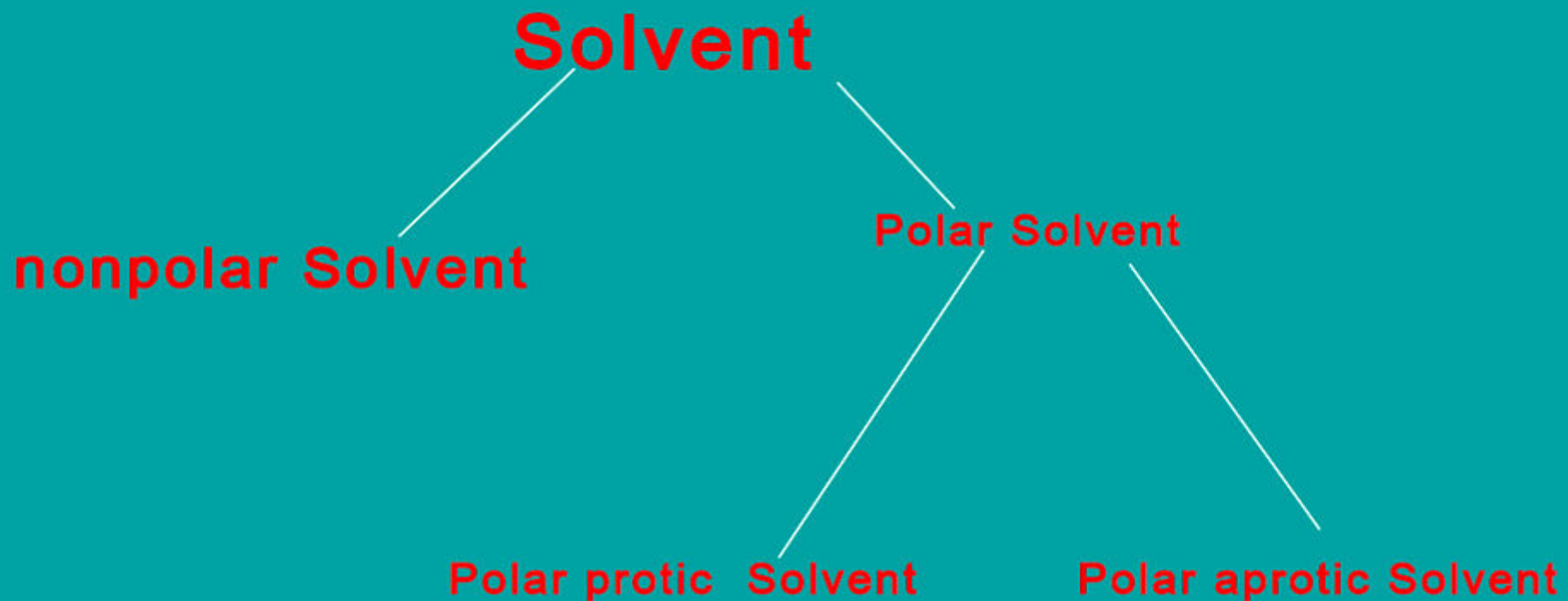
Example 2



- The most likely neighboring group participation leads to three, five, six membered rings
- Four membered ring neighboring group participation is higher in case of alkyl substitution on α or β carbon.
- The effect of halogen increase as going down the group ($I > Br > Cl$).

Some of the neighboring groups are COO^- , $COOR$, $COAr$, $OCOR$, OR , OH , O^- , NH_2 , NHR , $NHCOR$, SH , SR , I , Br , S^-

S_N2 : Effect of Solvent

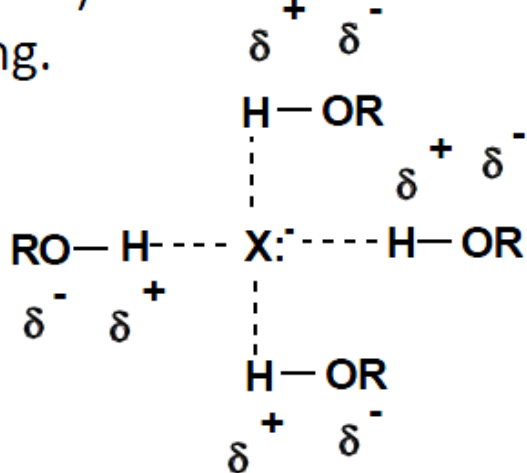


S_N2 reaction prefers polar aprotic solvent

S_N2: Effect of Solvent

- There are 3 classes of organic solvents:
 - ❑ Protic solvents, which contain -OH or -NH₂ groups. Protic solvents slow down S_N2 reactions.
 - ❑ Polar aprotic solvents like acetone, which contain strong dipoles but no -OH or -NH₂ groups. Polar aprotic solvents speed up S_N2 reactions.
 - ❑ Non polar solvents, e.g., hydrocarbons. S_N2 reactions are relatively slow in non polar solvents.

Protic solvents (e.g., H₂O, MeOH, EtOH, CH₃COOH, etc.) cluster around the Nu:- (solvate it) and lower its energy (stabilize it) and reduce its reactivity via H-bonding.

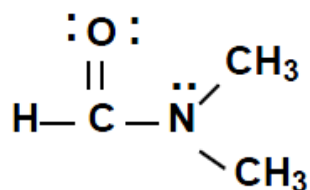


A solvated anion (Nu:-) has reduced nucleophilicity, reduced reactivity and increased stability

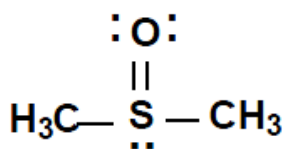
A solvated nucleophile has difficulty hitting the α -carbon.

S_N2: Effect of Solvent

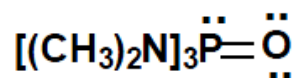
- ❑ Polar Aprotic Solvents solvate the cation counterion of the nucleophile but not the nucleophile.
- ❑ Examples include acetonitrile (CH₃CN), acetone (CH₃COCH₃), dimethylformamide (DMF) [(CH₃)₂NC=O], dimethyl sulfoxide, DMSO [(CH₃)₂SO], hexamethylphosphoramide, HMPA {[(CH₃)₂N]₃PO} and dimethylacetamide (DMA).



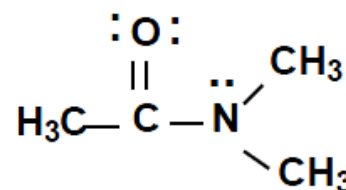
DMF



DMSO

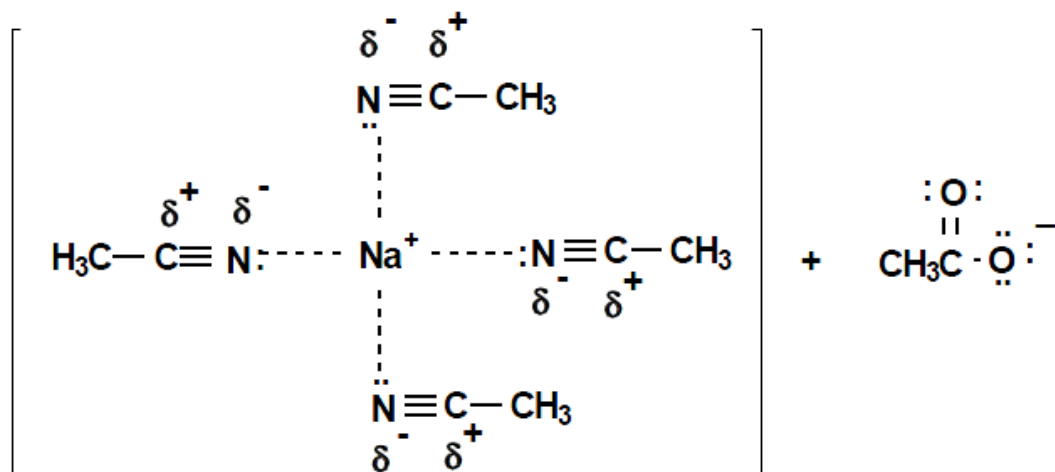
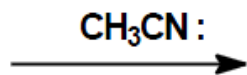
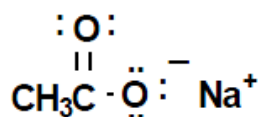


HMPA



DMA

Polar aprotic solvents solvate metal cations leaving the anion counterion (Nu: ⁻) bare and thus more reactive

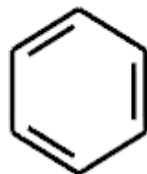


S_N2 : Effect of Solvent

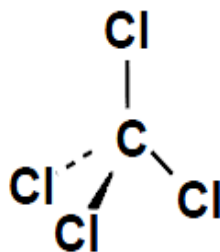
Effect of the solvent on rate of S_N2 reactions:

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

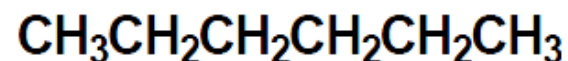
- S_N2 reactions are relatively slow in non polar solvents similar to that in protic solvents.



benzene



carbon
tetrachloride

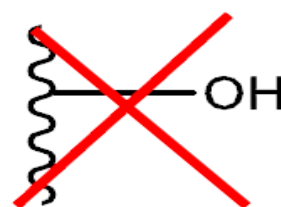


n-hexane

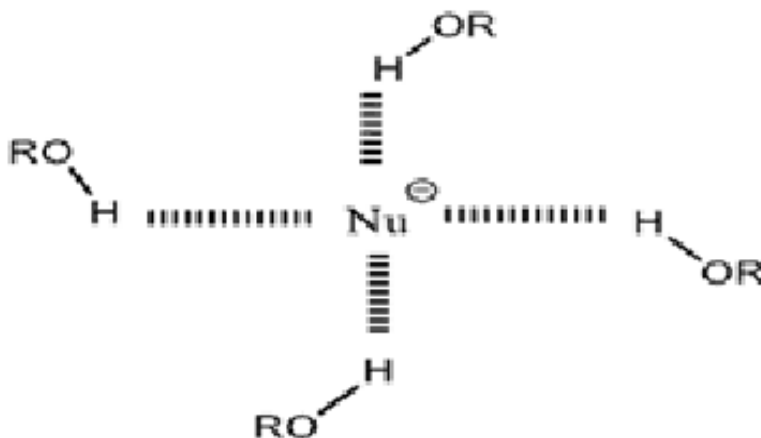
S_N2 : Effect of Solvent

- Requires a polar, aprotic solvent...

- NO alcohols or amines



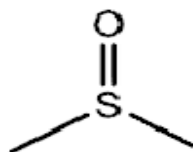
Why...because hydrogen bonding with the nucleophile can occur...slowing down the reaction



S_N2 : Effect of Solvent

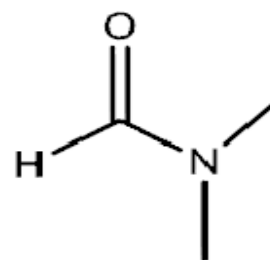
Polar, Aprotic Solvents

DMSO

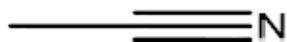


dimethyl sulfoxide

DMF

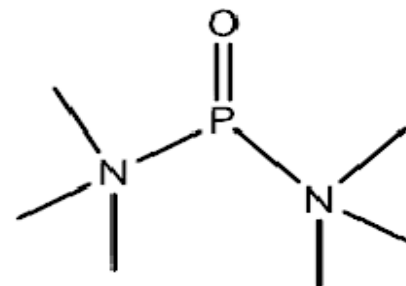


dimethyl formamide



acetonitrile

HMPA



hexamethyl phosphamide

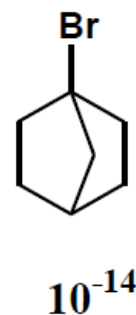
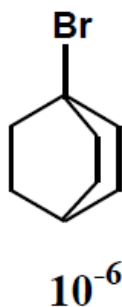
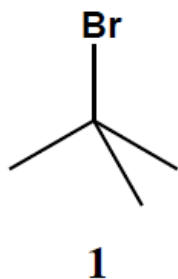
Problems :

1) S_N2 reaction by EtO⁻ in EtOH:

	CH ₃ CH ₂ -Br	CH ₃ CH ₂ CH ₂ -Br	Me ₂ HCCH ₂ -Br	Me ₃ CCH ₂ -Br	
relative rate	1	2.8X10 ⁻¹	3.0X10 ⁻²	24.2X10 ⁻⁶	Explain ?

2) Rate of solvolysis in EtOH :

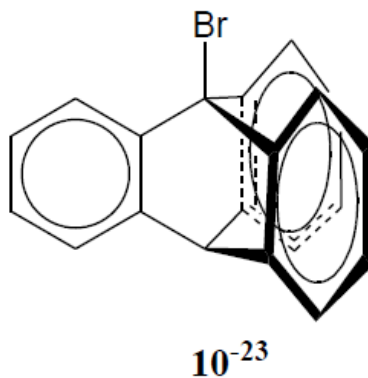
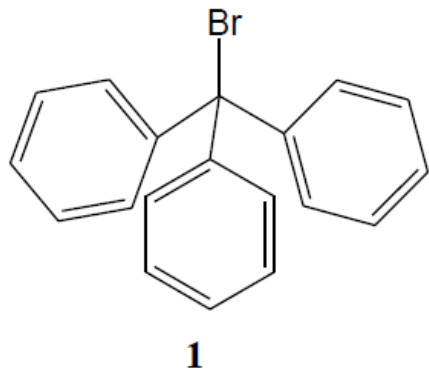
A)



Explain?

cc at bridge head, less stable, difficult to attain planarity due to rigidity


B)



Explain ?

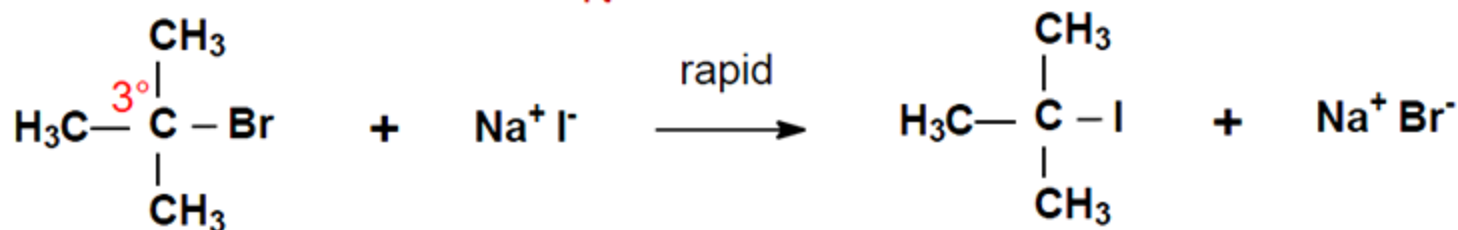
Rigid structure, cation empty p-orbitals are at right angles to π orbitals of Ph

1-bromotryptycene




SN1

1st Order Nucleophilic Substitution Reactions, i.e., S_N1 reactions



- ❑ 3° alkyl halides are essentially inert to substitution by the S_N2 mechanism because of steric hindrance at the back side of the α -carbon.
- ❑ Despite this, 3° alkyl halides do undergo nucleophilic substitution reactions quite rapidly, but by a different mechanism, i.e., the S_N1 mechanism.
- ❑ S_N1 = Substitution, Nucleophilic, 1st order (unimolecular).
- ❑ S_N1 reactions obey 1st order kinetics, i.e., $\text{Rate} = k \cdot [\text{RX}]$.
- ❑ The rate depends upon the concentration of only 1 reactant, the alkyl halide—not the nucleophile
- ❑ The order of reactivity of substrates for S_N1 reactions is the reverse of S_N2
 - $3^\circ > 2^\circ > 1^\circ > \text{vinyl} > \text{phenyl} > \text{Me}^\circ$
 - $\text{R}_3\text{C-Br} \quad \text{R}_2\text{HC-Br} \quad \text{RH}_2\text{C-Br} \quad \quad \text{CH}_2=\text{CH-Br} \quad \phi\text{-Br} \quad \text{H}_3\text{C-Br}$

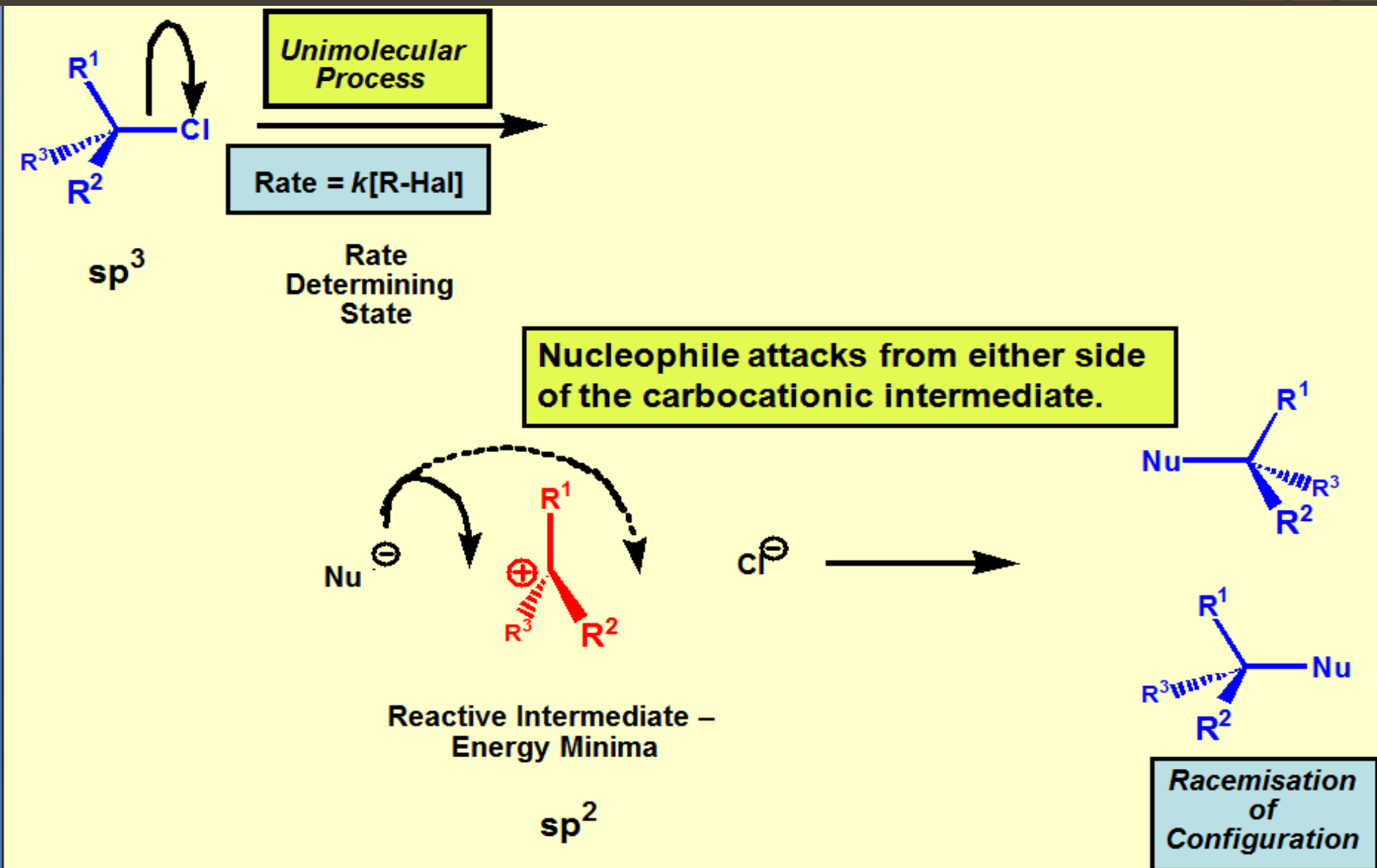


 increasing rate of S_N1 reactions

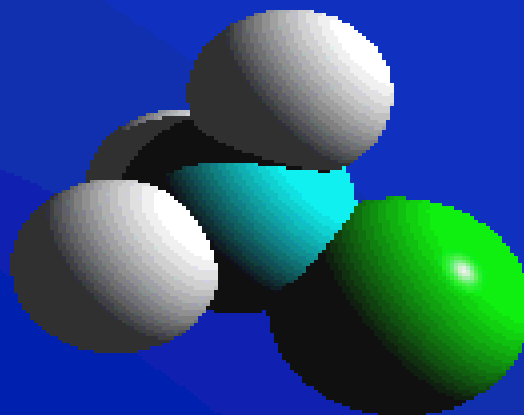
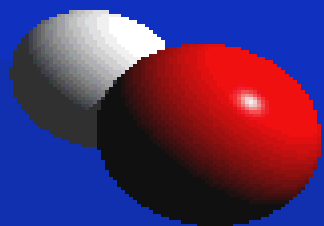
S_N1 Reaction: Kinetics

- The reactions follows first order (unimolecular) kinetics
- $\text{Rate} = k [\text{R-Br}]^1$

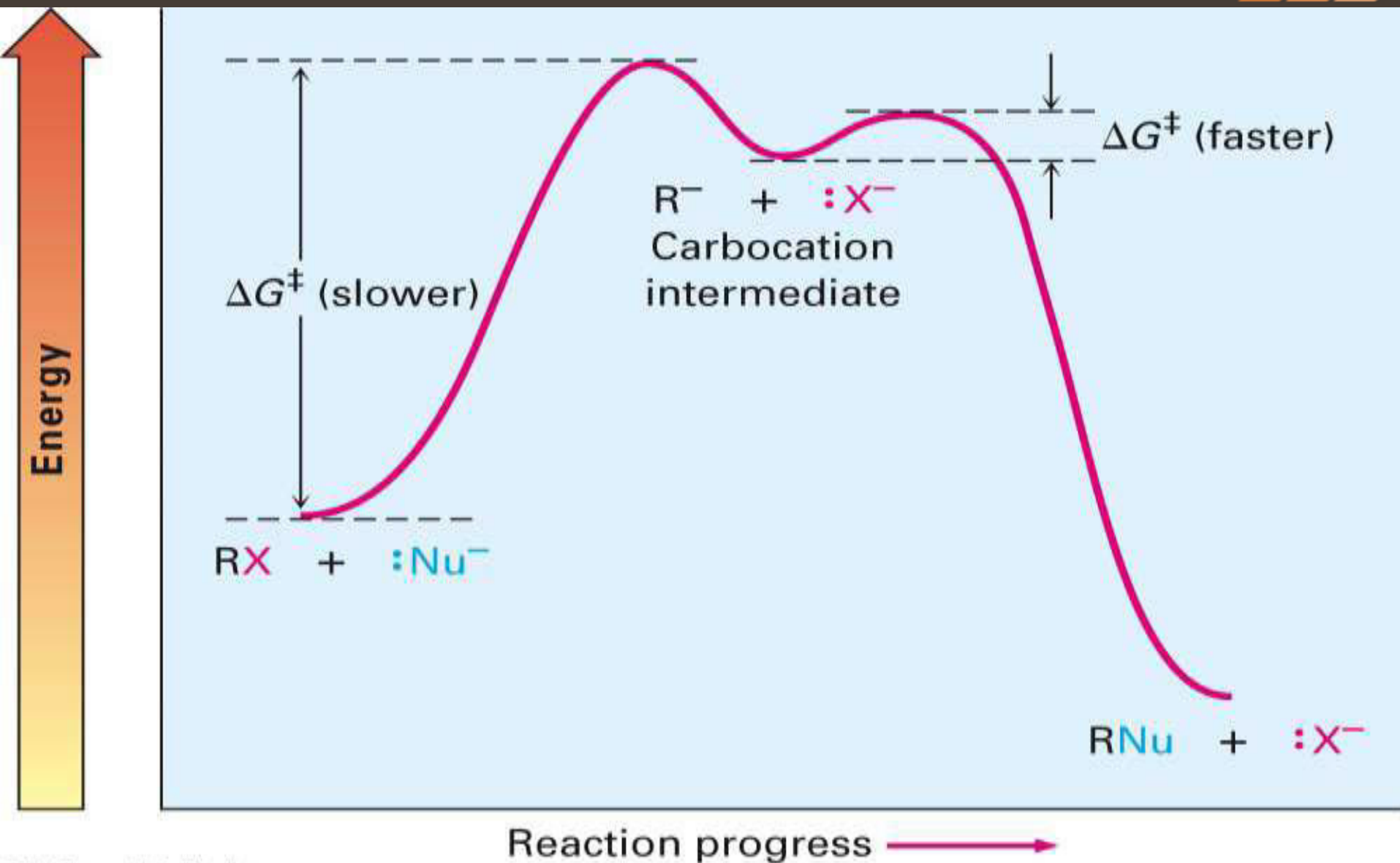
The S_N1 Reaction Mechanism



The S_N1 Reaction Mechanism



The S_N1 Reaction Mechanism



Transition States: Video Clip

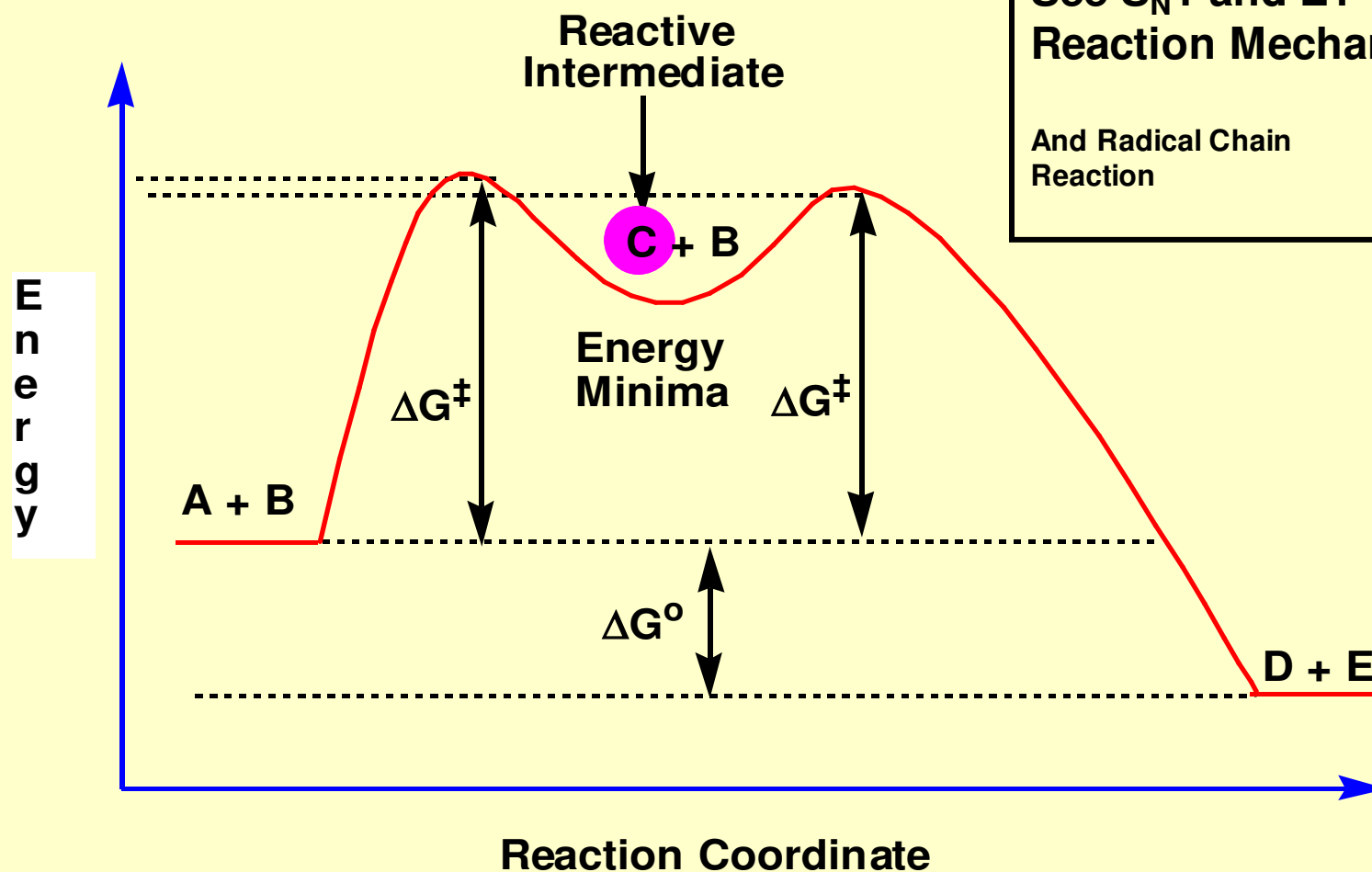


Reactive Intermediates

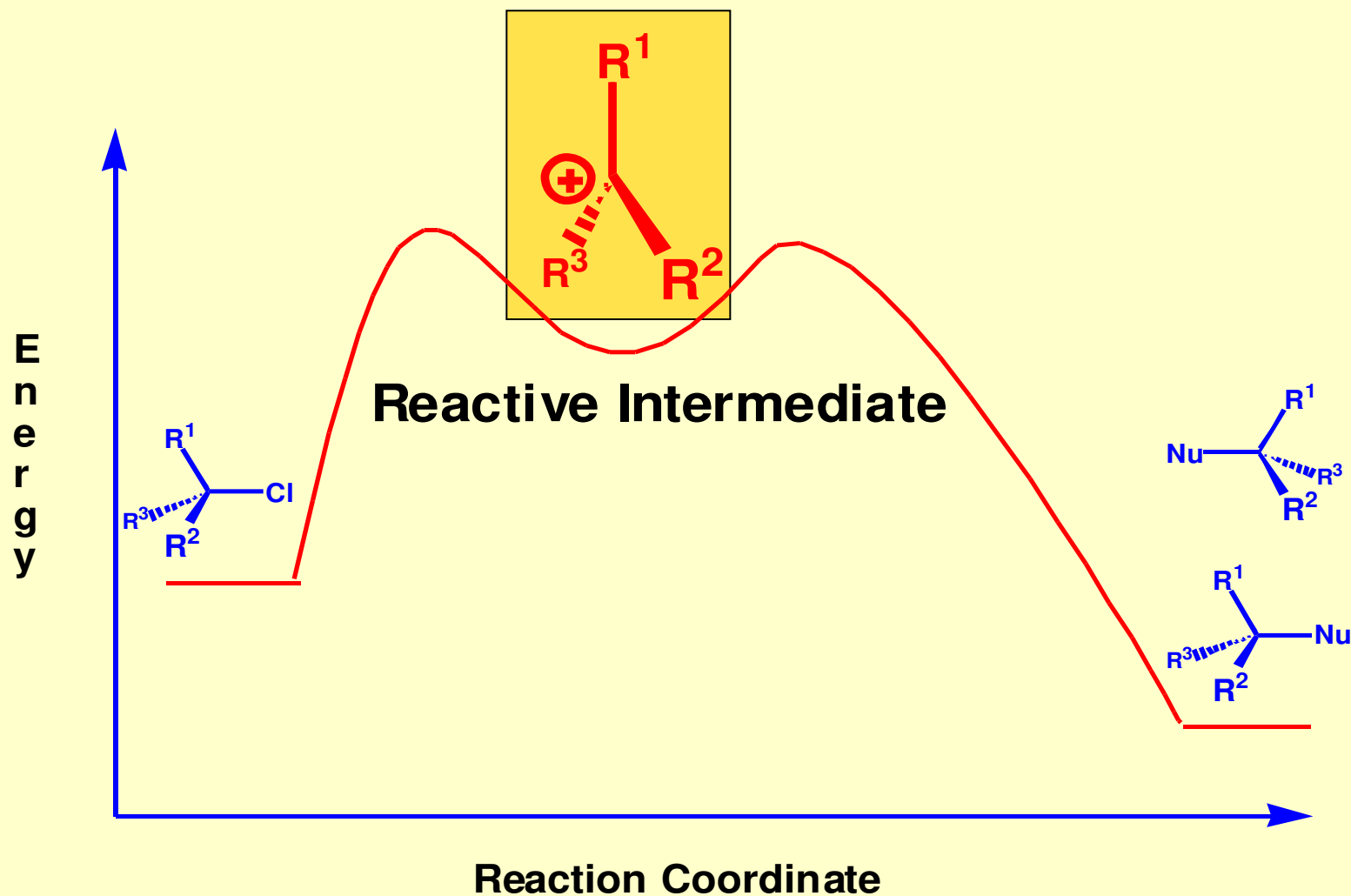
$$\text{Rate} = k[\text{A}]$$

See $\text{S}_{\text{N}}1$ and $\text{E}1$
Reaction Mechanisms

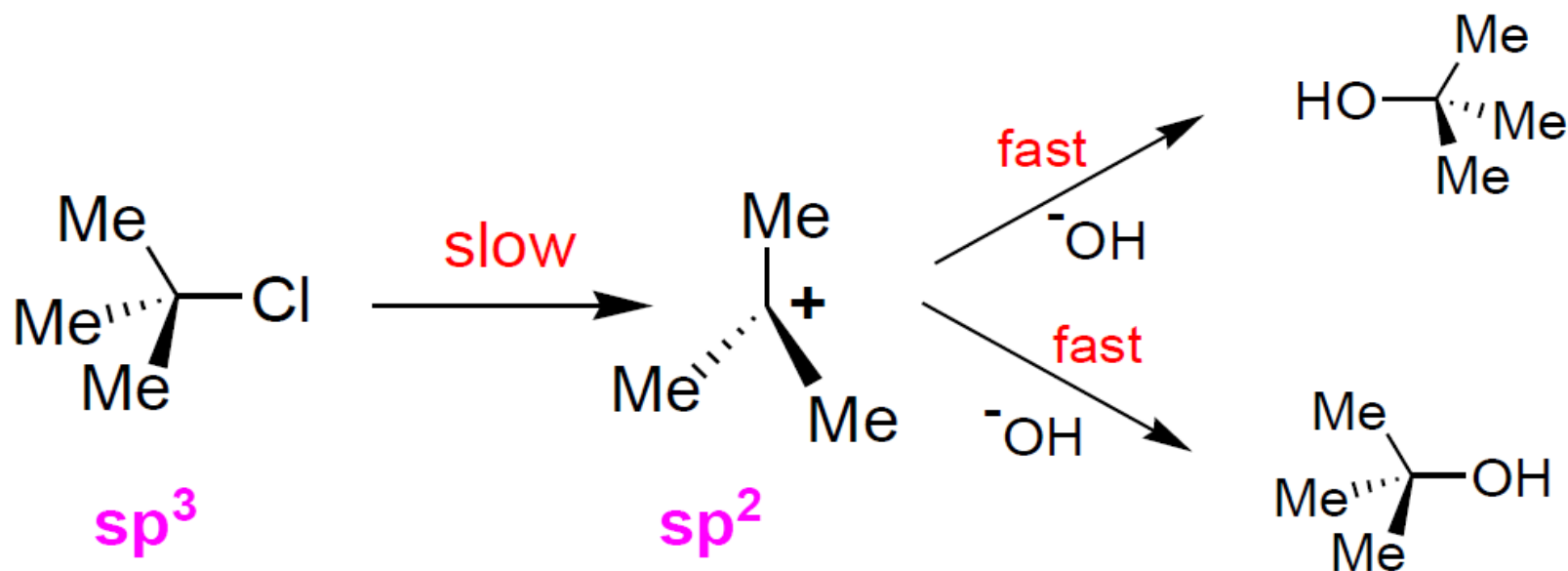
And Radical Chain
Reaction



Reactive Intermediates



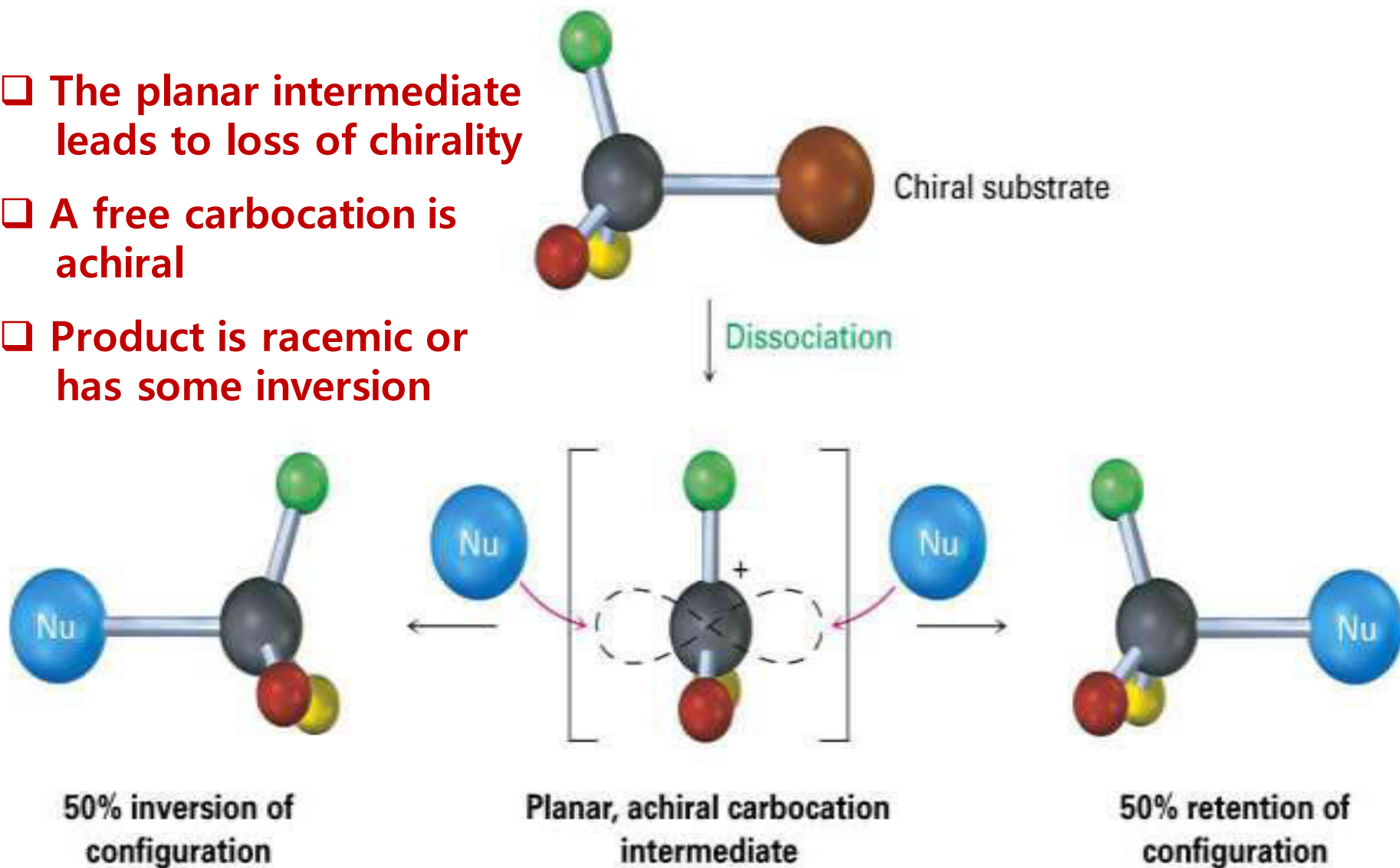
Stereochemistry of S_N1



1. Halide undergoes slow ionization to yield the ion pair R⁺ and Cl⁻ followed by first attack by ⁻OH or solvent or nucleophile.
2. The energy necessary to effect the initial ionization is largely recovered from the energy evolved through solvation of the resultant ion-pair.

Stereochemistry of S_N1

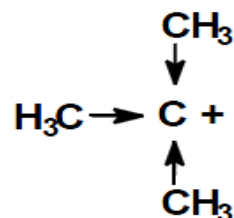
- ❑ The planar intermediate leads to loss of chirality
- ❑ A free carbocation is achiral
- ❑ Product is racemic or has some inversion



S_N1 : Effect of Nature of Substrate

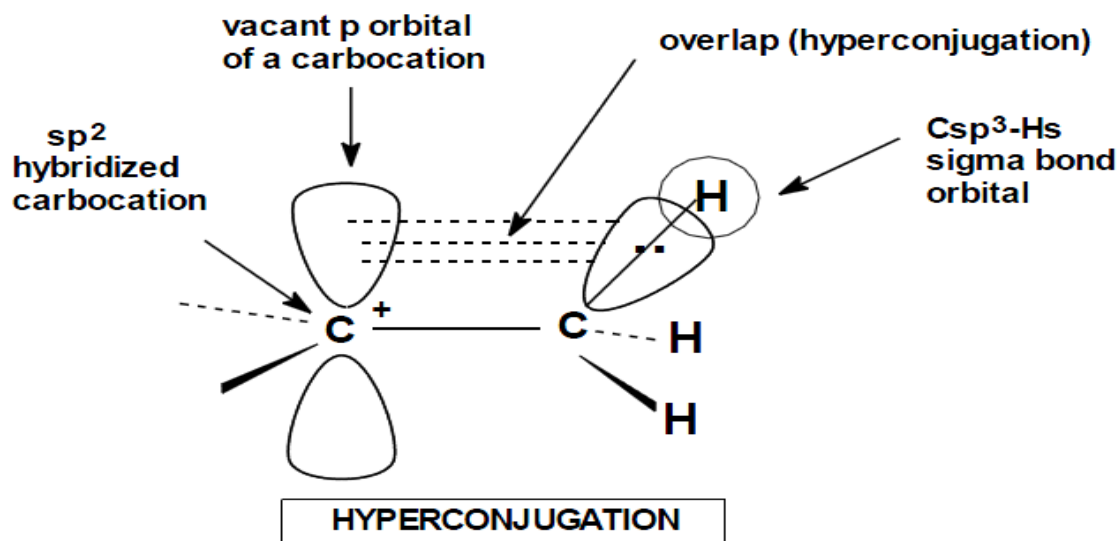
Stability of Carbocations

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



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

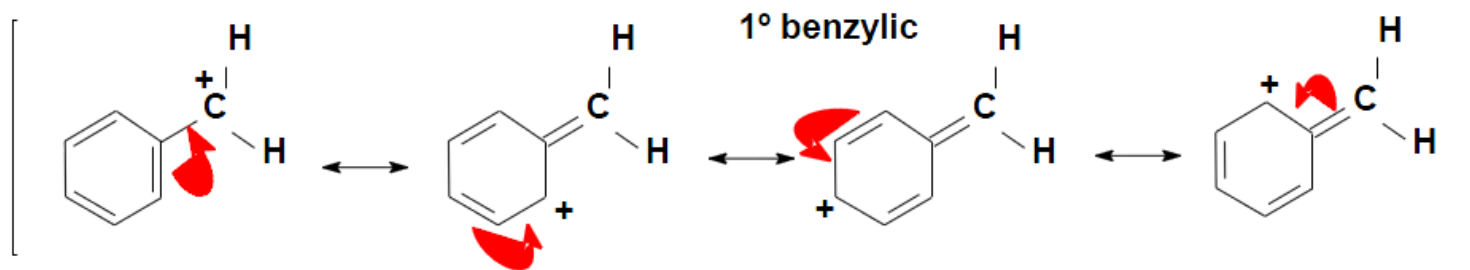
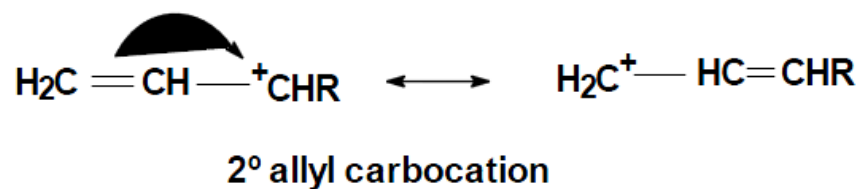
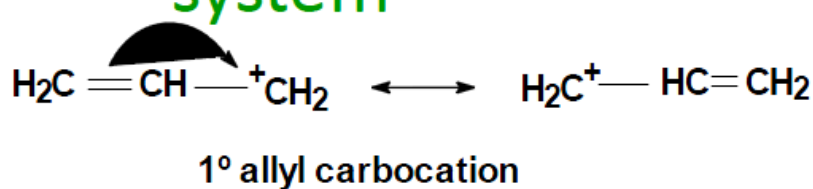
- They stabilize carbocations by hyperconjugation (by partial overlap of the alkyl C-to-H bonds with the empty p-orbital of the carbocation).



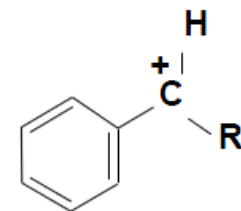
S_N1 : Effect of Nature of Substrate

Stability of Carbocations

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

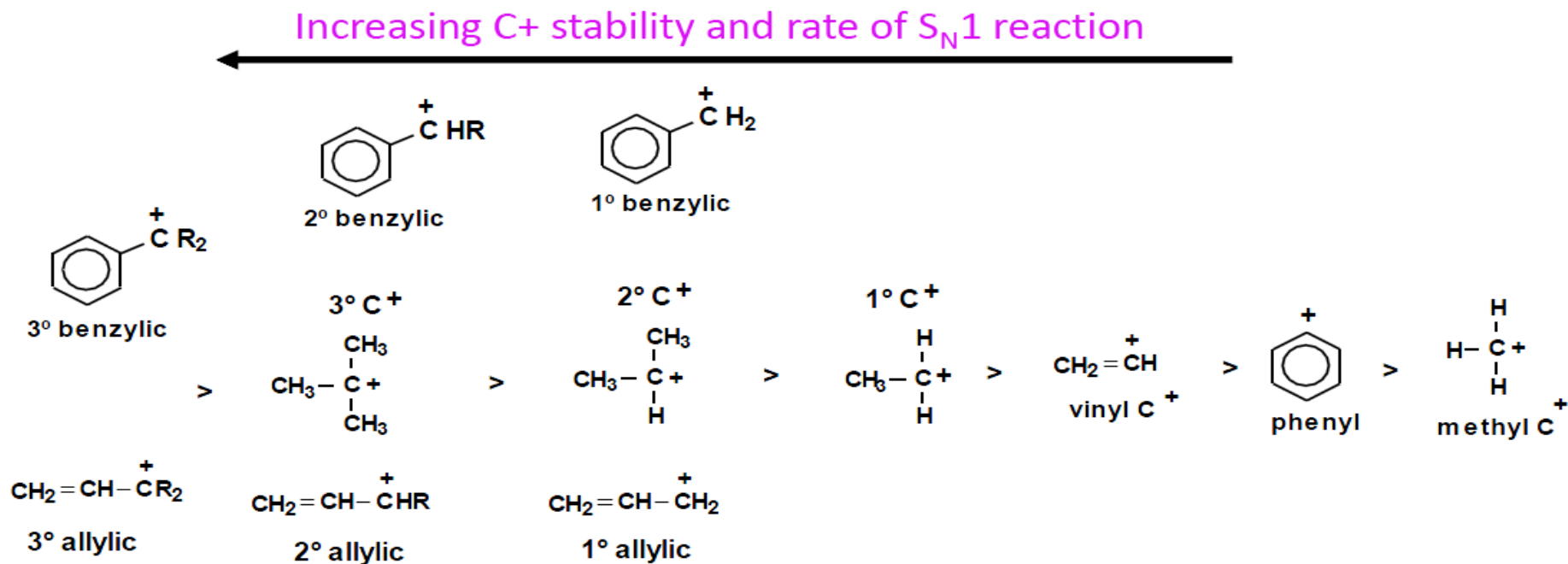


2° benzylic



S_N1 : Effect of Nature of Substrate

Relative Stability of All Types of Carbocations



Note that 1° allylic and 1° benzylic C^+ 's are about as stable as 2° alkyl C^+ 's.

Note that 2° allylic and 2° benzylic C^+ 's are about as stable as 3° alkyl C^+ 's.

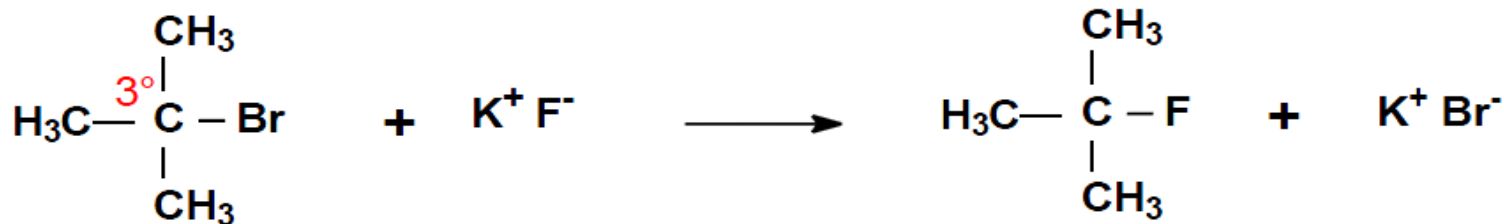
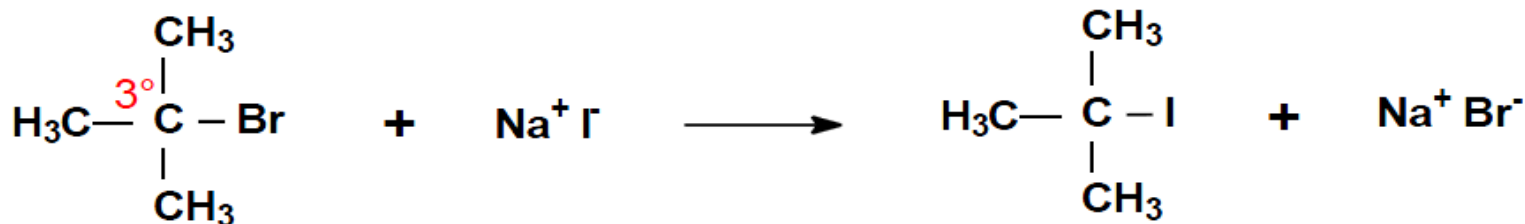
Note that 3° allylic and 3° benzylic C^+ 's are more stable than 3° alkyl C^+ 's.

Note that phenyl and vinyl C^+ 's are unstable. Phenyl and vinyl halides do not usually react by S_N1 or S_N2 reactions.

S_N1 : Effect of Nucleophile

- Consider the nature of the Nucleophile:

- Recall again that the nature of the nucleophile has no effect on the rate of S_N1 reactions because the slowest (rate-determining) step of an S_N1 reaction is the dissociation of the leaving group and formation of the carbocation.
- All carbocations are very good electrophiles (electron acceptors) and even weak nucleophiles, like H_2O and methanol, will react quickly with them.
- The two S_N1 reactions will proceed at essentially the same rate since the only difference is the nucleophile.



S_N1 : Effect of Leaving Group

- Leaving groups are the same as in S_N2 reactions:



Leaving group reactivity



S_N1 : Effect of Leaving Group

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

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

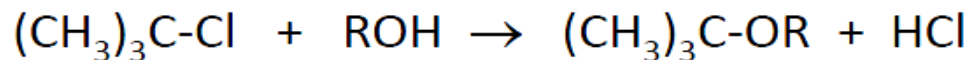
← Increasing leaving ability

- 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.

S_N1 : Effect of Solvent

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

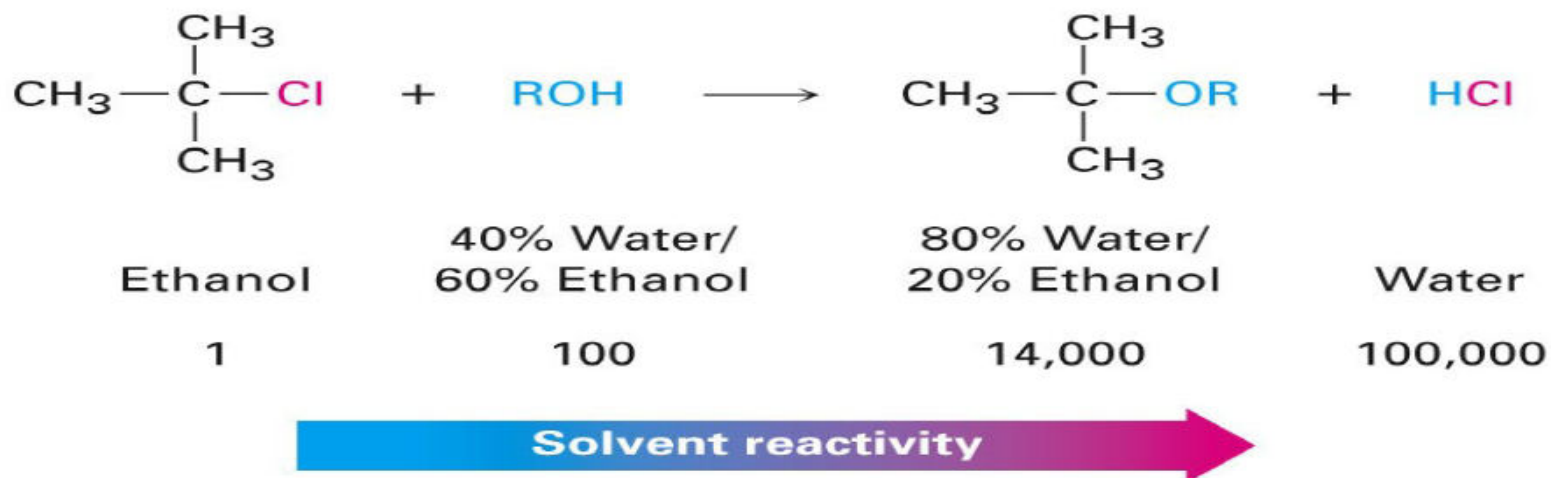
The relative rates of an S_N1 reaction due to solvent effects are given



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

reaction rate increases with polarity of solvent

S_N1 : Effect of Solvent



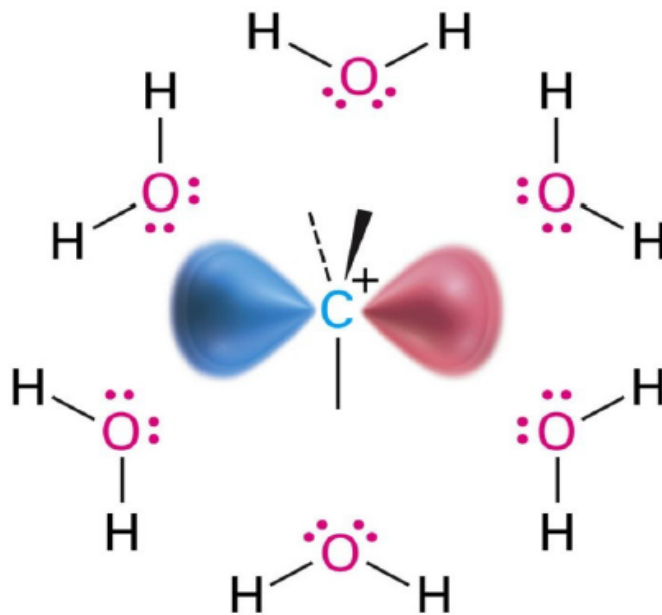
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Increase in dielectric constant and/or ion-solvating ability result in a marked **increase** in reaction rate

Dielectric constant (ϵ , at 25 C): H_2O **79**
EtOH **25**

S_N1 : Effect of Solvent

- Polar protic solvents favoring the S_N1 reaction since it stabilizes carbocation of the transition state
- Protic solvents disfavor the S_N2 reaction by stabilizing the ground state



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Transfer from polar, protic to polar, aprotic solvents can change the reaction mode from $S_N1 \rightarrow S_N2$

S_N1 : Effect of Solvent

Effect of the solvent on rate of S_N1 reactions:

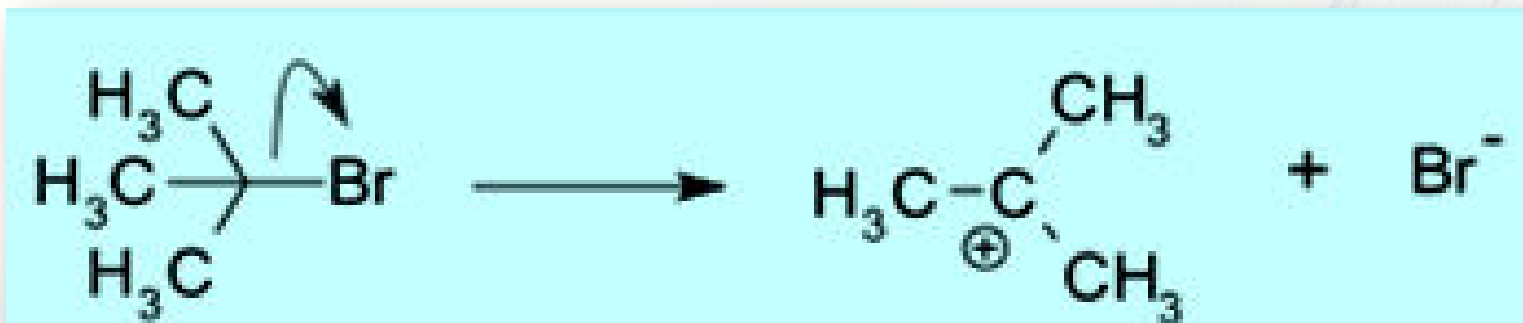
- ❑ Solvent polarity is usually expressed by the “dielectric constant”, ϵ , which is a measure of the ability of a solvent to act as an electric insulator.
- ❑ Polar solvents are good electric insulators because their dipoles surround and associate with charged species.
- ❑ Dielectric constants of some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

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

Examples of S_N1 reactions

- Hydrolysis of tert-butyl bromide with water forming tert-butyl alcohol:

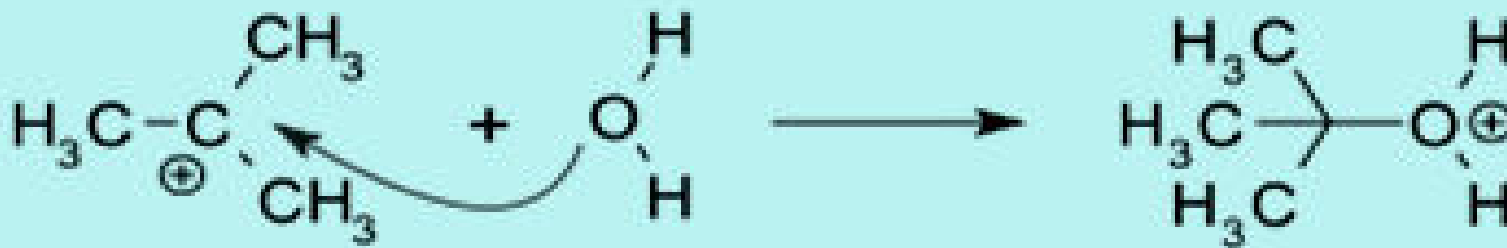
- Tert-butyl carbocation is formed by separating a leaving group (a bromide anion) from the carbon atom. This step is slow and reversible.



Examples of S_N1 reactions (contd.)

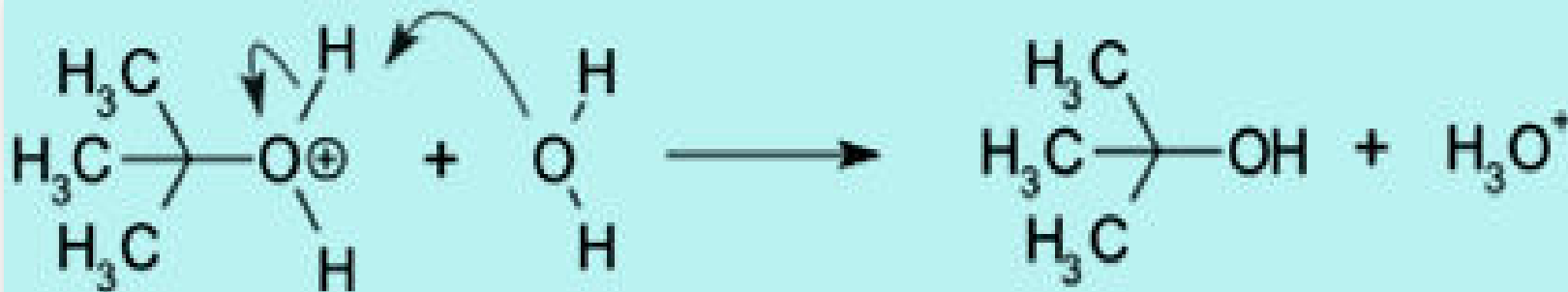
2. Nucleophilic attack: the carbocation reacts with the nucleophile.

A third step is required to complete the reaction if the nucleophile is a neutral molecule (a solvent). If the solvent is water, the intermediate is an oxonium ion. This is a fast step in the reaction.



Examples of S_N1 reactions(contd.)

3. Deprotonation: Water which acts as a base removes a proton on the protonated nucleophile to form alcohol and a hydronium ion. This is a fast step as well.





Things to remember

S_N2 vs S_N1 :



S_N2 reaction mechanism

One step mechanism

Bimolecular reaction

Product formation takes place by **TS**

No carbocation rearrangement

Reaction is favoured by **polar aprotic solvents**

Given mainly by **methyl halides**

Reactivity of RX; $CH_3X > 1^\circ > 2^\circ > 3^\circ$

Mechanism is favoured when **nucleophile is an anion**

Reaction velocity depends on the concentration of **nucleophile**. *i.e.*, mechanism is favored by high concentration of nucleophile

Inversion of configuration

S_N1 reaction mechanism

Two step mechanism

Unimolecular reaction

Product formation takes place by **carbocation intermediate**

Carbocation rearrangement

Reaction is favoured by **polar protic solvents**

Given mainly by **tertiary alkyl halides**

Reactivity of RX; $3^\circ > 2^\circ > 1^\circ > \text{methyl}$

Mechanism is favoured when **nucleophile is neutral**

Reaction velocity is independent of the concentration of **nucleophile**.

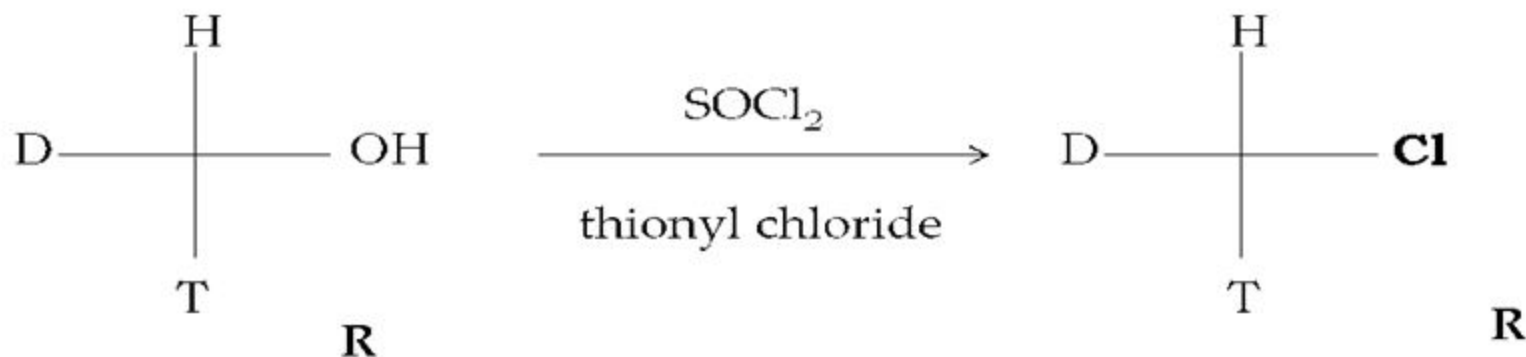
Racemisation



Sni

Nucleophilic Substitution S_Ni

This kind of reaction is seen only in one situation.



So, in S_Ni reactions, we have **retention of configuration**.

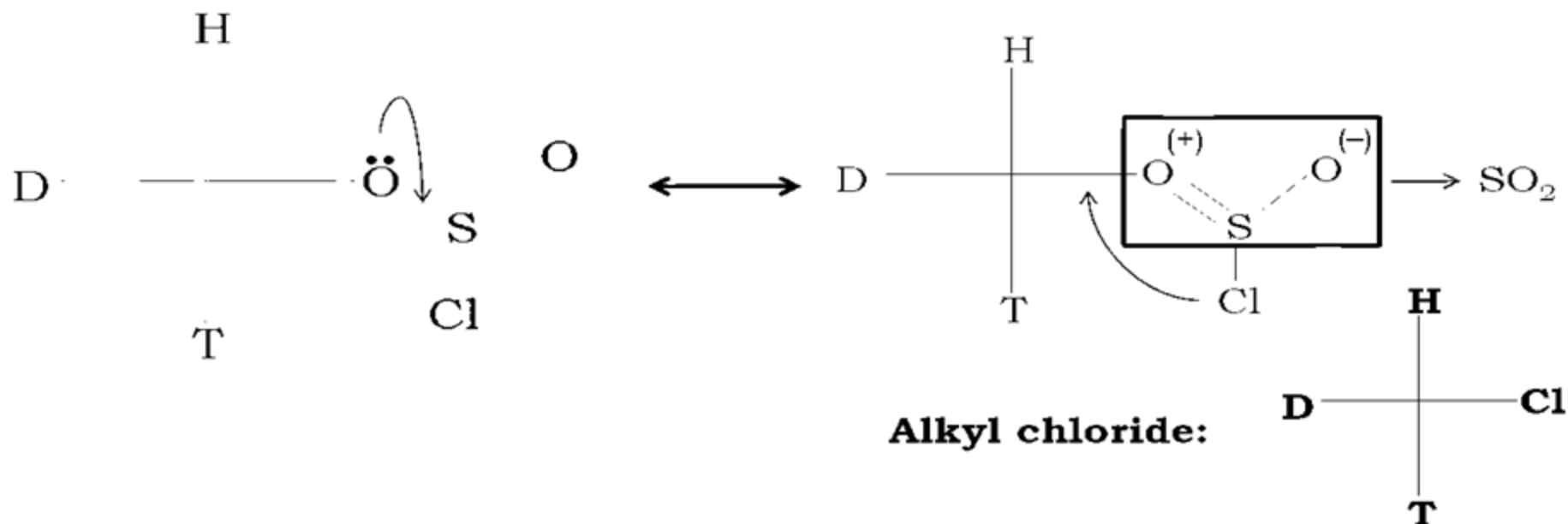
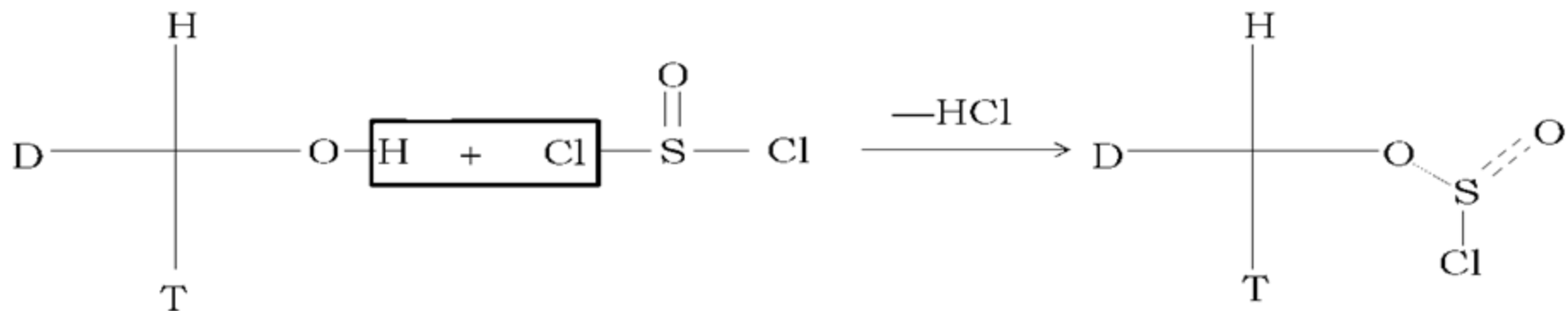
But this is different from S_N¹ reactions as there is no formation of a racemic mixture over here.

This is also different from S_N² reactions as in S_N², there is inversion of configuration, whereas over here, the stereochemistry of the reactant and the product is nearly the same.

Hence this reaction can be explained **neither by S_N¹ nor by S_N²**.

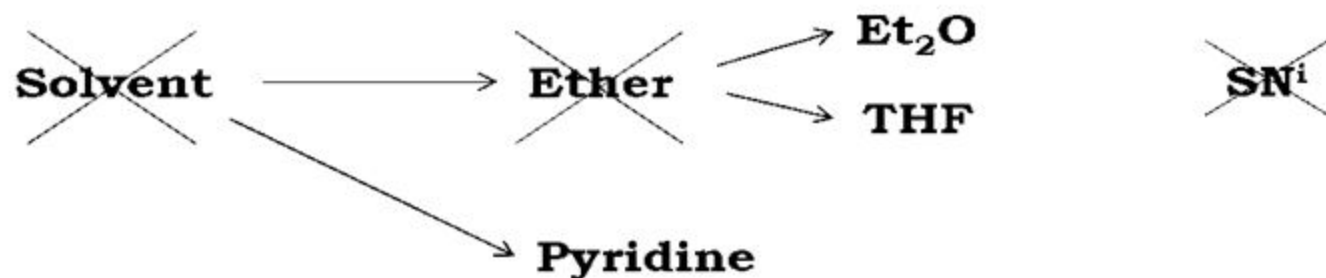
Nucleophilic Substitution Internal

Nucleophilic Substitution S_Ni

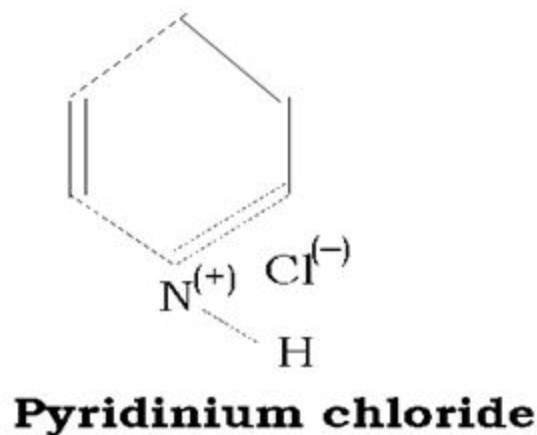


Nucleophilic Substitution S_Ni

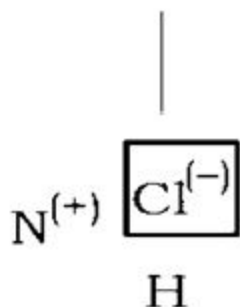
We conclude that in S_Ni reactions, we get a **retention of configuration**.



The principle mechanism of S_Ni reactions is based on the assumption that addition of pyridine to the reaction leads to **inversion of configuration**.

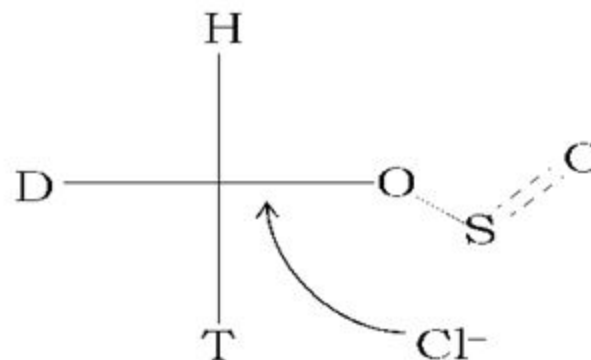


Nucleophilic Substitution S_N1



Pyridinium chloride

- Cl^- ion is **loosely bonded** and **free**



- Hence there is backward attack which results in **inversion** of configuration.

Hence if the solvent added in the medium of this reaction is pyridine, then the reaction will **no longer remain S_N1** as the mechanism will change to that of **S_N2** .

Nucleophilic Substitution S_Ni

Hence we can draw **four** important inferences:

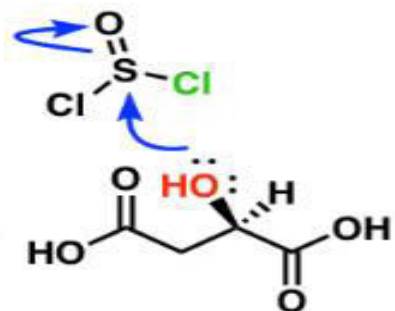
1. In ether medium, the reaction follows the rules of **SNⁱ** mechanism.
2. If pyridine is added as the medium solvent to this reaction, it will form a strong **nucleophile** in Pyridinium chloride, which will cause a **backward** attack on the system, eliminating Sulphur dioxide from it.
3. This type of reaction will be termed as SN² because there is **inversion** of configuration. In case of pyridine, the nature of the reaction changes from **SNⁱ** to **SN²**.
4. In case of SNⁱ reactions, the rate of the reaction is dependent on the concentration of both the alcohol and the thionyl chloride, i.e.,

$$\text{Rate } r \propto [\text{R} - \text{OH}] [\text{SOCl}_2],$$

as opposed to the case of SN¹ and SN² reactions.

S_Ni Reaction

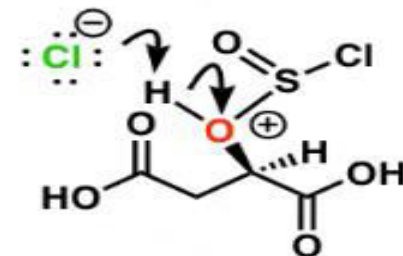
Why does SOCl₂ give retention ?



Attack of OH upon SOCl₂

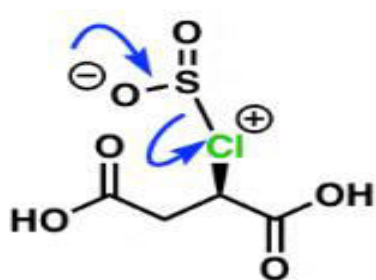


Expulsion of Cl⁻ to form protonated chlorosulfite

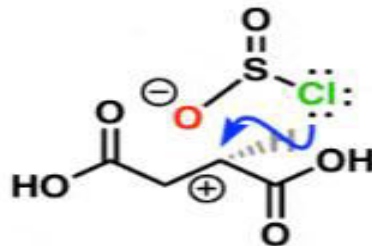


Neutralization to give chlorosulfite

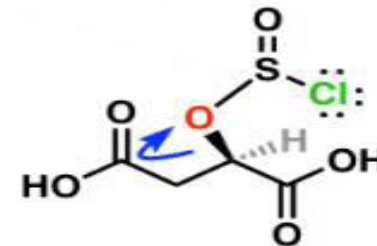
The alcohol attacks SOCl₂ and after expulsion of Cl⁻ and deprotonation of O, a "chlorosulfite" is formed. The C-O bond breaks with expulsion of Cl⁻, forming CO₂ and an "intimate" ion pair. Chloride then attacks the carbocation from the same face, resulting in "retention" of stereochemistry



Loss of SO₂



Chloride attacks carbocation on same face of "intimate" ion pair



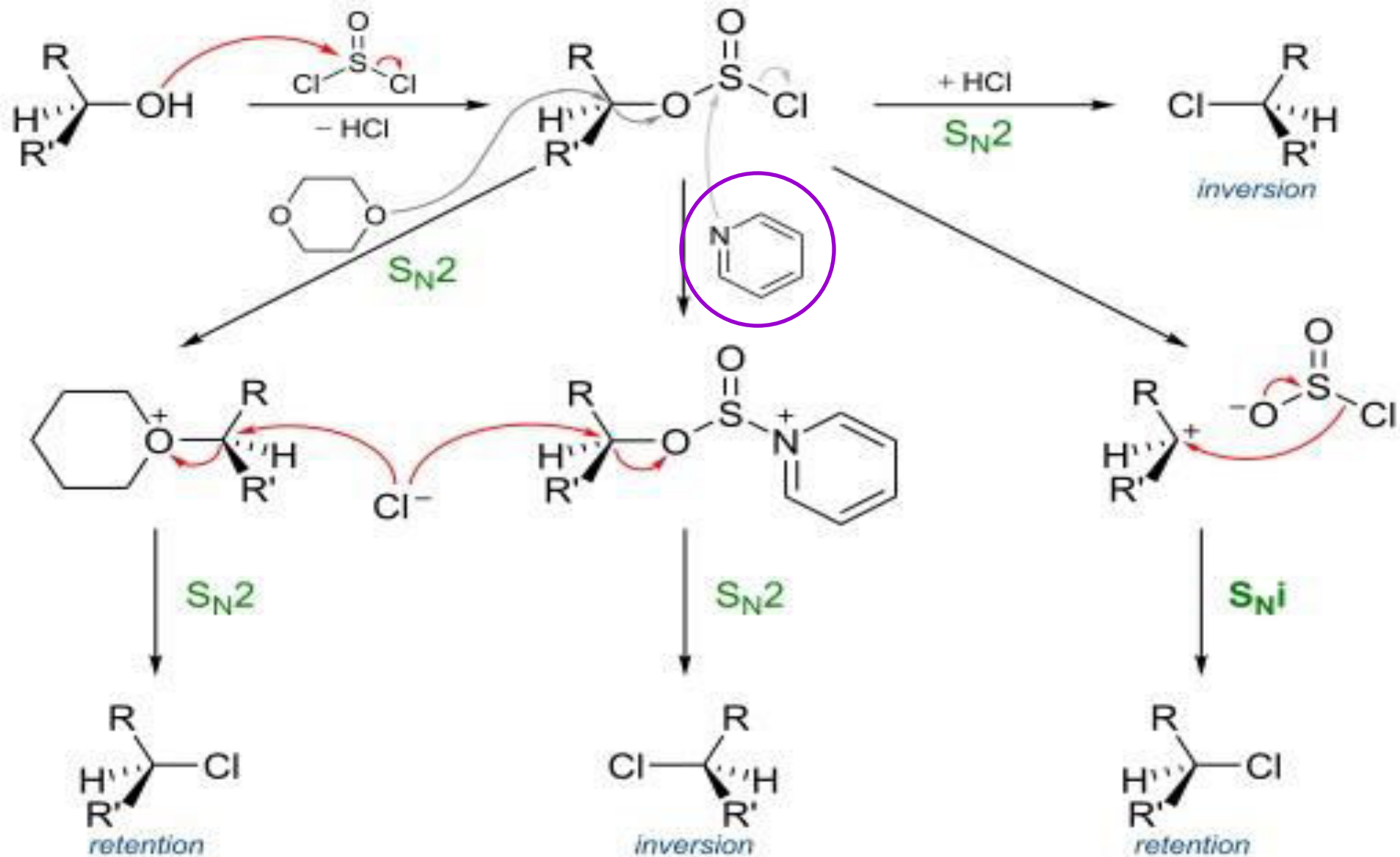
chlorosulfite

Departure of leaving group to form "intimate ion pair"

S_Ni Reaction

The most interesting thing to note is that when a chiral alcohol is reacted with $SOCl_2$, chlorination happens with *retention* of configuration, when no other solvent like pyridine is present. But when external agents are added (nucleophilic solvent like pyridine or NaCl) there is an inversion.

S_Ni Reaction





Exercise

Exercise 1: Substitution Reactions

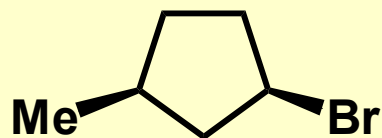
cis-1-Bromo, 3-methylcyclopentane reacts with NaSMe (MeS⁻ is an excellent nucleophile) to afford a product with molecular formulae C₇H₁₄S. The rate of the reaction was found to be dependent on both the bromoalkane and the NaSMe.

- (i) Identify the product(s), and
- (ii) propose an arrow pushing mechanism to account for the product formation.

Answer 1: Substitution Reactions

cis-1-Bromo, 3-methylcyclopentane reacts with NaSMe (MeS⁻ is an excellent nucleophile) to afford a product with molecular formulae C₇H₁₄S. The rate of the reaction was found to be dependent on both the bromoalkane and the NaSMe.

- (i) Identify the product(s), and
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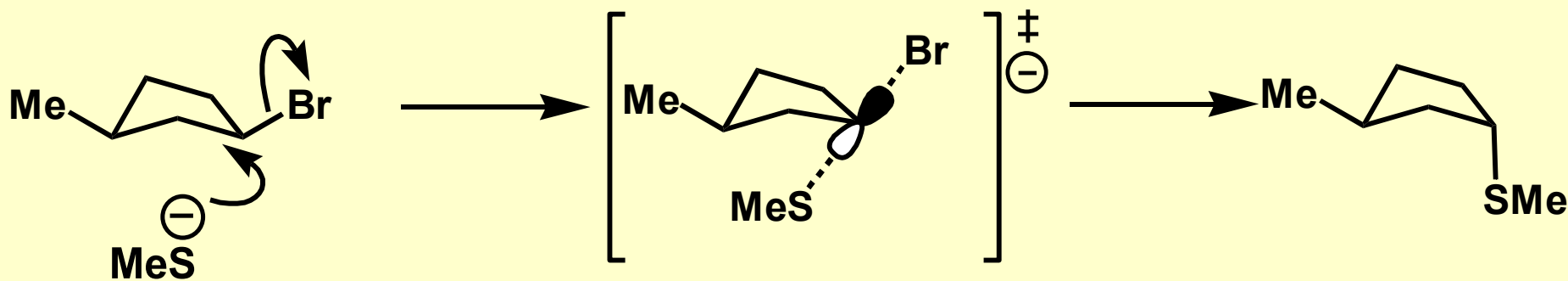


Starting material molecular formula = C₆H₁₁Br

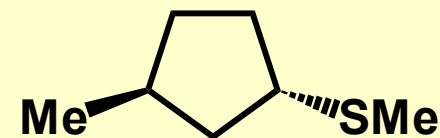
Product molecular formula = C₇H₁₄S

Lost Br, Gained SMe, Substitution Reaction

Rate equation indicates bimolecular process, S_N2



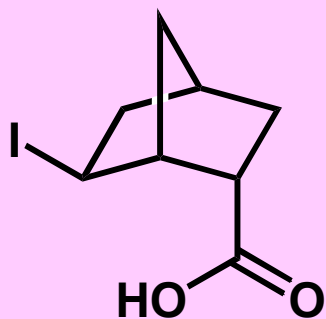
Envelope Conformation
of Cyclopentane



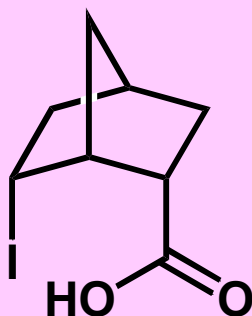
Exercise 2: Substitution Reactions

Compounds A and B when treated with a weak base are deprotonated to form the carboxylate anion. One of these carboxylate anions then reacts further to afford the lactone P, whilst the other carboxylate anion does not lead to P.

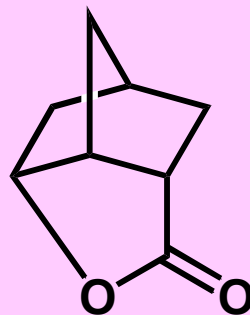
Identify the carboxylate anion which affords P, and rationalise its formation with an arrow pushing mechanism, as well as rationalising why the other carboxylate anion does not afford P.



A



B

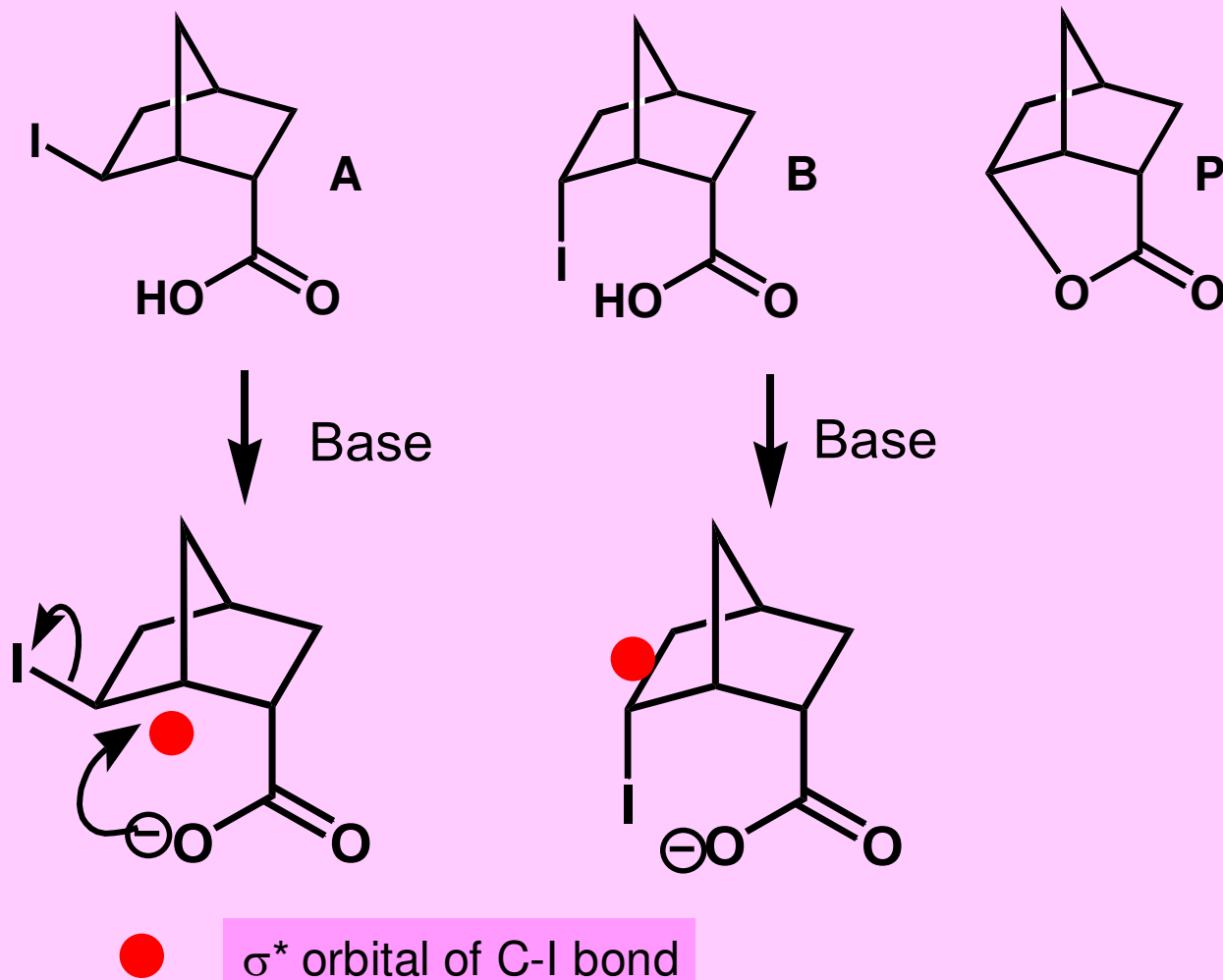


P

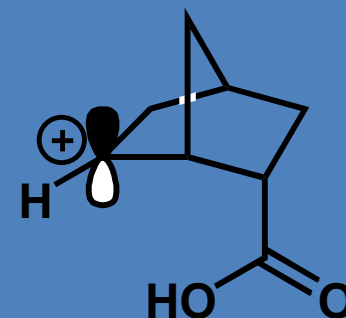
Answer 2: Substitution Reactions

Compounds A and B when treated with a weak base are deprotonated to form the carboxylate anion. One of these carboxylate anions then reacts further to afford the lactone P, whilst the other carboxylate anion is unaffected.

Identify the carboxylate anion which affords P, and rationalise its formation with an arrow pushing mechanism, as well as rationalising why the other carboxylate anion does not afford P.



Reaction must be S_N2 type, because if it was S_N1 like the carbocation below would be generated from both S1 and S2. Therefore both S1 and S2 would afford P



Thank you for your attention

