



NUCLEOPHILIC SUBSTITUTION

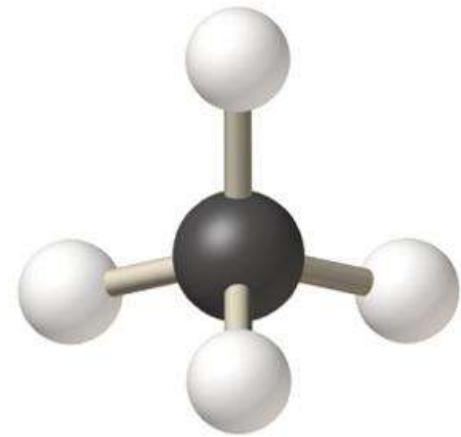
S_N1 and S_N2



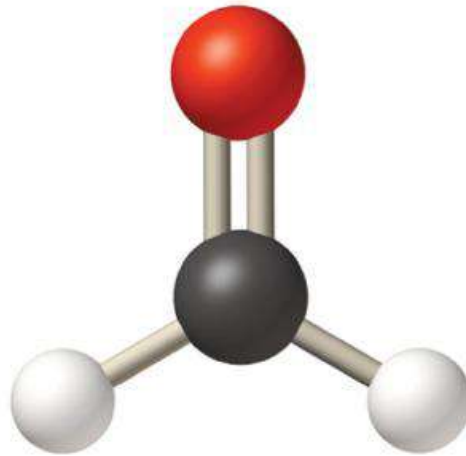
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Examples of Single and Multiple Bonds



Methane
(4 σ bonds)

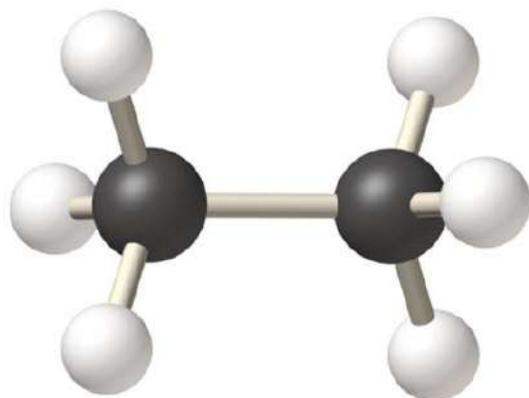
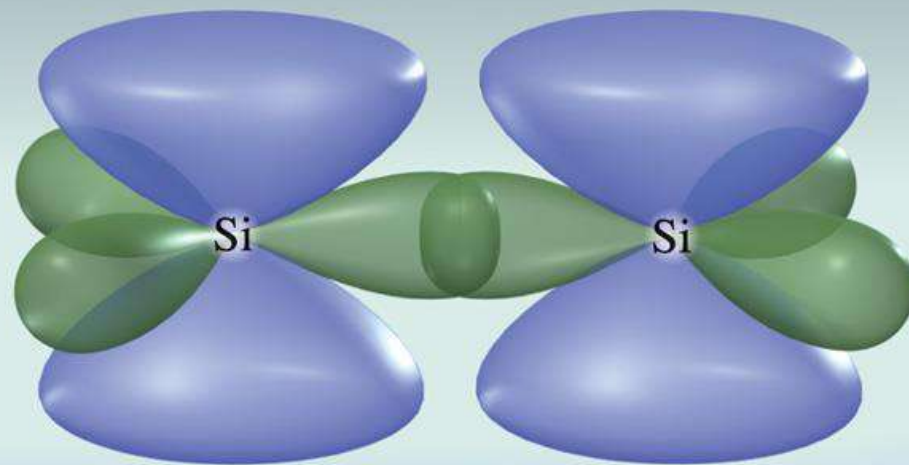
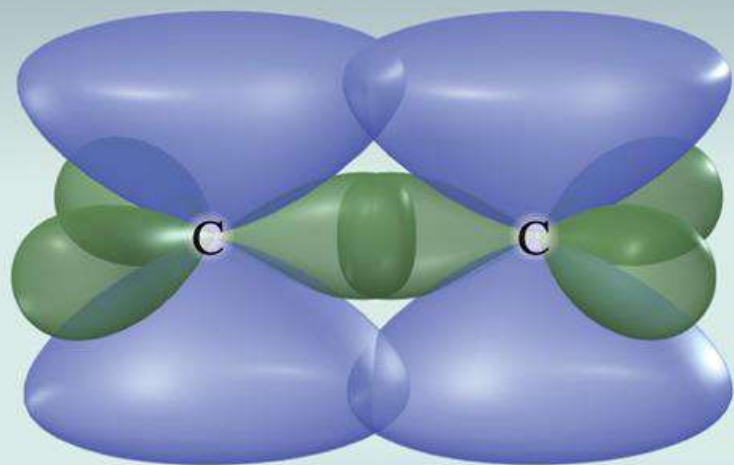


Formaldehyde
(3 σ bonds & 1 π bond)

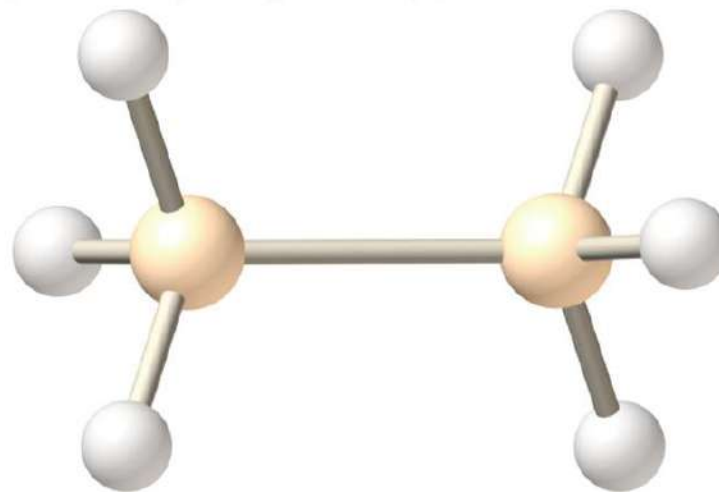


Carbon dioxide
(2 σ bonds & 2 π bonds)

Carbon's lack of *d* electrons enhances stability

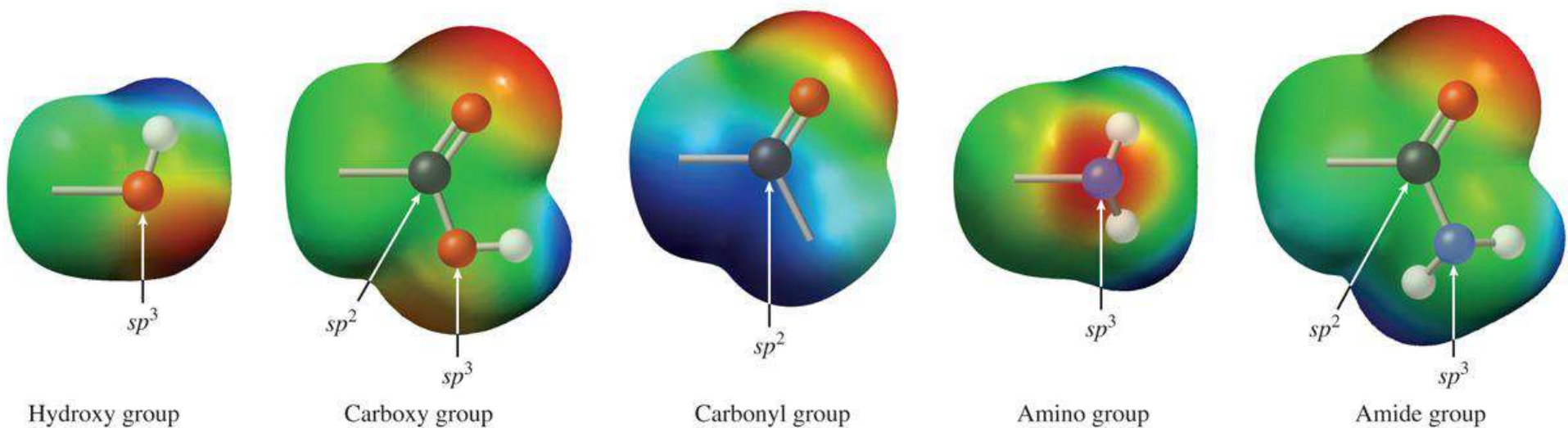


Ethane

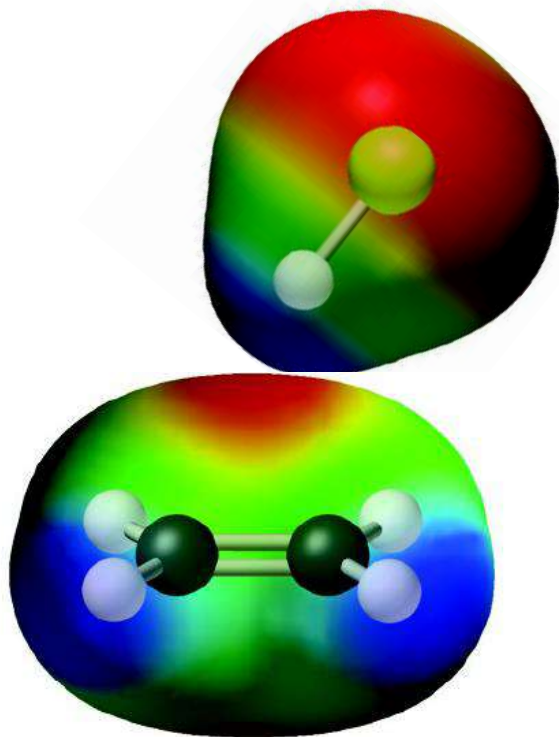
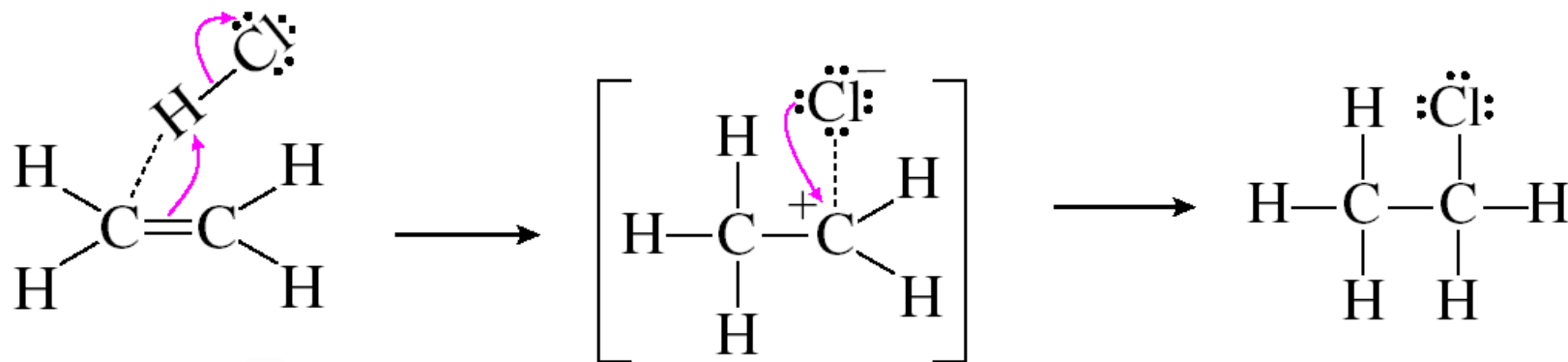


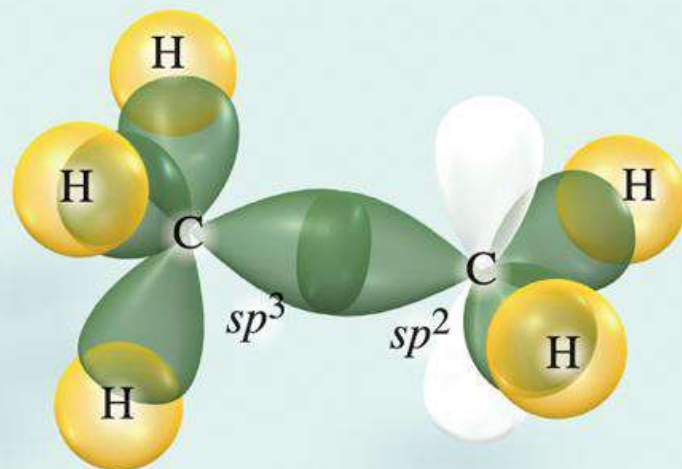
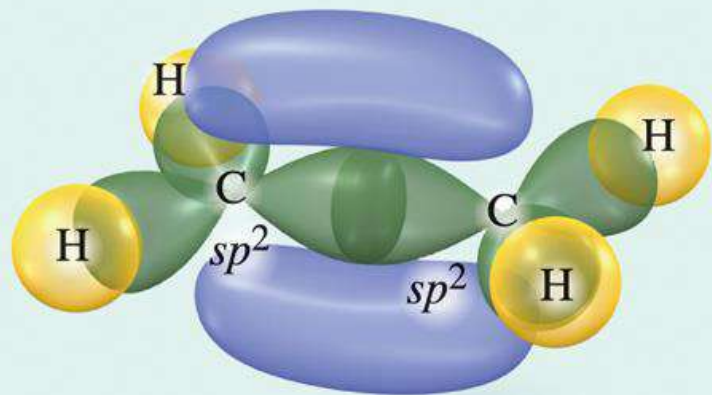
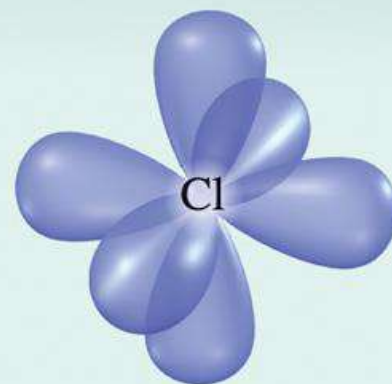
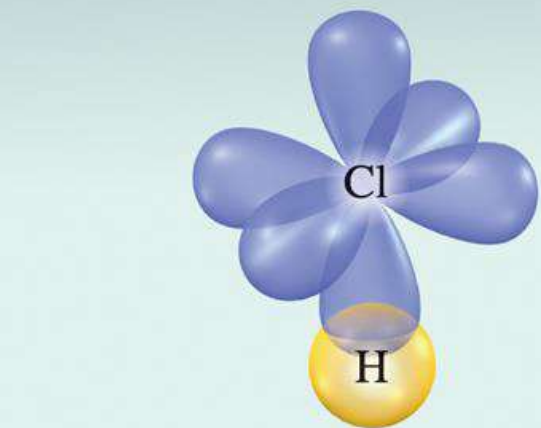
Disilane

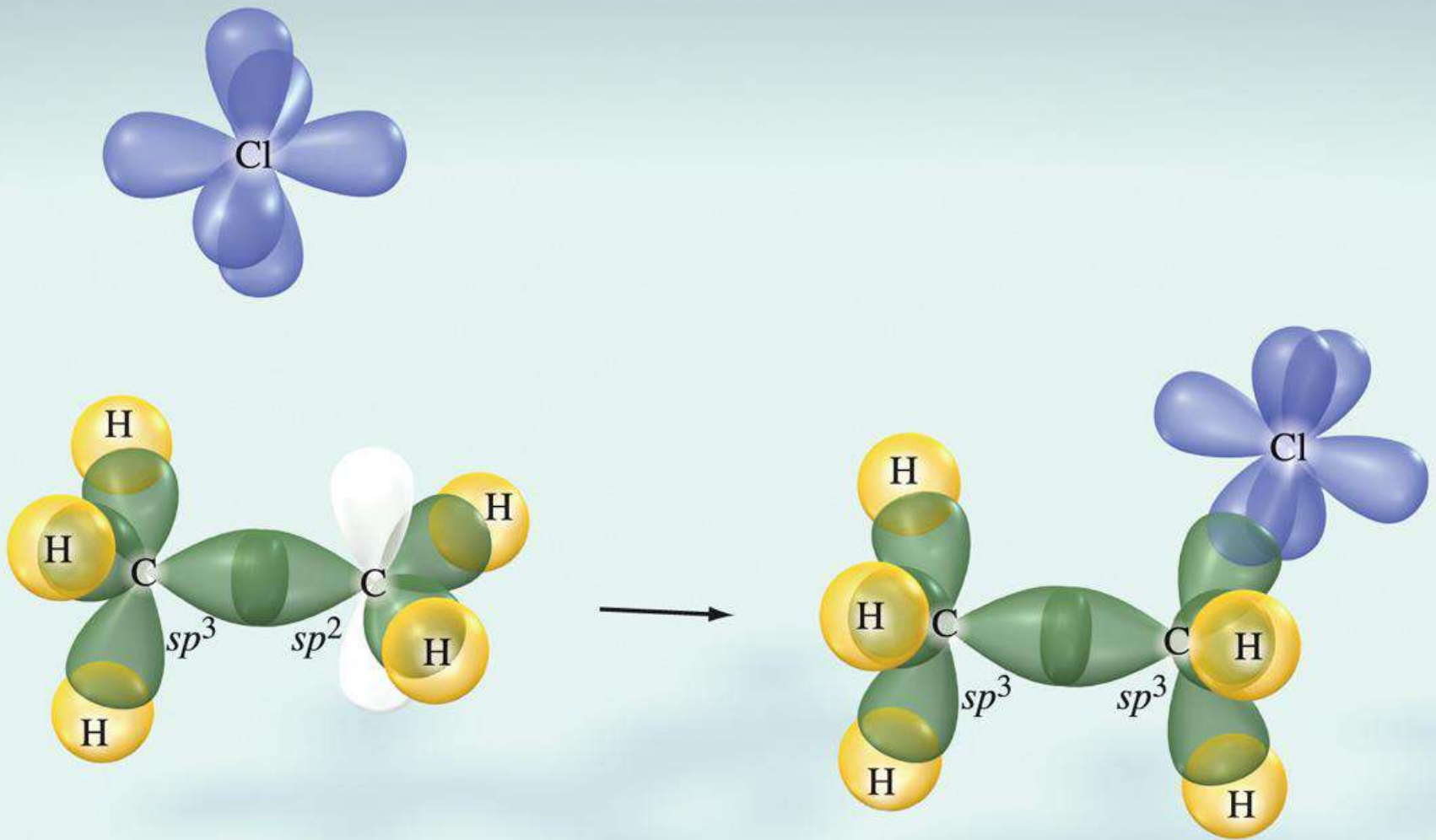
Electrostatic maps of selected functional groups

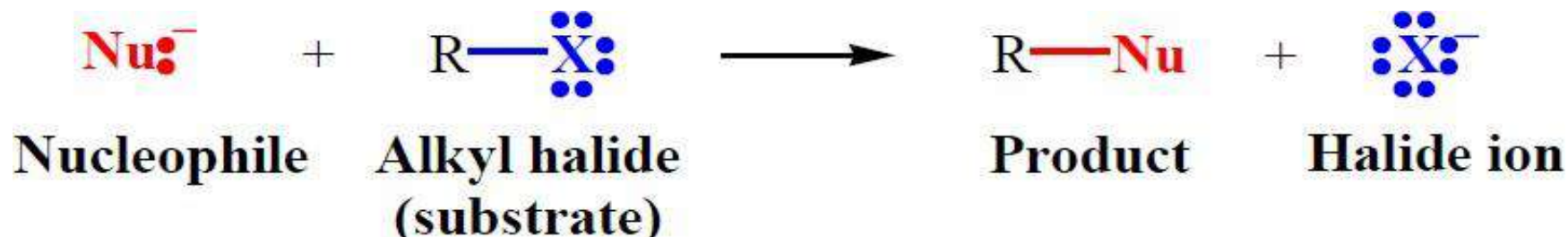


- Example: electrophilic addition



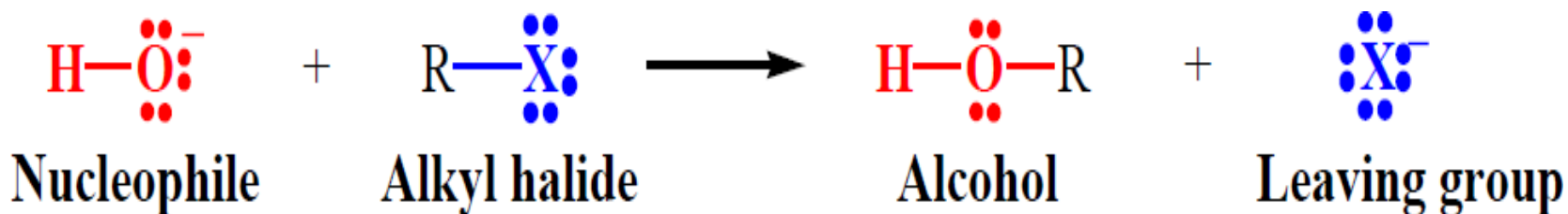






- **A nucleophile, a species with an unshared electron pair (lone-pair electrons), reacts with an alkyl halide (substrate) by replacing the halogen substituent (leaving group).**
- **In nucleophilic substitution reactions, the C–X bond of the substrate undergoes *heterolysis*, and the lone-pair electrons of the nucleophile is used to form a new bond to the carbon atom.**

A nucleophile is any negative ion or any neutral molecule that has at least one unshared electron pair-*General Reaction for Nucleophilic Substitution of an Alkyl Halide by Hydroxide Ion.*



- *To be a good leaving group the substituent must be able to leave as a relatively stable, weakly basic molecule or ion.*
- **In alkyl halides the leaving group is the halogen substituent — it leaves as a halide ion.**
- **Because halide ions are relatively stable and very weak bases, they are good leaving groups.**

NUCLEOPHILIC SUBSTITUTION REACTION AN S_N2 REACTION

- The rate of the reaction depends on the concentration of methyl chloride and the concentration of hydroxide ion
- The reaction is second order overall.
- The reaction is first order with respect to methyl chloride and first order with respect to hydroxide ion

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

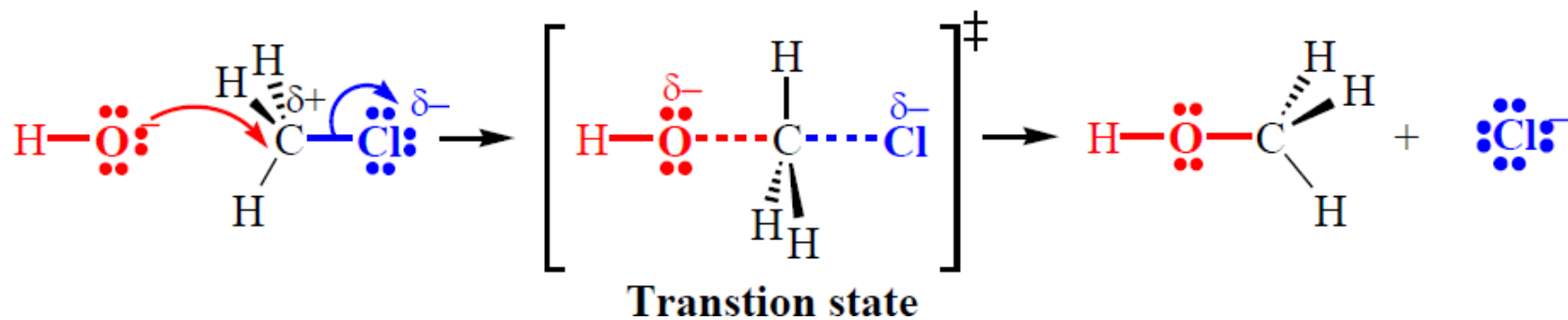
k is the rate constant.

MECHANISM FOR THE S_N2 REACTION

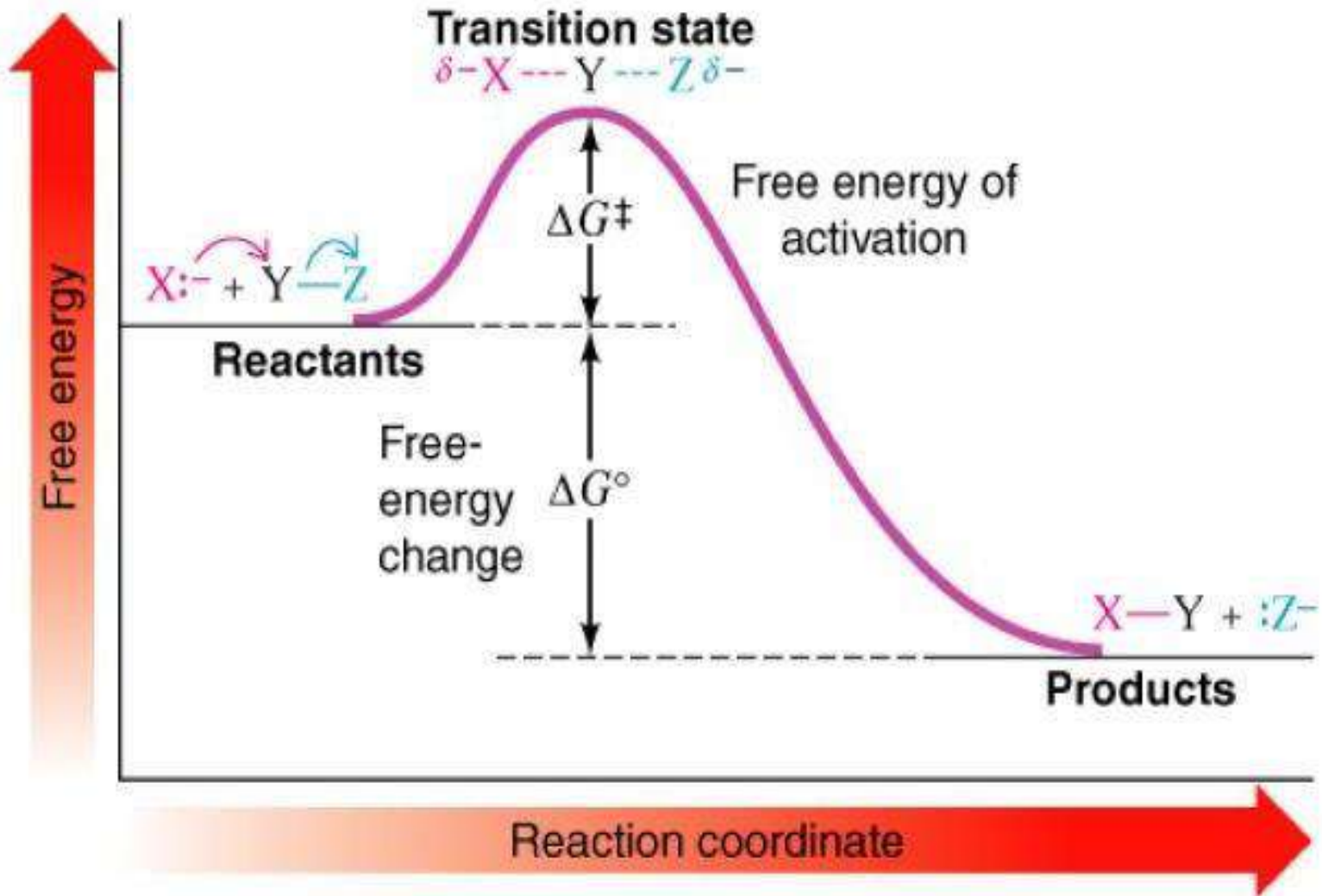
- The nucleophile attacks the carbon bearing the leaving group from the back side.
- The bond between the nucleophile and the carbon atom is forming, and the bond between the carbon atom and the leaving group is breaking.
- The configuration of the carbon atom becomes inverted during S_N2 reaction.
- Because bond formation and bond breaking occur simultaneously in a single transition state, the S_N2 reaction is a *concerted reaction*.

Mechanism

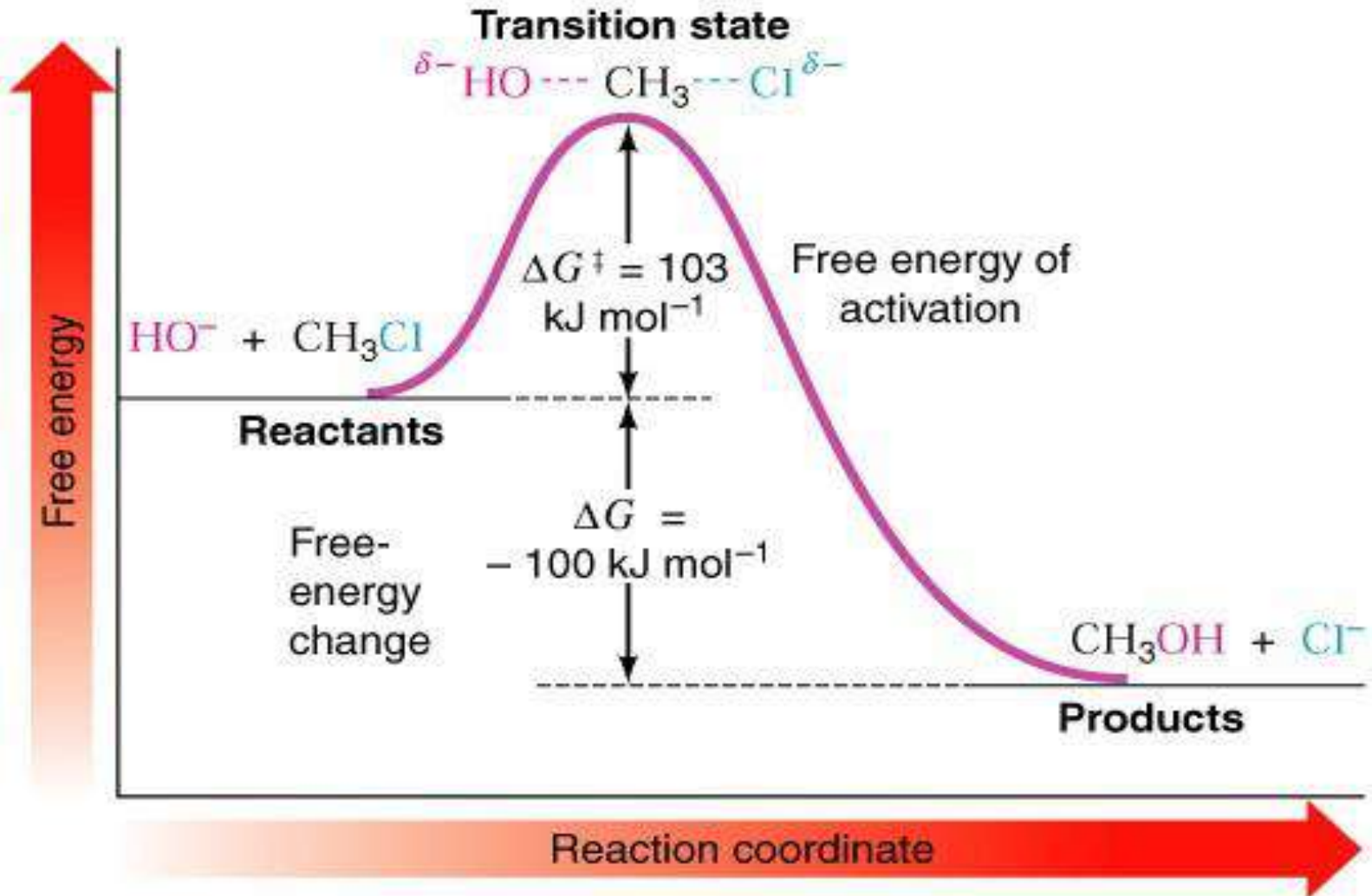
Mechanism:



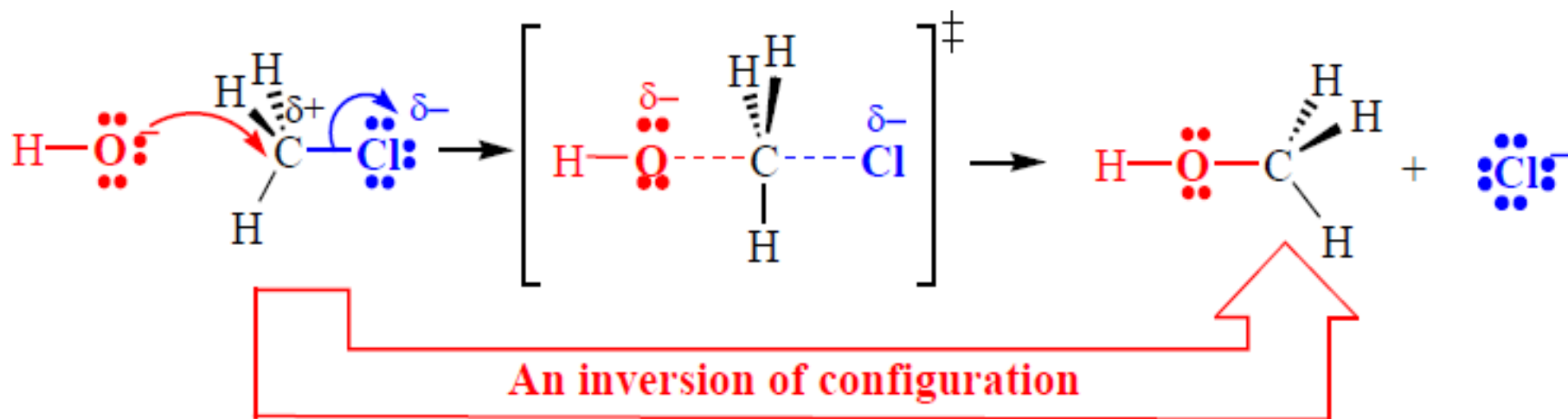
Free Energy Diagram



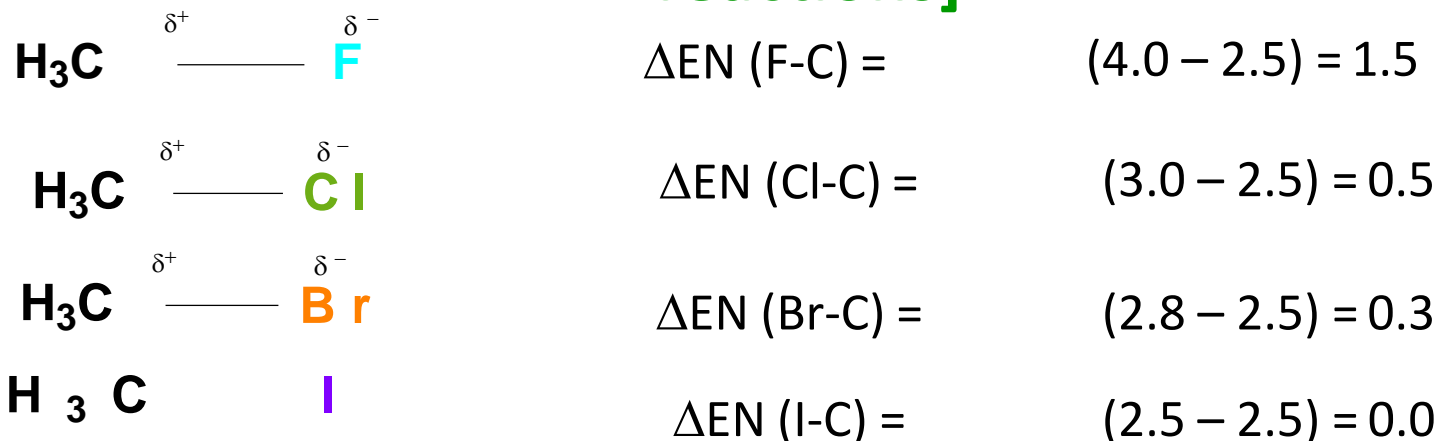
For Methanol



Stereo Chemistry



Reactions of Alkyl Halides (R-X): [SN1, SN2 reactions]



The α -carbon in an alkyl halide is electrophilic (electron accepting) for either or both of two reasons...

a) the C to X (F, Cl, Br) bond is polar making carbon δ^+

b) X (Cl, Br, I) is a leaving group

decreasing basicity, increasing stability

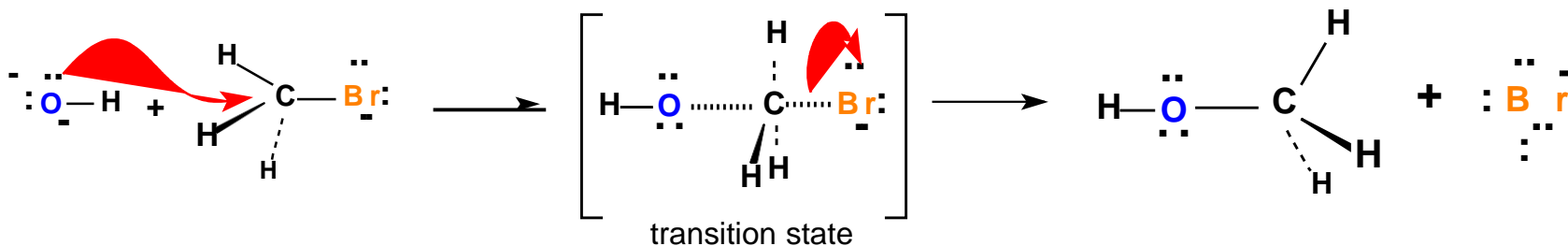
The best leaving groups are the weakest bases.

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

The poorest leaving groups are the strongest bases.

increasing leaving ability

2nd Order Nucleophilic Substitution Reactions, i.e., S_N2 reactions



The rate of an S_N2 reaction depends upon 4 factors:

1. The nature of the substrate (the alkyl halide)
2. The power of the nucleophile
3. The ability of the leaving group to leave
4. The nature of the solvent

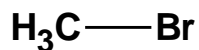
5. Consider the nature of the substrate:

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

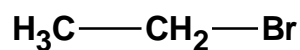


- While a methyl halides reacts quickly in S_N2 reactions, a 3° does not react. The back side of an α -carbon in a 3° alkyl halide is completely blocked.

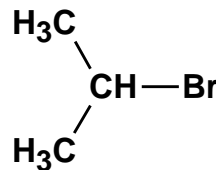
Effect of nature of substrate on rate of S_N2 reactions:



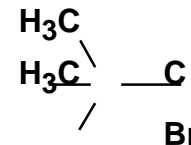
methyl bromide



ethyl bromide

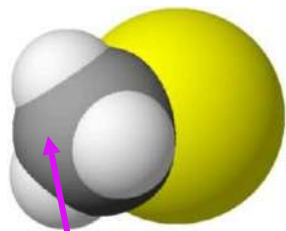


isopropyl bromide

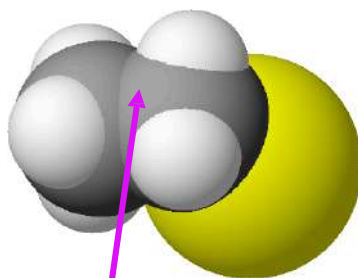


t-butyl bromide

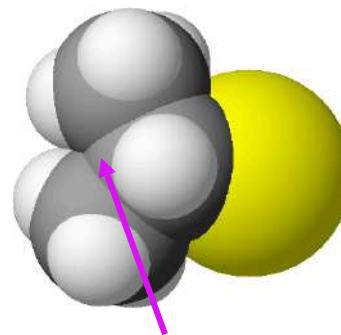
SPACE FILLING MODELS SHOW ACTUAL SHAPES AND RELATIVE SIZES



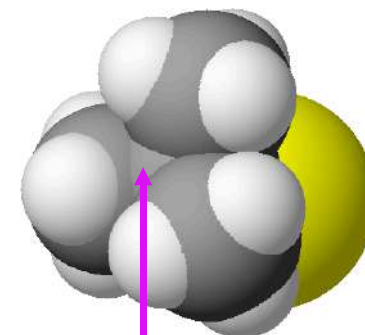
Back side of α -C of a methyl halide is unhindered.



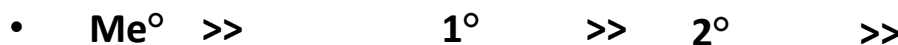
Back side of α -C of a 1° alkyl halide is slightly hindered.



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



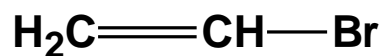
Back side of α -C of a 3° alkyl halide is completely blocked.



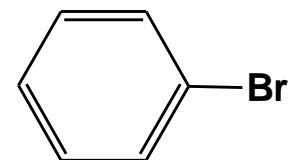
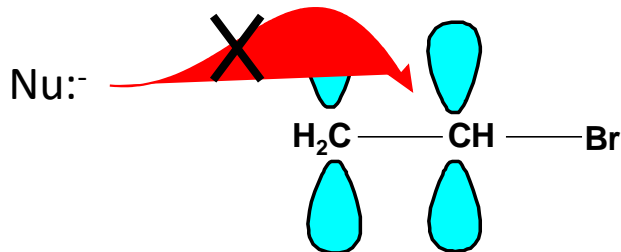
decreasing rate of S_N2 reactions

Effect of the nucleophile on rate of S_N2 reactions:

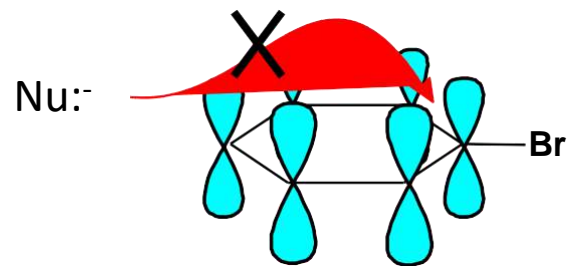
- The α -carbon in vinyl and aryl halides, as in 3° carbocations, is completely hindered and these alkyl halides do not undergo S_N2 reactions.



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.

Effect of nature substrate on rate of S_N2 reactions:

Consider the power of the nucleophile:

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

Reactivity	Nu: ⁻	Relative Reactivity
very weak	HSO ₄ ⁻ , H ₂ PO ₄ ⁻ , RCOOH	< 0.01
weak	ROH	1
	HOH, NO ₃ ⁻	100
fair	F ⁻	500
	Cl ⁻ , RCOO ⁻	20 × 10 ³
	NH ₃ , CH ₃ SCH ₃	300 × 10 ³
good	N ₃ ⁻ , Br ⁻	600 × 10 ³
	OH ⁻ , CH ₃ O ⁻	2 × 10 ⁶
very good	CN ⁻ , HS ⁻ , RS ⁻ , (CH ₃) ₃ P:, NH ₂ ⁻ , RMgX, I ⁻ , H ⁻	> 100 × 10 ⁶

↑
increasin
g

Effect of nature of the leaving group on rate of S_N2 reactions:

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

- The leaving group usually has a negative charge
- ❑ Groups which best stabilize a negative charge are the best leaving groups, i.e., the weakest bases are stable as anions and are the best leaving groups.
- ❑ Weak bases are readily identified. They have high 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 ₂ N ⁻
30,000	10,000	200	1	0	0	0



Increasing leaving ability

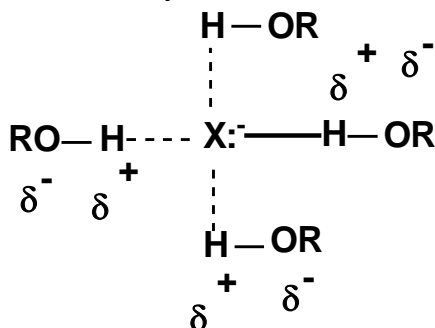
❑ Iodine (-I) is a good leaving group because iodide (I⁻) is non basic.

❑ The hydroxyl group (-OH) is a poor leaving group because hydroxide (OH⁻) is a strong base.

Effect of the solvent on rate of S_N2 reactions:

- **4. Consider the nature of the solvent:**
 - There are 3 classes of organic solvents:
 - ☐ **Protic solvents**, which contain $-OH$ or $-NH_2$ groups. Protic solvents slow down S_N2 reactions.
 - ☐ **Polar aprotic solvents** like acetone, which contain strong dipoles but no $-OH$ or $-NH_2$ groups. Polar aprotic solvents speed up S_N2 reactions.
 - ☐ **Non polar solvents**, e.g., hydrocarbons. S_N2 reactions are relatively slow in non polar solvents.

Protic solvents (e.g., H_2O , $MeOH$, $EtOH$, CH_3COOH , etc.) cluster around the $Nu:-$ (solvate it) and lower its energy (stabilize it) and reduce its bonding activity via H-bonding.

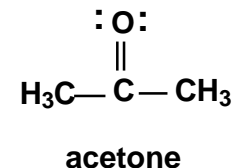


A solvated anion ($Nu:-$) has reduced nucleophilicity, reduced reactivity and increased stability

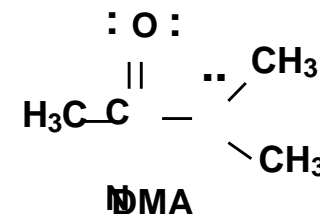
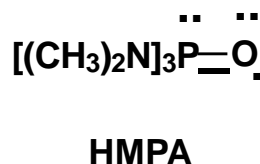
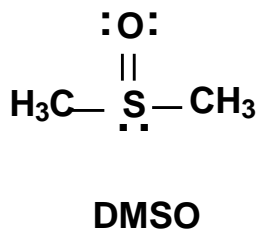
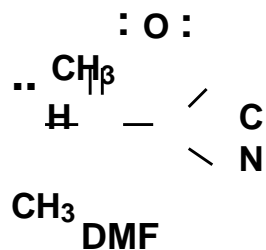
A solvated nucleophile has difficulty hitting the α -carbon.

CH₃—C≡N:
acetonitrile

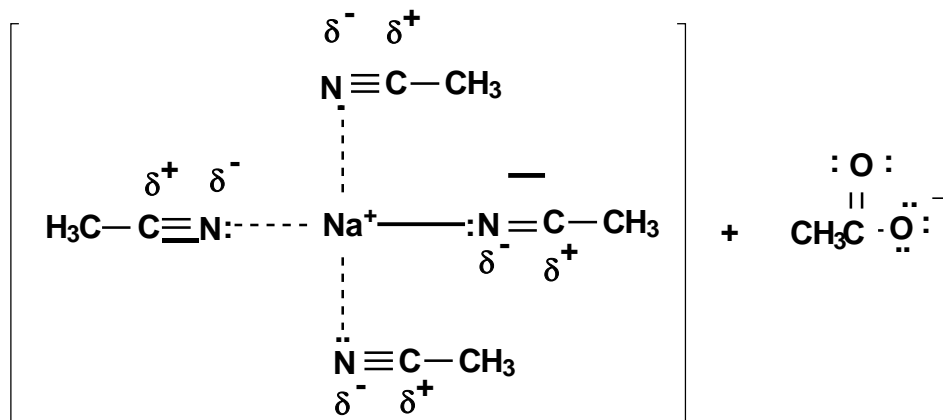
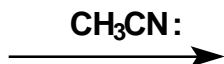
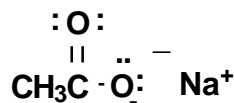
Effect of the solvent on rate of S_N2 reactions:



- ❑ 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).



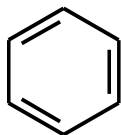
Polar aprotic solvents solvate metal cations leaving the anion counterion (Nu: ⁻) bare and thus more reactive



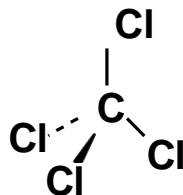
Effect of the solvent on rate of S_N2 reactions:

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

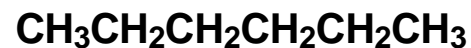
– S_N2 reactions are relatively slow in non polar solvents similar to that in protic solvents.



benzene



carbon
tetrachlorid
e

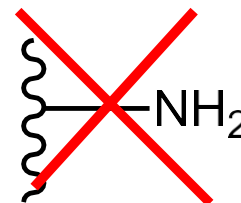
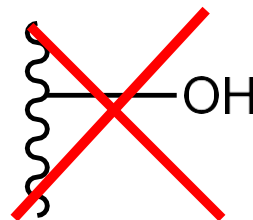


n-hexane

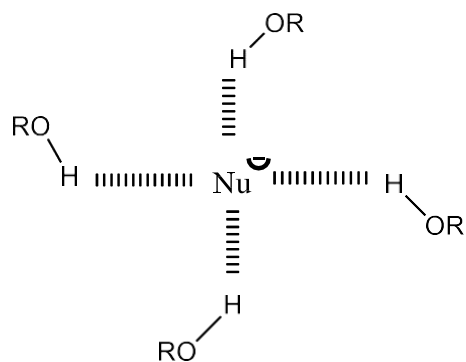
Solvent Effect for S_N2 reactions

- Requires a polar, aprotic solvent...

- NO alcohols or amines

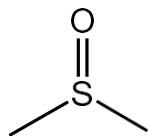


Why...because hydrogen bonding
with the nucleophile can
occur...slowing down the reaction



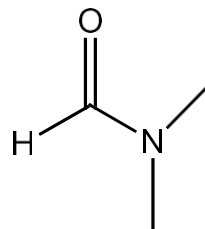
Polar, Aprotic Solvents

DMSO

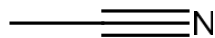


dimethyl sulfoxide

DMF

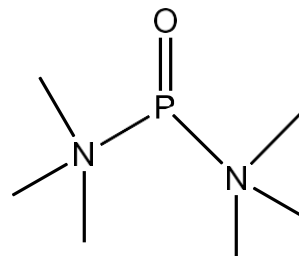


dimethyl formamide



acetonitrile

HMPA



hexamethyl phosphamide

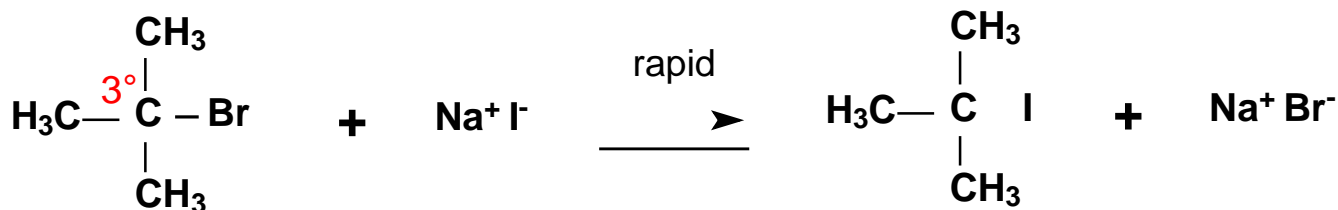
S_N2 Conditions Summary

- 1) Substrate (methyl > primary > secondary >> tertiary)
- 2) Nucleophile (negative charge > neutral)
- 3) leaving group (Y) (Y stabilizes a negative charge)
- 4) solvent (needs to be polar and aprotic)

AN S_N1 REACTION

- THE REACTION OF *TERT-BUTYL CHLORIDE* WITH HYDROXIDE ION

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

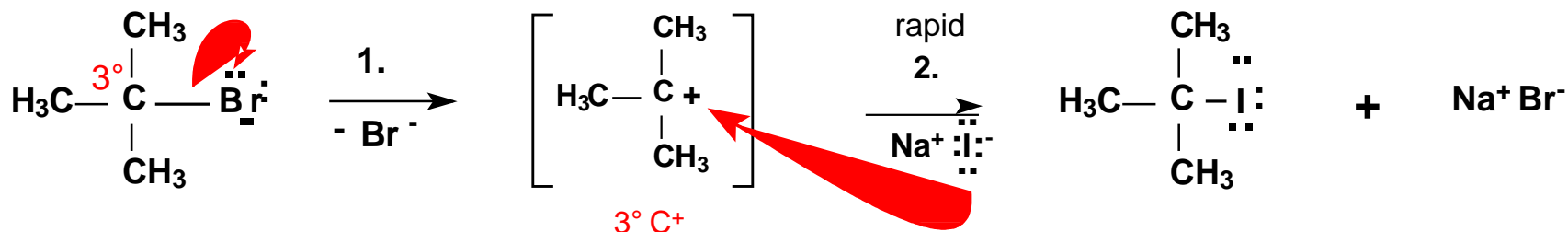


- ❑ 3° alkyl halides are essentially inert to substitution by the S_N2 mechanism because of steric hindrance at the back side of the α-carbon.
- ❑ Despite this, 3° alkyl halides do undergo nucleophilic substitution reactions quite rapidly, but by a different mechanism, i.e., the S_N1 mechanism.
- ❑ S_N1 = Substitution, Nucleophilic, 1st order (unimolecular).
- ❑ S_N1 reactions obey 1st order kinetics, i.e., Rate = k·[RX].
- ❑ The rate depends upon the concentration of only 1 reactant, the alkyl halide-not the nucleophile
- ❑ The order of reactivity of substrates for S_N1 reactions is the reverse of S_N2
 - 3° > 2° > 1° > vinyl > phenyl > Me°
 - R₃C-Br > R₂HC-Br > RH₂C-Br > CH₂=CH-Br > φ-Br > H₃C-Br

←
increasing rate of S_N1 reactions

Mechanism of S_N1 reactions

- The mechanism of an S_N1 reaction occurs in 2 steps:



- Reaction Steps ...

1. the slower, rate-limiting dissociation of the alkyl halide forming a C⁺ intermediate

2. rapid nucleophilic attack on the C⁺

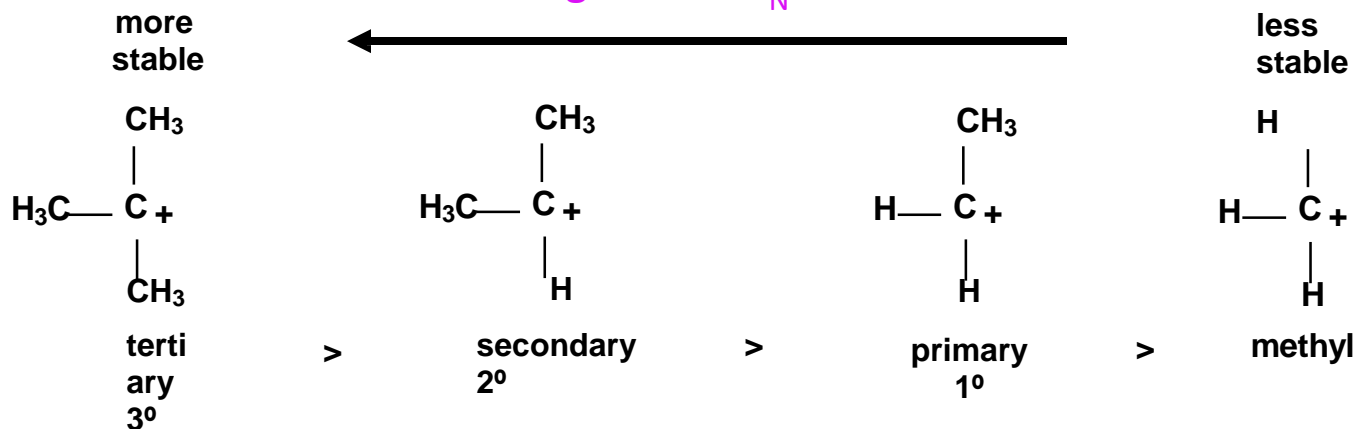
Note that the nucleophile is not involved in the slower, rate-limiting step.

The Rate of S_N1 reactions

- The rate of an S_N1 reaction depends upon 3 factors:
 1. The nature of the substrate (the alkyl halide)
 2. The ability of the leaving group to leave
 3. The nature of the solvent
- The rate is independent of the power of the nucleophile.

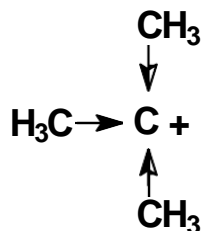
• 1. Consider the nature of the substrate:

Highly substituted alkyl halides (substrates) form more stable C⁺.



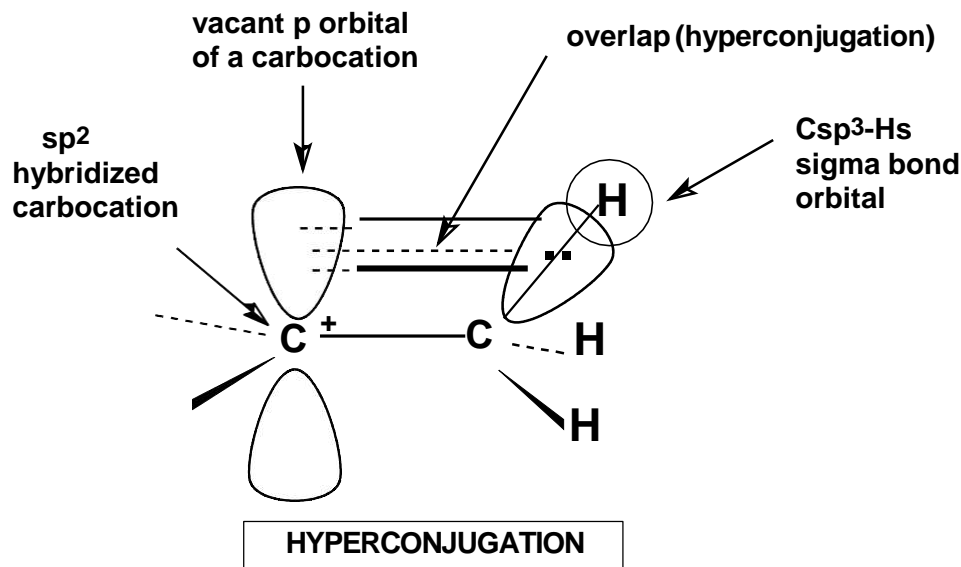
Stability of Carbocations

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



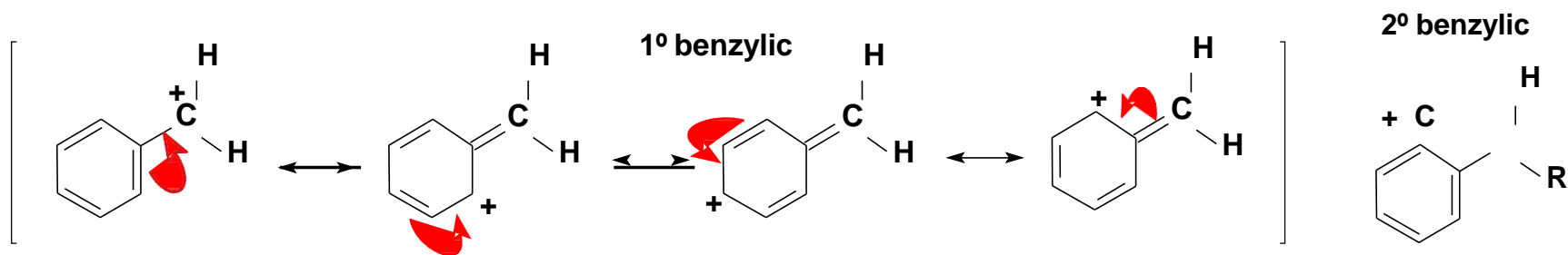
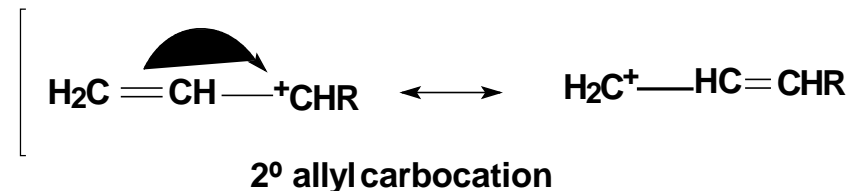
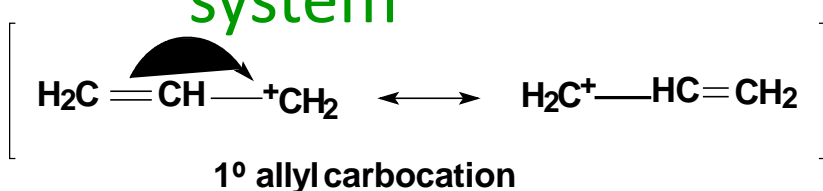
Inductive effects:
Alkyl groups donate (shift) electron density through sigma bonds to electron deficient atoms.
This stabilizes the carbocation.

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



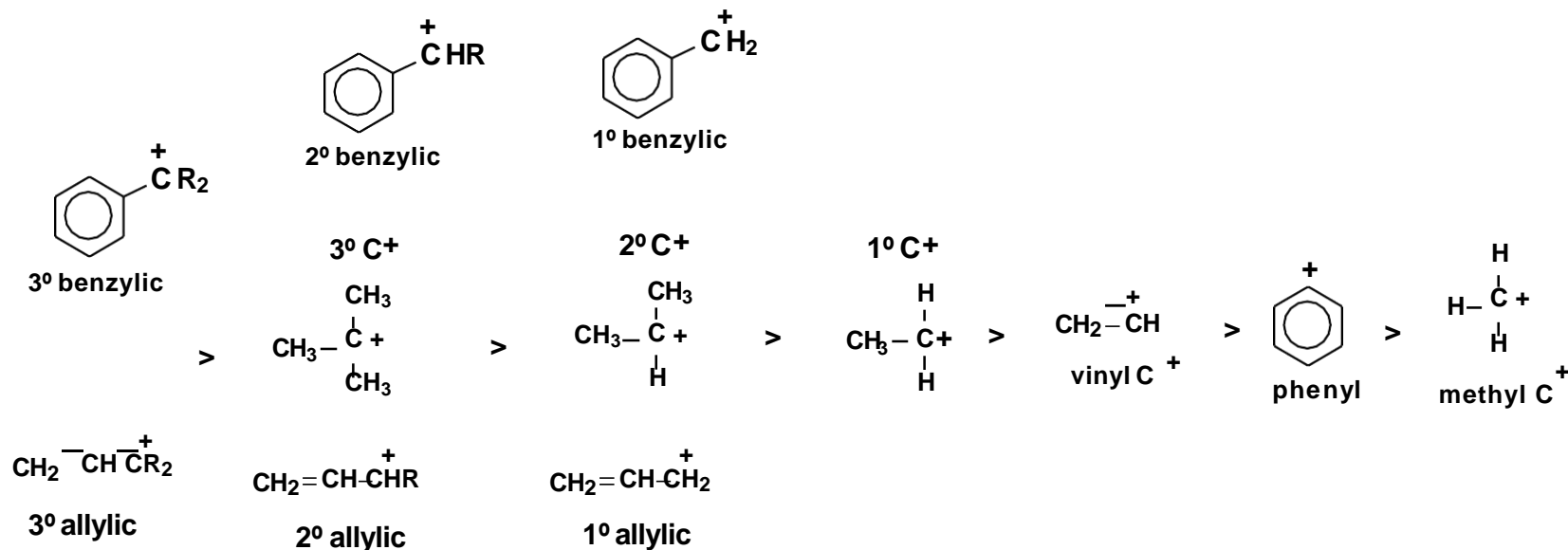
Stability of Carbocations

□ 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



Relative Stability of All Types of Carbocations

Increasing C⁺ stability and rate of S_N1 reaction



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.

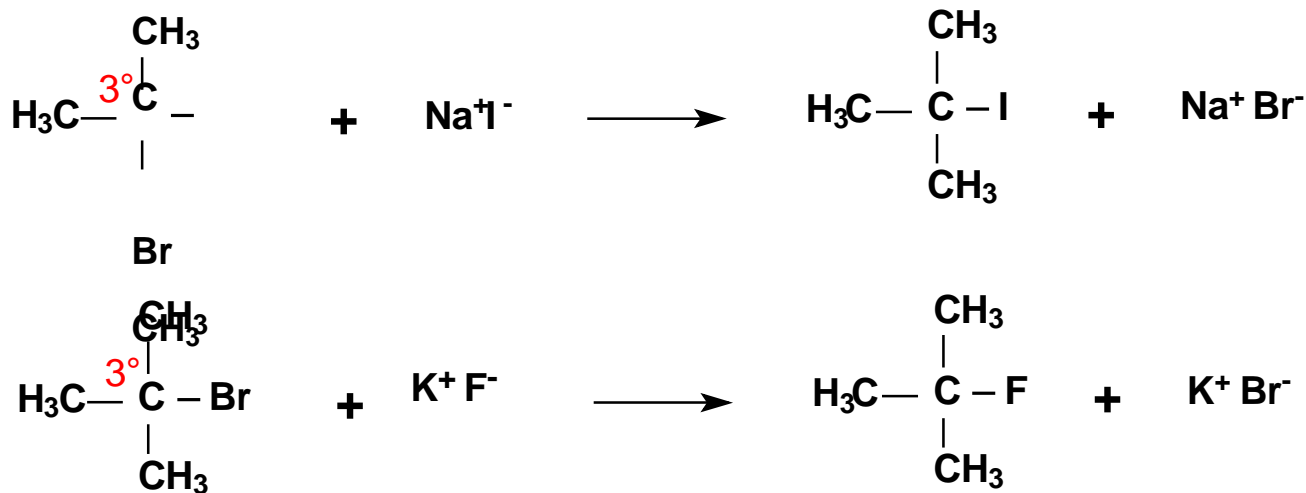
Note that 3° allylic and 3° benzylic C⁺'s are more stable than 3° alkyl C⁺'s.

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

Effect of the nucleophile on rate of S_N1 reactions:

- 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 H₂O 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.



Effect of nature of the leaving group on rate of S_N1 reactions:

- **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 ₂ N ⁻
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.

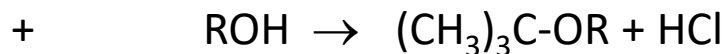
Effect of the solvent on rate of S_N1 reactions:

- 3. Consider the nature of the solvent:

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

relatively slower

The relative rates of an S_N1 reaction due to solvent effects are given $(CH_3)_3C-Cl$



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

reaction rate increases with polarity 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		

Reactivity of alkyl halides toward substitution and elimination

<i>Halide type</i>	<i>S_N1</i>	<i>S_N2</i>	<i>E1</i>	<i>E2</i>
Primary halide	Does not occur	Highly favored	Does not occur	Occurs when strong, hindered bases are used
Secondary halide	Can occur under solvolysis conditions in polar solvents	Favored by good nucleophiles in polar aprotic solvents	Can occur under solvolysis conditions in polar solvents	Favored when strong bases are used
Tertiary halide	Favored by nonbasic nucleophiles in polar solvents	Does not occur	Occurs under solvolysis conditions	Highly favored when bases are used

Effects of reaction variables on substitution and elimination reactions

<i>Reaction</i>	<i>Solvent</i>	<i>Nucleophile/base</i>	<i>Leaving group</i>	<i>Substrate structure</i>
S_N1	Very strong effect; reaction favored by polar solvents	Weak effect; reaction favored by good nucleophile/weak base	Strong effect; reaction favored by good leaving group	Strong effect; reaction favored by 3°, allylic, and benzylic substrates
S_N2	Strong effect; reaction favored by polar aprotic solvents	Strong effect; reaction favored by good nucleophile/weak base	Strong effect; reaction favored by good leaving group	Strong effect; reaction favored by 1°, allylic, and benzylic substrates
E1	Very strong effect; reaction favored by polar solvents	Weak effect; reaction favored by weak base	Strong effect; reaction favored by good leaving group	Strong effect; reaction favored by 3°, allylic, and benzylic substrates
E2	Strong effect; reaction favored by polar aprotic solvents	Strong effect; reaction favored by poor nucleophile/strong base	Strong effect; reaction favored by good leaving group	Strong effect; reaction favored by 3° substrates

Overall Summary of S_N1, S_N2, E1 and E2 Reactions

CH ₃ X Methyl	RCH ₂ X 1°	RR'CHX 2°	RR'R''CX 3°
	Bimolecular reactions only		S_N1/E1 or E2
Gives S _N 2 reactions	Gives mainly S _N 2 except with a hindered strong base [e.g., (CH ₃) ₃ CO ⁻] and then gives mainly E2	Gives mainly S _N 2 with weak bases (e.g., I ⁻ , CN ⁻ , RCO ₂ ⁻) and mainly E2 with strong bases (e.g., RO ⁻)	No S _N 2 reaction. In solvolysis gives S _N 1/E1, and at lower temperatures S _N 1 is favored. When a strong base (e.g., RO ⁻) is used E2 predominates