

NUCLEOPHILIC SUBSTITUTION REACTIONS (Part II)

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NUCLEOPHILIC SUBSTITUTION REACTION

S_N2 REACTION

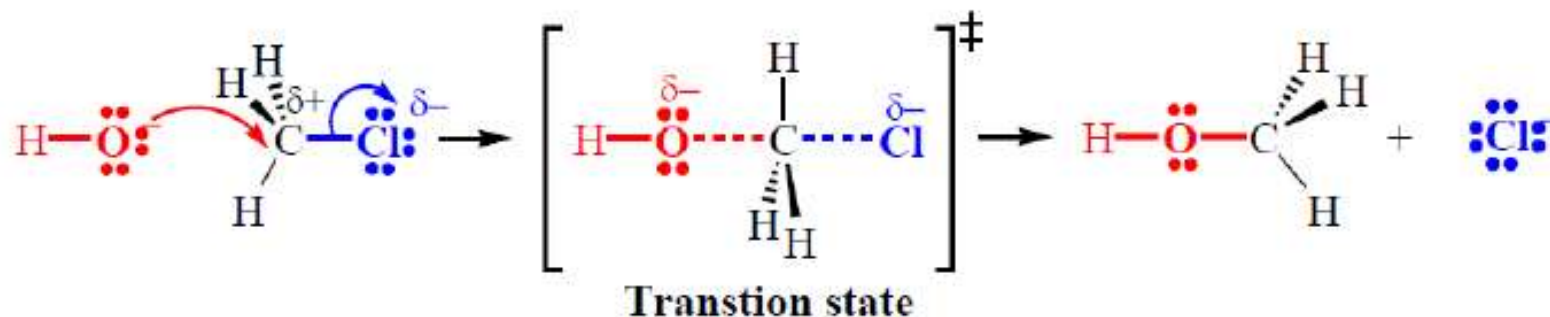
- ❑ 3° alkyl halides are essentially inert to substitution by the S_N2 mechanism because of steric hindrance at the back side of the carbon.
- ❑ S_N2 = Substitution, Nucleophilic, 2nd order (bimolecular).
- ❑ The rate of the reaction depends on the concentration of methyl chloride and the concentration of hydroxide ion.
- ❑ The reaction is first order with respect to methyl chloride and first order with respect to hydroxide ion.

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

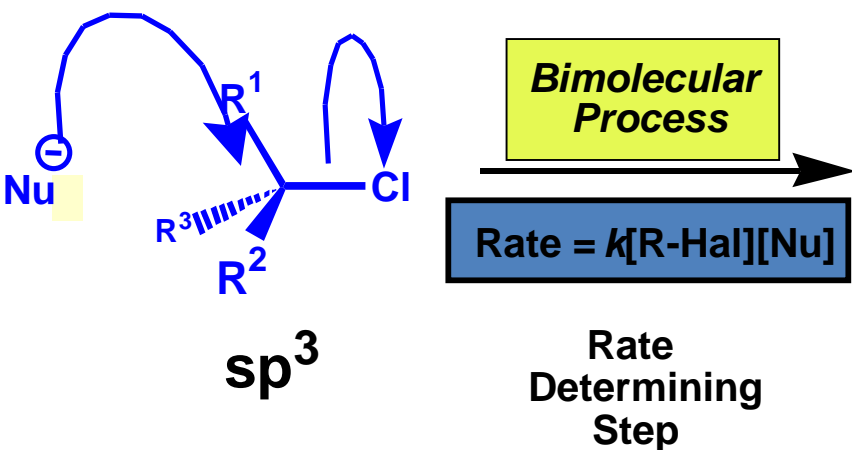
k is the rate constant.

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*.

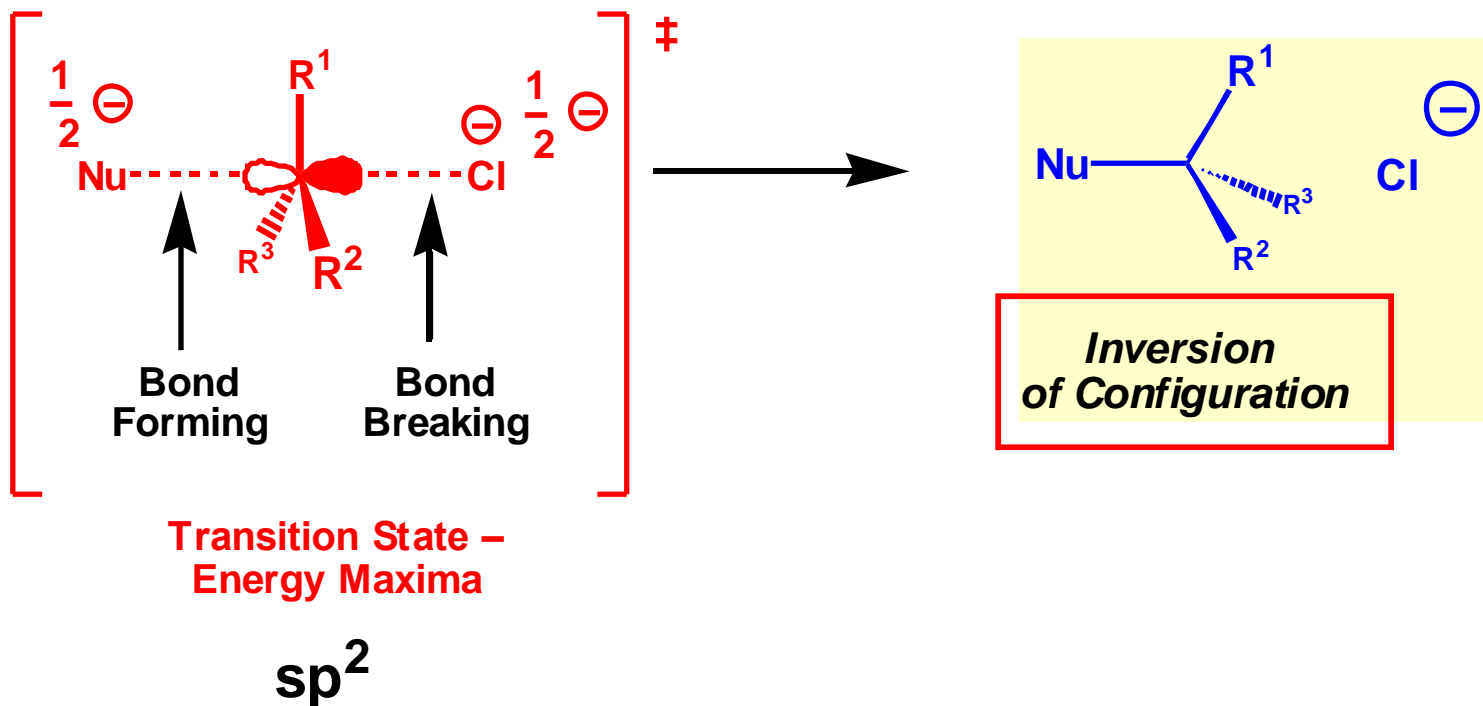


MECHANISM FOR THE S_N2 REACTION

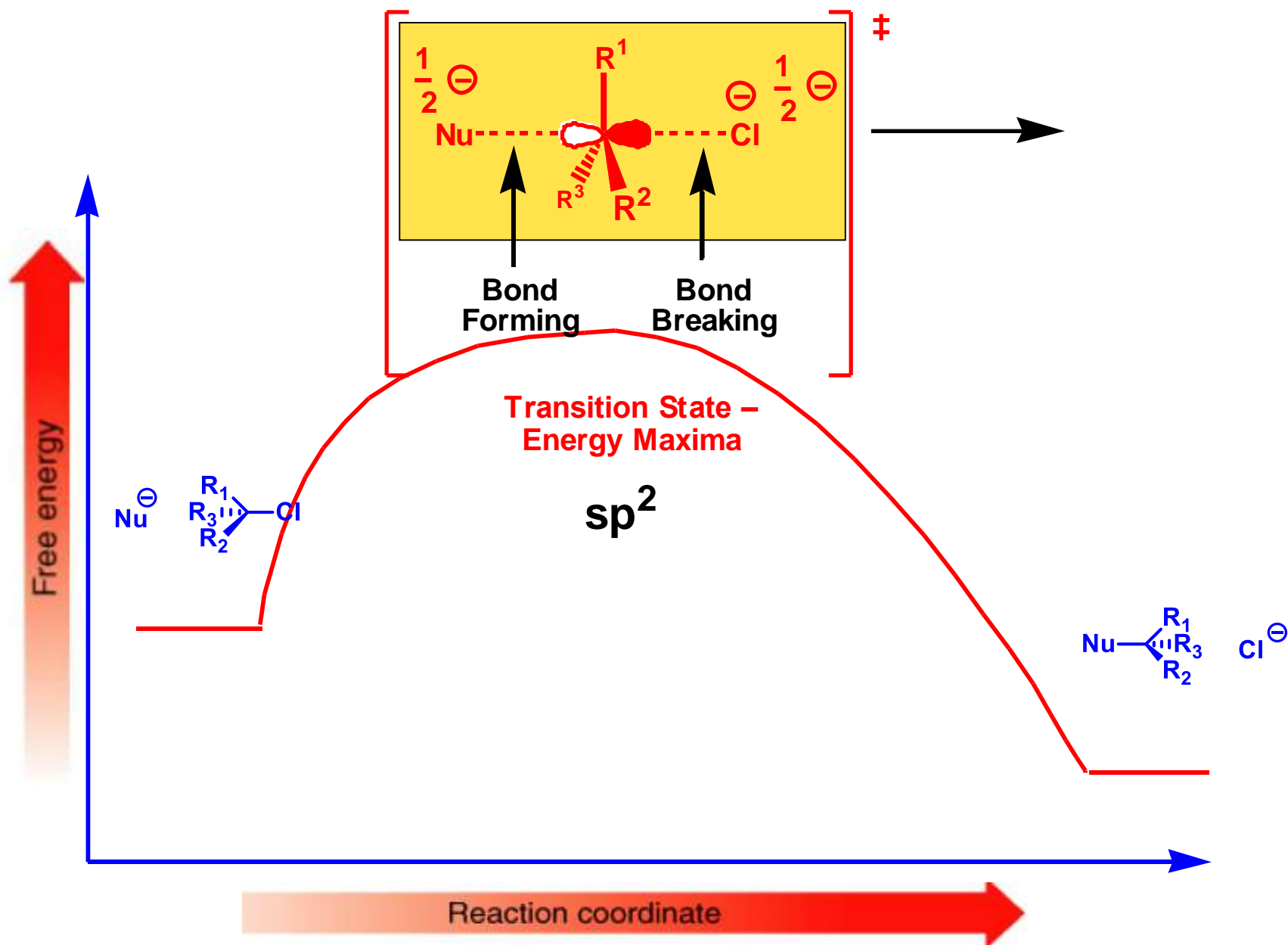


Nucleophile attacks from behind the C-Cl σ -bond.

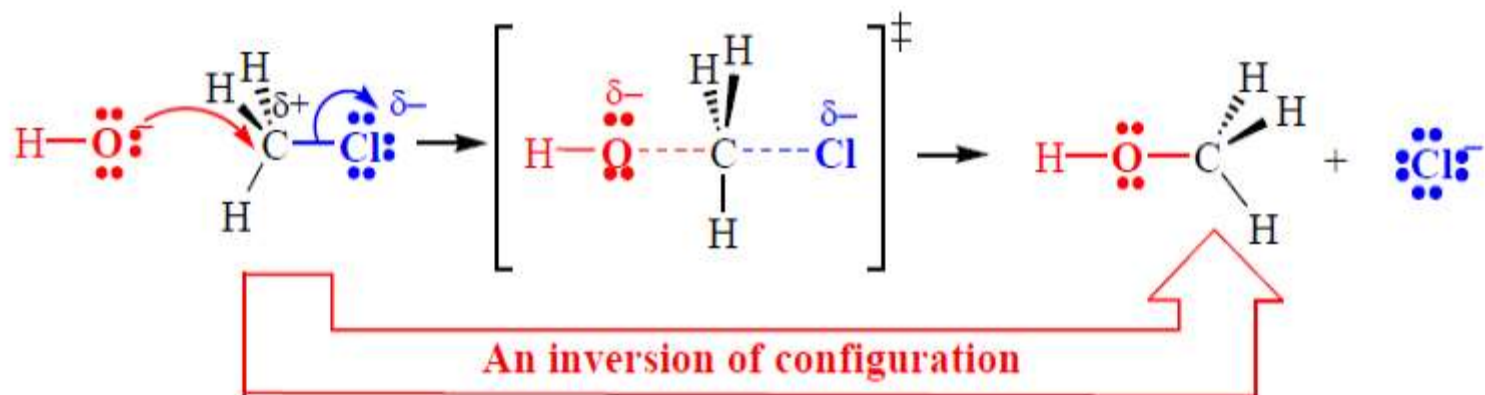
This is where the σ^* -antibonding orbital of the C-Cl bond is situated.



The Energy profile of S_N2 Reaction



Stereo Chemistry



Reactions of Alkyl Halides (R-X): [S_N2 reactions]

- The α -carbon in an alkyl halide is electrophilic (electron accepting) for either or both of two reasons...
- the C to X (F, Cl, Br) bond is polar making carbon C^+
 - X (Cl, Br, I) is a leaving group

decreasing basicity, increasing stability



The best leaving groups are the weakest bases.

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

The poorest leaving groups are the strongest bases.



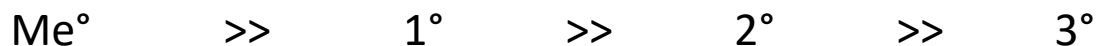
increasing leaving ability

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

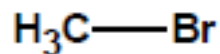
1) Nature of the substrate (the alkyl halide)

- ☐ 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:

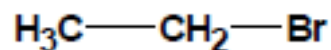


- ☐ While a methyl halides reacts quickly in S_N2 reactions, a 3° does not react. The back side of an α -carbon in a 3° alkyl halide is completely blocked.

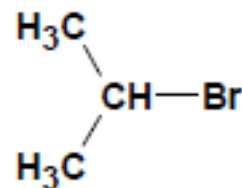
Effect of nature of substrate on rate of S_N2 reactions:



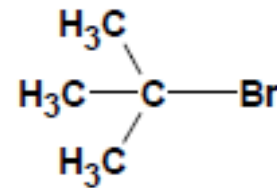
methyl bromide



ethyl bromide

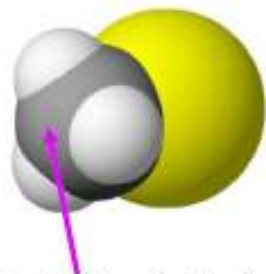


isopropyl bromide



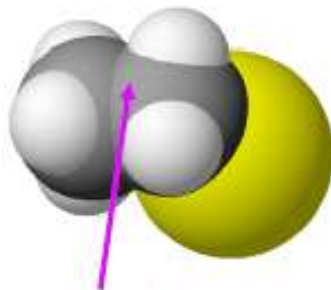
t-butyl bromide

Space filling models show actual shapes and relative sizes



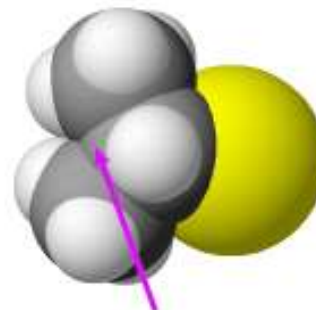
Back side of α -C of a methyl halide is unhindered.

Me° >>



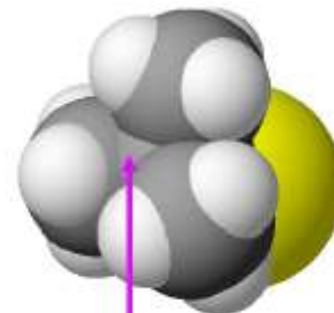
Back side of α -C of a 1° alkyl halide is slightly hindered.

1° >>



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

2° >>



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

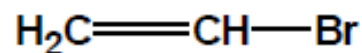
3°



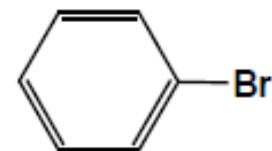
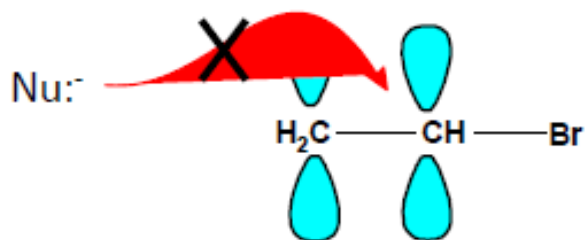
decreasing rate of S_N2 reactions

Effect of the nucleophile on rate of S_N2 reactions

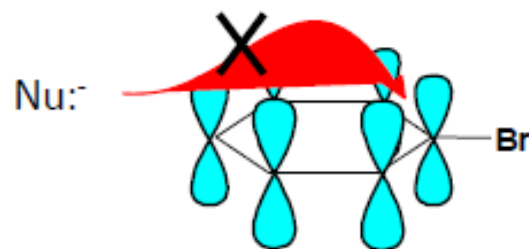
- The α -carbon in vinyl and aryl halides, as in 3° carbocations, is completely hindered and these alkyl halides do not undergo S_N2 reactions.



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.

2) 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_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

3) Nature of the leaving group

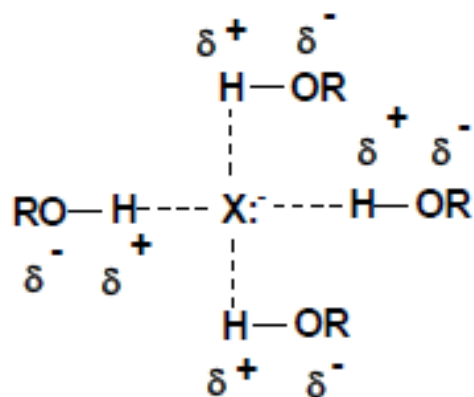
- The leaving group usually has a negative charge
- ❑ Groups which best stabilize a negative charge are the best leaving groups, i.e., the weakest bases are stable as anions and are the best leaving groups.
- ❑ Weak bases are readily identified. They have high pK_b values.
- ❑ Iodine ($-I$) is a good leaving group because iodide (I^-) is non basic.
- ❑ The hydroxyl group ($-OH$) is a poor leaving group because hydroxide (OH^-) is a strong base.

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

←
Increasing leaving ability

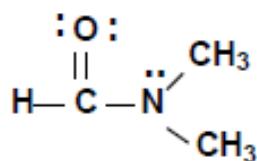
4) Nature of the solvent

- There are 3 classes of organic solvents:
 - ❑ Protic solvents, which contain -OH or NH_2 groups. Protic solvents slow down $\text{S}_\text{N}2$ reactions.
 - ❑ Polar aprotic solvents like acetone, which contain strong dipoles but no -OH or -NH_2 groups. Polar aprotic solvents speed up $\text{S}_\text{N}2$ reactions.
 - ❑ Non polar solvents, e.g., hydrocarbons. $\text{S}_\text{N}2$ 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 reactivity via H-bonding.

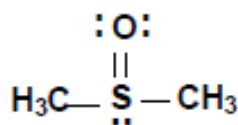


- A solvated anion (Nu:^-) has reduced nucleophilicity, reduced reactivity and increased stability.
- A solvated nucleophile has difficulty hitting the α -carbon.

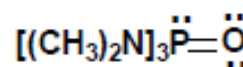
- ✓ **Polar Aprotic Solvents** solvate the cation counterion of the nucleophile but not the nucleophile. For examples: acetonitrile (CH_3CN), acetone (CH_3COCH_3), dimethylformamide (DMF) $[(\text{CH}_3)_2\text{NC=O}]$, dimethyl sulfoxide, DMSO $[(\text{CH}_3)_2\text{SO}]$, hexamethylphosphoramide, HMPA $\{[(\text{CH}_3)_2\text{N}]_3\text{PO}\}$ and dimethylacetamide (DMA).



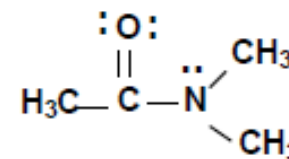
DMF



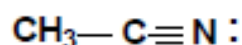
DMSO



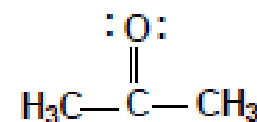
HMPA



DMA

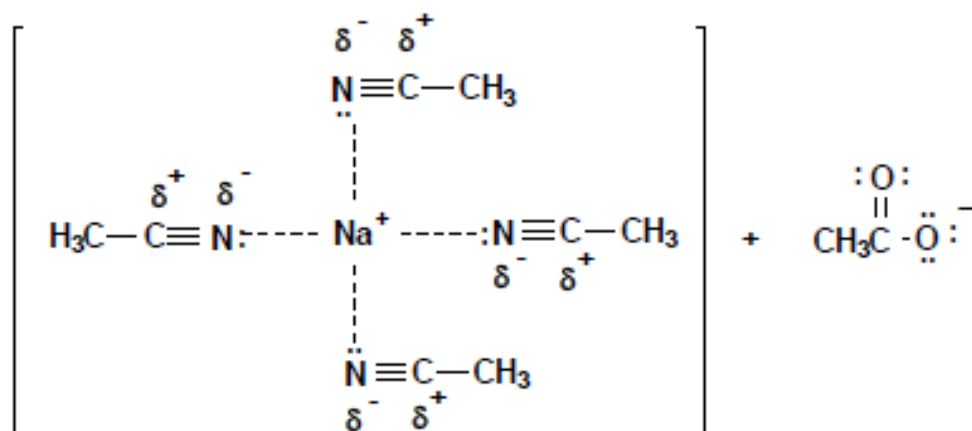
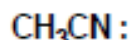
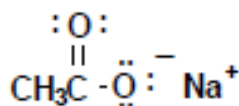


acetonitrile



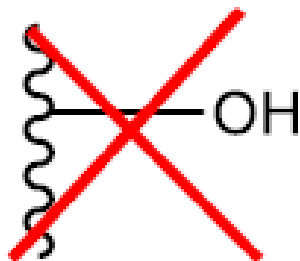
acetone

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

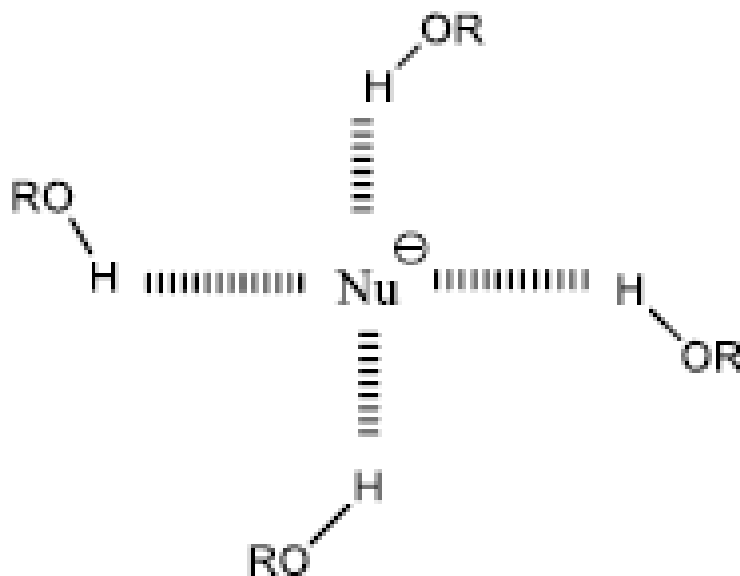


Solvent Effect for S_N2 reactions

- ✓ 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.
- ✓ Requires a polar, aprotic solvent...
- ✓ NO alcohols or amines



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



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)