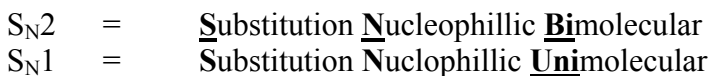


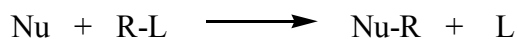
9. SUBSTITUTIONS: S_N1, S_N2

2 basic kinds of substitution reactions:



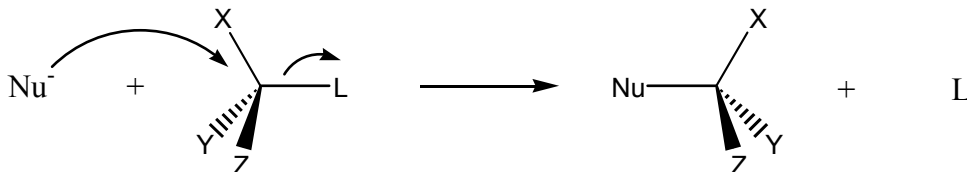
Lets deal with S_N2 first...

General substitution reaction scheme looks like...



Where R = alkyl group, Nu = nucleophile and L = leaving group.

A more detailed look at the reaction shows more details of the S_N2 reaction...

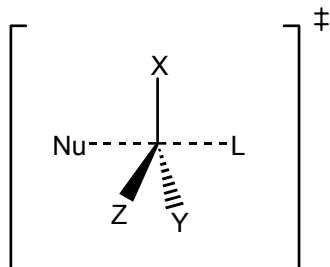


Nucleophile (anion or neutral with electron pair) attacks the carbon from the backside; displacing the leaving group as a free anion.

Reaction is **concerted**...meaning it happens all at once...in one deft motion...like pulling a table cloth out from under the dishes on the dining room table.

Result is a new compound with a stereo inversion about the carbon center.

The reaction has an unstable transition state...

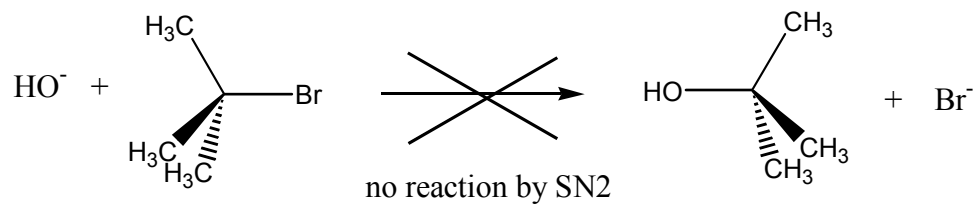
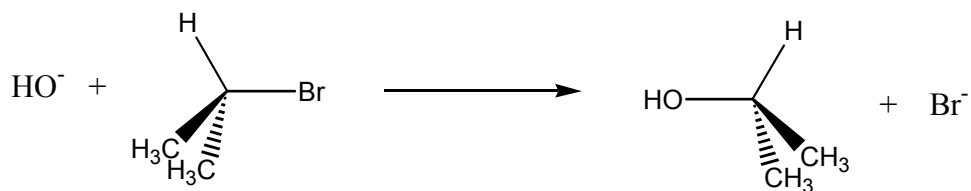
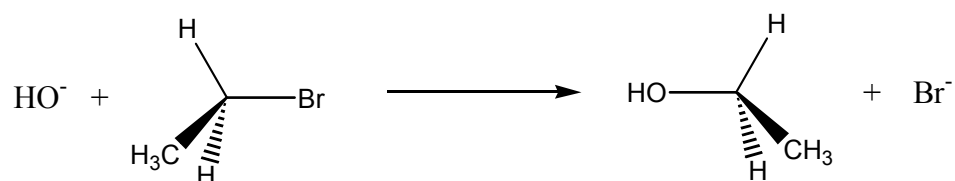
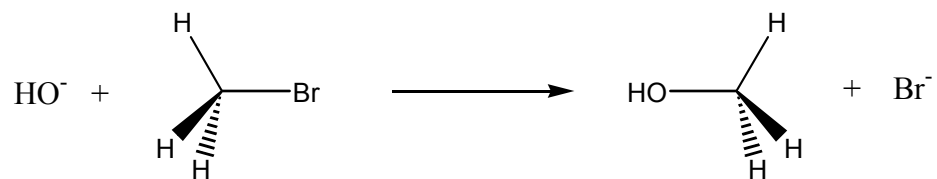


Such that X, Y and Z go trigonal planar with 120° bond angles, and Nu and L are only partially bound.

Rate of reaction depends on the nature of R, L and Nu.

PROPERTIES OF R...

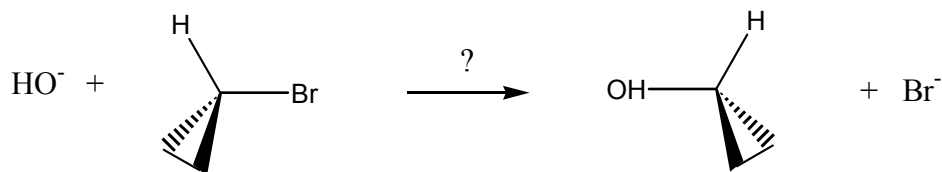
R can methyl, primary, or secondary.



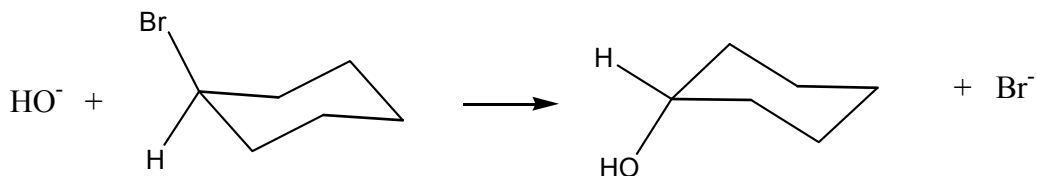
R cannot be tertiary. The size of the surrounding groups creates too much steric hinderence and therefore the reaction does not proceed by the $\text{S}_{\text{N}}2$ mechanism.

S_N2 with Rings...? Sure.

However, very difficult with C_3 and C_4 rings. Transition state wants to have the three substituents go trigonal planar with 120° bond angles. Cyclopropane and Cyclobutane have 60 and 90 degree bonds respectively. Ring strain significantly hinders the reaction so that if any reaction does occur, it is very slow...



For C_5 and C_6 and larger...no problem. One only needs to worry about steric hindrance.



Also, ring gets “flipped” during an S_N2 reaction.

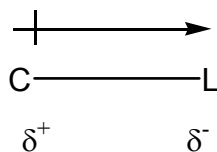
LEAVING GROUP CHARACTERISTICS.

Characteristics of a good leaving group include...

Stable anion formation (L^-)

Therefore L^- should be a weak base (HL is a strong acid with low pKa)

Useful to have a dipole setup between the carbon center and the leaving group...this encourages the flow of electrons to the leaving group during the substitution reaction...think of it in terms of a kind of “electronic momentum”, a driving force.



Good leaving groups include: I, Br, Cl, H_2O , TsO (tosylate group)

Not so good leaving groups: -F, -SH, -CN, -OH, -OR

Most common R-L for S_N2 reactions are alkyl halides.

NUCLEOPHILE CHARACTERISTICS.

A good nucleophile is...

A weak base (either an anion or a neutral compound with a lone pair of electrons)
 Reactive to partial positive (δ^+) carbon centers (more so than the leaving group)

General Trends in nucleophilicity...

- 1) Across a periodic row, nucleophilicity decreases. Increasing electronegativity decreases lone pair availability ($C^- > N^- > O^- > F^-$). Same as basicity
- 2) For the same atom, higher electron density increases nucleophilicity...ie, $HO^- > H_2O$. Same as basicity.
- 3) Down a group, nucleophilicity increases due to increased polarizability of the nucleophile. ($I^- > Br^- > Cl^- > F^-$) Bigger slosh factor. Opposite of basicity

common reagent	A- nucleophile	pKa (of HA)	relative nuc. (in MeOH)
HI	I ⁻	-10	1
H ₂ S	HS ⁻	7	1
KCN	NC ⁻	9.2	1
HBr	Br ⁻	-9	2
NH ₄ ⁺	:NH ₃	9.2	2
NaCN	NC ⁻	9.2	2
NaOCH ₃	CH ₃ O ⁻	15.5	2
NaOH	HO ⁻	15.7	2
KOH	HO ⁻	15.7	2
NaOCH ₂ CH ₃	CH ₃ CH ₂ O ⁻	15.9	2
NH ₂ R	:NH ₂ R	38	2
NaN ₃	N ₃ ⁻		2
HCl	Cl ⁻	-7	3
HF	F ⁻	3.2	3
KOAc	AcO ⁻	4.8	3
NH ₃	:NH ₃	38	3
H ₂ O	H ₂ O	-1.74	4
LiAlH ₄	H ⁻	35	?

Trends in nucleophilic character are highly dependent on the reaction partner (R-L) and the nature of the solvent.

For example, in protic solvents, weak bases are good nucleophiles because they are less likely to interact (react) with protons in the solvent...either by hydrogen bonding or by outright stripping of hydrogens off water or other species.

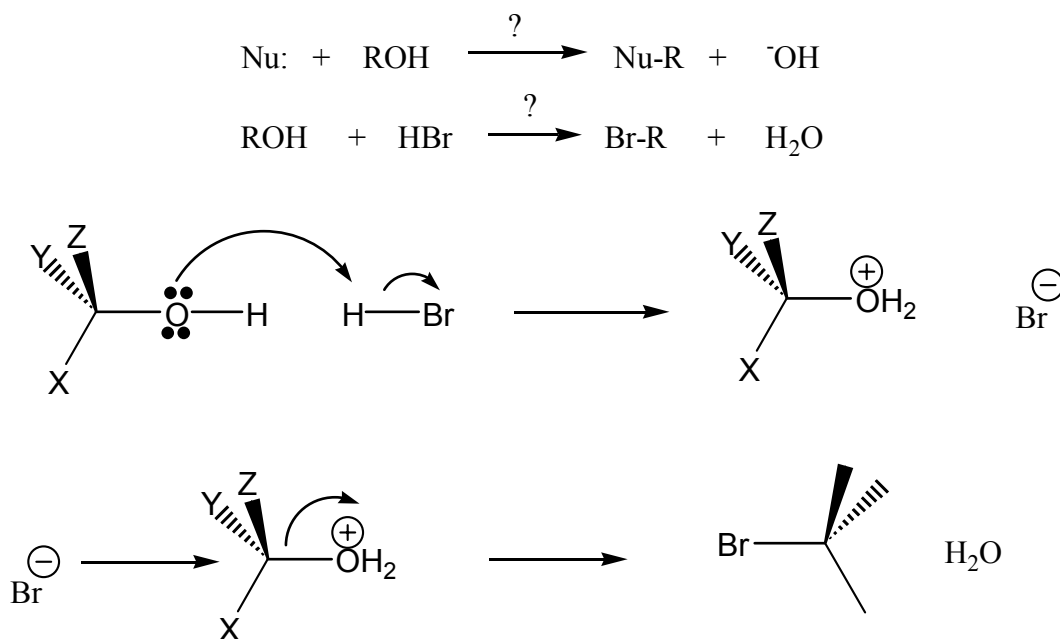
However, in aprotic solvents, the opposite is true.

Strong bases become better nucleophiles...and will readily attack the carbon center.

So, how can halides be both good leaving groups and good nucleophiles?

Remember, reactivity is relative. A good nucleophile need only be more nucleophilic than the leaving group.

TURNING A BAD LEAVING GROUP INTO A GOOD ONE...THE CASE OF -OH



Draw a similar mechanism for S_N2 reaction between HI and $\text{CH}_3\text{CH}_2\text{NH}_2$

Look at the derivatization of -OH to tosylate group (an excellent leaving group)

SOLVENT EFFECTS...

S_N2 reactions are very sensitive to solvent. Why? Polarity and Protons.

Requirements of the solvent...

- 1) get all the reagents into one phase so they can react
- 2) don't interfere with the reaction (react with the nucleophile, or R-L)
- 3) Stabilize the products (and intermediates)

polar protic solvents : H₂O, ROH

anions are solvated due to H-bonding

anions can react to form protonated species (NuH)

polar aprotic solvents : acetone, acetonitrile, DMSO, THF

no H-bonding interaction with Nu. (no solvation of L either)

Nu is free to react.

Apolar aprotic solvents: pentane, benzene, ether, chloroform, etc.

Non-combatants.

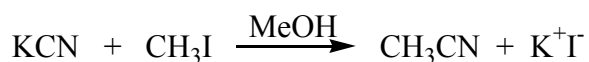
Effects:

- 1) Nucleophiles are more reactive in aprotic solvents as opposed to protic solvents.
- 2) Nucleophiles that are most strongly solvated ("deactivated) in polar protic solvents will benefit the most from aprotic polar solvents.

LAST WORD ON S_N2...

The "2" stands for bimolecular...as in bimolecular kinetics...as in the rate of the reaction depends on the concentration of both the nucleophile and the leaving group.

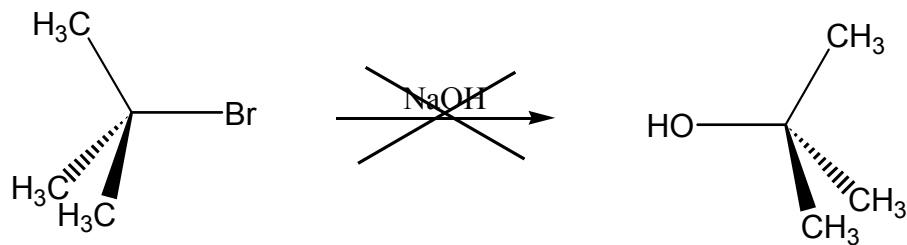
For the reaction...



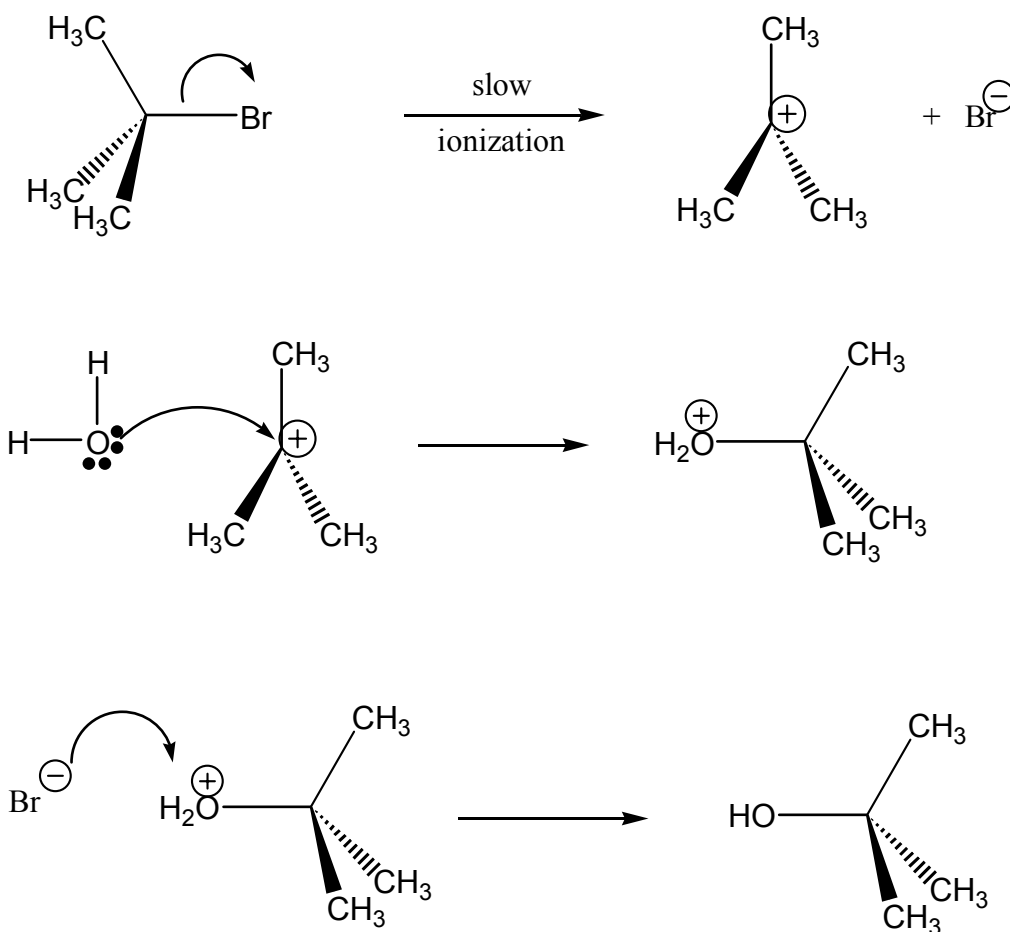
Rate of the reaction = k [CH₃I][KCN]

THE S_N1 REACTION.

We noted that tertiary centers do not undergo S_N2 reaction because of steric hindrance.



What does happen, is that t-butyl bromide reacts with water to give t-butyl alcohol. How does this happen?



The slow step in the reaction is the formation of a tertiary carbocation which is relatively stable under reaction conditions. Since the rate of a reaction is determined by its slowest step, the rate of the above reaction is...

$$R = k [t\text{-butylbromide}]$$

Ergo, Substitution Nucleophilic Unimolecular (or S_N1)

STEREOCHEMISTRY OF S_N1

Reaction mechanism above was written to give an inversion at the carbon center. However, S_N1 mechanisms give racemic mixtures at chiral centers, resulting in loss of optical activity for optically pure starting material.

The exception...excess of inversion product is usually present (+20 %). Due to ion pairing, the inversion pathway is preferentially left unhindered.

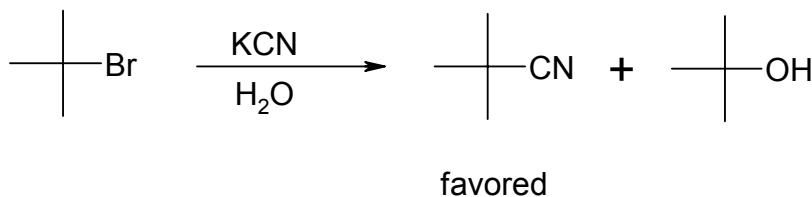
EFFECT OF R GROUP

Must be able to form a relatively stable carbocation in order to react via an S_N1 mechanism.

Tertiary > secondary >>> primary > methyl

NUCLEOPHILE...

Strength of nucleophile determines the bias of the product...DUH.



LEAVING GROUP...

Leaving group is crucial since the rate determining step is loss of the leaving group to give a carbocation. The more stable the L⁻, the better the leaving group...ie, weak base.

SOLVENT...

Solvent that favors (and stabilizes) the formation of carbocations and the anion leaving group. Polar solvents are a must, and the choice between protic or aprotic solvents depends on the Nu and the L groups.