Substitution Reactions

3 - Factors Affecting Substitution Reactions

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Factors Affecting S_N2 and S_N1 Reactions

Now we will look into the factors that affect the two types of reactions. What is it that makes them work well and give the desired product.

There are four main factors that affect substitution reactions.

1. Nature of the Substrate (Subs).
2. Strength of the Nucleophile (Nu^-).
3. Leaving group ability (LG).
4. Solvent used in the reaction.

We will study these in detail here.

1) Nature of Substrate (Subs)

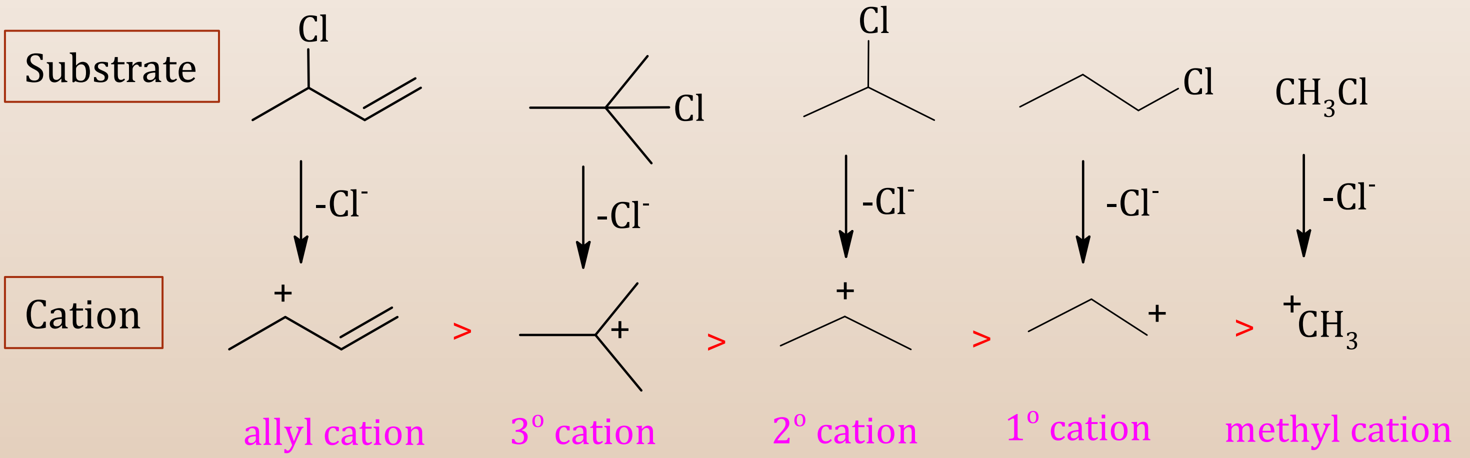
Nature of substrate can affect substitution reactions in different ways; the table below explains all the details of both mechanisms.

Reaction Type	S_N2	S_N1
Mechanism	Back side attack, so it is important for the carbon to be accessible.	Formation of carbocation, so carbocation must be stable.
Steric hinderance	The electrophilic carbon cannot be sterically hindered. It needs to be accessible to the nucleophile.	Crowding is not an issue since the carbocation forms a trigonal planar shape hence nucleophile accessibility is not a problem.
Reactivity of carbon*	CH_3X>> 1° > 2° > 3°	$C{=}C{-}C^+$ > 3° > 2° > 1° >> CH_3X

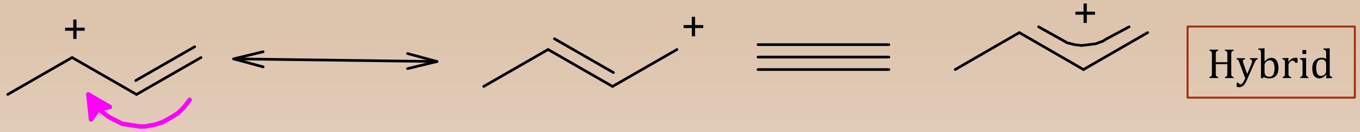
*****The opposite of reactivity is stability. The more stable the carbocation, the more it is able to exist on its own, hence the 3° is least reactive for S_N2 and most for S_N1 reaction.*

1a) Nature of Substrate – Stability of Carbocation

a) **<u>Stability of the Carbocation</u>:** Substrates can be an allylic halide, 3°, 2°, or 1°. Carbocations are formed as shown below.



Carbocation stability order is allylic cation as the most stable and a methyl cation as least stable. Allylic cation is the most stable due to resonance which causes delocalization of charges leading to its stability. Stability of tertiary carbocation is highest due to electron density around the cation, inductive effect, of alkyl groups. More alkyl groups stabilize the carbocation more.



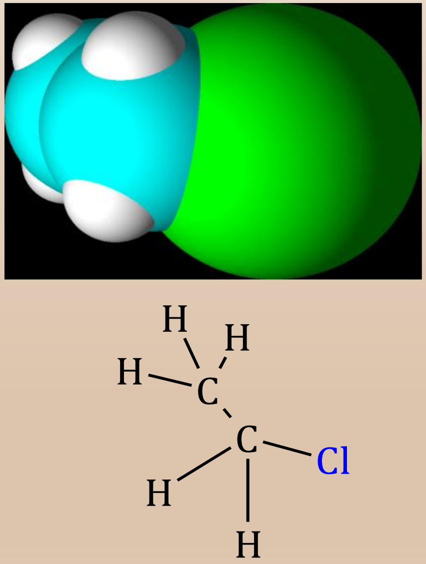
1b) Nature of Substrate – Steric Hinderance

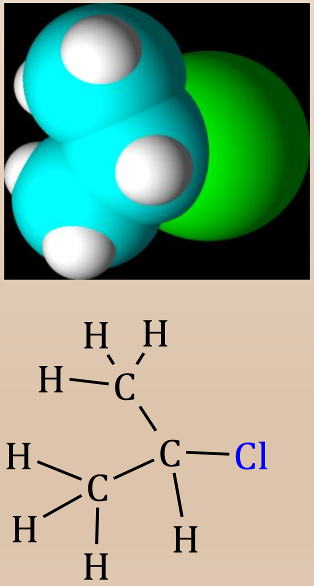
b) <u>Steric Hinderance</u>: Nucleophile approaches from the back side hence the electrophilic carbon should not be hindered/crowded in any way.

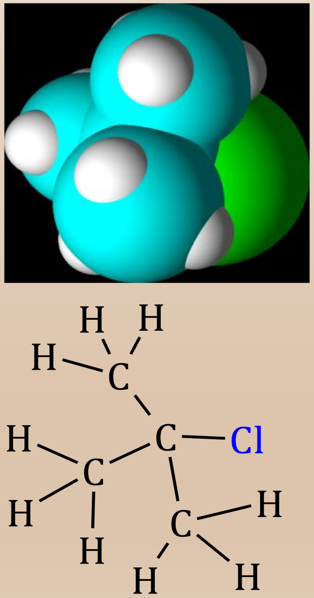
The green atom below is chlorine, while the blue and white represents carbons and hydrogens. The more alkyl groups there are, the harder it is to access the electrophile, the carbon with chlorine.

Best substrates for S_N^2 reactions are primary halides.

$1^o > 2^o > 3^o$







Solved Problem: Nature of Substrates

Classify the substrates below as primary, secondary or tertiary. Predict the mechanism of reaction it will follow and give a reason for it.

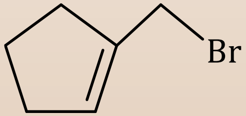
To answer this question you should draw the structure in case a name is given.

ANSWERS

a) 1-chlorobutane

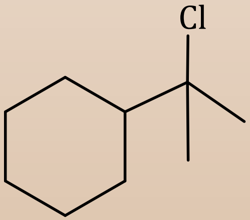
Substrate is 1°, and it should undergo S_N2. There is no steric hinderance and 1° cations are not stable.

b)



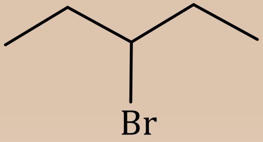
Substrate seems 1°, however, there is a double bond (allylic halide) hence it should undergo S_N1. There will be resonance when the cation forms which is very stable.

c)



Substrate is 3°, and it should undergo S_N1 since 1° cations are stable.

d) 3-bromopentane



Substrate is 2°, and it can undergo either S_N1 or S_N2. There is some steric hinderance however the 2° can be stable also. Reaction will depend on the Nu^-.

2) Nucleophilic (Nu^-) Strength

The nucleophile and leaving group are both electron rich, so why does the nucleophile substitute the leaving group? The nucleophile must be a stronger base/nucleophile than the leaving group.

Strong bases are mostly strong nucleophiles, but not all strong nucleophiles are strong bases*. Below are some criteria that can be used to determine the strength of the nucleophile.

- Charge: In a conjugate acid-base pair, the base (anion) is stronger:

  $OH^- > H_2O$; $NH_2^- > NH_3$
- Periodicity: Decreases left to right on the Periodic Table. More electronegative atoms less likely to form new bond:

  $OH^- > F^-$; $NH_3 > H_2O$
- Size of anion or atom: Increases down the Periodic Table, as size and polarizability increase:

  $I^- > Br^- > Cl^-$
- Electron density and Inductive effect: The more carbons there are on the anion, the more the electron density around the nucleophile and due to the inductive effect, electrons are pushed to the nucleophile making them stronger.

  $EtO^- > MeO^-$; $SH^- > OH^-$.

** Bases are characterized by their ability to abstract a proton while nucleophiles react with electrophiles.*

2) Nucleophile Strength - S_N1 vs S_N2

Size: Larger nucleophiles are not good for S_N2 because steric hinderance will not let them access the electrophilic carbon. E.g., EtO^- better than $tBuO^-$ even though $tBuO^-$ is a stronger nucleophile.

Strength: For S_N2 stronger Nu^- than LG is favorable for the reaction to occur. For S_N1 – strength of Nu^- does not matter, as it is not part of the rate determining step.

Some examples

Strong Nu	Moderate Nu	Weak Nu
$(CH_3CH_2)_3P:$	Br^-	F^-
SH^-	NH_3	H_2O
I^-	CH_3SCH_3	CH_3OH
$(CH_3CH_2)_2NH$	CH_3COO^-	
CN^-		
OH^-		
CH_3O^-		

2) Nucleophiles - How to Make Them

Using Salts for Nu$^-$

In case of simple Nu, like, I^- (NaI), SH^- (NaSH), CN^- (KCN), OH^- (NaOH) the ionic salts can be used. The cation counterions are washed away during the workup of the reaction.

Using Alkoxides (RO$^-$)

$CH_3O^-Na^+$, $CH_3CH_2O^-K^+$ - alkoxides are synthesized as salts: potassium or sodium. They are synthesized by dissolving solid sodium or potassium in the respective alcohol in a moisture and oxygen free environment.

$$CH_3OH + Na \longrightarrow CH_3O^-Na^+ + H_2$$

Alcohol with sodium or potassium hydroxides can also be used but these reactions are not favorable – why?

$$CH_3OH + NaOH \longrightarrow CH_3O^-Na^+ + H_2O$$

Nomenclature of Alkoxides:

Alk is the alkane part and oxide is the usual oxide, hence the nomenclature is easy. Since all these are ionic salts, use the ionic nomenclature of using cation first to name alkoxides. $CH_3O^-Na^+$, sodium methoxide, $CH_3CH_2O^-K^+$ potassium ethoxide, $(CH_3)_3CO^-Na^+$ sodium t-butoxide.

3) Leaving Group (LG)

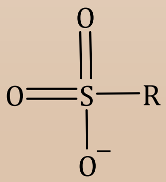
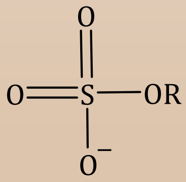
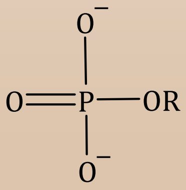
Leaving groups should have certain properties to be considered good.

- LG should be electron-withdrawing to create an electrophilic carbon.
- LG should be stable once it has left (a weak base is more stable than a strong base).
- A weaker base cannot displace stronger base (LG) in a S_N2 reaction.
- Halides are generally good LG.

Leaving group reactivity

$OH^-, NH_2^-, OR^- < F^- < Cl^- < Br^- < I^- < {}^*TsO^-$

Examples of leaving groups

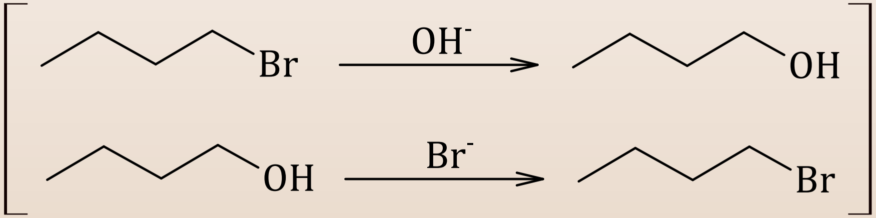
Ionic Nu:	Cl^-, Br^-, I^-	RSO_3^-,	$ROSO_3^-$,	$ROPO_3^{-2}$
	halides	*Sulfonate*	*sulfate*	*phosphate*
				
Neutral Nu:	H_2O,	ROH,	NR_3,	PR_3
	water	*alcohol*	*amines*	*phosphines*

* *Tosylates are organic sulfonates.*

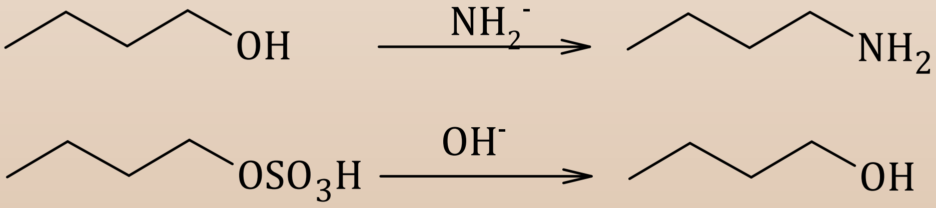
3) Leaving Group - Reaction Examples

Examples:

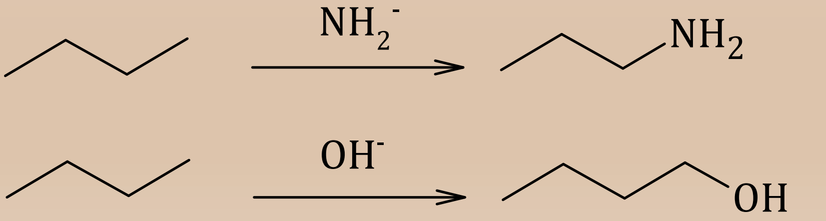
- OH^- can displace Br but Br cannot displace OH so the 2nd reaction will not occur as written.



- Both these reactions can occur since LG is weaker base than Nu^-.



- Some reactions will NOT occur as the LG is most strong of bases.



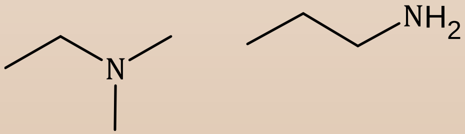
LG is CH_3^-

LG is H^-

Solved Problem: Nature of Nu and LG

Identify the better nucleophile or leaving group in following pairs and give an explanation for your choice.

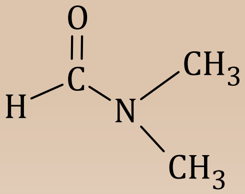
ANSWERS

a) OH^- SH^-	SH^- is better than OH^- because S has a larger size therefore more electron density.
b) 	The alkoxide is better than alcohol because it is negatively charged.
c) 	The first amine is 3° and is better than 1° because it has the inductive effect of all the alkyl groups around it.
d) $CH_3CH_2O^-$ $(CH_3)_2CHO^-$	The second alkoxide is more electron rich from the inductive effect of more CHs near the oxide.

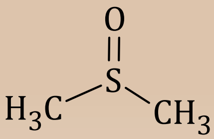
4) Solvents

There are three kinds of solvents: polar protic, polar aprotic and nonpolar.

Solvent	Polar Protic	Polar Aprotic	Nonpolar
Characteristic	Have an acidic proton High boiling points.	Polar solvent with no acidic proton High boiling points.	Nonpolar solvents Low boiling points.
Examples	H_2O CH_3OH, CH_3CH_2OH	DMF (dimethyl formamide), DMSO (dimethyl sulfoxide) *Shown below*.	Hexane Toluene Diethyl ether Dichloromethane
Comments	Will form H-bonds with Nu and are good for $S_N{}^1$ since they will	Does not form H-bond with Nu but still helps to solvate ions hence the best kind for S_N2	Not good for $S_N{}^2$ since they will not stabilize the ions formed.



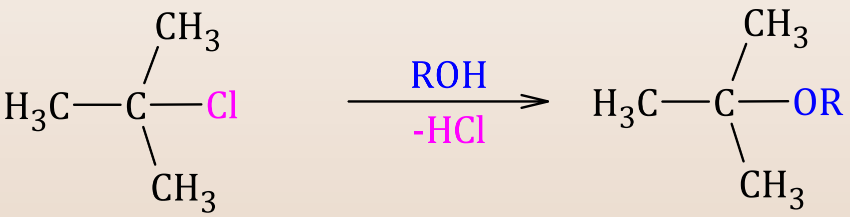
DMF



DMSO

4) Solvents – Rate of Reaction

Polar solvents help with ionization and stability of the carbocation.



	Ethanol	60% Ethanol in water	20% Ethanol in water	Water
Reactivity	1	100	14,000	100,000

S_N2 and S_N1 Characteristics

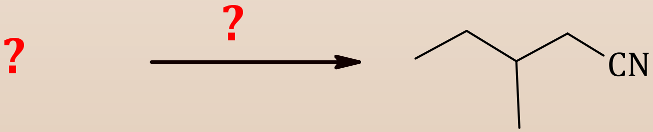
	S_N2	S_N1
Substrate	Primary or methyl	Tertiary
Nucleophile	Strong nucleophile	Weak nucleophile (may also be solvent)
Solvent	Polar aprotic solvent	Polar protic solvent
Kinetics	[substrate][Nu]	[substrate]
Stereochemistry	Inversion	Racemic mixture
Rearrangement	No	Yes

Solved Problem: Predicting reactants, Nu⁻, products and mechanism.
Predict the missing reagent, reactant or product (with proper stereochemistry) in the following reactions. Which substitution mechanism is being followed in each reaction.

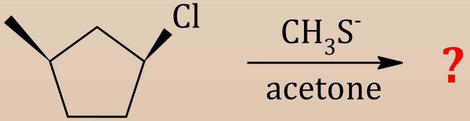
To answer this question, you should draw the structures of the reactant and/or product.

a) S-2-bromobutane $\xrightarrow{\text{methoxide}}$?

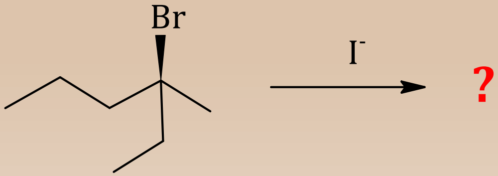
b)



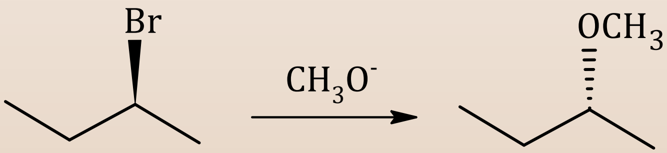
c)



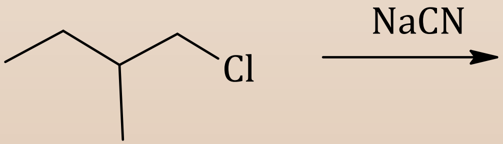
d)



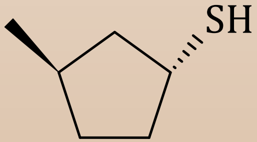
ANSWERS



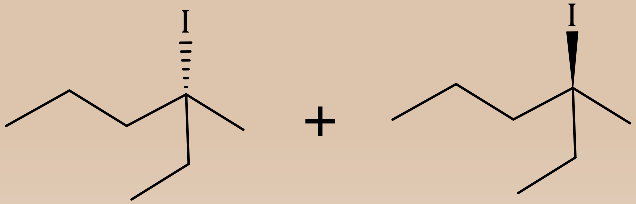
S_N2



S_N2



S_N2



S_N1

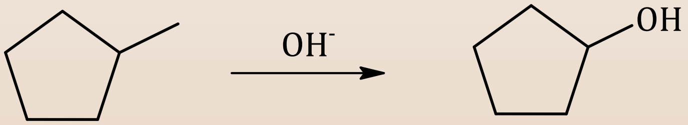
Solved Problem: Predicting occurrence of reactions.

Predict if the following reactions will occur or if there is anything wrong with them. What mechanism is expected? Explain your answer.

To answer this question, you should draw the structures of the reactant and/or product.

ANSWERS

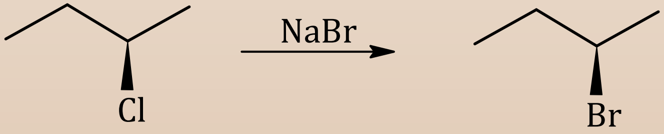
a)



This reaction cannot occur because the LG is CH_3^- which is a very strong base and OH^- is not strong enough to displace it.

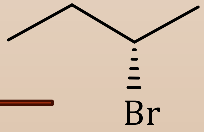
S_N2

b)

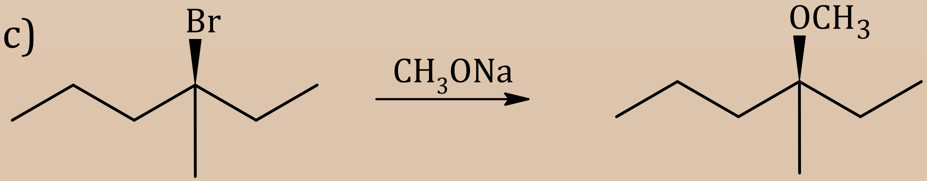


This reaction will occur as Br^- is stronger Nu^- than Cl^-, the product should have inversion of stereochemistry.

S_N2

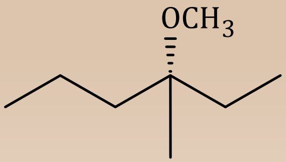


c)



This reaction will occur as written however, there is another product with inversion of stereochemistry.

S_N1



Key Words/Concepts

- Substitution Reaction
- Nucleophile
- Electrophile
- Leaving group
- 1st order reaction (unimolecular)
- 2nd order reaction (bimolecular)
- Transition state
- Rate determining step
- Carbocation
- Polar protic solvent
- Polar aprotic solvent
- Nonpolar solvent