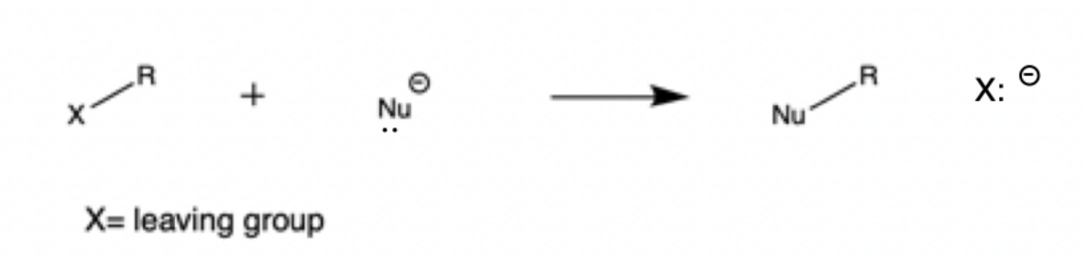
CHEM 261 February 28, 2023

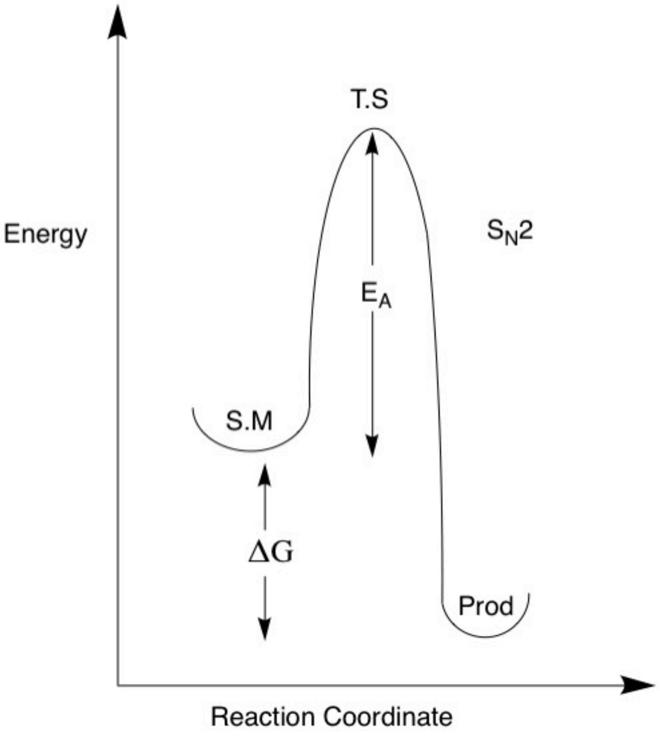
Recall the following about substitution reactions:



Characteristics of S_N2 reactions:

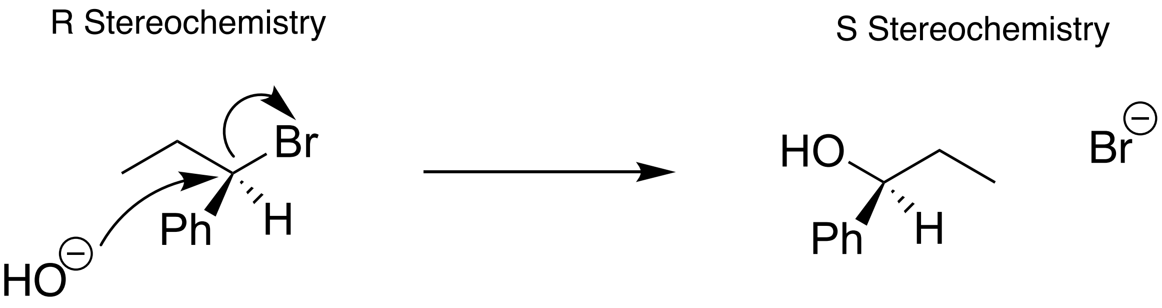
- Concerted
- Stereospecific
- Rate dependent on the concentration of nucleophile and substrate
- Works for 1° and 2° but not 3°

Energy Diagram of S_N2 Reaction



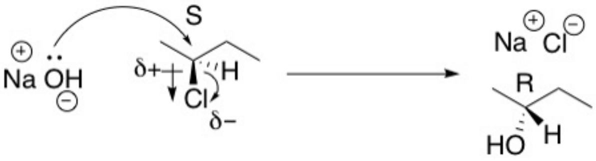
There is no intermediate in the S_N2 reaction, as it is concerted.
The only step is the rate determining step.

Mechanism of S_N2 Reaction



S_N2 always inverts stereochemistry
Favored conditions are with less steric bulk, primary best and secondary okay

S_N2 Mechanism Example 2



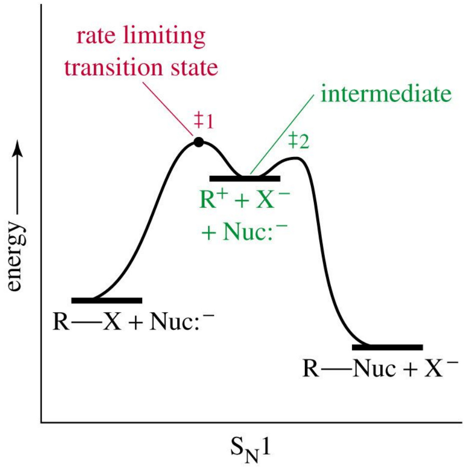
Reverse reaction will not occur.
Inversion of configuration.

- **Concerted**: The bonds of the starting material break at the same time that the product bonds form.
- **Stereospecific**: stereochemistry of the starting material determines the stereochemistry of the product.

Characteristics of S_N1 reactions:

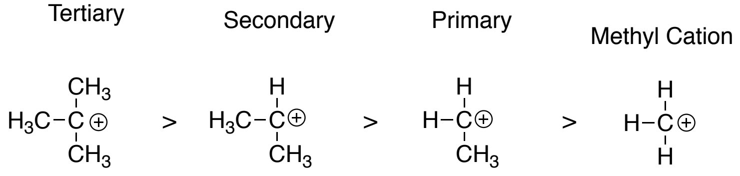
- Stepwise
- Carbocation intermediates
- Rate dependent on concentration of substrate only
- Not stereospecific
- Favoured by heat or acid
- Works for 3° and sometimes 2° but never 1°

Energy level diagram of S_N1



Favored conditions are with stabilized carbocation – more substitution

Carbocation Stability:


Tertiary

Secondary

Primary

Methyl Cation

$$(CH_3)_3C^{\oplus} > (CH_3)_2CH^{\oplus} > CH_3CH_2^{\oplus} > CH_3^{\oplus}$$

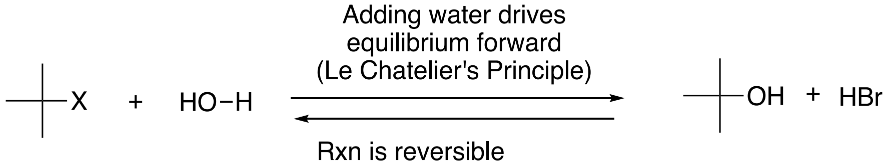
Most stable

The 3 alkyl groups donate e$^-$ density into the positive charge

Least stable (no S_N1)

Example: Tertiary Halide

-No S_N2 possible, sterically crowded – does work by S_N1


Adding water drives equilibrium forward (Le Chatelier's Principle)

Rxn is reversible

3° halide

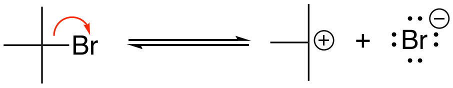
X = Br

No S_N2

S_N1 occurs

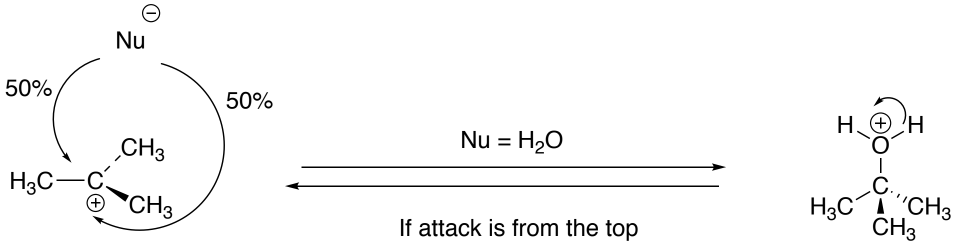
Mechanism of S_N1:

The bromine group leaves (Step 1) with its electrons from the covalent bond, leaving behind a reactive carbocation intermediate

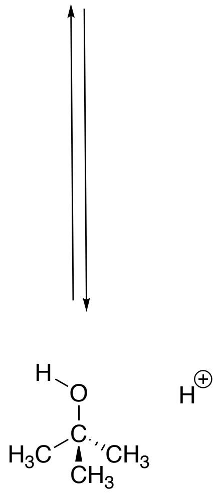


Carbocation intermediate

Carbocation intermediate is planar, so the nucleophile can attack from the top or bottom



Planar carbocation intermediate
sp^2, bond angle 120°



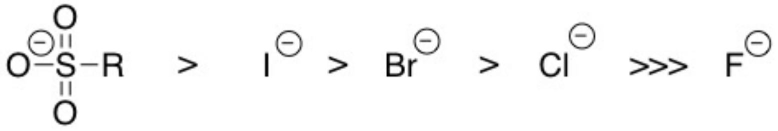
Due to the 50/50 chance of attcking from the top or bottom, the reaction is not stereospecific and stereochemistry is lost.

sp^3, tetrahedral, bond angle 109°

Summary of

S_N1 vs S_N2	***S_N1***	***S_N2***
RDS	Unimolecular	Bimolecular
Main barrier	Carbocation stability	Steric bulk
Alkyl halides	3° > 2° >> 1°	1° > 2° >> 3°
Nucleophile	Neutral/weak	Charged/strong
Stereochemistry	Mixture	Inversion

Good leaving groups



-OH or -OR can also act as leaving groups but they must first be transformed into H_2O or HOR by a strong acid

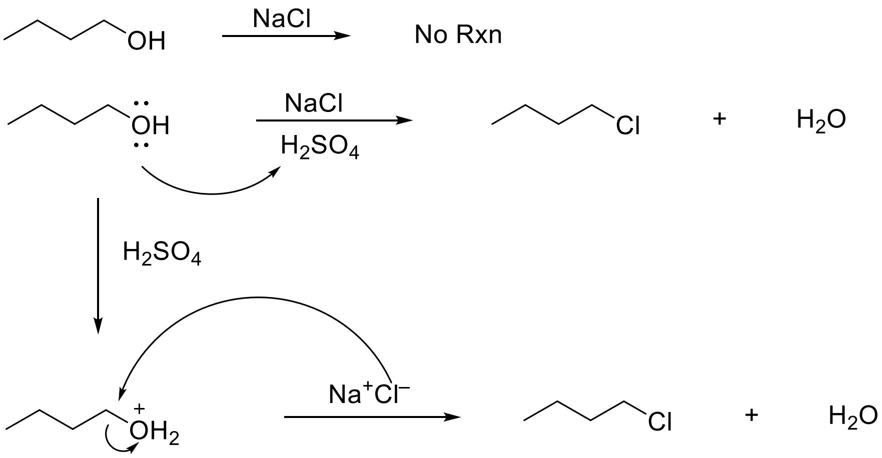
Never leaving groups: (negative charge not stabilized):


F^{-} $\quad {}^{-}OH$ $\quad {}^{-}OR$ $\quad {}^{-}NR_2$ $\quad R:^{-}$

Fluorine, though electronegative, is a bad leaving group as it is small and poorly solvated.

Leaving group activation:

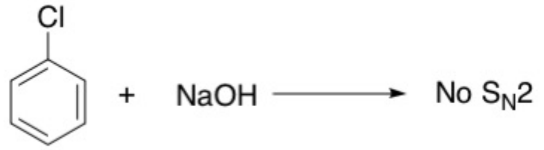
1) Protonation

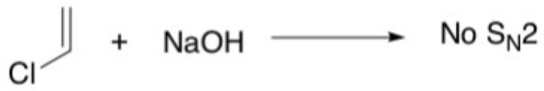


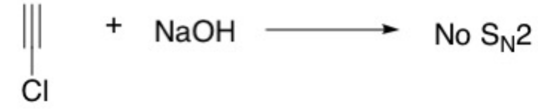
Highlights:

- H_2SO_4 is a proton (H^+) donor.
- ${}^{-}OH$ is transformed into a better leaving group via protonation of the O atom.
- Cl^{-} can then attack via S_N2, kicking off H_2O in the process.

S_N2 will **<u>not</u>** occur on carbon sites that have multiple bonds.

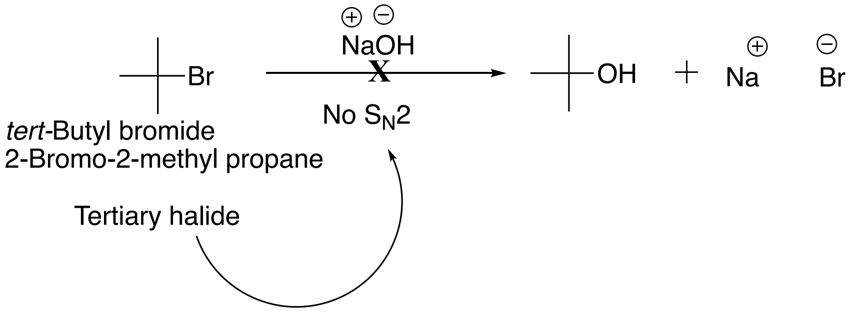






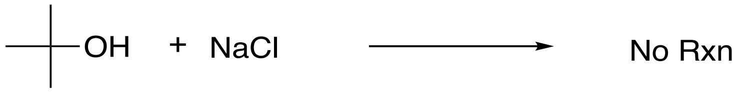
<u>REVIEW:</u> S_N yes or no? Examples

Ex #1) Will <u>NOT</u> proceed – no S_N



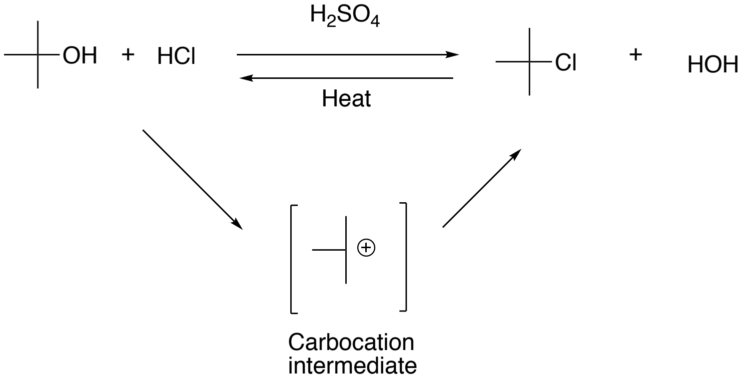
Note: alkyl groups stabilize carbocation intermediate by donating a negative charge
Note: will undergo elimination reaction (explanation of what this is comes later)

Ex #2)

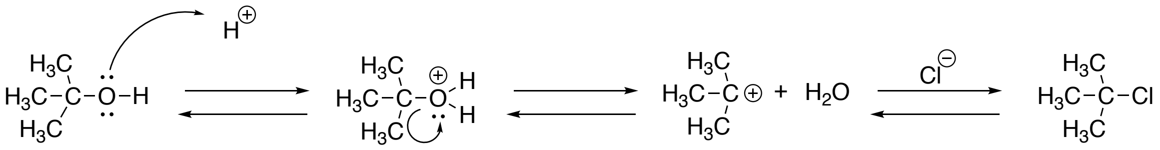


$^{\ominus}$OH is never a good leaving group

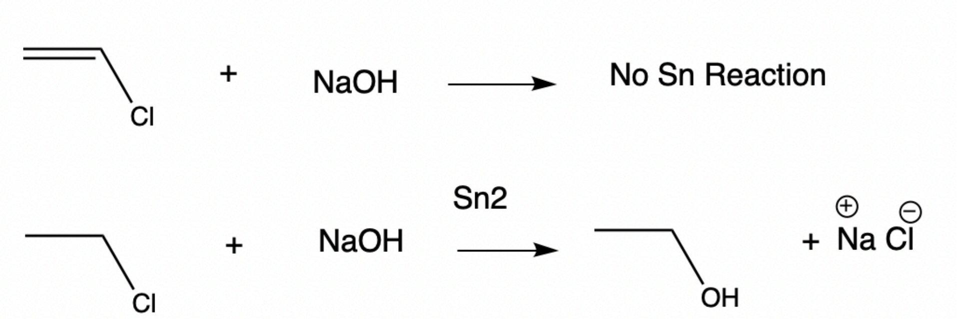
Ex #2a) Works with Acid as S_N1 Mechanism



Mechanism:

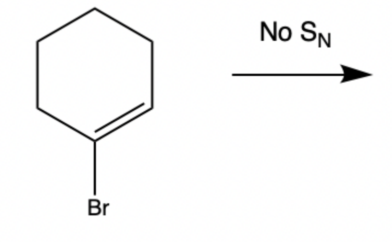


Ex #3)

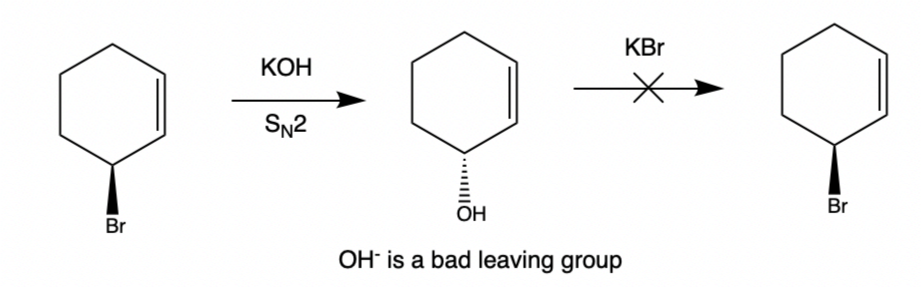


A carbon attached to a double bond cannot undergo a substitution reaction
The carbon with the leaving group must be sp^3 to undergo a substitution reaction

Ex #4)



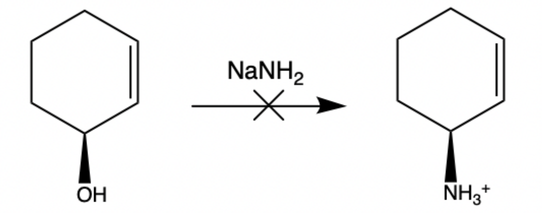
Ex #5)



OH$^-$ is a bad leaving group

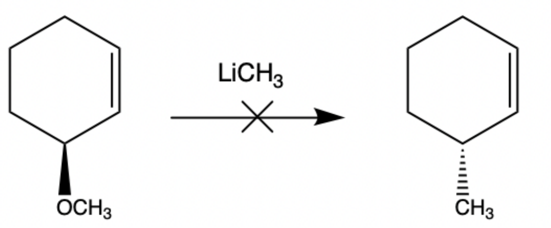
Inversion of stereochemistry indicates S_N2

Ex #6) Will not work



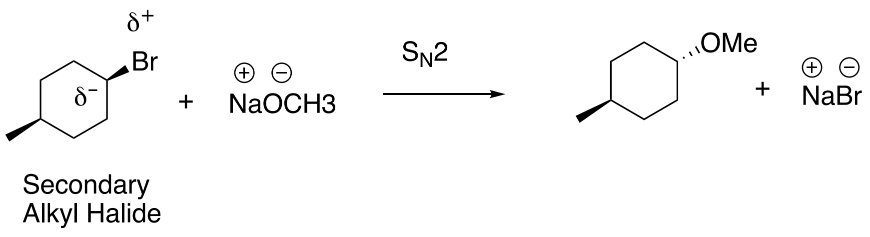
Note: these reagents will undergo an acid/base reaction rather than a substitution

Ex #7) will not work



$^-OCH_3$ is a BAD leaving group

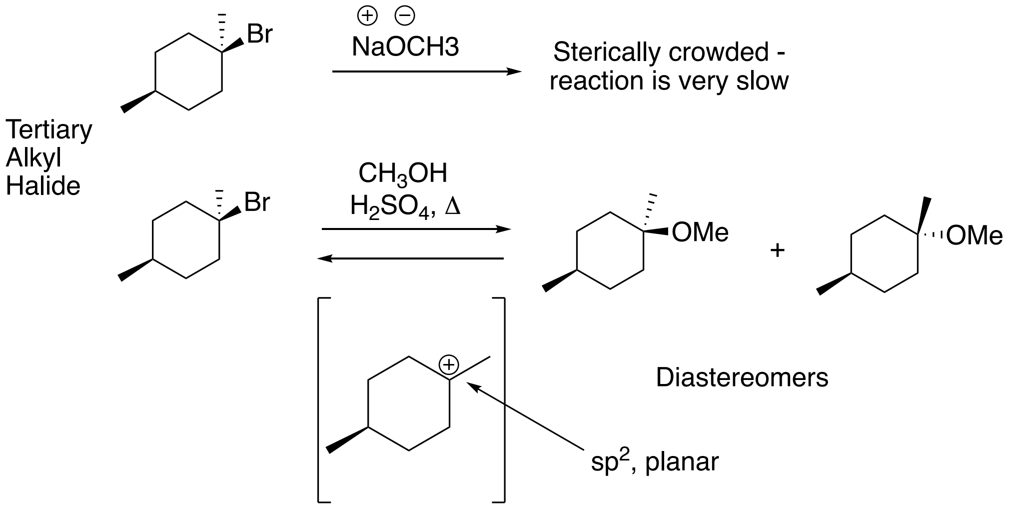
Ex #8)



Secondary
Alkyl Halide

–OCH_3 is a strong, negatively charged nucleophile, so it favors a S_N2 mechanism

Ex #9)



Tertiary Alkyl Halide

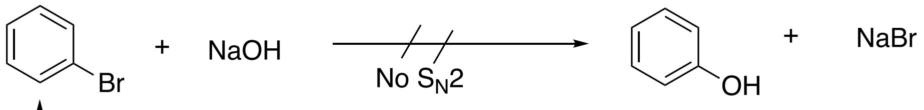
Sterically crowded - reaction is very slow

Diastereomers

sp^2, planar

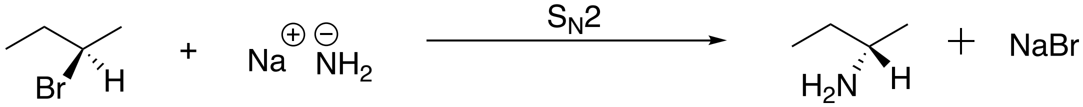
Note: the products are achiral

Extra examples:
Ex #1)



Halide attached to a double bond

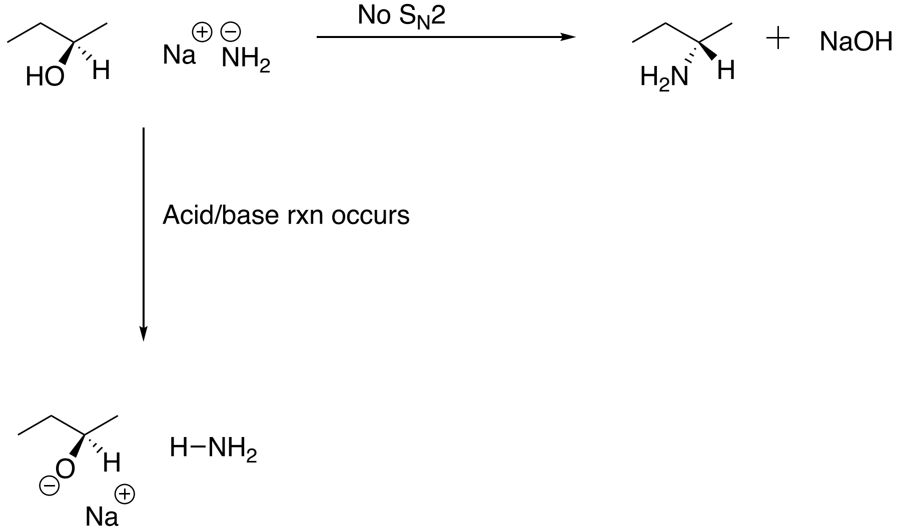
Ex #2) This one can work in principle



2-Bromobutane

Ex #3) The one below does NOT work

$^{\ominus}$OH, $^{\ominus}$OR, $^{\ominus}NR_2$ are never good leaving groups

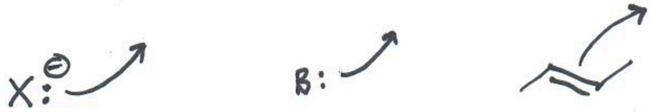


In this reaction, the NH_2 species will pull off the most acidic proton (the one on the alcohol) to from an **alkoxide** instead of undergoing an S_N2 reaction

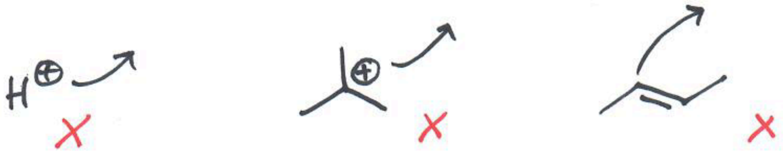
REACTION MECHANISMS

Curly arrows show movement of electrons

↑ negatively charged



NEVER

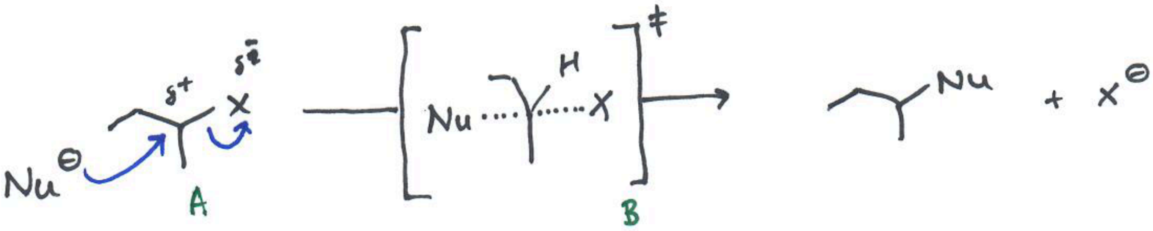


NUCLEOPHILIC SUBSTITUTION

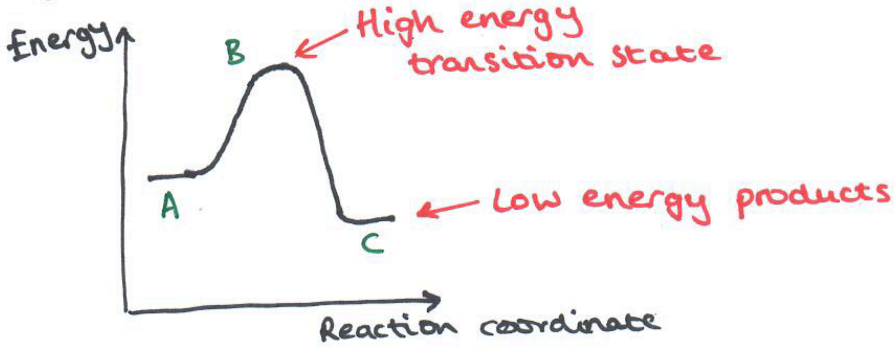
SN2

* Bimolecular nucleophilic substitution

CONCERTED (all at once)



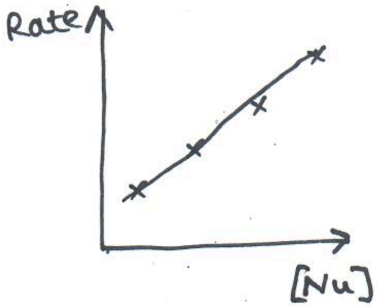
* Energy diagram

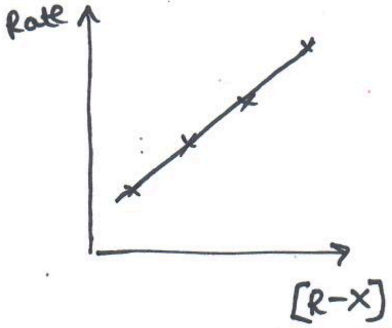


High energy transition state

Low energy products

* Rates of reaction



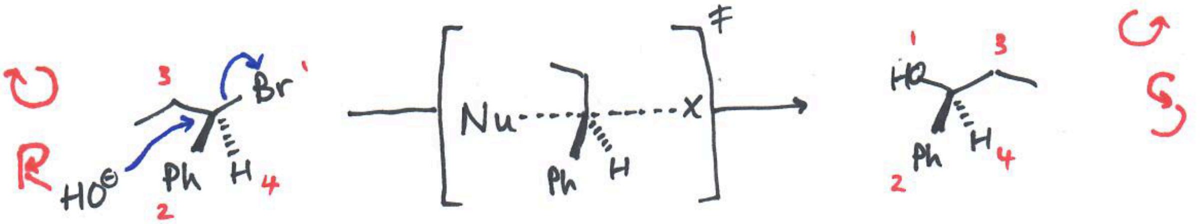


Increased rate with increased [Nu] and [R-X]

∴ Bimolecular – two components in RDS

↖ Rate determining step.

* Stereochemistry

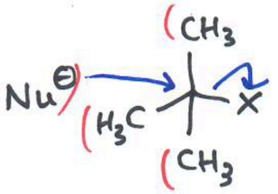


(Ph = phenyl = )

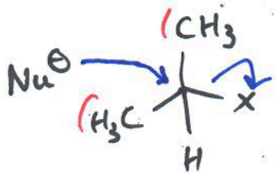
S_N2 always <u>inverts</u> stereochemistry

* Favoured conditions?

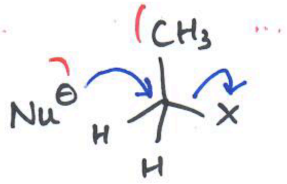
Less STERIC BULK



3°



2°

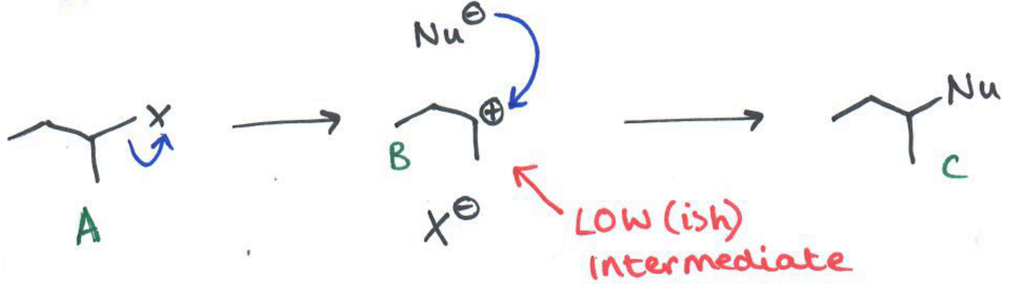


1°

S_N1

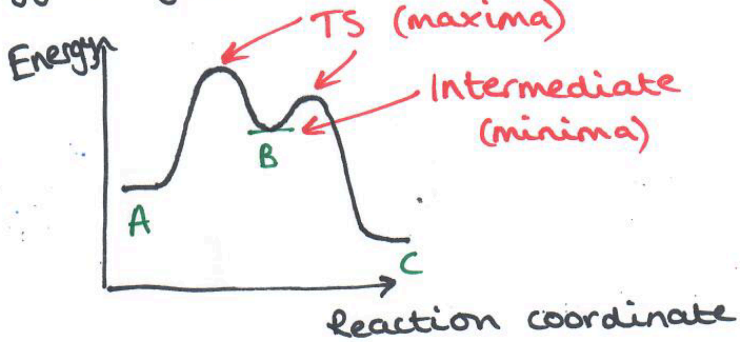
* Unimolecular nucleophilic substitution

STEPWISE mechanism (one at a time)



LOW (ish) intermediate

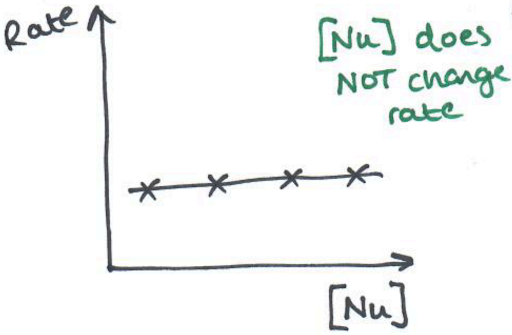
* Energy diagram



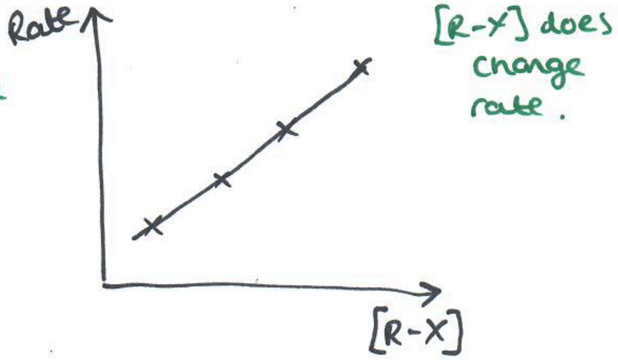
TS (maxima)

Intermediate (minima)

* Rates of reaction



[Nu] does NOT change rate

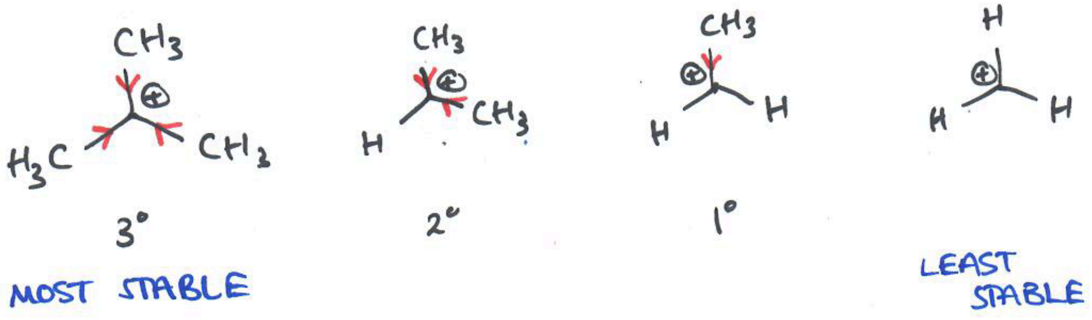


[R-X] does change rate.

∴ Unimolecular RDS

* favoured conditions?

Stabilise the CARBOCATION

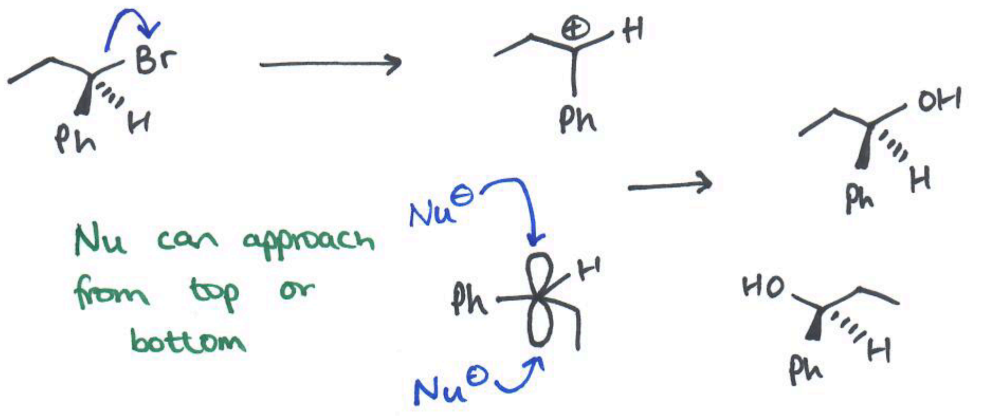


∴ S_N1 favoured for <u>more</u> substituted.

S_N1 vs. S_N2

	S_N1	S_N2
RDS	Unimolecular	Bimolecular
Main barrier	Carbocation stability	Steric bulk
Alkyl halides	3° > 2° >> 1°	1° > 2° >> 3°
Nucleophile	Neutral/weak	Charged/strong
Stereochemistry	Mixture	Inversion

S_N1 stereochemistry

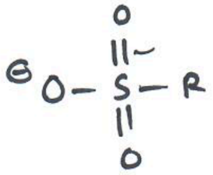


Nu can approach from top or bottom

S_N1 always gives both inversion + retention

LEAVING GROUPS

☺ Good leaving groups



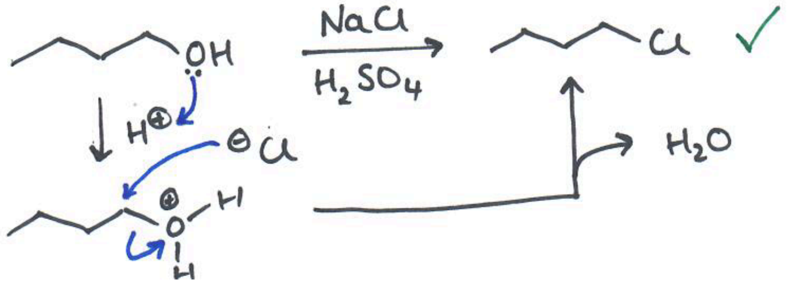
$^{\ominus}O-S(=O)_2-R > I^{\ominus} > Br^{\ominus} > Cl^{\ominus} \ggg F^{\ominus}$

(sulfonate)

☹ Bad leaving groups

$F^{\ominus}$ $^{\ominus}OH$ $^{\ominus}OR$ $^{\ominus}NR_2$ $R^{\ominus}$

Can we make any leaving groups better?



H_2O is a MUCH better LG than $^{\ominus}OH$

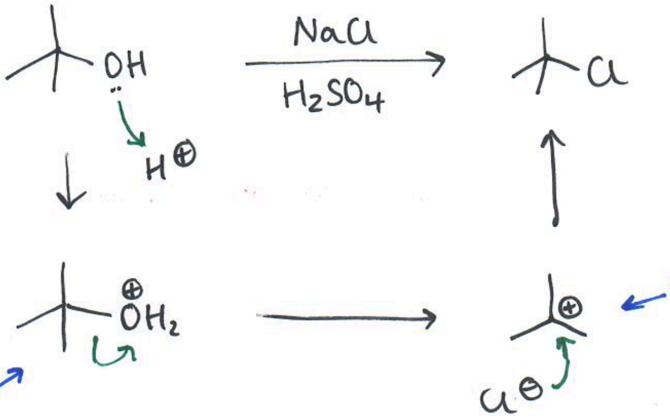
Examples

1)

No reaction

$^{\ominus}OH$ is not a good LG

2)



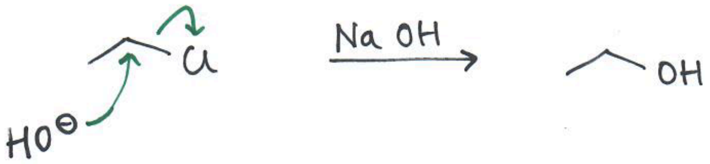
$H^{\oplus}$ helps OH become a good LG (H_2O)

Stable carbocation

3° so likely S_N1

3)

No reaction



S_N2 reaction because 1° halide + strong $Nu^{\ominus}$

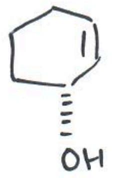
4)

No reaction

5)

Inversion indicates S_N2

6)



$\xrightarrow{KBr}$ No reaction

$^{\ominus}OH$ is a bad LG!

7)

$\xrightarrow{NaNH_2}$ No reaction

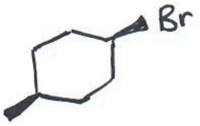
$^{\ominus}OH$ is a bad LG AND $^{\ominus}NH_2$ can act as a base

8)

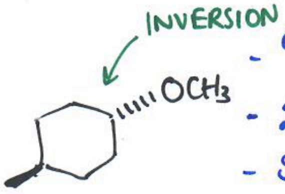
$\xrightarrow{LiCH_3}$ No reaction

$^{\ominus}OCH_3$ is a bad LG

9)



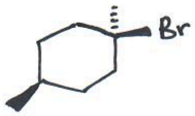
$\xrightarrow[S_N2]{NaOCH_3}$



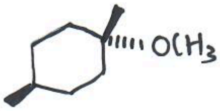
- $^{\ominus}Br$ good LG
- 2° alkyl halide
- Strong $Nu^{\ominus}$

Note - 2° are often hardest to determine S_N1/S_N2

10)



$\xrightarrow{NaOCH_3}$



S_N2 but v. slow!

↑ because of steric bulk

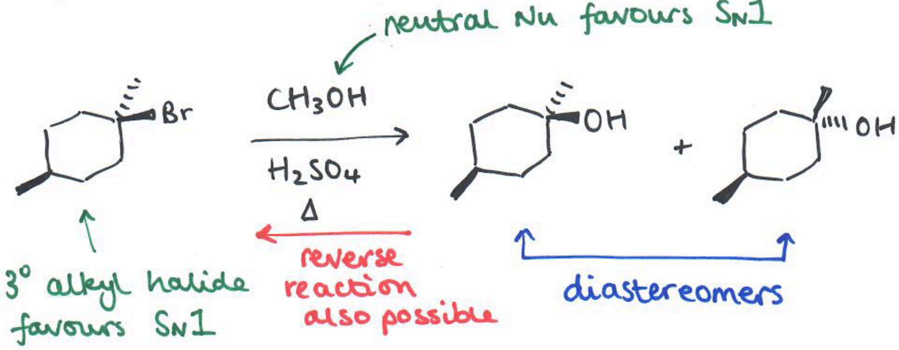
3° alkyl halide - so why not S_N1?

↳ charged nucleophile

Unlikely to form as a low energy intermediate in the presence of $^{\ominus}OCH_3$

11) How can we make the previous reaction work better?

↳ favour S_N1



neutral Nu favours S_N1

3° alkyl halide favours S_N1

reverse reaction also possible

diastereomers