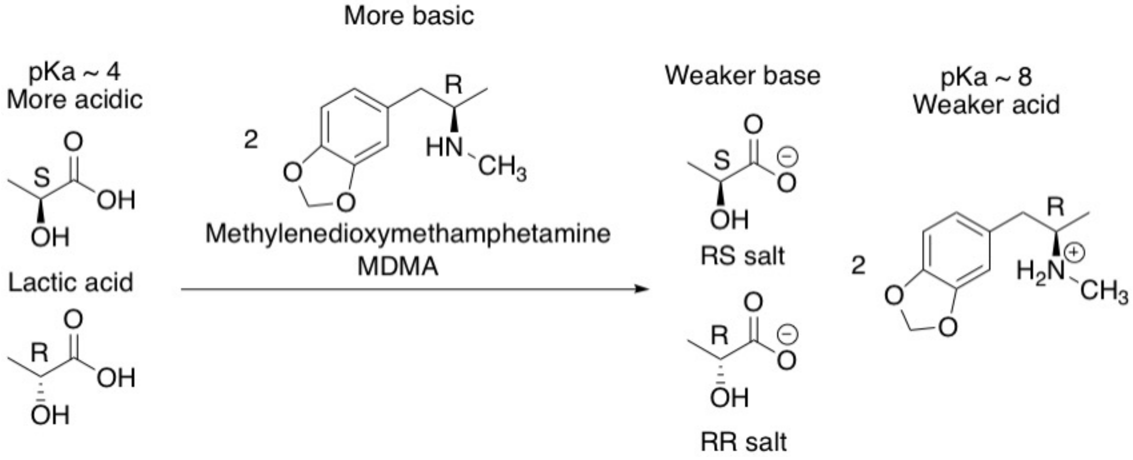
Resolution of Enantiomers

Definition: separation of two enantiomers

- Requires a chiral reagent to convert enantiomers to diastereomeric salts

Racemic mixture: 1:1 ratio of enantiomers in a mixture

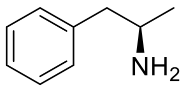
Example: Lactic Acid



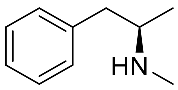
The starting material lactic acids are enantiomers of each other.

By reacting enantiomers to make a salt with an enantiomer of MDMA (another chiral molecule that is optically pure), also known as ecstasy, one can obtain salts which are now diastereomers of each other (RS and RR). The resulting diastereomers have different melting points, boiling points, solubilities, and can be separated by crystallization.

More examples of amines:

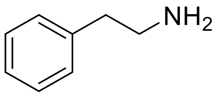


Amphetamine



Methamphetamine

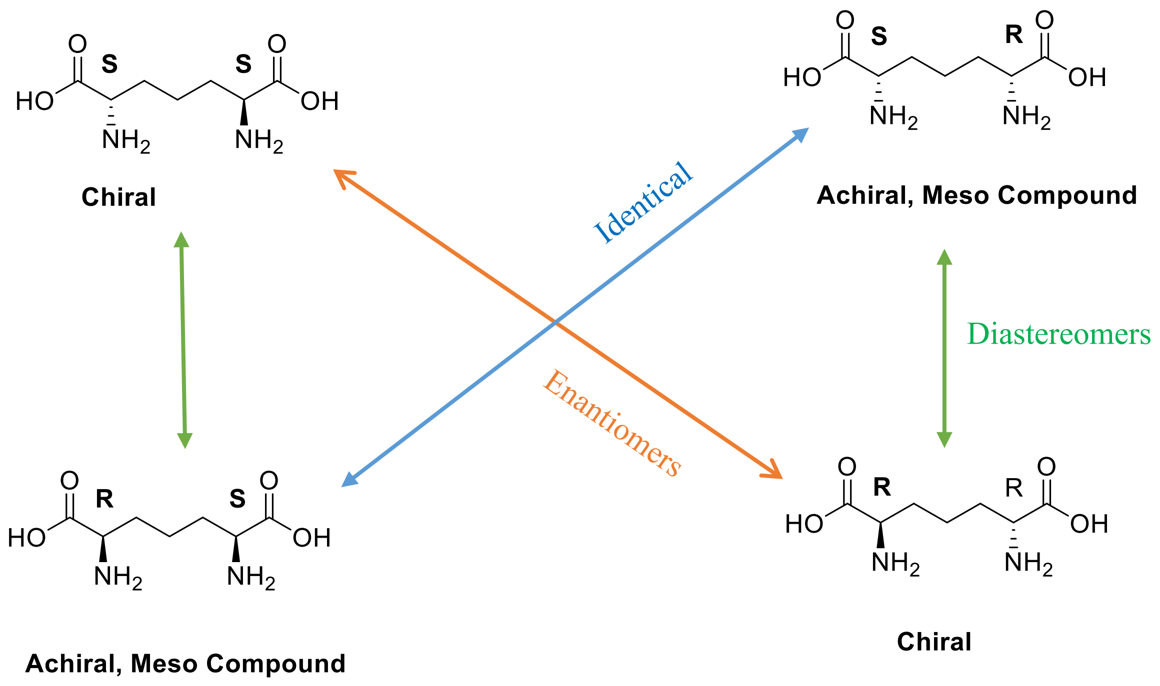
Methedrine= speed



Cannot be used for resolution of enantiomers.

Need a stereogenic centre

Review of concepts:



Substitution Reactions

Remember: Radical Substitution

1) Homolytic bond breaking

$$A{-}B \longrightarrow A\cdot \quad \cdot B$$

Example:

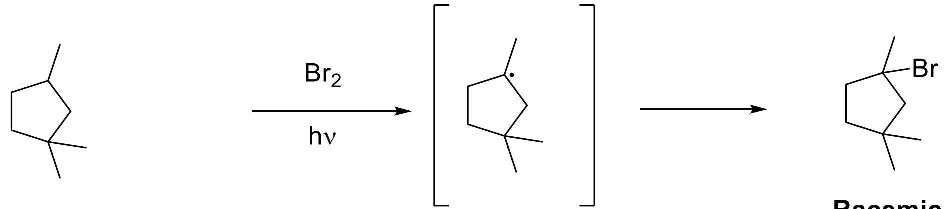
$$R\text{-}H \quad + \quad X_2 \xrightarrow{\text{light}} R\text{-}X \quad + \quad H\text{-}X$$

Proceeds by a radical mechanism

Alkane

X=F, Cl, Br
Not I

Alkyl Halide



1,1,3-trimethylcyclopentane

Racemic

Note: Although radicals are sp^3 hybridized, rapid inversion around the central C results in a loss of stereochemistry. Hence, the resulting product would be a racemic mixture.

2) Heterolytic Bond Breaking (<u>Ionic Substitution)</u>

$$\overset{\oplus}{M}\ \ Nu\overset{\ominus}{:}\ \ +\ \ R\text{-}X \longrightarrow Nu\text{-}R\ \ +\ \ \overset{\ominus}{:X}\ \ \overset{\oplus}{M}$$

Nucleophile
(Seeks positive
charge)

Alkyl Halide

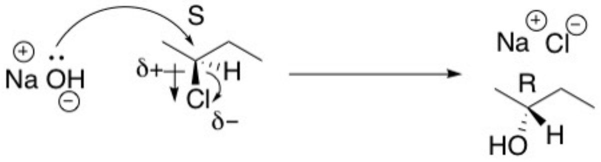
Nucleophile is a substance that seeks positive charge

Types of Nucleophilic Substitution (S_N)

S_N1 - rate depends on 1 concentration

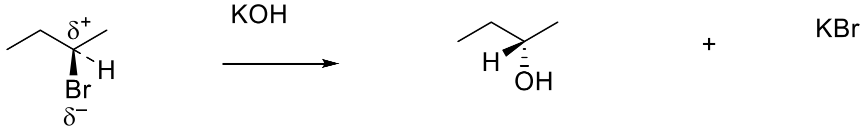
S_N2 - The rate is dependent on the concentration of the nucleophile and the electrophile (2 concentrations)

Sn2 Mechanism

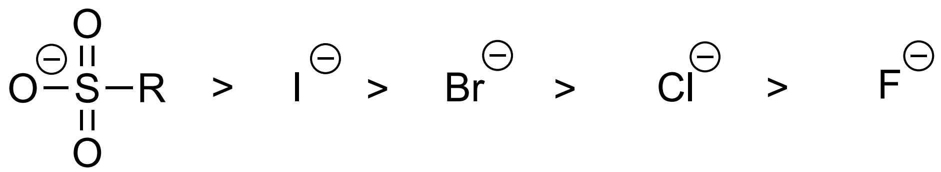


Reverse reaction will not occur.
OH^- is a terrible leaving group
- **Rate**: Depends on concentration

- Inversion of configuration (**Walden inversion)**
- **Concerted**: The bonds of the starting material break at the same time as the product bonds form.
- **Stereospecific**: stereochemistry of the starting material determines the stereochemistry of the product.
- Works for CH_3–X, R–CH_2X, R_1R_2CHX.



Good leaving groups:

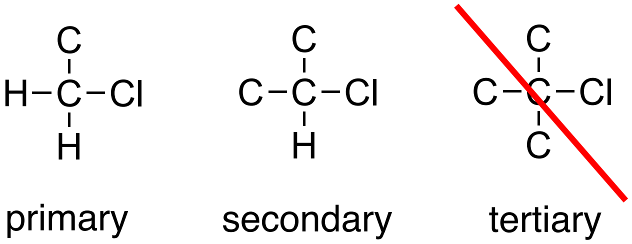


$^{\ominus}O-SO_2-R > I^{\ominus} > Br^{\ominus} > Cl^{\ominus} > F^{\ominus}$

Bad leaving groups:

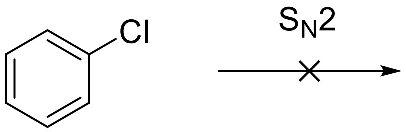
$H^{\ominus}$ $R^{\ominus}$ $NR_2^{\ominus}$ $OR^{\ominus}$ $OH^{\ominus}$

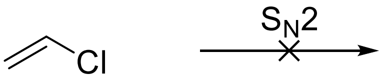
Leaving groups must be connected to a primary or secondary carbon (carbon that has at least one hydrogen, preferably 2)

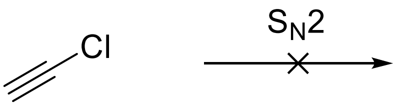


HOH, HOR are okay leaving groups, but need to protonate with acid before it can leave

Examples of reactions that do not proceed via S_N2

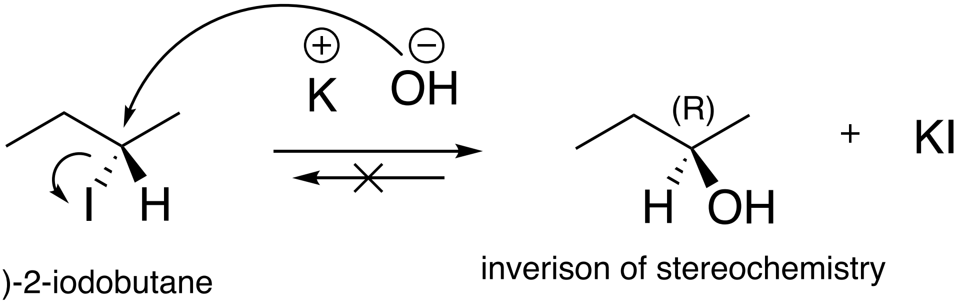


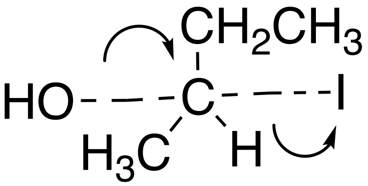




Another example of mechanism of S_N2 reaction

As such, the reaction below is not reversible:

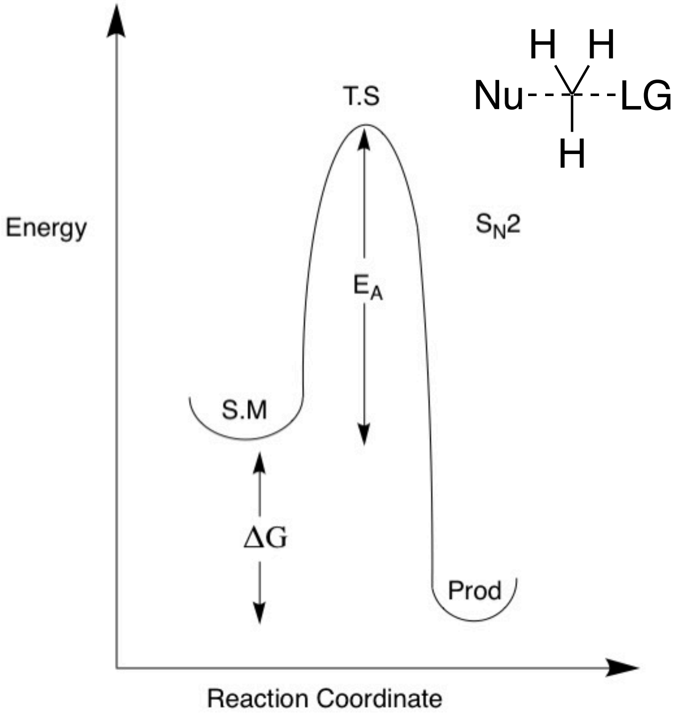




S_N2 always inverts stereochemistry, (Walden inversion)

Favored conditions are with less steric bulk, primary best and secondary okay

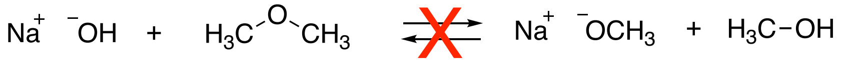
Energy Diagram of S_N2 Reaction



There is no intermediate in the S_N2 reaction, as it is concerted. S_N2 reactions are stereospecific.

Example:

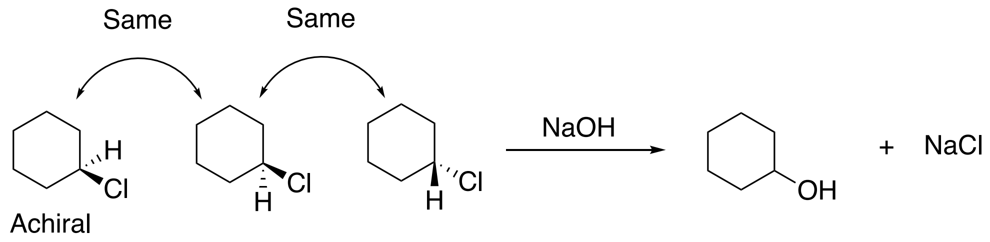
1)



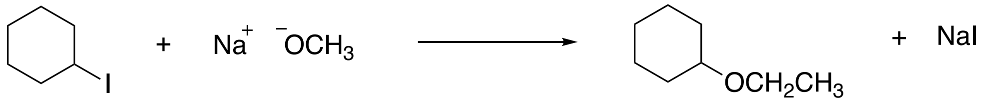
$Na^+ \; ^-OH + H_3C-O-CH_3 \; \cancel{\rightleftharpoons} \; Na^+ \; ^-OCH_3 + H_3C-OH$

Note: Methoxide (CH_3O^-) and hydroxide (^-OH) are bad leaving groups

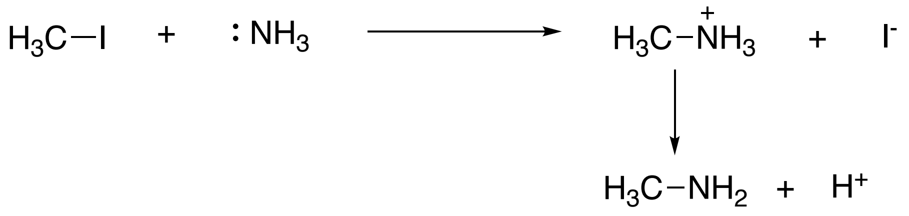
2)



3)



4) Neutral leaving group containing lone pair

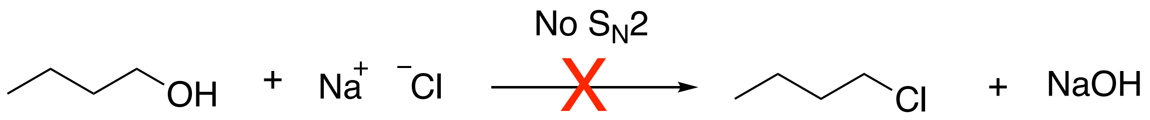


$H_3C-I + :NH_3 \longrightarrow H_3C-\overset{+}{N}H_3 + I^-$

$\downarrow$

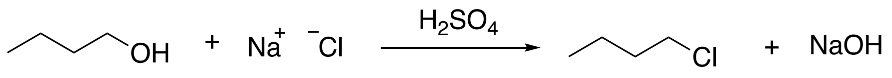
$H_3C-NH_2 + H^+$

5)

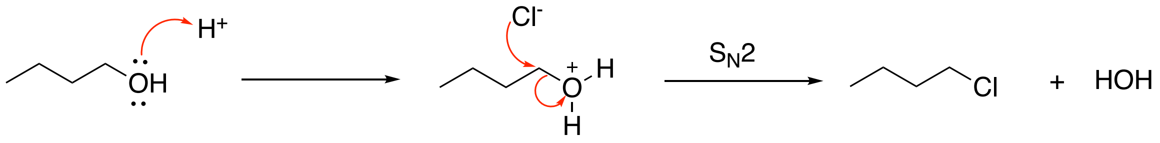


Note: OH is never a leaving group but if you add a strong acid or the reaction happen in a strongly acidic condition (see next example), the reaction will occur

6)

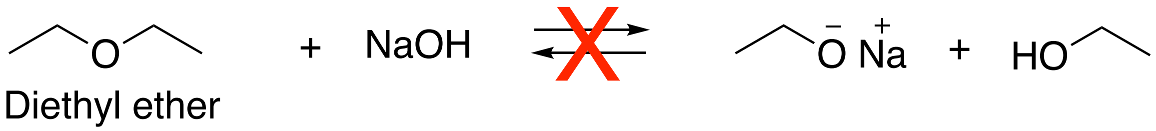


Mechanism:



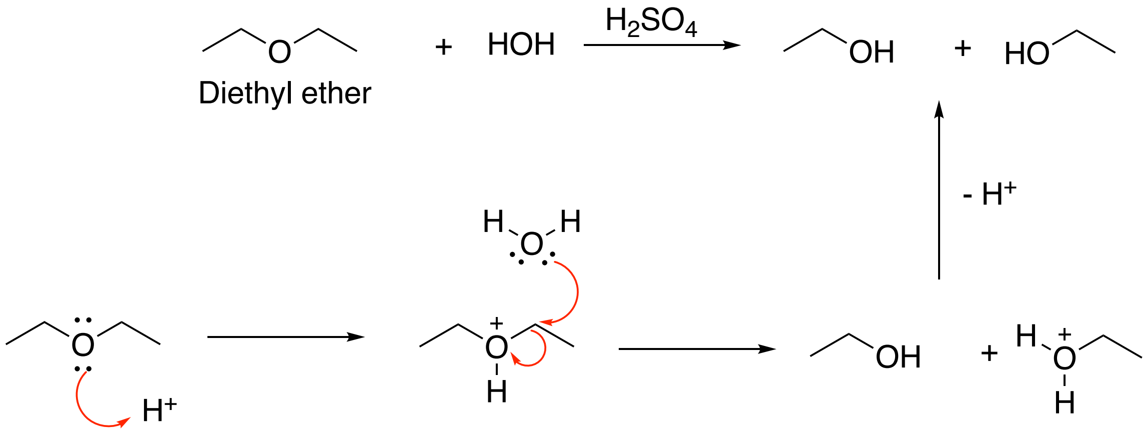
Note: The leaving group in this reaction is now HOH

7)

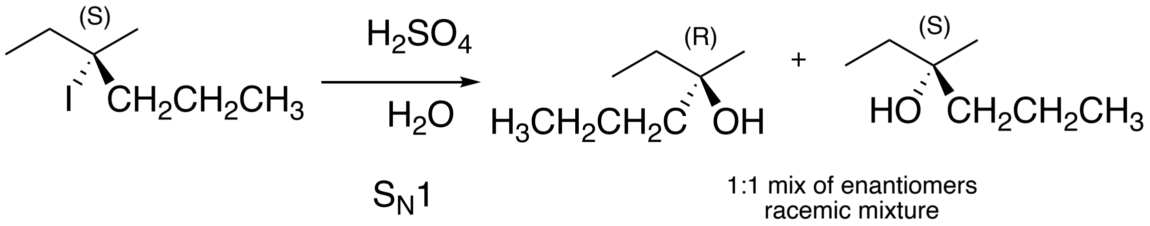


Note: Alkoxide ($^-$OR) or hydroxide ($^-$OH) are bad leaving group therefore no Sn2 reaction will occur on either direction. However, if the reaction happens in strongly acidic condition the reaction will occur. (see mechanism below)

8)

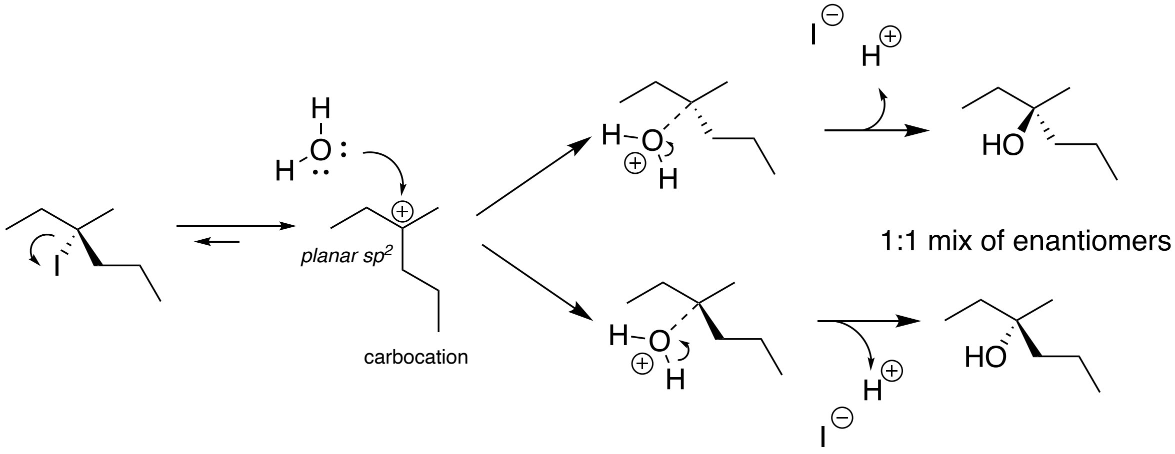


S_N1 Reaction:

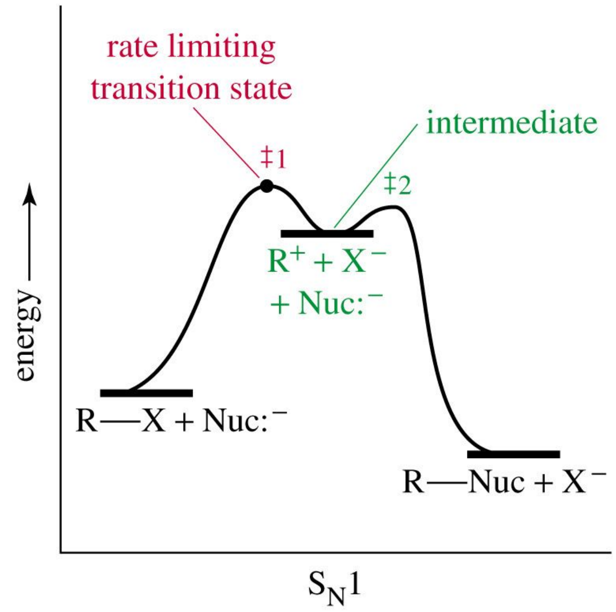


Characteristics of S_N1 reactions:

- 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°

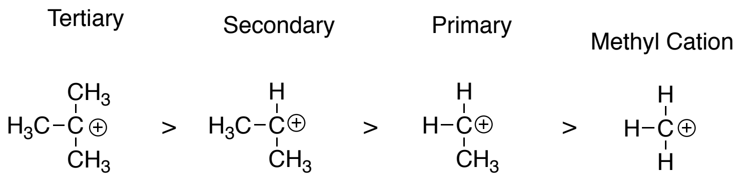


Energy level diagram of S_N1



Favored conditions are with stabilized carbocation – more substitution

Carbocation Stability:



$$H_3C-\overset{CH_3}{\underset{CH_3}{C}}\oplus > H_3C-\overset{H}{\underset{CH_3}{C}}\oplus > H-\overset{H}{\underset{CH_3}{C}}\oplus > H-\overset{H}{\underset{H}{C}}\oplus$$

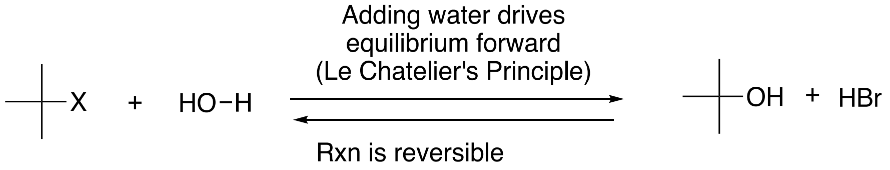
Most
stable

Least
stable
(no S_N1)

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

Example: Tertiary Halide

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

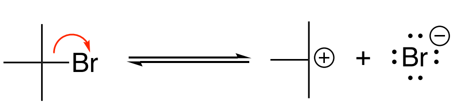


3° halide
X = Br
No S_N2

S_N1 occurs

Mechanism of S_N1:

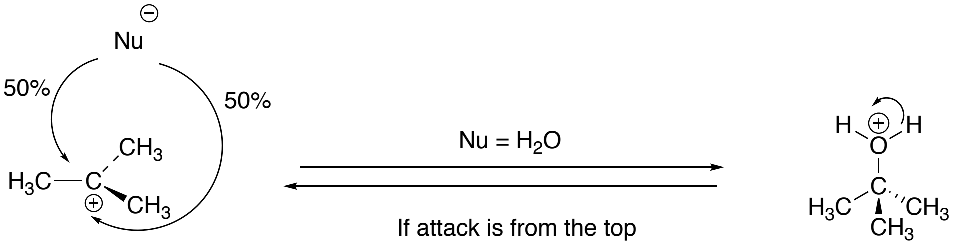
The bromine group leaves (Step 1) with its from the covalent bond, leaving behind a carbocation intermediate



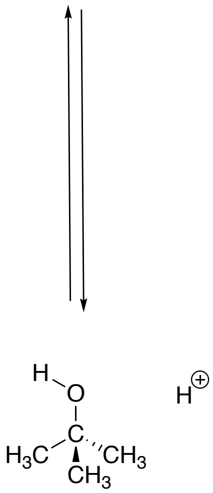
electrons
reactive

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°