Chem 240
10.9.18

Chapter 11: Nucleophilic Substitutions & Eliminations

Alkyl Halides - Halogen bonded to an sp^3 carbon

The carbon halogen bond in an alkyl halide is polar and the carbon atom is electron poor → therefore electrophilic

$\overset{\delta+}{R}-\overset{\delta-}{X}$

The carbon is electrophilic

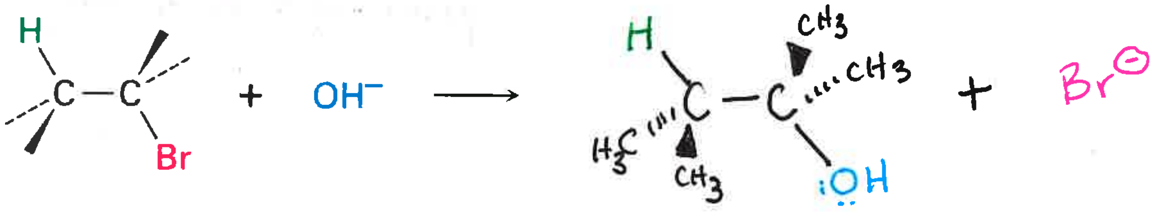
★ alkyl halides are electrophiles

Alkyl Halides React with Nucleophiles and Bases

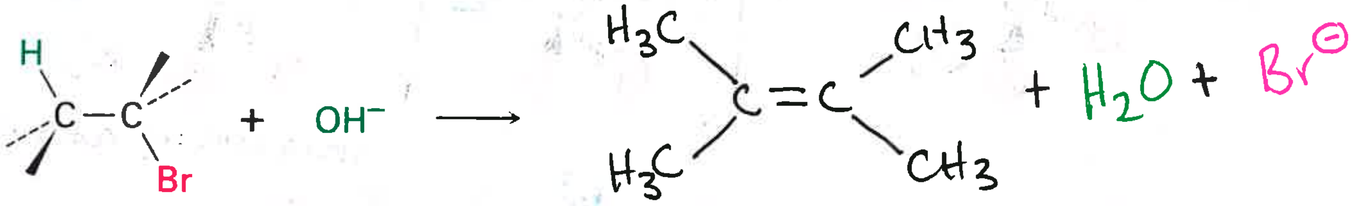
Alkyl halides are polarized at the carbon-halide bond, making the

carbon electropnilic and can act one of two ways:

Substitution: Nucleophiles will replace the halide in C-X bonds of many alkyl halides



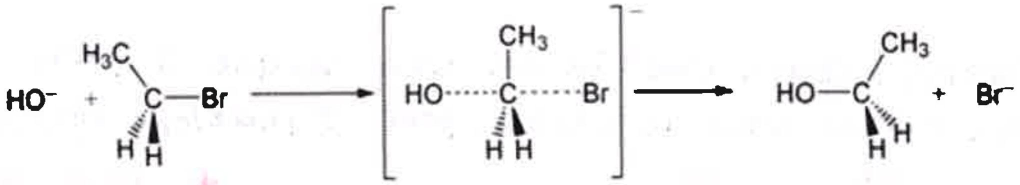
Elimination: Nucleophiles that are Brønsted bases produce elimination, forming water and a double bound



page 309 in 9th edition textbook

The Nature of Substitution

Substitution, by definition, requires that a leaving Group departs from the reacting molecule. A nucleophile is a reactant that can be expected to participate effectively in a substitution reaction.



Substitution Mechanisms

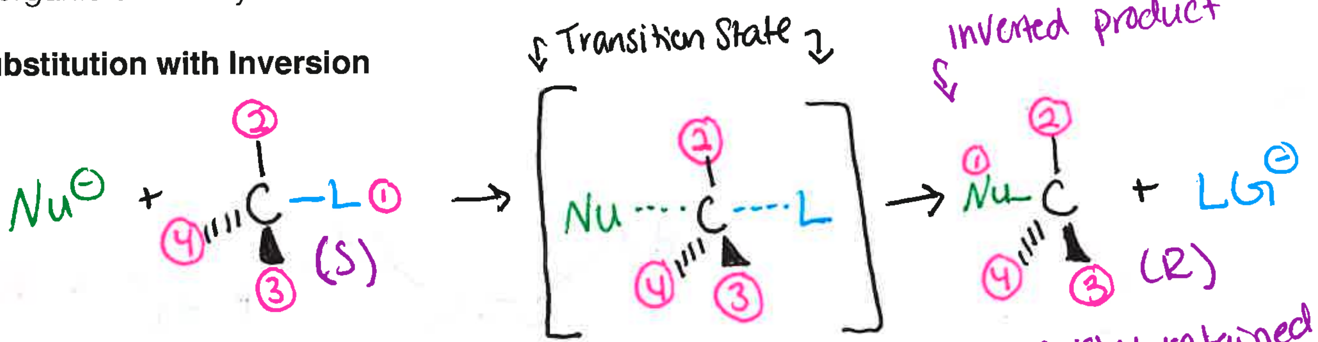
S_N1 Two steps with carbocation intermediate. Occurs in tertiary alkyls, allyls & benzyls

S_N2 Two steps combine - without intermediate. Occurs in primary & secondary alkyls

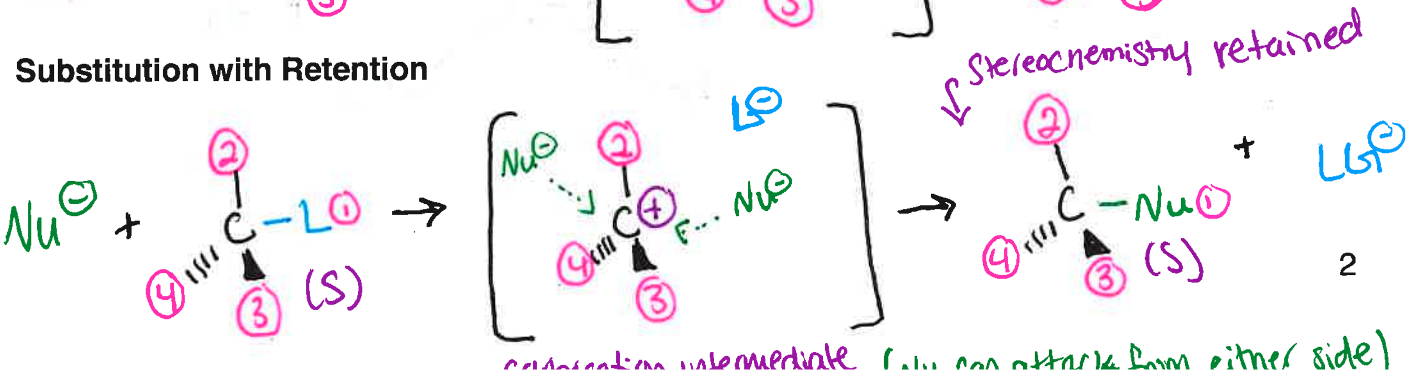
A mechanism that accounts for both the inversion of configuration and the second-order kinetics that are observed with the nucleophilic substitution reaction

Nucleophilic substitution reactions are one of the most common and versatile reaction types in organic chemistry

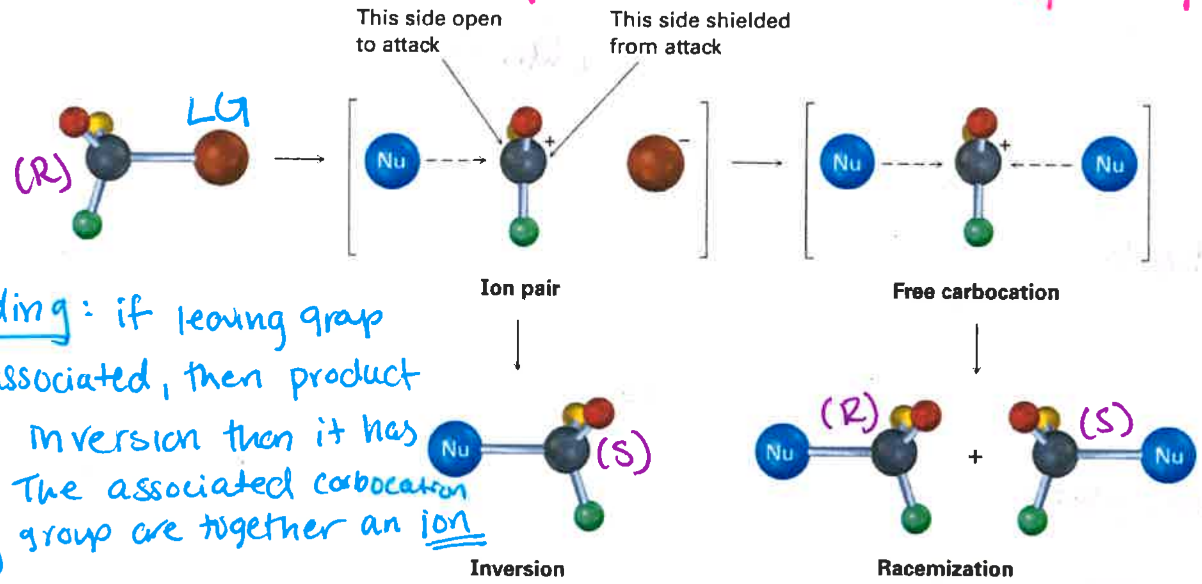
Substitution with Inversion



Substitution with Retention

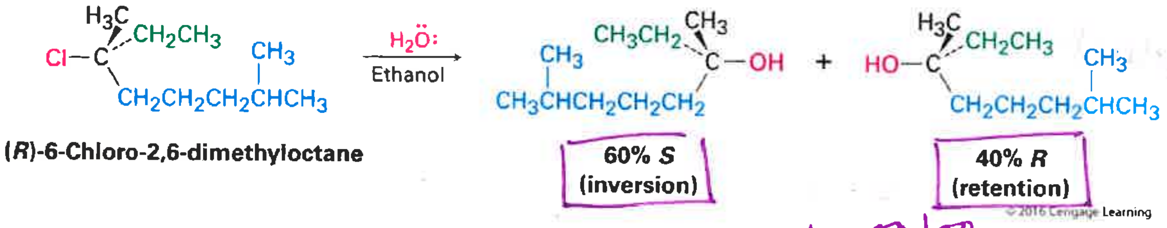


carbocation is effectively shielded from the reaction on one side by the departing anion



ion shielding: if leaving group remains associated, then product has more inversion than it has retention. The associated carbocation and leaving group are together an ion pair

mixture of both R and S



not always 50/50

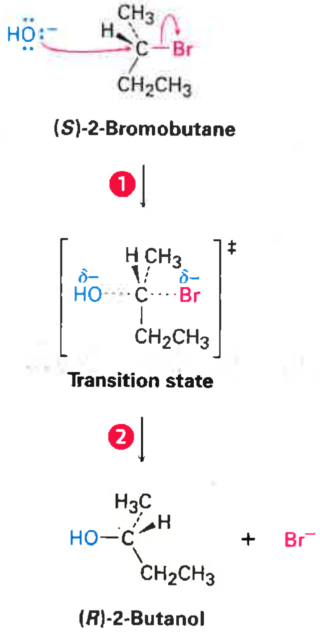
The S_N2 Reaction

* This reaction involves a transition state in which both reactants are together

* S_N2 reactions always have an inversion of stereochemistry

① The nucleophile ^-OH uses its lone-pair electrons to attack the alkyl halide carbon 180° away from the departing halogen. This leads to a transition state with a partially formed C–OH bond and a partially broken C–Br bond.

② The stereochemistry at carbon is inverted as the C–OH bond forms fully and the bromide ion departs with the electron pair from the former C–Br bond.

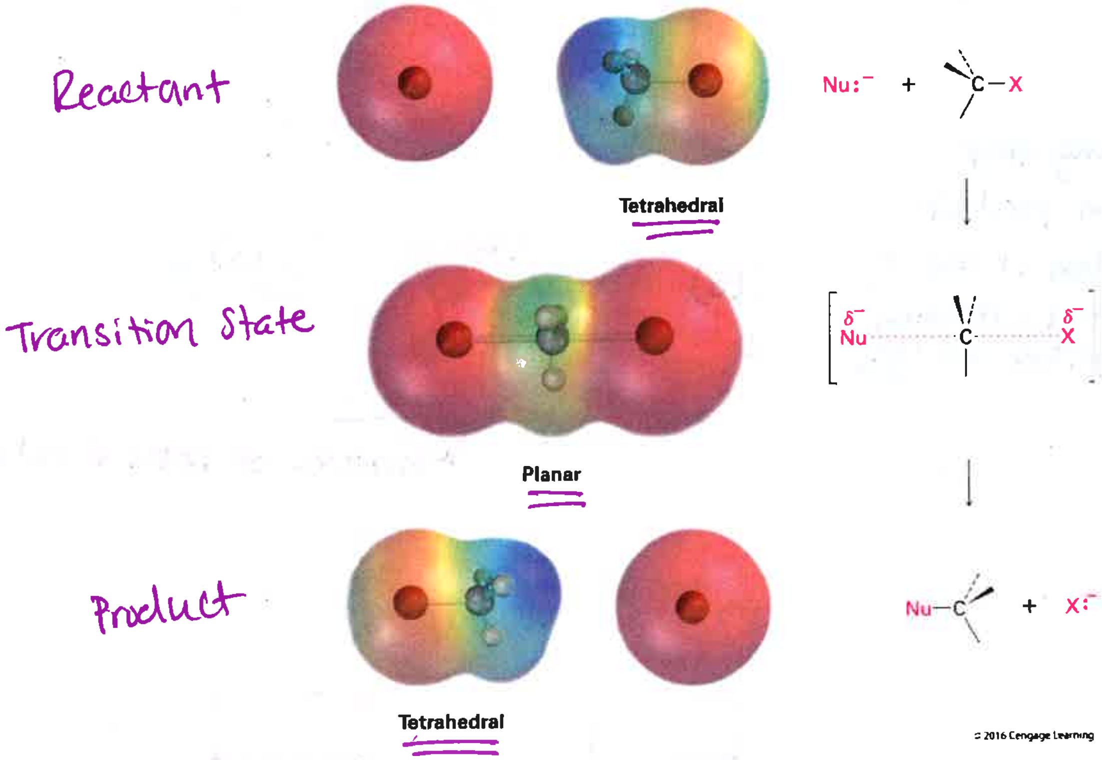


S_N2 = one single step!

S = substitution
N = nucleophilic
2 = bimolecular

page 314 in 9th edition textbook

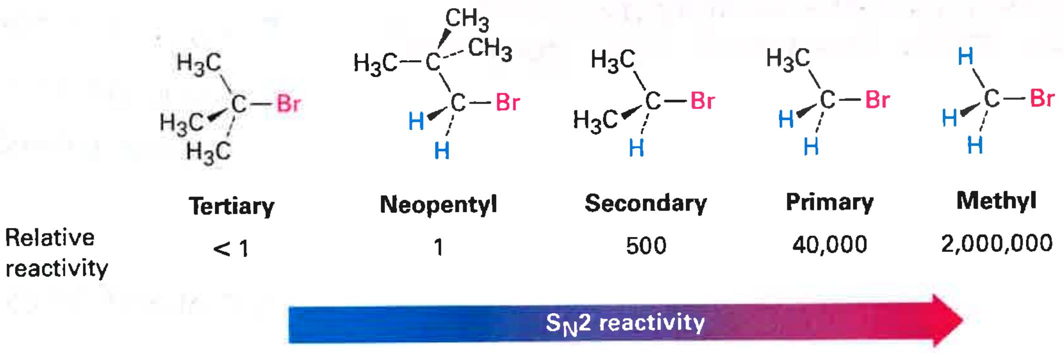
The transition state of an S_N2 reaction has a planar arrangement of the carbon atom and the remaining three groups



© 2016 Cengage Learning

Order of Reactivity in S_N2

The more alkyl groups connected to the reacting carbon, the slower the reaction



steric hindrance (in regards to the S_N2 reaction) slows down the Rxn.

Characteristics of the S_N2 Reaction

Sensitive to steric effects

Methyl halides are most reactive

Primary are next most reactive

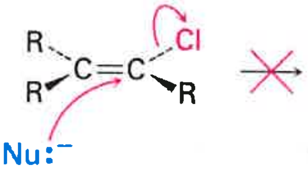
Secondary might react

Tertiary are unreactive by this path

No reaction at C=C (vinyl halides)

No reaction

Aryl halide



No reaction

Vinylic halide

The Leaving Group

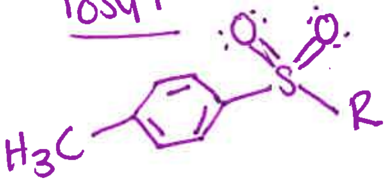
A good leaving group reduces the barrier to a reaction

Stable anions that are weak bases are excellent leaving groups and can delocalize charge

	$\underbrace{OH^-, NH_2^-, OR^-}$	F^-	Cl^-	Br^-	I^-	$TosO^-$
Relative reactivity	<<1	1	200	10,000	30,000	60,000

Leaving group reactivity →

Tosyl



Really good leaving group

Poor Leaving Groups

If a group is very basic or very small, it is prevents reaction

$$\underbrace{R-F \quad R-OH \quad R-OR' \quad R-NH_2}_{\text{These compounds do not undergo } S_N2 \text{ reactions.}}$$

The S_N2 Reaction Summary

	Good	Bad
Substrate	Methyl and primary substrates work best, secondary substrates will react slowly	Steric hindrance raises the energy of the transition state, so the reaction rate decreases, tertiary substrates do not react by an S_N2 reaction
Nucleophile	Basic, negatively charged nucleophiles are less stable & have a higher ground-state energy, decreasing the activation energy & increasing the S_N2 reaction rate	
Leaving Group	Stable anions are good leaving groups, they lower the energy of the transition state, which decreases the activation energy and increases the S_N2 reaction rate	
Solvent	Polar aprotic solvents surround the accompanying cation but not the nucleophilic anion, raising ground-state energy, decreasing the activation energy and increasing the reaction rate	Protic solvents solvate the nucleophile, which lowers the ground-state energy, increasing the activation energy and decreasing the S_N2 reaction rate

The S_N1 Reaction

- Tertiary alkyl halides react rapidly in **protic solvents** by a mechanism that involves departure of the leaving group prior to addition of the nucleophile
- Called an S_N1 reaction – occurs in two distinct steps while S_N2 occurs with both events in same step
- If nucleophile is present in reasonable concentration (or it is the solvent), then ionization is the slowest step (Rate determining step = Spontaneous removal of leaving group)
- Carbocation is biased to react on side opposite leaving group
- Suggests reaction occurs with carbocation loosely associated with leaving group during nucleophilic addition
- Alternative that S_N2 is also occurring is unlikely

Rate determining step is the spontaneous dissociation of the alkyl halide to create a carbocation intermediate. Reaction of the carbocation with

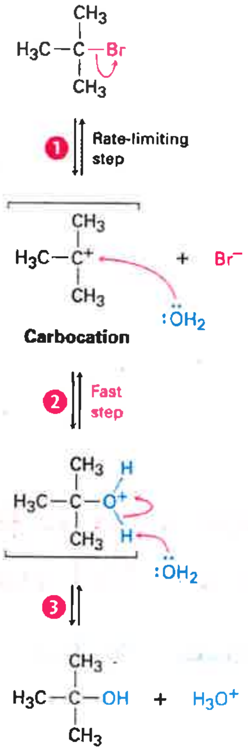
very quickly. much faster step

↓ when SN1 is carried out under acidic conditions with neutral water being the leaving group

① Spontaneous dissociation of the alkyl bromide occurs in a slow, rate-limiting step to generate a carbocation intermediate plus bromide ion.

② The carbocation intermediate reacts with water as a nucleophile in a fast step to yield protonated alcohol as product.

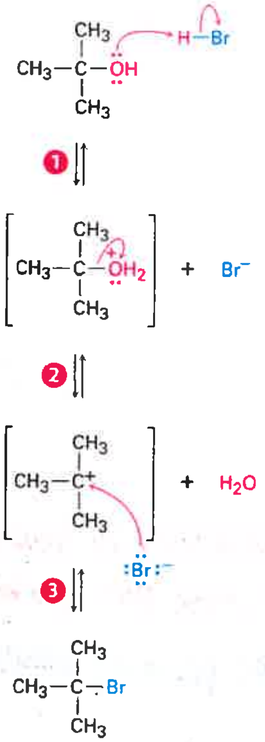
③ Loss of a proton from the protonated alcohol intermediate then gives the neutral alcohol product.



① The –OH group is first protonated by HBr.

② Spontaneous dissociation of the protonated alcohol occurs in a slow, rate-limiting step to yield a carbocation intermediate plus water.

③ The carbocation intermediate reacts with bromide ion in a fast step to yield the neutral substitution product.

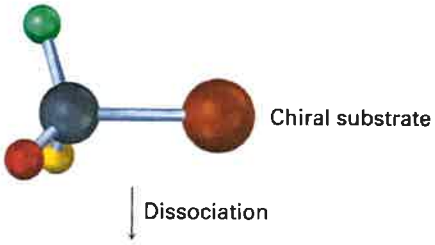


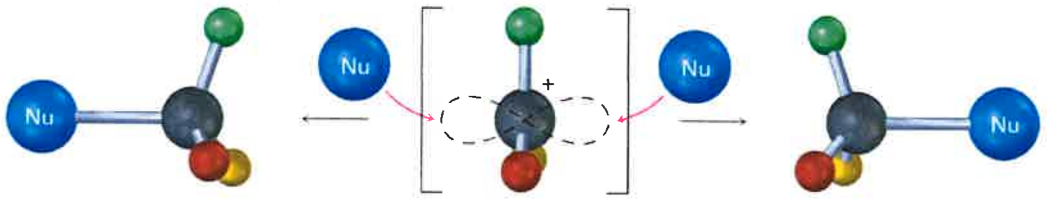
Stereochemistry of S_N1 Reaction

The planar intermediate leads to loss of chirality. A free carbocation is achiral

Product is racemic or has some inversion

you can start with a chiral molecule | pure chiral solution but after SN1 reaction you will nd up with a racemic mixture of nantiomers





50% inversion of configuration

Planar, achiral carbocation intermediate

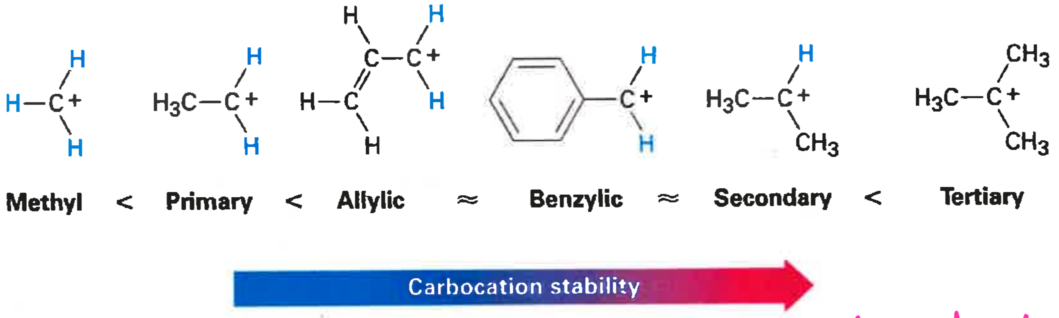
50% retention of configuration

© 2016 Cengage Learning

★ Resonance helps with stability!

Characteristics of the S_N1 Reaction

Tertiary alkyl halide is most reactive by this mechanism
Controlled by stability of carbocation

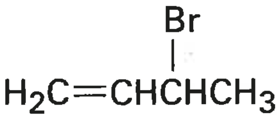


Reaction is favored when the stabilized carbocation is formed - the more stable the carbocation intermediate the faster the S_N1 reaction will occur

Note: primary allylic and benzylic substrates are also reactive to S_N2 reactions (along with S_N1)

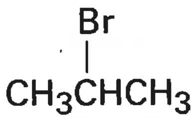
Rank the following substances in order of their expected S_N1 reactivity:

CH_3CH_2Br



$H_2C{=}CHCH(Br)CH_3$

$H_2C{=}CHBr$



$CH_3CH(Br)CH_3$

Effect of Leaving Group on S_N1

Critically dependent on leaving group
Reactivity: the larger halides ions are better leaving groups

In acid, OH of an alcohol is protonated and leaving group is H_2O, which is still less reactive than halide

p-Toluensulfonate (TosO-) is excellent leaving group

$HO^- < Cl^- < Br^- < I^- \approx TosO^- < H_2O$

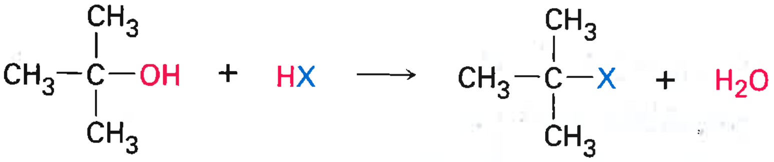
*The nature of the nucleophile plays a major role in S_N2 reactions but does not affect S_N1

Nucleophiles in S_N1

Since nucleophilic addition occurs *after* formation of carbocation, reaction rate is not affected by the nature or concentration of nucleophile

The reactions occur through a rate limiting step in which the added nucleophile has no part, the nucleophile can not affect the reaction rate

*S_N1 reactions occur through a rate limiting step in which the added nucleophile has no part, the nucleophile concentration does not affect the reaction rate



2-Methyl-2-propanol (Same rate for X = Cl, Br, I)

Summary of S_N1 Reactions

Substrate	Tertiary, allylic, and benzylic halides
Nucleophile	Nucleophile must be non-basic to prevent the competition of elimination of HX reactions, Neutral nucleophiles work well
Leaving Group	Stable anions are good leaving groups, they lower the energy of the transition state, which decreases the activation energy and increases the S_N1 reaction rate
Solvent	Polar solvents stabilize the carbocation intermediate by solvation and therefore increasing the reaction rate

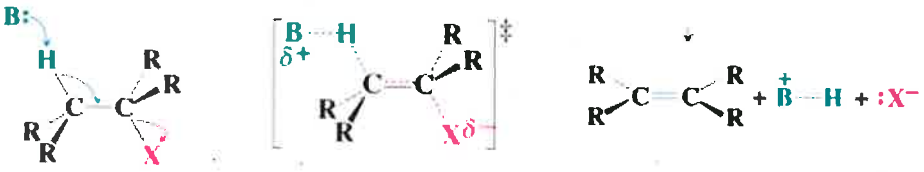
Alkyl Halides: Elimination

Elimination is an alternative pathway to substitution

Opposite of addition

Generates an alkene

Can compete with substitution and decrease yield, especially for S_N1 processes



Elimination, bimolecular: occurs when an alkyl halide reacts with a strong base such as hydroxide or alkoxide ion ($RO^{\ominus}$)

The E$_2$ Reaction Mechanism

A proton is transferred to base as leaving group begins to depart

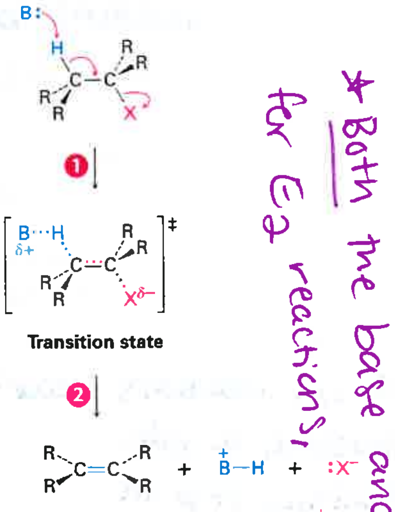
Transition state combines leaving of X and transfer of H

Product alkene forms stereospecifically

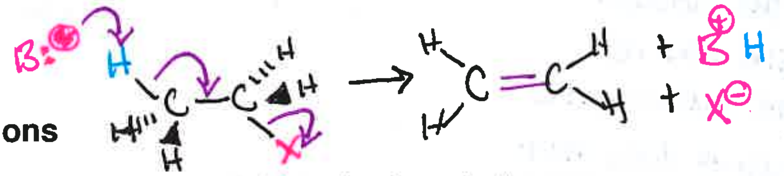
E2 reaction (similar to S_N2): C-H and C-X bonds break simultaneously, giving the alkene in a single step without intermediates

① Base (B:) attacks a neighboring hydrogen and begins to remove the H at the same time as the alkene double bond starts to form and the X group starts to leave.

② Neutral alkene is produced when the C–H bond is fully broken and the X group has departed with the C–X bond electron pair.



Transition state

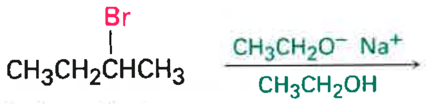


* Both the base and the alkyl halide reactant take part in the rate limiting step for E2 reactions, so both concentrations will impact the rate of the reaction.
↳ If you double the base, you double the rate (for example)

Zaitsev's Rule for Elimination Reactions

In the elimination of HX from an alkyl halide, the more highly substituted alkene product predominates

↳ more stable

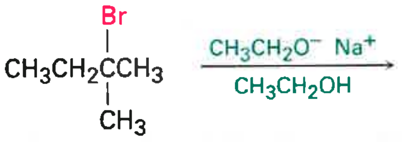


$$CH_3CH_2CH(Br)CH_3 \xrightarrow[CH_3CH_2OH]{CH_3CH_2O^- \ Na^+} CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CH_2$$

2-Bromobutane

2-Butene (81%)

1-Butene (19%)



$$CH_3CH_2C(Br)(CH_3)CH_3 \xrightarrow[CH_3CH_2OH]{CH_3CH_2O^- \ Na^+} CH_3CH{=}C(CH_3)CH_3 + CH_3CH_2C(CH_3){=}CH_2$$

2-Bromo-2-methylbutane

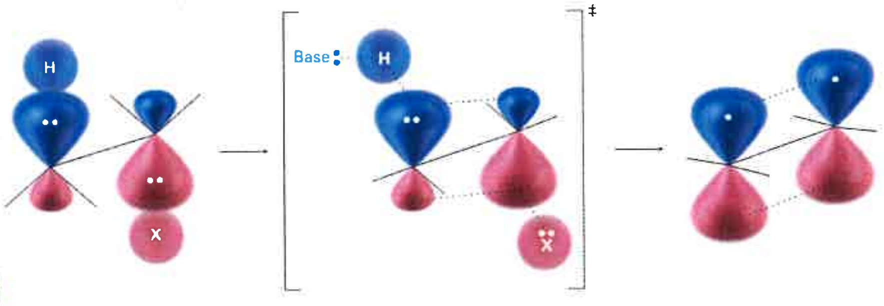
2-methyl-2-butene (70%)

2-methyl-1-butene (30%)

* Elimination reactions pretty much always result in a mixture of products but we can predict the major and minor products

E$_2$ Stereochemistry

Overlap of the developing π orbital in the transition state requires periplanar geometry, anti arrangement



Anti periplanar reactant

Anti transition state

Alkene product

the sp3 sigma orbitals in the C-H and C-X bonds of the reactant must overlap and become pi orbitals in the alkene product

* This occurs easily if they are all in the same plane

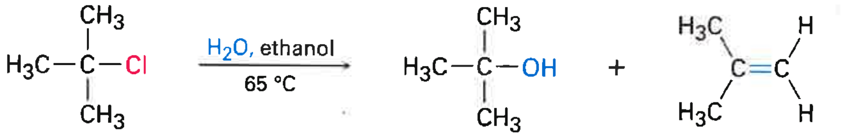
E_1 Reaction (similar to S_N1): C-X bond breaks first to give a carbocation intermediate followed by base removal of a proton to yield an alkene

Stereochemistry of E_1 Reactions

Just as in S_N1, the first step of E_1 Rxns is the rate limiting step (dissociation of leaving group)

- ★ E_1 is not stereospecific and there is no requirement for alignment
- ★ Product has Zaitsev orientation because step that controls product is loss of proton after formation of carbocation

no geometric requirement in the E1 Rxn because the halide and the hydrogen are lost in seperate steps.



2-Chloro-2-methylpropane **2-Methyl-2-propanol (64%)** **2-Methylpropene (36%)**

E1 = Begins with the same loss of the leaving group to create a carbocation (like S_N1) but the 2nd step is the loss of a proton (H^+) from the adjacent carbon rather than a substitution.

Comparing E_1 and E_2

- ★ Strong base is needed for E_2 but not for E_1
- ★ E_2 is stereospecifc, E1 is not
- ★ E_1 gives Zaitsev orientation

Summary of Reactivity: S_N1, S_N2, E_1, E_2

Substrate	SN1	SN2	E1	E2
1°	X	Yes	X	w/strong base
2°	Benzylic and allylic	w/E2	Benzylic and allylic	Favored w/ strong base
3°	Favored in hydroxylic solvents	X	w/SN1	Favored w/ bases

Primary – mostly SN2

Secondary – SN2 w/ non-basic solvents or E2 w/ strong bases

Tertiary – Mostly E2 (SN1 and E1 in non-basic solvents)

Solvents

Polar aprotic solvents (no NH, OH, SH) form weaker interactions with substrate and permit faster reaction (solvate + better than -)

raise energy = increase the rate of S_N2 reactions

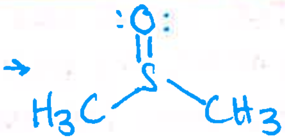
$$CH_3CH_2CH_2CH_2{-}Br + N_3^- \longrightarrow CH_3CH_2CH_2CH_2{-}N_3 + Br^-$$

Solvent	CH_3OH	H_2O	DMSO	DMF	CH_3CN	HMPA
Relative reactivity	1	7	1300	2800	5000	200,000

Solvent reactivity →

*these are polar & do not hydrogen bond

DMSO = Dimethylsulfoxide →



DMF →

Protic solvents (-OH or –NH) can donate hydrogen bonds slow S_N2 reactions by associating with reactants

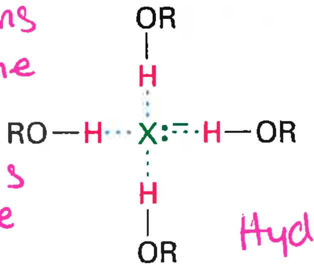
↳ hydrogen bonding = bad for S_N2 Rxns

Energy is required to break interactions between reactant and solvent

methanol = CH_3OH

ethanol = CH_3CH_2OH

*protic solvents slow down S_N2 reactions by solvation of the reactant nucleophile. The solvent molecules hydrogen bond to the $Nu^{\ominus}$ (form a cage)



A solvated anion (reduced nucleophilicity due to enhanced ground-state stability)

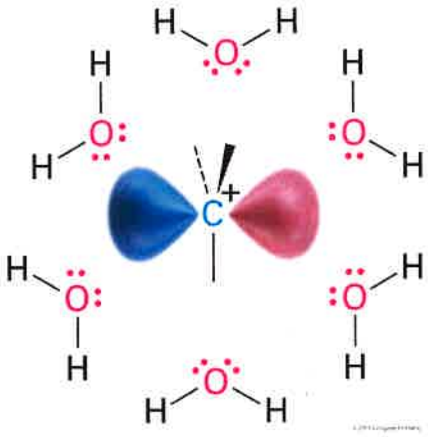
Hydrogen bonds create a cage lowers energy = less reactive

solvent molecules orient around the carbocation so that

Solvent is Critical in S_N1

Stabilizing carbocation also stabilizes associated transition state and controls rate

*protic solvents increase S_N1 reactions



*electron rich oxygen atoms of a solvent will orient around the positive charge of carbocation and stabilize it

* solvent effects in S_N2 reactions are due to stabilization and destabilization of the nucleophile reactant

* solvent effects in S_N1 reactions are due to stabilization and destabilization of the Transition State