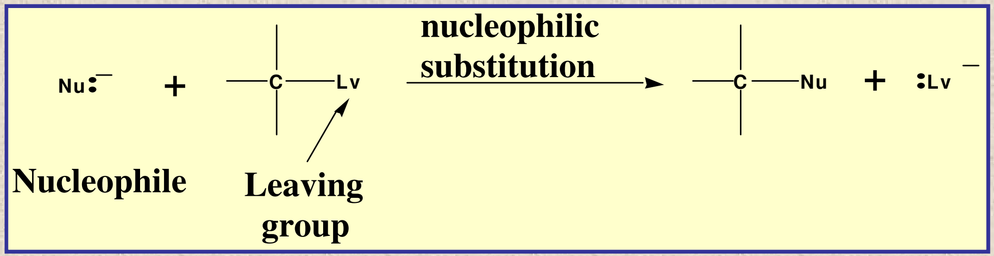
Nucleophilic Substitution and β-Elimination

Chapter 9

Nucleophilic Substitution

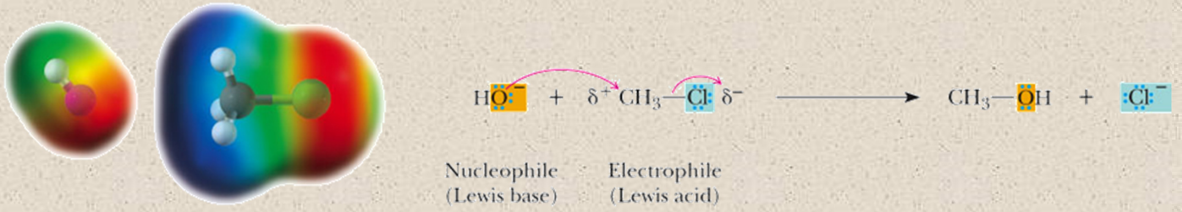


Nucleophile: From the Greek meaning nucleus loving. A molecule or ion that donates a pair of electrons to another atom or ion to form a new covalent bond; a Lewis base.

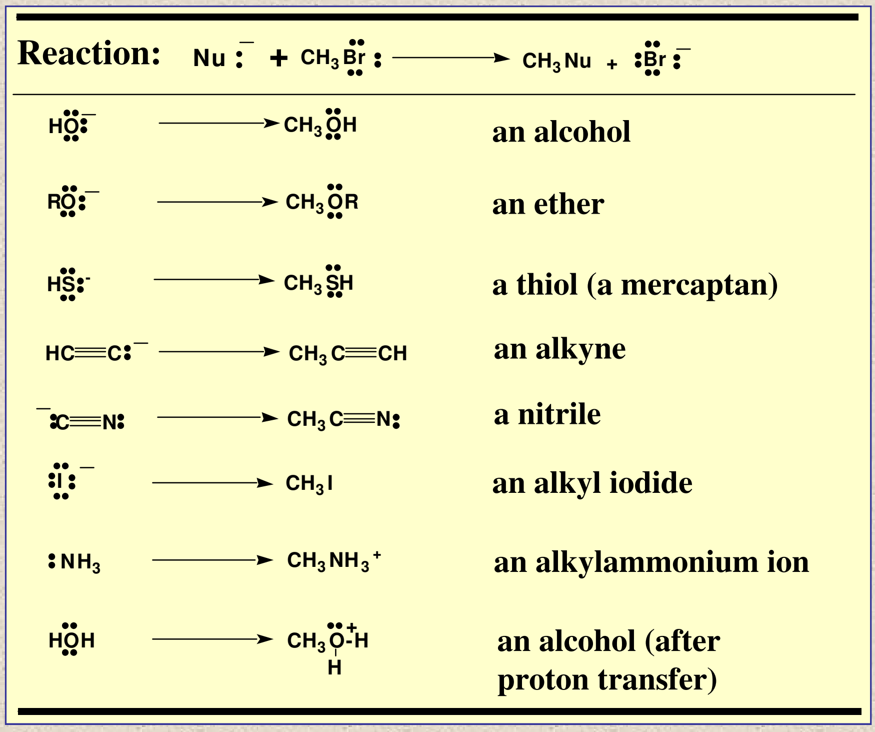
Nucleophilic substitution: Any reaction in which one nucleophile substitutes for another at a tetravalent carbon.

Nucleophilic Substitution

- Electrostatic potential map showing the nucleophile (OH^-) reacting at its negative (red) end with the electrophilic carbon (blue) in the reaction of hydroxide with chloromethane.



Nucleophilic Substitution-Haloalkanes



Reaction: $Nu:^- + CH_3Br: \longrightarrow CH_3Nu + :Br:^-$

$HO:^-$	$\longrightarrow$	CH_3OH	an alcohol
$RO:^-$	$\longrightarrow$	CH_3OR	an ether
$HS:^-$	$\longrightarrow$	CH_3SH	a thiol (a mercaptan)
$HC{\equiv}C:^-$	$\longrightarrow$	$CH_3C{\equiv}CH$	an alkyne
$^-:C{\equiv}N:$	$\longrightarrow$	$CH_3C{\equiv}N:$	a nitrile
$:I:^-$	$\longrightarrow$	CH_3I	an alkyl iodide
$:NH_3$	$\longrightarrow$	$CH_3NH_3^+$	an alkylammonium ion
HOH	$\longrightarrow$	$CH_3\overset{+}{O}{-}H$ with H below O	an alcohol (after proton transfer)

Mechanisms

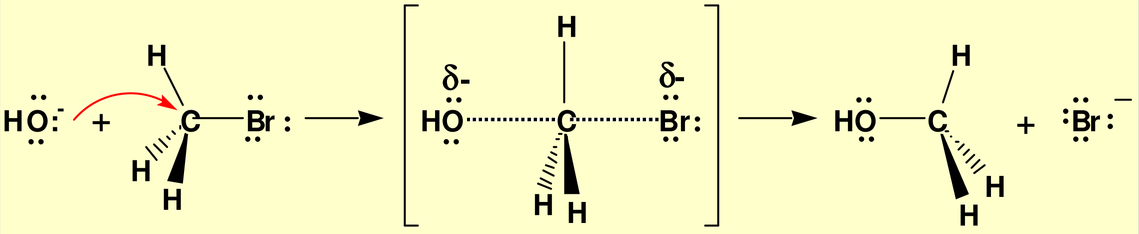
- Chemists propose two limiting mechanisms for nucleophilic substitution.
  - A fundamental difference between them is the **timing of bond-breaking and bond-forming steps.**

Mechanisms

- At one extreme, the two processes take place simultaneously; designated S_N2.
  - S = substitution
  - N = nucleophilic
  - 2 = bimolecular (two species are involved in the rate- determining step)

Mechanisms S_N2

– Both reactants are involved in the transition state of the **rate-determining step.**

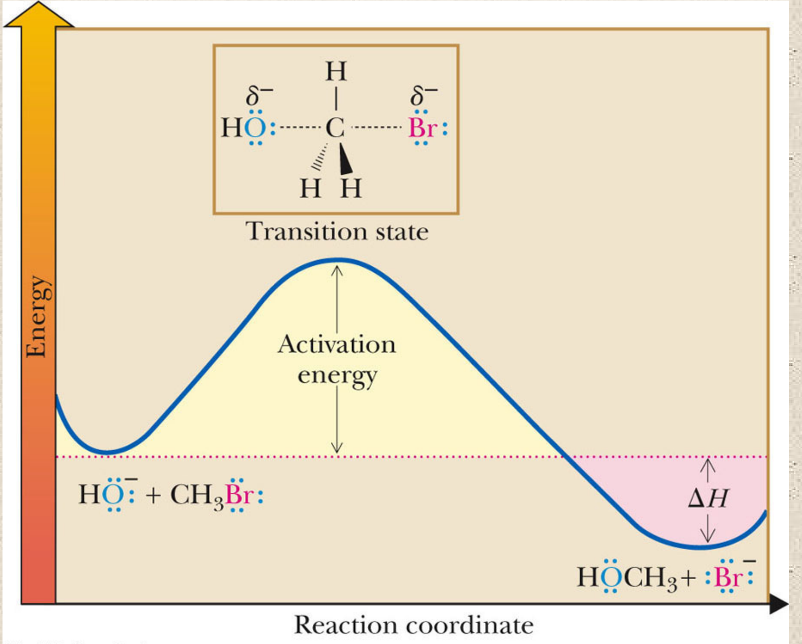


Transition state with simultaneous bond breaking and bond forming

---

Mechanisms S_N2

- An energy diagram for an S_N2 reaction. There is one transition state and no reactive intermediate.



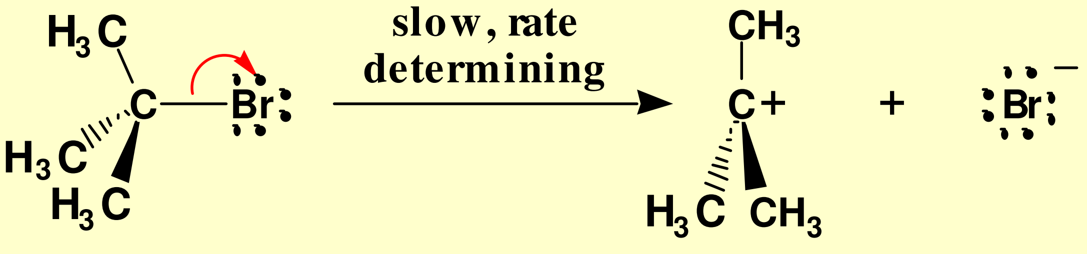
© Brooks/Cole, Cengage Learning

Mechanisms S_N1

- Bond breaking between carbon and the leaving group is **entirely completed** before bond forming with the nucleophile begins.
- This mechanism is designated S_N1 where
  - S = substitution
  - N = nucleophilic
  - 1 = unimolecular (only one species is involved in the rate-determining step)

Mechanisms S_N1

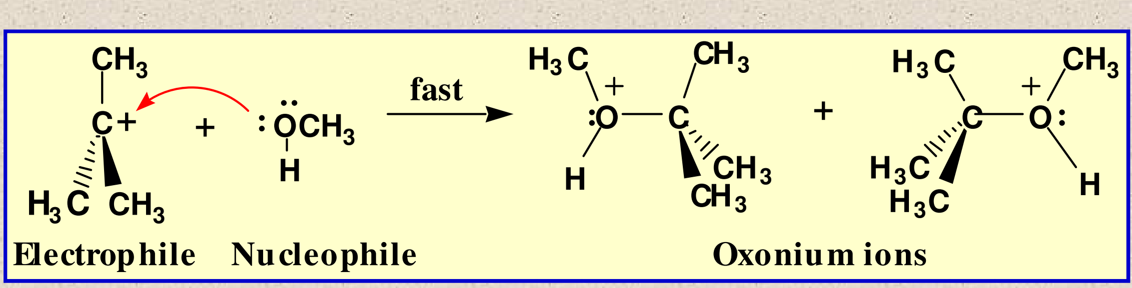
- **Step 1: Ionization** of the C-X bond gives a carbocation intermediate.



A carbocation intermediate; its shape is trigonal planar

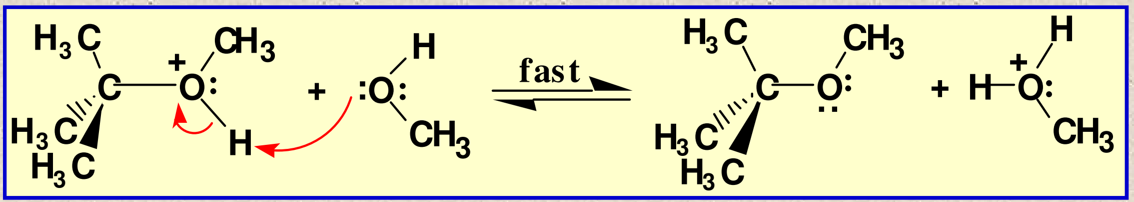
Mechanisms S_N1

–Step 2: Reaction of the carbocation (an electrophile) on either side with methanol (a nucleophile) gives an oxonium ion.



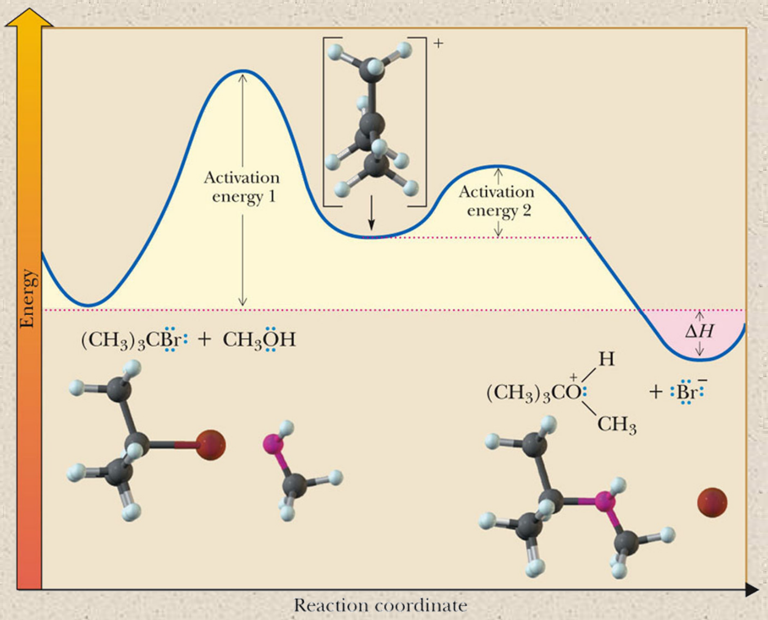
Mechanisms S_N1

Step 3: Proton transfer completes the reaction.



Mechanisms S_N1

- Energy diagram for an S_N1 reaction. Step 1 crosses the higher energy barrier and therefore is rate-determining.

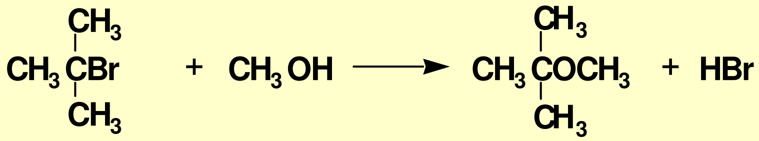


Evidence of S_N reactions

1. What is relationship between the rate of an S_N reaction and
   - the structure of Nu?
   - the structure of RLv?
   - the structure of the leaving group?
   - the solvent?
2. What is the stereochemical outcome if the leaving group is displaced from a chiral center?
3. Under what conditions are skeletal rearrangements observed (carbocation?)

Kinetics

- For S_N1
  - Reaction occurs in two steps.
  - The reaction leading to formation of the transition state for the carbocation intermediate involves only the haloalkane and not the nucleophile.
  - The result is a first-order reaction.



$$CH_3\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{CBr}} + CH_3OH \longrightarrow CH_3\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}OCH_3 + HBr$$

2-Bromo-2-methylpropane | Methanol | 2-Methoxy-2-methylpropane

$$\text{Rate} = -\frac{d[(CH_3)_3CBr]}{dt} = k[(CH_3)_3CBr]$$

Kinetics

- For S_N2
  - Reaction occurs in one step.
  - The reaction leading to the transition state involves the haloalkane and the nucleophile.
  - The result is a second-order reaction; first order in haloalkane and first order in nucleophile.

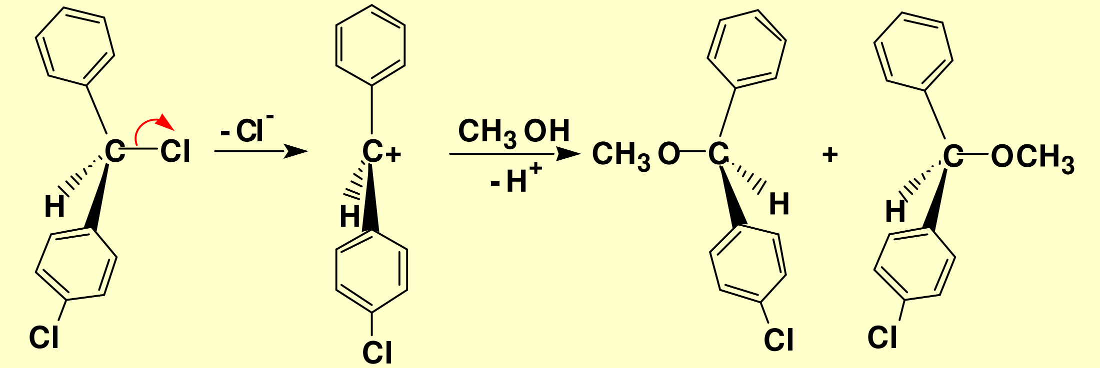
$$CH_3Br + Na^+OH^- \longrightarrow CH_3OH + Na^+Br^-$$

Bromomethane | Methanol

$$\text{rate} = -\frac{d[CH_3Br]}{dt} = k[CH_3Br][OH^-]$$

Stereochemistry

- For an S_N1 reaction at a chiral center, the *R* and *S* enantiomers are formed in equal amounts, and the product is a racemic mixture.



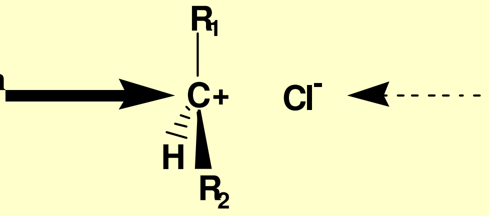
R Enantiomer **Planar carbocation (achiral)** **S Enantiomer** **R Enantiomer**

A racemic mixture

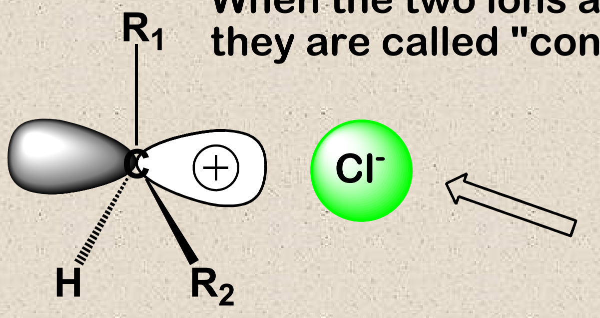
Stereochemistry

- For S_N1 reactions at a chiral center
  - examples of complete racemization have been observed, but
  - partial racemization with a slight excess of inversion is more common.

Approach of the nucleophile from this side is less hindered

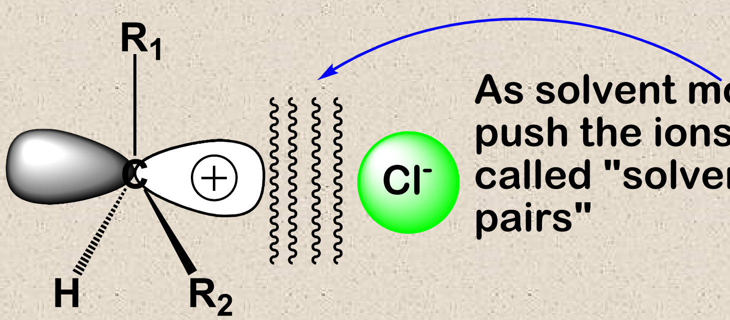


Approach of the nucleophile from this side is partially blocked by leaving group, which remains associated with the carbocation as an ion pair



When the two ions are close to each other, they are called "contact ion pairs"

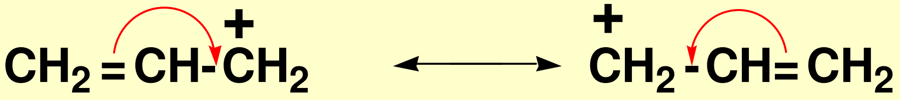
Chloride ion can partially block this face of the ion pair



As solvent molecules interact to push the ions apart, they are called "solvent separated ion pairs"

Carbocation Stability

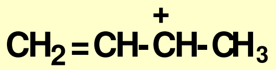
- Allylic cations are stabilized by resonance delocalization of the positive charge.
  - A 1° allylic cation is about as stable as a 2° alkyl cation.



$$CH_2=CH-\overset{+}{C}H_2 \longleftrightarrow \overset{+}{C}H_2-CH=CH_2$$

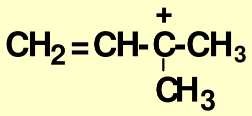
Allyl (propenyl)cation
(a hybrid of two equivalent contributing structures)

Carbocation Stability



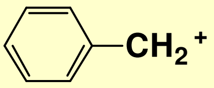
$CH_2=CH-\overset{+}{C}H-CH_3$

A 2° allylic carbocation



$CH_2=CH-\overset{+}{\underset{CH_3}{C}}-CH_3$

A 3° allylic carbocation



Benzyl cation
(a benzylic carbocation)

$C_6H_5-CH_2^+$

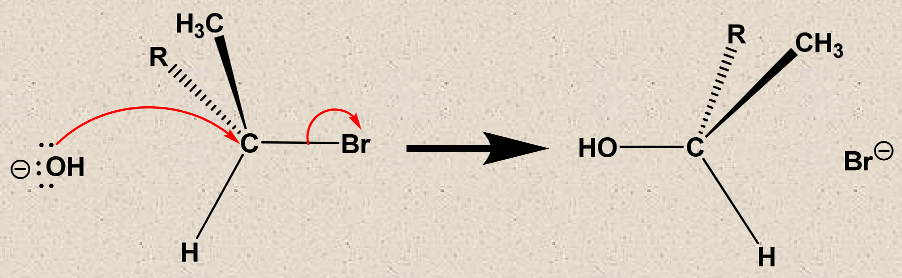
The benzyl cation is also written
in this abbreviated form

methyl < 1° alkyl < {2° alkyl, 1° allylic, 1° benzylic} < {3° alkyl, 2° allylic, 2° benzylic} < {3° allylic, 3° benzylic}

Increasing stability of carbocations

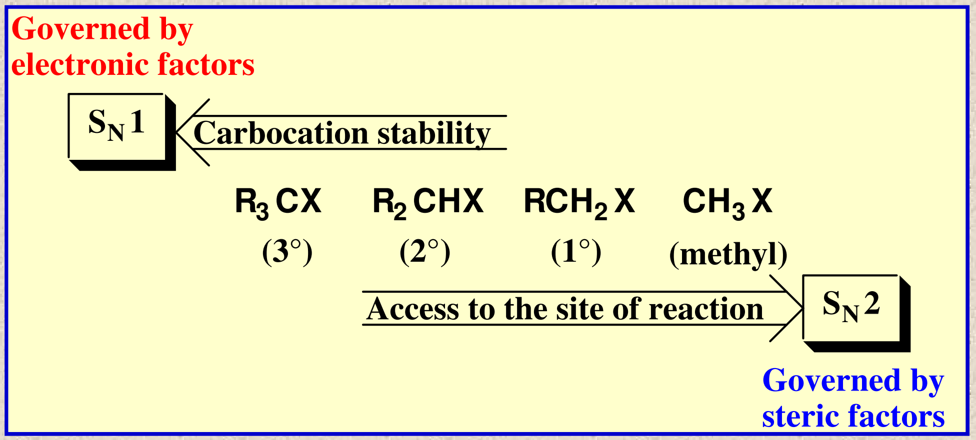
Stereochemistry of Sn2

For an S_N2 reaction at a chiral center, there is inversion of configuration at the chiral center.



Structure of R-X

- S_N1 reactions: governed by electronic factors
  - namely, the relative stabilities of the carbocation intermediates.
- S_N2 reactions: governed by steric factors
  - namely, the relative ease of approach of a nucleophile to the reaction site.


Governed by electronic factors

S_N1 ← Carbocation stability

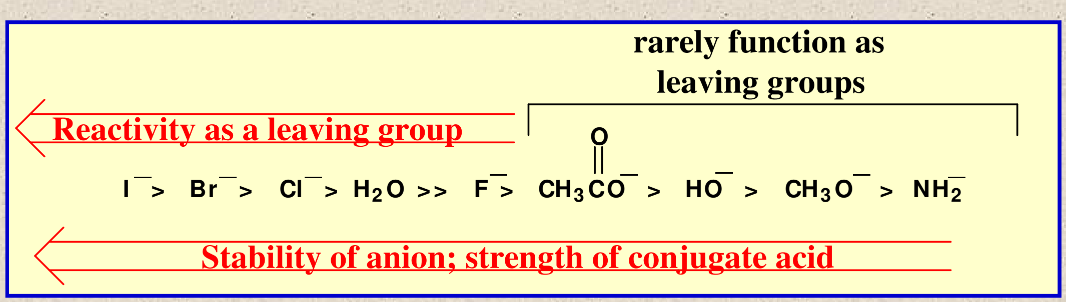
R_3CX (3°) R_2CHX (2°) RCH_2X (1°) CH_3X (methyl)

Access to the site of reaction → S_N2

Governed by steric factors

The Leaving Group

- The more stable the anion, the better the leaving ability.
  - **The most stable anions are the conjugate bases of strong acids.**


rarely function as leaving groups

← Reactivity as a leaving group

$I^- > Br^- > Cl^- > H_2O >> F^- > CH_3\overset{O}{\overset{\|}{C}}O^- > HO^- > CH_3O^- > NH_2^-$

← Stability of anion; strength of conjugate acid

Solvents

- Protic solvent: A solvent that is a hydrogen bond donor.
  - The most common protic solvents contain -OH groups.
- Aprotic solvent: A solvent that cannot serve as a hydrogen bond donor.
  - Nowhere in the molecule is there a hydrogen bonded to an atom of high electronegativity.

Dielectric Constant

- **Solvents are classified as polar and nonpolar**
  - The most common measure of solvent polarity is dielectric constant.
- Dielectric constant: A measure of a solvent's ability to insulate opposite charges from one another.
  - The greater the value of the dielectric constant of a solvent, the smaller the interaction between ions of opposite charge dissolved in that solvent.
  - **Polar solvent: dielectric constant > 15.**
  - **Nonpolar solvent: dielectric constant < 15.**

Aprotic Solvents

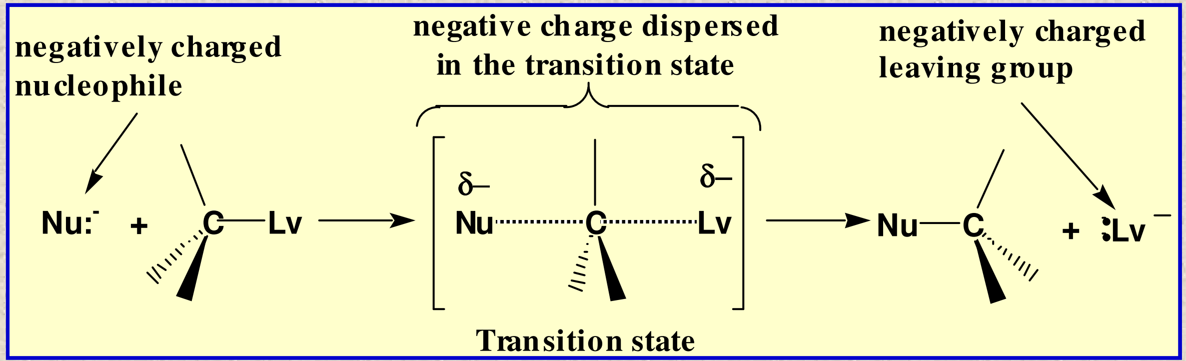
Solvent	Structure	Dielectric Constant
Polar		
Dimethyl sulfoxide (DMSO)	$(CH_3)_2S{=}O$	48.9
Acetonitrile	$CH_3C{\equiv}N$	37.5
N,N-Dimethylformamide (DMF)	$(CH_3)_2NCHO$	36.7
Acetone	$(CH_3)_2C{=}O$	20.7
Nonpolar		
Dichloromethane	CH_2Cl_2	9.1
Diethyl ether	$CH_3CH_2OCH_2CH_3$	4.3
Toluene	$C_6H_5CH_3$	2.3
Hexane	$CH_3(CH_2)_4CH_3$	1.9

Protic Solvents

Solvent	Structure	Dielectric Constant (25°C)
Water	H_2O	79
Formic acid	$HCOOH$	59
Methanol	CH_3OH	33
Ethanol	CH_3CH_2OH	24
Acetic acid	CH_3COOH	6

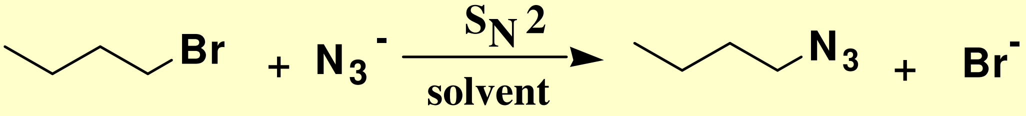
The Solvent – S_N2

- The most common type of S_N2 reaction involves a negative $Nu:^-$ and a negative leaving group.



  - – The weaker the solvation of $Nu:^-$, the less the energy required to remove it from its solvation shell and the greater the rate of S_N2.

The Solvent – S_N2

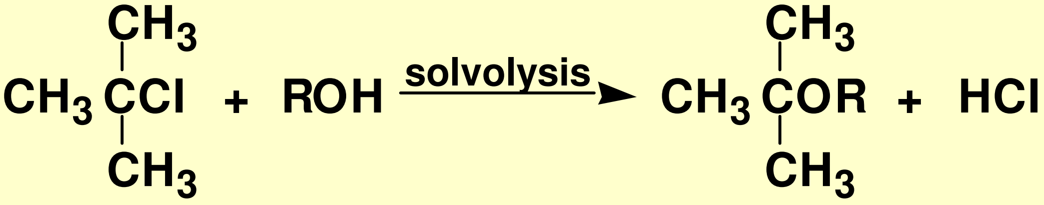


Solvent Type	Solvent	$\frac{k_{(solvent)}}{k_{(methanol)}}$
polar aprotic	$CH_3C{\equiv}N$	5000
	$(CH_3)_2NCHO$	2800
	$(CH_3)_2S{=}O$	1300
polar protic	H_2O	7
	CH_3OH	1

The Solvent – S_N1

- S_N1 reactions involve creation and separation of unlike charges in the transition state of the rate-determining step.
- **Rate depends on the ability of the solvent to keep these charges separated and to solvate both the anion and the cation.**
- **Polar protic solvents (formic acid, water, methanol) are the most effective solvents for S_N1 reactions.**

The Solvent – S_N1



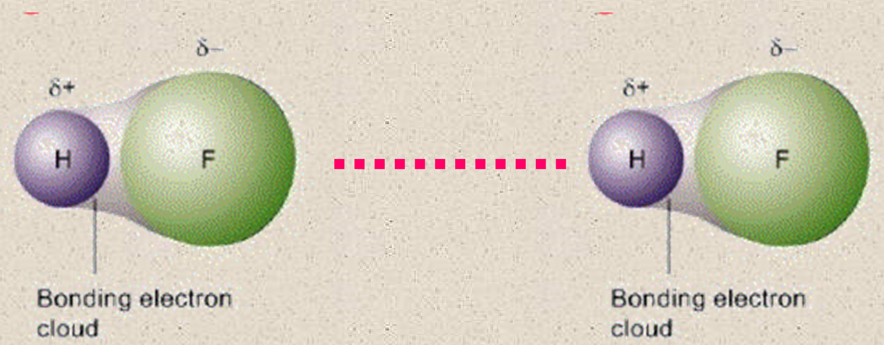
$$CH_3\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{CCl}} + ROH \xrightarrow{\text{solvolysis}} CH_3\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{COR}} + HCl$$

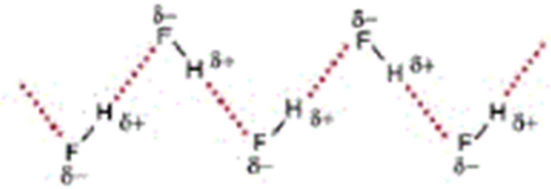
Solvent	$\frac{k_{(solvent)}}{k_{(ethanol)}}$
water	100,000
80% water: 20% ethanol	14,000
40% water: 60% ethanol	100
ethanol	1

Nucleophilicity

- **Nucleophilicity:** A **kinetic property** measured by the rate at which a Nu: causes a nucleophilic substitution under a standardized set of experimental conditions.
- **Basicity**: A **equilibrium property** measured by the position of equilibrium in an acid-base reaction.
- Because all nucleophiles are also bases, correlations between nucleophilicity and basicity are studied.

Effectiveness	Nucleophile
Good	Br^-, I^-
	CH_3S^-, RS^-
	HO^-, CH_3O^-, RO^-
	CN^-, N_3^-
Moderate	Cl^-, F^-
	CH_3COO^-, $RCOO^-$
	CH_3SH, RSH, R_2S
	NH_3, RNH_2, R_2NH, R_3N
Poor	H_2O
	CH_3OH, ROH
	CH_3COOH, $RCOOH$





Hydrogen fluoride (HF)

Nucleophilicity

- Polar protic solvents (e.g. H_2O, methanol)
  - **Anions are highly solvated by hydrogen bonding with the solvent.**
  - The more concentrated the negative charge of the anion, the more tightly it is held in a solvent shell.
  - The nucleophile must be at least partially removed from its solvent shell to participate in S_N2 reactions.

F^- is most tightly solvated and I^- the least:

nucleophilicity is $I^- > Br^- > Cl^- > F^-$

Nucleophilicity

- A guiding principle:

the “freer” the nucleophile, the greater its nucleophilicity.

- Polar aprotic solvents (e.g., DMSO, acetone, acetonitrile, DMF)
  - are very effective in solvating cations, but not nearly so effective in solvating anions.
  - because anions are only poorly solvated, they participate readily in S_N2 reactions, and

nucleophilicity parallels basicity:

$$F^- > Cl^- > Br^- > I^-$$

Nucleophilicity

- Generalization
  - In a series of reagents with the same nucleophilic atom, **anionic reagents are stronger nucleophiles than neutral reagents**; this trend parallels the basicity of the nucleophile.

Increasing Nucleophilicity

H_2O	<	OH^-
ROH	<	RO^-
NH_3	<	NH_2^-
RSH	<	RS^-

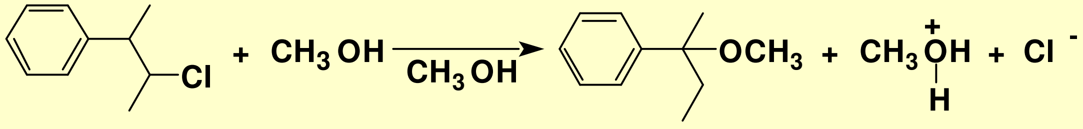
Nucleophilicity

- Generalization
  - When comparing groups of reagents in which the nucleophilic atom is the same, **the stronger the base, the greater the nucleophilicity.**

Nucleophile	$RCOO^-$ Carboxylate ion	HO^- Hydroxide ion	RO^- Alkoxide ion
	Increasing Nucleophilicity →		
Conjugate acid	RCOOH	HOH	ROH
pK_a	4-5	15.7	16-18
	← Increasing Acidity		

Rearrangements in S_N1

- Rearrangements are common in S_N1 reactions if the initial carbocation can rearrange to a more stable one.

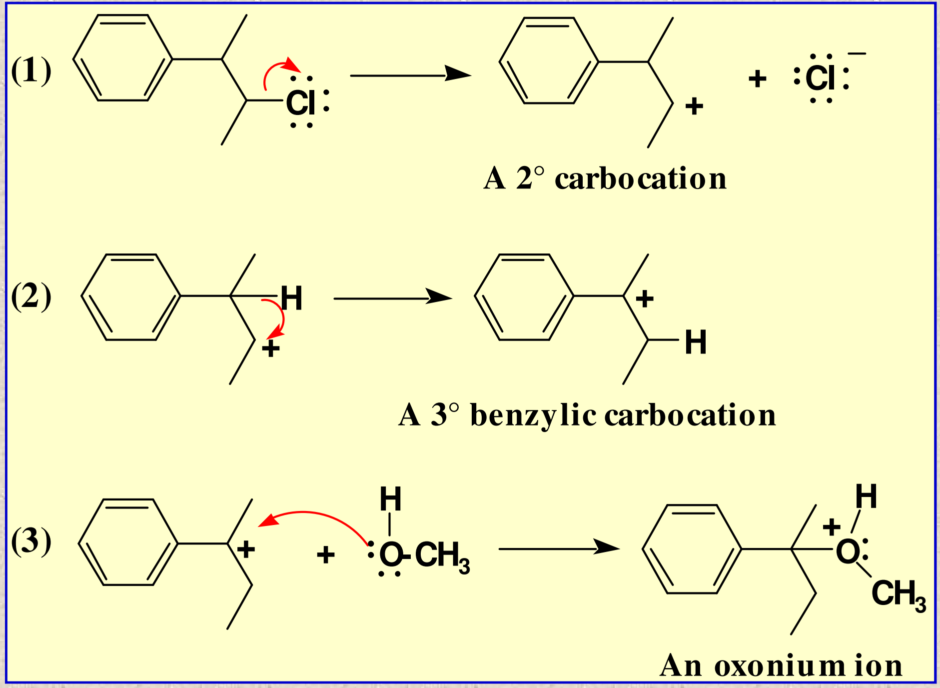


2-Chloro-3-phenylbutane

2-Methoxy-2-phenylbutane

Rearrangements in S_N1

- Mechanism of a carbocation rearrangement

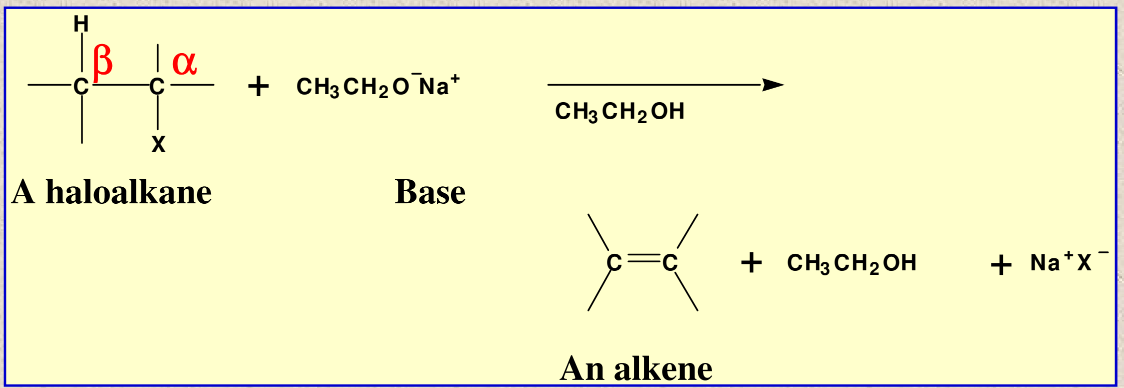


Summary of S_N1 & S_N2

Type of Alkyl Halide	S_N2	S_N1
Methyl CH_3X	**S_N2 is favored.**	**S_N1 does not occur.** The methyl cation is so unstable, it is never observed in solution.
Primary RCH_2X	**S_N2 is favored.**	**S_N1 rarely occurs.** Primary cations are so unstable, that they are never observed in solution.
Secondary R_2CHX	**S_N2 is favored** in aprotic solvents with good nucleophiles.	**S_N1 is favored** in protic solvents with poor nucleophiles. Carbocation rearrangements may occur.
Tertiary R_3CX	**S_N2 does not occur** because of steric hindrance around the reaction center.	**S_N1 is favored** because of the ease of formation of tertiary carbocations.
Substitution at a stereocenter	**Inversion of configuration.** The nucleophile attacks the stereocenter from the side opposite the leaving group.	**Racemization is favored.** The carbocation intermediate is planar, and attack of the nucleophile occurs with equal probability from either side. There is often some net inversion of configuration.

β-Elimination

β-Elimination: A reaction in which a small molecule, such as HCl, HBr, HI, or HOH, is split out or eliminated from adjacent carbons.

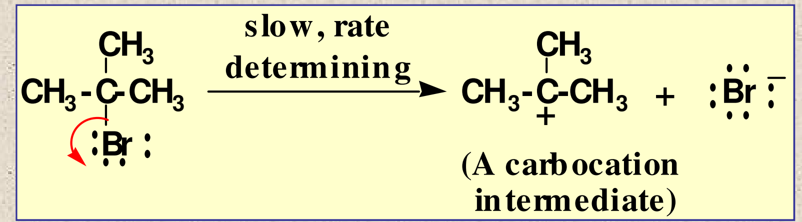


β-Elimination

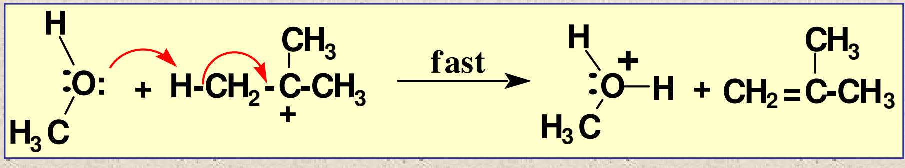
- There are two limiting mechanisms for β-elimination reactions.
- E1 mechanism: At one extreme, breaking of the R-Lv bond to give a carbocation is complete before reaction with base to break the C-H bond.
  - Only R-Lv is involved in the rate-determining step.
- E2 mechanism: At the other extreme, breaking of the R-Lv and C-H bonds is concerted.
  - Both R-Lv and base are involved in the rate-determining step.

E1 Mechanism

– Rate-determining ionization of the C-Lv bond gives a carbocation intermediate.

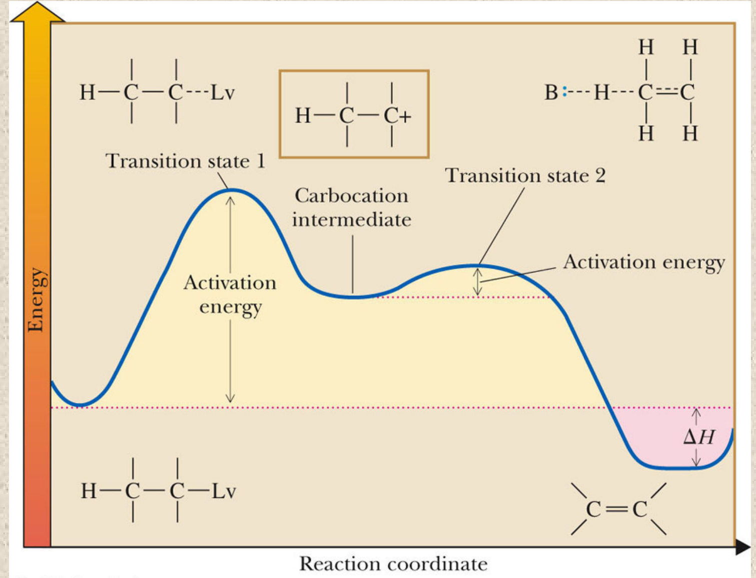


– Proton transfer from the carbocation intermediate to the base (in this case, the solvent) gives the alkene.



E1 Mechanism

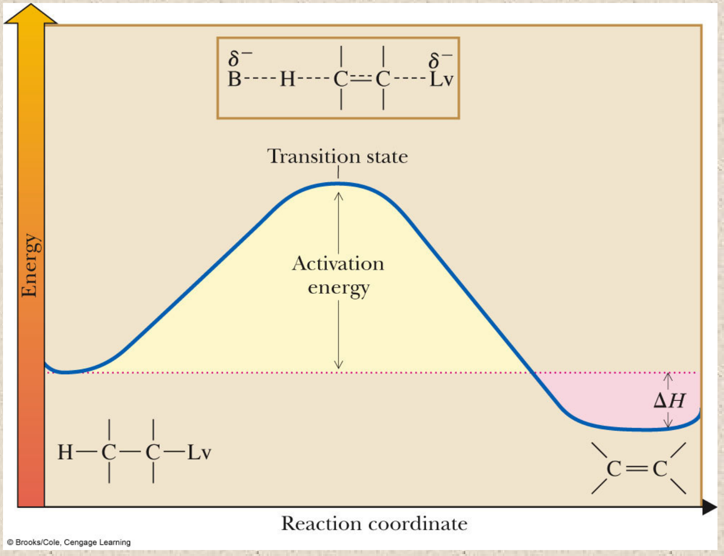
- Energy diagram for an E1 reaction. Two transition states and one reactive intermediate.



© Brooks/Cole, Cengage Learning

E2 Mechanism

- Energy diagram for an E2 reaction. There is considerable double bond character in the transition state.



© Brooks/Cole, Cengage Learning

Kinetics of E1 & E2

- E1 mechanism
  - Reaction occurs in two steps.
  - The rate-determining step is carbocation formation.
  - Reaction is 1st order in RLv and zero order is base.

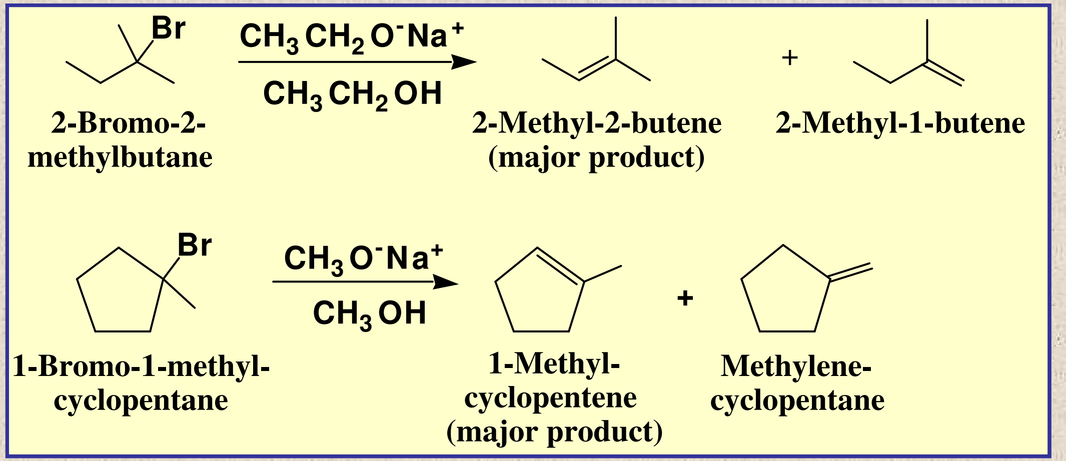
$$\text{Rate} = -\frac{d[\text{RLv}]}{dt} = k[\text{RLv}]$$

- E2 mechanism
  - Reaction occurs in one step.
  - Reaction is 2nd order; first order in RLv and 1st order in base.

$$\text{Rate} = -\frac{d[\text{RLv}]}{dt} = k[\text{RLv}][\text{Base}]$$

β-Elimination

- Zaitsev rule: The major product of a β-elimination is the **more stable (the more highly substituted) alkene.**



2-Bromo-2-methylbutane

2-Methyl-2-butene (major product)

2-Methyl-1-butene

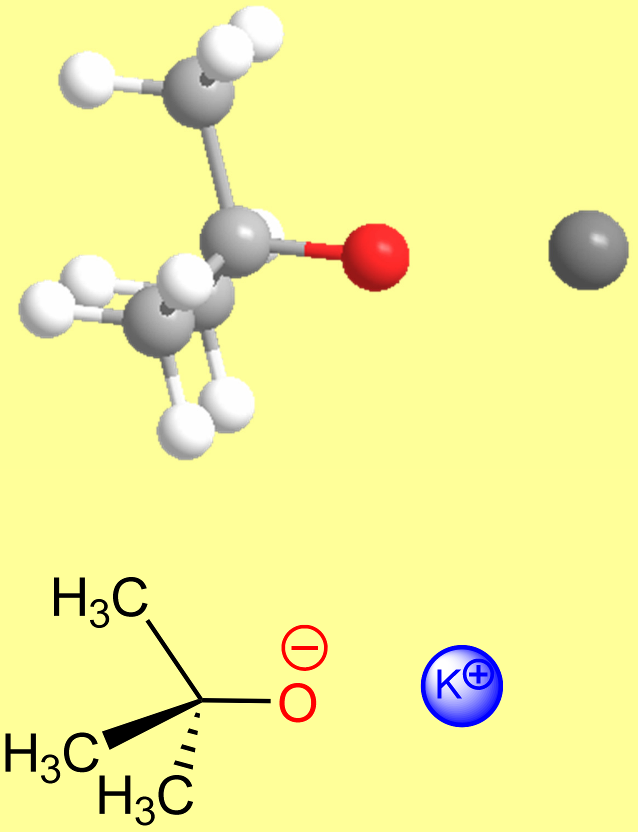
1-Bromo-1-methyl-cyclopentane

1-Methyl-cyclopentene (major product)

Methylene-cyclopentane

Regioselectivity of E1 & E2

- E2: with strong base, the major product is the more stable (more substituted) alkene.
  - Double bond character is highly developed in the transition state.
  - Thus, the transition state of lowest energy is that leading to the most stable (the most highly substituted) alkene.
- E2: with a strong, sterically hindered base such as *tert*-butoxide, the major product is often the less stable (less substituted) alkene.



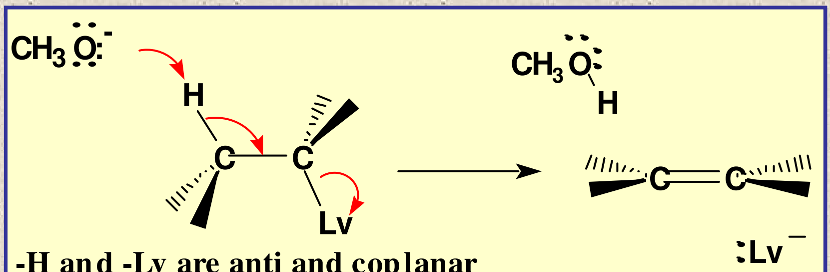
Regioselectivity of E1 & E2

E1: major product is the more stable alkene.

- Zaitsev rule: The major product of a β-elimination is the **more stable (the more highly substituted) alkene.**

Stereoselectivity of E2

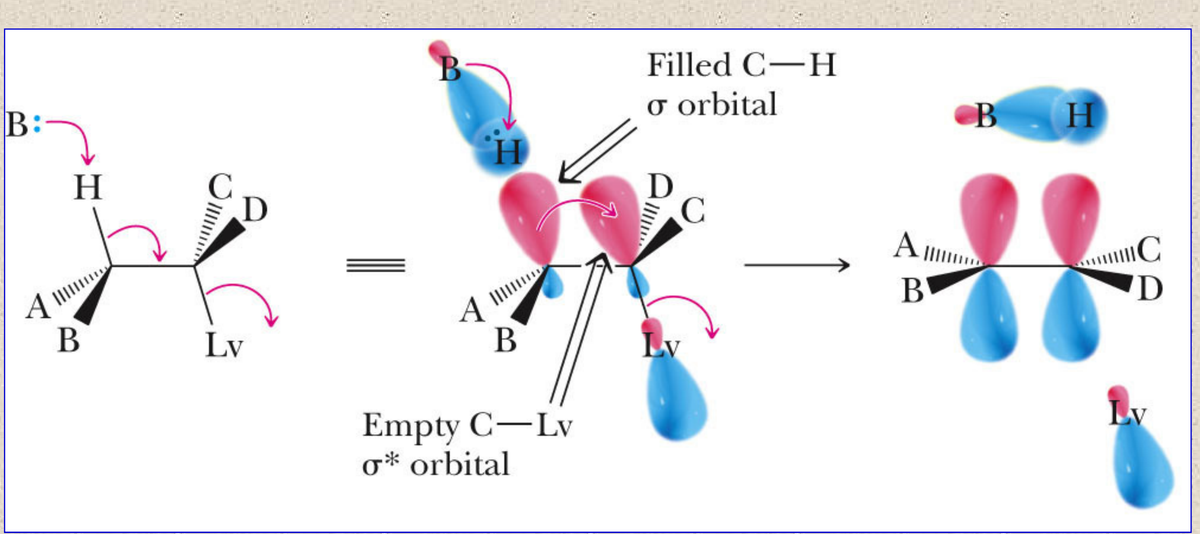
- E2 is most favorable (lowest activation energy) when H and Lv are oriented **anti and coplanar**.



-H and -Lv are anti and coplanar
(dihedral angle 180°)

Stereoselectivity of E2

- There is an orbital-based reason for the anti and coplanar arrangement of -H and -Lv involved in an E2 reaction.

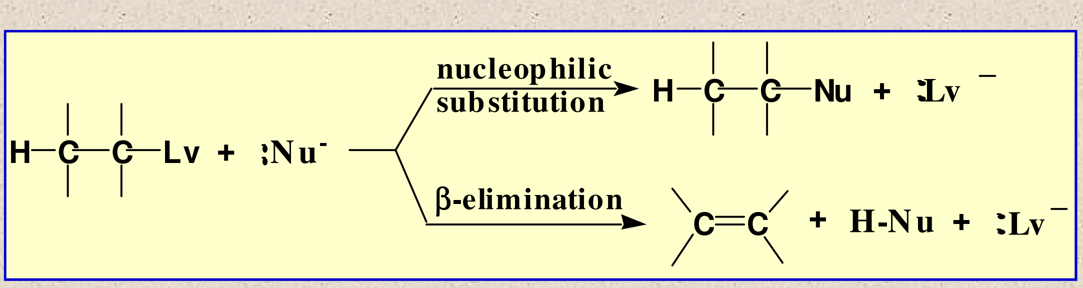


Summary of E2 vs E1

Alkyl halide	E1	E2
Primary RCH_2X	E1 does not occur. Primary carbocations are so unstable, they are never observed in solution.	E2 is favored.
Secondary R_2CHX	Main reaction with weak bases such as H_2O, ROH.	Main reaction with strong bases such as OH and OR.
Tertiary R_3CX	Main reaction with weak bases such as H_2O, ROH.	Main reaction with strong bases such as OH and OR.

S_N vs E

- Many nucleophiles are also strong bases (OH^- and RO^-) and S_N and E reactions often compete.
- The ratio of S_N/E products depends on the relative rates of the two reactions.



S_N vs E

Halide	Reaction	Comments
Methyl CH_3X	S_N2	S_N1 reactions of methyl halides are never observed. The methyl cation is so unstable that it is never formed in solution.
Primary RCH_2X	S_N2	The main reaction with good nucleophiles/weak bases such as I^- and CH_3COO^-.
	E2	The main reaction with strong, bulky bases such as potassium *tert*-butoxide.
		Primary cations are never observeded in solution and, therefore, S_N1 and E1 reactions of primary halides are never observed.

⟹

S_N vs E

Secondary R_2CHX	S_N2	The main reaction with bases/nucleophiles where pK_a of the conjugate acid is 11 or less, as for example I^- and CH_3COO^-.
	E2	The main reaction with bases/nucleophiles where the pK_a of the conjugate acid is 11 or greater, as for example OH^- and $CH_3CH_2O^-$.
	S_N1/E1	Common in reactions with weak nucleophiles in polar protic solvents, such as water, methanol, and ethanol.
Tertiary R_3CX	E2	Main reaction with strong bases such as HO^- and RO^-.
	S_N1/E1	Main reactions with poor nucleophiles/weak bases. S_N2 reactions of tertiary halides are never observed because of the extreme crowding around the 3° carbon.