

11. Reactions of Alkyl Halides: Nucleophilic Substitutions and Eliminations

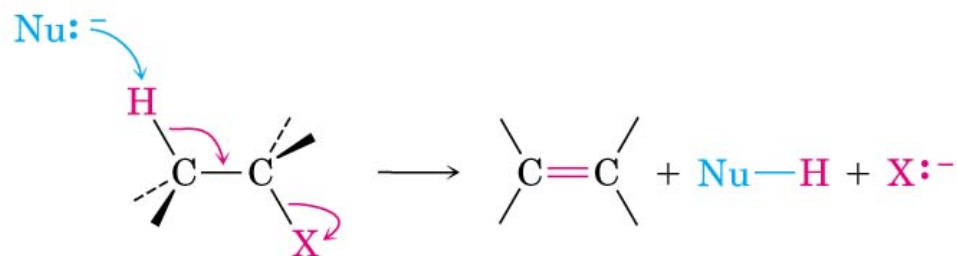
Alkyl Halides React with Nucleophiles and Bases

- Alkyl halides are polarized at the carbon-halide bond, making the carbon electrophilic
- Nucleophiles will replace the halide in C-X bonds of many alkyl halides (reaction as Lewis base)
- Nucleophiles that are Brønsted bases produce elimination rather than substitution

Substitution

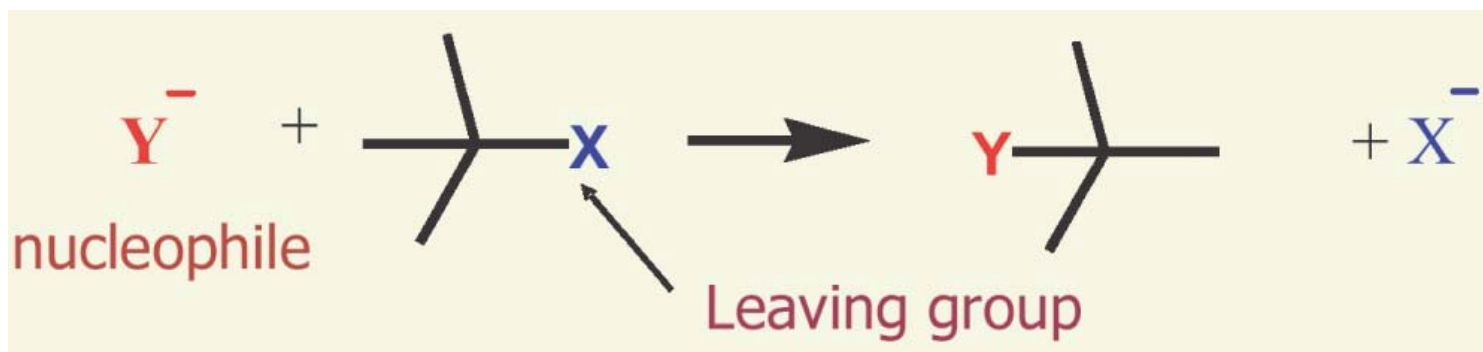


Elimination



The Nature of Substitution

- Substitution, by definition, requires that a "leaving group", which is also a Lewis base, 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 3°, allyl, benzyl (stable carbocations)

- S_N2
 - Two simultaneous steps combine - without intermediate
 - Occurs in primary, secondary (minimal steric hindrance)

11.3 Kinetics of Nucleophilic Substitution

- **Rate** (V) is change in concentration with time
- Depends on concentration(s), temperature, inherent nature of reaction (barrier on energy surface)
- A **rate law** describes relationship between the concentration of reactants and conversion to products
- A rate constant (k) is the proportionality factor between concentration and rate

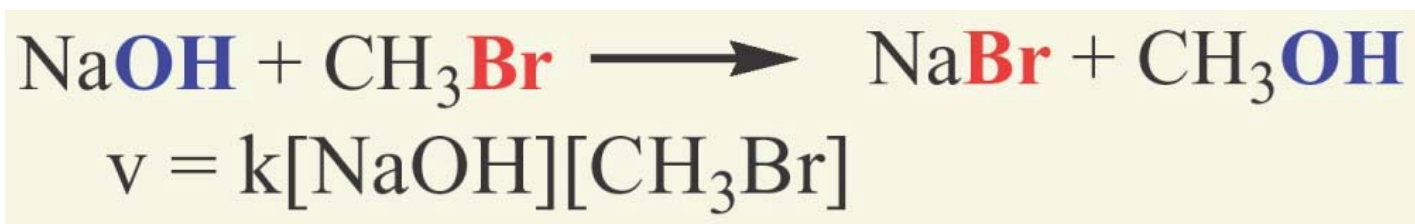
Example: for S converting to P

$$V = d[S]/dt = k [S]$$

Reaction Kinetics

- The study of rates of reactions is called *kinetics*

- Rates decrease as concentrations decrease (probability of two molecules colliding decreases) but the rate constant does not
- Rate units: [concentration]/time such as Mol/(L x s)
- The *rate law* is a result of the mechanism
- The *order* of a reaction is sum of the exponents of the concentrations in the rate law – the example is second order ($1 + 1 = 2$) In this example, the rate of the reaction depends on the concentration of both reagents, increasing the conc. of one increases the rate, increasing the conc. of both increases the rate even more.



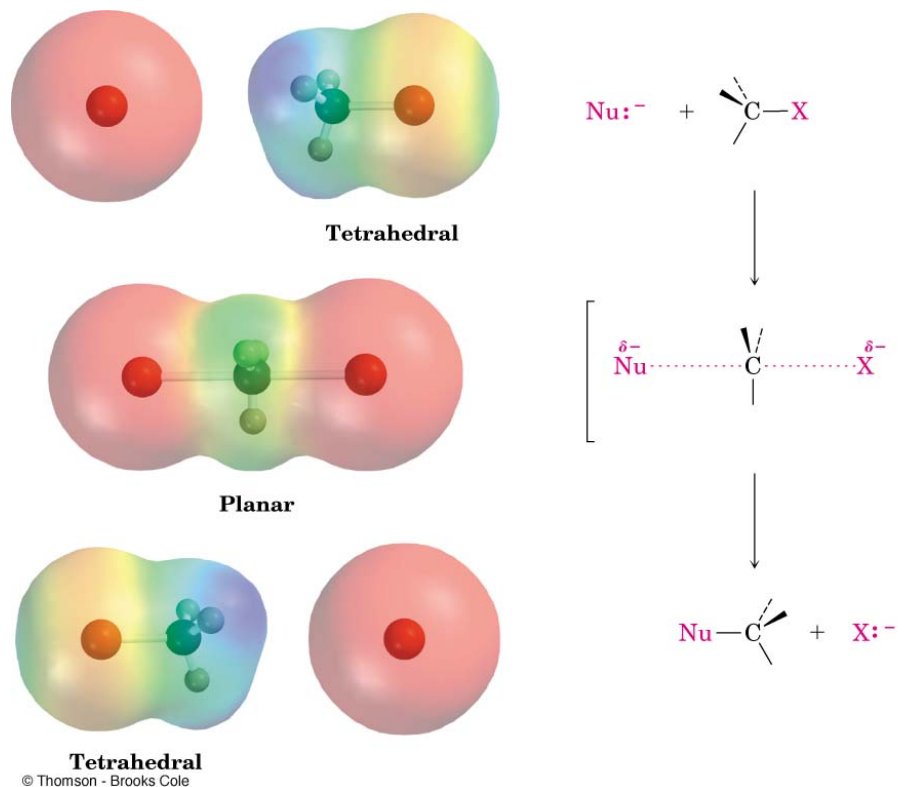
11.4 The S_N2 Reaction

- Reaction is with inversion of configuration at reacting center
- Follows second order reaction kinetics
- Ingold nomenclature to describe characteristic step:
 - S = substitution, N (subscript) = nucleophilic

- 2 = both nucleophile and substrate in characteristic step (bimolecular)

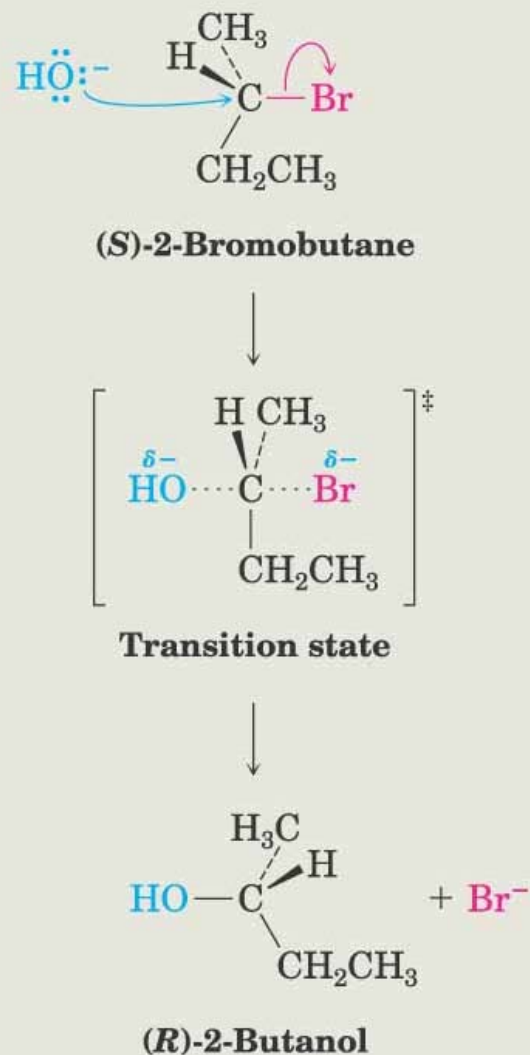
S_N2 Process

- The reaction involves a transition state in which both reactants are together
- The transition state of an S_N2 reaction has a planar arrangement of the carbon atom and the remaining three groups



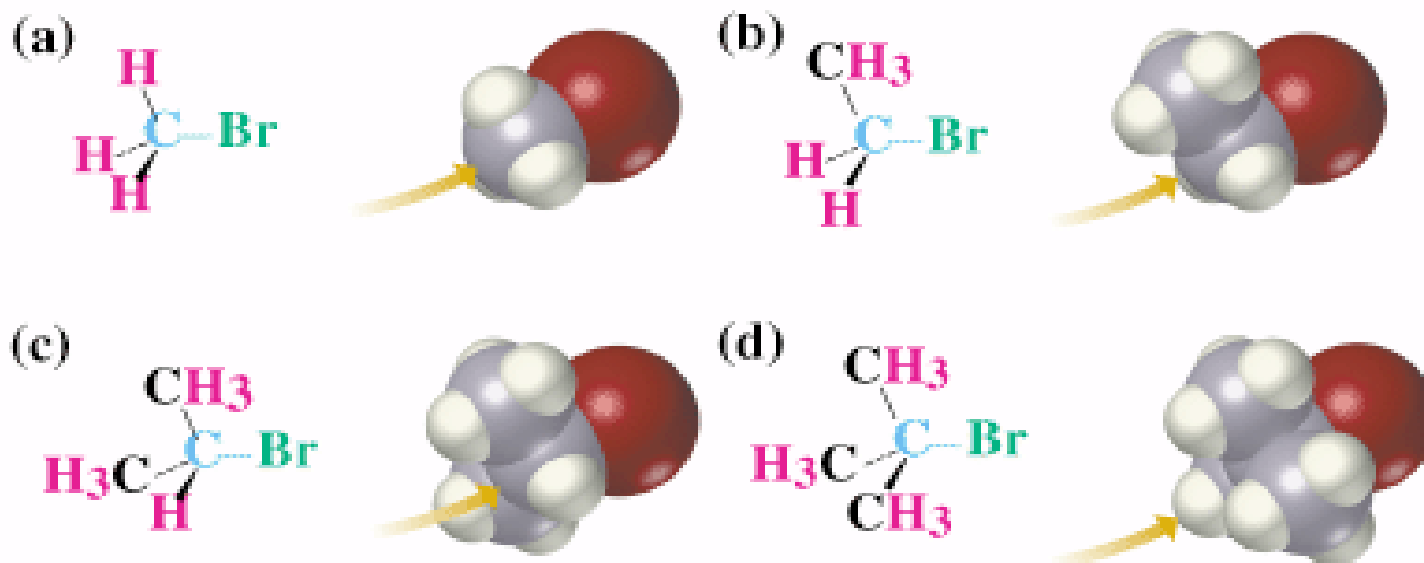
The nucleophile OH^- uses its lone-pair electrons to attack the alkyl halide carbon 180° away from the departing halogen. This leads to a transition state with a partially formed $\text{C}-\text{OH}$ bond and a partially broken $\text{C}-\text{Br}$ bond.

The stereochemistry at carbon is inverted as the $\text{C}-\text{OH}$ bond forms fully and the bromide ion departs with the electron pair from the former $\text{C}-\text{Br}$ bond.



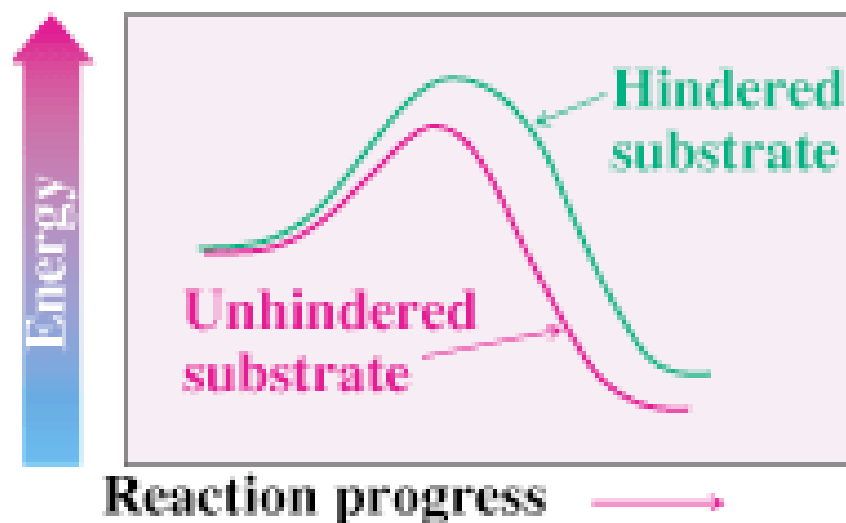
11.5 Characteristics of the S_N2 Reaction (how do the following affect the S_N2 reaction)

1) The Substrate: Steric Effects on S_N2 Reactions



The carbon atom in (a) bromomethane is readily accessible resulting in a fast S_N2 reaction. The carbon atoms in (b) bromoethane (primary), (c) 2-bromopropane (secondary), and (d) 2-bromo-2-methylpropane (tertiary) are successively more hindered, resulting in successively slower S_N2 reactions.

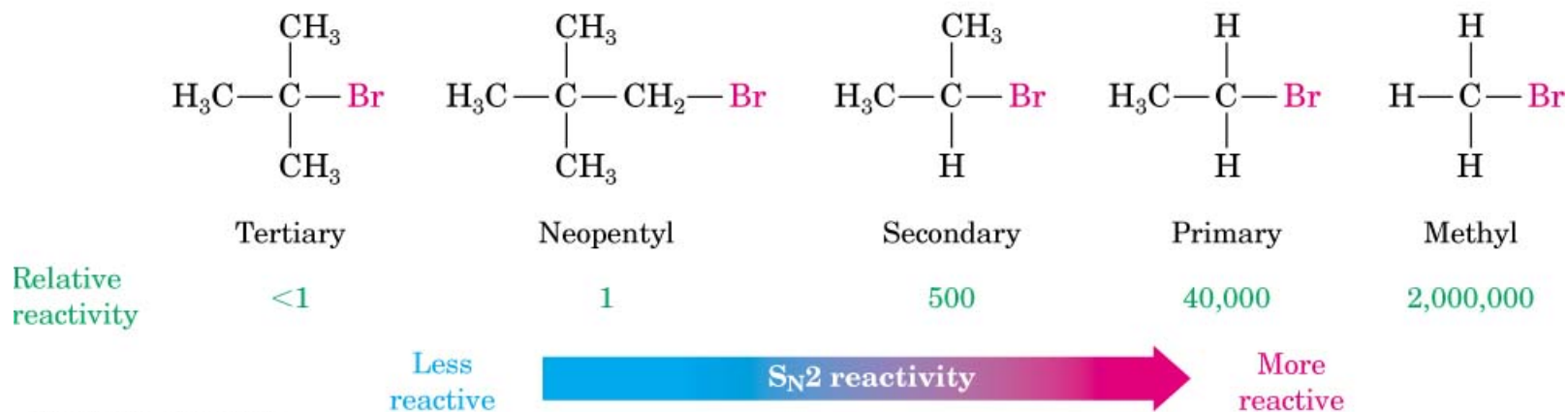
Steric Hindrance Raises Transition State Energy



- Steric effects destabilize transition states
- Severe steric effects can also destabilize ground state

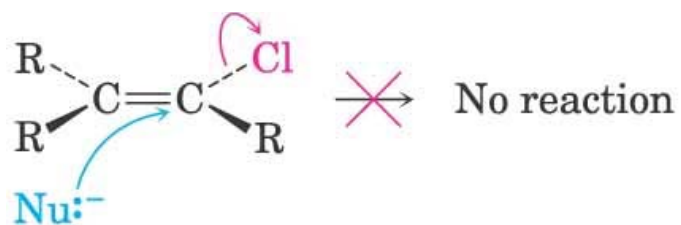
Order of Reactivity in S_N2

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



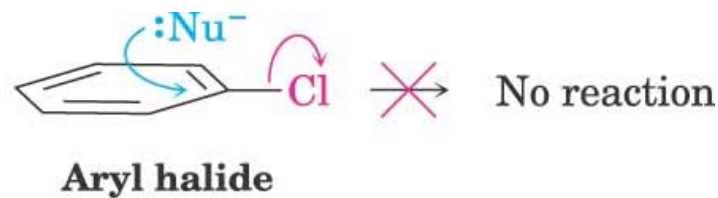
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Vinyllic and aryl halides are not reactive towards $\text{S}_{\text{N}}2$ reactions.



Vinyllic halide

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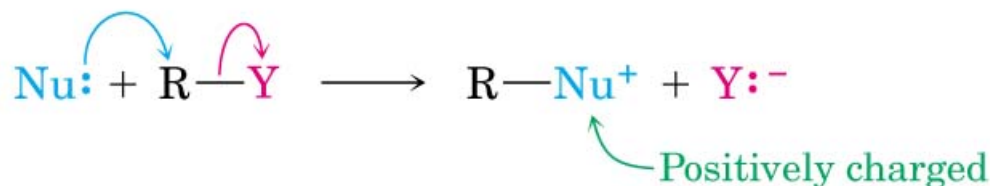
2) The Attacking Nucleophile

- Neutral or negatively charged Lewis base can act as nucleophiles in S_N2 reactions as long as it has a lone pair of electrons.
 - Neutral nucleophile yields a positively charged product
 - Anionic nucleophile yields a neutral product
 - See Table 11-1 for an illustrative list

**Negatively charged
Nu:⁻**



Neutral Nu:



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**An acetylide anion
(nucleophile)**

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TABLE 11.1 Some S_N2 Reactions with Bromomethane: $\text{Nu}^- + \text{CH}_3\text{Br} \longrightarrow \text{Nu}-\text{CH}_3 + \text{Br}^-$

| Nucleophile | | Product | |
|---------------------------------------|-----------------|---|-----------------------------|
| Formula | Name | Formula | Name |
| $\text{CH}_3\ddot{\text{S}}^-$ | Methanethiolate | CH_3SCH_3 | Dimethyl sulfide |
| HS^- | Hydrosulfide | HSCH_3 | Methanethiol |
| $\text{N}\equiv\text{C}^-$ | Cyanide | $\text{N}\equiv\text{CCH}_3$ | Acetonitrile |
| $\text{N}=\text{N}=\ddot{\text{N}}^-$ | Azide | N_3CH_3 | Azidomethane |
| $:\ddot{\text{I}}^-$ | Iodide | ICH_3 | Iodomethane |
| $\text{CH}_3\ddot{\text{O}}^-$ | Methoxide | CH_3OCH_3 | Dimethyl ether |
| HO^- | Hydroxide | HOCH_3 | Methanol |
| $:\ddot{\text{Cl}}^-$ | Chloride | ClCH_3 | Chloromethane |
| $\text{H}_3\text{N}:$ | Ammonia | $\text{H}_3\text{N}^+\text{CH}_3 \text{ Br}^-$ | Methylammonium bromide |
| CH_3CO_2^- | Acetate | $\text{CH}_3\text{CO}_2\text{CH}_3$ | Methyl acetate |
| $(\text{CH}_3)_3\text{N}:$ | Trimethylamine | $(\text{CH}_3)_3\text{N}^+\text{CH}_3 \text{ Br}^-$ | Tetramethylammonium bromide |
| H^- | Hydride | CH_4 | Methane |

Relative Reactivity of Nucleophiles

Nucleophilicity is not very precise, however general rules do apply keeping in mind that there are exceptions.

a- Nucleophilicity roughly parallels basicity

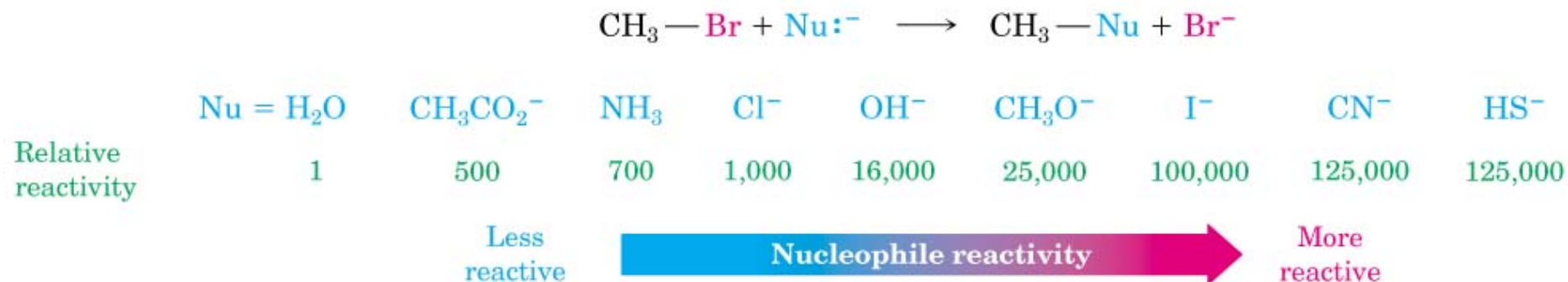
TABLE 11.2 Correlation of Basicity and Nucleophilicity

| Nucleophile | CH ₃ O ⁻ | HO ⁻ | CH ₃ CO ₂ ⁻ | H ₂ O |
|---|--------------------------------|-----------------|--|------------------|
| Rate of S _N 2 reaction with CH ₃ Br | 25 | 16 | 0.5 | 0.001 |
| pK _a of conjugate acid | 15.5 | 15.7 | 4.7 | -1.7 |

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b- Nucleophilicity usually increases going down a column in the PT, the order can change depending on the solvent.

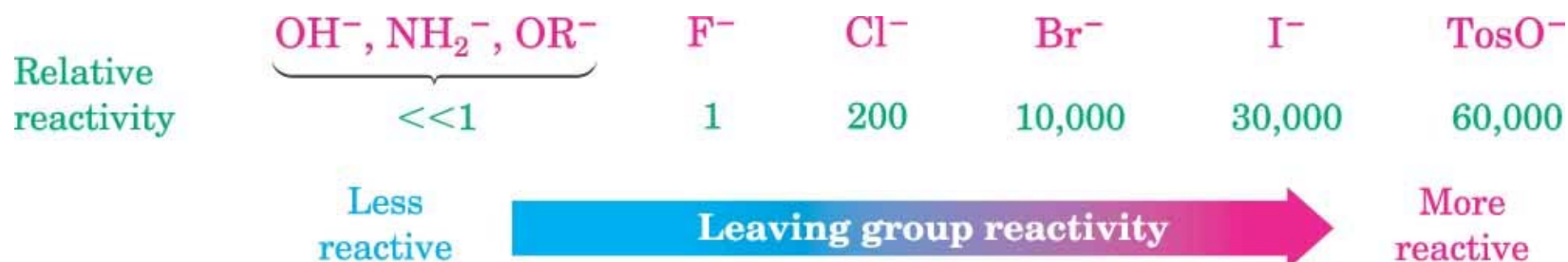
c- Negatively charged nucleophiles are usually more reactive than neutral ones.



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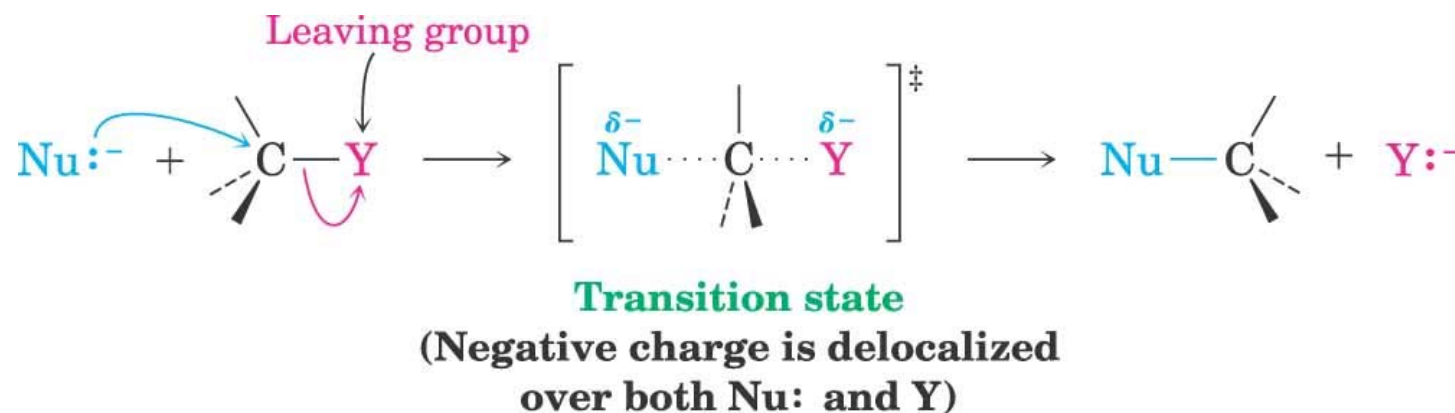
3) The Leaving Group

- A good leaving group reduces the barrier to a reaction
- Stable anions that are weak bases are usually excellent leaving groups (can delocalize charge) the best leaving groups are those that best stabilize the negative charge.



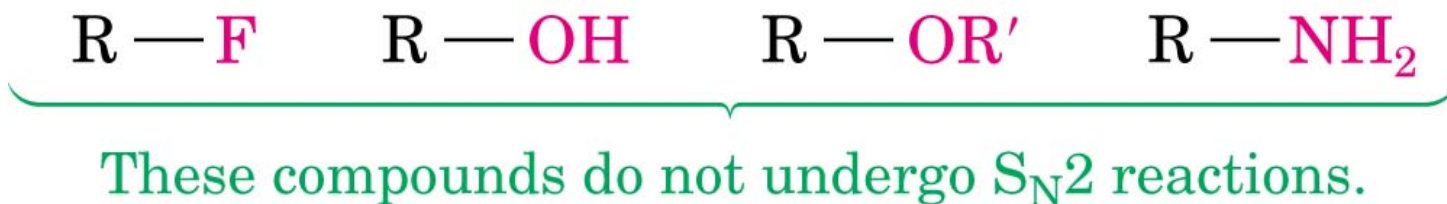
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The greater the extent of charge stabilization by the LG, the lower the energy of the transition state and thus the more rapid the reaction.



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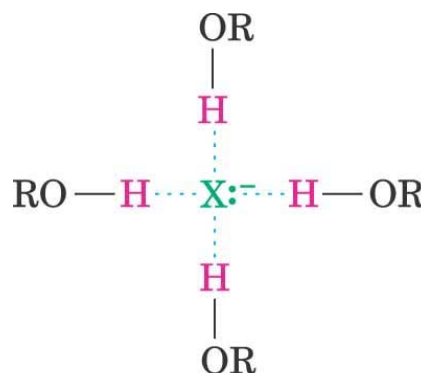
- If a group is very basic or very small, it prevents reaction



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4) The Solvent

- Solvents that can donate hydrogen bonds (-OH or -NH) slow S_N2 reactions by associating with reactants
- Energy is required to break interactions between reactant and solvent
- Polar aprotic solvents (no NH, OH, SH) form weaker interactions with substrate and permit faster reaction



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

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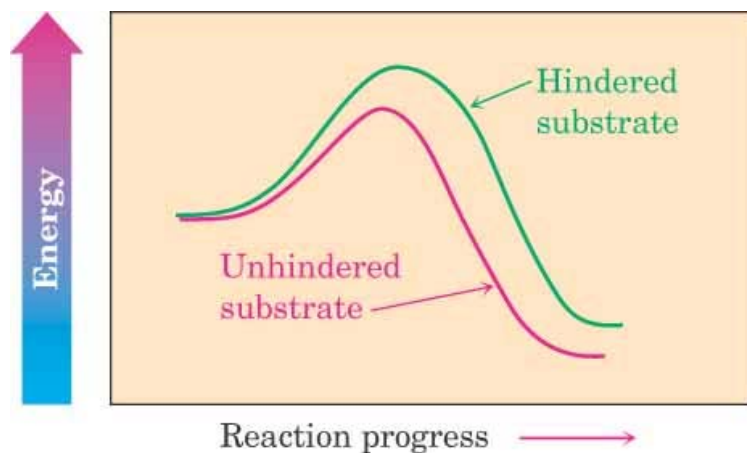
| Solvent | CH ₃ OH | H ₂ O | DMSO | DMF | CH ₃ CN | HMPA |
|---------------------|--------------------|------------------|-------|-------|--------------------|---------|
| Relative reactivity | 1 | 7 | 1,300 | 2,800 | 5,000 | 200,000 |

Less reactive

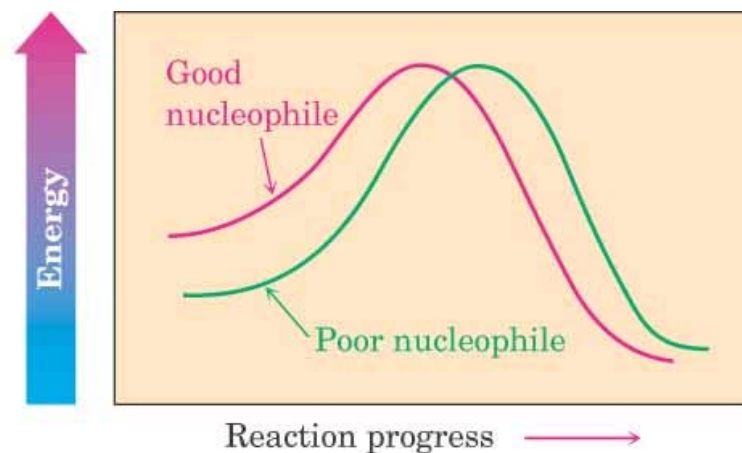
More reactive

Solvent reactivity

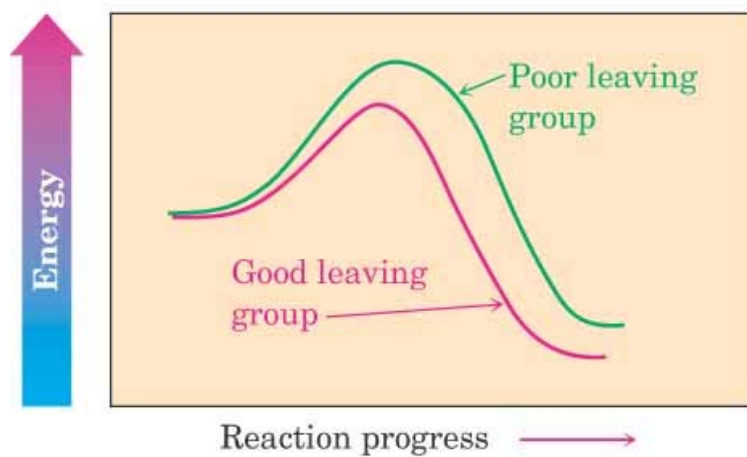
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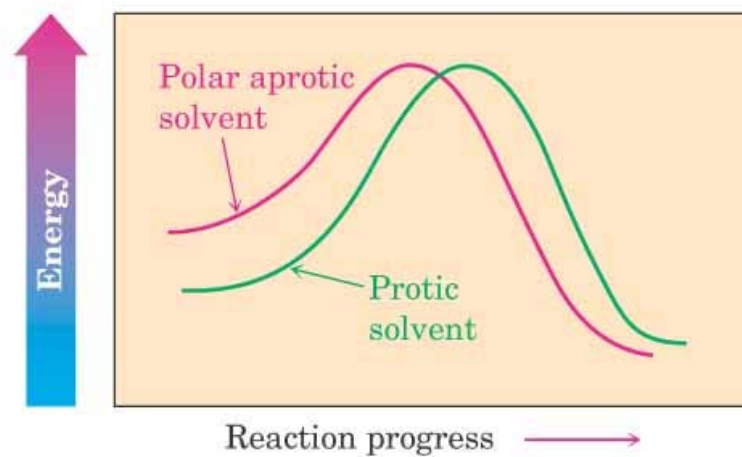
(a)



(b)



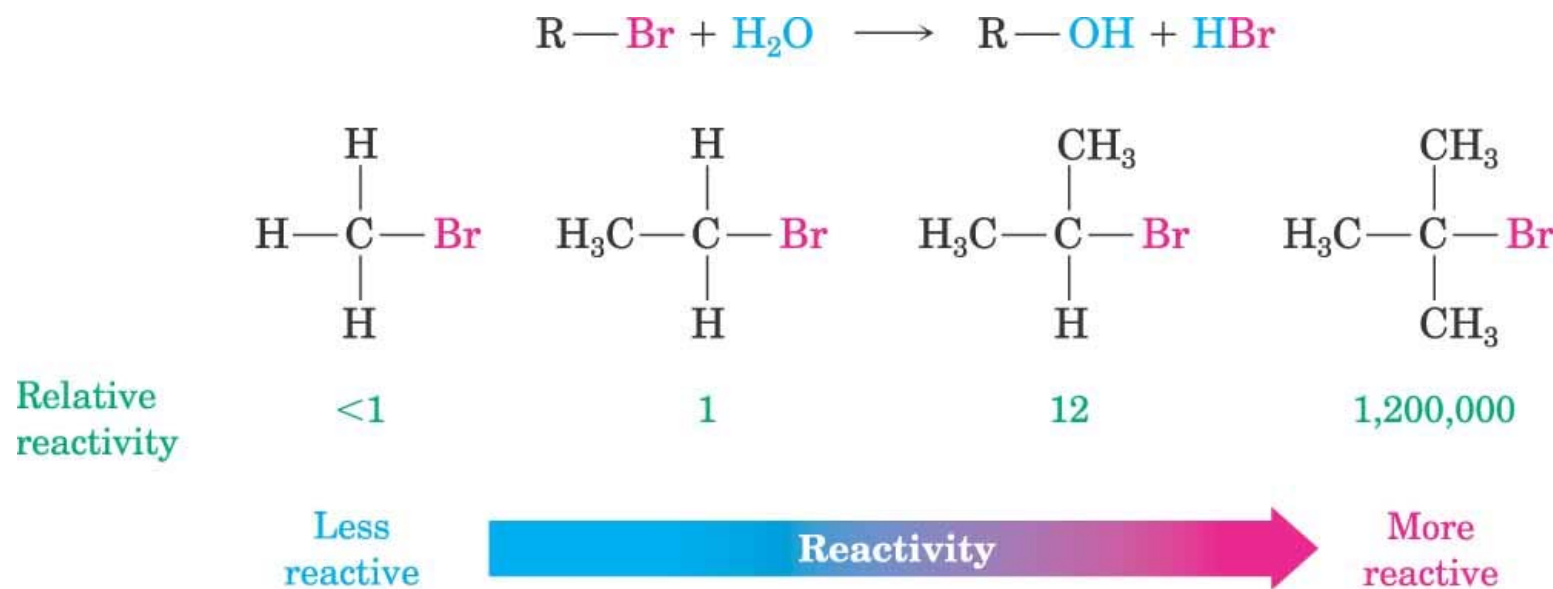
(c)



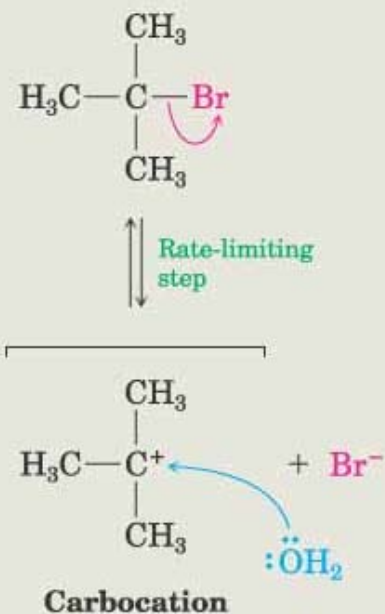
(d)

11.6 The S_N1 Reaction

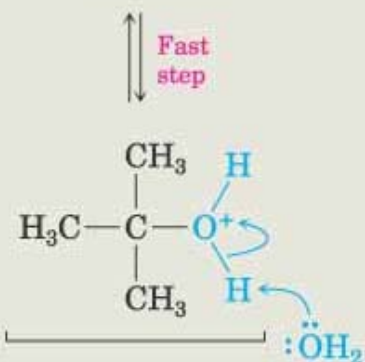
- Tertiary alkyl halides react rapidly in protic solvents by a mechanism that involves spontaneous departure of the leaving group prior to addition of the nucleophile
- Called an S_N1 reaction – occurs in two distinct steps while S_N2 occurs with both events in same step
- If nucleophile is present in reasonable concentration (or if it is the solvent), then ionization is the slowest step and thus the rate determining step.



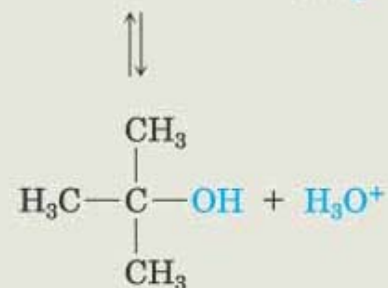
Spontaneous dissociation of the alkyl bromide occurs in a slow, rate-limiting step to generate a carbocation intermediate plus bromide ion.



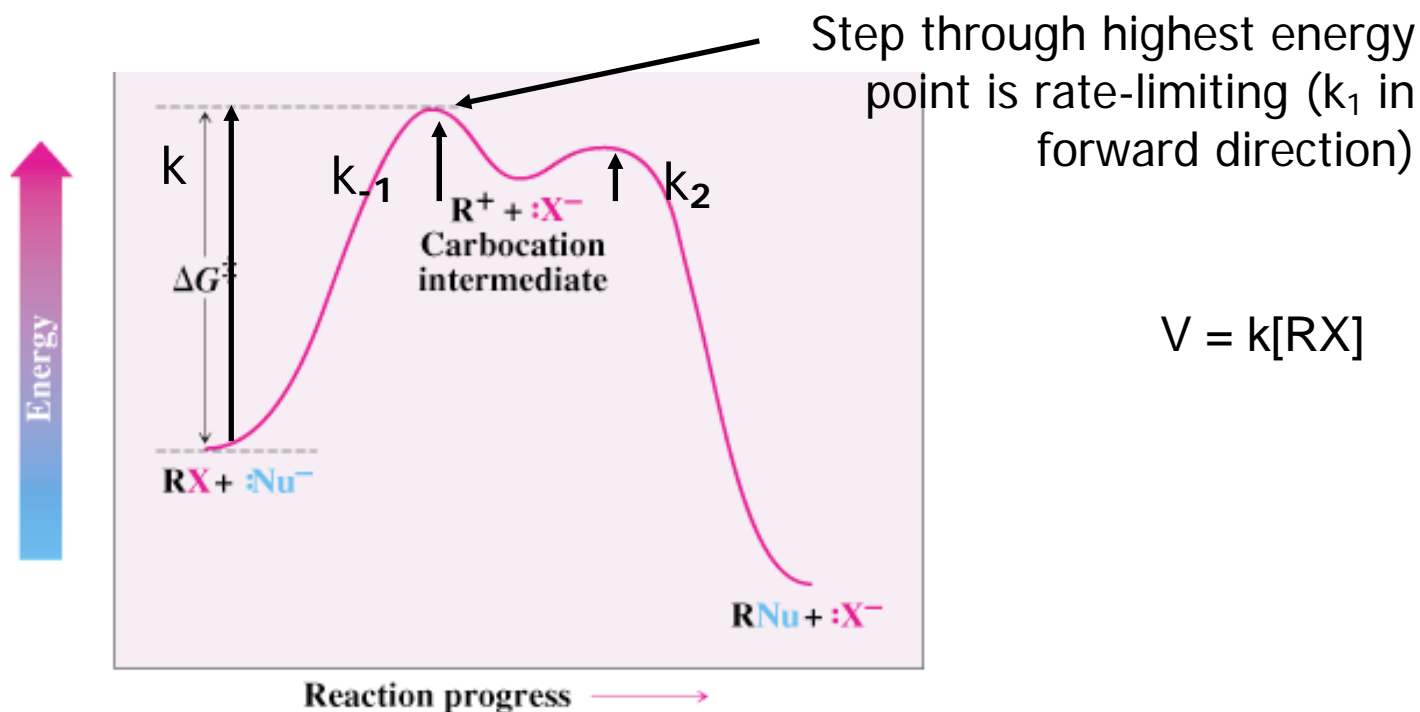
The carbocation intermediate reacts with water as nucleophile in a fast step to yield protonated alcohol as product.



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



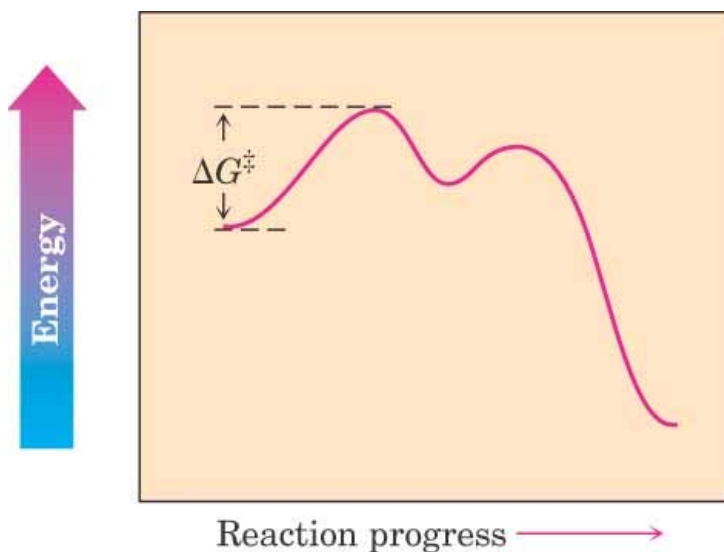
11.7 Kinetics of The S_N1 Reaction, Energy Diagram



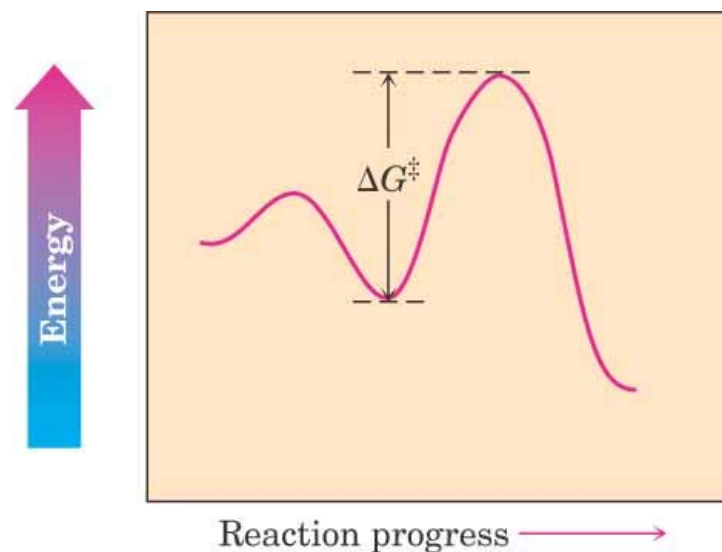
- Rate-determining step is formation of carbocation. Reaction rate is equal to the rate of disappearance of alkyl halide.

Rate-Limiting (Determining) Step (No reaction can proceed faster than its rate determining step. Traffic jam or bottle neck.)

- The overall rate of a reaction is controlled by the rate of the slowest step. **Reaction rate is dependant on $[R-X]$ and k only, first-order process.**
- The highest energy transition state point on the diagram is that for the rate determining step
- The overall reaction rate measured in a kinetics experiment is determined by the height of the highest energy barrier between a low point and a subsequent high point (it may be either the first or a subsequent step).



(a)

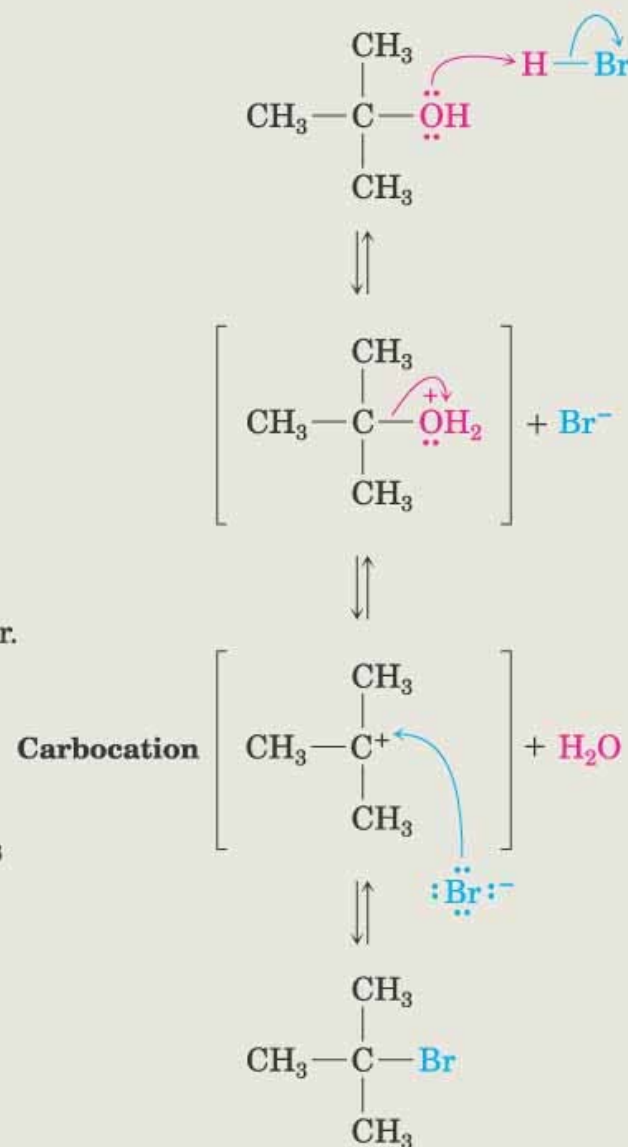


(b)

The —OH group is first protonated by HBr.

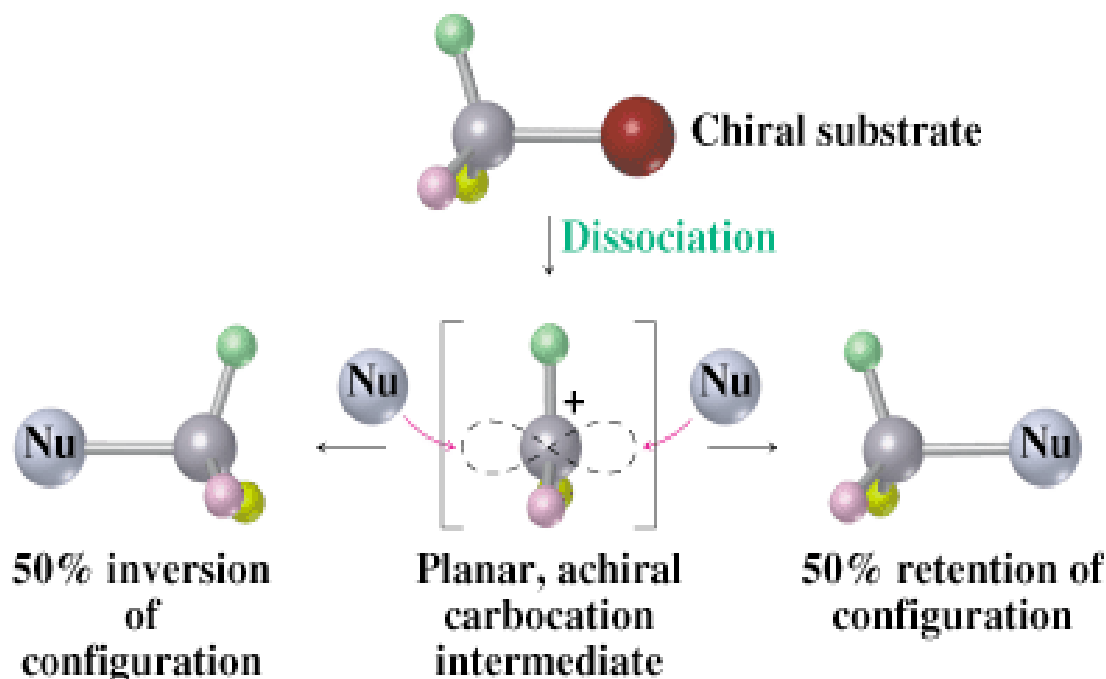
Spontaneous dissociation of the protonated alcohol occurs in a slow, rate-limiting step to yield a carbocation intermediate plus water.

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



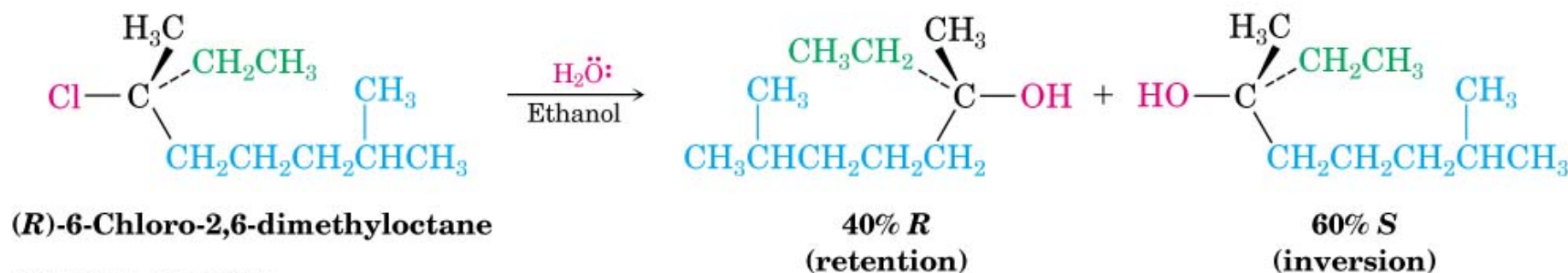
11.8 Stereochemistry of S_N1 Reaction

- In an S_N1 reaction, if the starting material is chiral, then the planar and SP² intermediate (carbocation) is not chiral. A free carbocation is achiral
- Product is racemic (a 50/50 mixture of enantiomers) or has some inversion



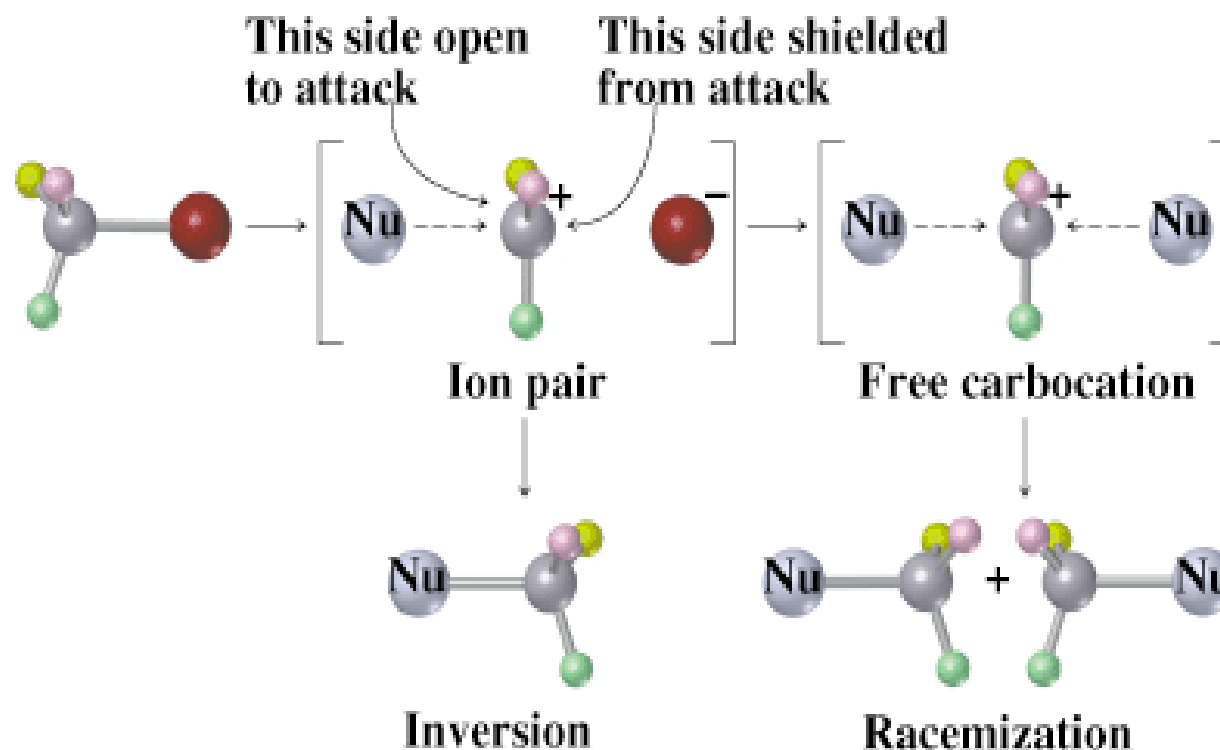
In many cases though, there is a bias and a minor excess of one enantiomer.

- Carbocation is biased to react on side opposite leaving group
- Suggests reaction occurs with carbocation loosely associated with leaving group during nucleophilic addition (S_N2 taking place is unlikely).



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- If leaving group remains associated, then product has more inversion than retention
- Carbocation and associated leaving group form an **ion pair**

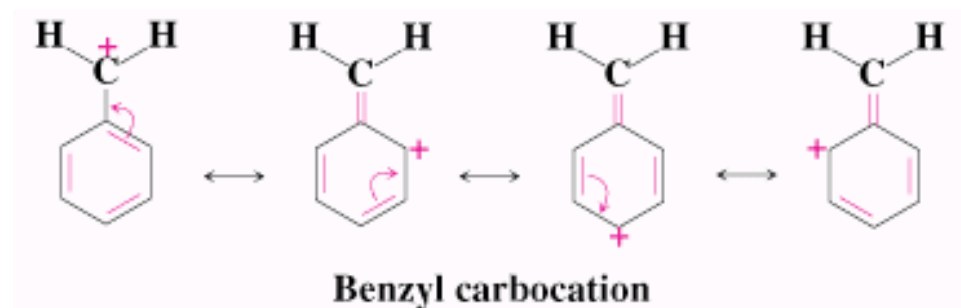
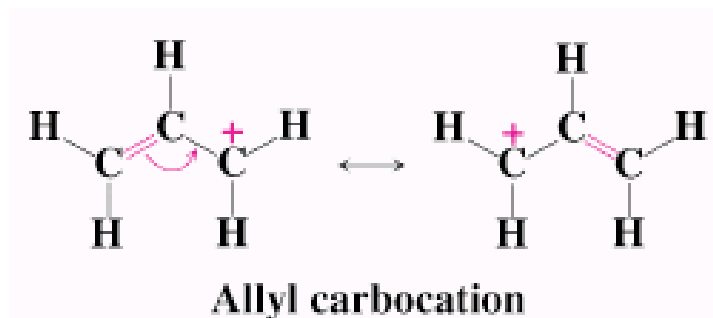


11.9 Characteristics of the S_N1 Reaction

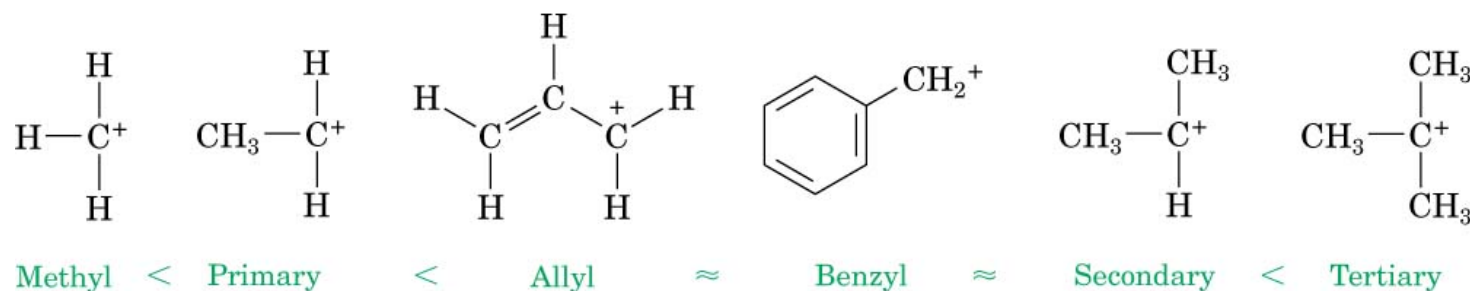
Much like the S_N2 reaction, in the S_N1 reaction, factors that lower the ΔG^\ddagger favor faster S_N1 reactions. Once again the substrate, leaving group, nucleophile and solvent play roles in lowering (or increasing) ΔG^\ddagger .

1) The substrate: the more stable the carbocation intermediate, the faster the S_N1 reaction.

- Delocalization of cationic charge enhances stability, primary allyl is more stable than primary alkyl, primary benzyl is more stable than allyl



- Tertiary alkyl halide is most reactive by this mechanism

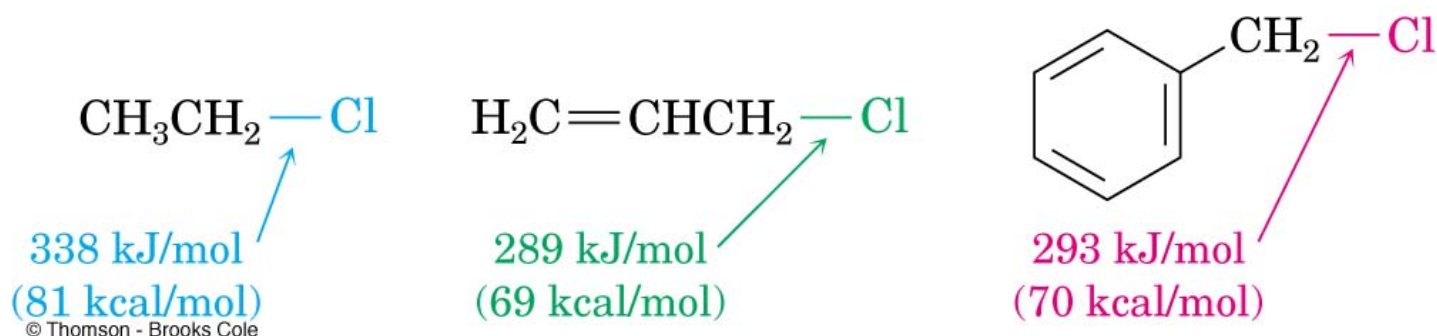


Less
stable

Carbocation stability

More
stable

- Allylic and benzylic intermediates stabilized by delocalization of charge
- Primary allylic and benzylic are also more reactive in the S_N2 mechanism.
- The allylic and benzylic C-X bonds are about 50 KJ/mol weaker than the corresponding saturated bonds and are therefore more easily broken.



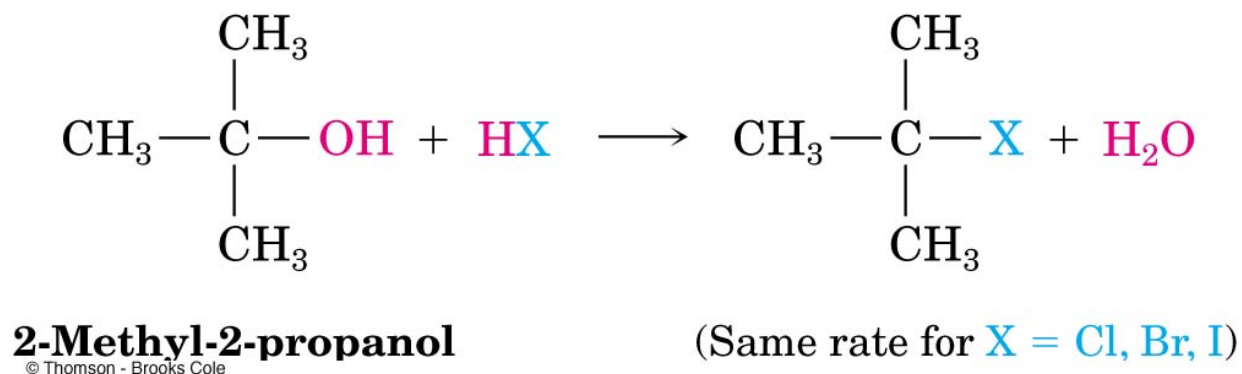
2) Leaving Group:

- 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 halides
- p-Toluenesulfonate (TosO^-) is excellent leaving group



3) Nucleophiles in SN1

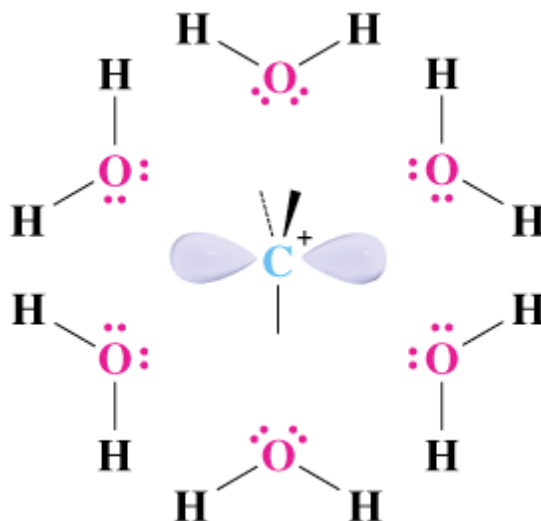
- Since nucleophilic addition occurs *after* formation of carbocation, reaction rate is not normally affected by nature or concentration of nucleophile



4) Solvent Is Critical in SN1

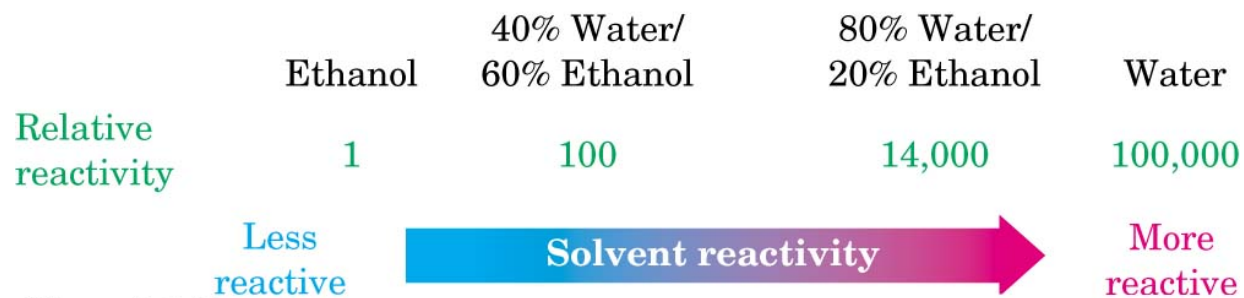
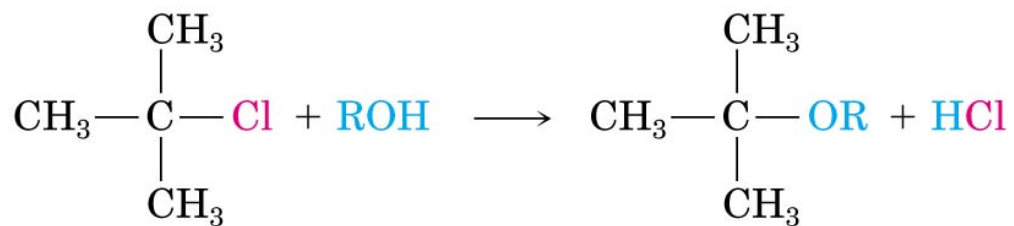
Solvents that stabilize carbocations also stabilize associated transition state and increases rate

Solvation of a carbocation by water



Polar Solvents Promote Ionization

- Polar, protic and unreactive Lewis base solvents facilitate formation of R^+
- Solvent polarity is measured as **dielectric polarization (P)** (Table 11-3)
 - Nonpolar solvents have low P , Polar solvents have high P values



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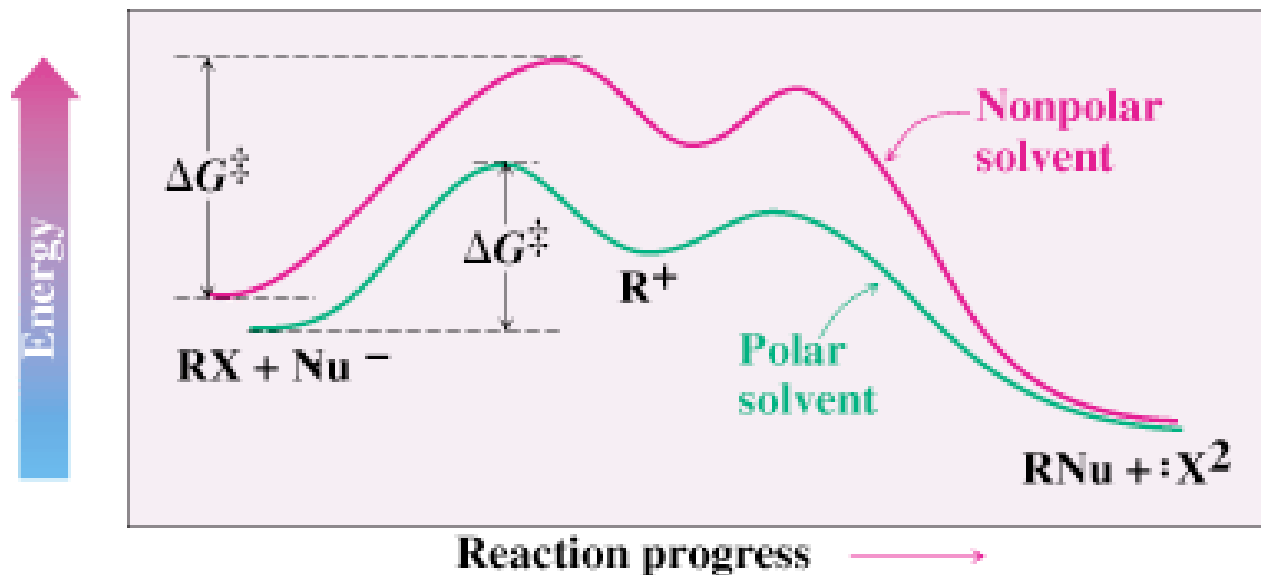
TABLE 11.3 Dielectric Polarizations of Some Common Solvents

| Name | Dielectric polarization | Name | Dielectric polarization |
|--------------------------------|-------------------------|------------------------|-------------------------|
| Aprotic solvents | | Protic solvents | |
| Hexane | 1.9 | Acetic acid | 6.2 |
| Benzene | 2.3 | Ethanol | 24.3 |
| Diethyl ether | 4.3 | Methanol | 33.6 |
| Chloroform | 4.8 | Formic acid | 58.0 |
| Hexamethylphosphoramide (HMPA) | 30 | Water | 80.4 |
| Dimethylformamide (DMF) | 38 | | |
| Dimethyl sulfoxide (DMSO) | 48 | | |

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Effects of Solvent on Energies

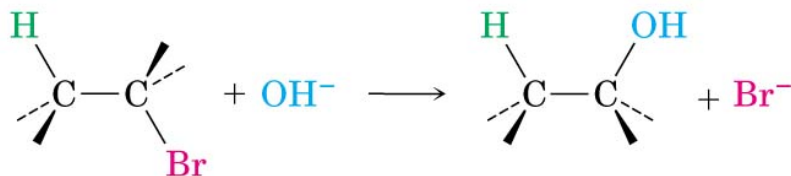
- Polar solvent stabilizes transition state and intermediate more than reactant and product



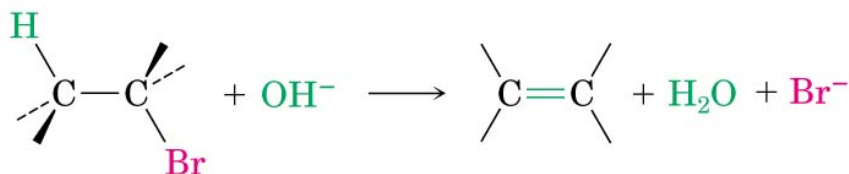
11.10 Alkyl Halides: Elimination

- Elimination is an alternative pathway to substitution
- Opposite of addition
- Generates an alkene
- Can compete with substitution and decrease yield, especially for SN1 processes

Substitution

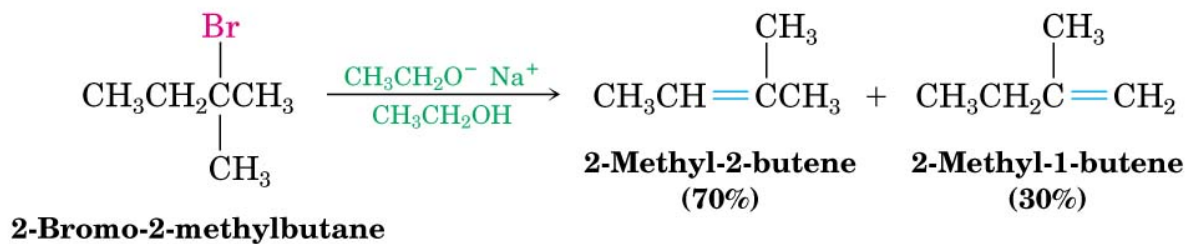
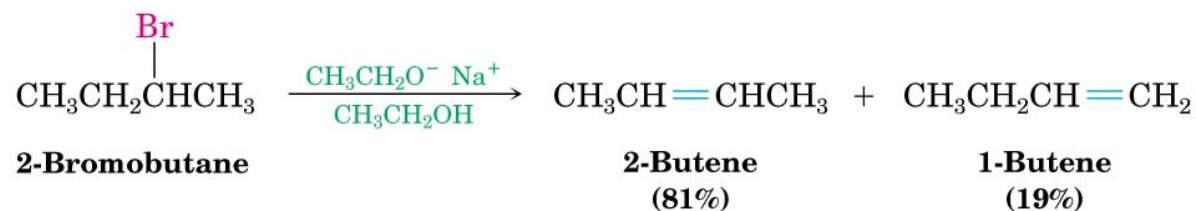


Elimination



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Zaitsev's Rule for Elimination Reactions (1875): In the elimination of HX from an alkyl halide, the more highly substituted alkene product predominates



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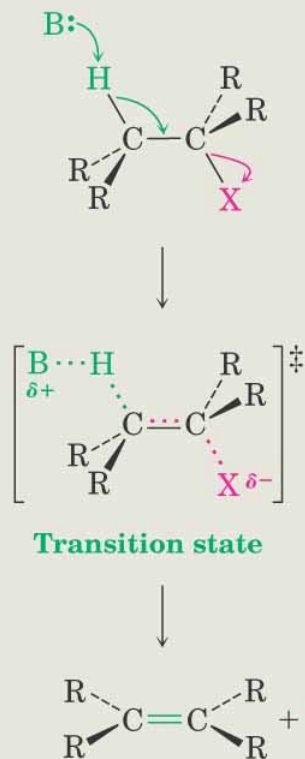
Mechanisms of Elimination Reactions

- Ingold nomenclature: E – “elimination”
- E1: X- leaves first to generate a carbocation
 - a base abstracts a proton from the carbocation
- E2: Concerted transfer of a proton to a base and departure of leaving group

11.11 The E2 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

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.



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.

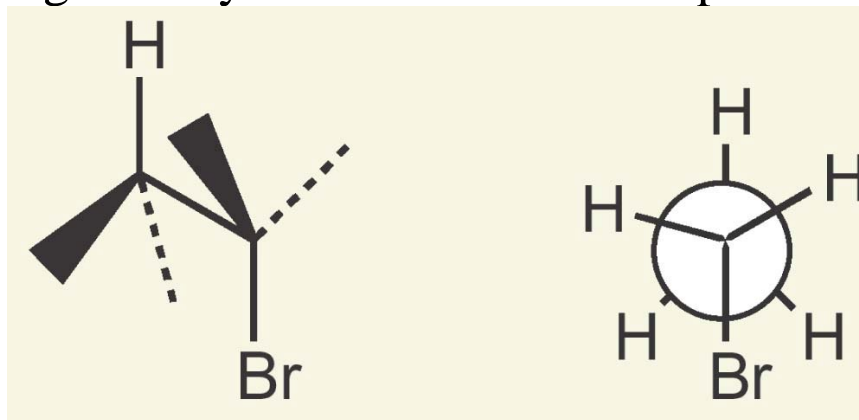
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E2 Reaction Kinetics

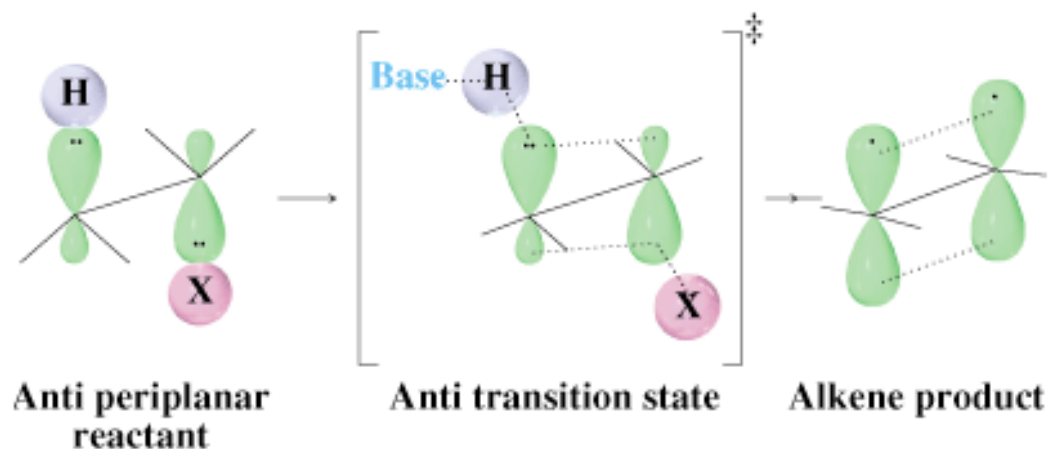
- One step – rate law has base and alkyl halide
- Transition state bears no resemblance to reactant or product
- $V = k[R-X][B]$
- Reaction goes faster with stronger base, better leaving group

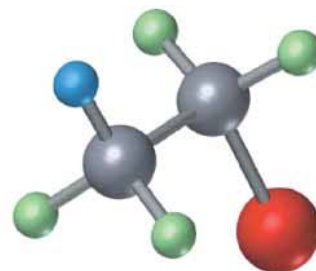
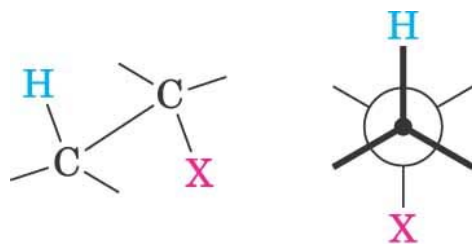
Geometry of Elimination – E2

- Antiperiplanar geometry allows orbital overlap and minimizes steric interactions

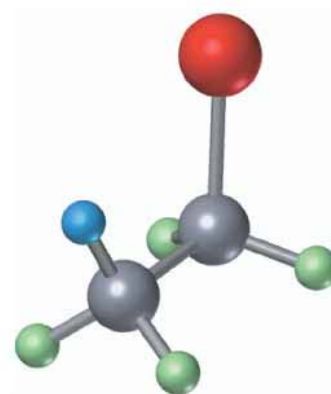
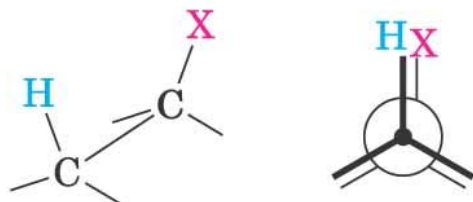


Overlap of the developing π orbital in the transition state requires periplanar geometry, anti arrangement





Anti periplanar geometry
(staggered, lower energy)



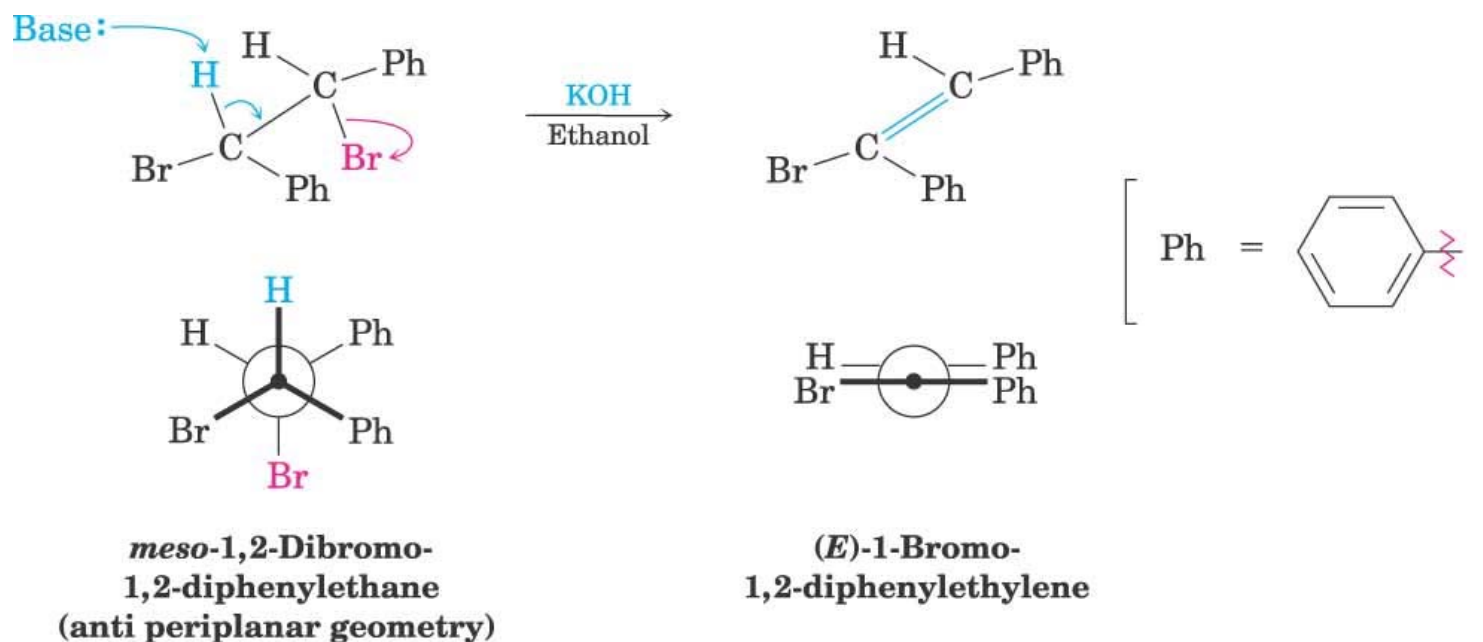
Syn periplanar geometry
(eclipsed, higher energy)

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E2 Stereochemistry & Predicting Product

- E2 is stereospecific (stereochemically different reactants react differently to yield stereochemically different products)

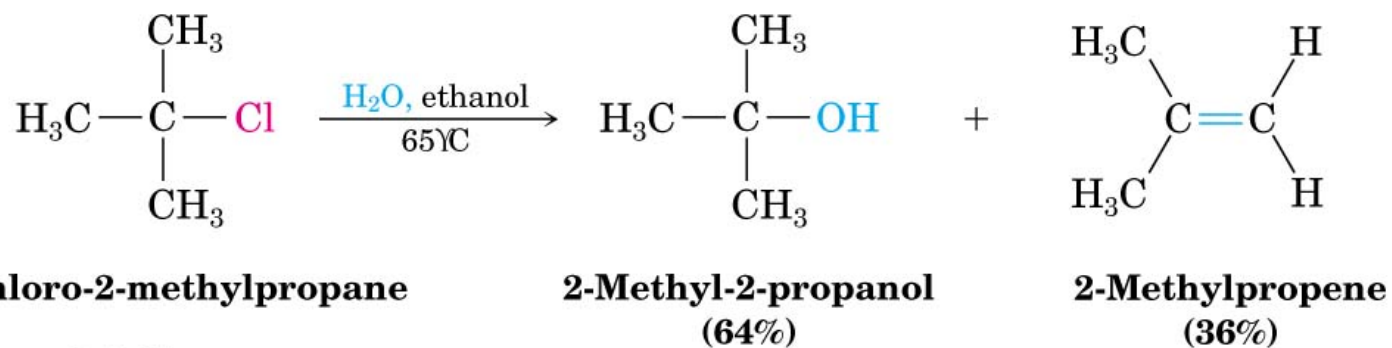
- Meso-1,2-dibromo-1,2-diphenylethane with base gives (E) 1,2-diphenyl
- RR or SS 1,2-dibromo-1,2-diphenylethane gives (Z) 1,2-diphenyl



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11.14 The E1 Reaction

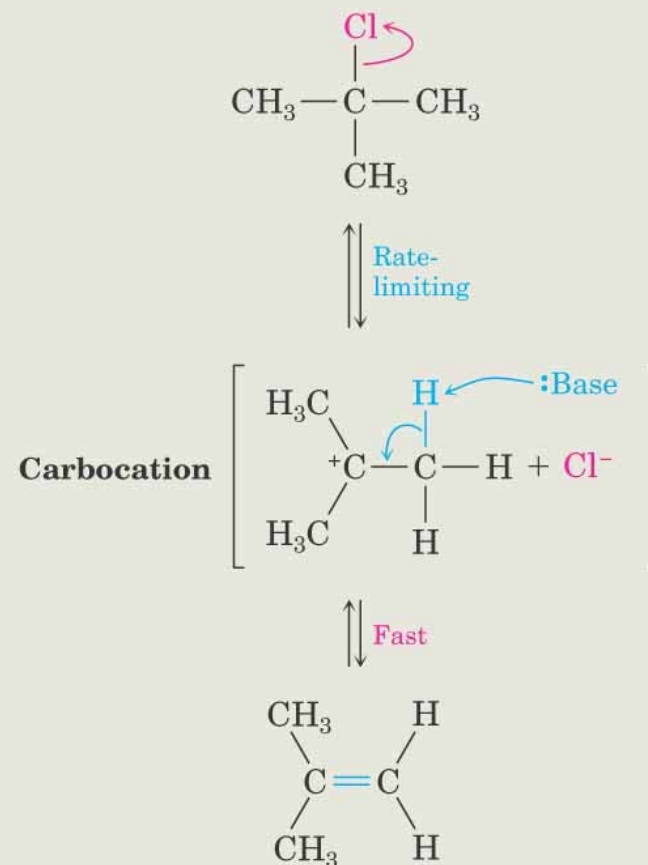
- Competes with $\text{S}_{\text{N}}1$ and $\text{E}2$ at 3° centers
- $V = k [\text{RX}]$



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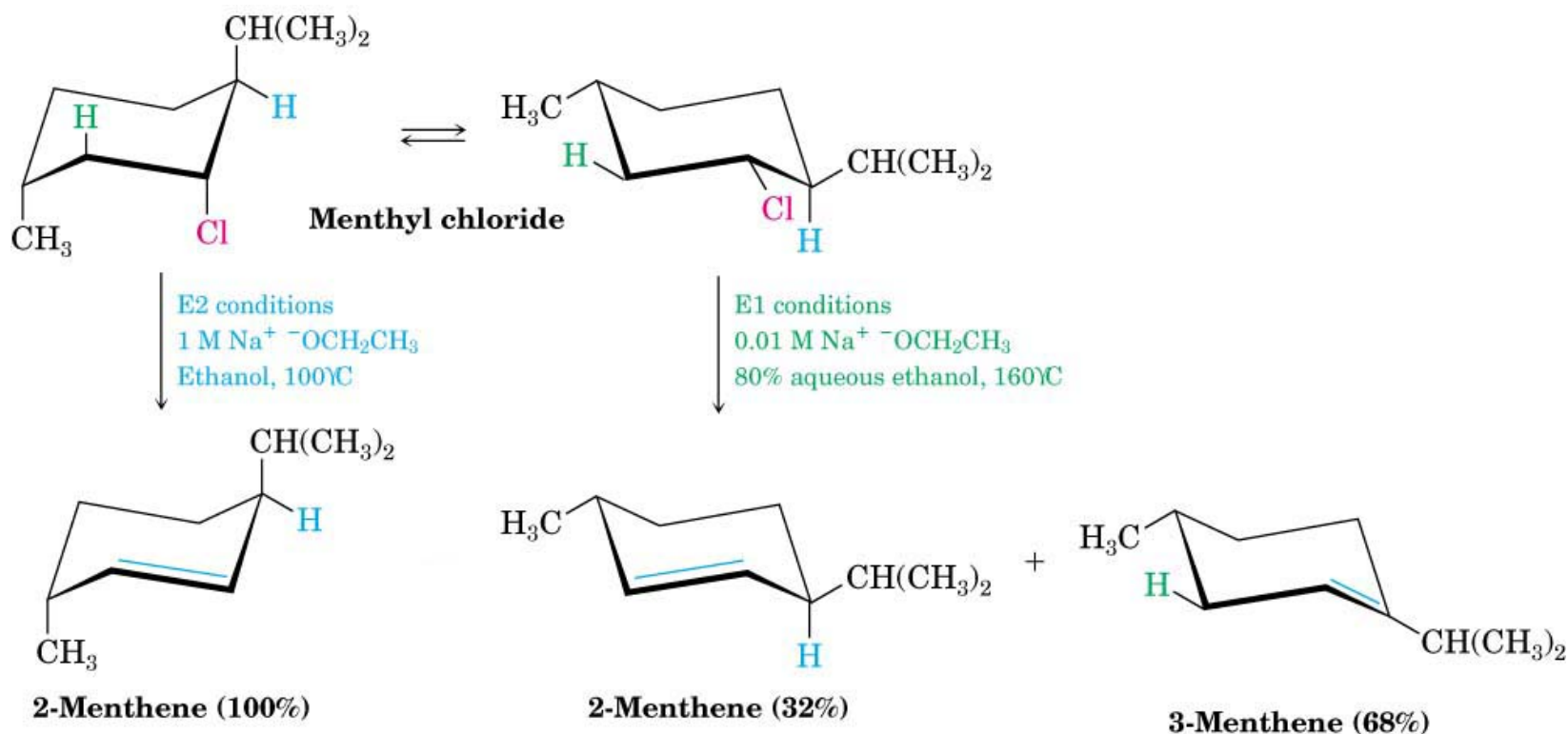
Spontaneous dissociation of the tertiary alkyl chloride yields an intermediate carbocation in a slow, rate-limiting step.

Loss of a neighboring H^+ in a fast step yields the neutral alkene product. The electron pair from the $\text{C}-\text{H}$ bond goes to form the alkene π bond.



Stereochemistry of E1 Reactions

- E1 is not stereospecific and there is no requirement for alignment
- Product has Zaitsev orientation (more highly substituted alkene predominates) because step that controls product is loss of proton after formation of carbocation



Comparing E1 and E2

- Strong base is needed for E2 but not for E1
- E2 is stereospecific, E1 is not
- E1 gives Zaitsev orientation

TABLE 11.4 A Summary of Substitution and Elimination Reactions

| Halide type | S _N 1 | S _N 2 | E1 | E2 |
|-----------------------------------|---|--|--|------------------------------------|
| RCH ₂ X (primary) | Does not occur | Highly favored | Does not occur | Occurs when strong bases are used |
| R ₂ CHX (secondary) | Can occur with benzylic and allylic halides | Occurs in competition with E2 reaction | Can occur with benzylic and allylic halides | Favored when strong bases are used |
| R ₃ CX (tertiary) | Favored in hydroxylic solvents | Does not occur | Occurs in competition with S _N 1 reaction | Favored when bases are used |