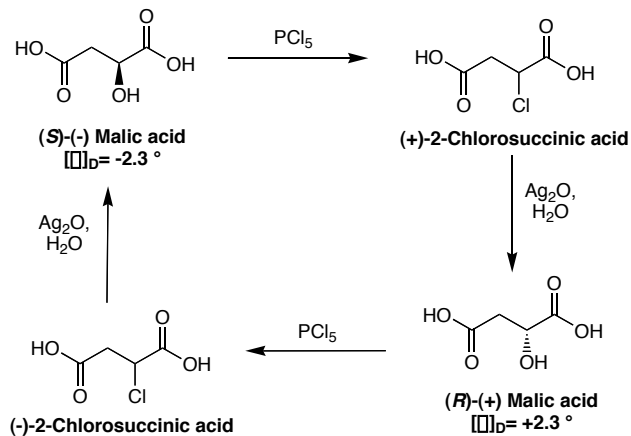


Chapter 11: Nucleophilic Substitution and Elimination

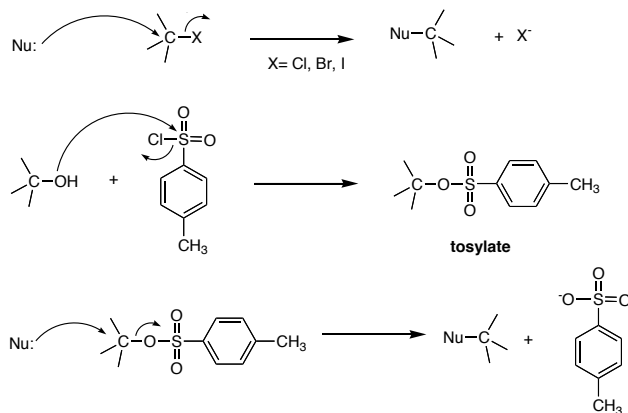
Walden Inversion

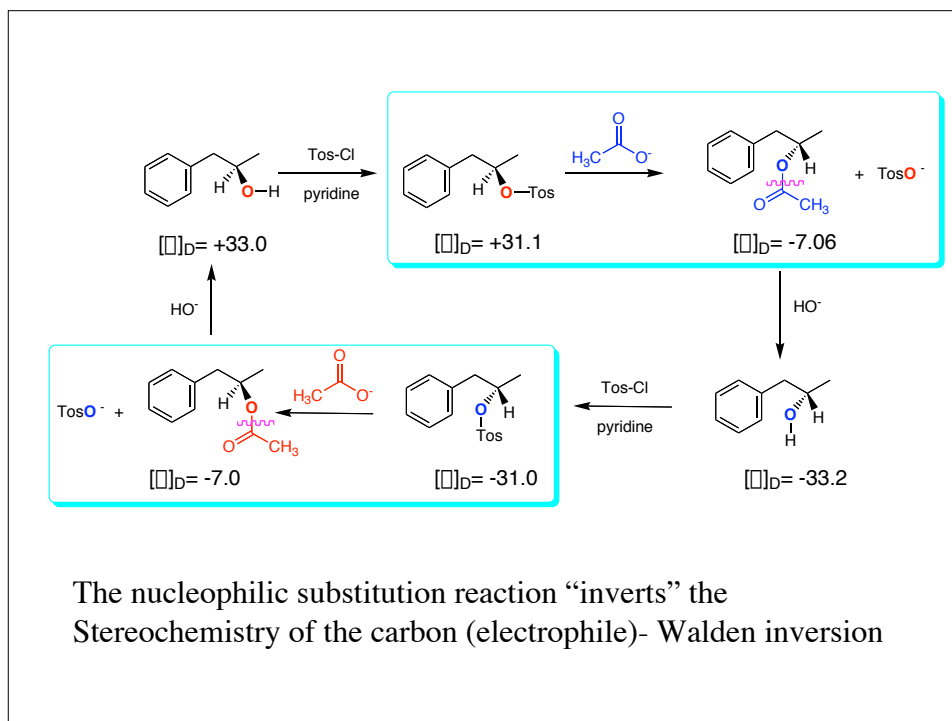


The displacement of a leaving group in a nucleophilic substitution reaction has a defined stereochemistry

Stereochemistry of nucleophilic substitution

p-toluenesulfonate ester (tosylate): converts an alcohol into a leaving group; tosylates are excellent leaving groups. abbreviates as Tos

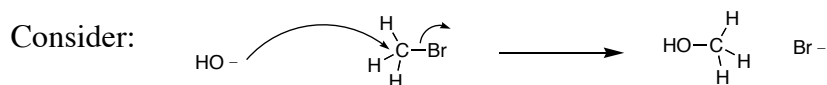




Kinetics of nucleophilic substitution

Reaction rate: how fast (or slow) reactants are converted into product (kinetics)

Reaction rates are dependent upon the concentration of the reactants. (reactions rely on molecular collisions)

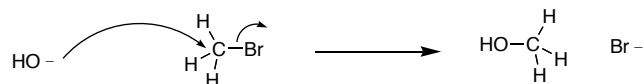


At a given temperature:

If $[\text{OH}^-]$ is doubled, then the reaction rate may be doubled

If $[\text{CH}_3\text{-Br}]$ is doubled, then the reaction rate may be doubled

A linear dependence of rate on the concentration of two reactants is called a second-order reaction (molecularity)



Reaction rates (kinetic) can be expressed mathematically:
 reaction rate = disappearance of reactants (or appearance of products)

For the disappearance of reactants:

$$\text{rate} = k [\text{CH}_3\text{Br}] [\text{OH}^-]$$

$[\text{CH}_3\text{Br}] = \text{CH}_3\text{Br}$ concentration

$[\text{OH}^-] = \text{OH}^-$ concentration

$k = \text{constant}$ (rate constant)

$$\frac{\text{L}}{\text{mol}\cdot\text{sec}}$$

For the reaction above, product formation involves a collision between both reactants, thus the rate of the reaction is dependent upon the concentration of both.

Nucleophilic Substitution comes in two reaction types:

S_N2

S= substitution
 N= nucleophilic
 2= bimolecular

$$\text{rate} = k [\text{R-X}] [\text{Nu:}]$$

S_N1

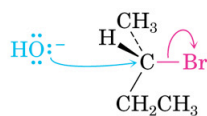
S= substitution
 N= nucleophilic
 1= unimolecular

$$\text{rate} = k [\text{R-X}]$$

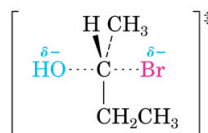
The S_N2 Reaction: Mechanism

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.

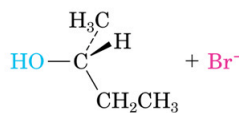
The stereochemistry at carbon is inverted as the C–OH bond forms fully and the bromide ion departs with the electron pair from the former C–Br bond.



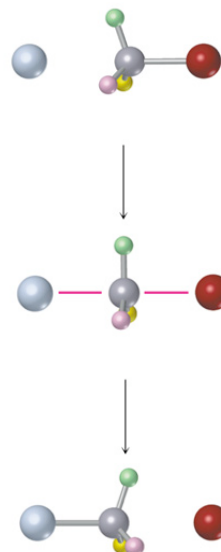
(*S*)-2-Bromobutane



Transition state



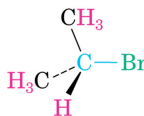
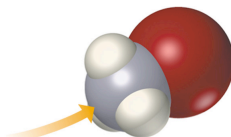
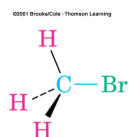
(*R*)-2-Butanol



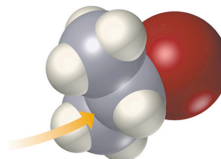
Steric effects in the S_N2 reaction:

- For an S_N2 reaction, the nucleophile approaches the electrophilic carbon at an angle of 180 ° from the leaving group (backside attack)
- the rate of the S_N2 reaction decrease as the steric hindrance (substitution) of the electrophile increases.

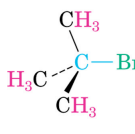
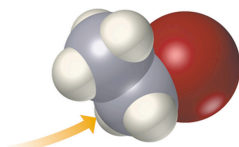
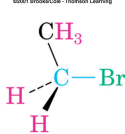
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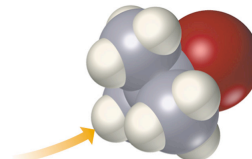
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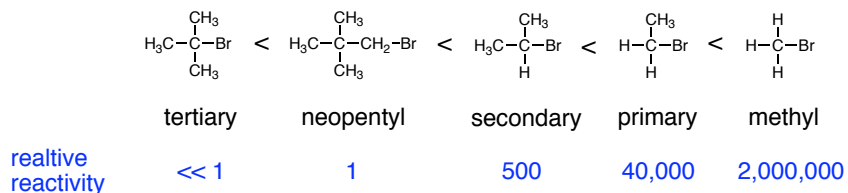
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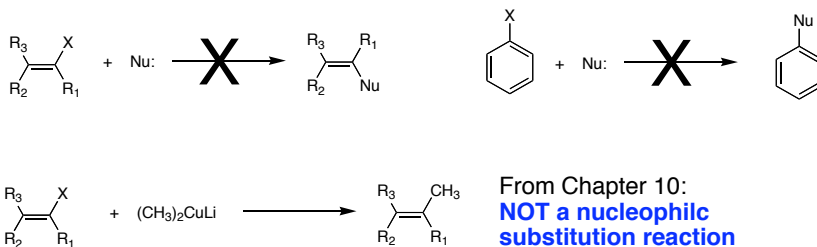
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Increasing reactivity in the S_N2 reaction

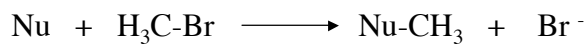


Vinyl and aryl halides do not react in nucleophilic substitution reactions



The nature of the nucleophile in the S_N2 Reaction:

The measure of *nucleophilicity* is imprecise.



Nu =	H ₂ O	relative reactivity =	1
	CH ₃ CO ₂ ⁻		500
	NH ₃		700
	Cl ⁻		1,000
	HO ⁻		16,000
	CH ₃ O ⁻		25,000
	I ⁻		100,000
	N≡C ⁻		125,000
	HS ⁻		125,000

Nucleophiles are Lewis bases

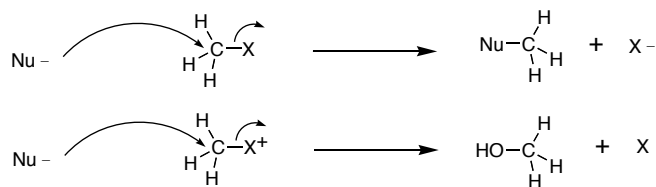
Nucleophilicity roughly parallels basicity when comparing nucleophiles that have the same attacking atom

Nu:	CH ₃ O ⁻	HO ⁻	CH ₃ CO ₂ ⁻	H ₂ O
relative reactivity:	25,000	16,000	500	1
pKa of the conj. acid:	15.5	15.7	4.7	-1.7

Nucleophilicity usually increases going down a column of the periodic chart. Thus, sulfur nucleophiles are more reactive than oxygen nucleophiles. I⁻ > Br⁻ > Cl⁻.

Negatively charged nucleophiles are usually more reactive than neutral nucleophiles.

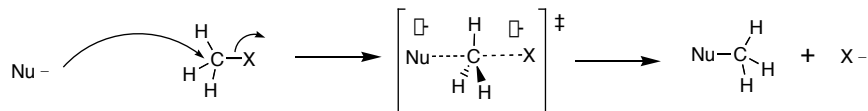
The role of the leaving group in S_N2 reactions:



The leaving group is usually displaced with a negative charge
The best leaving groups are those with atoms or groups that can best stabilize a negative charge.
Good leaving groups are the conjugate bases of strong acids



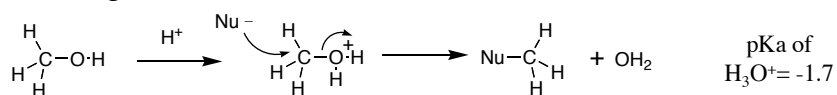
the lower the pKa of H-X, the stronger the acid.



Increasing reactivity in the S_N2 reaction

LG:	HO ⁻ , H ₂ N ⁻ , RO ⁻	F ⁻	Cl ⁻	Br ⁻	I ⁻	TosO ⁻
Relative Reactivity:	<<1	1	200	10,000	30,000	60,000
pKa:	>15	3.45	-7.0	-8.0		

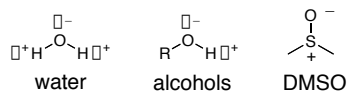
Charged Leaving Groups: conversion of a poor leaving group to a good one



The role of the solvent in S_N2 reactions:

Descriptor 1:

polar: "high" dipole moment

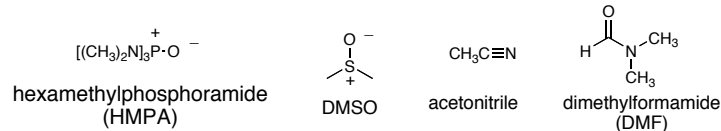


non-polar: low dipole moment (hexanes)

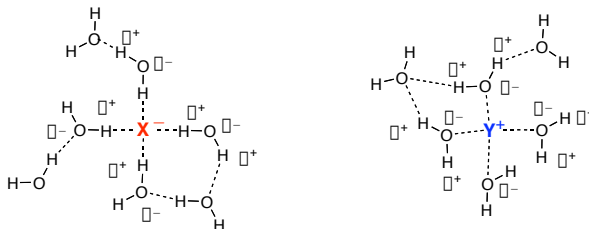
Descriptor 2:

protic: acidic hydrogens that can form hydrogen bonds
(water, alcohols)

aprotic: no acidic hydrogens

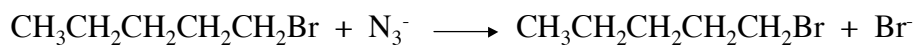


Solvation: solvent molecules form “shells” around reactants and dramatically influence their reactivity.

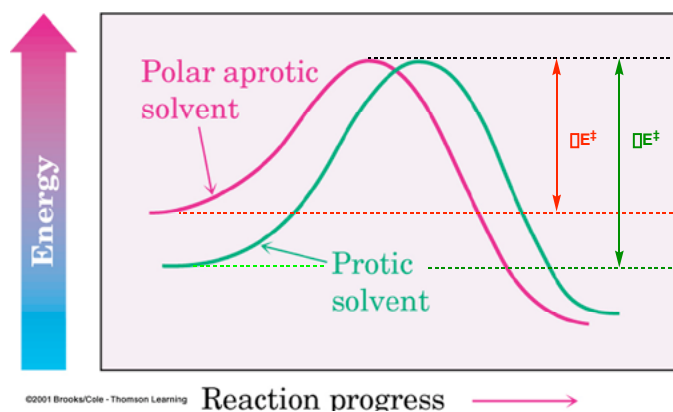


Polar protic solvents stabilize the nucleophile, thereby lowering its energy. This will raise the activation energy of the reactions. S_N2 reactions are not favored by polar protic solvents.

Polar aprotic solvents selectively solvate cations. This raises the energy of the anion (nucleophile), thus making it more reactive. S_N2 reactions are favored by polar aprotic solvents.



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



The S_N1 Reaction:

kinetics: first order reaction (unimolecular)

$$\text{rate} = k [\text{R-X}] \quad [\text{R-X}] = \text{alkyl halide conc.}$$

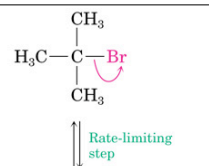
The nucleophile does not appear in the rate expression-
changing the nucleophile concentration does not affect
the rate of the reaction!

Must be a two-step reaction

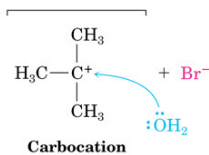
The overall rate of a reaction is dependent upon the slowest
step: rate-limiting step

The Mechanism of the S_N1 Reaction

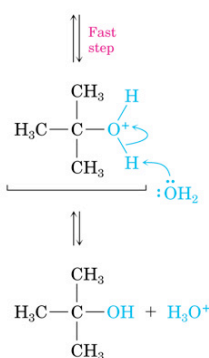
Spontaneous dissociation of the
alkyl bromide occurs in a slow,
rate-limiting step to generate a
carbocation intermediate plus
bromide ion.



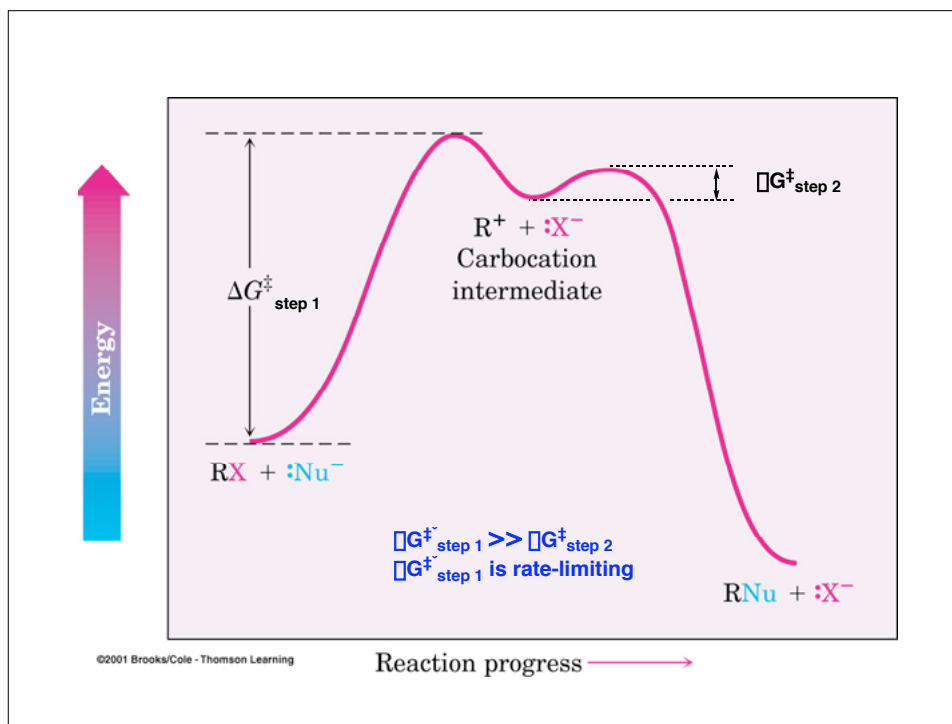
The carbocation intermediate reacts
with water as nucleophile in a fast
step to yield protonated alcohol as
product.



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

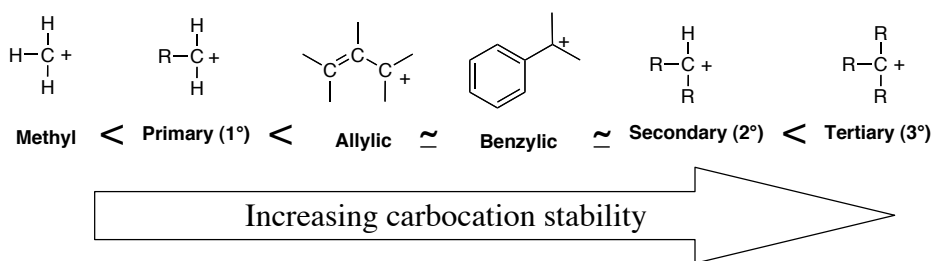


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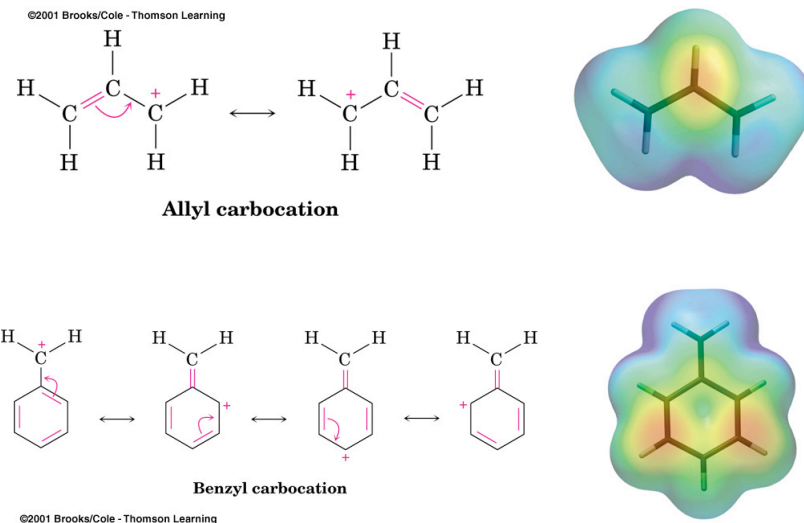
Reactivity of the Alkyl Halide in the S_N1 Reaction:

Formation of the carbocation intermediate is rate-limiting.
Thus, carbocation stability greatly influence the reactivity.



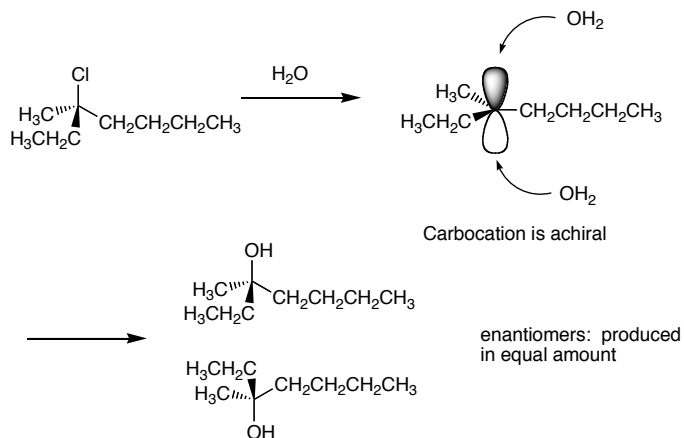
The order of reactivity of the alkyl halide in the S_N1 reaction exactly parallels the carbocation stability

Allylic and benzylic carbocations are stabilized by resonance



Stereochemistry of the S_N1 Reaction: it is actually a complicated issue.

For the purpose of Chem 220a, sect. 2 the stereochemistry of the S_N1 reaction gives racemization. A chiral alkyl halide will undergo S_N1 substitution to give a racemic product

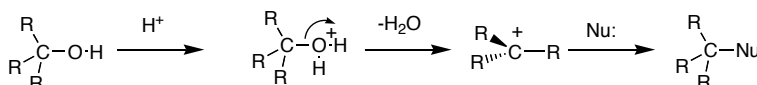


The role of the leaving group in S_N1 reactions:

same as for the S_N2 reaction



Charged Leaving Groups: conversion of a poor leaving group to a good one

**The role of the nucleophile in S_N1 reactions: None**

Involvement of the nucleophile in the S_N1 reaction is *after* the rate-limiting step. Thus, the nucleophile *does not* appear in the rate expression. The nature of the nucleophile plays **no** role in the rate of the S_N1 reaction.

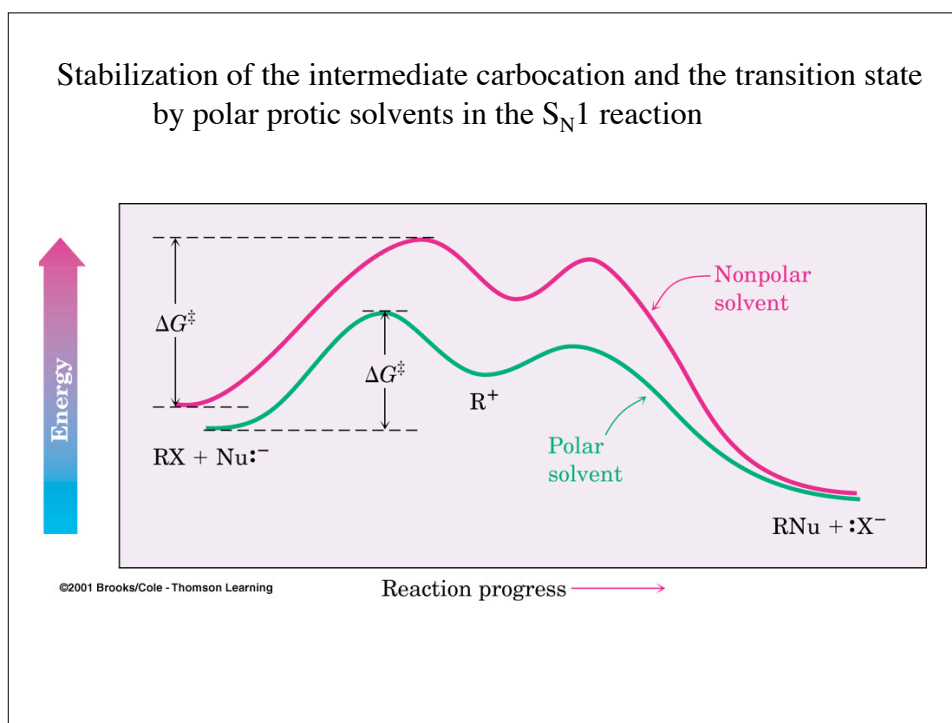
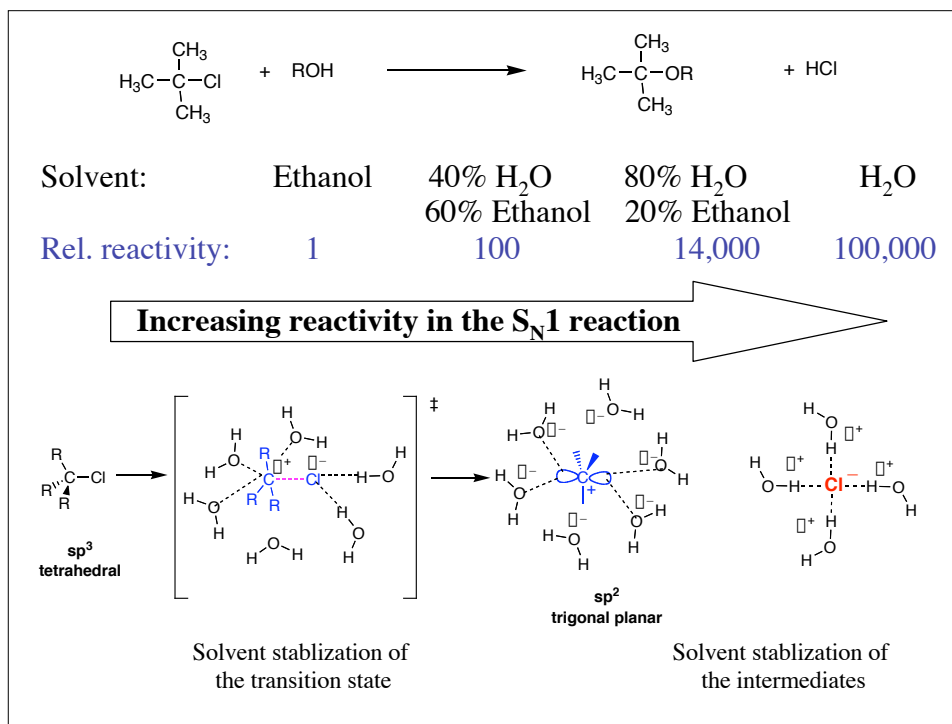
The role of the solvent in S_N1 reactions:

polar solvents are favored over non-polar for the S_N1 reaction

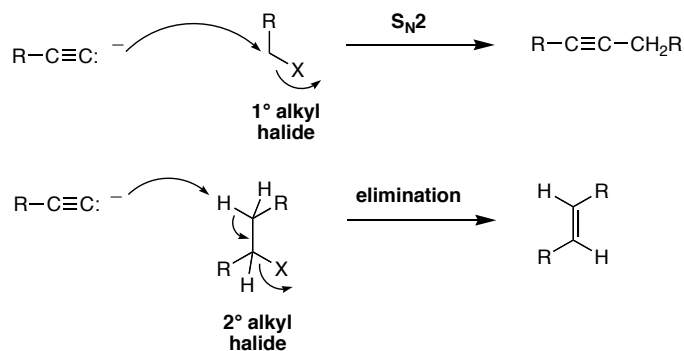
protic solvents are favored over aprotic for the S_N1 reaction

Solvent polarity is measured by dielectric constant (ε)

Hexane	ε = 1.9	} nonpolar	} aprotic
(CH ₃ CH ₂) ₂ O	4.3		
HMPA	30	} polar	
DMF	38		
DMSO	48	} protic	
CH ₃ CH ₂ OH	24		
CH ₃ OH	34		
H ₂ O	80		

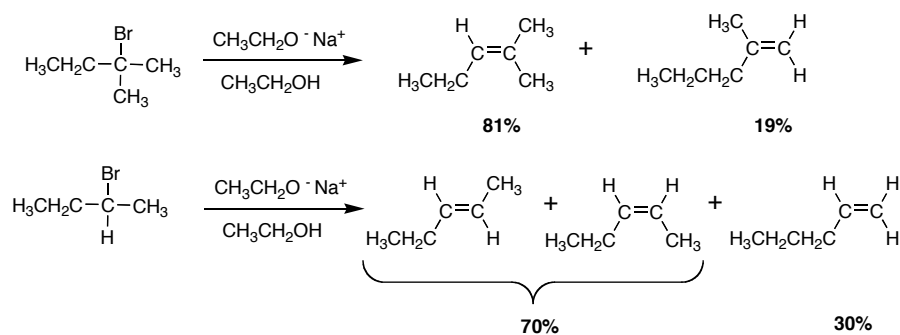


Elimination Reactions: Nucleophiles are Lewis bases. In the reaction with alkyl halides, they can also promote elimination reactions rather than substitution.



Elimination is a competitive reaction with nucleophilic substitution.

Zaitsev's Rule: When more than one alkene product is possible from the base induced elimination of an alkyl halide, the most highly substituted (most stable) alkene is usually the major product.



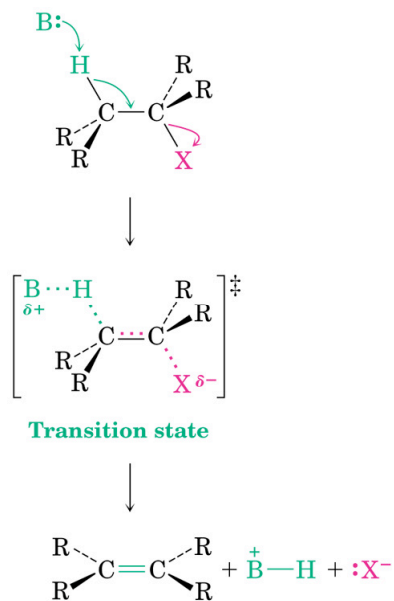
The E2 Elimination:

$$\text{rate} = k [\text{R-X}] [\text{Base}]$$

Base (B^{\ominus}) 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.

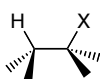
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The E2 elimination takes place in a single step with no intermediate

Stereochemistry of the E2 Elimination:

The H being abstracted and the leaving group must be in the same plane



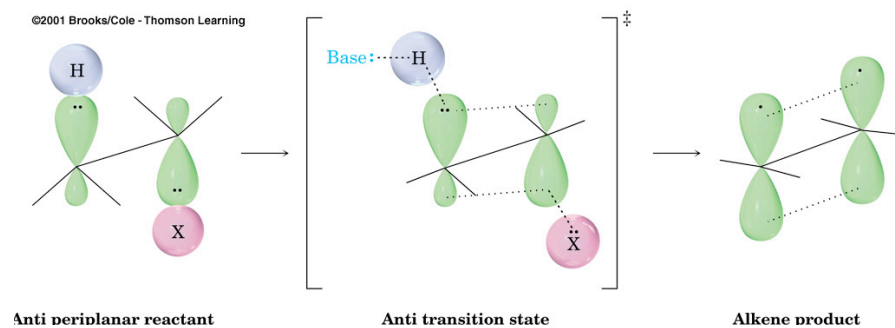
Syn periplanar:
the H and X
are eclipsed
dihedral angle = 0°



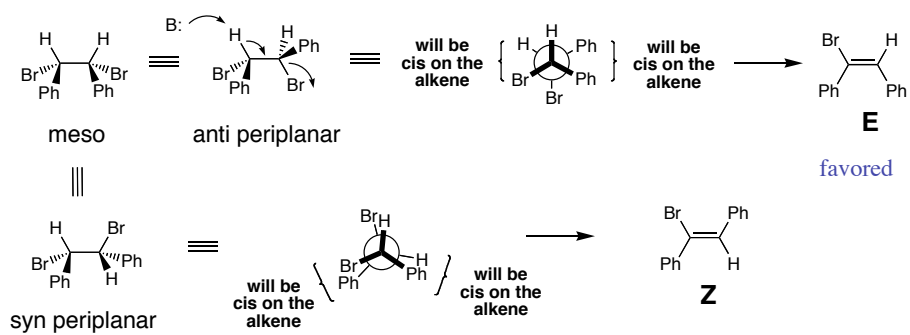
Anti periplanar:
the H and X are
anti staggered
dihedral angle = 180°

Generally, the anti periplanar geometry is energetically preferred (staggered conformation vs eclipsed)

In the periplanar conformation, the orbitals are already aligned for π -bond formation



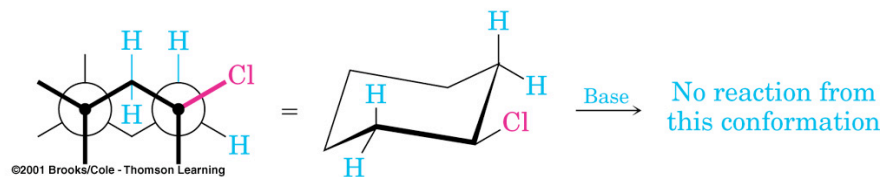
The E2 elimination has a defined geometric (stereochemical) outcome:



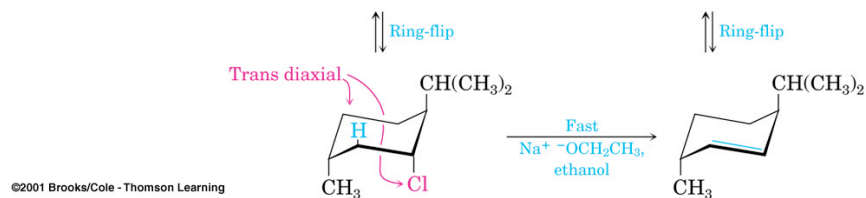
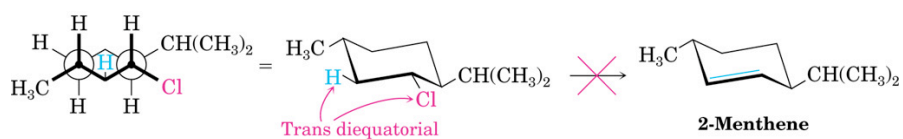
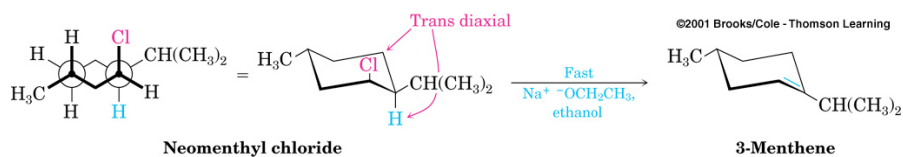
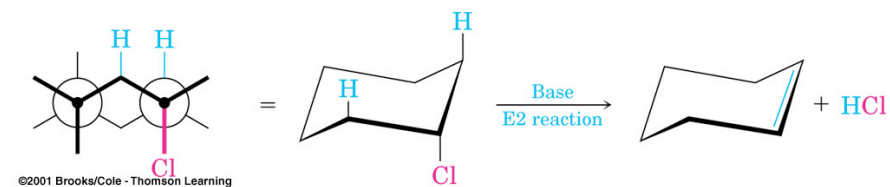
Anti periplanar geometry is usually preferred for E2 elimination

E2 elimination with halocyclohexane reactants

Equatorial chlorine: H and Cl are not anti periplanar



Axial chlorine: H and Cl are anti periplanar



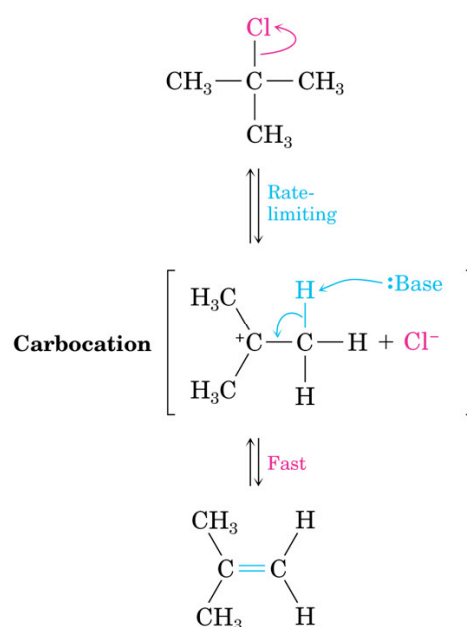
The E1 Elimination:

$$\text{rate} = k [\text{R-X}]$$

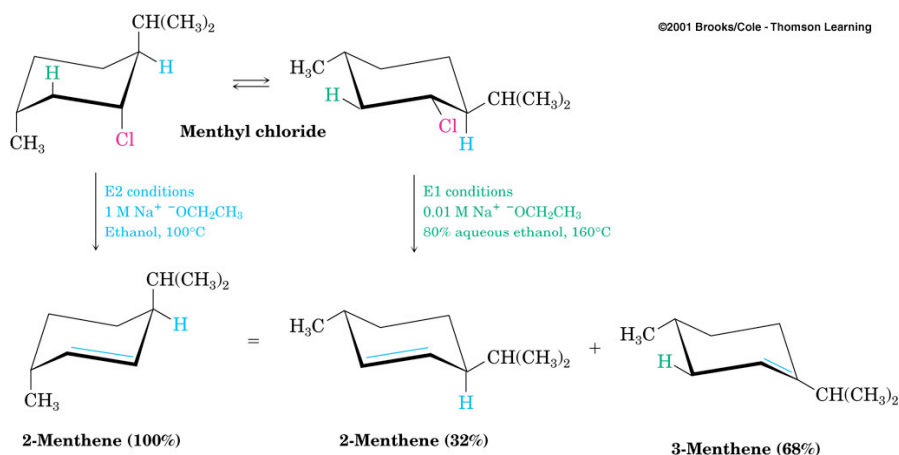
Spontaneous dissociation of the tertiary alkyl chloride yields an intermediate carbocation in a slow, rate-limiting step.

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

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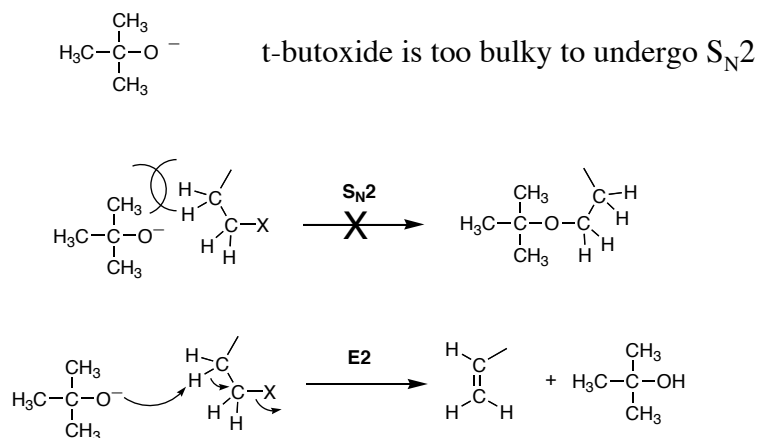
No geometric requirements for E1 elimination.
Usually follows Zaitsev's Rule



S_N2 vs E2

For primary alkyl halides S_N2 is favored with most nucleophiles

E2 is favored with “bulky” bases (t-butoxide)



Secondary halides: E2 is competitive with S_N2 and often gives a mixture of substitution and elimination products

Tertiary Halides:

E2 elimination occurs with strong bases such as HO^- , RO^- , H_2N^- (strongly basic conditions)

E1 elimination occurs with heat and weak bases such as H_2O or ROH . (neutral conditions)

The E1 elimination product is often a minor product with the major product arising from S_N1 reaction.

S_N2 reaction does not occur with 3° halides