

Advanced Organic Chemistry Notes# Reactions of Alkenes## Addition of Peroxyacid to Alkene* Epoxide → ether in which oxygen is incorporated into 3-member ring

- Is a carboxylic acid with extra oxygen atom # Substitution Reactions of Alkyl Halides## Stereochemistry Nomenclature Review* Spatial method → Right-hand rule
- Rank groups 1-4
- Orient right thumb from asymmetric carbon towards #4 substituent
- If can curl fingers from #1 to #2 to #3 in order → R configuration
- If not, S configuration



Figure 1: Chair Conformers

Basics* Substitution reaction → electronegative atom/group replaced by another atom/group

- Elimination reaction → eliminate the electronegative group + an adjacent hydrogen
- Leaving group is substituted/eliminated

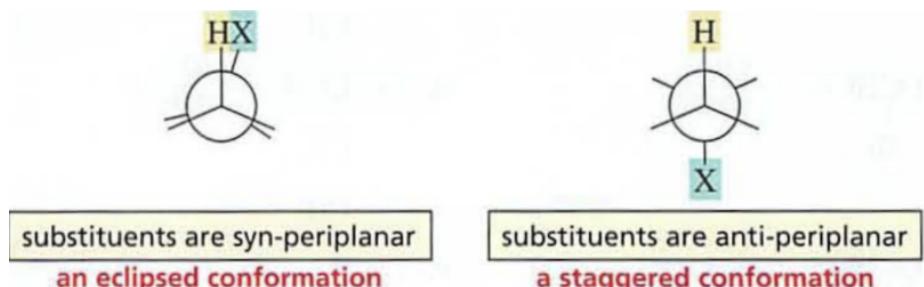


Figure 2: Overview

- Alkyl halide → leaving group is F⁻, Br⁻, etc ## Alkyl Halide Reactions* Halogen attached to carbon → polar bond with partial positives δ⁺ and δ⁻

- Nucleophilic → a nucleophile approaches carbon and causes break of halogen-carbon bond
- Two possible mechanisms for nucleophilic substitution

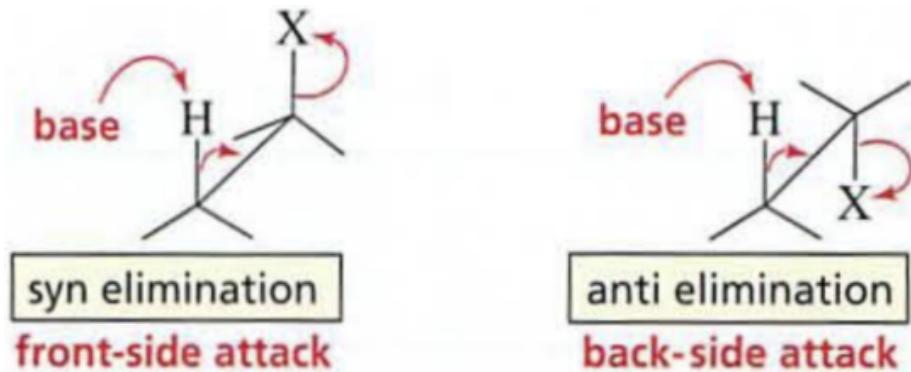


Figure 3: SN2

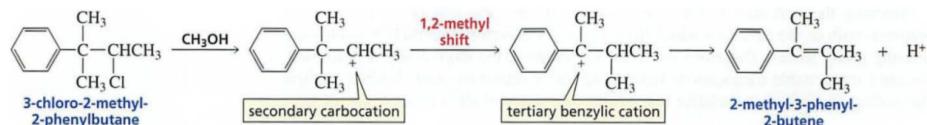


Figure 4: SN1

- Predominant mechanism depends on
 - Structure of halide
 - Reactivity of nucleophile
 - Concentration of nucleophile
 - Solvent of reaction ## SN2 Reaction Mechanism* Rate of nucleophilic substitution depends on concentration of reagents
 - i.e. rate $\propto [r_1][r_2]$ where $[r_1], [r_2]$ are rate constants with some proportionality k
 - Thus a second-order reaction
- SN2 reaction → substitution, nucleophilic, and bimolecular
 - Bimolecular → 2 molecules involved in transition state of rate-det-step
 - Concerted so no intermediates → nucleophile attacks carbon with leaving group, displaces
- Productive collision → nucleophile must hit carbon opposite to leaving group in back-side attack
- MO theory explanation → HOMO of nucleophile interacts with LUMO of C-X bond
 - When approaching front, there is a bonding and antibonding interaction, thus not favorable
 - Also not sterically favorable

Mechanism of the E1 reaction

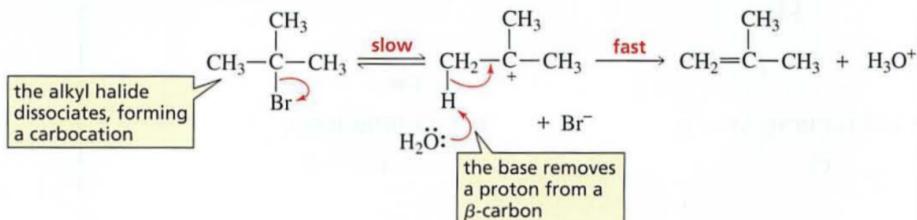


Figure 5: Leaving group

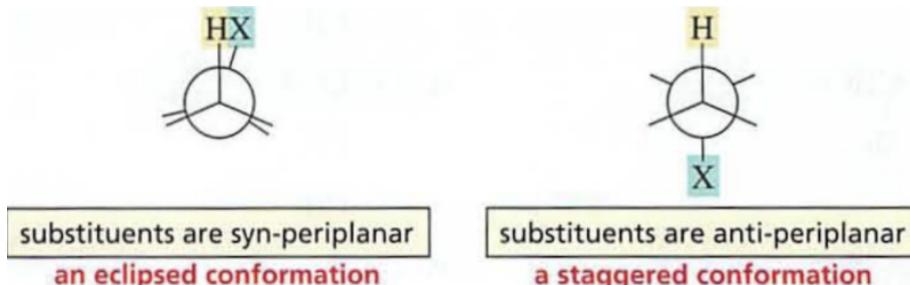


Figure 6: Reactivity of alkyl halides

- Rate of SN2 reaction depends on number of alkyl groups attached to carbon undergoing attack and size of them

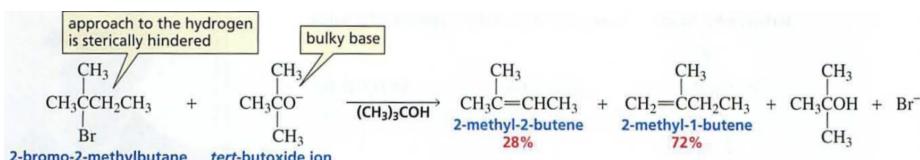


Figure 7: Walden inversion

- C–H bonds can switch direction to move away from nucleophile
- Inversion is called Walden inversion
 - Thus, only one substitution product is formed when alkyl halide with halogen bonded to asymmetric center undergoing SN2 rxn
- Draw mirror image, replace halogen with nucleophile ## Factors Affecting SN2 Reactions* Leaving group in SN2 rxn → More electronegative, harder to leave so worse rxn
 - Weaker base (proton acceptor) → better leaving ability, do not share electrons well due to stability
- Nucleophile in SN2 rxn

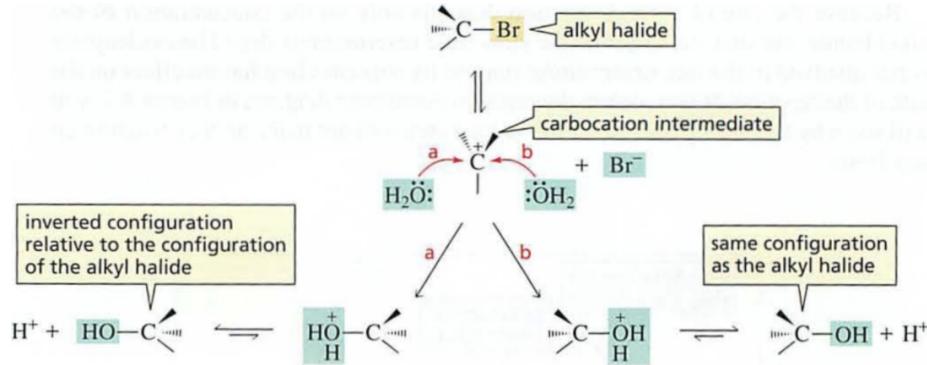


Figure 8: Stereochemistry of Walden inversion

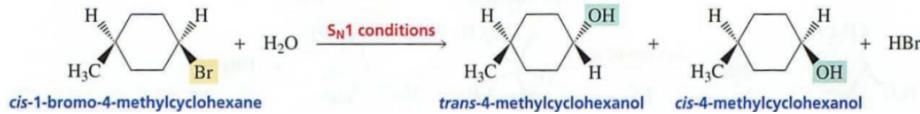


Figure 9: Rxn rates

- Nucleophilicity measure of nucleophile ability to attack electron-deficient atom, measured by rate constant k
- Stronger bases are better nucleophiles when attacking atom is the same and when attacking atoms are similar in size
- If attacking atoms are different in size → polarizability of atom is important
 - * More polarizable → better nucleophile, overlapping of MO from farther away

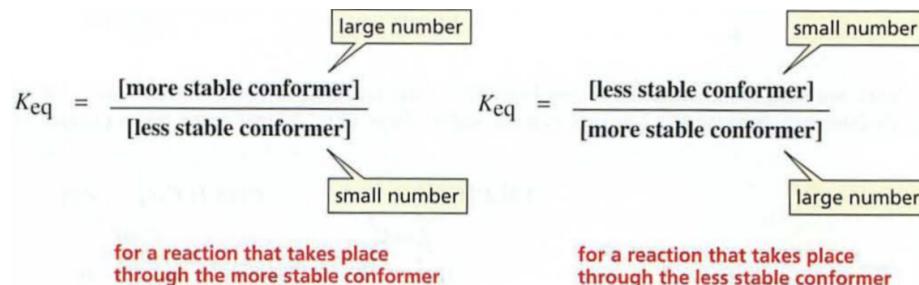


Figure 10: Polarizability

- If rxn is carried out in aprotic polar solvent (no hydrogen on O or N)
 - Relationship b/w basicity and nucleophilicity maintained → stronger bases are best nucleophiles, iodide is worst nucleophile
- Protic solvent used → inverted relationship

- Largest atom is best nucleophile even though is weakest base, so iodide ion is best nucleophile

$$\text{rate} = k_2[\text{alkyl halide}][\text{nucleophile}] + k_1[\text{alkyl halide}]$$

Figure 11: Nucleophilicity

- Nucleophilicity affected by solvent → ion-dipole interactions formed

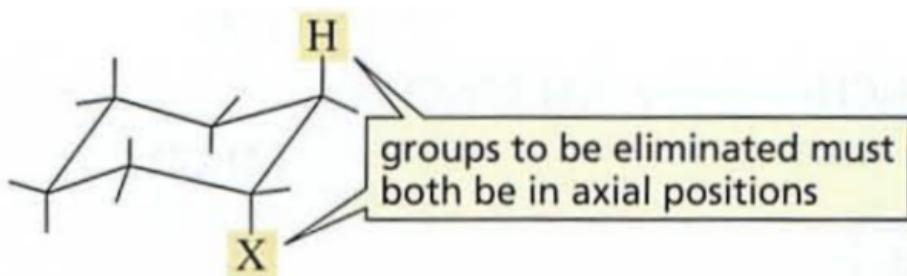


Figure 12: Nucleophilicity

- Solvent shields nucleophile → must break reactions, so a weaker base is a better nucleophile due to less shielding
- Aprotic polar solvents → DMSO or DMF, δ^+ not easily accessible → solvates cations > anions
- Steric effects → bulky nucleophile cannot approach carbon effectively, despite basicity ## Reversibility of SN2 Reactions* Can synthesize wide variety of organic compounds due to multiple nucleophiles reacting with alkyl halides
- Reaction can only be reversed if basicity of leaving group is less than that of nucleophile
 - E.g. chloride ion can't engage in substitution for OH group in ex. 1, so it better leaving group
 - SN2 proceeds in direction that allows stronger base to displace weaker base
 - Reversible → b), irreversible → a)
- If difference in basicity is small → can reverse
- If concentration of C = [C] is decreased, A and B generate more product to maintain K_{eq}
- If rxn is carried out in neutral solution → protonated product can lose proton and push rxn to products due to equilibrium disturbance ## Mechanism of SN1 Reaction
- Given above, there is no steric hindrance affecting the speed of the rxn so it is not SN2

Table 9.6 Summary of the Products Expected in Substitution and Elimination Reactions

Class of alkyl halide	S _N 2 versus E2	S _N 1 versus E1
Primary alkyl halide	Primarily substitution, unless there is steric hindrance in the alkyl halide or nucleophile, in which case elimination is favored	Cannot undergo S _N 1/E1 reactions
Secondary alkyl halide	Both substitution and elimination; the stronger and bulkier the base and the higher the temperature, the greater the percentage of elimination	Both substitution and elimination
Tertiary alkyl halide	Only elimination	Both substitution and elimination

Figure 13: Reversing rxns

$$\text{rate} = k[\text{alkyl halide}][\text{base}]$$

Figure 14: Rxn coordinate diagram

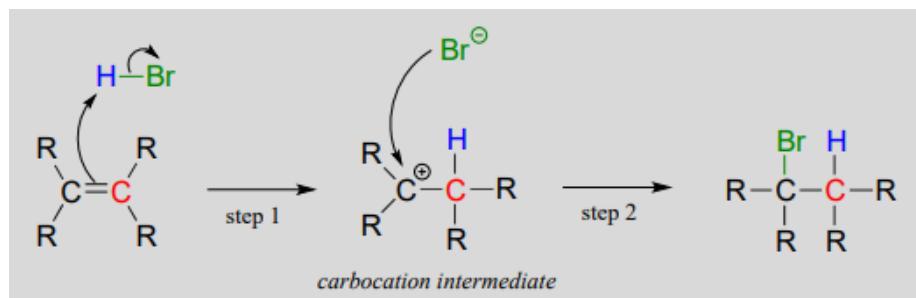


Figure 15: Equilibrium

Table 8.5 Comparison of S_N2 and S_N1 Reactions

S _N 2	S _N 1
A one-step mechanism	A stepwise mechanism that forms a carbocation intermediate
A bimolecular rate-determining step	A unimolecular rate-determining step
No carbocation rearrangements	Carbocation rearrangements
Product has inverted configuration relative to the reactant	Products have both retained and inverted configurations relative to the reactant
Reactivity order: methyl > 1° > 2° > 3°	Reactivity order: 3° > 2° > 1° > methyl

Figure 16: SN1 overview

- Changing concentration of nucleophile has no effect → rate = $k[\text{alkyl halide}]$
 - Is a first-order SN1 rxn
- Unimolecular → one molecule in transition state

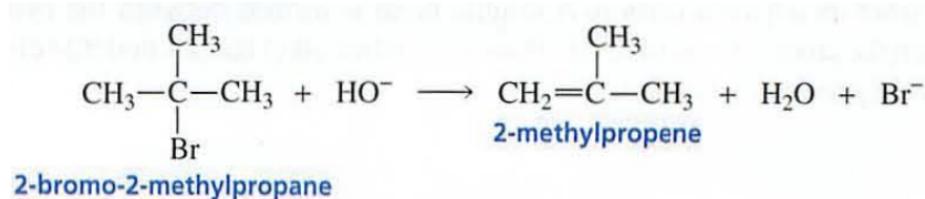


Figure 17: SN1 mechanism

- Experimental evidence
 - Rate law shows that rxn only depends on [alkyl halide] → thus rate-determining step only involves alkyl halide
 - As methyl groups replaced by hydrogens → rxn rate decreases
 - * Stability of carbocations

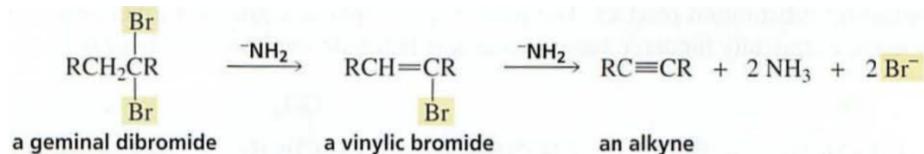


Figure 18: Reactivity for SN1

- Substitution rxn where halogen is on asymmetric center forms 2 stereoisomers → same relative config + inverted config
- Mechanism

an intramolecular reaction

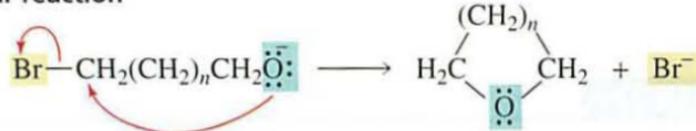


Figure 19: Inversions

- Carbocation intermediate formed in C–halogen bond break
 - * Slow → rate-determining step
- Protonated alcohol formed
- pH of soln determines alcohol result in protonated or neutral form

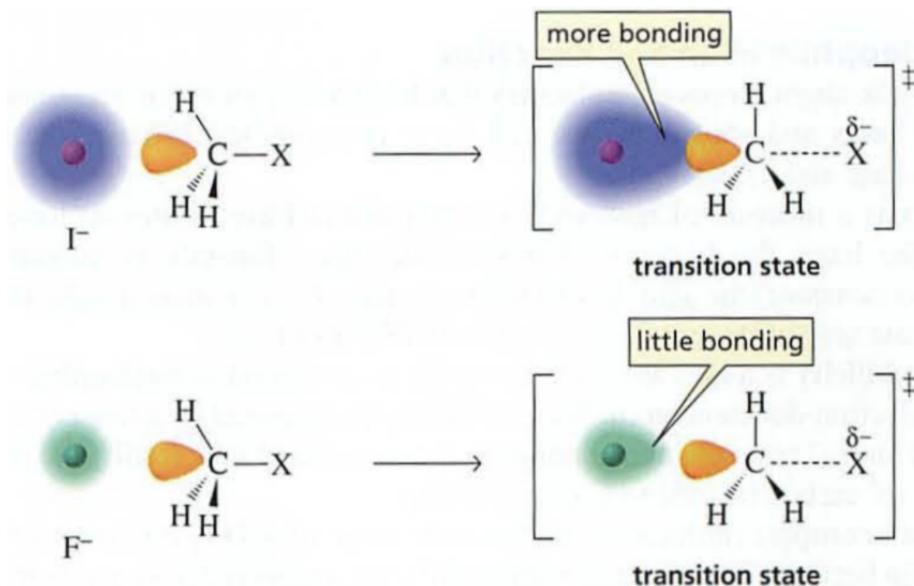


Figure 20: Mechanism rxn coordinate diagram

Factors Affecting SN1 Reactions* Leaving group in SN1 rxn

- Ease with which it disassociates from carbon and stability of carbocation formed affect rate of rxn
- Tertiary alkyl halides more reactive as more stable → better rxn
- Primary alkyl halides do not undergo SN1
- Weaker base → easier to break halogen-carbon bond
 - Alkyl iodide » alkyl fluoride
- Nucleophile role → does not participate until after rate-determining step

so no effect on reactivity

- Solvent is nucleophile in most SN1
- Carbocation rearrangements can occur

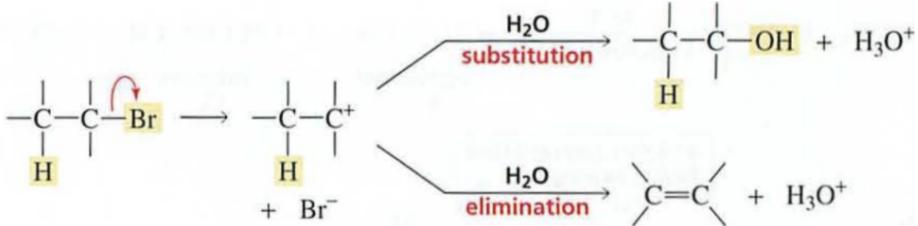


Figure 21: Carbocation rearrangement

Stereochemistry of SN2 and SN1 Reactions* SN1 rxn results in pair of enantiomer products

- Can only predict stereoisomers formed through reactant configuration and type of rxn
 - E.g. for SN2 → inverted configuration of reactant
- SN1 forms both inverted and non-inverted → either complete or partial racemization

$$\text{rate} = k[\text{alkyl halide}]$$

Figure 22: Stereochemistry

Benzyllic Halides, Allylic Halides, Vinylic Halides, Aryl Halides* Benzyllic and allylic halides

- Readily undergo SN2 unless tertiary due to sterics
- Also undergo SN1 well → carbocations stabilized by electron delocalization
- If resonance contributors have diff. groups bonded to sp² carbons → two substitution products due to electron delocalization
- Vinylic + aryl halides → halogen attached to aromatic ring → do not undergo SN1,2 rxns
- Vinylic and aryl halides reason for non-reactive
 - Unstable due to +ve charge on sp carbon, and bonded to a stronger sp² carbon ## Competition between SN2 and SN1 Reactions
- If alkyl halide can undergo SN1 and SN2 → simultaneous rxns
 - Conditions determine predominant rxn

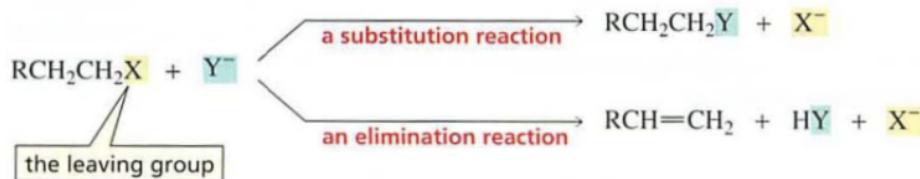


Figure 23: Example

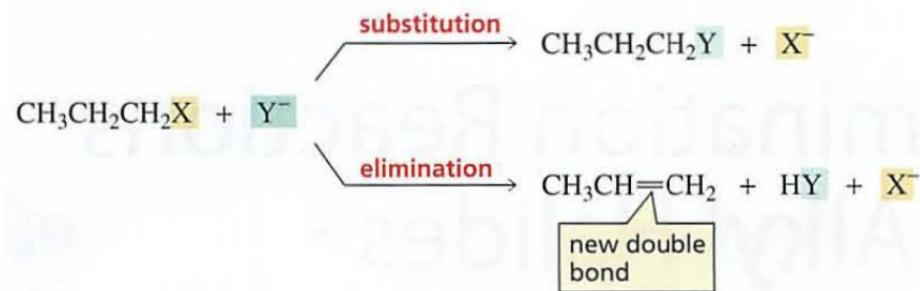


Figure 24: Vinylic and aryl halides

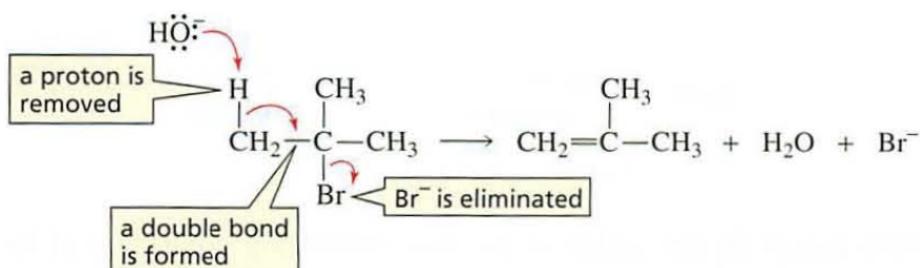


Figure 25: Reaction summary

- * Concentration of nucleophile, reactivity of nucleophile, solvent of rxn
- Rate law for simultaneous rxn is by contribution → rate = $k_2[\text{alkyl halide}][\text{nucleophile}] + k_1[\text{alkyl halide}]$
 - Increasing [nucleophile] increases SN2 fraction
 - Increasing rate constant k_2 of SN2 = increasing reactivity of nucleophile
- High concentration of good nucleophile → favors SN2 rxn
- SN1 rxn favored by poor nucleophile ## Role of Solvent in SN2 and SN1 Reactions* Dielectric constant of solvent measures how well polar opposite charges are insulated
 - Cluster around a charge to insulate
 - Positive poles → surround –ve, etc.
- Ion interacting with polar solvent → spread to surrounding solvent molecules for stability
 - Protic solvents → H bonded to O or N → hydrogen bond donors
 - Aprotic solvents → lack this bonding
- Solvation in polar solvent allows for dissociation of C–X bond → provides energy, cannot take place in nonpolar solvent
- Solvent and rxn rates
 - Increasing polarity of solvent will decrease rate if ≥ 1 reactants are charged in rate-det-step
 - Will increase rate of rxn if none of reactants in rate-det-step are charged
- If charge on reactants > charge of transition states → polar solvent stabilizes reactants more
 - Bigger energy difference → more polar solvent decreases rate
- If charge on transition state > charge on reactants → polar solvent stabilizes transition state more
 - Smaller energy difference → more polar solvent increase rate
- Solvent effect on SN1 rxn rate
 - Transition state involving carbon-halogen bond has higher charge → polar solvent increases rate
- Solvent effect on SN2 rxn rate
 - Stabilizes nucleophile more than transition state because transition state distributes charge over 2 atoms → decrease rxn rate with polarity
 - Will increase rate if between alkyl halide and neutral nucleophile

- For substitution rxn → solvent effect depends on whether reactant in rate-det-step is charged ## Intermolecular vs. Intramolecular Reactions
- Molecule with 2 functional groups → bifunctional molecule
 - 2 rxns occur if two functional groups can react → intermolecular rxn or between
 - If products subsequently react → form a polymer

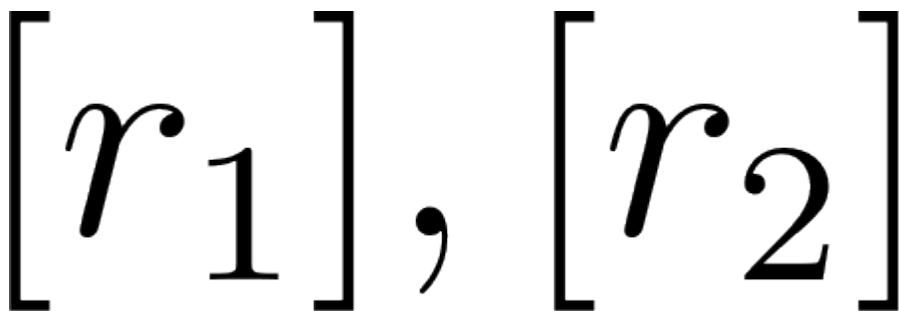


Figure 26: Intramolecular rxn

- Intramolecular rxn → occurs within the molecule
- Preference depends on concentration of molecule and size of ring formed
 - 5 or 6 membered rings favored over others
 - Low concentration favors intramolecular rxn ## Biological Methylation Reagents* Methyl iodide best possible leaving group if choosing a methyl group on a nucleophile
- Organic molecules → SAM and SAF methylating agents
 - Soluble in water
 - Transfer methyl group to a nucleophile
- Very good leaving groups # Elimination of Alkyl Halides* Elimination rxn → atoms/groups removed from reactant to generate a product

E2 Reaction* Is bimolecular elimination rxn with rate dependent on concentrations of both alkyl halide + hydroxide ion (rate = $k[\text{alkyl halide}][\text{base}]$)

- Second order rxn → both alkyl halide + hydroxide involved in transition state
- Can portray the rxn as concerted single-step
- Removal of proton and halide ion → dehydrohalogenation
- alpha-carbon → carbon to which halogen is bonded
- beta-carbon → adjacent to alpha-carbon
 - E2 initiated by deprotonating a beta-carbon → beta-elimination rxn
- In alkyl halide series → weaker bases are better leaving groups

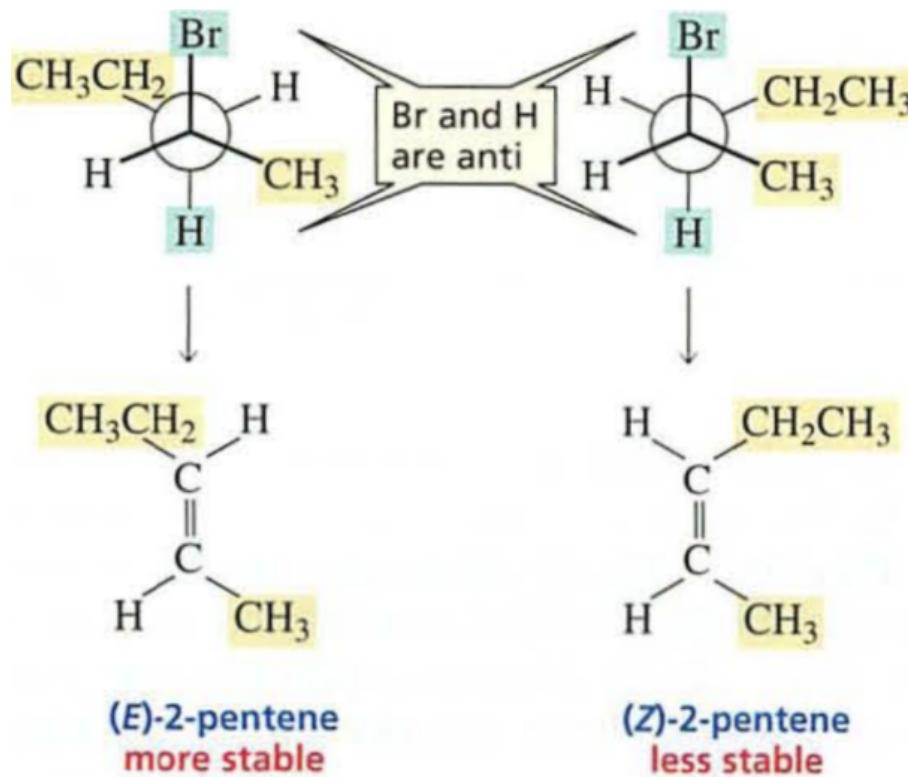


Figure 27: Elimination overview

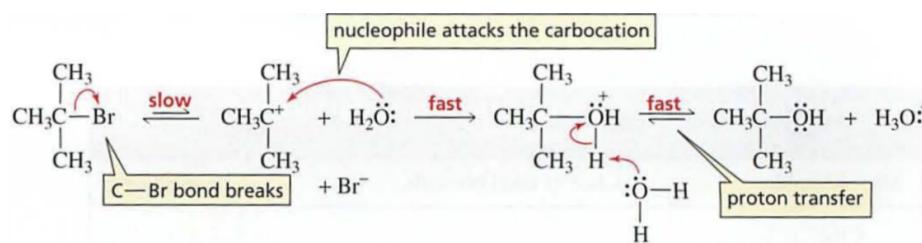


Figure 28: Elimination example

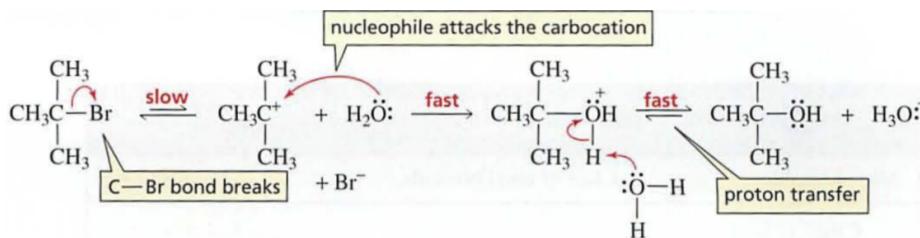


Figure 29: E2 mechanism

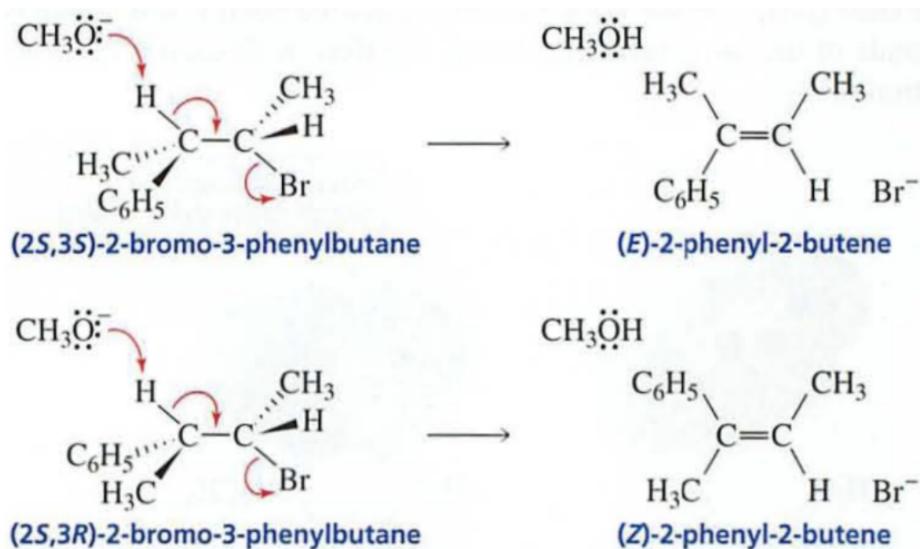


Figure 30: E2 mechanism with carbon labeling

- RI > RBr > RCl > RF ## Regioselective E2 Rxn

Table 9.4 Stereochemistry of Substitution and Elimination Reactions

Reaction	Products
S _N 1	Both stereoisomers (<i>R</i> and <i>S</i>) are formed (more inverted than retained).
E1	Both <i>E</i> and <i>Z</i> stereoisomers are formed (more of the stereoisomer with the bulkiest groups on opposite sides of the double bond).
S _N 2	Only the inverted product is formed.
E2	Both <i>E</i> and <i>Z</i> stereoisomers are formed (more of the stereoisomer with the bulkiest groups on opposite sides of the double bond) unless the β -carbon of the reactant is bonded to only one hydrogen, in which case only one stereoisomer is formed; its configuration depends on the configuration of the reactant.

Figure 31: Regioselectivity

- 2-bromobutane \rightarrow 2 structurally different β -carbons from which proton can be removed
 - Therefore forms 2 elimination products
- Alkene-like transition state \rightarrow the more stable alkene will predominate
- Shortcut to predicting most substituted alkene \rightarrow Zaitsev's rule
 - More substituted alkene will be formed by removing proton from beta-carbon bonded to least hydrogens, not more stable alkene necessarily
 - Does not work if alkyl halide has double bond or ring
- Exceptions to stability rule \rightarrow rxn prefers less steric hindrance given a bulky base, but only if steric hindrance is large

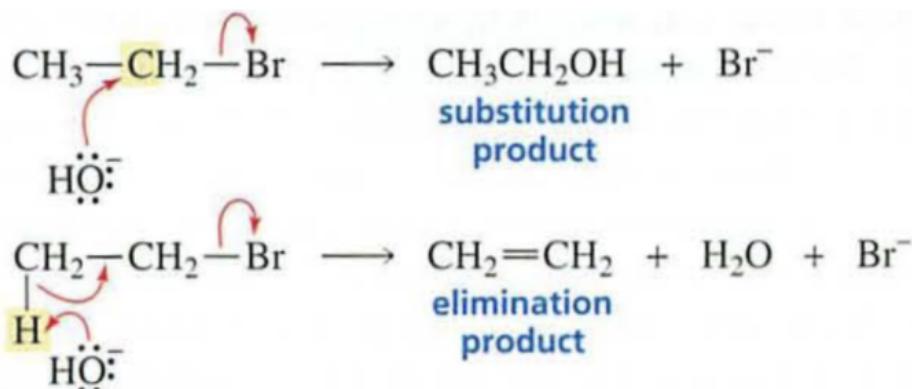


Figure 32: Steric hindrance

- In below case, steric hindrance not enough to overcome general stability rule

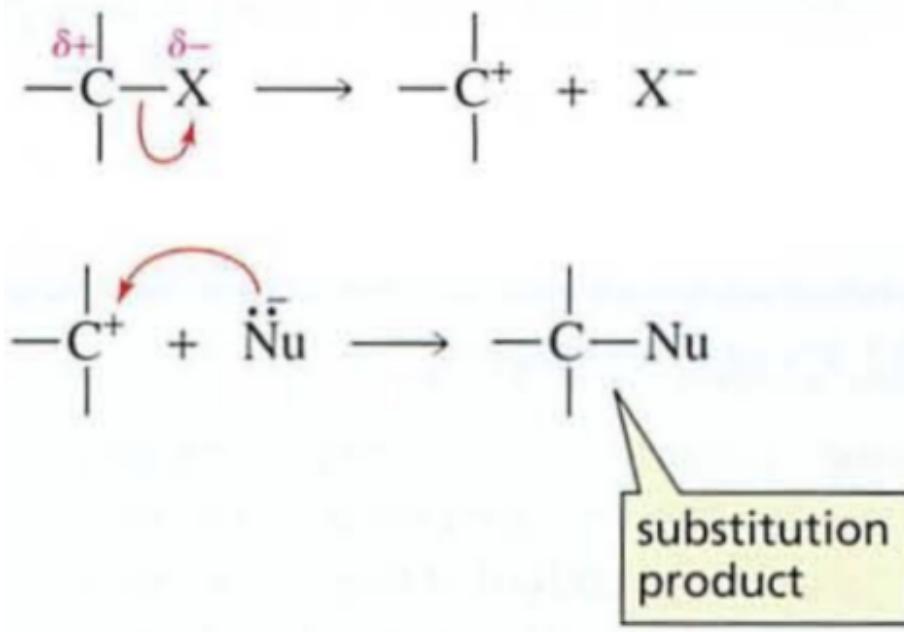


Figure 33: Steric regioselectivity

- Major product of dehydrohalogenation of alkyl fluorides is less substituted alkene
 - Strongest leaving base = poorest leaving group
 - Negative charge builds on alpha-carbon → carbanion transition state
- Carbanion stability → destabilized by electron-donating alkyl groups
- Summary → major product of E2 elimination rxn = more stable alkene except when reactants sterically hindered || poor leaving group (e.g. alkyl fluoride) ## E1 Reaction* Unimolecular elimination rxn
- First order elimination → rate of rxn depends only on concentration of alkyl halide
 - rate = $k[\text{alkyl halide}]$
- Alkyl halide takes part in rate-determining step of rxn
 - E1 rxn has ≥ 2 steps
 - First step is rate-determining
- E1 rxn mechanism
 - Alkyl halide disassociates → forms carbocation
 - Base forms elimination product → removes the beta-carbon
- pKa → larger means weaker acid \implies higher Ka → stronger acid
 - pKa reduced by +ve carbon in 2nd step → can accept electrons left by deprotonation
 - Carbon adjacent to +vely charged carbon (beta) shares charge due



Figure 34: E1 mechanism

- to hyperconjugation
 - * Drains electron density from C-H bond → weakens it
 - Rxn is regioselective → more substituted alkene is the major product

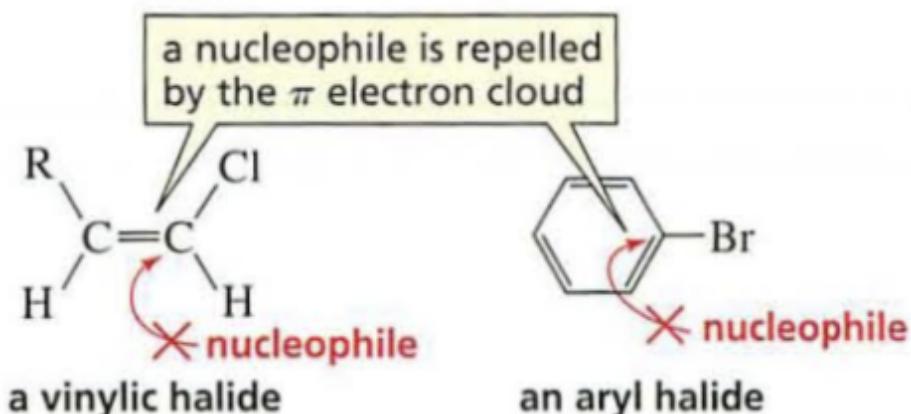


Figure 35: Hyperconjugation

- More stable carbocation → easier to form
- Weakest bases are best leaving groups → RI > RF in reactivity
- For both E2 and E1 rxn
 - Major product is most stable alkene
 - Tertiary alkyl halides most reactive > primary alkyl halides
- E1 rxn forms carbocation intermediate → carbocation rearrangement can occur for more stability
- Comparison with electrophilic addition
 - Addition → need acid to react w/ nucleophilic alkene (recall)
- Elimination → need base to remove proton from carbocation to form alkene

E1 and E2 Competition* Primary alkyl halides undergo only E2 rxn → not E1 as primary carbocations too unstable for formation

- Secondary/tertiary undergo both E1 and E2
- Correspondence with substitution \implies E1 = SN1 and E2 = SN2

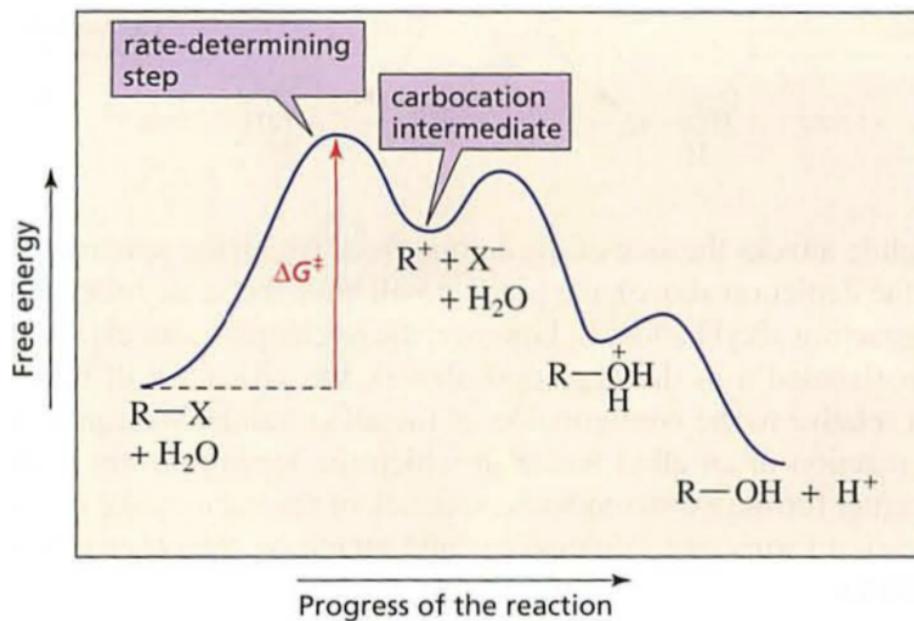


Figure 36: Benzylic shift

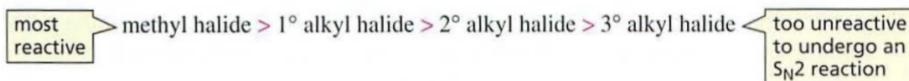


Figure 37: Electrophilic addition

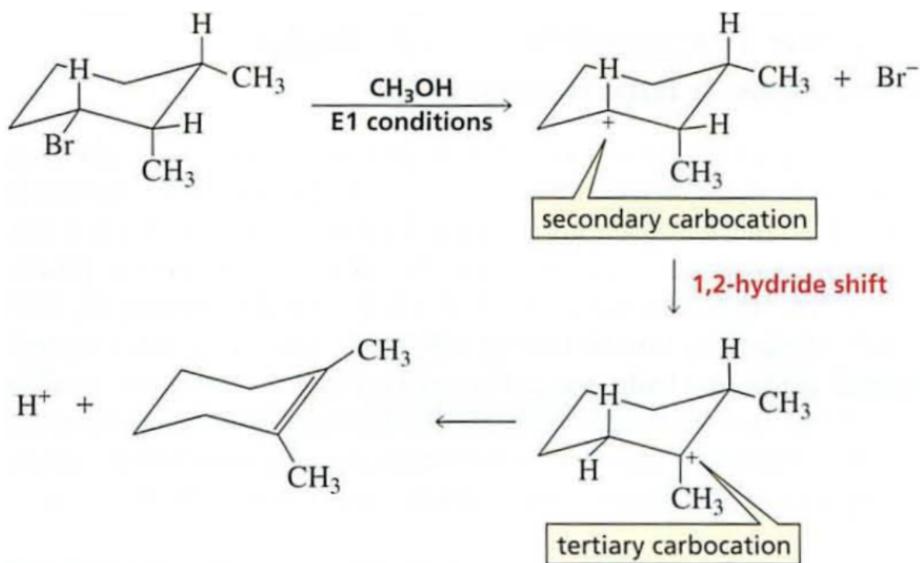


Figure 38: Elimination and addition

- E2 rxn favored by high concentration of strong base (nucleophile) + aprotic polar solvent
- E1 rxn favored by weak base and protic polar solvent ## Stereoselective E1 and E2s* C-X and C-H bonds must be in same plane[a] → orbitals of each of these carbons become overlapping p orbitals in transition state
- Optimal overlap ⇒ parallel orbitals
- Can be parallel on same side of molecule (syn-periplanar) or on opposite sides (antiperiplanar)
 - Elimination from opposite/same sides of C-C bond → anti/syn elimination
 - Syn elimination much slower, anti favored in an E2 rxn
 - Syn requires an eclipsed (unstable) conformation over staggered (anti)
- Sawhorse projections[b]
- Syn elimination → electrons of removed H move to front of C-X carbon
- Anti elimination → electrons of removed H move to back of C-X carbon
 - Best interacting orbital overlap
 - Electron rich base spared repulsion
- Thus, E2 is stereoselective in favoring E/trans over Z/cis
- If reactant has 2 hydrogens bonded to beta-carbon (from which H is removed) → E and Z products formed → 2 conformers from which eliminated groups are anti
- Alkene with bulkiest groups on opposite sites of == bond formed in greater

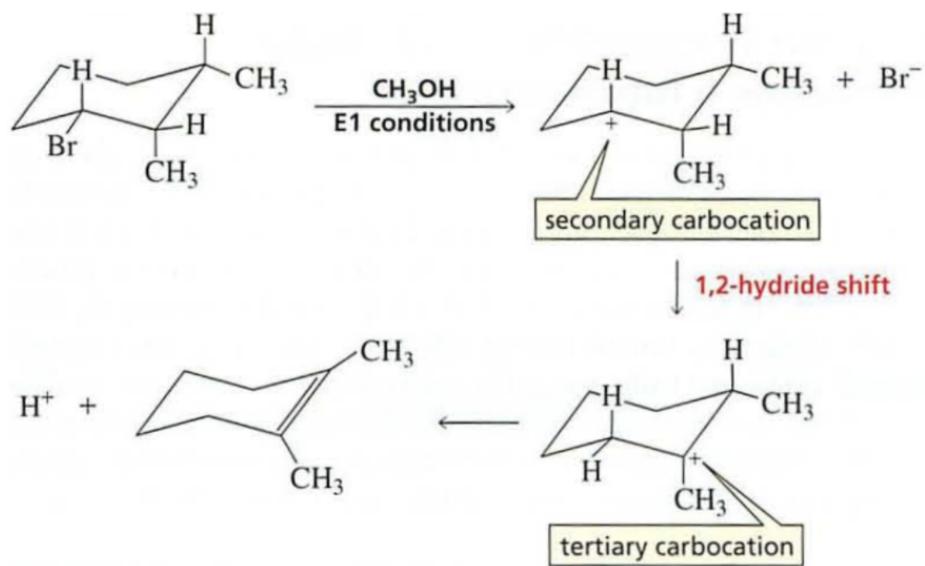


Figure 39: Newton projections

$$\text{rate} \propto [r_1][r_2]$$

Figure 40: Attack

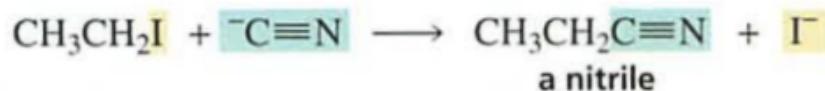
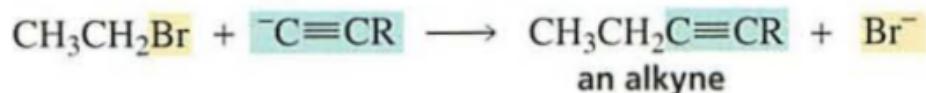
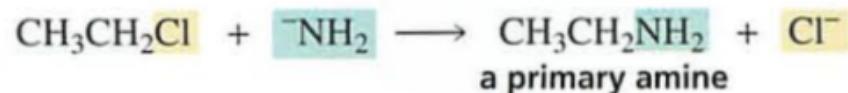
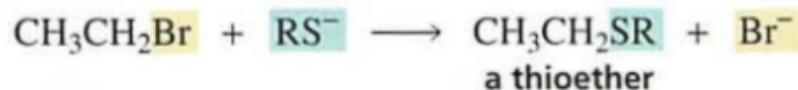
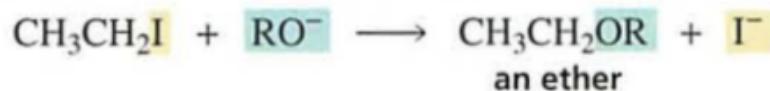
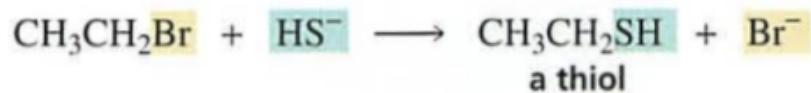
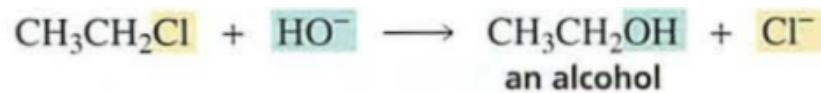


Figure 41: Antiperiplanar addition

yield → more stable If due to sterics

- If beta-carbon bonded to only 1 hydrogen → only one conformer from which eliminated groups are anti → 1 alkene product

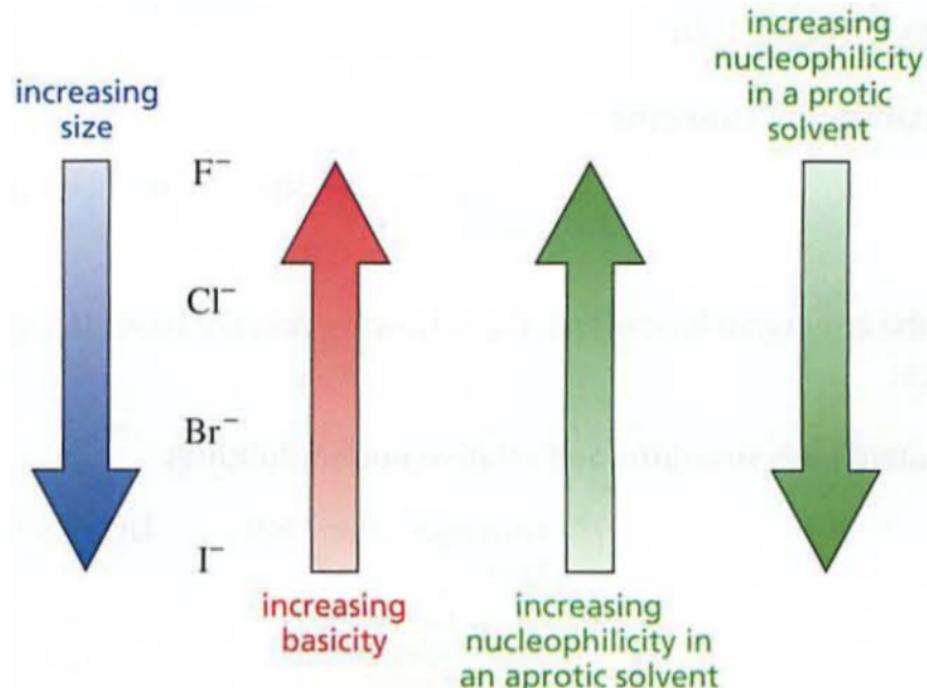


Figure 42: Stereochemistry of elimination

- Non-eliminated groups retain spatial positions
- E1 stereochemistry → major product will have bulkiest products on opposite sides of bonds
 - Both syn and anti elimination can occur due to carbocation being planar, electrons from departing proton can move towards +ve carbon from either side
- E and Z products formed regardless of beta-carbon having 1 or 2 hydrogens, contrast w/ E2

Elimination from Substituted Cyclohexanes* Follows same stereochemical rules as elimination from open-chain compounds

- Must have parallel groups for elimination → axial positions
 - More stable conformer of chlorocyclohexane has equatorial groups, but does not undergo E2
- Rate constant given by K_{eq} → larger means faster rxn

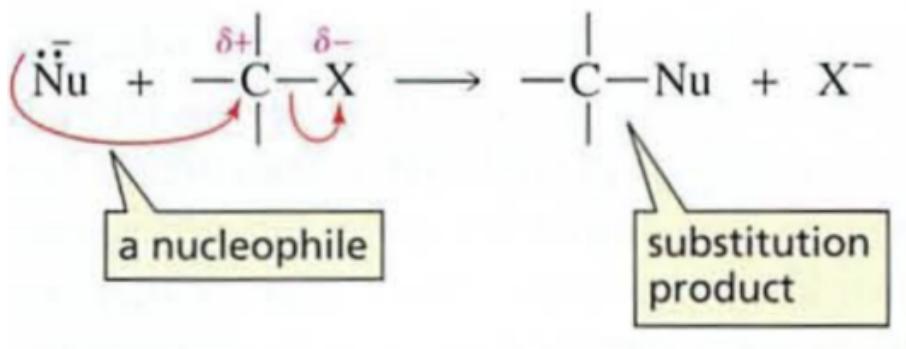


Figure 43: E and Z product example

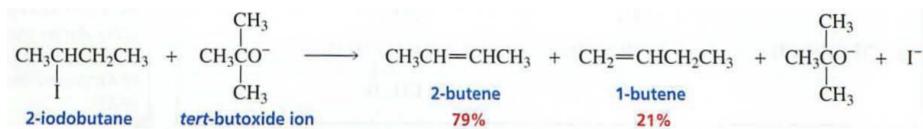


Figure 44: Axial positioning

relative reactivities of alkyl halides in an S_N1 reaction

most reactive	>	3° alkyl halide	>	2° alkyl halide	>	1° alkyl halide	too unreactive to undergo an S_N1 reaction
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Figure 45: Importance of antiperiplanar addition

Table 9.5 Relative Reactivities of Alkyl Halides

In an S_N2 reaction: $1^\circ > 2^\circ > 3^\circ$ In an S_N1 reaction: $3^\circ > 2^\circ > 1^\circ$
 In an E2 reaction: $3^\circ > 2^\circ > 1^\circ$ In an E1 reaction: $3^\circ > 2^\circ > 1^\circ$

Figure 46: Conformer stability

- Hydrogen eliminated may not be from beta-carbon bonded to fewest hydrogens → rule states that when there is more than one beta-carbon from which H can be removed, it is removed from C with min carbons
 - H in this case must be in axial position, and for below ex. there is only one beta-carbon with axial H

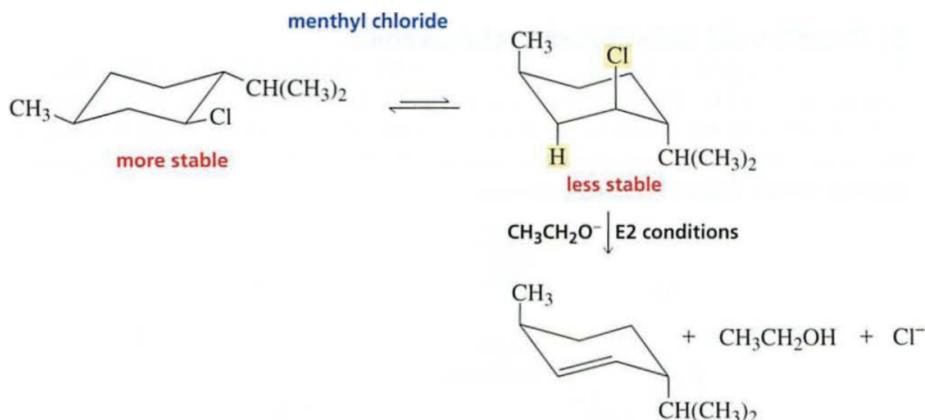


Figure 47: Elimination example on ring

- Stereochemistry of E1 rxns
 - Eliminated groups do not have to be in axial positions → elimination rxn is not concerted
 - Carbocation loses proton from beta-carbon bonded to fewest hydrogens → follows Zaitsev's rule
 - Example below has carbocation shift

Kinetic Isotope effect to Determine Mechanism* Deuterium kinetic isotope effect = $\frac{k_H}{k_D}$ where H represents a reactant with H and D represents reactant with deuterium replacing hydrogen

- Replace a H with D and compare observed rates
 - C-D bond harder to break than C-H
 - A non-unity ratio indicates that C-H or C-D bond is broken in rate-determining step → consistent with E2 mechanism ## Competition be-

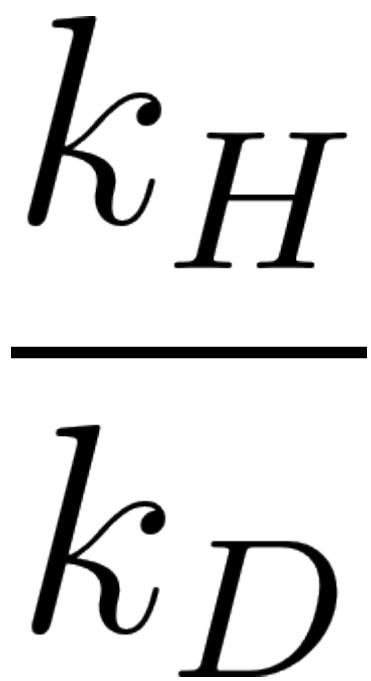


Figure 48: Carbocation shift in ring elimination

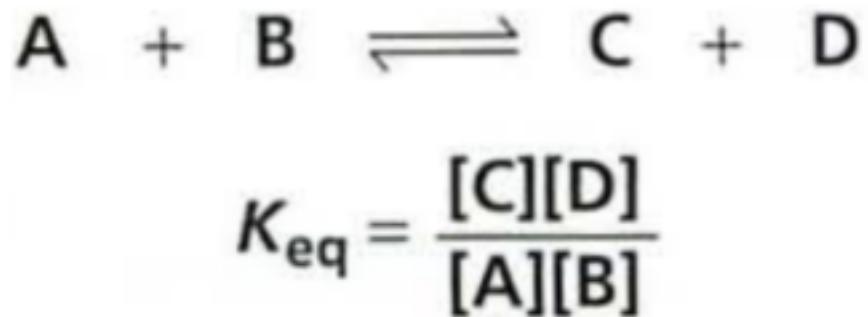


Figure 49: Stereochemistry summary for substitution and elimination

tween Elimination and Substitution* Terminology → In substitution, OH⁻ is a nucleophile but is called base in elimination

- Primary alkyl halide undergoes only SN₂/E₂ rxns due to unstable carbocation
 - Undergoes either if secondary or tertiary alkyl halide
 - Good nucleophile encourages SN₂/E₂ and poor nucleophile encourages SN₁/E₁
 - SN₂/E₂ Conditions → high conc. of good nucleophile/strong base

relative rates of reaction

Figure 50: Preference

- Primary alkyl halide most reactive in SN2 due to unhindered back of alpha-carbon and least in E2
 - Substitution favored given conditions favoring SN2/E2

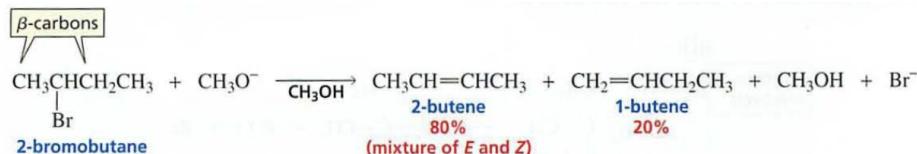


Figure 51: Alkyl halide reactivities overall

- If tertiary alkyl halide or nucleophile/base sterically hindered → elimination preferred
 - Secondary alkyl halides can form both substitution and elimination products under SN2/E2
 - Stronger and bulkier base \Rightarrow greater percentage of elimination product
 - Higher temperatures favor elimination due to greater ΔS value for elimination rxn as it forms more product molecules > substitution
 - For tertiary alkyl halides → only elimination product formed under SN2/E2 conditions
 - SN1/E1 conditions → poor nucleophile/weak base
 - Alkyl halide dissociates to form carbocation, then either elimination or substitution product
 - Will give both substitution and elimination products

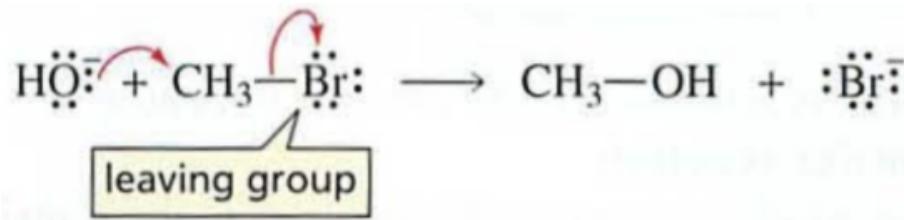


Figure 52: Example

- Primary alkyl halides do not undergo either rxn due to instability

Williamson ether synthesis



Figure 53: Summary of expected products

Substitution and Elimination Reactions in Synthesis* Substitution rxns to synthesize compounds

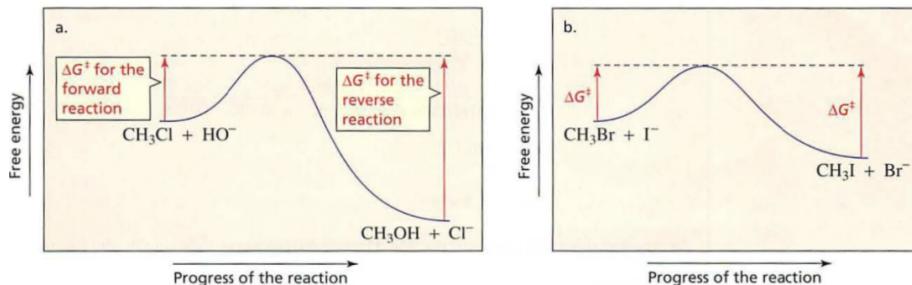


Figure 54: Williamson ether synthesis

- Williamson ether synthesis → nucleophilic substitution rxn, needs a good nucleophile conc. → therefore is SN2
 - Can't use tertiary alkyl halide as would only form elimination product (SN2/E2)
- Acetylide anion + alkyl halide synthesis for alkynes → also SN2 rxn
- Elimination rxn to synthesize compounds
 - Choose most hindered alkyl halide to maximize elimination product ## Consecutive E2 Elimination Reactions* Alkyl dihalides can undergo 2 dehydrohalogenations → 2 double bonds (diene)

- Zaitsev's rule products stable product of first but not 2nd step due to a conjugated diene being more stable than isolated (separated by 1 single bond)

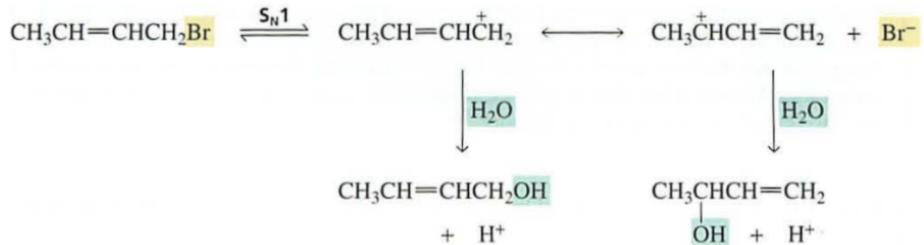
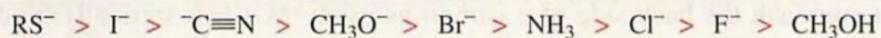


Figure 55: Consecutive E1/E2 rxns

- If 2 halogens on same carbon (geminal dihalide) → alkyne is formed
- Strong base needed to perform elimination on vinylic halide
- Reacting alkene with Br₂ or Cl₂ forms vicinal dihalide → converts double to triple bond

Table 8.2 Relative Nucleophilicity Toward CH₃I in Methanol



increasing nucleophilicity

Figure 56: Converting a double bond to a triple bond

Designing Synthesis II* Read Section 9.11.