

*Substitution
and
Elimination Reactions*

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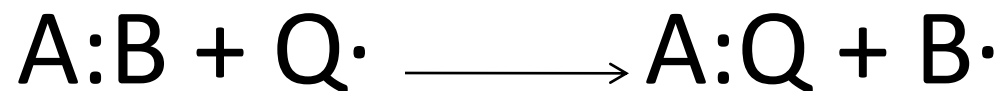
Substitution Reactions-Definition

- Reactions which involve the **replacement or substitution** of one or more atoms or groups of a compound by other atoms or groups are known as ***SUBSTITUTION REACTIONS.***

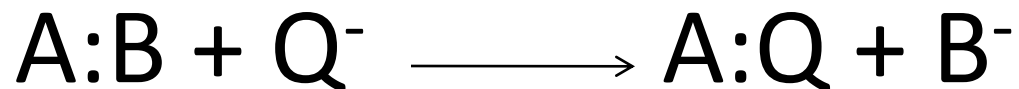
Classification

- Based on the *nature of substituents* involved:

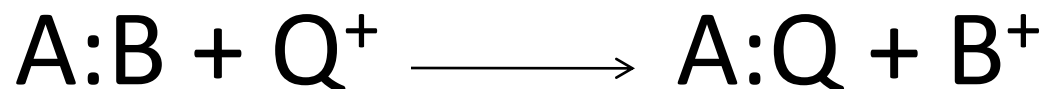
1. Free Radical Substitution



2. Electrophilic Substitution



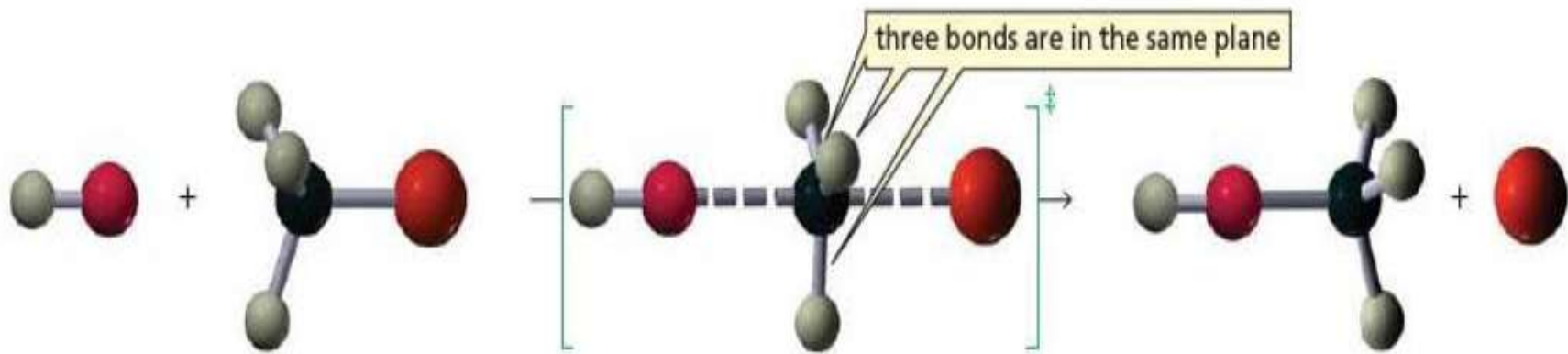
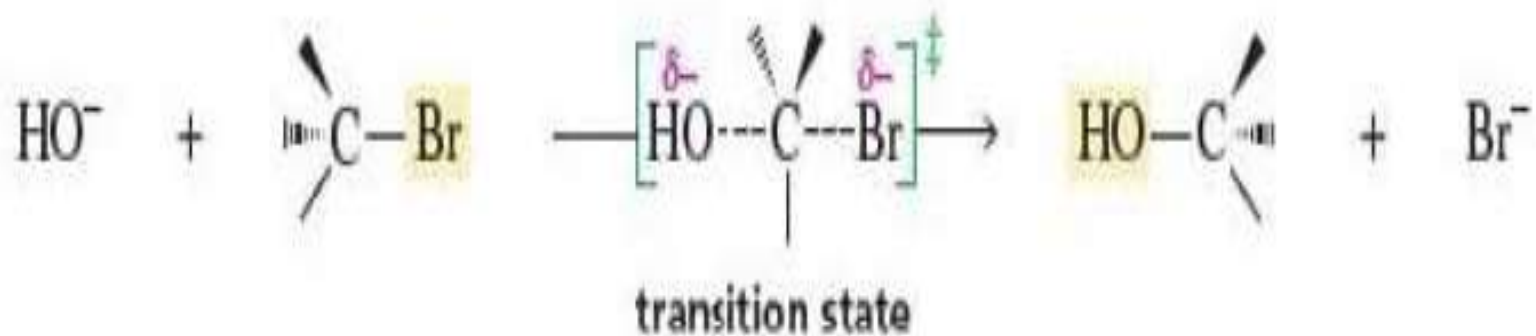
3. Nucleophilic Substitution

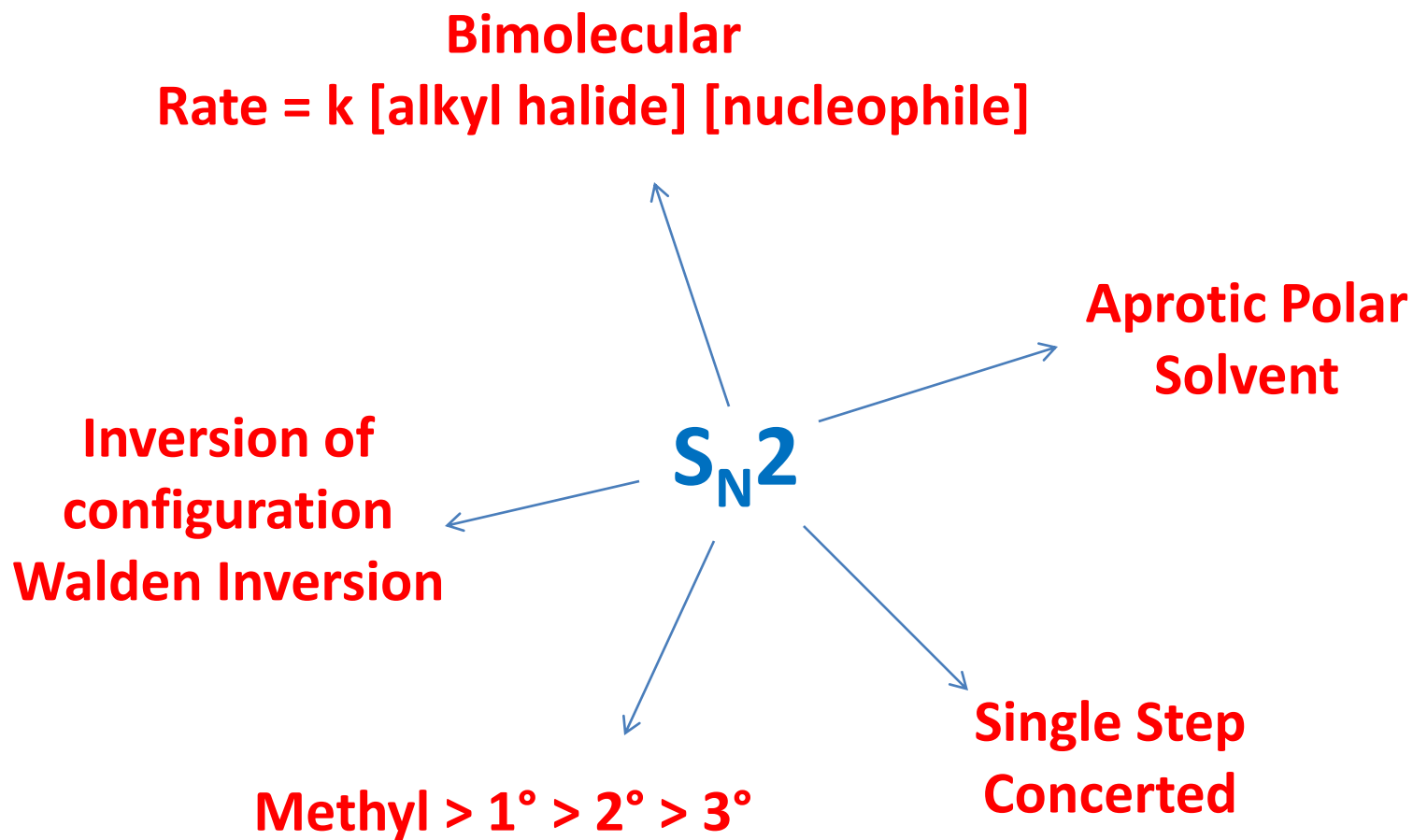


Aliphatic Nucleophilic substitution

- In 1935, **Edward D. Hughes** and **Sir Christopher Ingold** studied nucleophilic substitution reactions of alkyl halides and related compounds.
- They proposed two main mechanisms—
the **S_N1 reaction** and the **S_N2 reaction**.
- S stands for chemical substitution, N stands for nucleophilic, and the number represents the kinetic order of the reaction.

S_N2 Mechanism

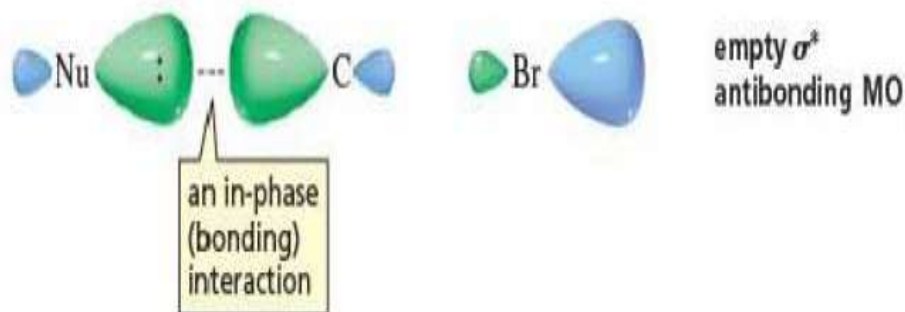




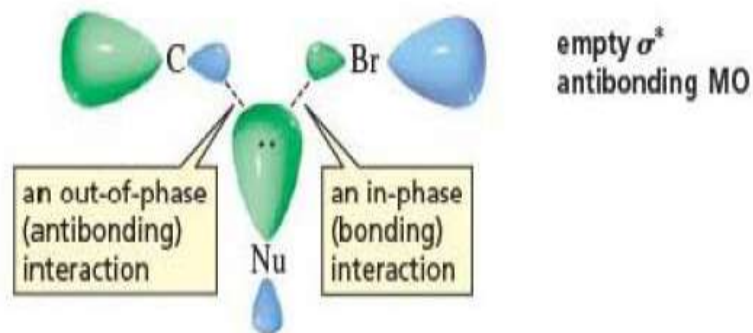
Attack of Nucleophile

- Nucleophile attacks the carbon from the side opposite to the leaving group because of blockade by leaving group.
- Also front side attack results in formation of a bonding and anti-bonding interaction that cancel each other

a. Back-side attack

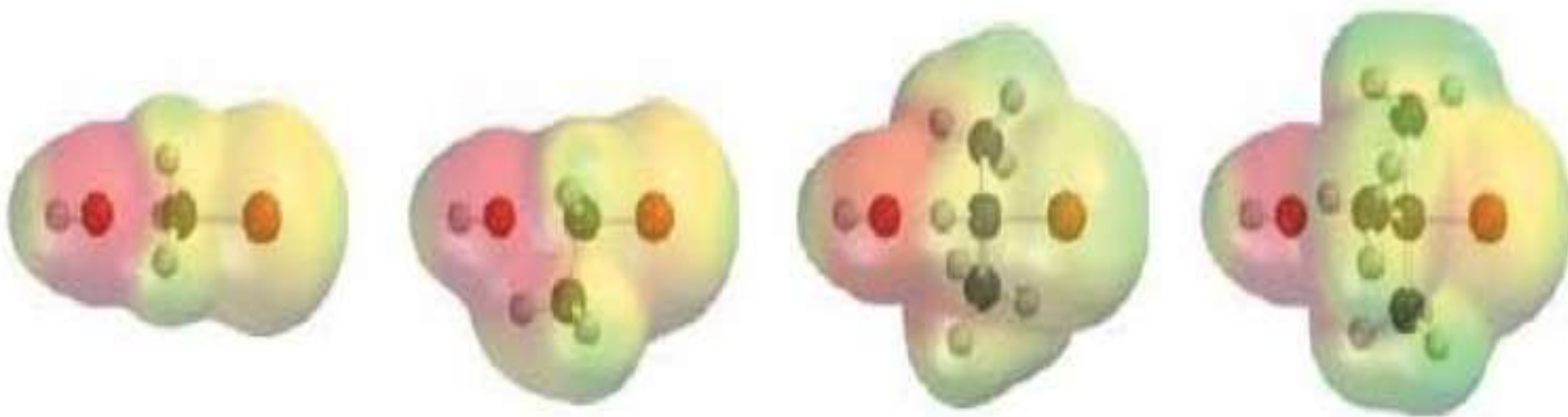


b. Front-side attack

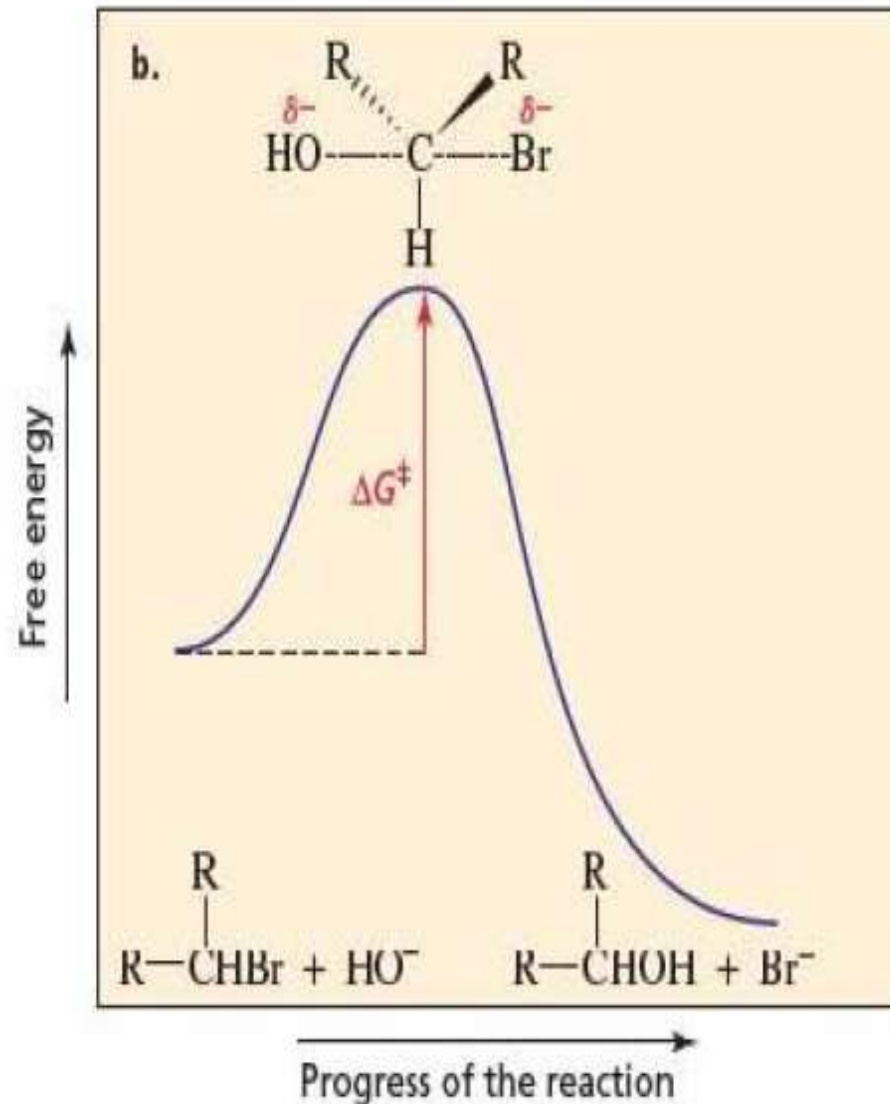
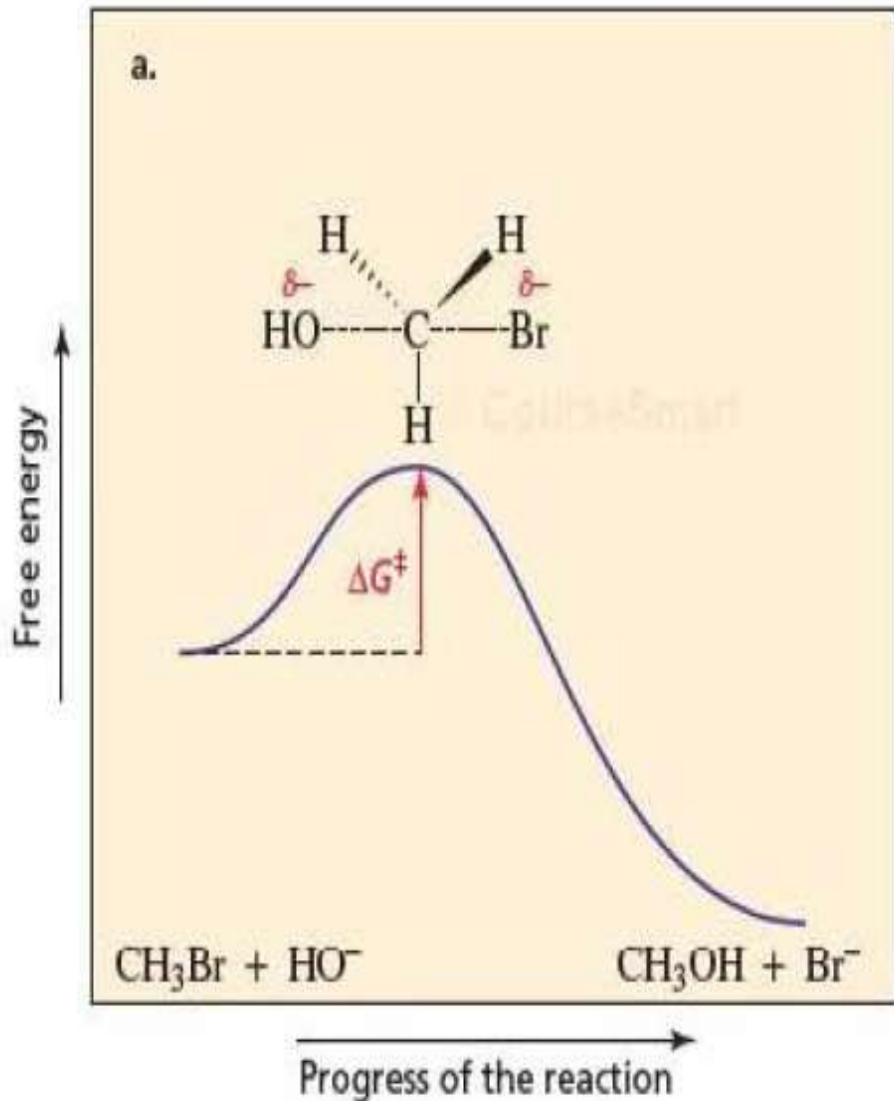


Relative Reactivities of different halides to S_N2 reaction

- Methyl Halide > 1° Halide > 2° Halide > 3° Halide
- Reason : Steric Hindrance



The approach of HO^- to a methyl halide, a primary alkyl halide, a secondary alkyl halide, and a tertiary alkyl halide



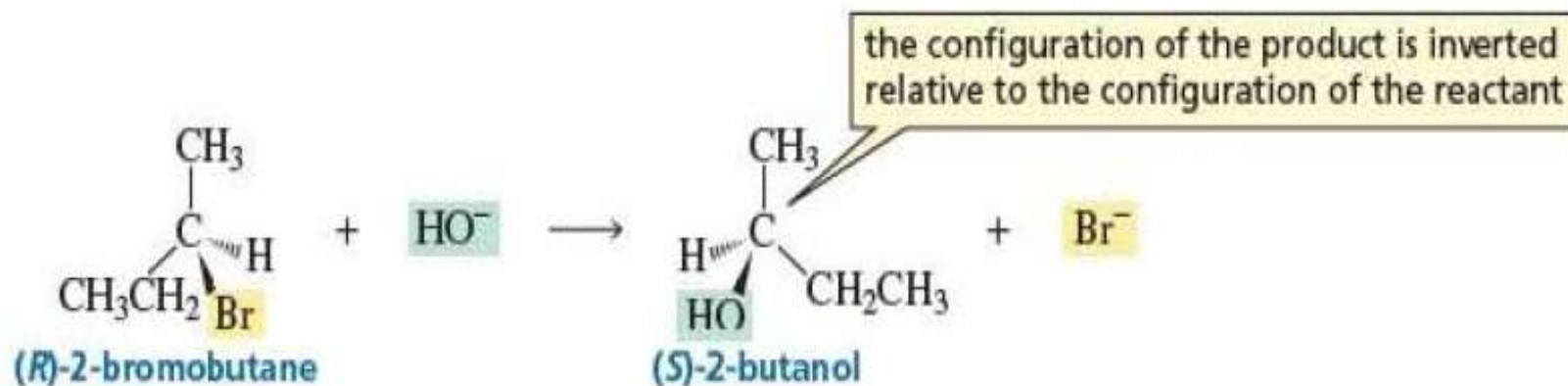
Reaction coordinate diagrams for

(a) the $\text{S}_{\text{N}}2$ reaction of bromomethane with hydroxide ion;

(b) an $\text{S}_{\text{N}}2$ reaction of a sterically hindered secondary alkyl bromide with hydroxide ion.

Walden Inversion

- Inverted product relative to reactant is formed in S_N2 .
- Because of Back-side attack of the nucleophile.
- Example:



Factors affecting S_N2 reaction

- Leaving group:

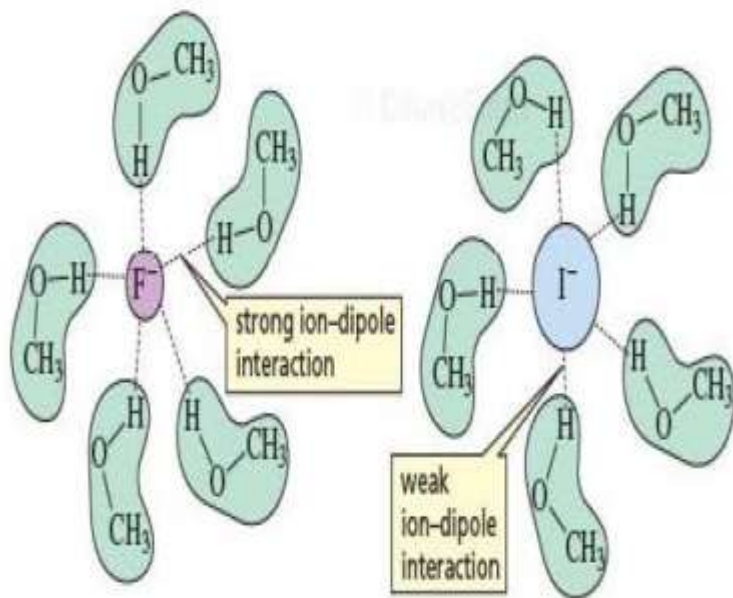
The weaker the basicity of a group, the better is its leaving propensity.



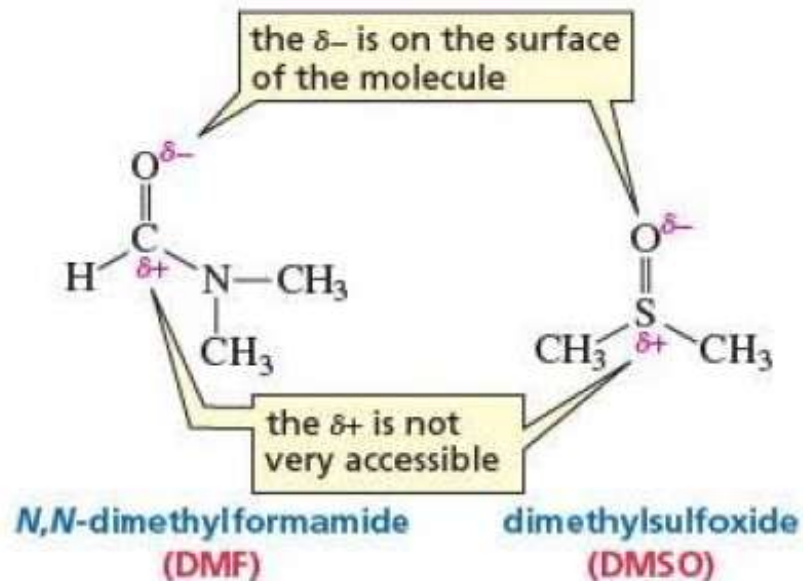
- Attacking Nucleophile:
 - Nucleophilicity
 - Size of the nucleophile
 - Solvent employed (aprotic polar solvent)
 - Steric factors of the nucleophile

Role of solvent in S_N2

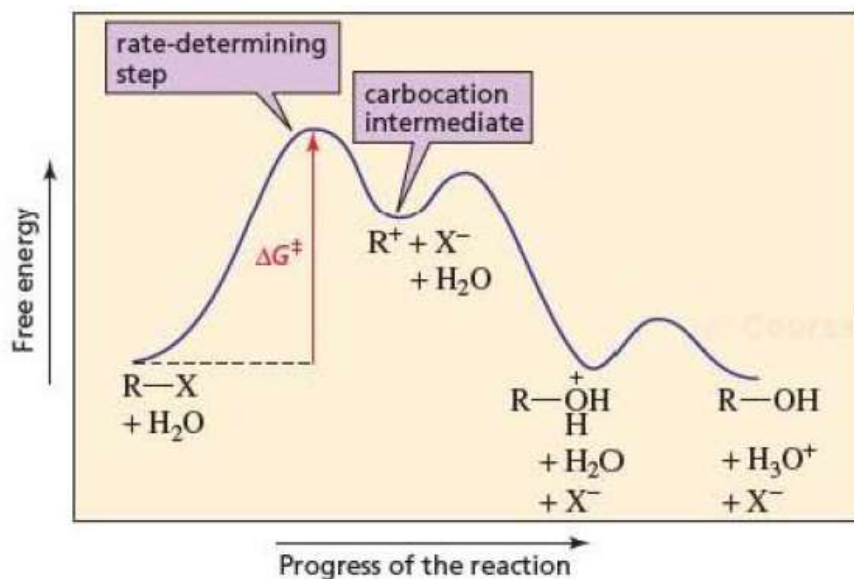
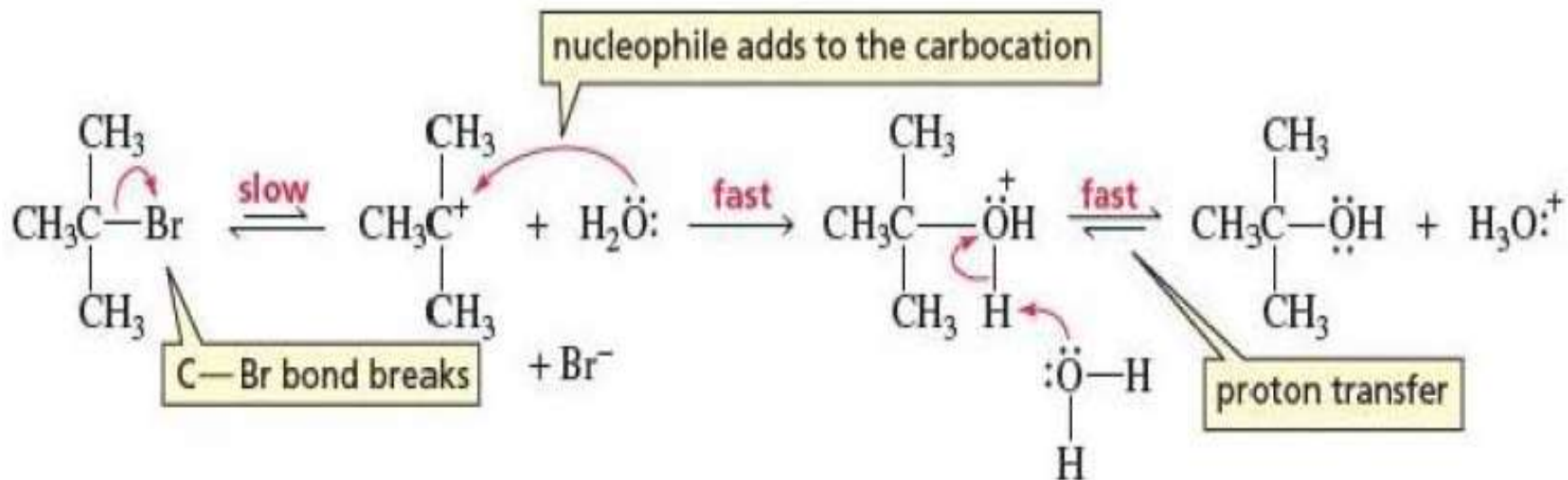
- Non-polar solvents: Ionic compounds are usually insoluble and hence not used.
- Protic polar solvents:

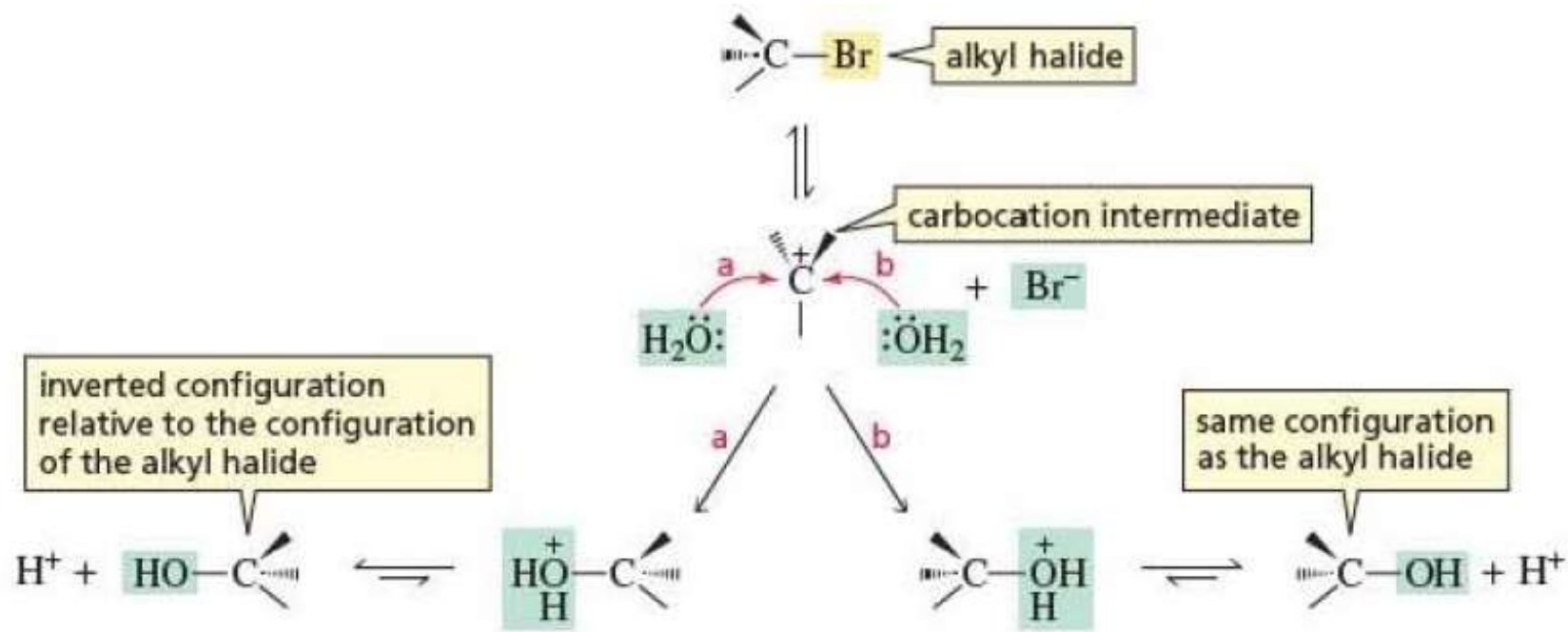


Aprotic Polar solvents:



S_N1 Mechanism





Generally more of inverted product is formed.

Unimolecular
Rate = k [alkyl halide]

**A pair of
Enantiomers
formed**

S_N1

```
graph TD; S_N1((S_N1)) --> A[Unimolecular Rate = k [alkyl halide]]; S_N1 --> B[Protic Polar Solvent]; S_N1 --> C[Two-Step]; S_N1 --> D["3° > 2° > 1° > methyl"]; S_N1 --> E[A pair of Enantiomers formed];
```

Protic Polar Solvent

Two-Step

3° > 2° > 1° > methyl

Relative Reactivities of different halides to S_N1 reaction

- **3° Halide > 2° Halide > 1° Halide > Methyl Halide**
- Reactivity depends on stability of carbocation formed in step 1.
- Carbocation stability: **$3^\circ > 2^\circ > 1^\circ$**

Stability of Carbocations

1. Increasing substitution by carbon stabilizes carbocations



Reasons:

- Electron release by adjacent carbons by inductive effect i.e a carbon (electronegativity 2.5) connected to hydrogen (electronegativity 2.2) will be electron rich, and can donate some of those electrons to the neighboring carbocation.
- Hyper conjugation invokes stabilization through donation of the electrons in C-H sigma bonds to the empty p orbital of the carbocation.

Factors affecting S_N1 reaction

- Leaving group:

Similar to S_N2 reaction, *The weaker the basicity of a group, the better is its leaving propensity.*

- Stability of Carbocation
- Solvent (protic polar solvent)
- Nucleophile:

No effect as it has no part to play in rate-determining step.

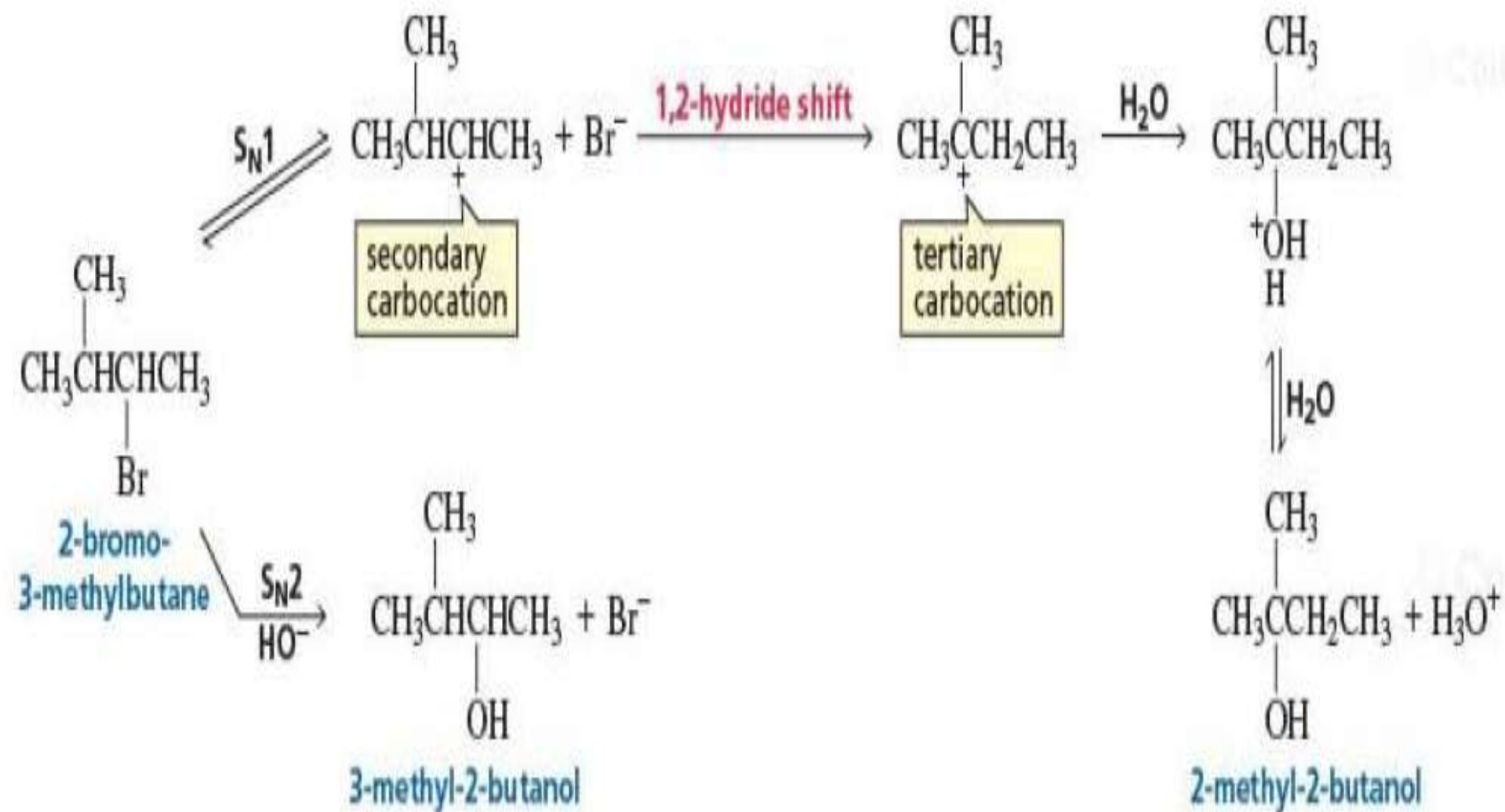
Role of solvent in S_N1

- Protic polar solvents: proton reacts with the leaving group and eliminates its influence.
- Generally solvent is the nucleophile.
- Thus solvolysis is the reaction.
- For example, water acts as both nucleophile and solvent.

Factor	S _N 1	S _N 2
Kinetics	Rate = k[RX]	Rate = k[RX][Nuc]
No. of steps	Two step	One step
Primary alkyl	Never	Good
Secondary alkyl	Moderate	Moderate
Tertiary alkyl	Excellent	Never
Leaving group	Less Basic	Less Basic
Nucleophilicity	Unimportant	Important
Preferred Solvent	Polar protic	Polar aprotic
Stereochemistry	Racemisation(more inversion possible)	Walden Inversion
Rearrangements	Common	Rare

Carbocation Rearrangements

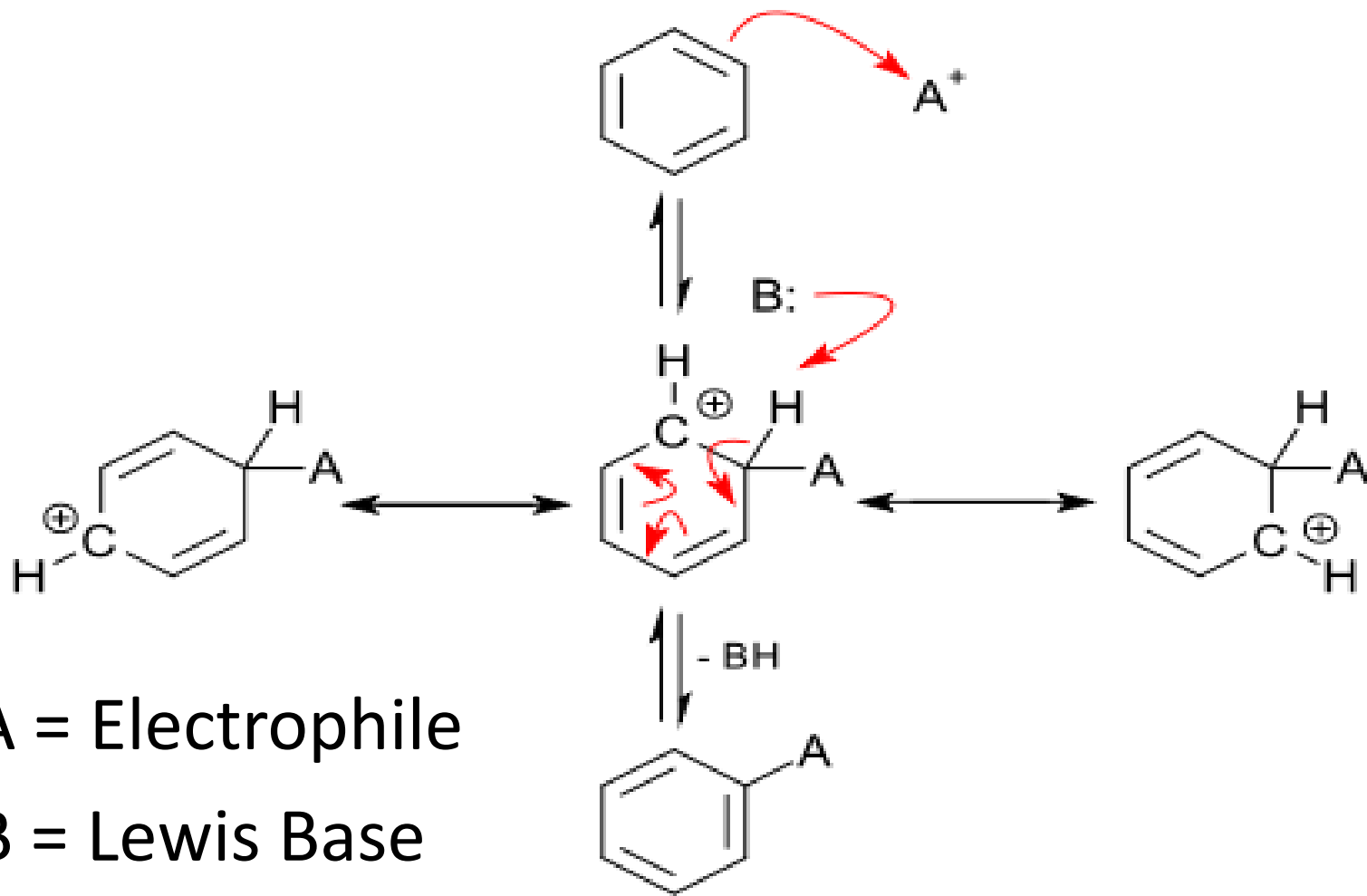
- In S_N1 , a carbocation will rearrange if it becomes more stable in the process.
- If a secondary carbocation formed initially undergoes a 1,2-hydride shift to form a more stable tertiary carbocation; this changes the carbon skeleton of the reactant.
- S_N1 and S_N2 reactions of the same alkyl halide can produce different constitutional isomers as products. since a carbocation is not formed in an S_N2 reaction and therefore the carbon skeleton cannot rearrange.



Examples

- *Organic reductions* with hydrides, for example
$$\text{R-X} \rightarrow \text{R-H using LiAlH}_4 \quad (\text{S}_{\text{N}}2)$$
- *Hydrolysis* reactions such as
$$\text{R-Br} + \text{OH}^- \rightarrow \text{R-OH} + \text{Br}^- \quad (\text{S}_{\text{N}}2) \text{ or}$$
$$\text{R-Br} + \text{H}_2\text{O} \rightarrow \text{R-OH} + \text{HBr} \quad (\text{S}_{\text{N}}1)$$
- *Williamson ether synthesis*
$$\text{R-Br} + \text{OR}'^- \rightarrow \text{R-OR}' + \text{Br}^- \quad (\text{S}_{\text{N}}2)$$
- The *Wenker synthesis*, a ring-closing reaction of aminoalcohols.
- The *Finkelstein reaction*, a halide exchange reaction
- The *Kolbe nitrile synthesis*, the reaction of alkyl halides with cyanides.

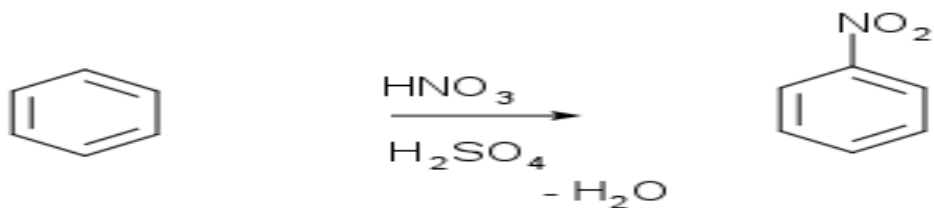
Electrophilic Aromatic Substitution



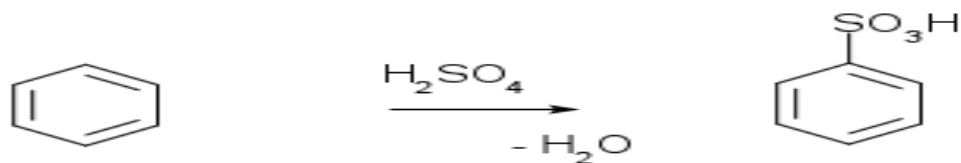
- A = Electrophile
- B = Lewis Base

Examples

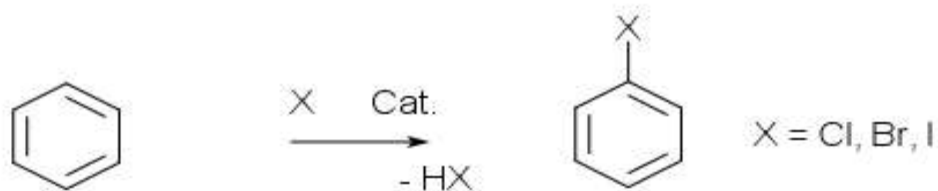
- **Nitration:**



- **Sulphonation:**

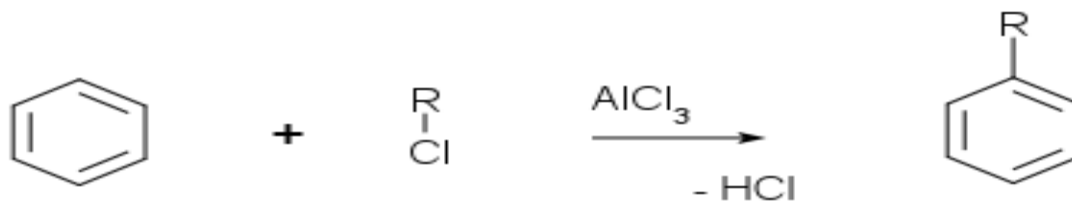


- **Halogenation:**

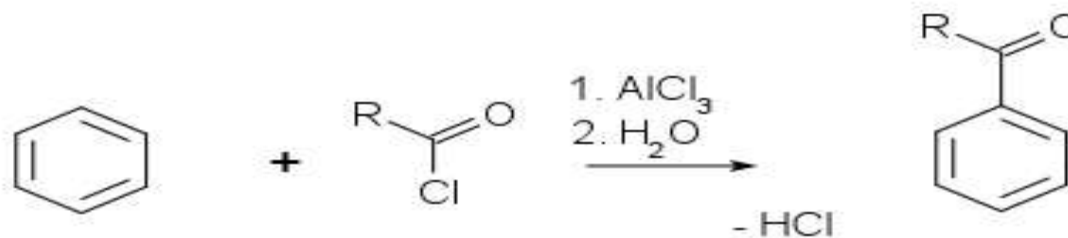


Examples

- Friedel-Craft's alkylation:



- Friedel-Craft's acylation:



Effect of Substituents

- Any substituents, if present, affect both the **regioselectivity** and **speed** of the reaction.
- In terms of regioselectivity, the substituents may be **ortho-para directing** or **meta directing**.
- In terms of kinetics, substituents may **increase (activating)** or **decrease (deactivating)** the rate of reaction.

Activating Substituents:

- They *stabilize* the cationic intermediate formed during the substitution by *donating* electrons into the ring system, by either inductive effect or resonance effects.

Examples are *toluene*, *aniline* and *phenol*

Deactivating Substituents:

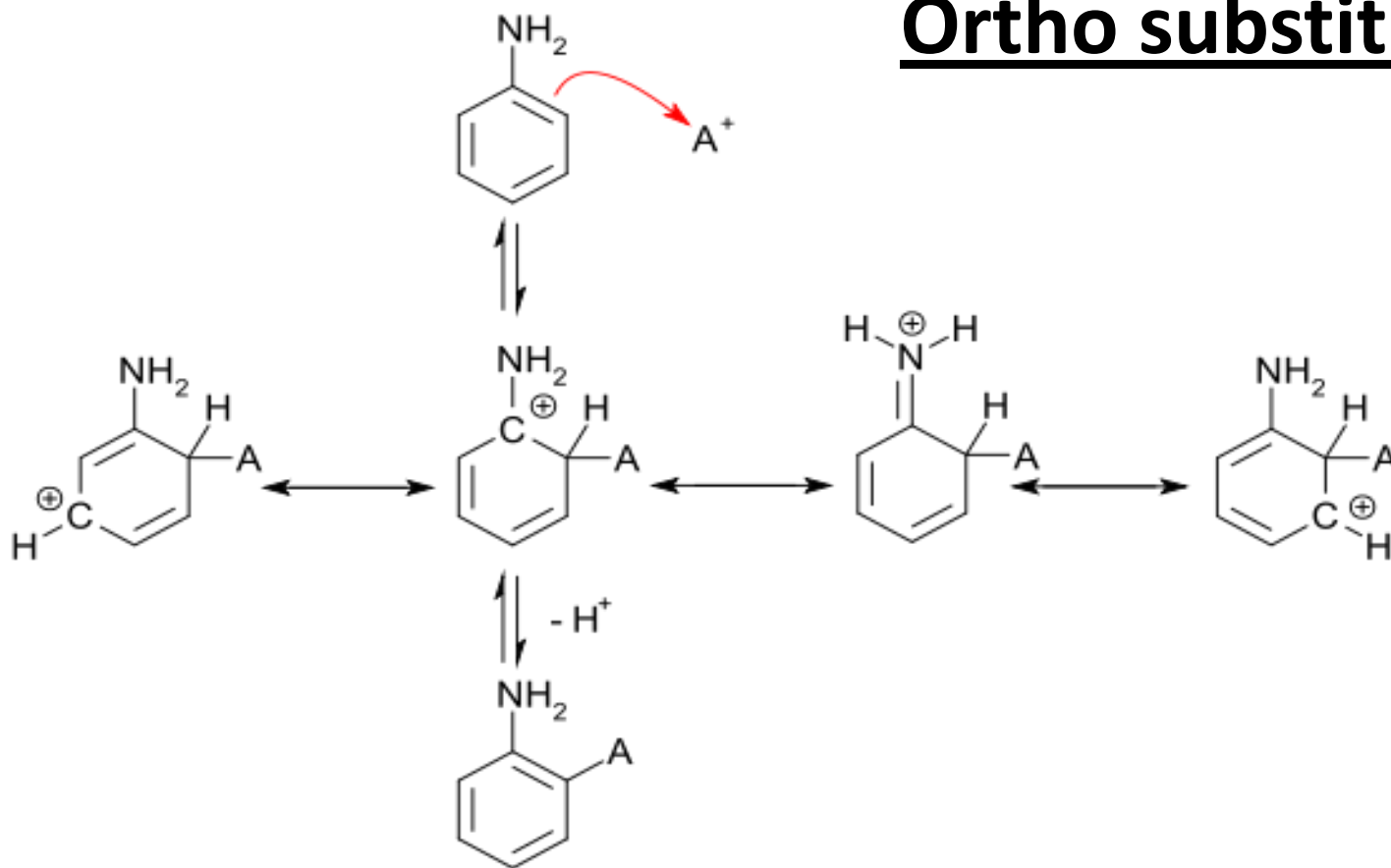
- These *destabilize* the intermediate cation and thus decrease the reaction rate by *withdrawing* electron density from the aromatic ring.

Examples are *nitrobenzene*, *benzaldehyde* and *trifluoromethylbenzene*

<p>ACTIVATING GROUPS ELECTRON RELEASING GROUPS</p>	Strongly activating groups	-OH, -OR, -NH ₂ , NHR
	Moderately activating groups	-NHCOR, -OCOR
	Weak activating groups	-R, -Ar, -CH=CHR
<p>DEACTIVATING GROUPS ELECTRON WITHDRAWING GROUPS</p>	Weak deactivating groups	-F, -Cl, -Br, -I
	Moderate deactivating groups	-CHO, -COR, -COOR, -COOH, -COCl
	Strong deactivating groups	-SO ₃ H, -NH ₂ R, -NR ₃ , -NO ₂ , -NHR ₂ , -NH ₃ , -CN

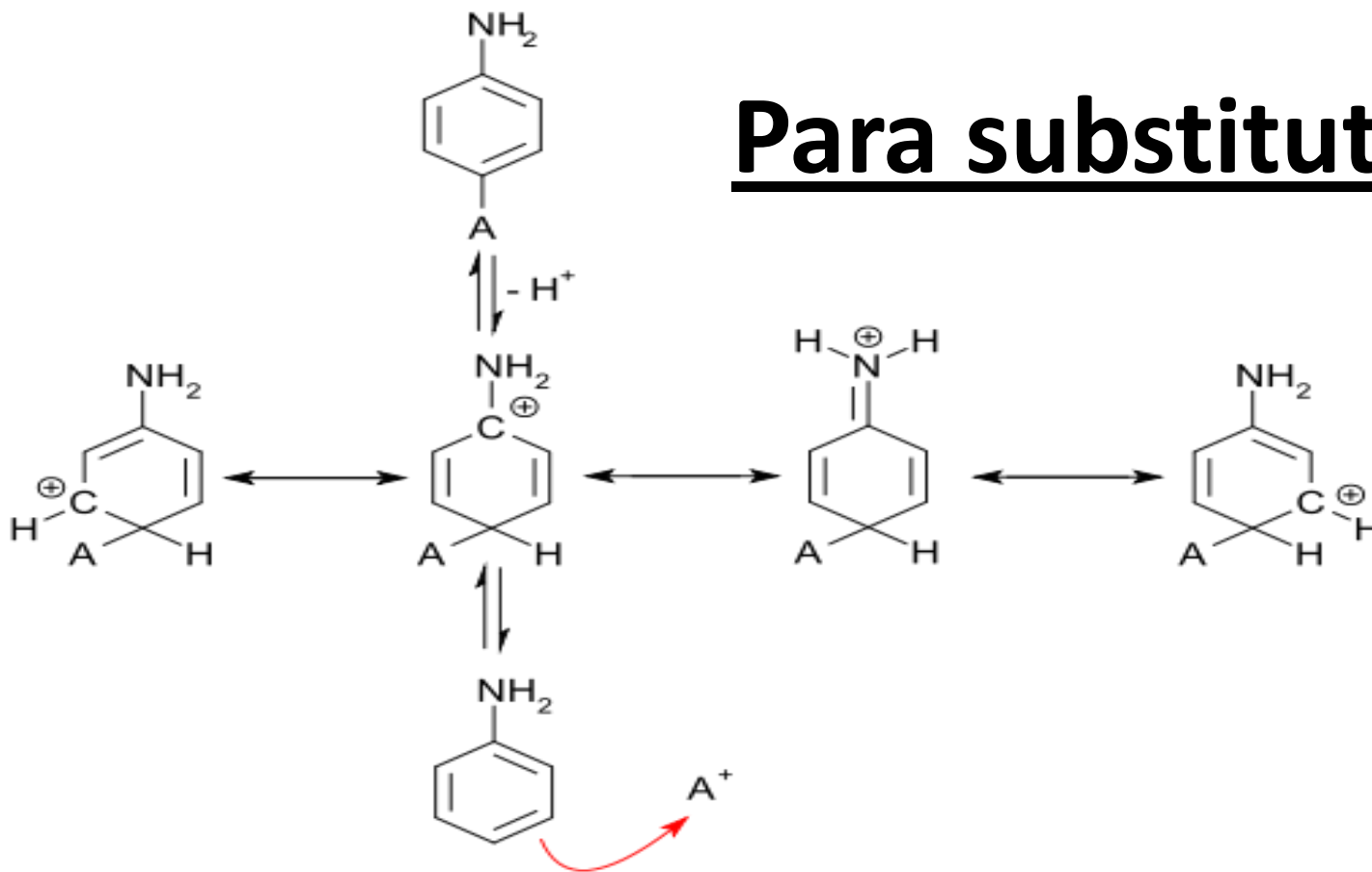
Ortho/para directors

Ortho substitution



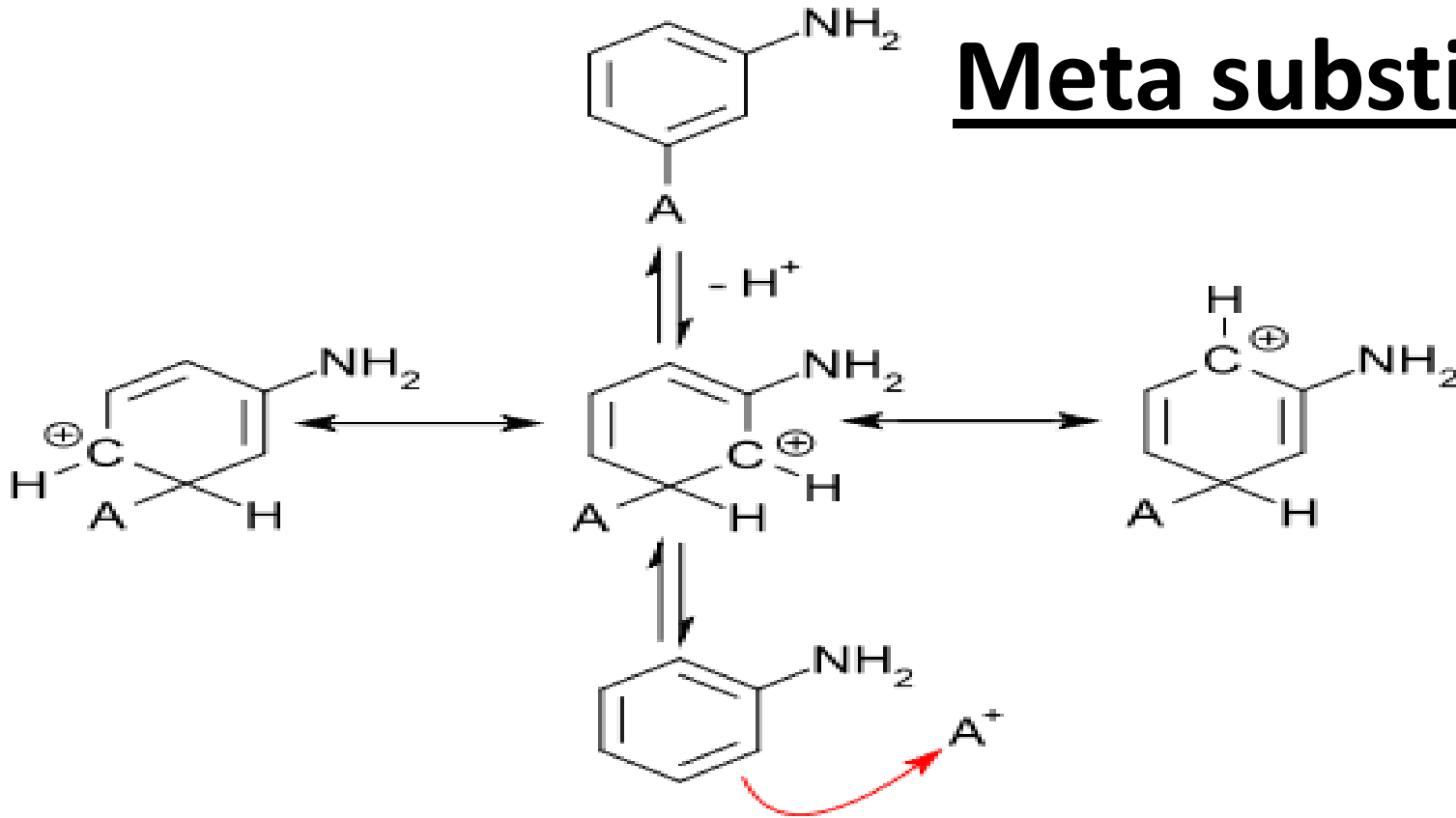
Ortho/para directors

Para substitution



Ortho/para directors

Meta substitution



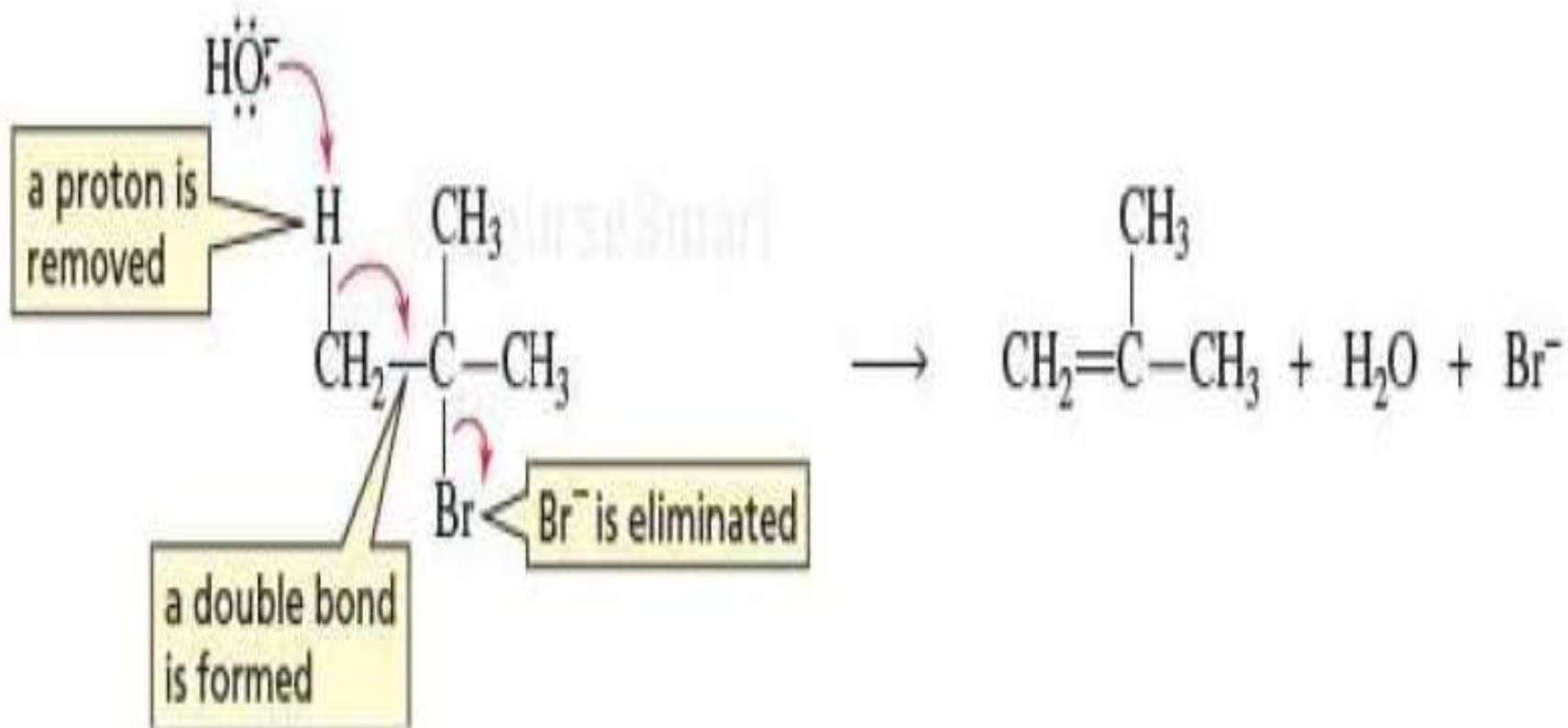
Meta directors

- Non-halogen groups with atoms that are more electronegative than carbon, such as a carboxylic acid group (CO_2H) draw substantial electron density from the *pi* system.
- These groups are strongly deactivating groups.
- Additionally, since the substituted carbon is already electron-poor, the resonance contributor with a positive charge on this carbon (produced by *ortho/para* attack) is less stable than the others.
- Therefore, these electron-withdrawing groups are *meta* directing

Elimination Reactions

- In an elimination reaction, atoms or groups are removed from a reactant.
- For example, when an alkyl halide undergoes an elimination reaction, the halogen (X) is removed from one carbon and a hydrogen is removed from an adjacent carbon and a double bond is formed between the two carbons from which the atoms are eliminated.
- The product of an elimination reaction is an alkene.
- Two important elimination reactions: E1 and E2.

The E2 Reaction



$3^\circ > 2^\circ > 1^\circ$

Bimolecular

Rate = k [alkyl halide][base]

1,2-elimination

E2

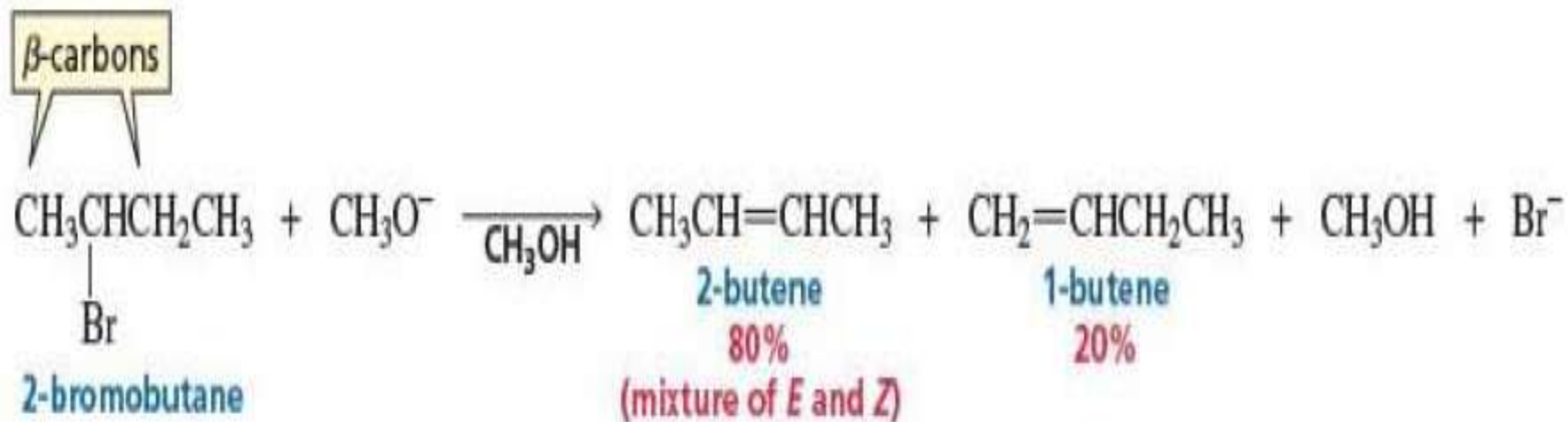
Regioselective

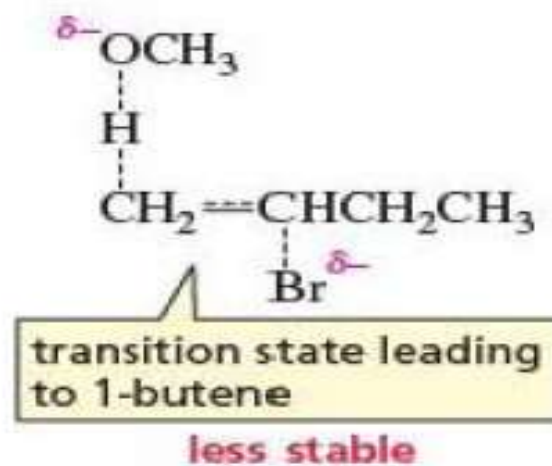
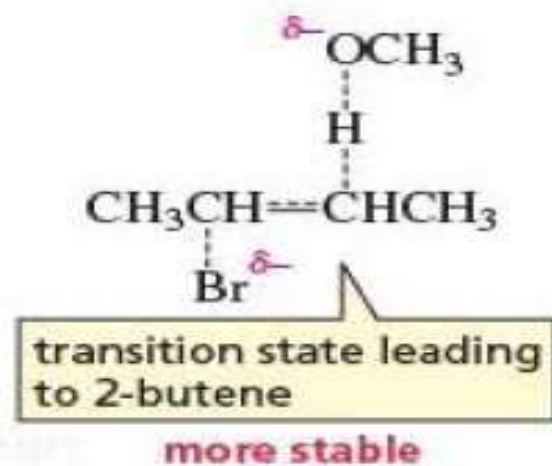
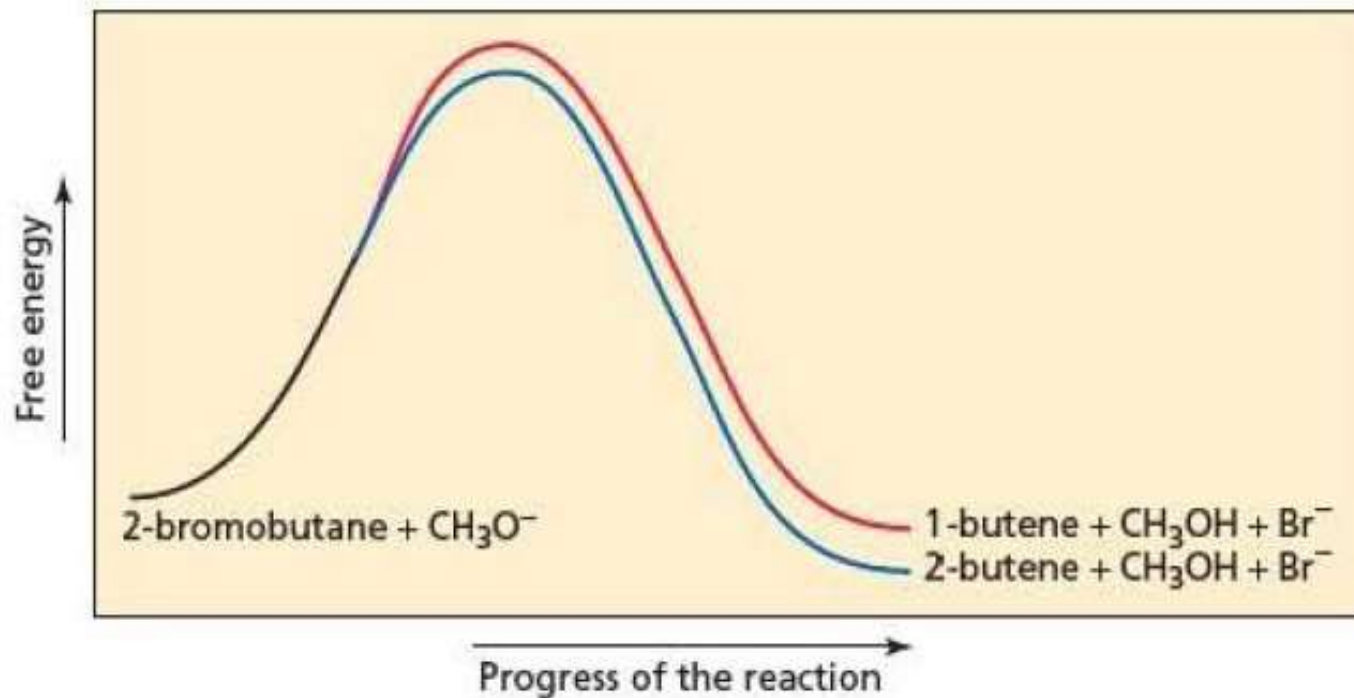
B-elimination

**Single Step
Concerted**

Regioselectivity

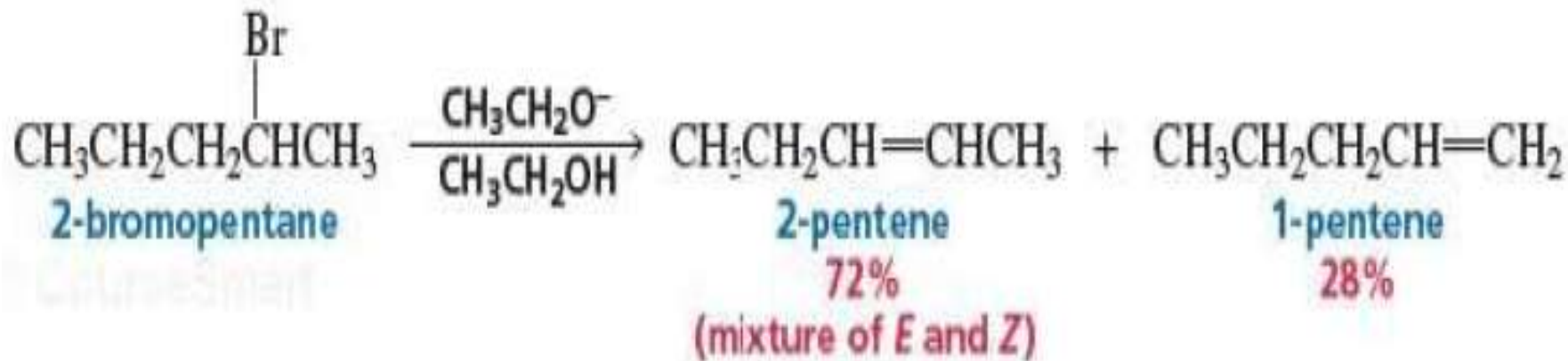
- When two structurally different β -carbons are available from which hydrogen can be eliminated, more stable alkene is formed as major product.





Greater the number of alkyl substituents on alkene, more stable it is.

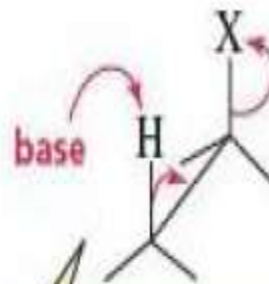
Stereoselectivity of E2 (Anti-elimination)



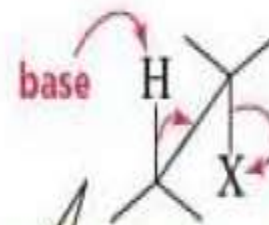
substituents are syn-periplanar
an eclipsed conformation



substituents are anti-periplanar
a staggered conformation

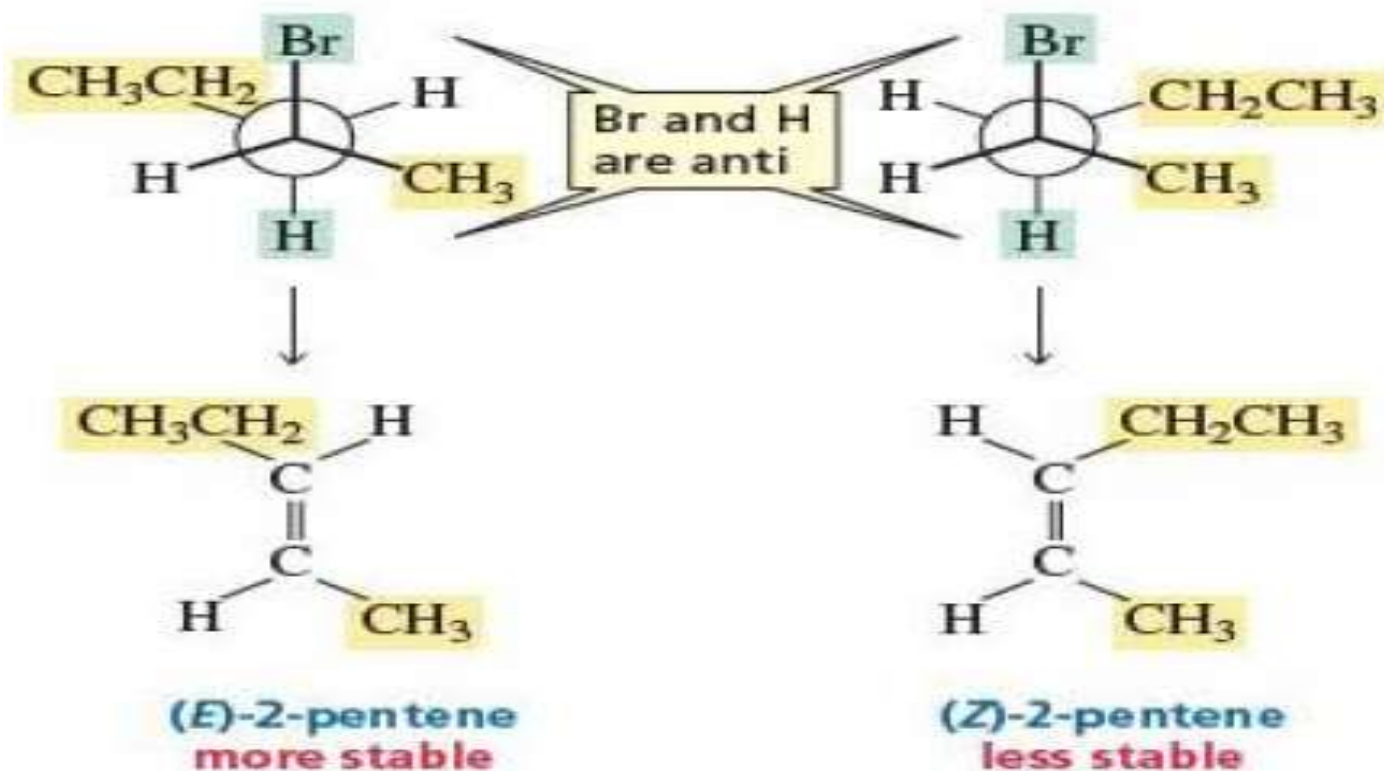


syn elimination
front-side attack



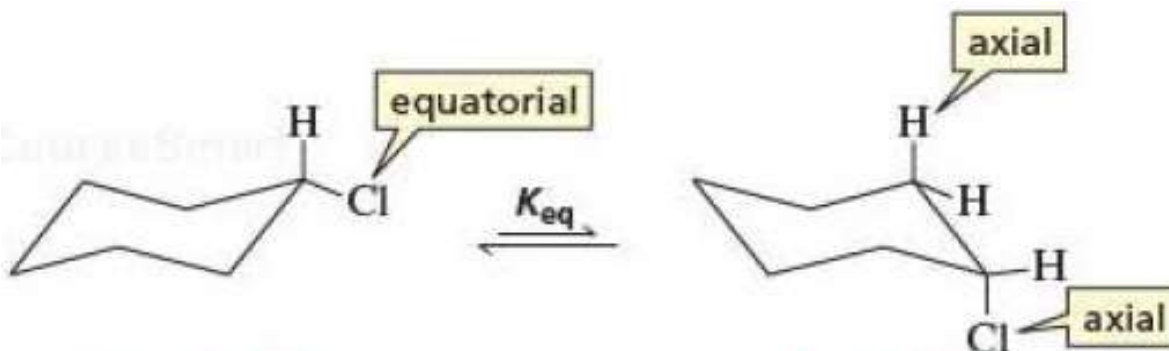
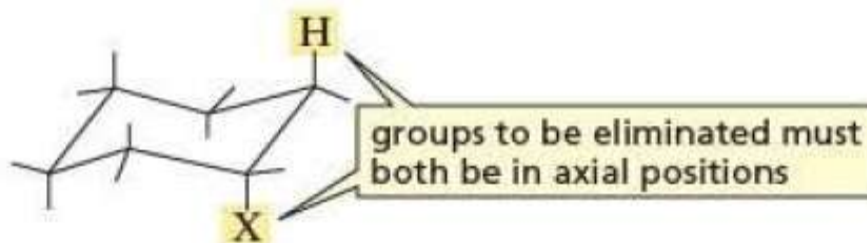
anti elimination
back-side attack

If the reactant has *two hydrogens bonded to the carbon from which a hydrogen is to be removed* both the *E* and *Z* products will be formed, because the reactant has two conformers in which the groups to be eliminated are anti.



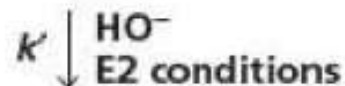
The alkene with the *bulkiest groups on opposite sides of the double bond* will be *formed* in greater yield because it is the more stable alkene, so it will have the more stable transition state leading to its formation.

E2 reaction of substituted cyclohexanes



more stable

less stable

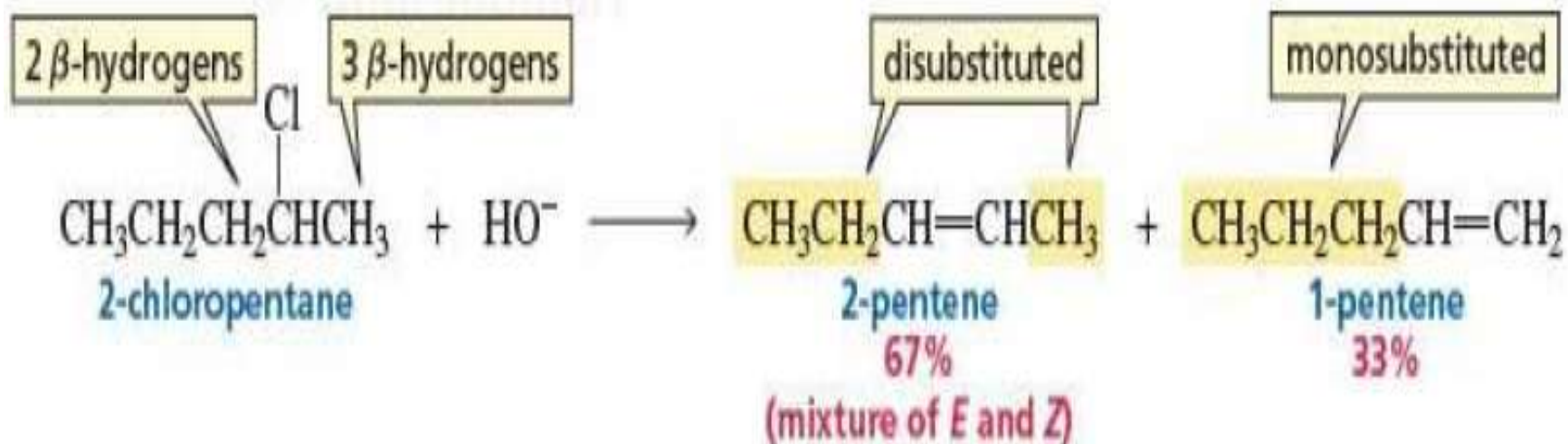


no reaction



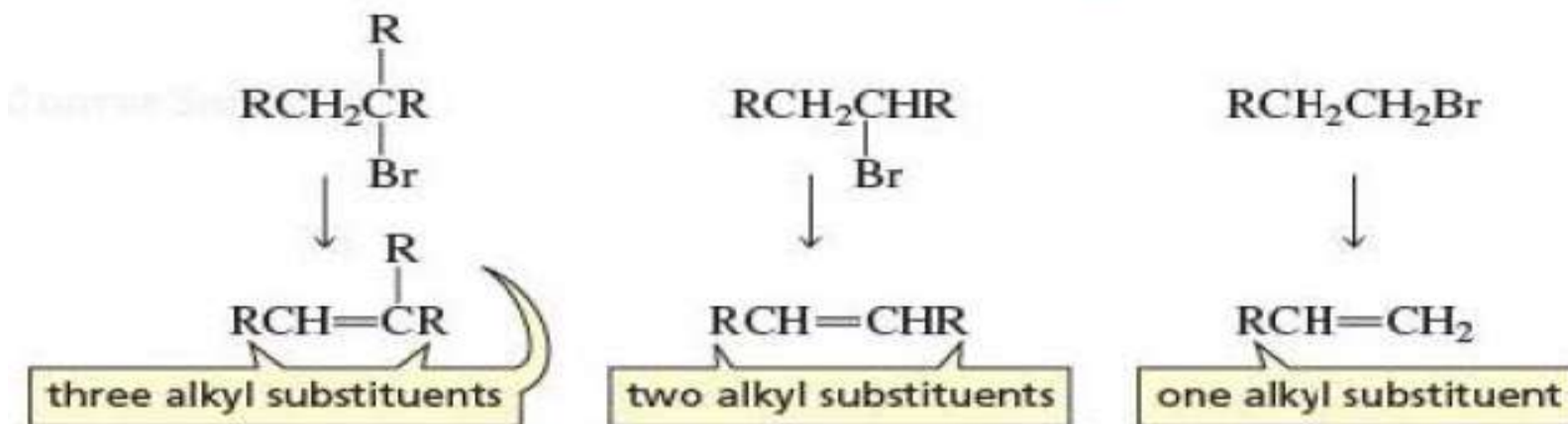
Saytzeff's Rule

- The more substituted alkene is obtained when hydrogen is removed from the β -carbon that is bonded to the fewest hydrogens.



- Hence as per saytzeff rule, elimination from a tertiary alkyl halide leads to a more substituted product than secondary alkyl halide, and a secondary alkyl halide more than a primary alkyl halide.
- Thus, relative reactivities in an E2 reaction are:

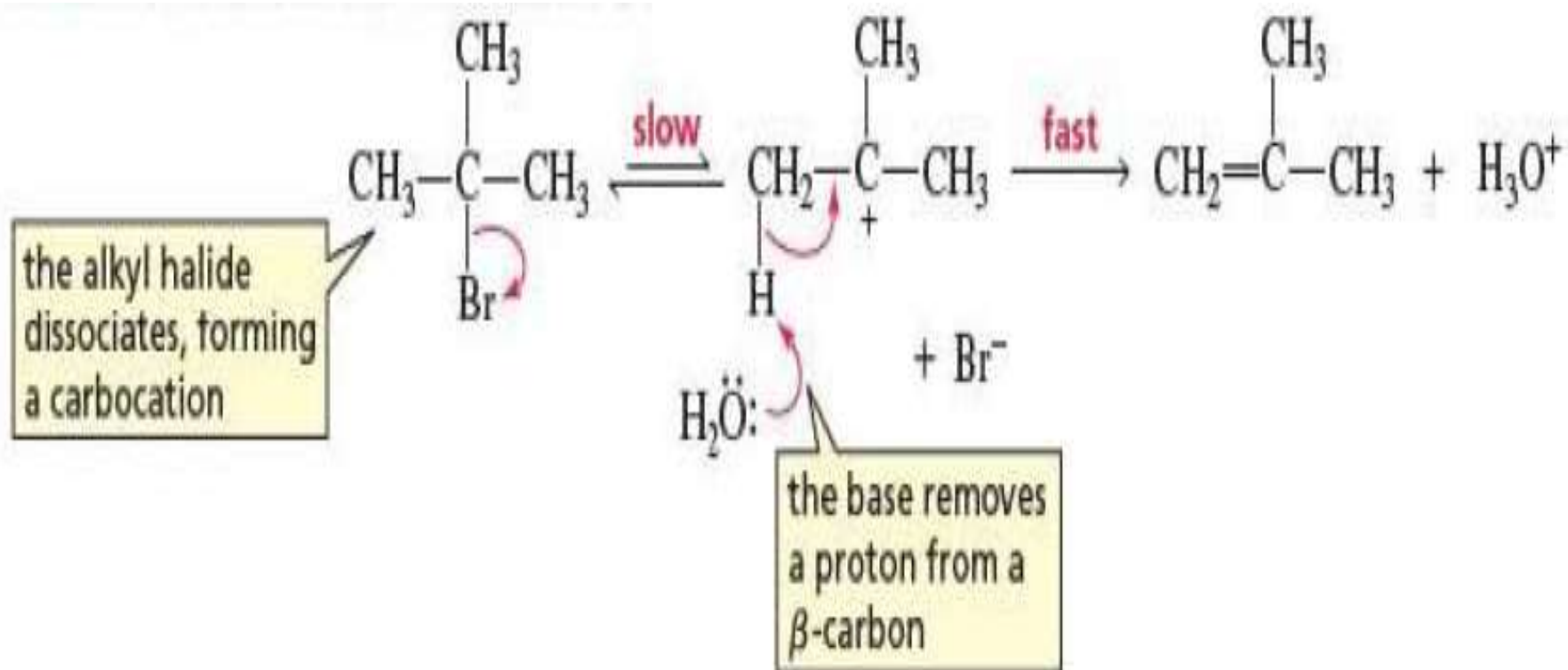
tertiary alkyl halide > secondary alkyl halide > primary alkyl halide

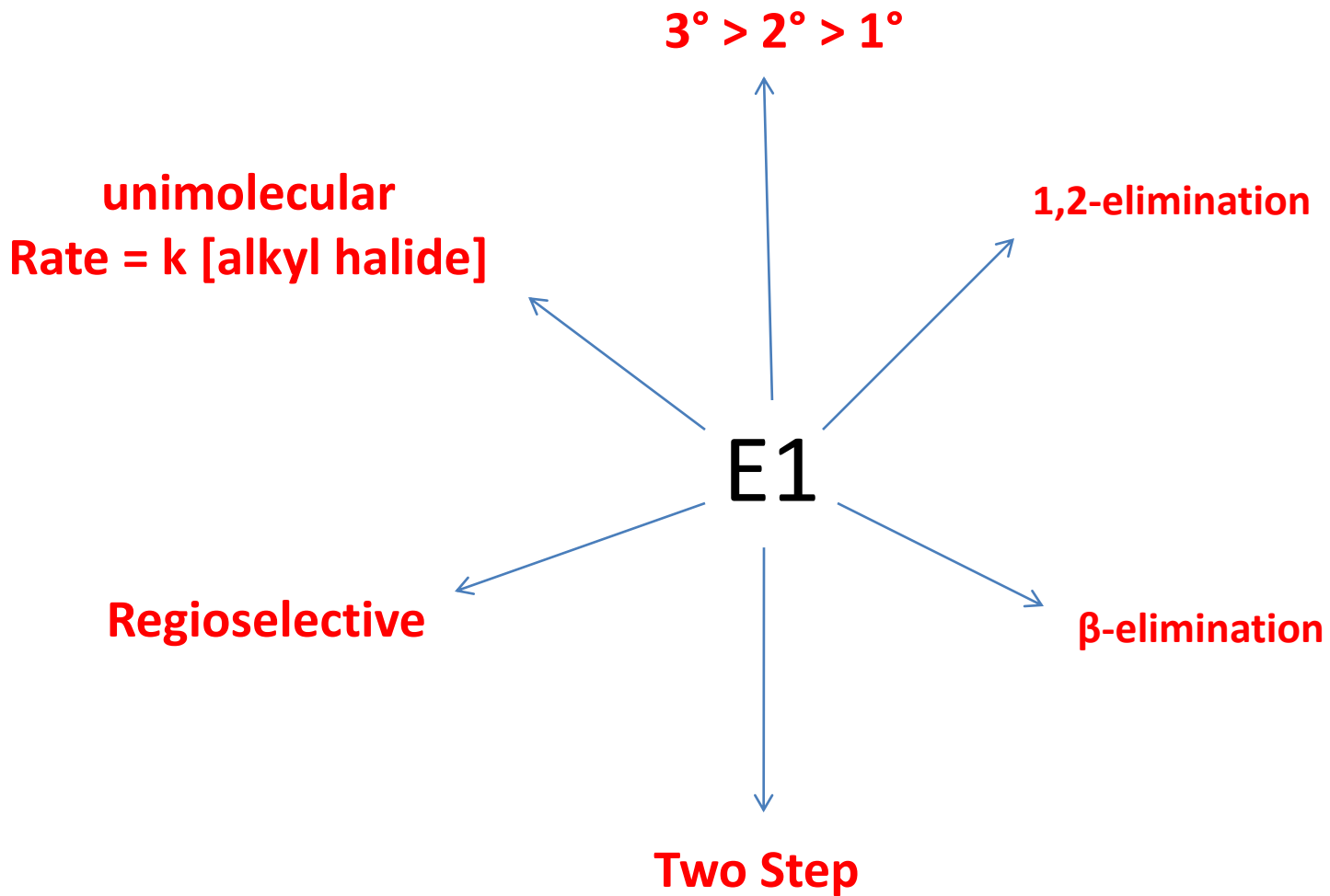


Deviations from Saytzeff rule

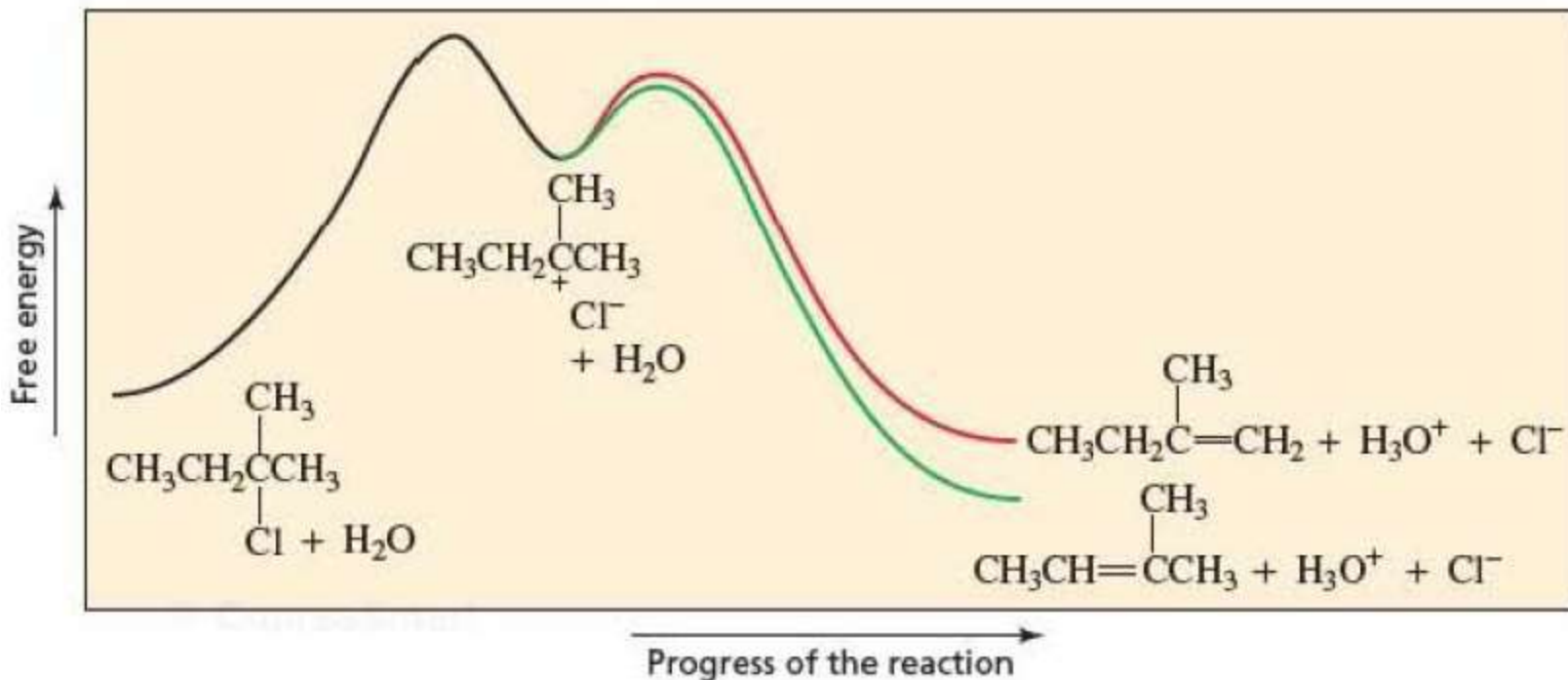
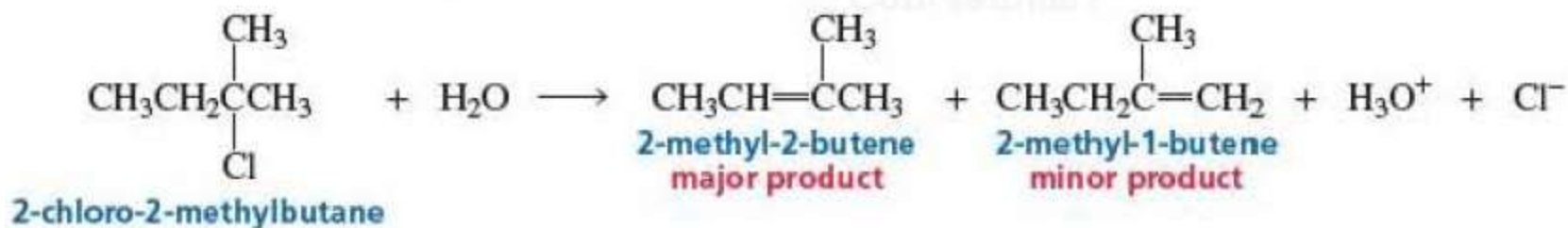
- When fluoride ion is the leaving group,
- When base is sterically hindered,
- When the product of elimination may lead to formation of a conjugated diene, even though the product is a less substituted one.

The E1 reaction

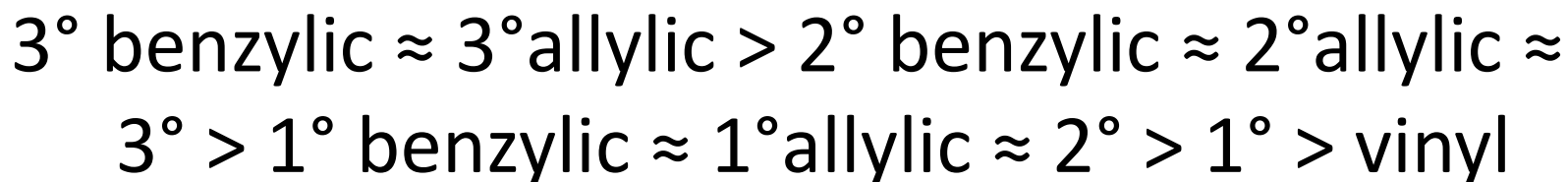




- Similar to E2, more substituted product is formed as major product in accordance with Saytzeff rule.



- Relative reactivity of alkyl halide in E1 depends on stability of carbocation formed in the 1st step. Thus,

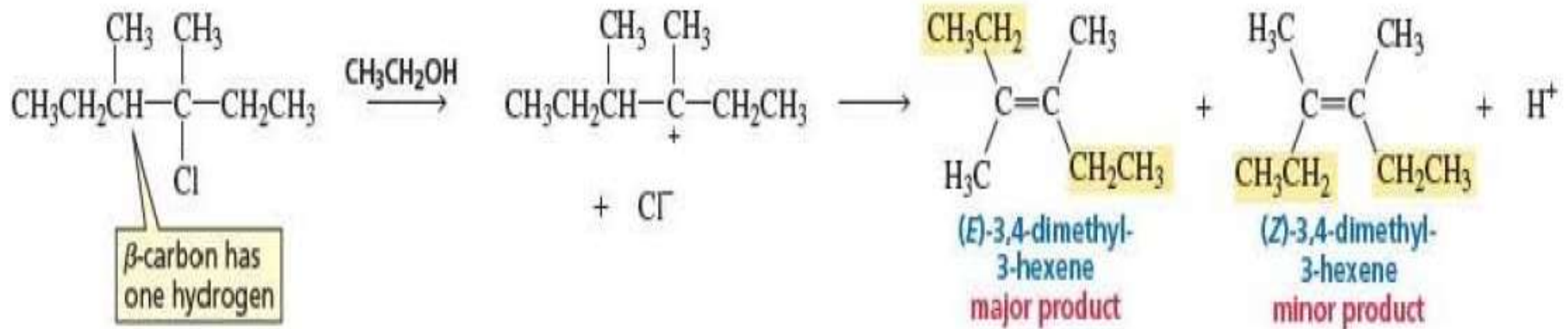


- Since weak bases are better leaving groups,



Factor	E1	E2
Kinetics	Rate = $k[\text{RX}]$	Rate = $k[\text{RX}][\text{Base}]$
No. of steps	Two step	One step
Primary alkyl	Never	Good
Secondary alkyl	Moderate	Moderate
Tertiary alkyl	Excellent	May happen
Leaving group	Less Basic	Less Basic
Basicity of the attacking base	weak	strong

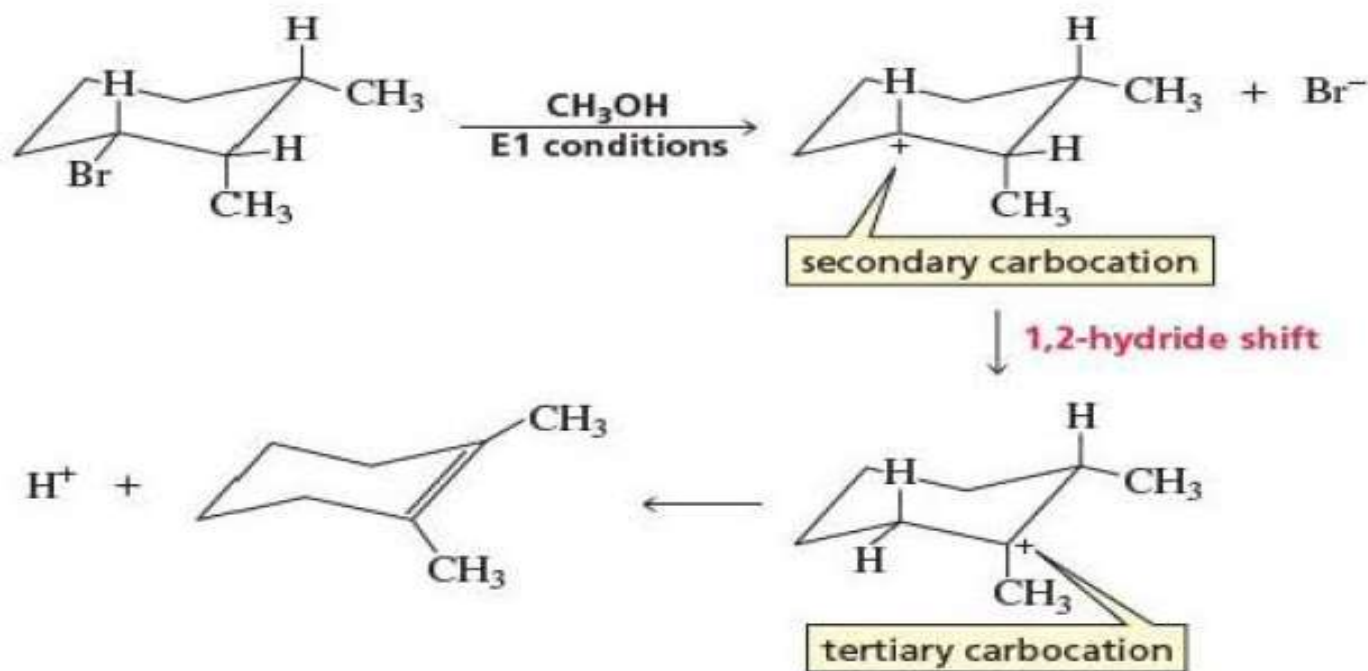
Stereoselectivity of E1



- The carbocation created in the first step is planar. so the electrons from a departing proton can move toward the positively charged carbon from *either side*. Therefore, both *syn* and *anti* elimination can occur.
- The major product is the one with the bulkiest groups on opposite sides of the double bond. because that is the more stable alkene .

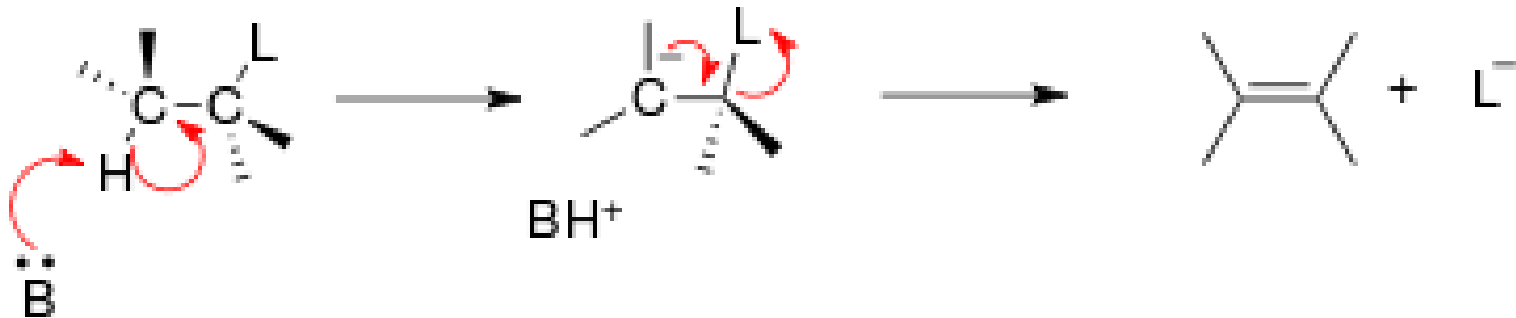
E1 reaction of substituted cyclohexanes

- The two groups that are eliminated do not both have to be in axial positions because the elimination reaction is not concerted.
- Saytzeff rule is followed



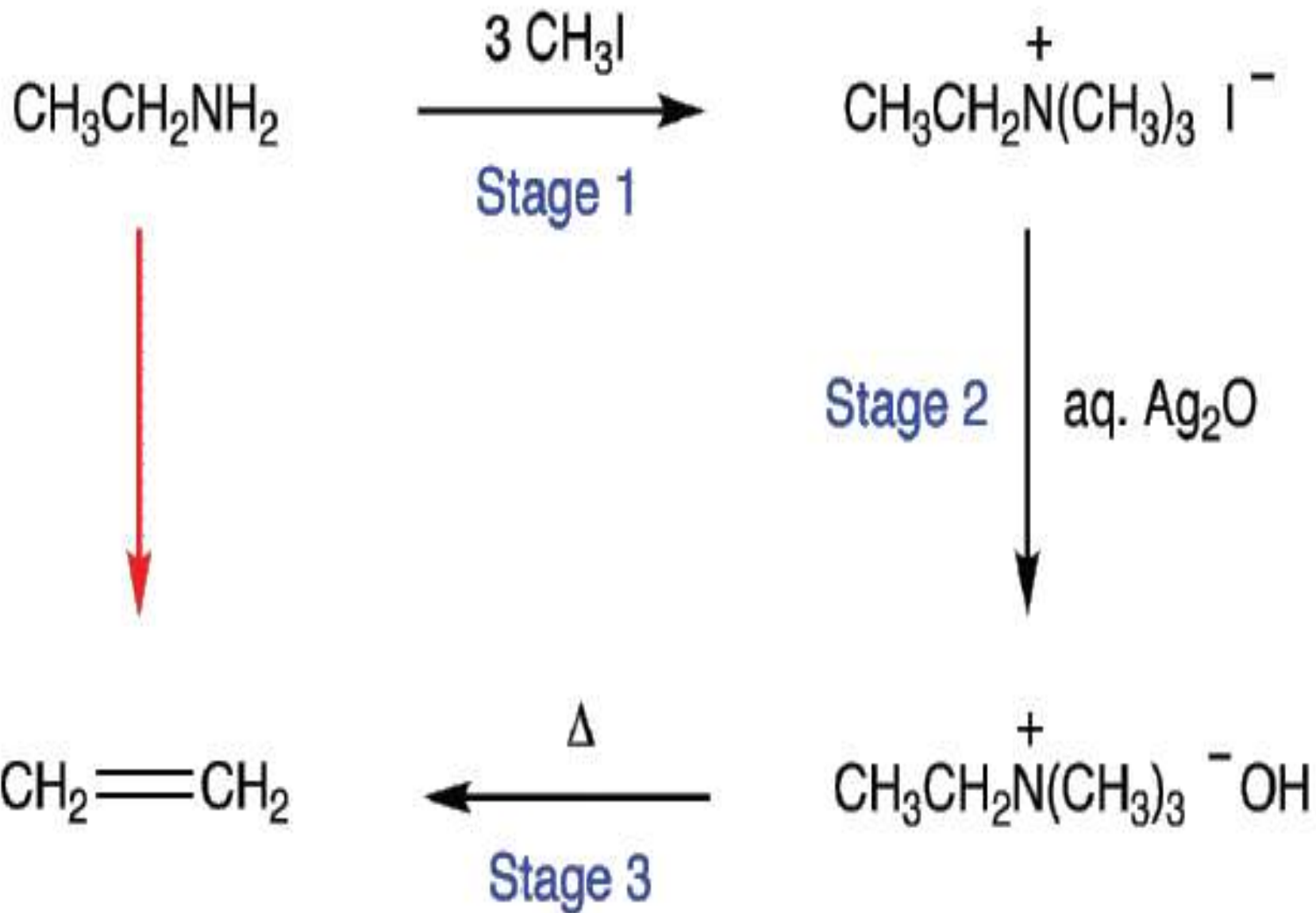
E1cB-elimination reaction

- Elimination **U**nimolecular conjugate **B**ase
- The reaction takes place around a sp^3 - sp^3 carbon to carbon covalent bond with an α -acidic hydrogen atom substituent and a β -leaving group.
- Carbanion intermediate is formed.



Hofmann Elimination

- When a primary amine bearing one or more beta hydrogens is treated with methyl iodide, followed by aqueous silver oxide, followed by heat, the primary amine is converted to an alkene.
- Occurs in 3 steps and the product is usually anti-saytzeff because of the E1CB reaction in the 3rd step.



Substitution	Elimination
Less sterically hindered nucleophile	Sterically hindered nucleophile
Lewis base acts as nucleophile attacking the carbon	Lewis base abstracts proton from β carbon
Weak base	Strong base
Increase in temperature increases rate of reaction but is not favourable	Increase in temperature significantly increases rate of reaction
Lowest practical temperature with considerable reaction rates	Higher temperatures

REFERENCES

- Organic Chemistry by P.Bruice; 6th edition
- Organic Chemistry by Carey; 8th edition
- Wikipedia

A blue glass bottle with a metal spring around its neck, set against a background of chemical structures. The bottle is tilted, and the spring is wrapped around the neck. The background features several chemical structures, including amino acids and other organic molecules, rendered in black lines on a light blue background. The text "Thank You" is centered on the bottle in a white serif font.

Thank You