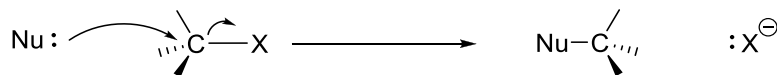


S_N2 – Substitution, Nucleophilic Bimolecular

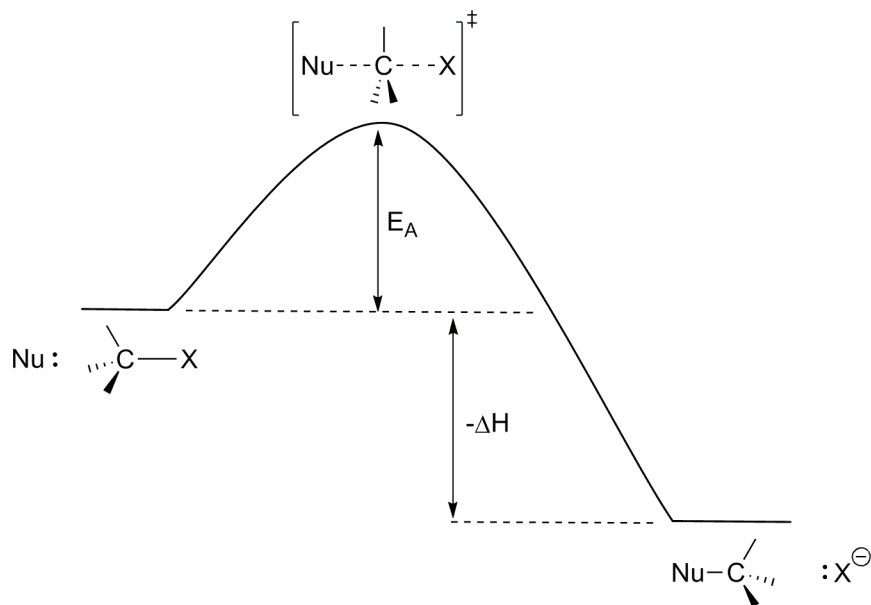
One step, concerted reaction where both nucleophile and substrate participate in this rate limiting step (bimolecular)

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

Mechanism:



Reaction Coordinate:



Conclusion: According to Hammond postulate, \ddagger resembles the starting alkyl halide (or R-LG) and Nu:

- Less crowded carbon lowers E_A : $\text{CH}_3\text{-X} > \text{RCH}_2\text{-X} > \text{R}_2\text{CH-X} > \text{R}_3\text{C-X}$
fastest fast slow never
- Smaller, charged nucleophile forms tighter, stronger bond faster; stronger base closer to \ddagger in E.
- Polar aprotic solvent stabilizes \ddagger and does not reduce nucleophilicity

Stereochemistry: If the carbon being attacked is an *R* or *S* center, it is physically inverted through the reaction. In applying nomenclature, *R* usually becomes *S* and vice-versa. Be sure to check if the priority order has changed!

Summary:

Substrate Type	Conditions for S_N2
$\text{CH}_3\text{-X}$	Only reaction pathway regardless of Nu or solvent
1° C-X	Preferred reaction pathway unless Nu is a strong, bulky base (E2 competes to a small extent)
2° C-X	Use a small, strong Nu however, E2 will compete (Zaitsev & Hoffmann rules apply) * S_N2 will be the only pathway for 2° C-X if I^- , Br^- , HS^- , CN^- or RCOO^- are the nucleophile
3° C-X	NOT OBSERVED
Allyl-X, Benzyl-X	Inspect C center and apply conditions above; i.e. a center can be benzyl and 2° .

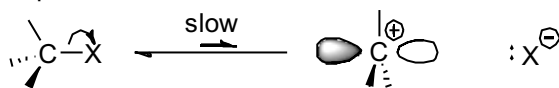
S_N1 – Substitution, Nucleophilic Unimolecular

Two step reaction where only the substrate participates in this rate limiting step (unimolecular)

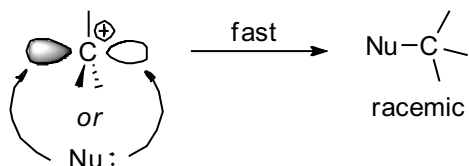
$$\text{Rate} = k[\text{R-X}]$$

Mechanism:

Step 1

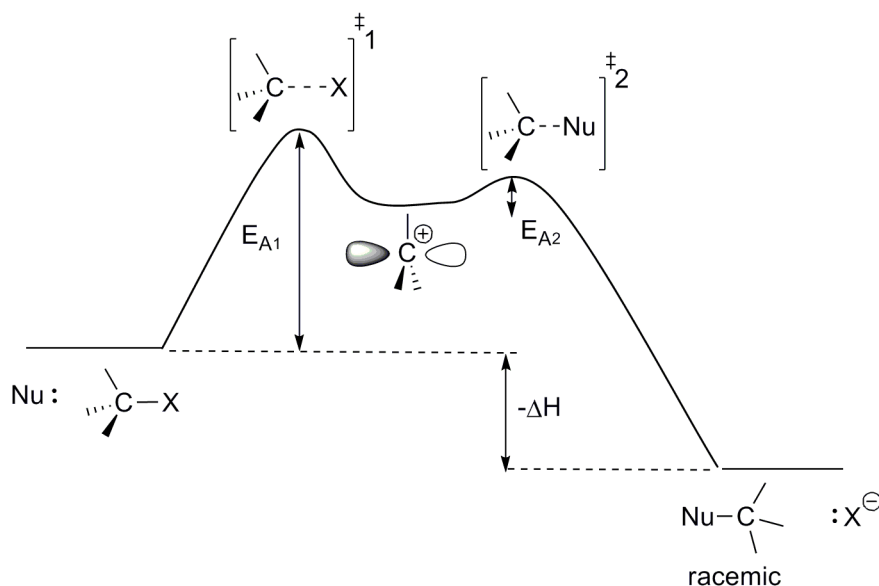


Step 2



For nucleophiles of the type H-Nu there is a third deprotonation step usually to give H-X

Reaction Coordinate:



Conclusion: According to Hammond postulate, ‡₁ resembles the carbocation intermediate

- Stabilization of C⁺ lowers E_A: > R₃C⁺ > R₂CH⁺, allyl C⁺, benzyl C⁺ > RCH₂⁺ > CH₃⁺
fast slow never
- Neutral nucleophile, usually a protic solvent (solvolysis)
- Polar protic solvent stabilizes and separates charged species acting as nucleophile
- S_N1 and E1 are always paired with the same optimum conditions

Stereochemistry: If the carbon being attacked is an R or S center, it is racemized (no longer pure R or S)

Summary:

Substrate Type

Conditions for S_N1

CH₃-X

NEVER OBSERVED

1° C-X

NEVER OBSERVED

2° C-X

Weak nucleophile in polar protic solvent, competes with E1 as T increases

3° C-X

Weak nucleophile in polar protic solvent, competes with E1 as T increases

Allyl-X, Benzyl-X

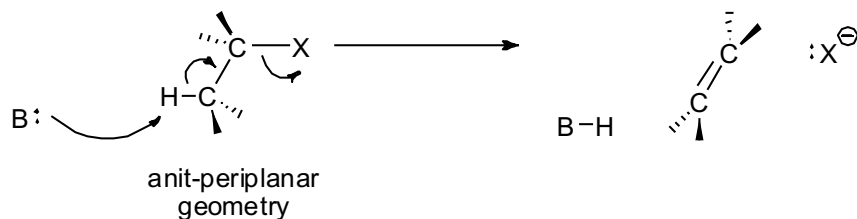
Inspect C center and apply conditions above, allyl and benzyl cations are resonance stabilized!

E2 – Elimination, Bimolecular

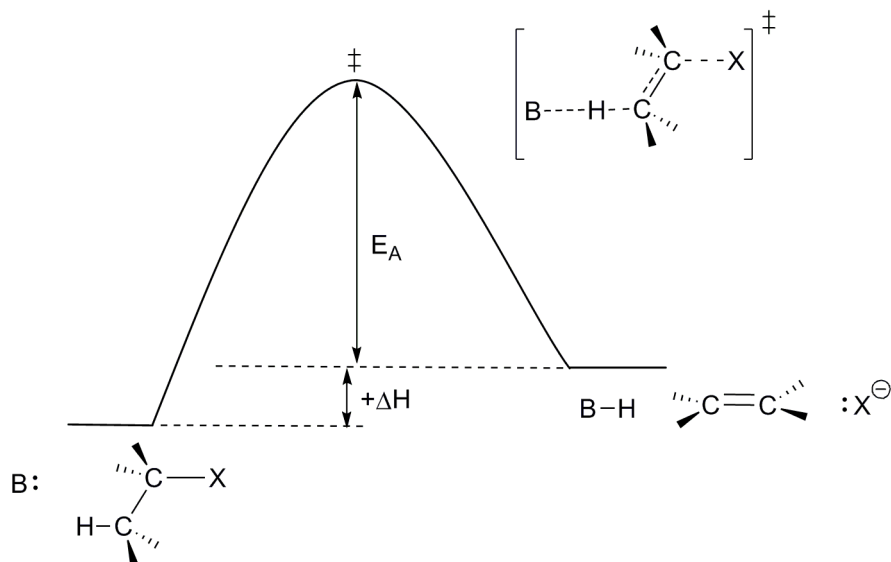
One step, concerted reaction where both base and substrate participate in this rate limiting step (bimolecular)

$$\text{Rate} = k[\text{B:}][\text{R-X}]$$

Mechanism:



Reaction Coordinate:



Conclusion: According to Hammond postulate, ‡ resembles the product alkene thermodynamically

- More substituted carbon lowers energy of C=C $3^\circ > 2^\circ > 1^\circ$
fastest fast slow
- Bigger, bulkier bases do not act as nucleophiles
- Polar aprotic solvent stabilizes ‡ but does not reduce basicity

Stereochemistry:

- Both *cis*- and *trans*-alkenes can be formed;
- When leaving group is on ring, it must be thermodynamically able to be axial through ring-flip, and possess an anti-periplanar geometry with the H being abstracted

All β-hydrogens can be abstracted by a base and produce an alkene product; **major product** depends on base:

- **Zaitsev Rule:** Product has the greatest number of carbon groups on the C=C
- **Hoffmann Rule:** Product has the least number of carbon groups on the C=C

Summary:

Substrate Type

Conditions for E2

CH₃-X

No elimination possible

1° C-X

Slow; use a big, bulky base, otherwise S_N2 will predominate

2° C-X

Use a big, bulky base – Hoffmann E2; small base Zaitsev E2 (S_N2 will compete at low T)

3° C-X

*S_N2 will be the only pathway for 2° C-X if I⁻, Br⁻, HS⁻, ⁻CN or RCOO⁻ are the nucleophile
Preferred reaction pathway with any charged base (⁻OH and ⁻OR most common)

Allyl-X, Benzyl-X

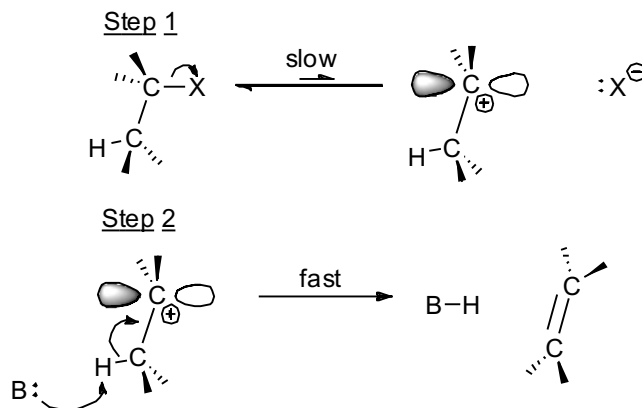
β-hydrogens will be abstracted opposite the existing C=C or -Ph

E1 – Elimination Unimolecular

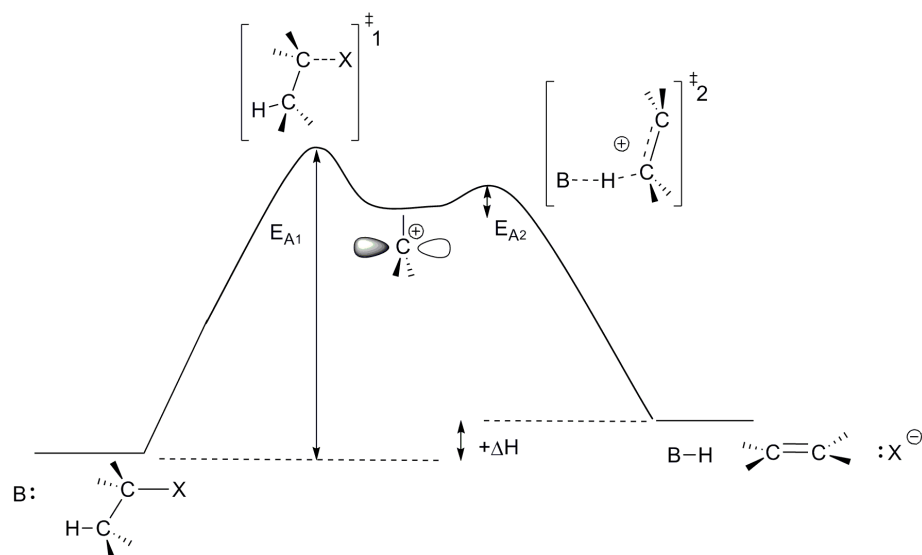
Two step reaction where only the substrate participates in this rate limiting step (unimolecular)

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

Mechanism:



Reaction Coordinate:



Conclusion: According to Hammond postulate, \ddagger_1 resembles the carbocation intermediate as in S_N1

- Stabilization of C^+ lowers E_A : $R_3C^+ > R_2CH^+$, allyl C^+ , benzyl C^+ $> RCH_2^+ > CH_3^+$
 fast slow never
- C^+ is so reactive, even a neutral nucleophile (like a protic solvent) can act as base
- Polar protic solvent stabilizes charged species
- S_N1 and $E1$ are always paired with the same optimum conditions

Stereochemistry: Both *cis*- and *trans*-alkenes formed; ring conformation unimportant due to planar C^+ species

Zaitsev Rule: All β -hydrogens can be abstracted by a base and produce an alkene product, the **major** product has:

- The greatest number of carbon groups on the $C=C$
- The least steric crowding (*trans*- more stable than *cis*-)

Summary:

Substrate Type

Conditions for E1

CH₃-X

NEVER OBSERVED

1° C-X

NEVER OBSERVED

2° C-X

Weak nucleophile in polar protic solvent, competes with S_N1 – heat for more $E1$

3° C-X

Weak nucleophile in polar protic solvent, competes with S_N1 – heat for more $E1$

Allyl-X, Benzyl-X

β -hydrogens will be abstracted opposite the existing $C=C$ or $-Ph$