

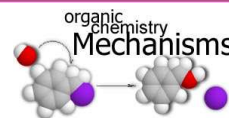
CHEM 344

ORGANIC REACTION MECHANISM

FOR CHEMISTRY' STUDENTS, COLLEGE OF SCIENCE

PRE-REQUISITES COURSE; CHEM 241

CREDIT HOURS; 2 (2+0+0)



Prof. Mohamed El-Newehy

<http://fac.ksu.edu.sa/melnewehy>

Dr. Zainab Almarhoon

<https://fac.ksu.edu.sa/zalmarhoon>

Dr. Monirah A. Al-Shaikh

<https://faculty.ksu.edu.sa/ar/mshaikh>

Chemistry Department, College of Science, King Saud University

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Elimination Reactions

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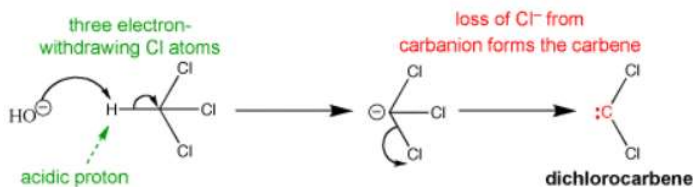
ELIMINATION REACTIONS

TYPES OF ELIMINATION REACTIONS

- **Elimination reactions**, are those reactions in which hydrogen along with a leaving group will be eliminated.
- **Elimination reactions** are used for the generation of double and triple bonds from a saturated compounds.
- **Based on the position of eliminating groups, elimination reactions are classified as:**

- **α -Elimination**

Both groups are lost from the same atom to give a carbene.



Unstable species are formed, which undergo further reactions.

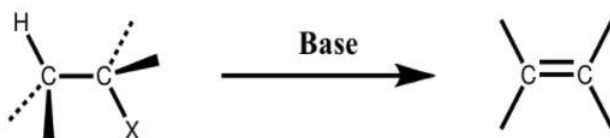
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ELIMINATION REACTIONS

TYPES OF ELIMINATION REACTIONS

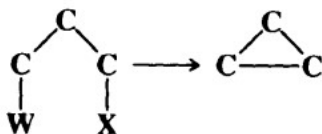
- **β -Elimination**

Both groups are lost from the two adjacent carbon atoms to give alkene.



- **γ -Elimination**

A three-membered ring is formed

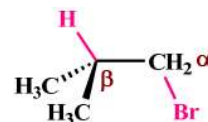


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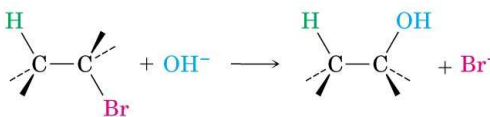
ELIMINATION REACTIONS

B-ELIMINATIONS

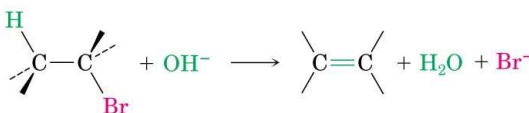
- β -elimination proceeds through two mechanisms;
 - E2 biomolecular elimination reactions
 - E1 unimolecular elimination reactions
- E2 & E1 mechanism differ in the *timing of bond cleavage and bond formation*, analogous to the S_N^2 & S_N^1 mechanisms
- E2 & S_N^2 reactions have some features in common, as do E1 & S_N^1 reactions.



Substitution



Elimination



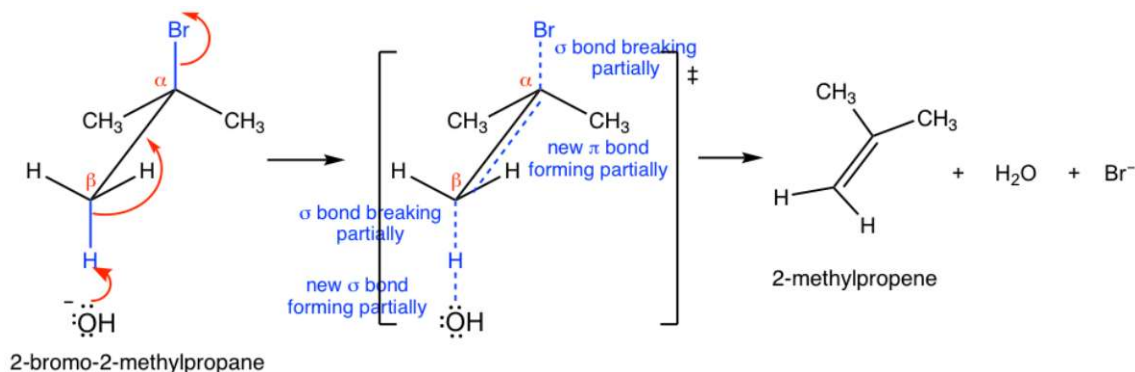
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E2 REACTION

REACTION MECHANISM

- E2 reaction is a **single step** elimination, with a **single transition state**



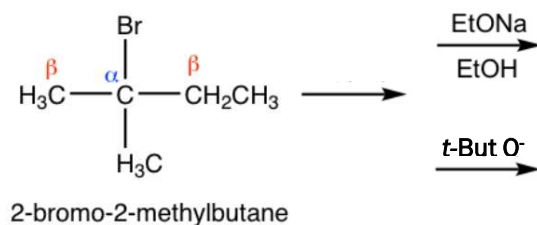
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E2 REACTION

REGIOSELECTIVITY OF E2 REACTION:

For alkyl halides, if there are *different β -carbons* in the substrate, then the elimination reaction may yield *more than one products*.

- **Example:** Dehydrohalogenation of 2-bromo-2-methylbutane can produce two products, *2-methyl-2-butene* and *2-methyl-1-butene*



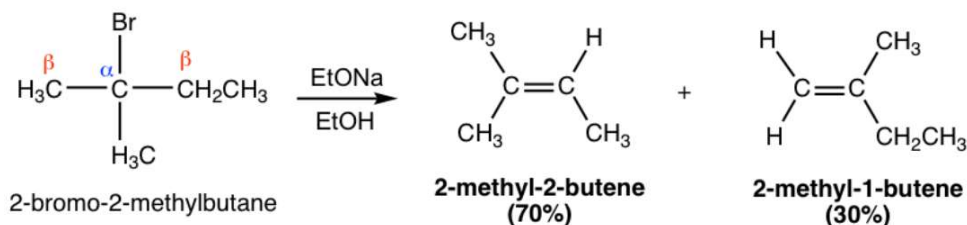
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E2 REACTION

REGIOSELECTIVITY OF E2 REACTION:

Zaitsev's Rule

When *small base, such as OH^- , CH_3O^- , EtO^-* , is applied, the elimination products can be predicted by *Zaitsev's rule*, i.e. the major product is the more stable product - the one with the *more substituted double bond*.



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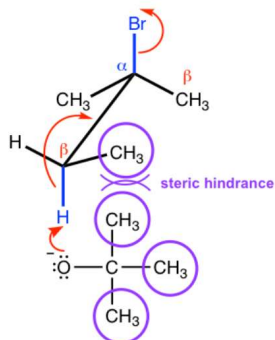
E2 REACTION

REGIOSELECTIVITY OF E2 REACTION:

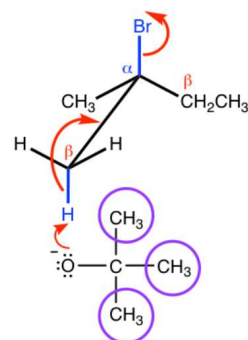
Hofmann's Rule

If a *bulky base such as t-BuOK*, is applied in the elimination, the reaction favors the formation of *less substituted double bond*.

This is mainly because of *Steric Hindrance*.



pathway (a): bulky base $t\text{-BuO}^-$ is more hindered



pathway (b): bulky base $t\text{-BuO}^-$ is less hindered

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E2 REACTION

REACTION KINETICS

- The E2 reaction is a *concerted process* (one step reaction), with a *bimolecular rate-determining step*.

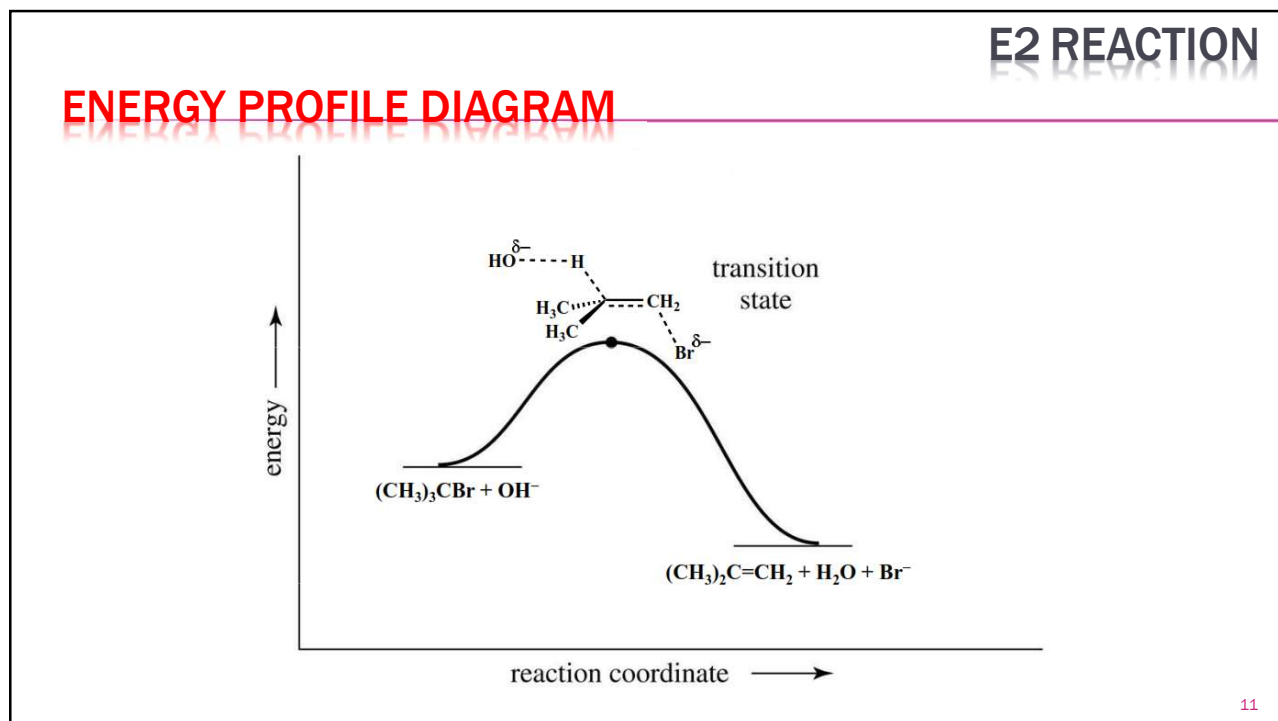
"*Concerted*" means that the formation of a double bond, and departure of the leaving group (X^- and H^+) all occur in one step.

- The reaction rate is *second order*, because it's influenced by both the *alkyl halide* and *the base* (bimolecular).

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

- Reaction goes faster with *stronger base* and *better leaving group*.

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E2 REACTION

FACTORS AFFECTING THE RATE OF E2 REACTION

- E2 & S_N² reactions have some features in common in how the identity of the *base*, the *leaving group* and the *solvent affect the rate*.
- The rate of the E2 reaction increases with
 - the *strong, negatively charged bases* like ⁻OH and ⁻OR.
 - the *Polar aprotic solvents*
 - the *better the leaving group*.
- Rate of reaction follows the order,

most reactive → RI > RBr > RCl > RF ← least reactive

- Alkyl iodides are the most reactive
- alkyl fluorides the least reactive

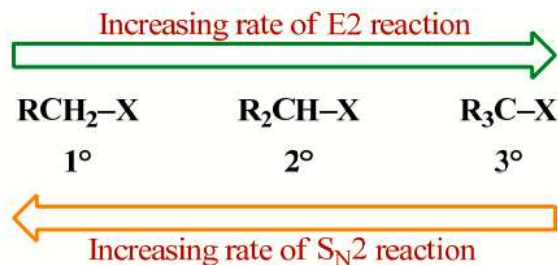
} because weaker bases are better leaving groups

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E2 REACTION

FACTORS AFFECTING THE RATE OF E2 REACTION

- The S_N^2 and E2 mechanisms differ in how the **R group** affects the reaction rate.
As the number of R groups on the carbon with the leaving group increases, the rate of the E2 reaction increases.



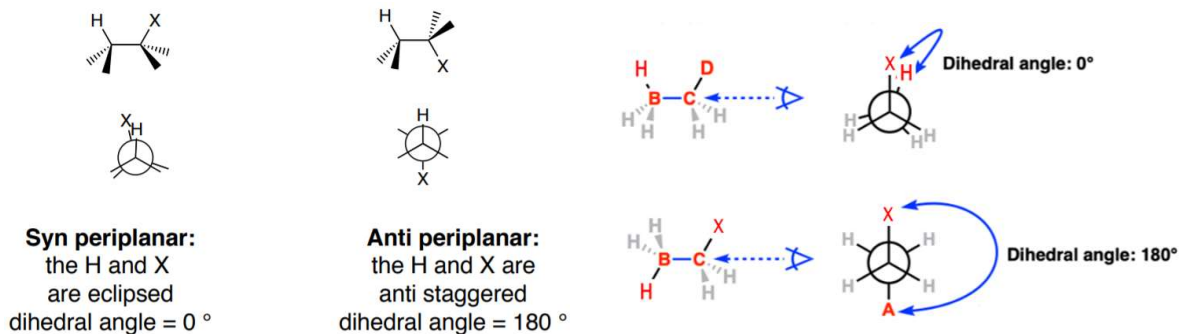
- In the transition state;
 - The double bond is partially formed.
Thus, the transition state for a more substituted alkene is lower in energy, reducing the activation energy for the reaction and making the reaction faster.

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E2 REACTION

STEREOCHEMISTRY

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



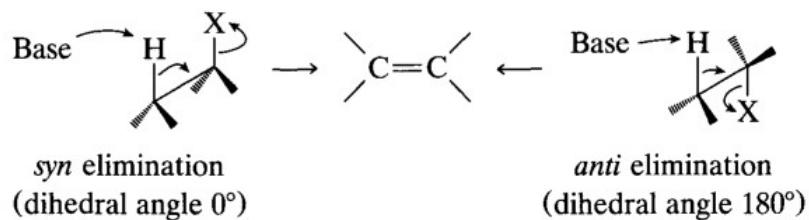
- Staggered conformation has a lower potential energy
- Whereas eclipsed conformation has the maximum potential energy.

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E2 REACTION

STEREOCHEMISTRY

- The term **anti elimination** means that the proton and leaving group depart from opposite sides of the bond, which then becomes a double bond.
- The term **syn elimination** means that they depart from the same side.



- **E2 reactions** are highly stereospecific and **anti elimination** is preferred over syn elimination
 - In **anti E substrate** has **staggered** conformation while that of in **syn** is **eclipsed**.

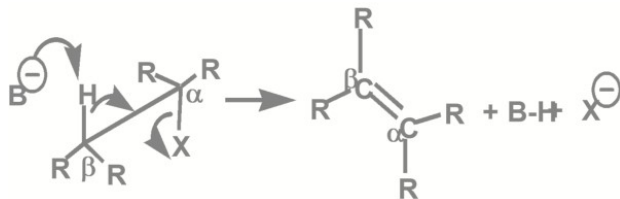
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E2 REACTION

STEREOCHEMISTRY

Anti Elimination in E2

- **Antiperiplanar**; the H and X groups must be anti to each other and be in the same plane with each other and the carbon atoms to which they are attached.



- The **anti-position** allows the transition state of the reaction is in the more stable **staggered conformation** (helps to lower down the energy level of the transition state and speed up the reaction).

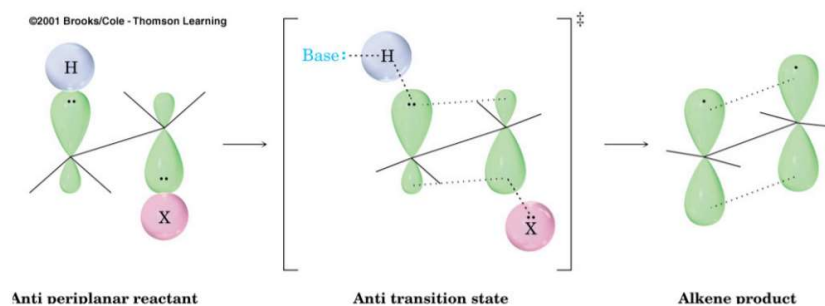
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E2 REACTION

STEREOCHEMISTRY

Anti Elimination in E2

- **Antiperiplanar** allows orbital overlap and minimizes steric interactions



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

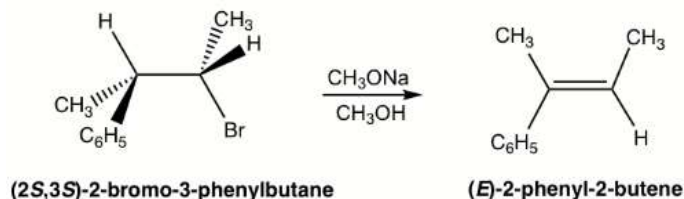
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E2 REACTION

STEREOCHEMISTRY

Anti Elimination in E2

- **E2 reactions** are stereoselective, resulting in the formation of *trans-double bonds* preferably.
- **Example**; the elimination of (2*S*,3*S*)-2-bromo-3-phenylbutane produces the *E* isomer specifically, not the *Z* isomer at all.



This is because when H is in anti-position to the leaving group Br, the whole compound is in staggered conformation, and the other groups retain their relative position in elimination that leads to the *E* isomer.

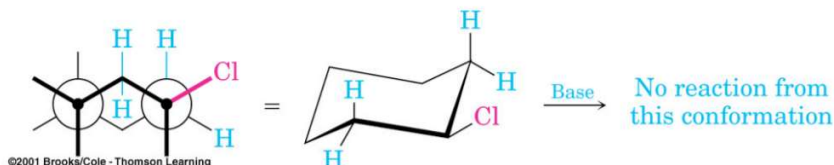
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E2 REACTION

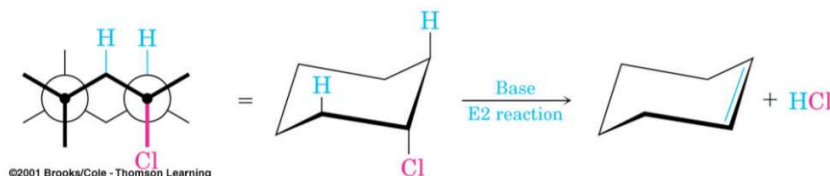
STEREOCHEMISTRY

E2 Elimination with Halocyclohexane Reactants

Equatorial chlorine: H and Cl are not anti periplanar



Axial chlorine: H and Cl are anti periplanar



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E2 REACTION

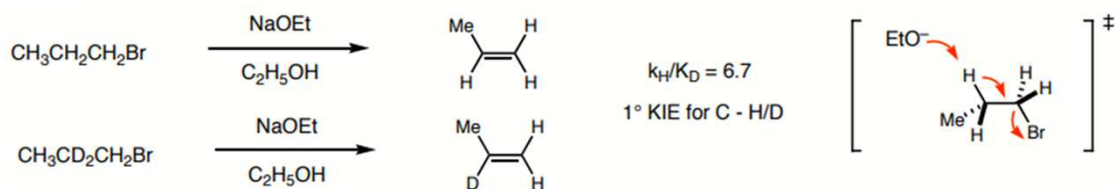
KINETIC ISOTOPE EFFECTS (KIEs)

- **A kinetic isotope effect (KIEs);**
 - is a mechanistic phenomenon wherein isotopically substituted molecules react at different rates.
 - can provide information that traditional kinetics can not, about broken/formed and change in hybridization that occur during the rate-determining step of a reaction.
- **There are several different classifications for KIE's**
 - **Primary isotope effect:** Occurs when labelled bond is made or broken in the rate-determining step
 - **Secondary isotope effect:** Occurs when labelled bond is not made or broken in the rate-determining step
- **Normal isotope effect:** Occurs when K_H/K_D is greater than 1
- **Inverse isotope effect:** Occurs when K_H/K_D is less than 1

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E2 REACTION

KINETIC ISOTOPE EFFECTS (KIEs)

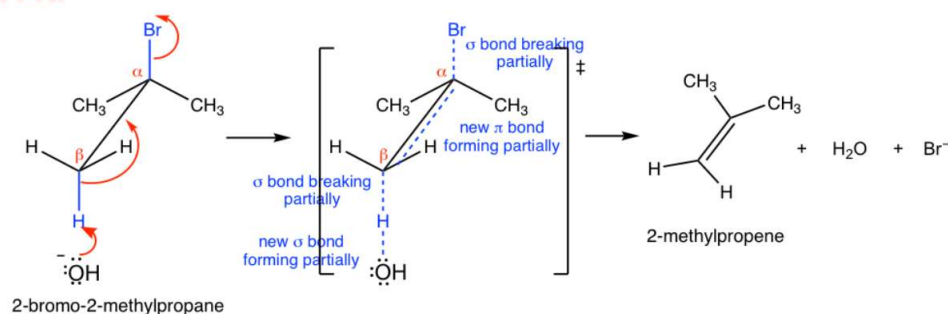


- This **KIE is consistent with an E2 elimination** in which the C - H/D bond is broken in the rate determining step.
- **Rate is reduced in E2 reaction**
 - Heavier isotope bond is slower to break
 - Shows C-H bond is broken in or before rate-limiting step

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E2 REACTION

SUMMARY



- **Reaction is:**
 - Stereospecific (Anti-periplanar geometry preferred, Syn-periplanar geometry possible)
 - Concerted - all bonds form and break at the same time
 - Bimolecular - rate depends on concentration of both base and substrate
 - Favored by strong bases

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E1 REACTION

REACTION

- When *t*-butyl bromide reacts with ethanol, small amount of elimination products obtained via E1 mechanism.



$$\text{Reaction Rate} = k \times [(\text{CH}_3)_3\text{Br}]$$

first-order reaction

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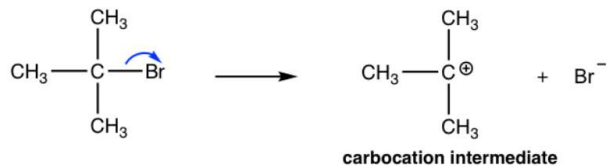
E1 REACTION

REACTION MECHANISM

- The overall elimination involves two steps:

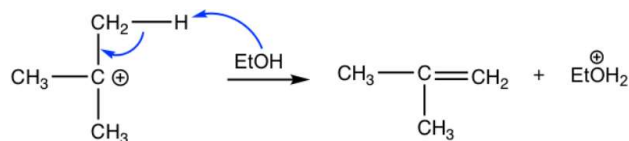
Step 1: Cleavage of C-Br bond **slowly** to form the carbocation intermediate.

Spontaneous dissociation of the tertiary alkyl bromide yields carbocation intermediate in a slow, rate-determining step



Step 2: base (Et-OH) removes H from β -carbon, and double bond produced.

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.

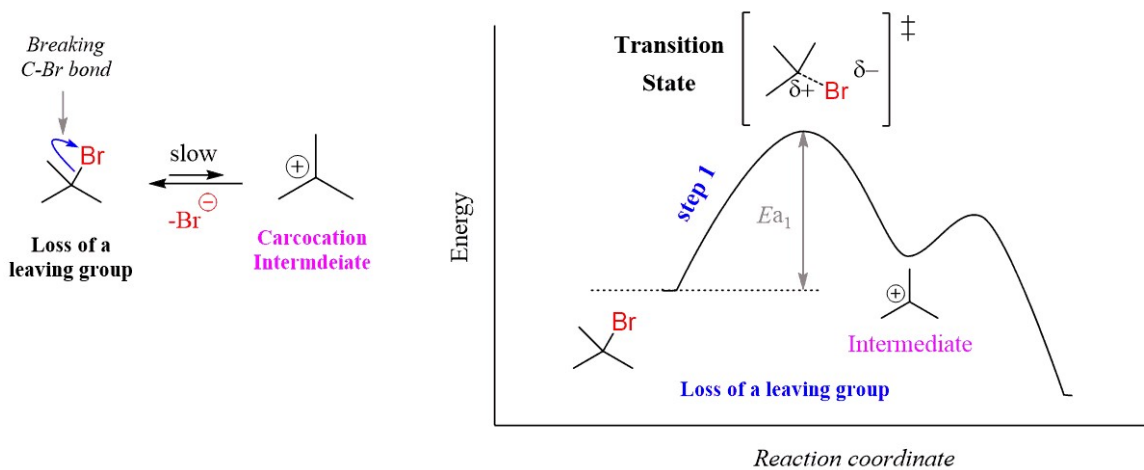


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E1 REACTION

ENERGY PROFILE DIAGRAM

The energy diagram showing the first step of the E1 mechanism

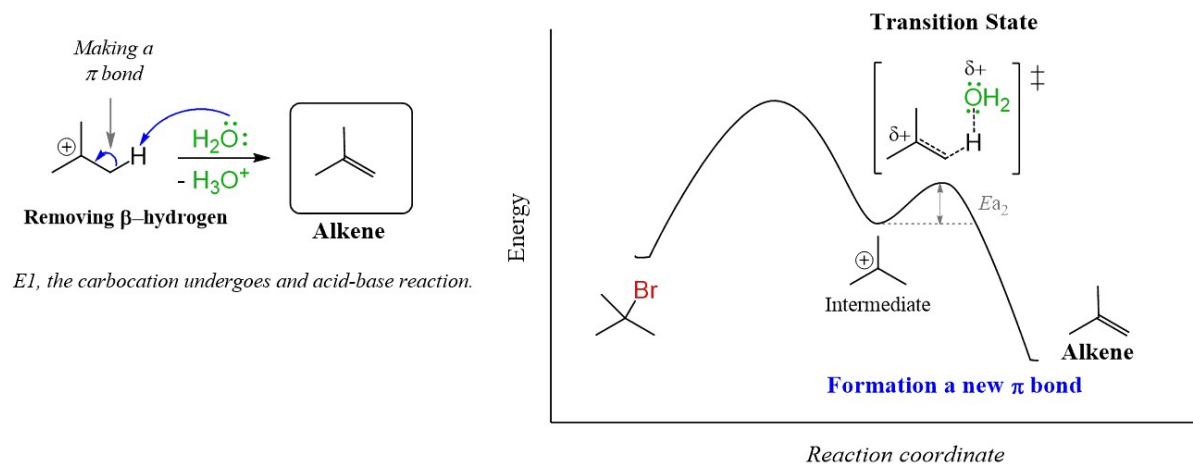


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E1 REACTION

ENERGY PROFILE DIAGRAM

The energy diagram showing the formation of the π bond



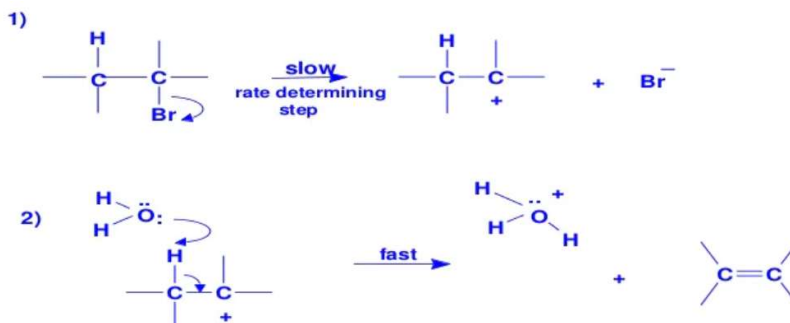
E1, the carbocation undergoes an acid-base reaction.

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E1 REACTION

REACTION KINETICS

- E1 reactions follow first order (unimolecular) kinetics.
- Rate = $k [R-X]$
- The solvent helps to stabilize the carbocation, but it does not appear in the rate law



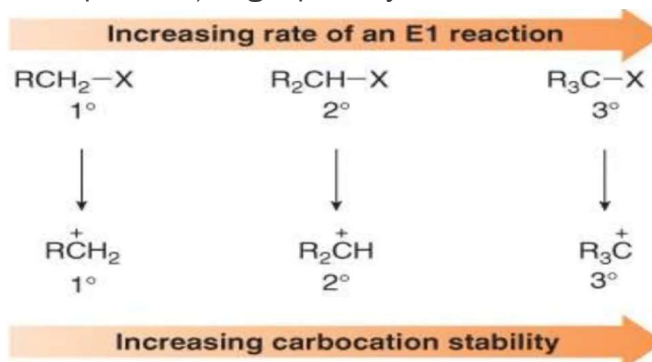
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E1 REACTION

FACTORS AFFECTING THE RATE OF E1 REACTION

1) Substrate Effect

- The order of the reactivity of the alkyl groups is: Tertiary > Secondary > Primary
- This is because the rate-determining step is the formation of carbocation and the stability of these ions increases; Tertiary > Secondary > Primary
- It is hard (but not impossible) to get primary carbocations are not stable.



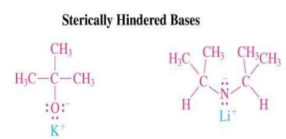
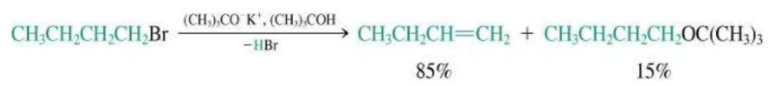
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E1 REACTION

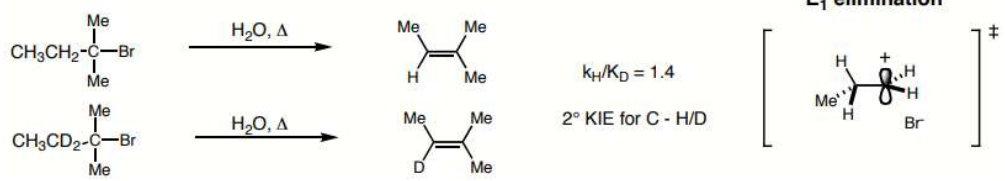
FACTORS AFFECTING THE RATE OF E1 REACTION

2) Base Effect

- Bulky bases favor elimination



3) Kinetic Isotope Effects (KIEs)



- This KIE is consistent with an E1 solvolysis in which the C - H/D bond is not broken in the rate-determining step.

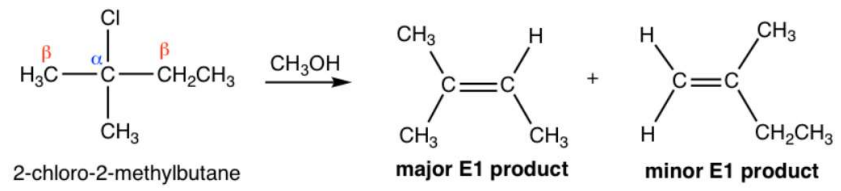
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E1 REACTION

FACTORS AFFECTING THE RATE OF E1 REACTION

4) Orientation of Elimination: Zaitsev's Rule

- E1 reactions follow Zaitsev's rule
- The major product should be the product that is the most highly substituted.

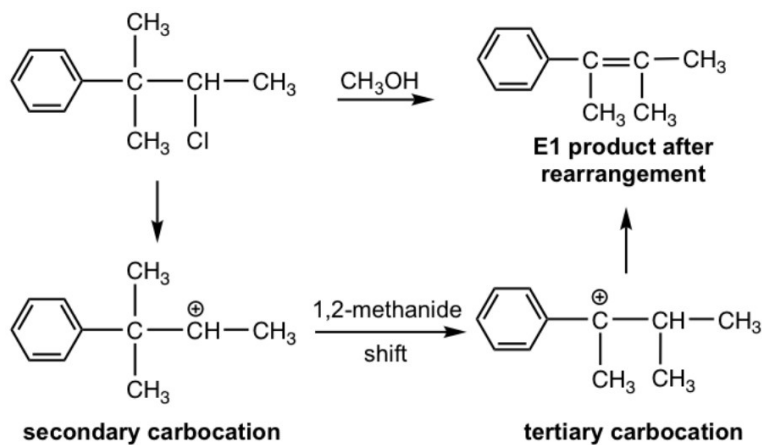


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E1 REACTION

REARRANGEMENTS

- Since **E1 reaction** involves a carbocation intermediate, the carbocation rearrangement might occur if such rearrangement leads to a more stable carbocation.

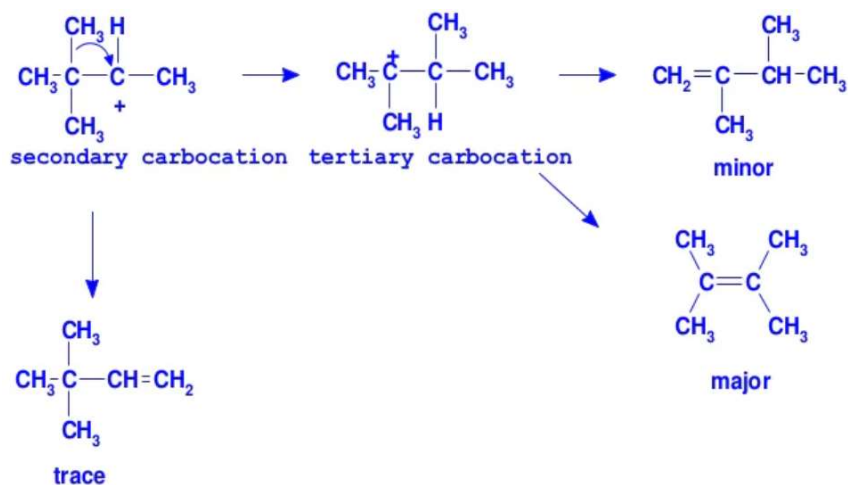


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E1 REACTION

REARRANGEMENTS

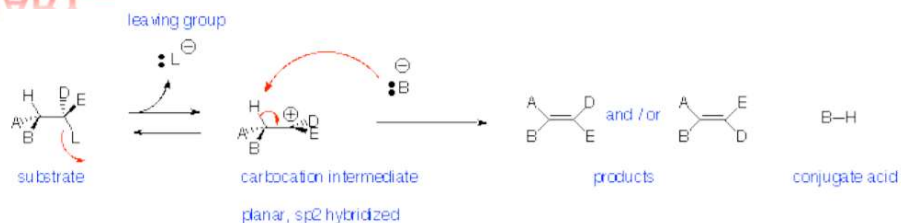
- Alkyl groups and hydrogen can migrate in rearrangement reactions to give the more stable intermediate carbocations.



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E1 REACTION

SUMMARY



○ Reaction is:

- Non-stereospecific- follows Zaitsev (Saytseff) Rule
- Non-concerted - has carbocation intermediate - favoured for tertiary leaving groups
- Unimolecular - rate depends on concentration of only the substrate
- Does NOT occur with primary alkyl halides (leaving groups)
- Strong acid can promote loss of OH as H₂O or OR as HOR if tertiary or
- conjugated carbocation can be formed

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COMPARISON BETWEEN S_N¹ AND S_N² REACTIONS

	E1	E2
Rate law	Rate = k[substrate]	Rate = k[substrate][base]
Mechanism	Multiple steps with carbocation intermediate	One-step, concerted
Product	More substituted, more stable alkenes	Small base: more substituted alkenes (Zaitsev's rule) Bulky base: less substituted alkenes (Hofmann rule)
Substrate	Tertiary (3°) > Secondary (2°) > Primary (1°) (no E1)	Primary (1°) > Secondary (2°) > Tertiary (3°)
Base	Weak base, (H ₂ O, ROH), solvolysis	Strong base (OH ⁻ , RO ⁻ , or NH ₂ ⁻)
Solvent	Polar protic solvent; H ₂ O, ROH	Polar aprotic solvent
Leaving group	Good leaving group	Good leaving group

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COMPARISON BETWEEN S_N^1 AND S_N^2 REACTIONS

	S_N^1	S_N^2
Rate law	Rate = $k[\text{substrate}]$	Rate = $k[\text{substrate}][\text{base}]$
Mechanism	Multiple steps with carbocation intermediate	One-step, concerted
Stereochemistry	Racemic mixture	Walden Inversion
Substrate	Tertiary (3°) > Secondary (2°) > Primary (1°)	Primary (1°) > Secondary (2°) > Tertiary (3°)
Nucleophile	Weak nucleophile, (H_2O , ROH) solvolysis	Strong nucleophile (OH^- , RO^- , or NH_2^-)
Solvent	Polar protic solvent; H_2O , ROH	Polar aprotic solvent
Leaving group	Good leaving group	Good leaving group

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SUBSTITUTION or ELIMINATION

FACTORS TO CONSIDER

- How basic is the nucleophile?
- Steric Hindrance at reacting carbon
- Steric Hindrance at nucleophile

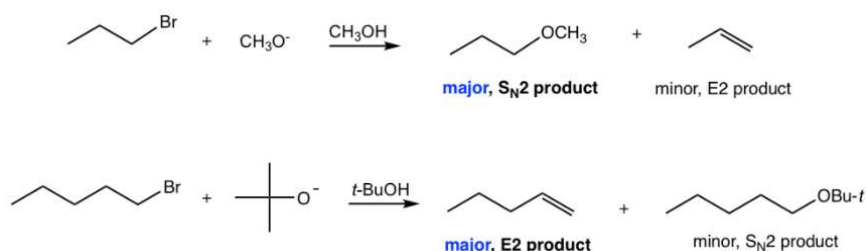
Type of haloalkane	Type of nucleophile (base)			
	Poor nucleophile (e.g., H_2O)	Weak base/good nucleophile (e.g., I^-)	Strong base/unhindered nucleophile (e.g., CH_3O^-)	Strong base/hindered nucleophile (e.g., $(CH_3)_3CO^-$)
Methyl	No Reaction	S_N^2	S_N^2	S_N^2
Primary				
Unhindered	No Reaction	S_N^2	S_N^2	E2
Branched	No Reaction	S_N^2	E2	E2
Secondary	Slow S_N^1 , E1	S_N^2	E2	E2
Tertiary	S_N^1 , E1	S_N^1 , E1	E2	E2

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COMPARISON and COMPETITION BETWEEN S_N^1 , S_N^2 , E1 & E2

STRUCTURAL NATURE OF A SUBSTRATE (PRIMARY, SECONDARY OR TERTIARY)

- **Methyl substrate** only go with S_N^2 reaction,
- **Primary (1°) substrates**
 - cannot go with any unimolecular reaction, (e.g. no S_N^1 /E1),
because primary carbocations are too unstable to be formed.
 - S_N^2 is the predominant pathway when **good nucleophile** is used; Cl^- , Br^- , I^- , RS^- , N_3^- , CN^- , RCO_2^- .
 - **E2** becomes the major reaction when **big bulky base/nucleophile** is used; $t\text{-BuO}^-$ and LDA

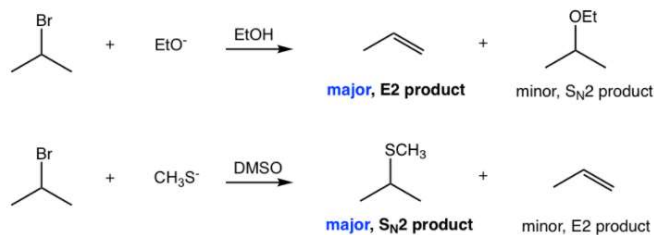


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COMPARISON and COMPETITION BETWEEN S_N^1 , S_N^2 , E1 & E2

STRUCTURAL NATURE OF A SUBSTRATE (PRIMARY, SECONDARY OR TERTIARY)

- **Secondary (2°) substrates**
 - It is most complicated or challenging because all the pathways are possible.
 - **E2**: favored by a **strong base**; OH^- , RO^- (R: small size alkyl group), NH_2^-
 - S_N^2 : favored by a **good nucleophile (relatively weaker base)**; Cl^- , Br^- , I^- , RS^- , N_3^- , CN^- , RCO_2^- .
 - S_N^1 /E1: It is hard to separate S_N^1 and E1 completely apart, because they both go through **carbocation intermediates**, and are favored by **poor nucleophile/weak base**; H_2O or ROH (solvolysis).
 S_N^1 and E1 usually occur together for secondary substrates, and increasing the reaction temperature favors E1 over S_N^1 .



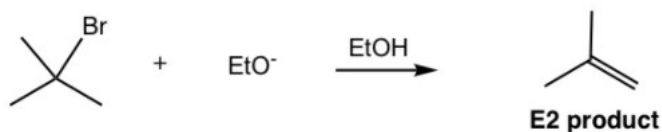
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COMPARISON and COMPETITION BETWEEN S_N^1 , S_N^2 , E1 & E2

STRUCTURAL NATURE OF A SUBSTRATE (PRIMARY, SECONDARY OR TERTIARY)

○ Tertiary (3°) substrates

- do not go with S_N^2 reactions because of **steric hindrance**.
- **E2** reaction is the choice when **strong base** applied; ^-OH , RO^- (R: small size alkyl group), NH_2^-
- $S_N^1/E1$ pathway with neutral condition (**poor nucleophile/weak base**); H_2O or ROH (solvolysis).
E1 always combine together with S_N^1 , and it is almost impossible to avoid the substitution product.



NOTES:

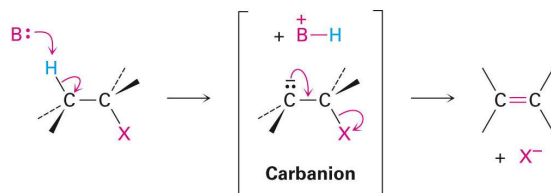
- The relative stronger bases have the stronger tendency to act as base.
- The relative weaker base, with small size and good polarizability, have the better tendency to act as nucleophile.
- Bulky bases, such as $t-BuO^-$ and LDA, always favor E2 and generate elimination products that follow Hofmann rule, because they are too big to do back-side attack in S_N^2 .

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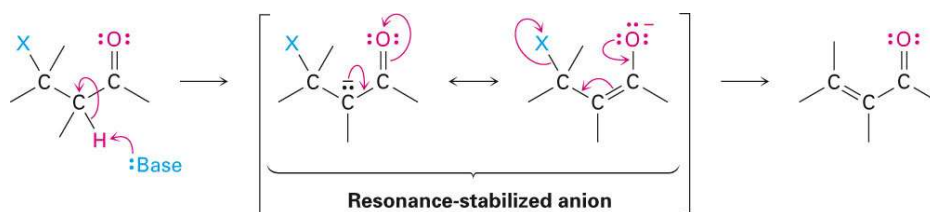
E1 cB REACTION

REACTION MECHANISM

- **E1 cB Reaction**; Elimination Unimolecular conjugate Base.
- **E1 cB Reaction**: is a type of elimination reaction which occurs under basic conditions, where C-H bond breaks first, giving a carbanion intermediate that loses X^- to form the alkene.



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E1 cB REACTION

REACTION MECHANISM

o E1 cB Reaction;

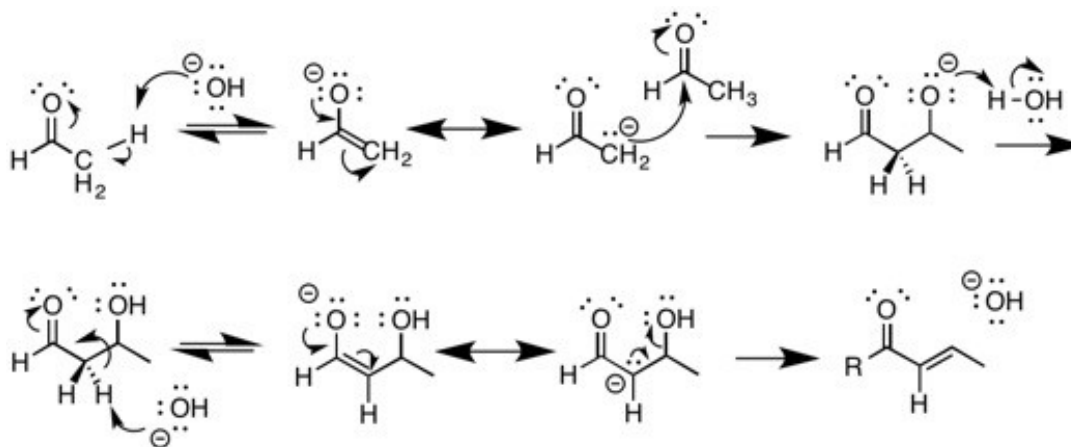
- is 1,2-elimination occurring via E1 cB mechanism.
- takes place through a carbanion intermediate.
- is preferred, with strong base and very poor leaving group is (F⁻ and ⁻OH groups).
- HO-C-C=O fragment often involved.
- is not common reaction.
- has a complex rate law, meaning that the rate-determining step is the second step.

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(E1 cB REACTION)

EXAMPLE:

Aldol Reaction and E1cB Mechanism



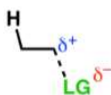
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COMPARING THE E1, E2 & E1cB MECHANISMS

E1

Two steps

- 1) C-LG breaks
- 2) C-H breaks
C-C (pi) forms



Carbocation intermediate

Carbocation stabilized by electron **donating** groups

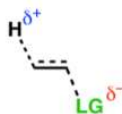
Assisted by **good** leaving groups

No strict requirement on stereochemistry of C-H and C-LG

E2

One step

- C-H breaks, C-C (pi) forms
C-LG breaks, all at same time



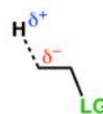
No intermediate (concerted)

C-H and C-LG are **anti**

E1cB

Two steps

- 1) C-H breaks
- 2) C-LG breaks
C-C (pi) forms



Carbanion intermediate

Carbanion stabilized by electron **withdrawing** groups

Assisted by **poor** leaving groups

No strict requirement on stereochemistry of C-H and C-LG