

CHEM F111: General Chemistry Semester II: AY 2017-18

Lecture 39 (27-04-2018)

Summary of Lecture 38



Nucleophilic Aromatic Substitution (S_NAr)

Nucleophilic Substitution Reactions

X = CI, Br, I, OTs etc.

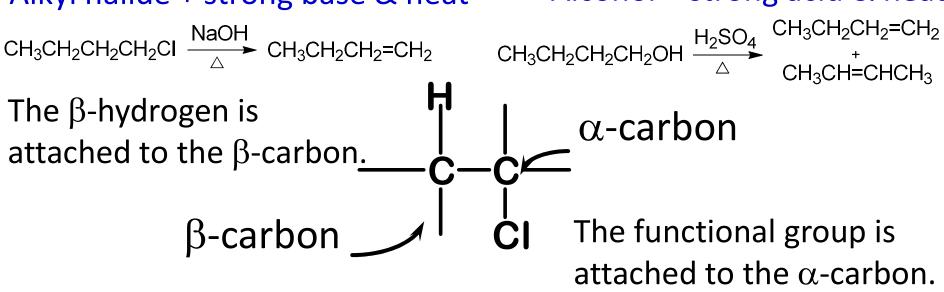
- The structure of the substrate
- Reactivity of the nucleophile
- Nature of the solvent
- The nature of the leaving group

Elimination Reactions



Alkyl halide + strong base & heat

Alcohol + strong acid & heat



Since the β -hydrogen is lost this reaction is called a β -elimination

The stability of an alkene increases as the number of R groups bonded to the double bond carbons increases.

$$CH_2=CH_2$$
 < $RCH=CH_2$ < $R_2C=CH_2$ ~ $RCH=CHR$ < $R_2C=CHR$ < $R_2C=CR_2$

Mechanisms of Elimination



There are two mechanisms of elimination E2 and E1

- E2 mechanism bimolecular elimination
- E1 mechanism unimolecular elimination

Both the mechanisms differ in the timing of bond cleavage and bond formation

E2 reactions are generally run with strong, negatively charged bases like OH and OR.

The reaction exhibits second-order kinetics, and both the alkyl halide and the base appear in the rate equation i.e.

rate =
$$k[(CH_3)_3CBr][-OH]$$

The reaction is concerted—all bonds are broken and formed in a single step.

E2-Elimination Reaction



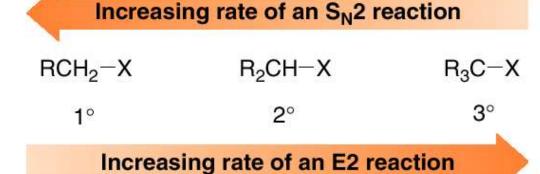
Because the bond to the leaving group is partially broken in the transition state, the better the leaving group the faster the E2 reaction.

Increasing leaving group ability Increasing rate of E2 rexn.



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.



E2-Elimination Reaction

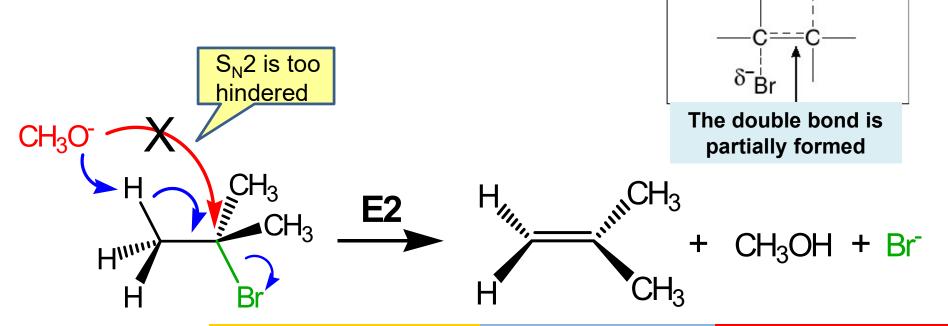


The increase in E2 reaction rate with increasing alkyl substitution can be rationalized in terms of transition state stability & steric hindrance for $S_N 2$

In the transition state, the double bond is partially formed.

Thus, increasing the stability of the double bond with alkyl

substituents stabilizes the transition state.



Regioslectivity & Stereochemistry of E2 Rexn



If more than one elimination product is possible, the most-substituted alkene is the major product (most stable)- Zaitsev's (Saytzeff) rule

$$H_3C$$
 CH_3
 $CH_3O^ CH_3C$
 CH_3C
 CH_3

E2-elimination occurs most often in the anti-periplanar geometry. This arrangement allows the molecule to react in the lower energy staggered conformation, and allows the incoming base and leaving group to be further away from each other.

anti elimination

base

Stereochemistry of E2 Rexn



E2 is both stereoselective and stereospecific.

Stereochemistry of E2 Rexn



$$Br$$
 H_3C
 Ph
 Ph
 H_3C
 Ph
 H_3C

What about (2R, 3R) and (2R, 3S) isomers?

cis- reacts faster than trans- as activation energy for cis- is lower.

Formation of Hofmann Product



Bulky bases abstract the least hindered H⁺ to give least substituted alkene as major product.

Zaitsev product

Hofmann product

$$\xrightarrow{\text{-OCH}_2\text{CH}_3}$$

$$\xrightarrow{\text{CH}_3\text{CH}_2\text{OH}}$$

$$C = C$$
 CH_3
 $C = C$
 CH_3
 CH_3

$$\xrightarrow{\text{-OC(CH}_3)_3} \xrightarrow{\text{(CH}_3)_3\text{COH}}$$

$$C = C$$
 $C = C$
 CH_3
 $C = C$
 CH_3
 CH_3

$$CH_3$$
 CH_2 $C=C$
 H_3C T_2
 T_3

Some bulky bases:

They are strong base, poor nucelophile.

$$CH_3$$
 CH_3
 CH_3
 CH_3
 CH_3
 t -butoxide

$$H_3C$$
 $\stackrel{..}{N}$
 CH_3

2,6-dimethylpyridine

E1-Elimination reaction



An E1 reaction exhibits first-order kinetics:

rate =
$$k[(CH_3)_3CI]$$

The E1 reaction proceed via a two-step mechanism.

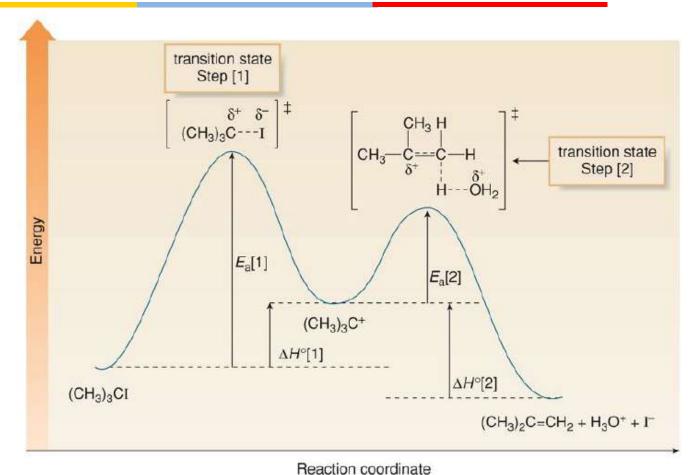
The bond to the leaving group breaks first before the π bond is formed.

The slow step is unimolecular, involving only the alkyl halide. Intermediate carbocation is formed.

The strength of the base usually determines whether a reaction follows the E1 or E2 mechanism. Strong bases like [¬]OH and [¬]OR favor E2 reactions, whereas weaker bases like H₂O and ROH favor E1 reactions.

Free Energy Diagram of E1 Reactions





The rate of an E1 reaction increases as the number of R groups on the carbon with the leaving Increasing rate of an E1 reaction

group increases.

E1-Elimination reaction



- These reactions proceed under neutral conditions where a
 polar solvent helps to stabilize the carbocation intermediate.
- This solvent also acts as a weak base and removes a proton in the fast step.
- These types of reactions are referred to as solvolysis reactions.
- Tertiary substrates go by E1 in polar solvents, with little or no base present!
- Typical polar solvents are water, ethanol, methanol and acetic acid
- E1 reactions also occur in a low concentration of base (i.e. 0.01M NaOH).

E1-Elimination reaction



E1 reactions are regioselective, favoring formation of the more substituted, more stable alkene. E1 reactions follow the Zaitsev's rule.

CH₃ H₂O + minor product

Rearrangements occur in E1 reactions.

E1 reactions do not require an *anti coplanar* orientation of H and X.

Diastereomers give the same products with E1 reactions, including cis- and trans products.

E1 reactions usually give the thermodynamically most stable product as the major product.

Hofmann Elimination



■ Hofmann elimination, also known as exhaustive methylation, is a process where an amine is reacted to create a tertiary amine and an alkene by treatment with excess methyl iodide/primary halide followed by treatment with silver oxide, water, and heat.

$$CH_{3}CH_{2}CH_{2}NH_{2} + \underbrace{CH_{3}I}_{\text{excess}} \xrightarrow{\textbf{K}_{2}CO_{3}} CH_{3}CH_{2}CH_{2}NCH_{3} \xrightarrow{\textbf{Ag}_{2}O} CH_{3}I^{-}$$

$$CH_{3}CH_{2}CH_{2} \xrightarrow{\textbf{CH}_{3}} CH_{3} \xrightarrow{\textbf{CH}_{3}CH_{2}CH_{2}} CH_{3} \xrightarrow{\textbf{CH}_{3}CH_{2}CH_{2}} CH_{3} \xrightarrow{\textbf{CH}_{3}CH_{2}CH_{2}} + \underbrace{CH_{3}}_{NCH_{3}} + \underbrace{H_{2}O_{3}CH_{2}CH_{2}}_{CH_{3}} + \underbrace{CH_{3}CH_{2}CH_{2}}_{CH_{3}} + \underbrace{CH_{3}CH_{2}CH_{2}}_{CH_{3}} + \underbrace{CH_{3}CH_{2}CH_{2}}_{CH_{3}} + \underbrace{CH_{3}CH_{2}CH_{2}CH_{2}}_{CH_{3}} + \underbrace{CH_{3}CH_{2}CH_{2}}_{CH_{3}} + \underbrace{CH_{3}CH_{2}CH_{2}CH_{2}}_{CH_{3}} + \underbrace{CH_{3}CH_{2}CH_{2}}_{CH_{3}} + \underbrace{CH_{3}CH_{2}}_{CH_{3}} + \underbrace{CH_{3}CH_{2}CH_{2}}_{CH_{3}} + \underbrace{CH_{3}CH_{2}CH_{2}}_{CH_{3}} + \underbrace{CH_{3}CH_{2}CH_{2}}_{CH_{3}} + \underbrace{CH_{3}CH_{2}}_{CH_{3}} + \underbrace{$$

A Hofmann elimination is an E2 reaction

Hofmann Elimination



Heating quaternary ammonium hydroxide produces the least substituted alkene.

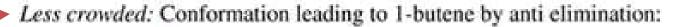
A quaternary ammonium salt is a good leaving group as neutral amine.

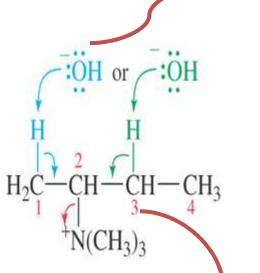
The leaving group of a quaternary ammonium ion has about the same leaving tendency as a protonated amino group.

N,N,N-trimethyl-N-(2-butyl) ammonium hydroxide

Hofmann Elimination







1-Butene (major product)

More crowded: Conformation leading to trans-2-butene by anti elimination:

Cope Elimination

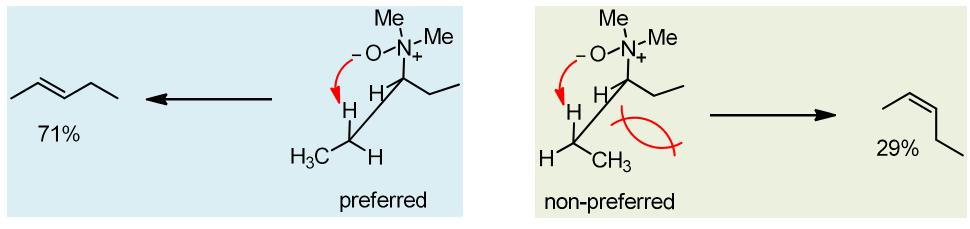


The Cope elimination of N-oxides, which can easily be prepared in situ from tertiary amines with an oxidant such as peracid is a *syn* periplanar elimination in which six electrons move in a five-membered ring according to a concerted, thermally-induced mechanism to yield an alkene and a hydroxylamine in aprotic solvents.

The sterically demanding amine oxide function reacts preferentially with the more easily accessible hydrogens, and often gives good selectivity favoring the less-substituted alkene. Thus, for simple alkenes, the reaction follows the Hofmann Rule

Cope Elimination





Comparison of E1 and E2 Elimination



E2 mechanism

- Much more common and useful.
- Favored by strong, negatively charged bases, especially OH and OR.
- The reaction occurs with 1°, 2°, and 3° alkyl halides. Order of reactivity: R₃CX > R₂CHX > RCH₂X.

E1 mechanism

- Much less useful because a mixture of S_N1 and E1 products usually results.
- Favored by weaker, neutral bases, such as H₂O and ROH.
- This mechanism does not occur with 1° RX because they form highly unstable 1° carbocations.

Summary for predicting SN1, SN2, E1 & E2

Halide	Conditions	Mechanism
1°	strong nucleophile strong bulky base	SN2 E2
2 °	strong base & nucleophile strong bulky base weak base and nucleophile	SN2 & E2 E2 SN1 & E1
3 °	weak base and nucleophile strong base	SN1 & E1 E2