Lecture 14

Organic Chemistry 1

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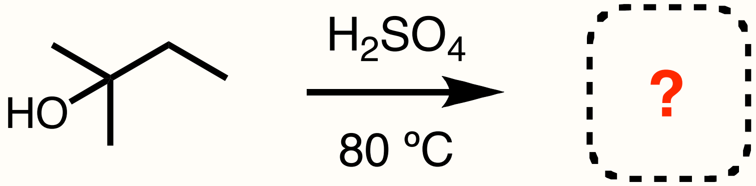
02/09/2010

Regioselectivity & Stereoselectivity of Dehydration

Section 5.10-5.11

Self Test Question

What is the product(s) of the following reaction?



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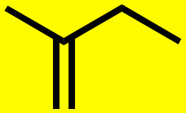
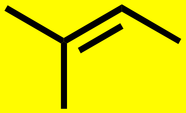
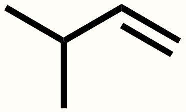
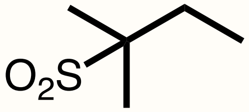
B. 

C. 

D. 

E. 

Types of Selectivity in Organic Chemistry

There are three forms of selectivity to consider . . . .

- ☑ Chemoselectivity: *which* functional group will react
- ☑ Regioselectivity: *where* it will react
- ☑ Stereoselectivity: *how* it will react with regards to stereochemical outcome

. . . for each transformation, always question which of these are factors are at play.

Regioselectivity of Elimination

Regioselectivity: *Where* Will It React?

Preferential reaction at one site of a single functional group over other sites that could undergo the same reaction

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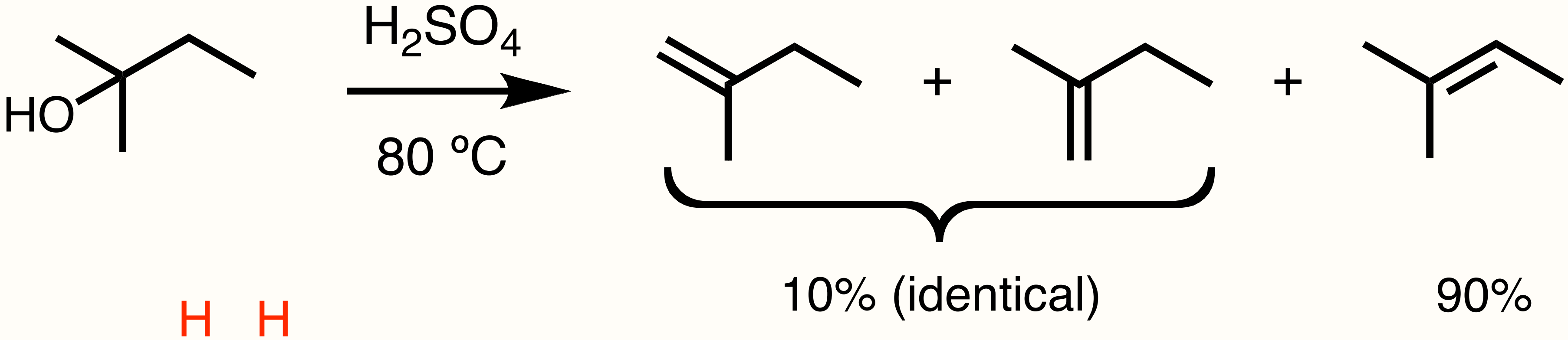
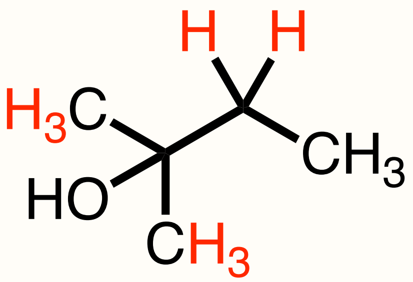
CHEM 232 Definition, 2009





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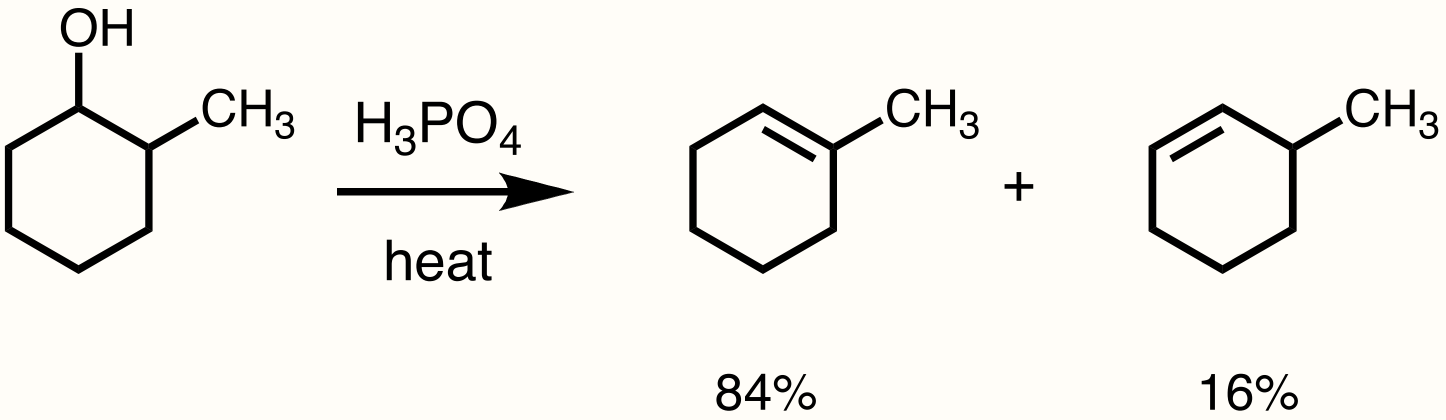
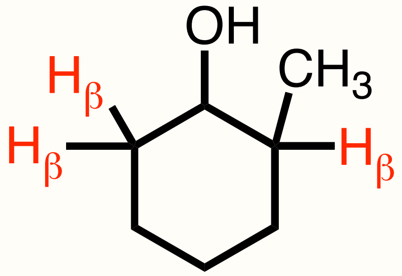


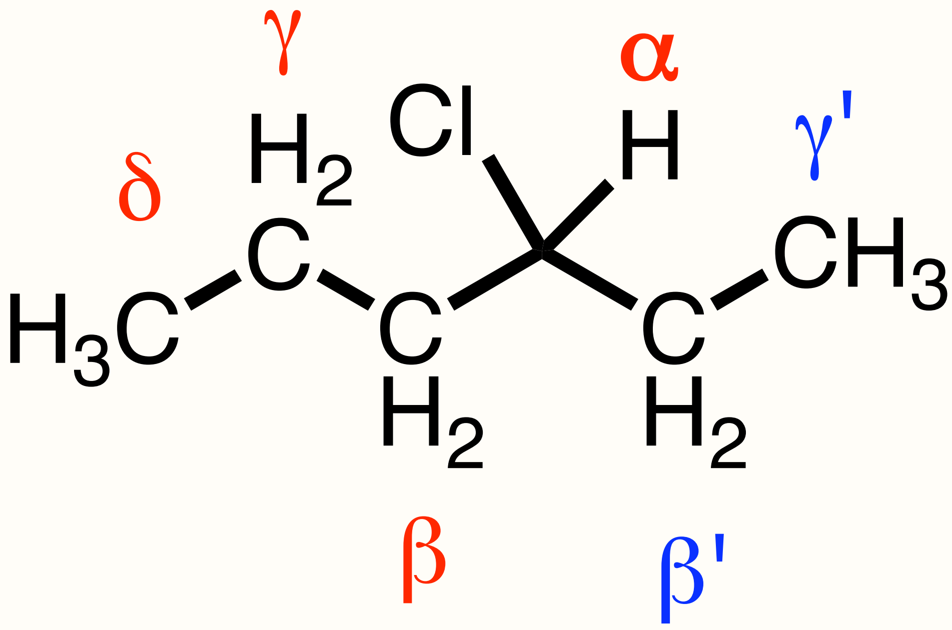


2 different leaving group/H_β relationships

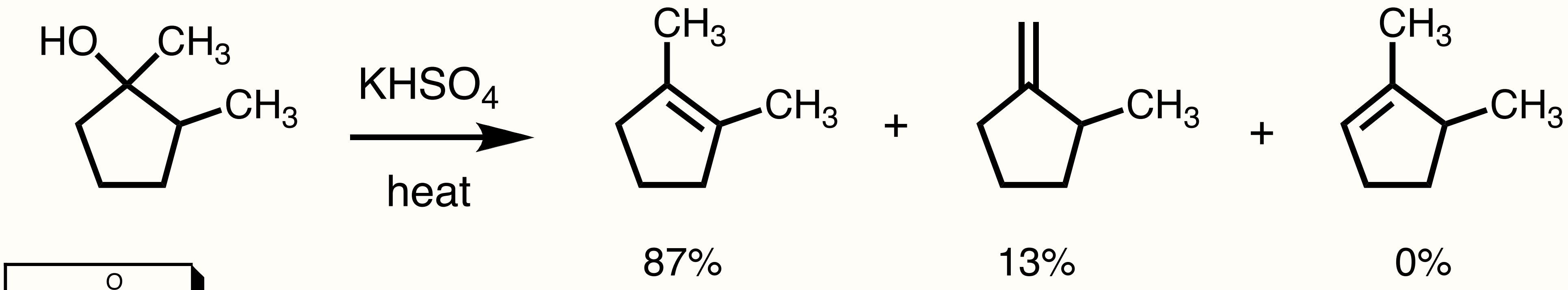
Greek Lettering & Elimination Reactions

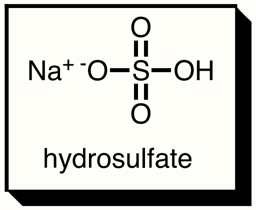
Nomenclature

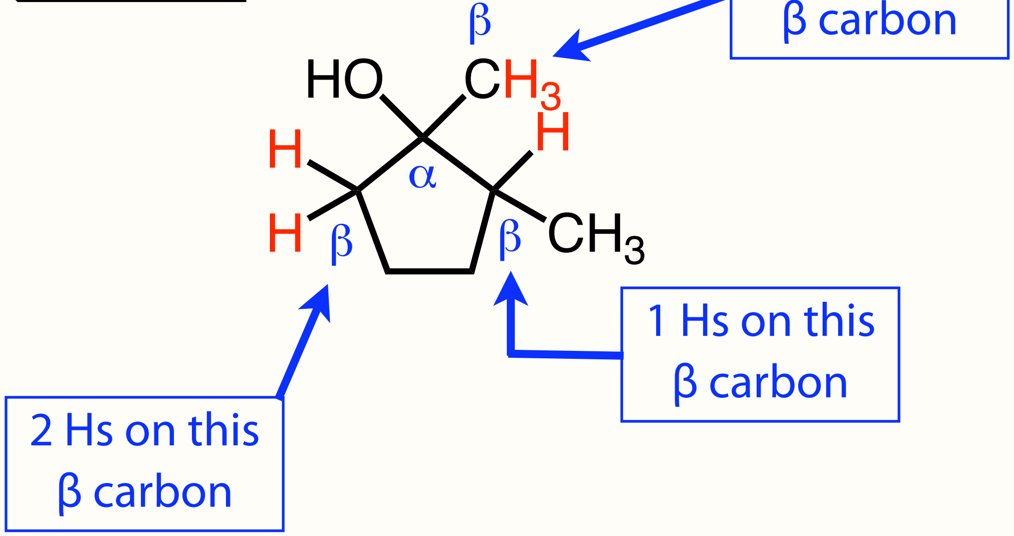
The α-carbon is the one to which the leaving group is initially bonded, and the carbon chain from this may be labelled β (beta), γ (gamma), δ (delta) etc, following Greek alphabet. Use primed letters for chains branching at α-carbon



Regioselectivity of Elimination
Zaitsev Rule







3 Hs on this β carbon

1 Hs on this β carbon

2 Hs on this β carbon

Zaitsev Rule
When elimination can occur in more than one direction, the major alkene is the one formed by loss of a H atom from the β carbon having the *fewest* hydrogens

Dehydration is Stereoselective

Stereoselectivity: *How* It Will React With Regard to Stereochemical Outcome?

Preferential formation of one stereoisomer when two or more stereoisomers are potential products of a given chemical reaction

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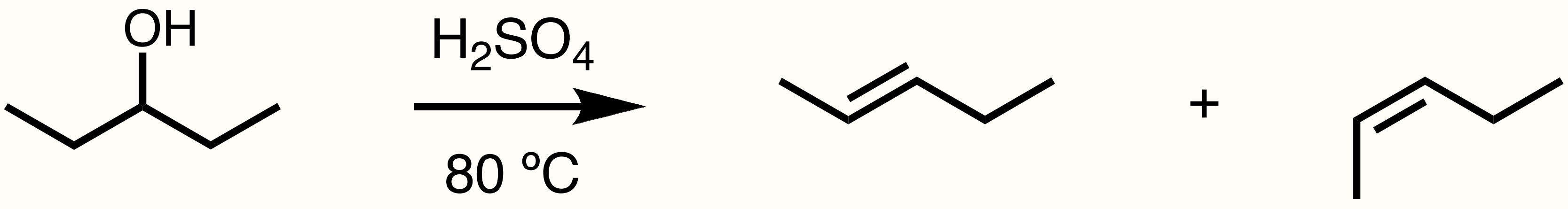
CHEM 232 Definition, 2009

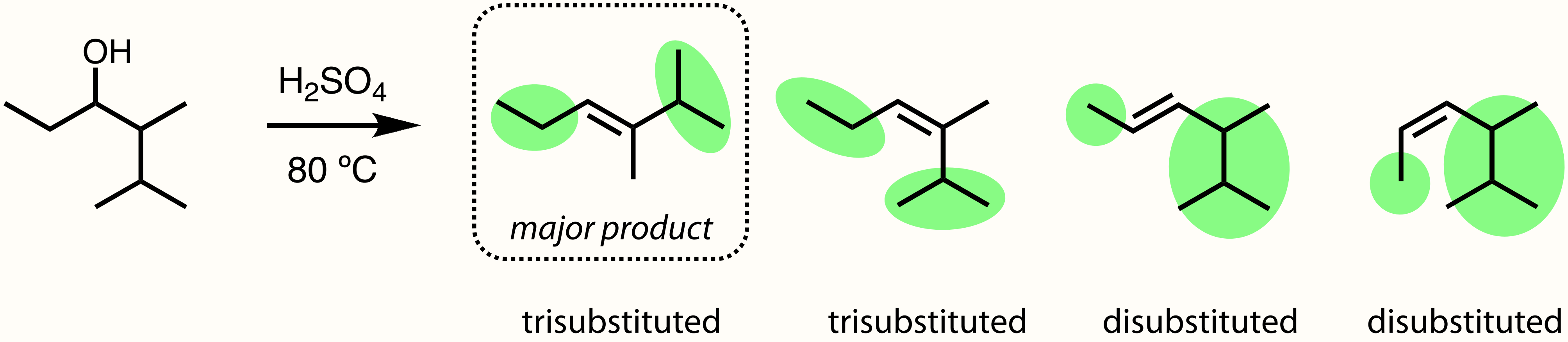


E (75%)   *Z* (25%)

trans alkenes are formed in greater amounts in dehydration reactions compared to *cis* alkenes

Considering Stereo & Regioselectivity

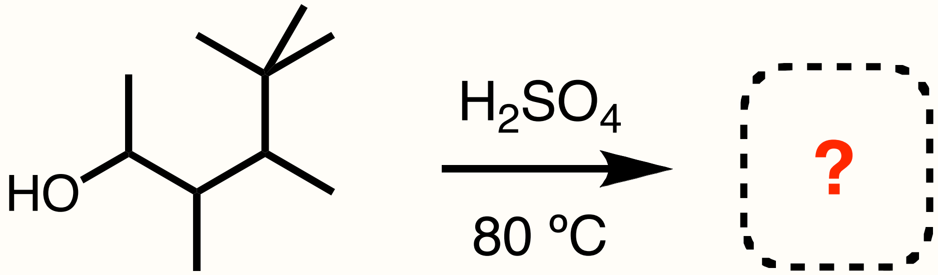
Combine Zaitsev's Rule and observations about stereoselectivity to predict the major products of dehydration (elimination)

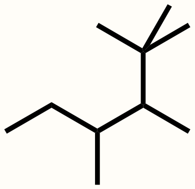


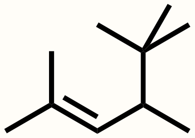
most stable alkenes have largest groups on each carbon *trans* to each other

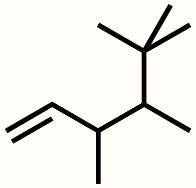
Self Test Question

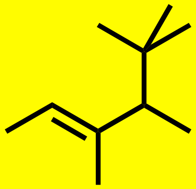
What is the major product expected for the reaction scheme below?

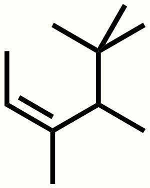


A. 

B. 

C. 

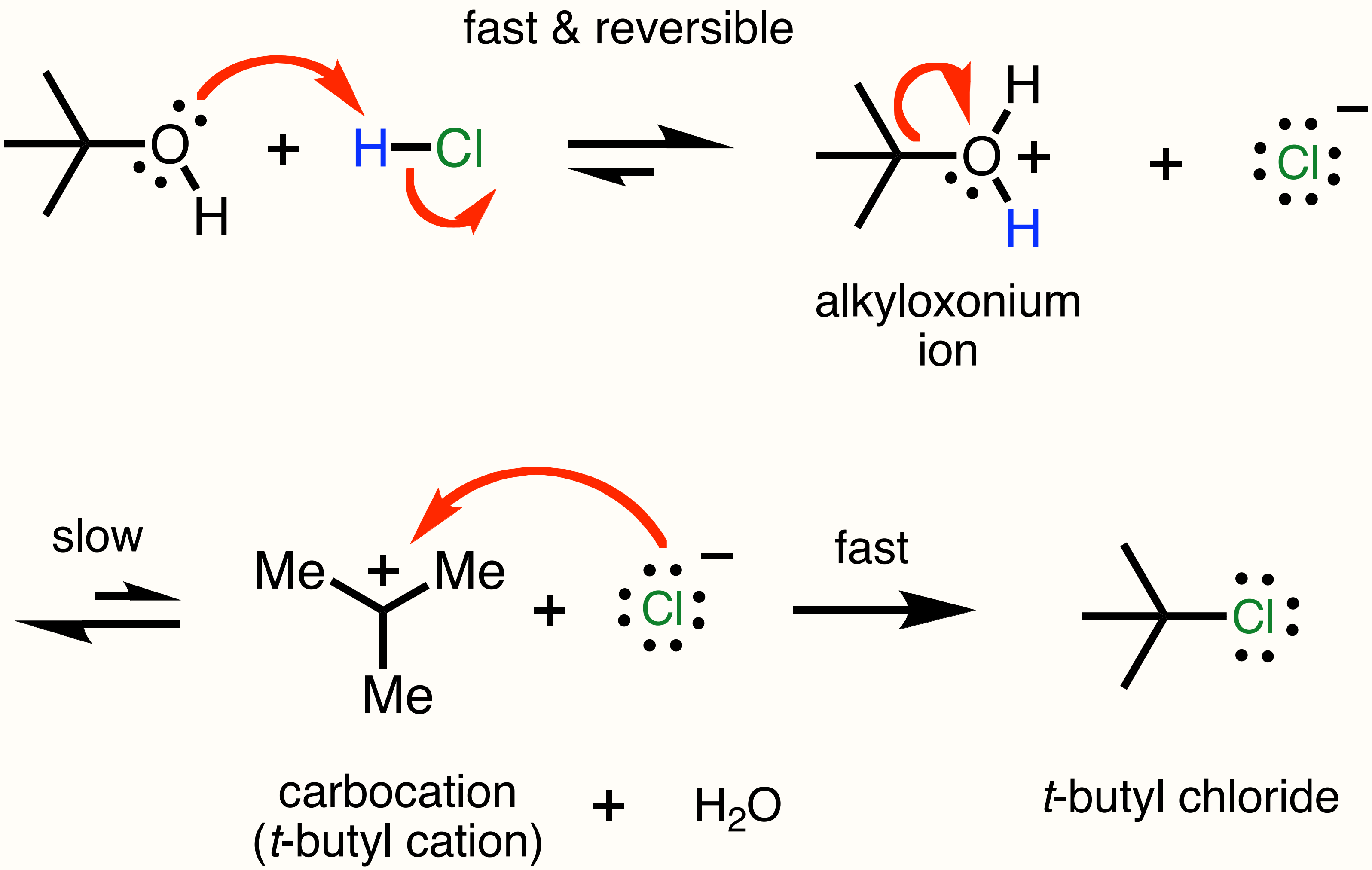
D. 

E. 

E1 & E2 Mechanisms of Alcohol Dehydration

Section: 5.12

Organic Mechanisms (S_N1)



alkyloxonium ion

carbocation (*t*-butyl cation) + H_2O

t-butyl chloride

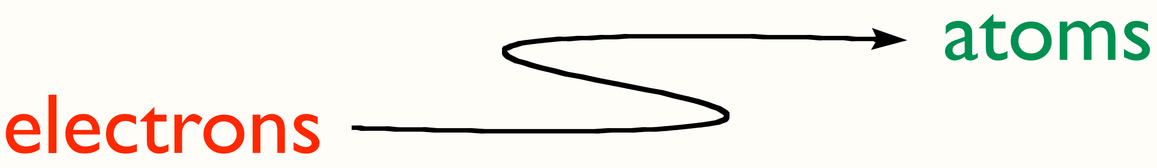
curved arrows: show direction of electron flow in each bond making and bond breaking

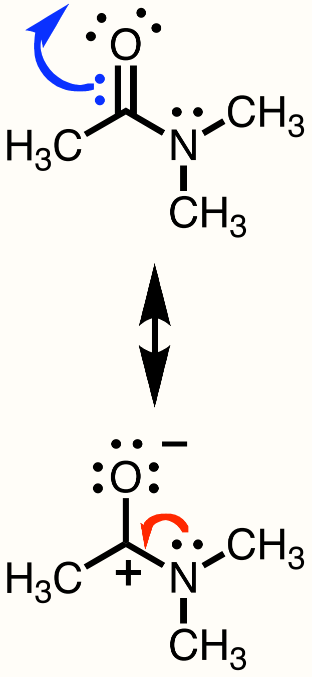
elementary steps: involves bond making/breaking that proceeds through one transition state

intermediates (i.e. carbocations, oxonium ions)

Remember Curved Arrow Notation?

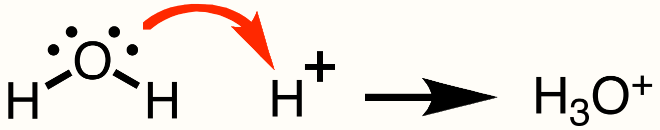
curved arrows show the movement of electrons; never atoms



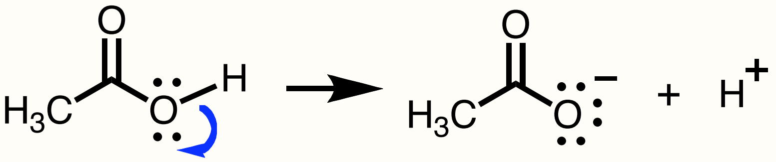


resonance: electrons in a covalent bond moving out to an atom

resonance: lone pair of electrons moving in between two atoms to form a new covalent bond



bond making: lone pair of electrons forming a new bond to another atom

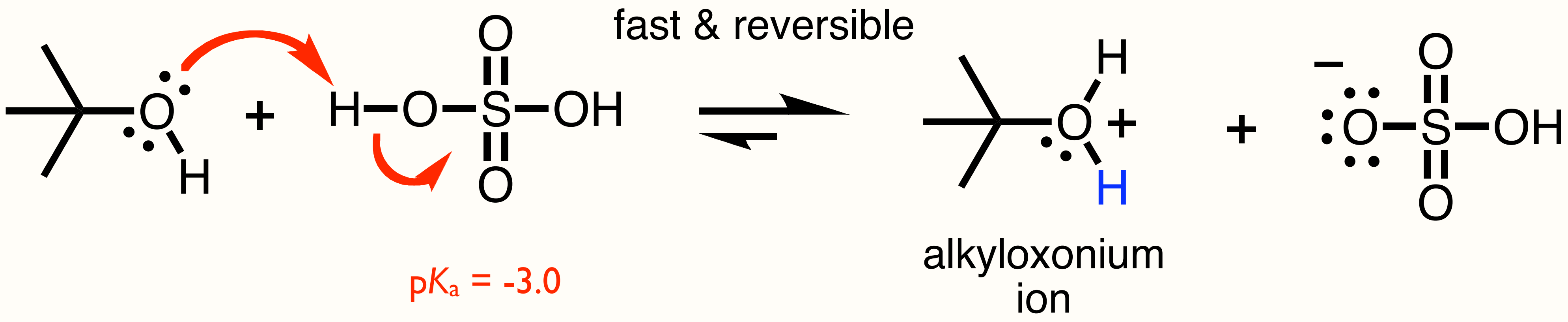


bond breaking: electrons in a bond leaving to most electronegative atom

Mechanism of Dehydration (E1)

Step One

Proton Transfer (Protonation)



this is an acid–base reaction; product is an alkoxonium ion

exothermic and fast (proton transfer is among the fastest processes in organic chemistry)

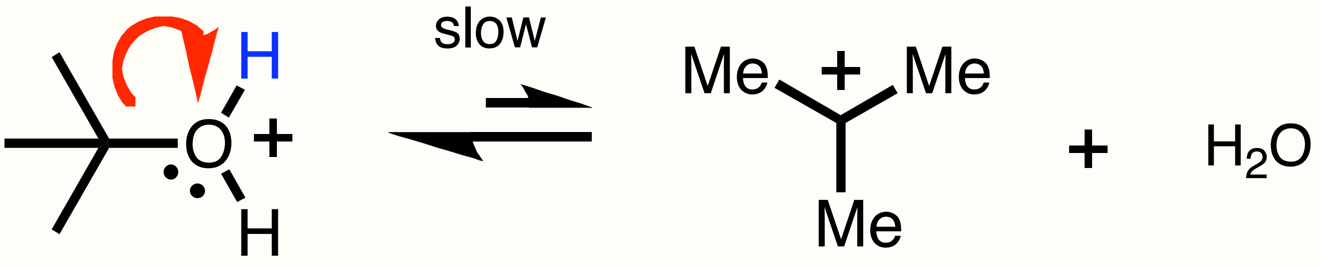
rate of individual step =k x [alcohol] x [HX]; two reactants = bimolecular (2nd order)

oxonium ion is an intermediate in the overall reaction

Mechanism of Dehydration (E1)

Step Two

Dissociation



carbocation
(*t*-butyl cation)

breaking a carbon–oxygen bond

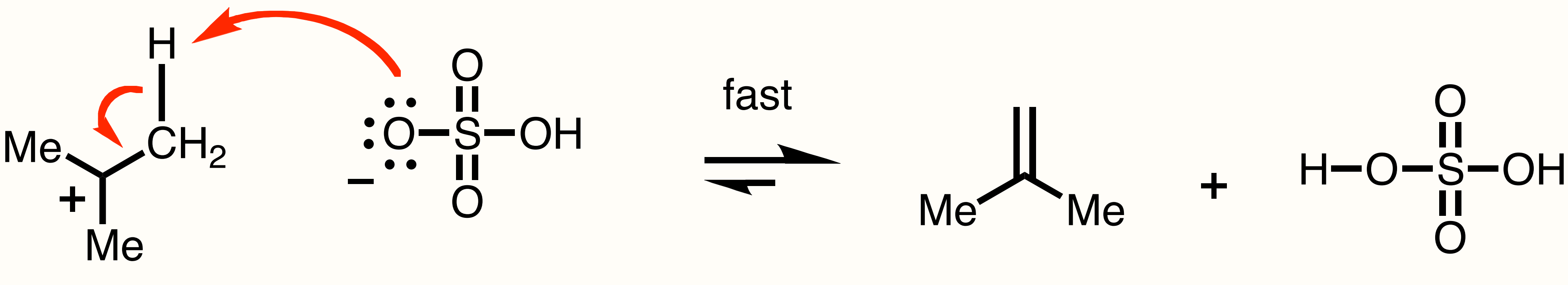
slowest (rate determining) step in entire mechanism; endothermic

rate=k[oxonium ion]; one reactant = unimolecular (1st order)

Mechanism of Dehydration (E1)

Step Three

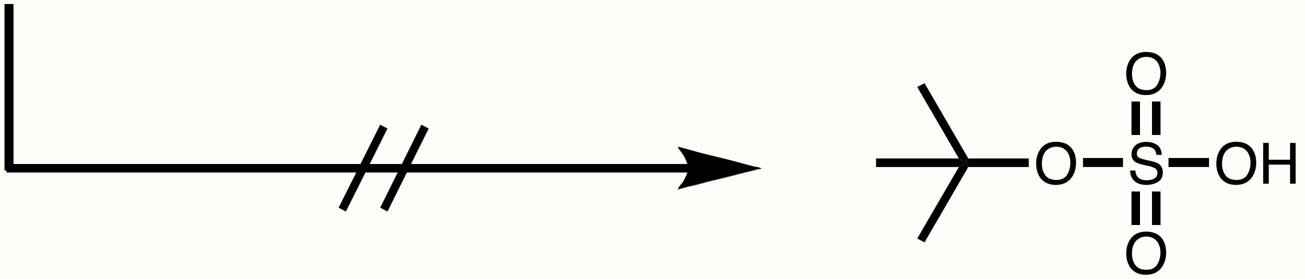
~~Carbocation Capture~~ β-Deprotonation!



carbocation
(*t*-butyl cation)

alkene
(2-methylpropene)

sulfuric acid
(regenerated)



alkyl hydrogen
sulfate
(product of S_N1)

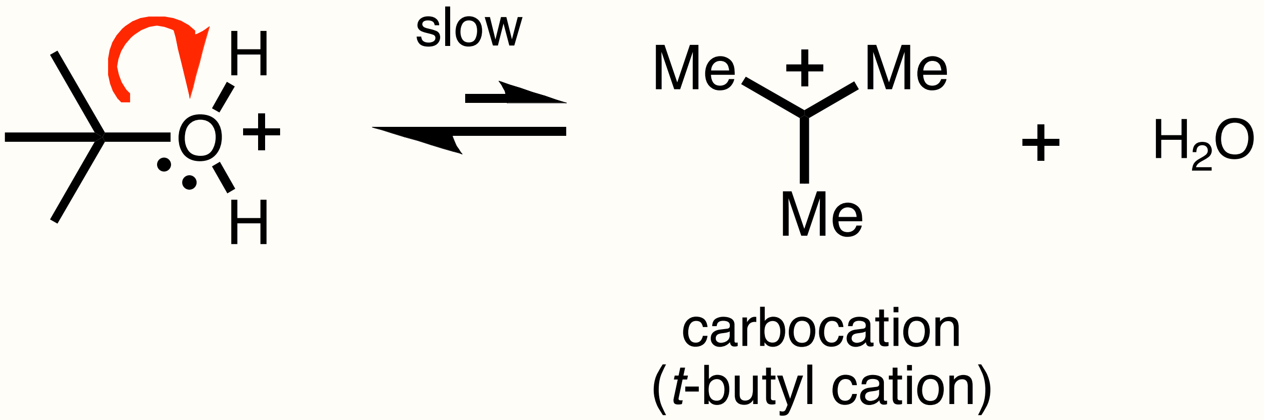
exothermic and fast; neutral products much lower in NRG

small activation energy; negative charge to positive charge

transition state looks most like carbocation since they are closest in energy

rate = k x [carbocation][halide]; two reactants = bimolecular

Hughes-Ingold Nomenclature



carbocation
(*t*-butyl cation)

E1

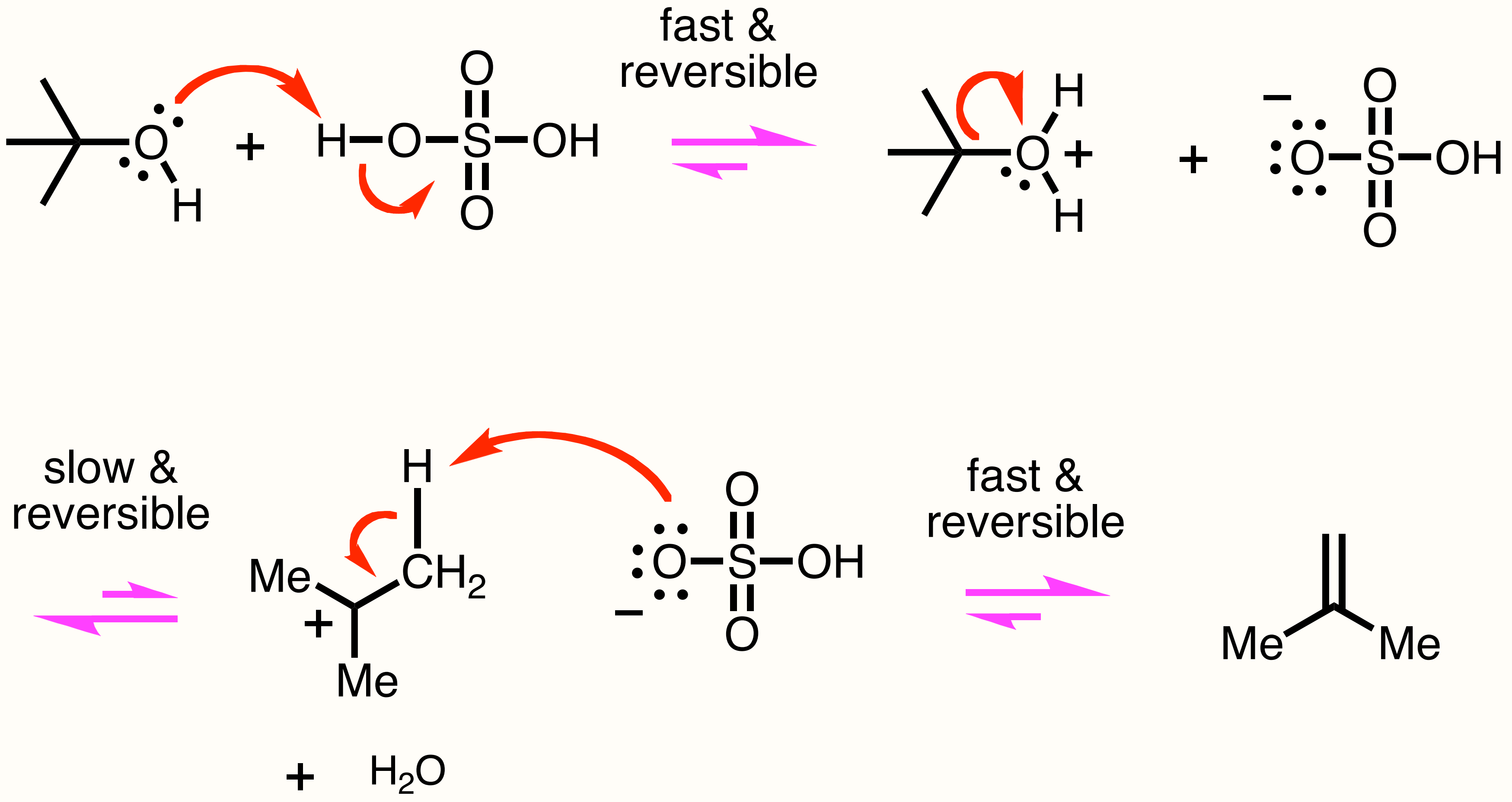
elimination
unimolecular

overall reaction = β-Elimination

rate determining step (RDS) involves on species = unimolecular

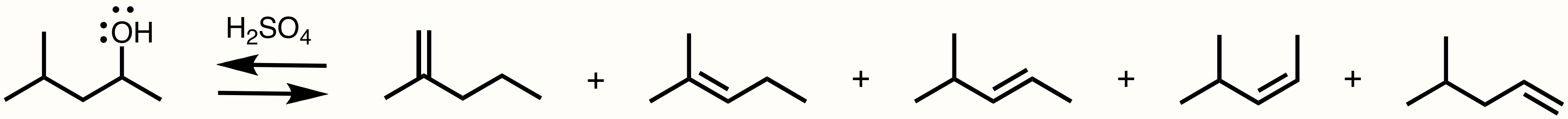
rate = *k*[alkyl oxonium ion] = first order

Each Step of E1 Mechanism is Reversible



If all steps in E1 are reversible, what drives the reaction forward?

Alkenes Isolated from Dehydration Reactions by Distillation



4-methyl-2-pentanol
bp = 132 °C

2-methyl-1-pentene
bp = 62 °C

2-methyl-2-pentene
bp = 67 °C

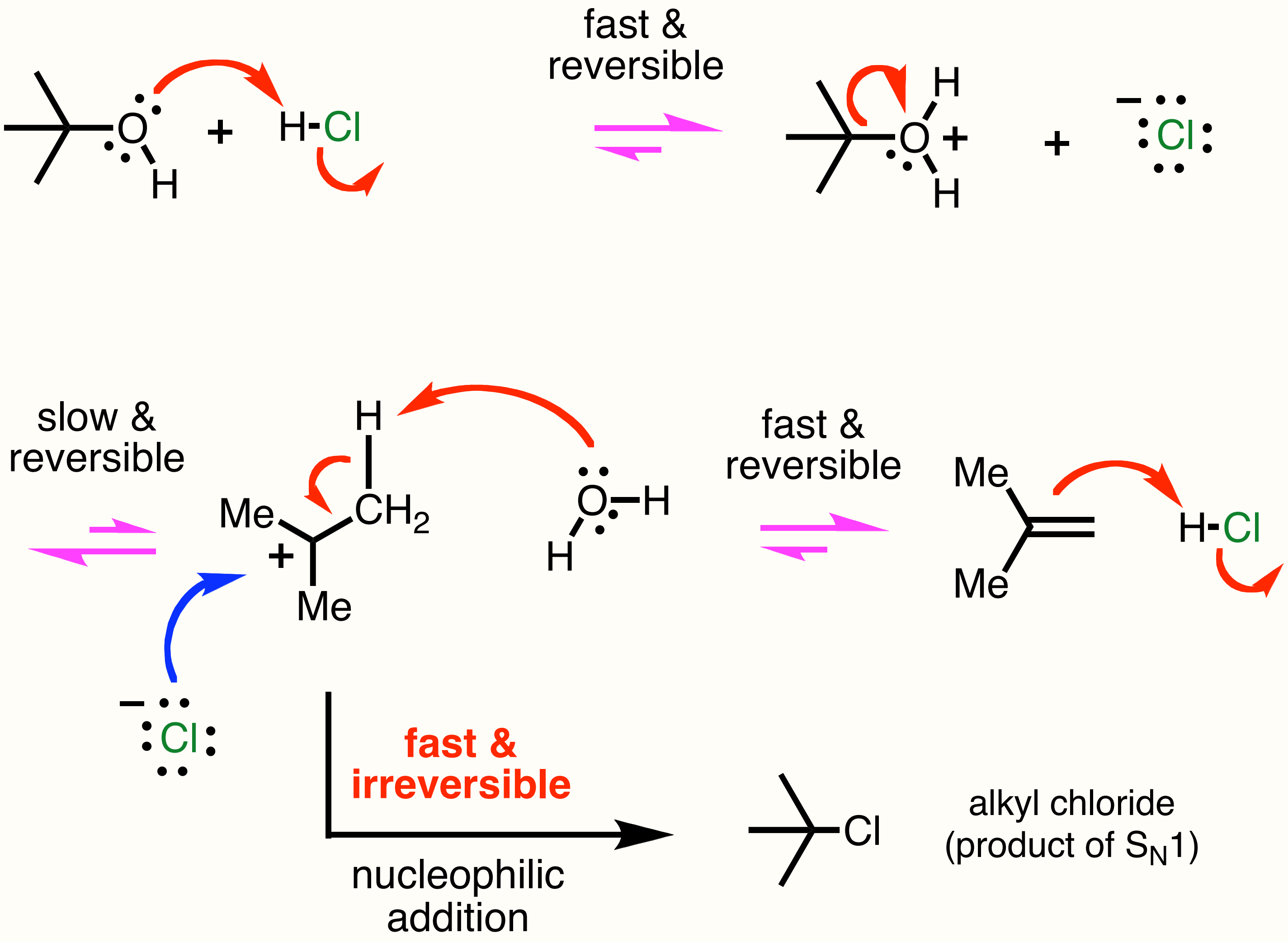
trans-4-methyl-2-pentene
bp = 59 °C

cis-4-methyl-2-pentene
bp = 58 °C

4-methyl-1-pentene
bp = 54 °C

- alkenes have much lower boiling points than alcohols
- alcohols have higher boiling points (b.p.) because of larger van der Waals forces, including strong hydrogen-bonding
- by removing alkenes through distillation (boiling), equilibrium is shifted toward products (LeChatlier Principle) until no more reactants remain

Why Can't Hydrogen Halides Be Used for Elimination Reactions?



fast & reversible

slow & reversible

fast & reversible

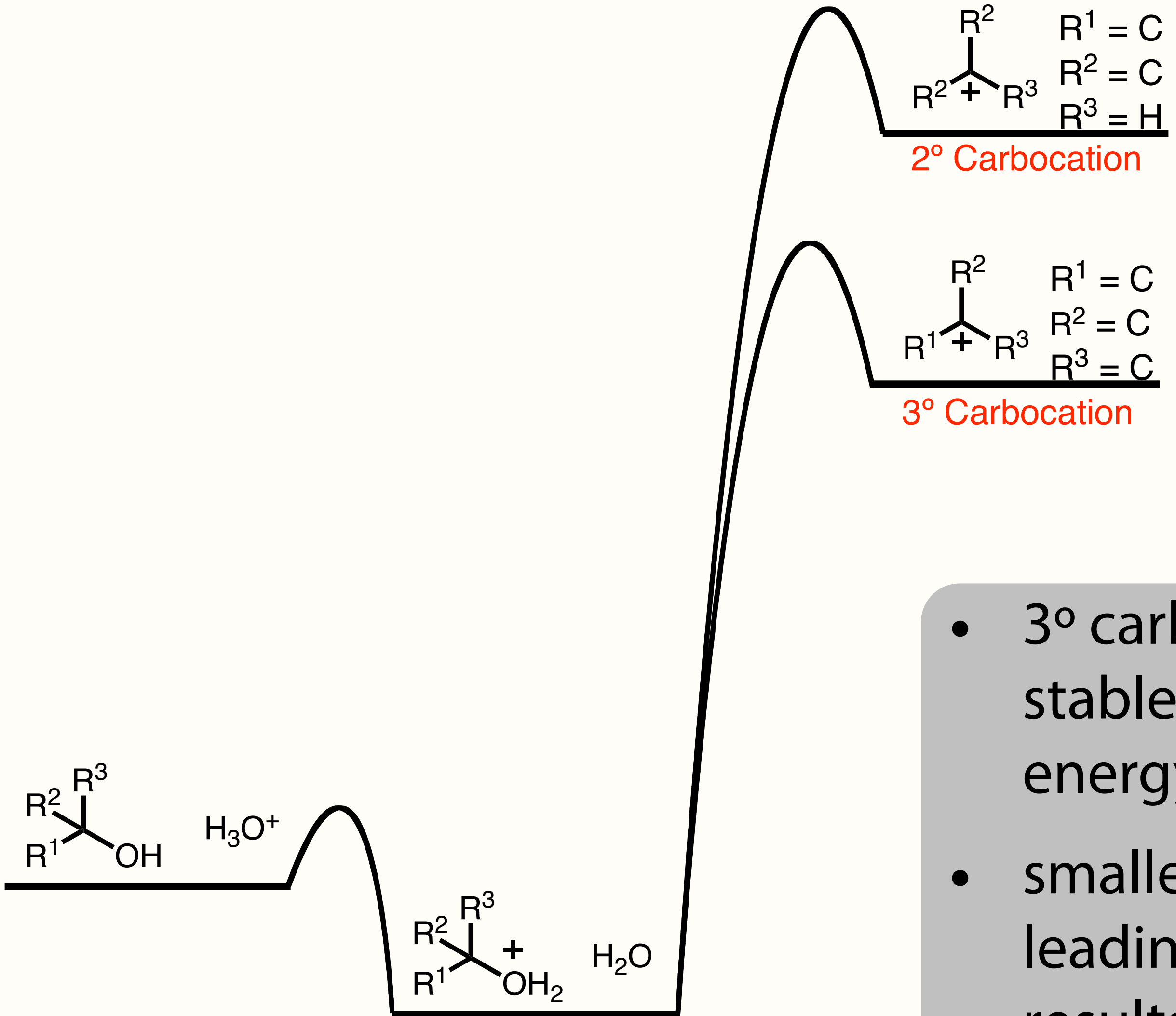
fast & irreversible

nucleophilic addition

alkyl chloride (product of S_N1)

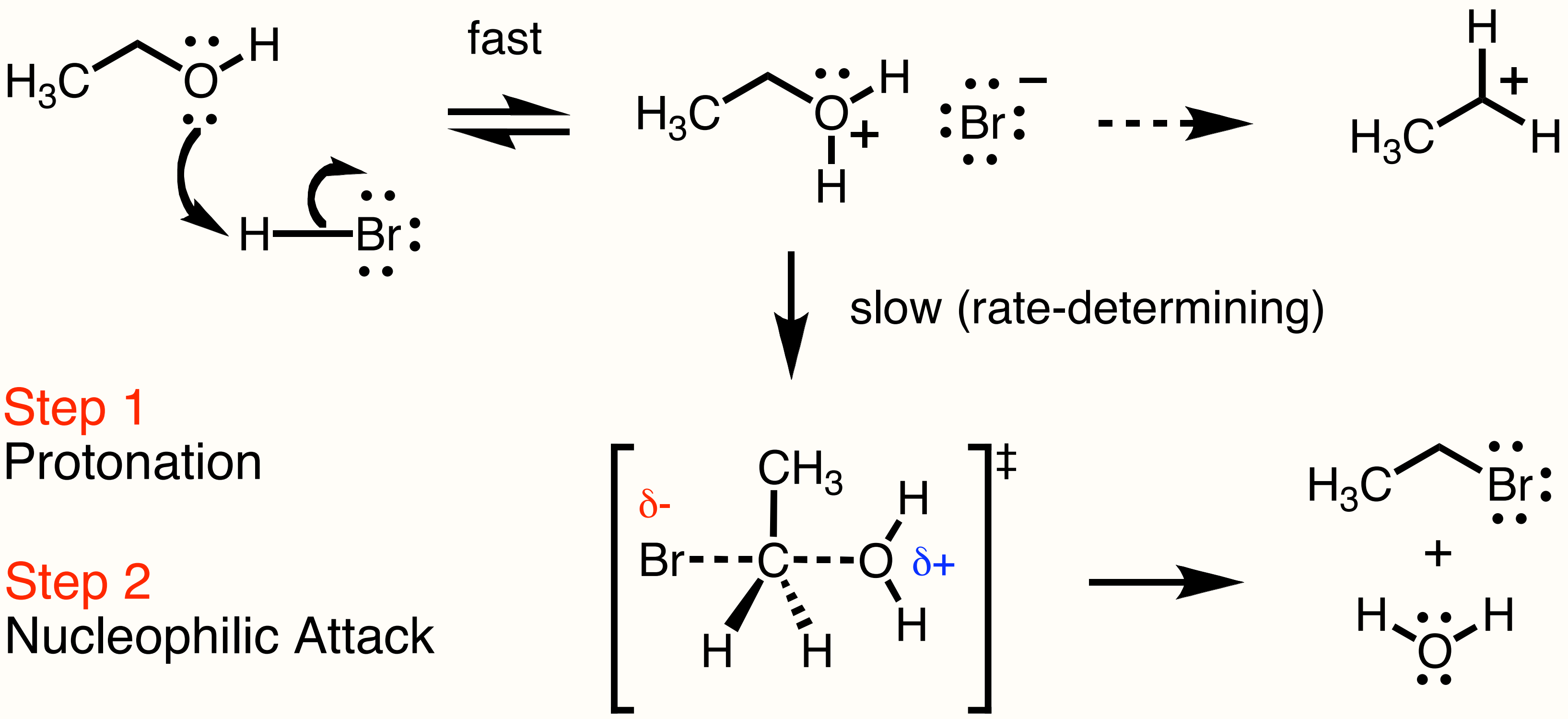
Nucleophilic addition of chloride (Cl^-) to a carbocation is not reversible

Reactivity Explained



- 3° carbocations are more stable than 2° = 3° lower in energy
- smaller activation energy leading to 3° carbocation results in faster reaction

Bimolecular Substitution - S_N2 Mechanism (from Lecture 8)

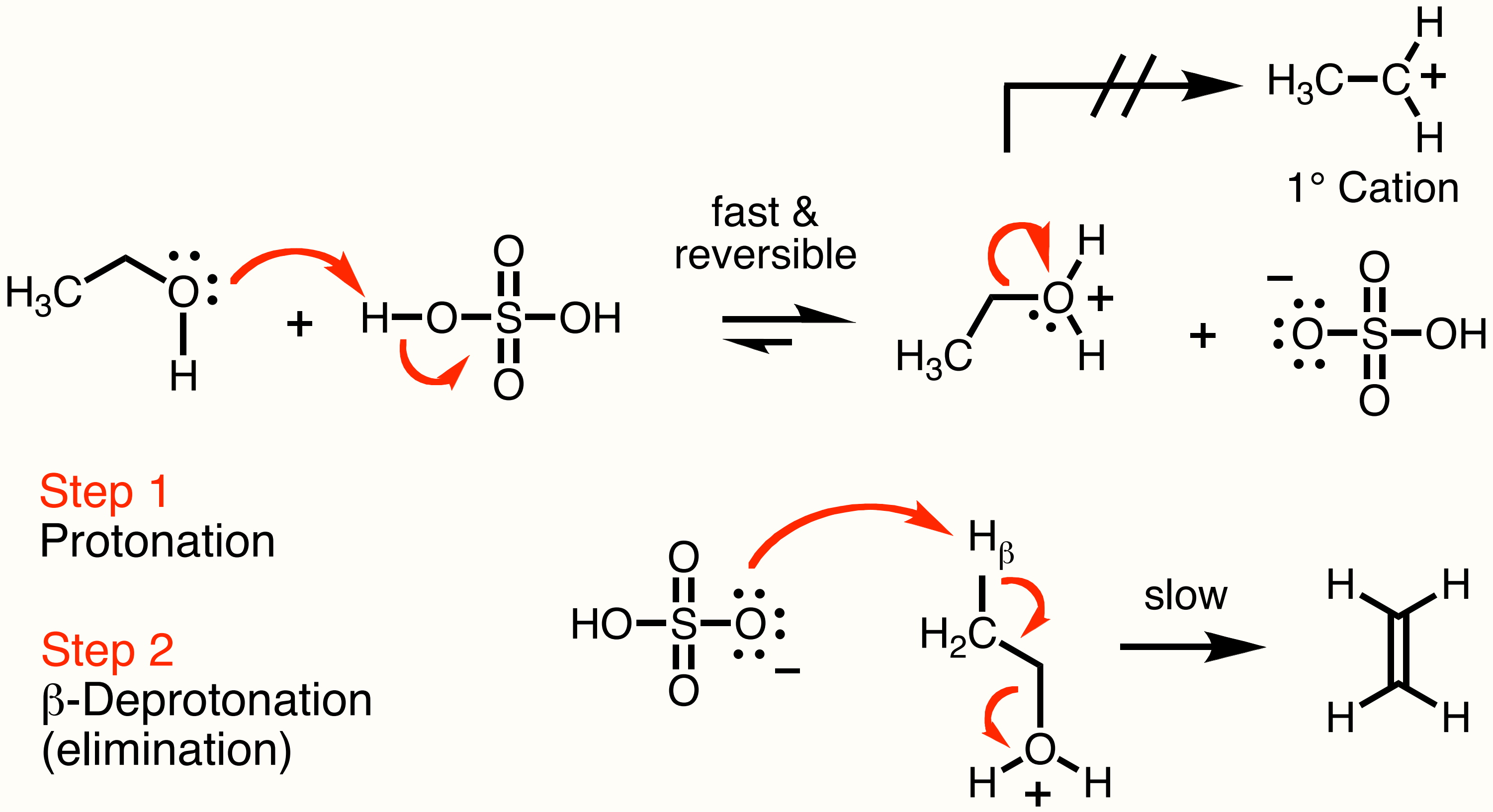


Step 1
Protonation

Step 2
Nucleophilic Attack

- C-O bond breaks at the **same time** the nucleophile (Br) forms the C-X bond
- RDS is nucleophilic attack; bimolecular, therefore Ingold notation = **S_N2**
- fewer steps does not mean faster reaction

Dehydration of Primary Alcohols Proceeds via E2 Mechanism



Step 1
Protonation

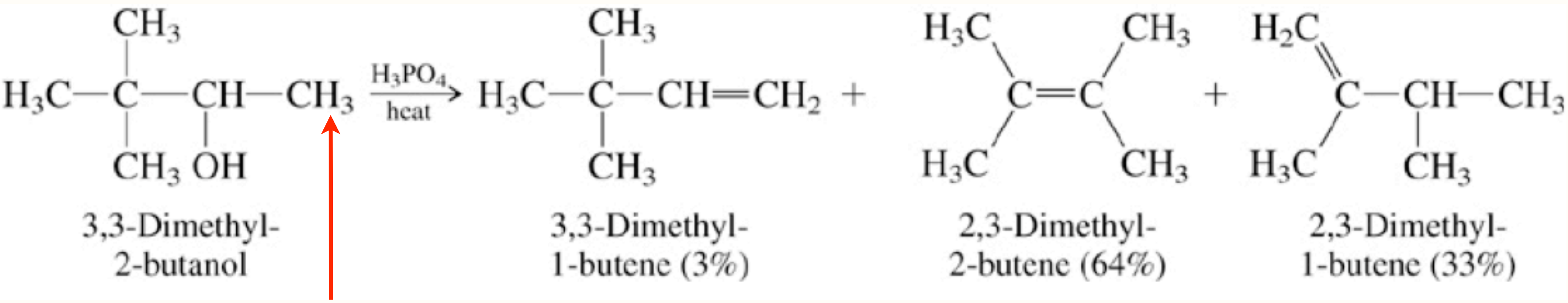
Step 2
β-Deprotonation
(elimination)

- C-O bond breaks at the **same time** the nucleophile (Br) forms the C-X bond
- RDS is nucleophilic attack; bimolecular, therefore Ingold notation = **S_N2**
- fewer steps does not mean faster reaction

Rearrangement During Alcohol Dehydration

Section 5.13

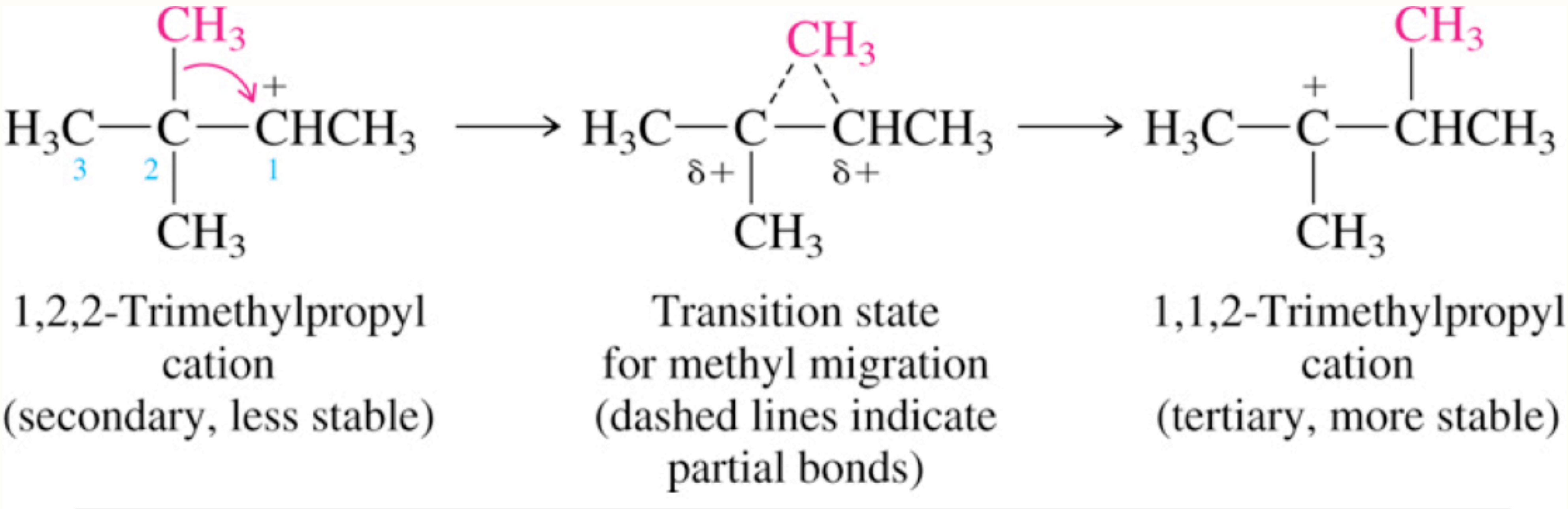
Rearrangements



only β-hydrogens!

- arrangement (connectivity) of the carbons atoms in the some of the products is <u>different</u> than in the reactant
- change in connectivity = rearrangement
- rearrangement takes place at the carbocation intermediate

Rearrangements via 1,2-Methyl Shift



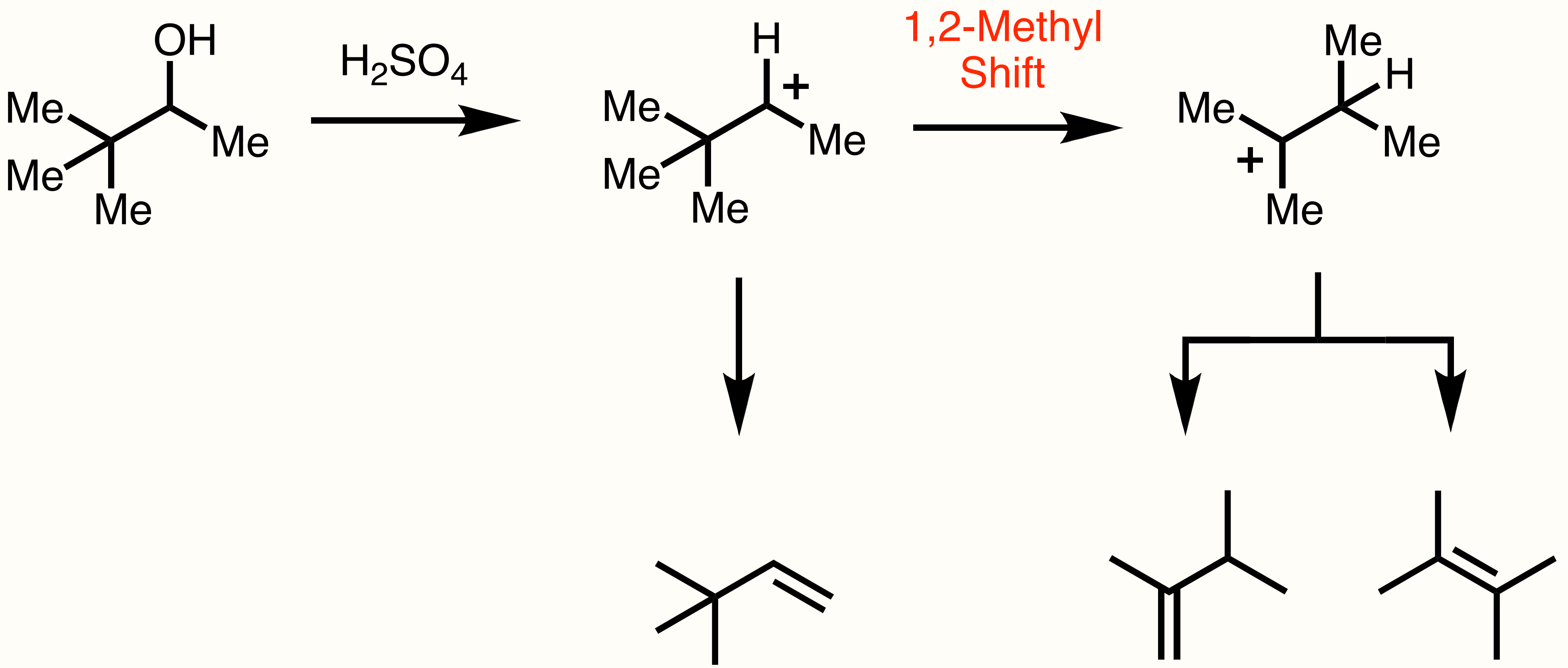
1,2,2-Trimethylpropyl cation (secondary, less stable)

Transition state for methyl migration (dashed lines indicate partial bonds)

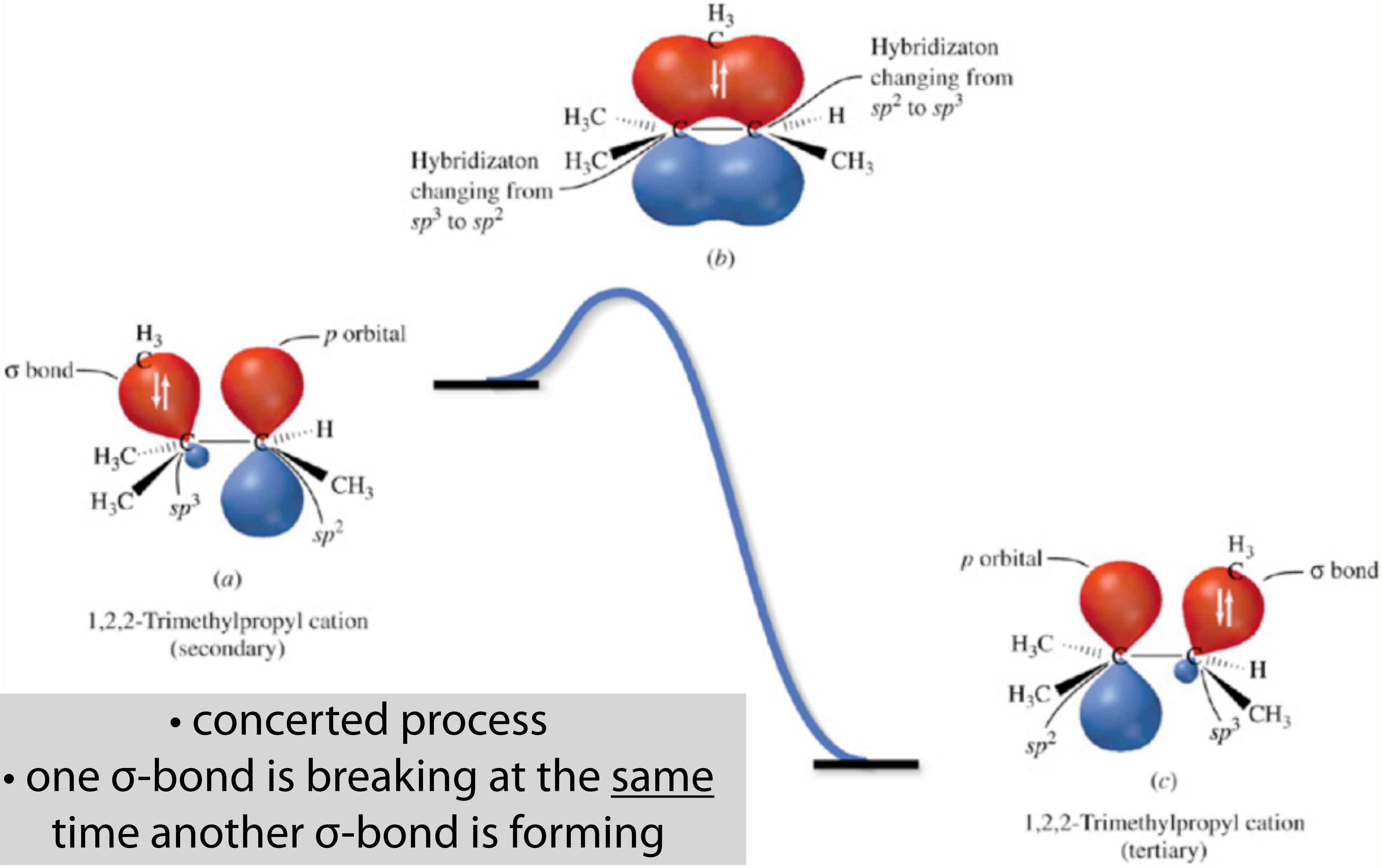
1,1,2-Trimethylpropyl cation (tertiary, more stable)

- methyl group migrates to adjacent (1,2) carbocation with its electrons
- driving force is generation of a more stable carbocation intermediate
- β-elimination can then take place from both carbocation intermediates
- the most stable carbocation will give rise to the major products

Example of 1,2-Methyl Shift

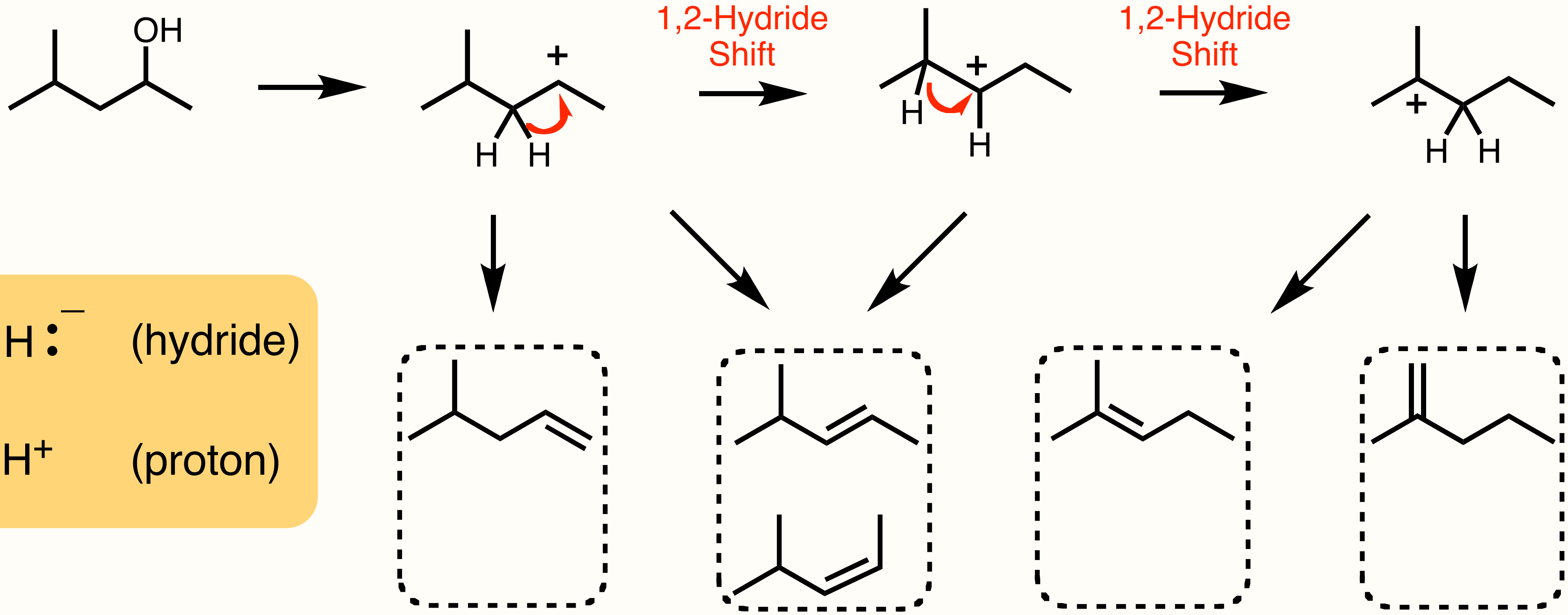


Valence Orbital Picture of Rearrangement



- concerted process
- one σ-bond is breaking at the <u>same</u> time another σ-bond is forming

Rearrangements: 1,2-Hydride Shift

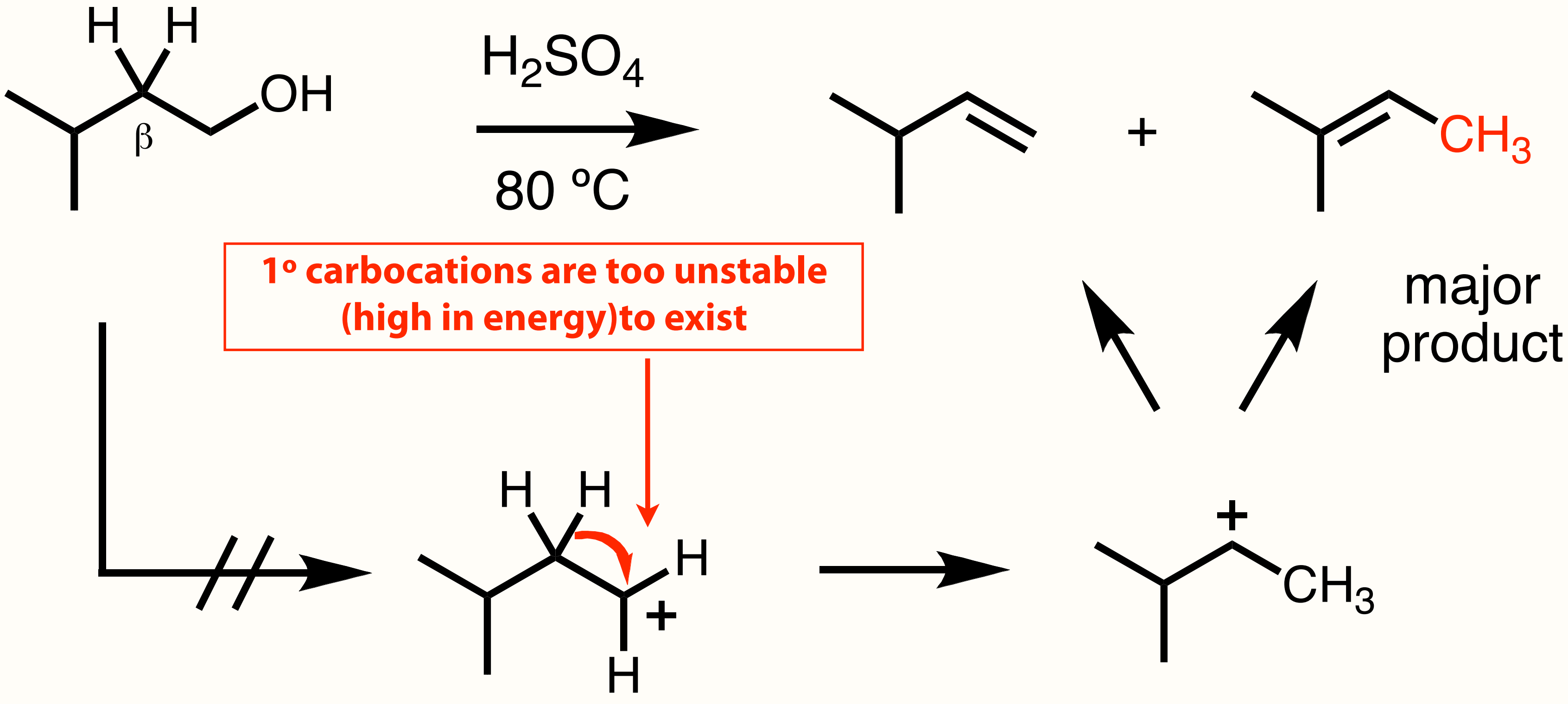


$H:^-$ (hydride)

H^+ (proton)

- hydride (hydrogen with the electrons in the sigma bond) migrates by the same mechanism as methyl
- formation of more stable carbocation drives rearrangement; multiple migrations are possible

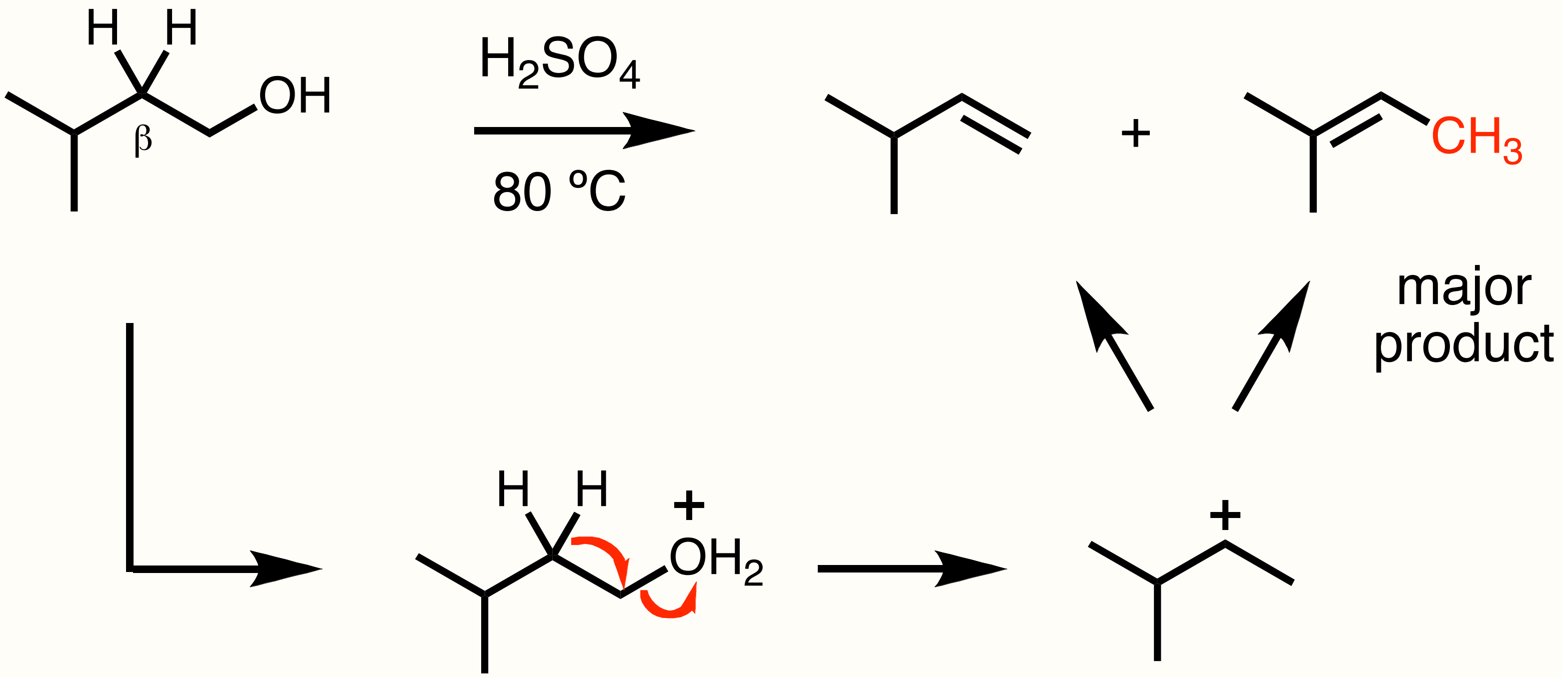
Hydride Shifts in 1° Alcohols Do Not Proceed via Primary Carbocations



1° carbocations are too unstable (high in energy)to exist

- no carbocation intermediate is possible when the alcohol is primary (mechanism is E2; deprotonation concerted with C-O breakage)
- primary carbocation are too high in energy to be viable intermediates

Hydride Shift in 1° Alcohol



- therefore, hydride migrates at the same time, as water leaves (C-O bond heterolysis) from alkyl oxonium ion intermediate
- concerted process: σ-bond cleavage simultaneous with σ-bond formation

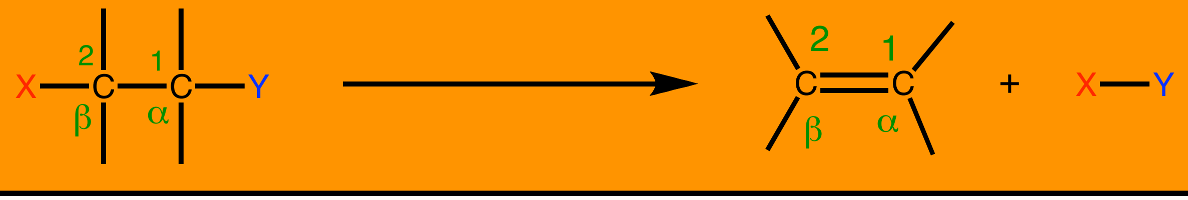
Dehydrohalogenation

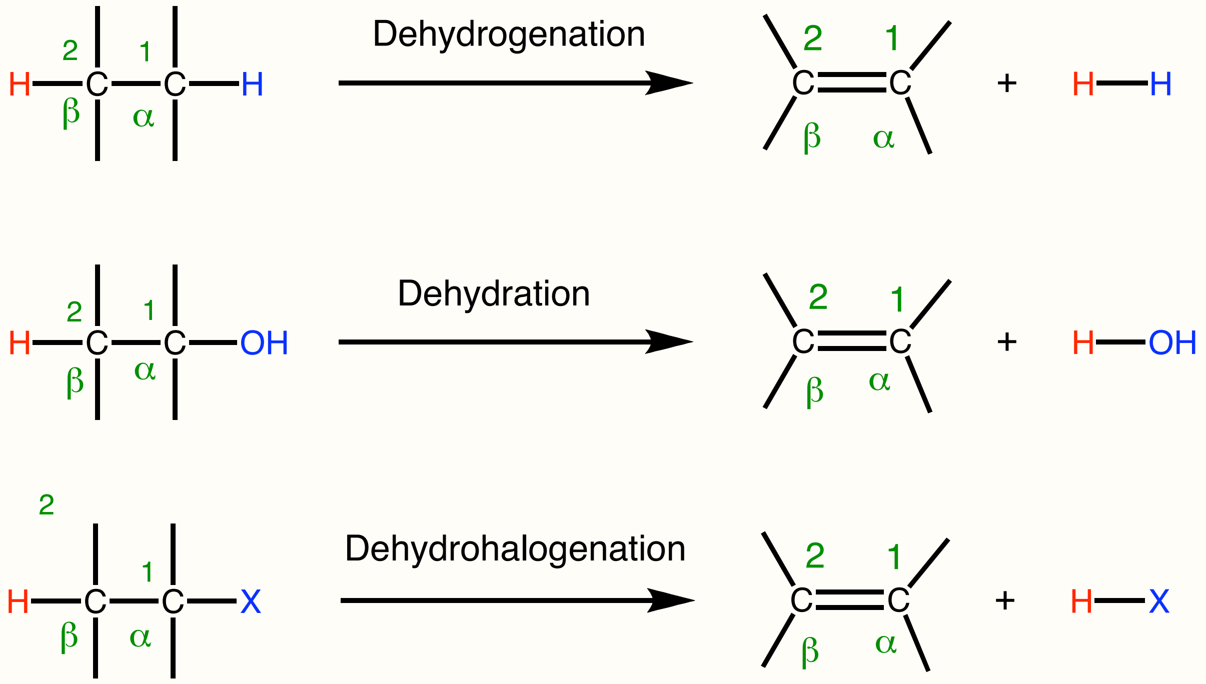
Sections: 5.14-5.16, 5.18

You are responsible for sections 5.17 & 5.18

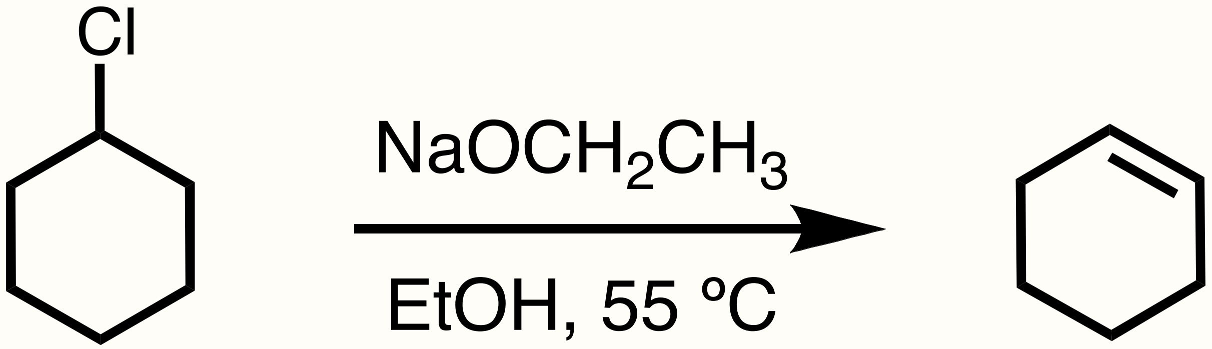
Dehydrohalogenation
An Elimination Process

Summary of β-elimination (1,2-elimination) Reactions



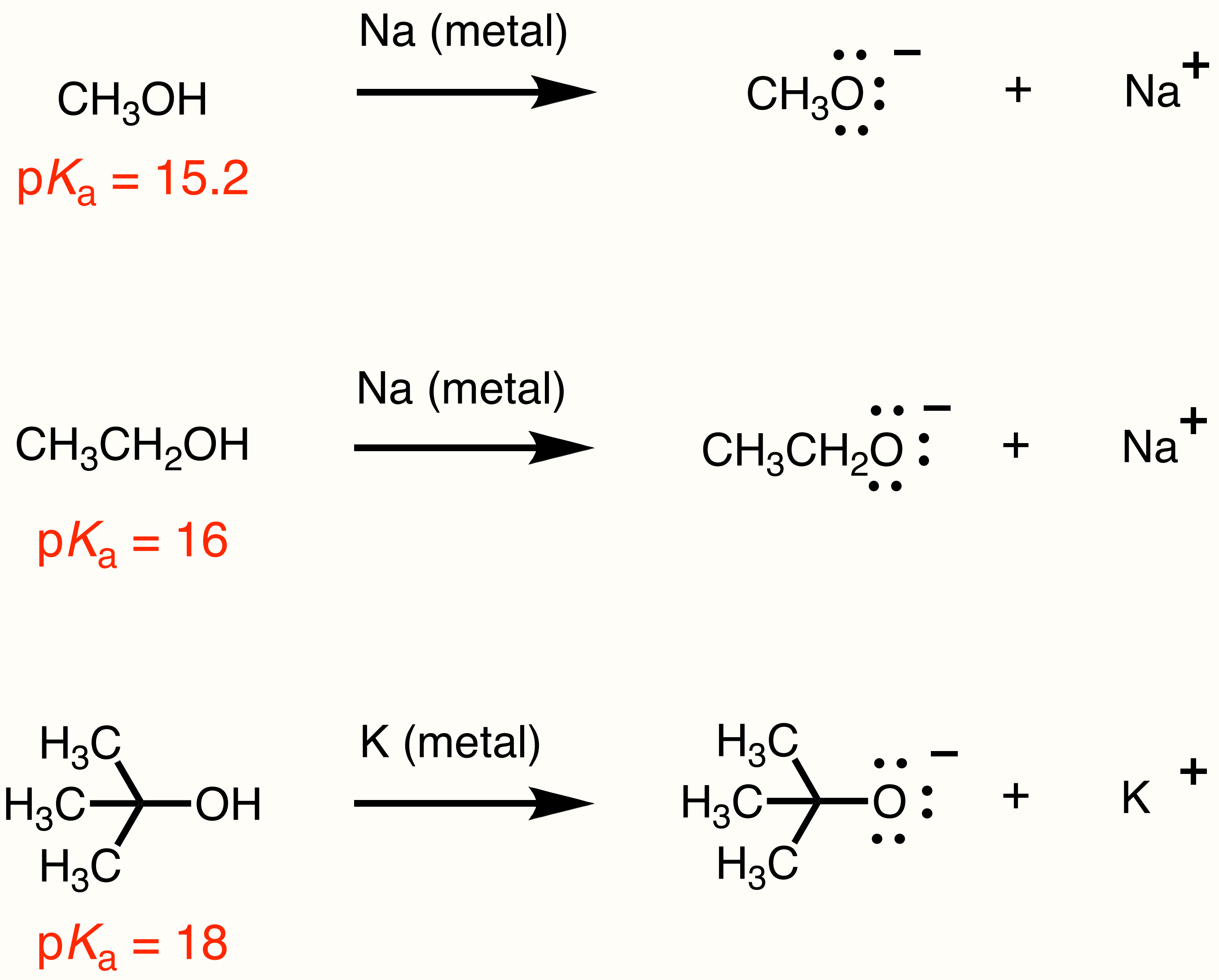


Brønsted Bases Mediate Dehydrohalogenation



- requires strong bases
- most common are conjugate bases of alcohols (alkoxides)
- solvent (liquid the reaction is conducted in) is generally the conjugate acid of the base being used

Generation of Alkoxide Bases



sodium methoxide

$NaOCH_3$

sodium ethoxide

$NaOCH_2CH_3$

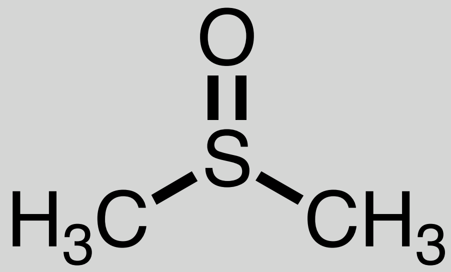
potassium *tert*-butoxide

$KOC(CH_3)_3$

Dimethyl Sulfoxide as Solvent

$$CH_3(CH_2)_{15}CH_2CH_2Cl \xrightarrow[\text{DMSO, 25°C}]{KOC(CH_3)_3} CH_3(CH_2)_{15}CH{=}CH_2$$

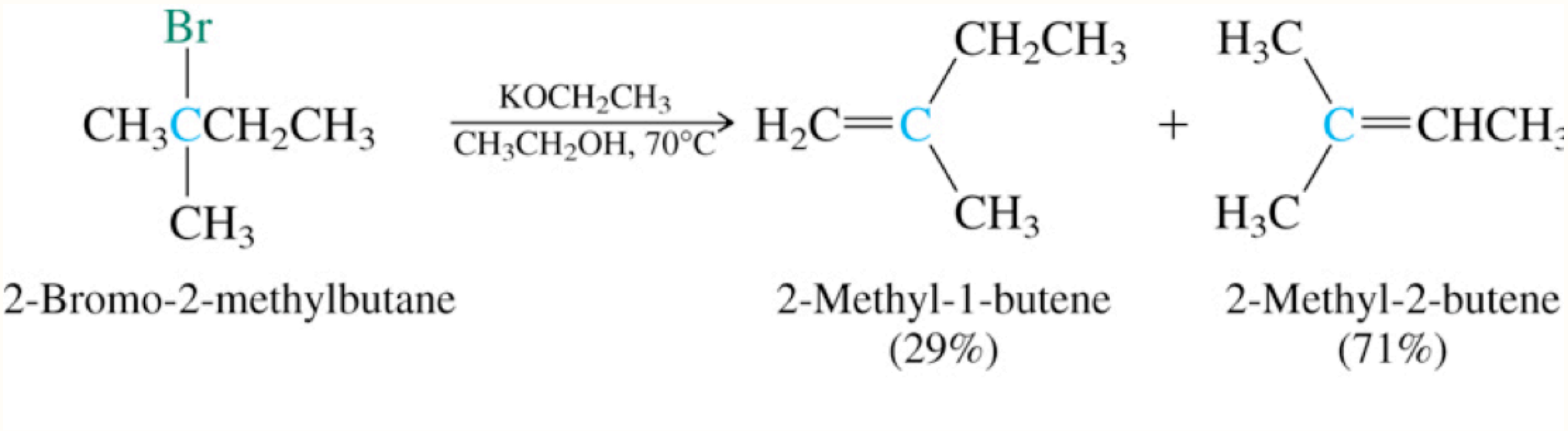
1-Chlorooctadecane 1-Octadecene (86%)



dimethyl sulfoxide (DMSO)

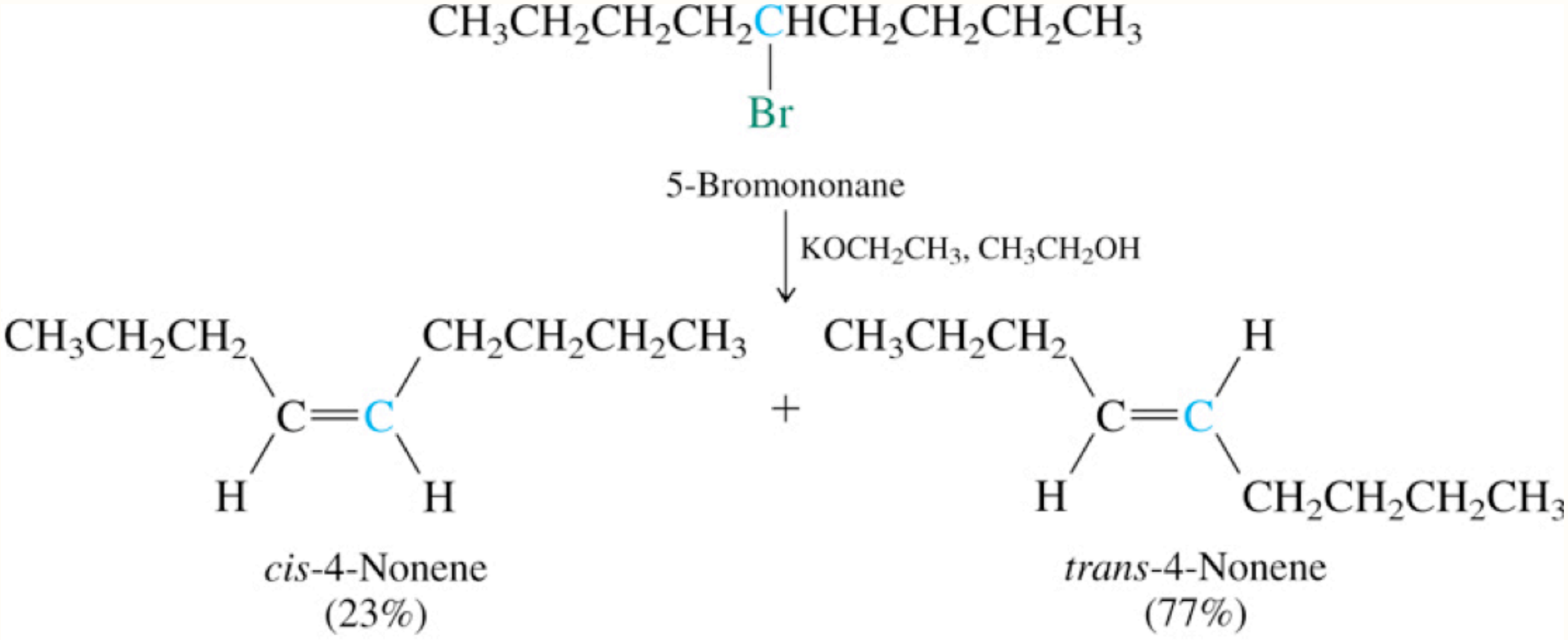
- common solvent for dehydrohalogenations
- very polar; readily dissolves large ionic organic molecules such as $KOC(CH_3)_3$
- relatively non-toxic; safe
- does not participate in the reaction

Dehydrohalogenation is Regioselective



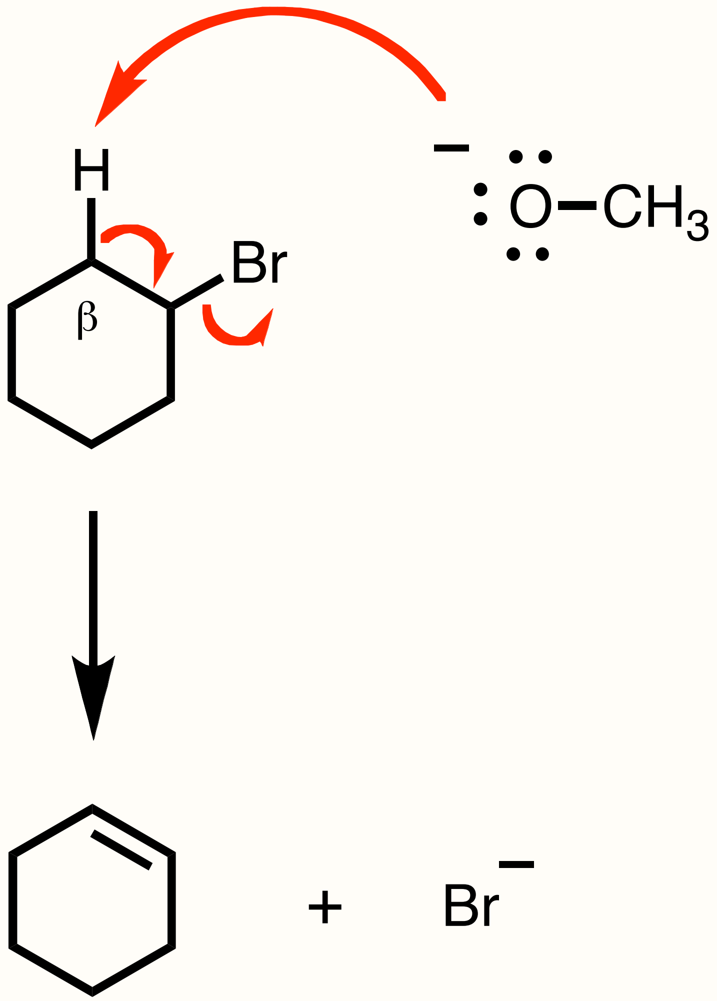
- dehydrohalogenation is regioselective
- Zaitsev's Rule is still followed
- most substituted alkenes are preferred

Dehydrogenation is Stereoselective



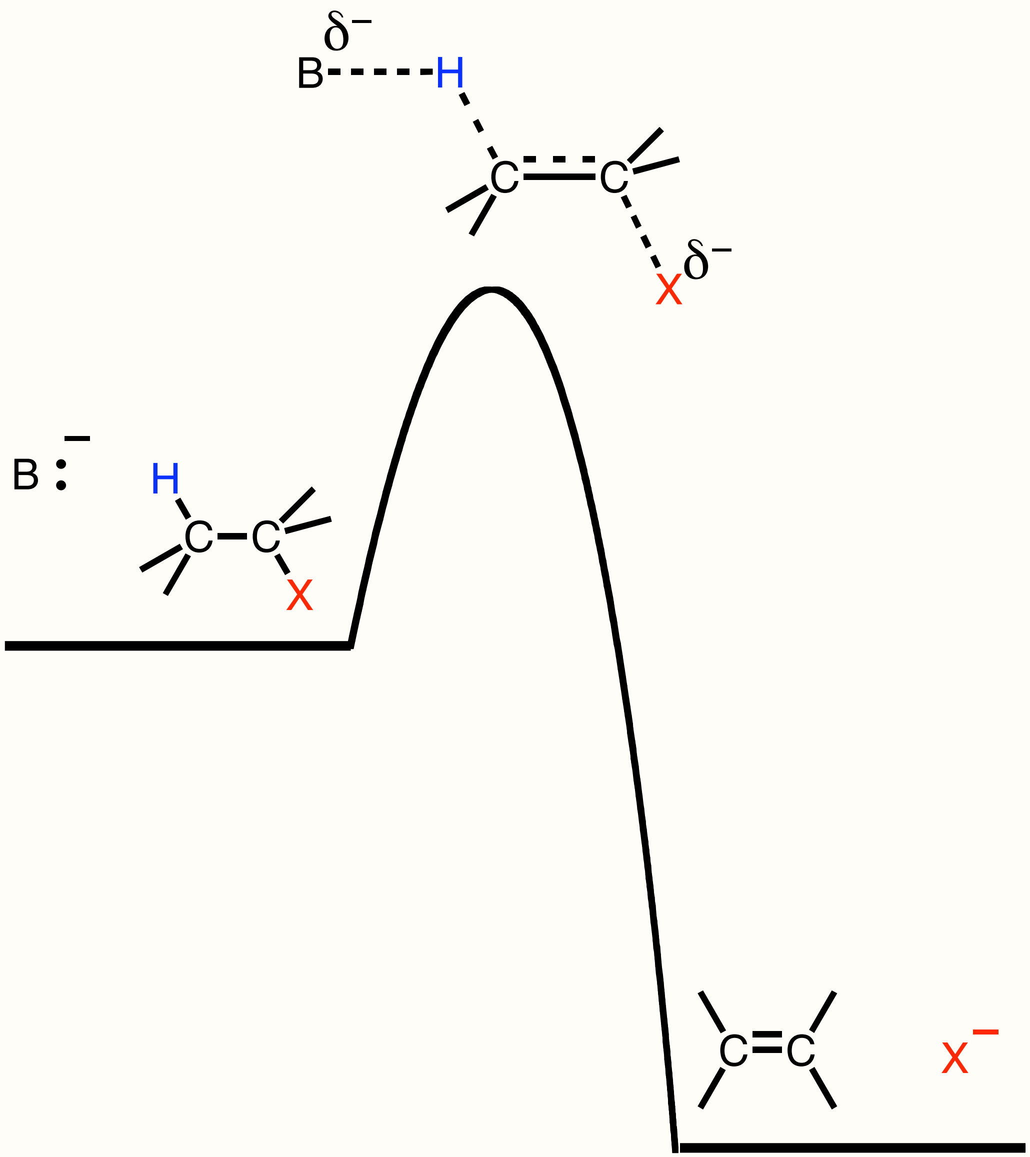
- dehydrohalogenation is stereoselective
- *trans* (E) alkenes are preferred

E2 Mechanism for Dehydrohalogenation



- E2: Elimination, 2nd order (bimolecular)
- dehydrohalogenation is second order (bimolecular)
- two molecules involved in RDS (halide & base)
- rate = k[alkyl halide][base]
- concerted process

Consider Structure of E2 Transition State



Observations

Four key elements in transitions state:

a. B-H σ-bond making

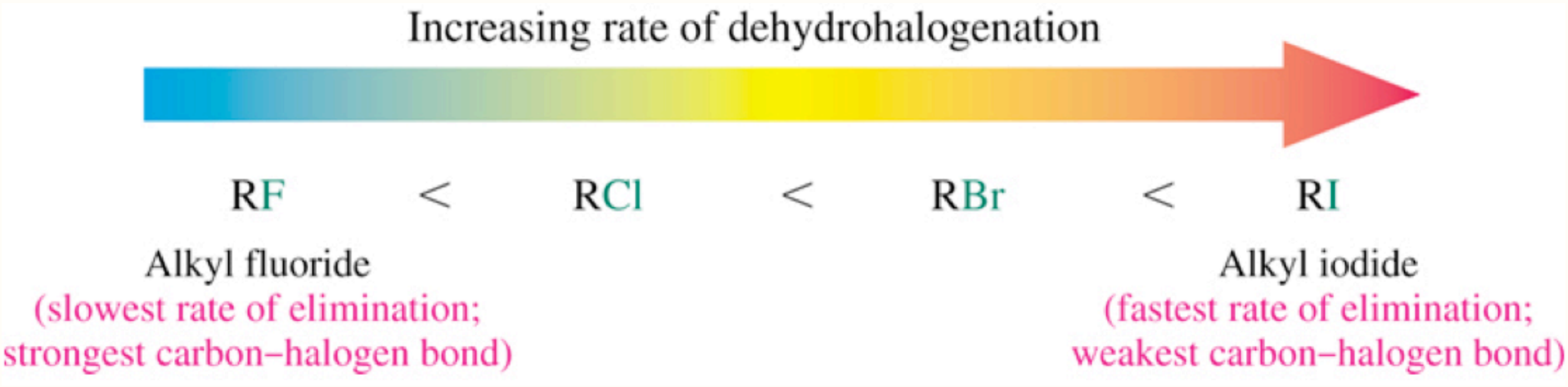
b. C-H σ-bond breaking

c. C-C π-bond making

d. C-X σ-bond breaking

All four processes are concerted (same time)

Leaving Group Ability & Reactivity

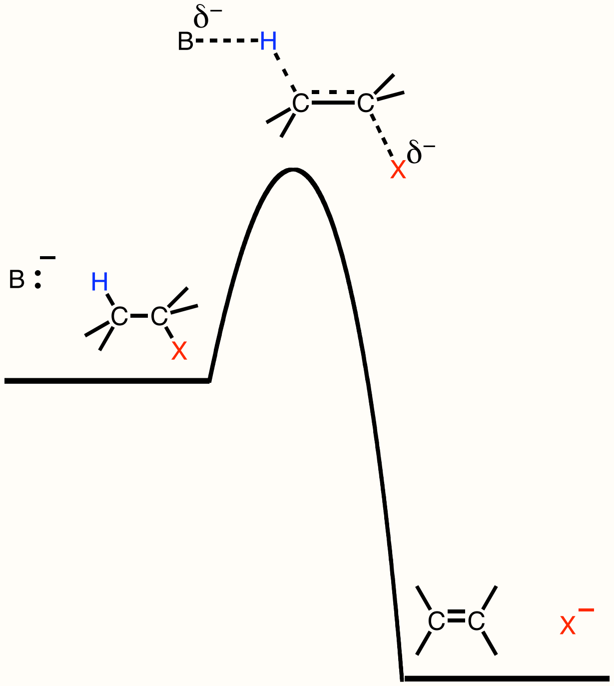


Increasing rate of dehydrohalogenation

RF < RCl < RBr < RI

Alkyl fluoride (slowest rate of elimination; strongest carbon–halogen bond)

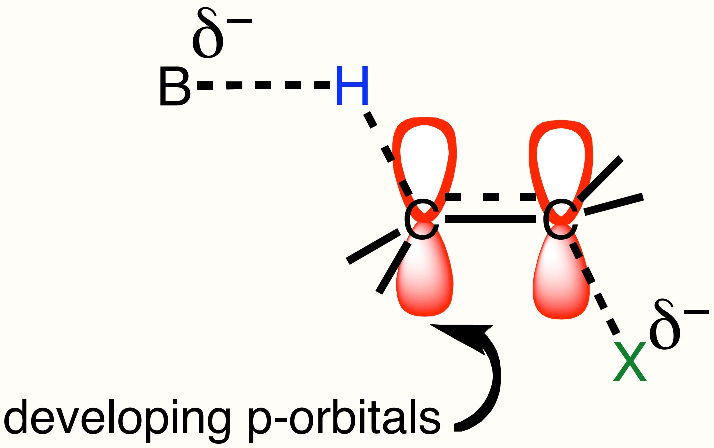
Alkyl iodide (fastest rate of elimination; weakest carbon–halogen bond)



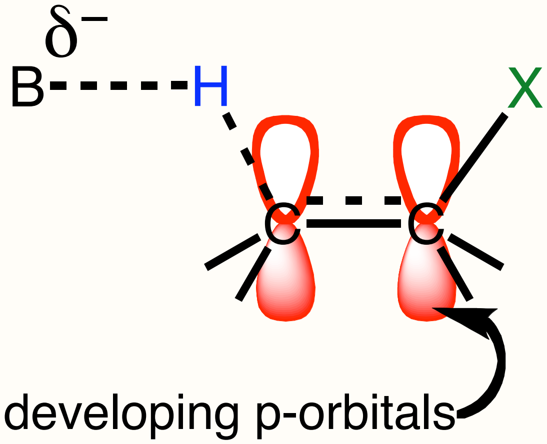
- X orbital size increases down group
- C-X bond strength decreases down group
- weaker C-X bond = breaks faster = faster reaction

Transition States of E2 Eliminations

- π-bond is forms from the 2 σ-bonds being broken
- formation of a π-bond requires that the C-H σ-bond and the C-X σ-bond be planar (parallel)
- two conformations satisfy this stereoelectronic requirement

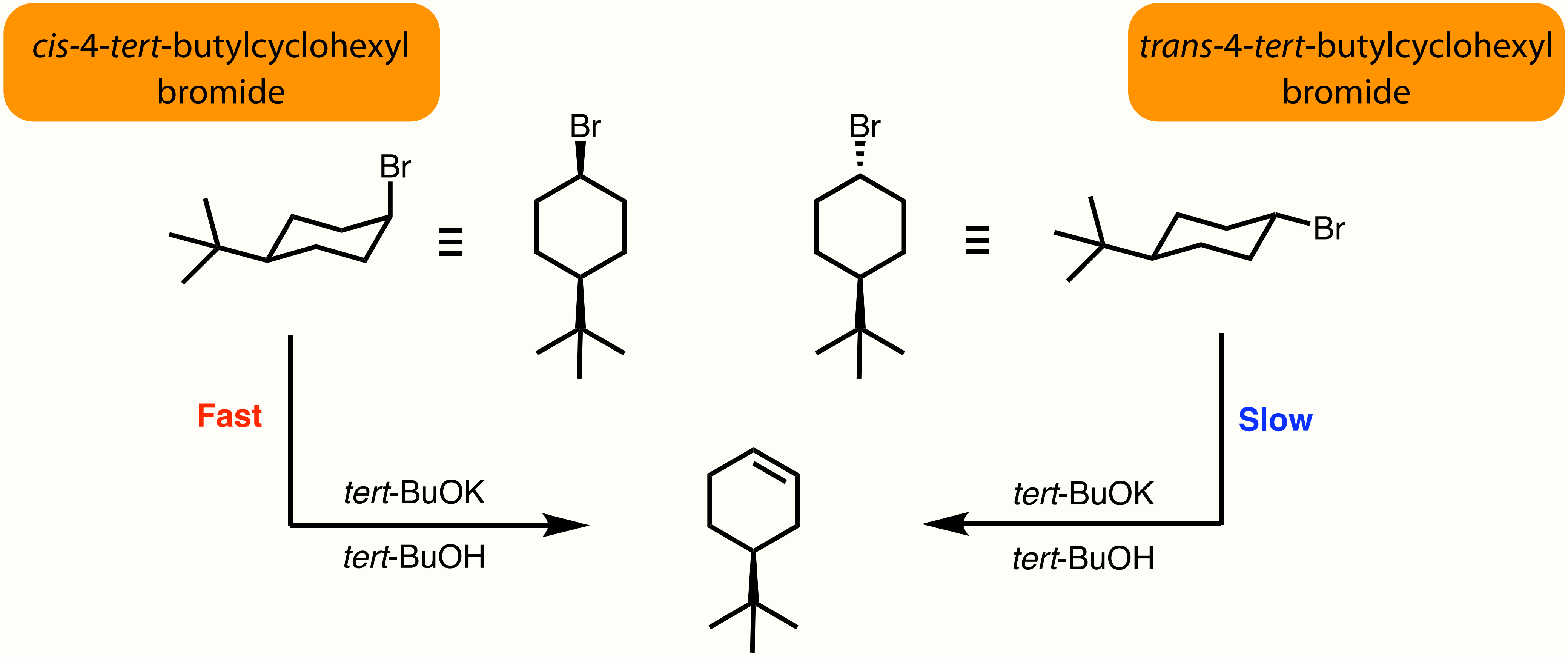


anti periplanar
(anti coplanar)



syn periplanar
(syn coplanar)

E2 Elimination From Cyclohexanes

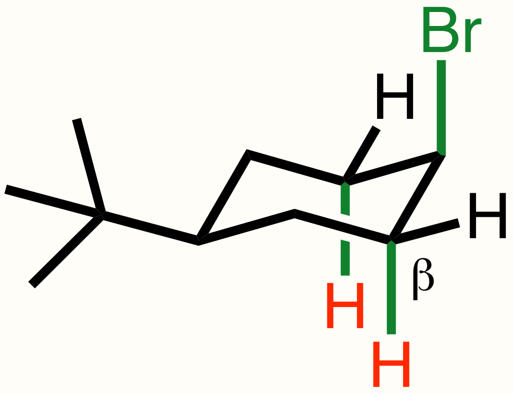


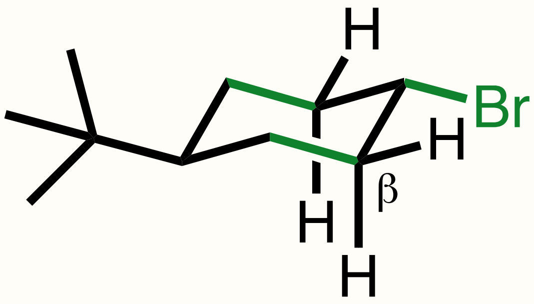
Observation: the *cis* isomer undergoes dehydrogenation faster than the *trans* isomer.

Origin of

cis-4-*tert*-butylcyclohexyl bromide

trans-4-*tert*-butylcyclohexyl bromide



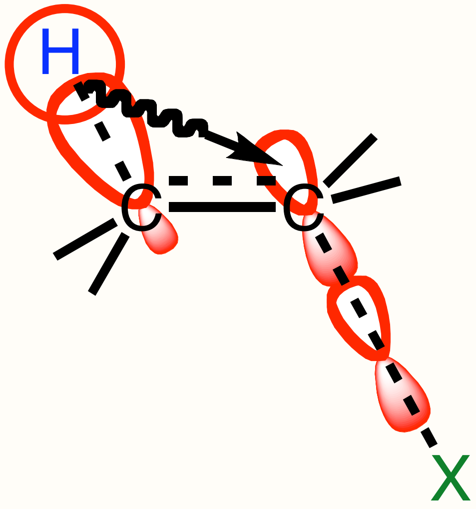


For E2 elimination in cyclohexanes, both C-H and C-X bonds must be *axial*. In case above, only the *cis* isomer satisfies this requirement.

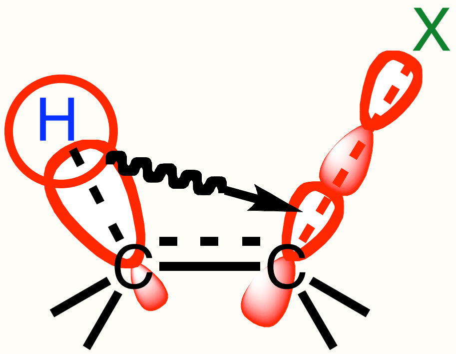
Why *is* E2 elimination fastest when the adjacent groups are anti coplanar? There are two possible rationales. . . .

Rationale One (Best)

Antiperiplanar



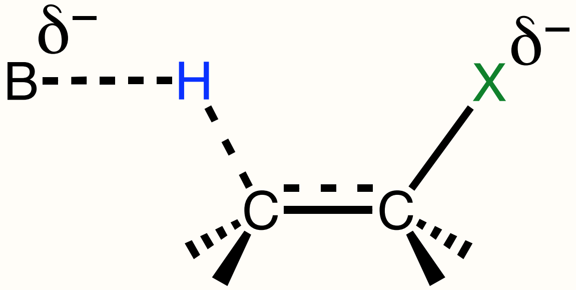
Synperiplanar



- antiperiplanar conformer is favored
- best orbital overlap between C-H σ (bonding) orbitals and C-X σ* (antibonding) orbitals
- better overlap = weaker C-X bond = faster reaction
- stereoelectronic effect = preference for one spatial arrangement of electrons or orbitals over another arrangement

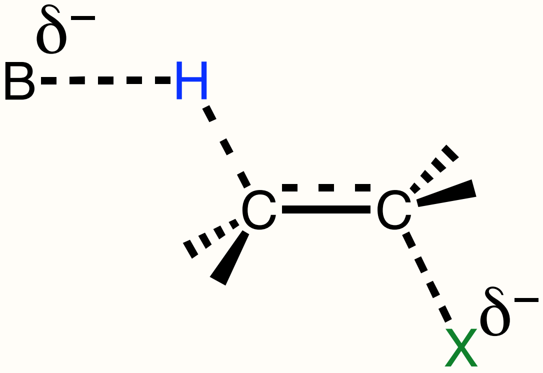
Rationale Two

Synperiplanar



- eclipsed conformation
- all adjacent bonds eclipsed

Antiperiplanar



- anti, staggered conformation
- all adjacent bonds gauche

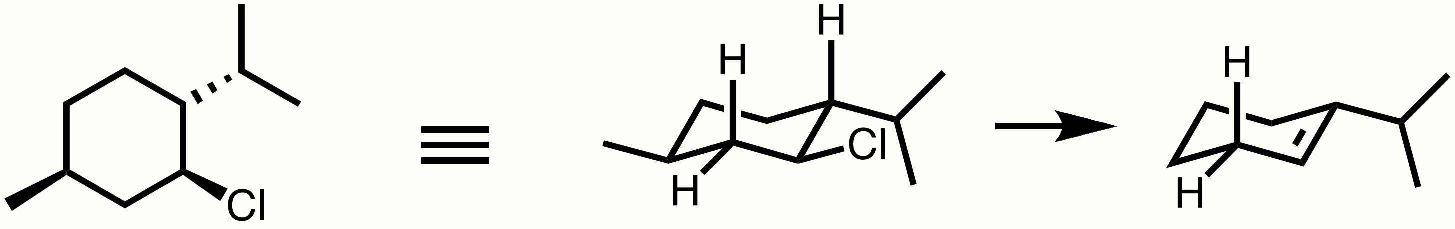
- antiperiplanar conformer favored
- lowest energy transition state conformation is *anti*
- lower transition states energy = faster reaction

Self Test Question

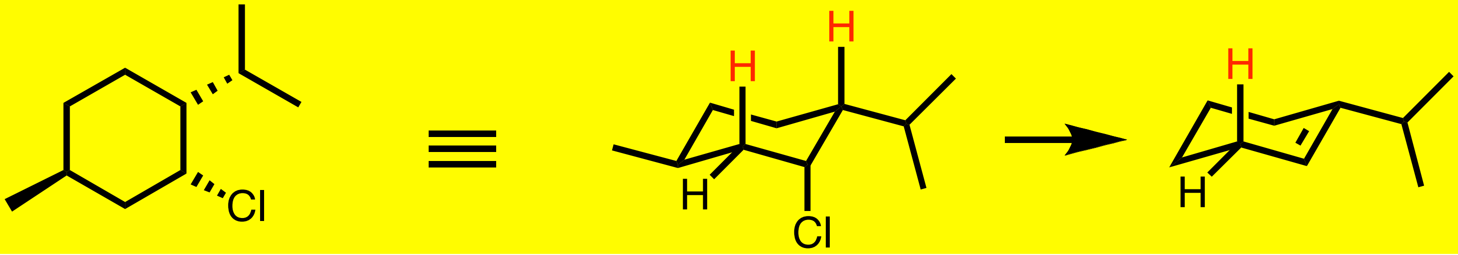
Which cyclohexyl chloride undergoes elimination most rapidly upon treatment with sodium ethoxide?

Hint: Draw the most stable chair conformation of each.

A

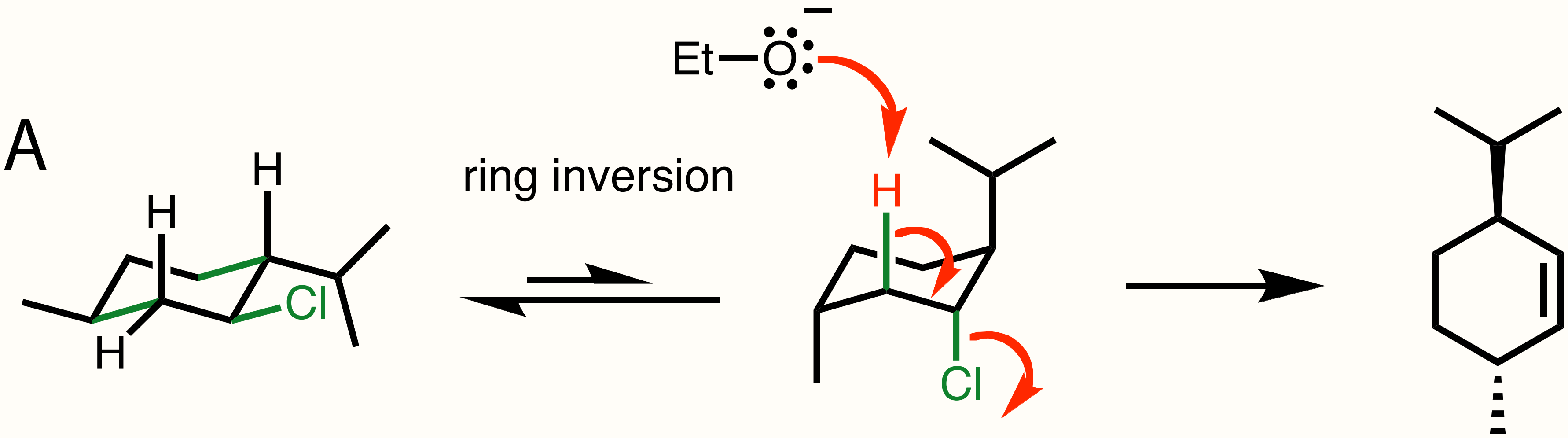


B



Compound A Must Undergo Ring Inversion *Before* E2 Elimination

A



equatorial chloride is anti-periplanar to only **C-C bonds** and cannot be eliminated by E2 mechanism

axial chloride is anti-periplanar to only **C-H bonds** so E2 elimination is possible

Next Lecture...

Chapter 6: Sections 6.1-6.11

Exam One

- Monday, February 15
- 6:00-7:15 p.m.
- 250 SES
- Chapters 1-5 (everything!)
- Makeup Exam: Monday, Feb. 22, time t.b.a.

Makeup policy: There are no makeup exams without **prior** approval. Only students showing proof of a class conflict will have the option to take a makeup exam. To be added to the makeup list, you must email me no later than Friday, Feb. 12.

Exam One Grade Distribution

Q1. Ranking (50 points)

Q2. Predict the Products (50 points)

Q3. Arrow-Pushing Mechanism (50 points)

Q4. Nomenclature (20 points)

Q5. Drawing & Conformational Analysis (50 points)

Q6. Functional Groups (30 points)

Exam One Policies

- Non-scientific calculators allowed only
- No cell phones, ipods or others electronic devices
- No molecular models
- Periodic table will be provided
- Seating will be assigned
- **Bring Your I.D.**