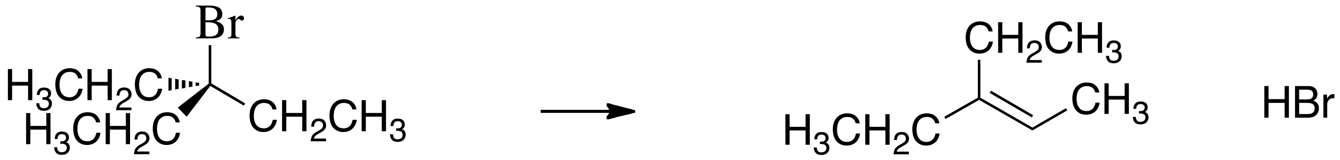
Eliminations

Instead of substitution reactions, another reaction that can occur
when a leaving group is present is an elimination reaction

An elimination is when the leaving group and another atom (typically a hydrogen)
leave the molecule and no new atoms are added

- Two species have therefore been eliminated

An elimination results in the formation of a new π bond



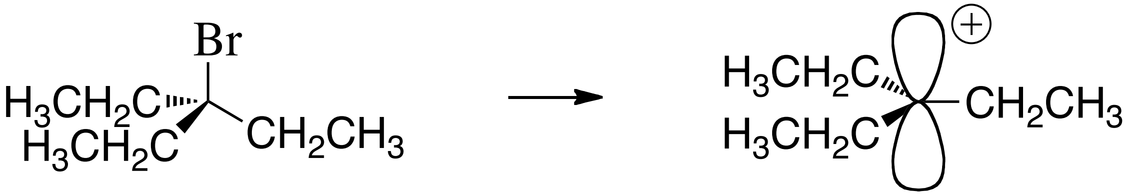
A convenient method to form alkenes
(actually this is the reverse of an hydrogen halide addition to an alkene)

Elimination Reactions

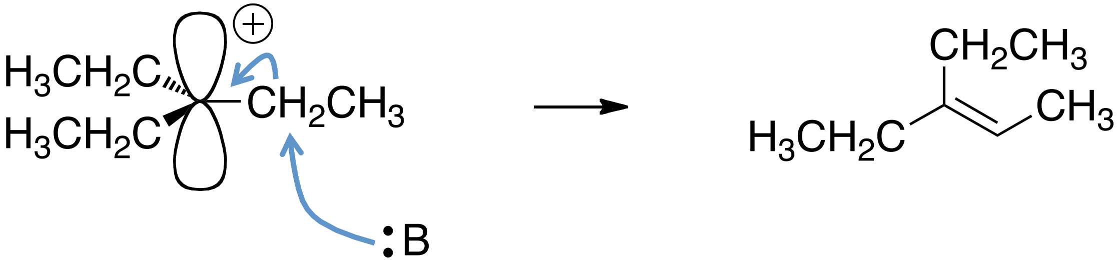
There are three versions of an elimination reaction: E1, E2 and E1cB
(the E1cB mechanism is very rare and only occurs under very select conditions)

E1: Elimination, Unimolecular

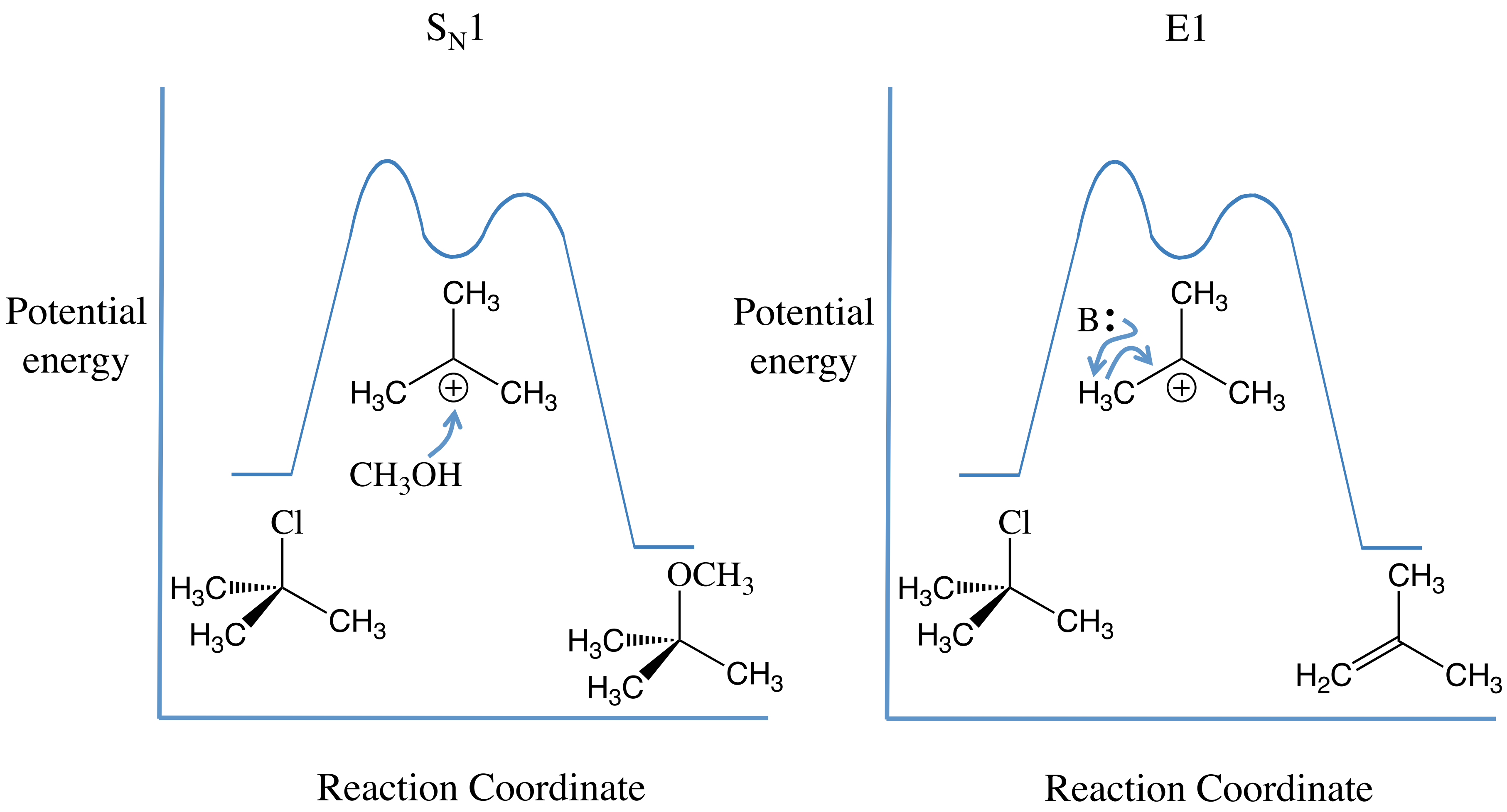
This mechanism is similar to the S_N1 mechanism
The leaving group departs in the rate determining step to generate a carbocation



A base then abstracts a hydrogen from a carbon ADJACENT to the carbocation
to form a new π bond



S_N1 and E1 Reactions Have Identical Energy Diagrams for Rate Determining Step

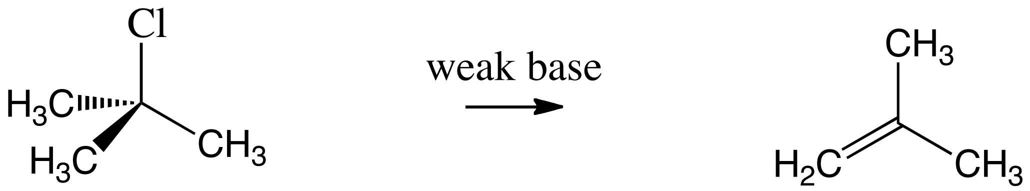


Rate = k [substrate]

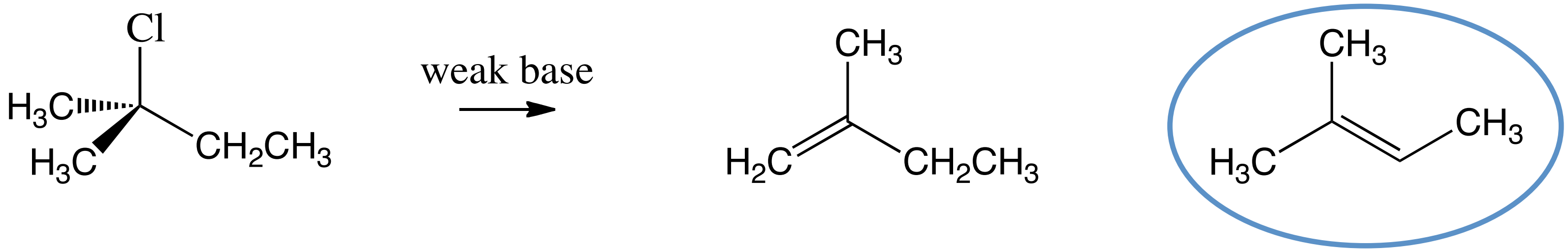
Rate = k [substrate]

Regioselectivity in E1 Reactions

With the t-Butyl Chloride starting material shown, only one possible E1 product is possible as all three methyl groups are symmetrically equivalent



With an unsymmetrical tertiary chloride, however, different products can be obtained

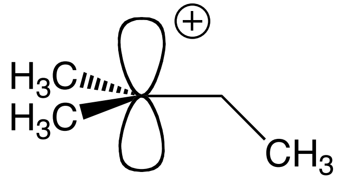


In an E1 reaction, the more substituted alkene is favored

Saytzeff Elimination

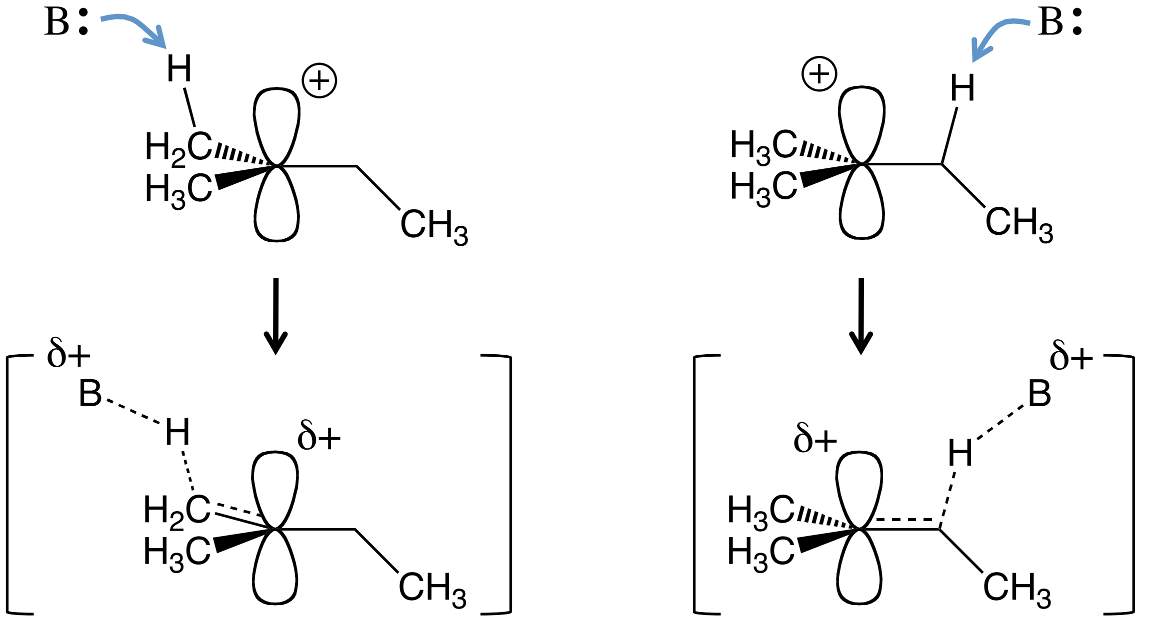
This preference for the more substituted alkene is referred to as the “Saytzeff” rule
(Sometimes translated as Zaitsev, Zaitzev, Saytzev)

The preference for the more substituted alkene is due to the lower energy transition state



First obtain 3° cation

The cation could have the base abstract
either of the adjacent hydrogens

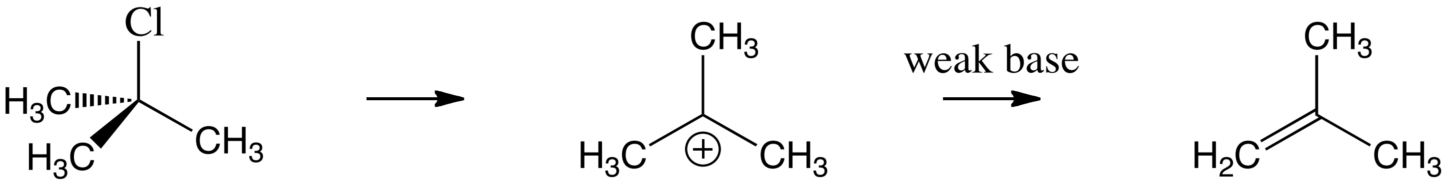


As seen with alkenes, the more alkyl substituents the more stable,
thus the more substituted alkene transition state is favored

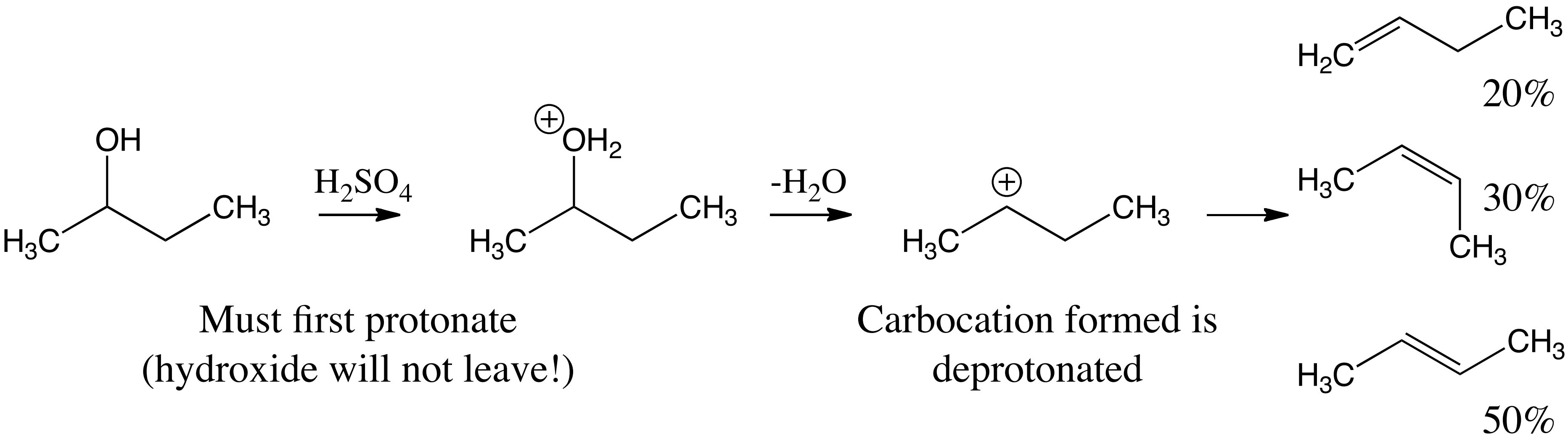
Elimination Reactions

E1 reactions can occur whenever a cation intermediate is generated

Have observed this with alkyl halides



Also observe this reaction with alcohols under acidic conditions



Must first protonate
(hydroxide will not leave!)

Carbocation formed is
deprotonated

Still have Saytzeff preference

Elimination Reactions

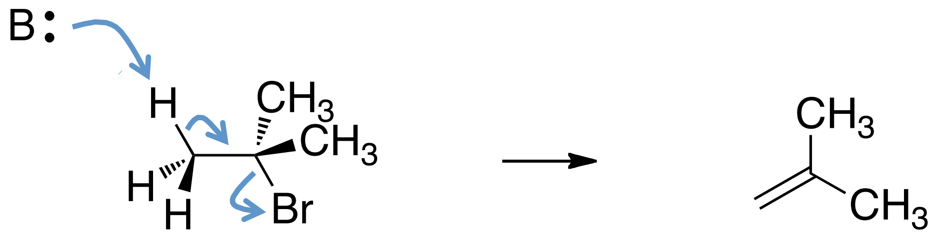
Eliminations can also occur in a single step

E2: Elimination, Bimolecular

Rate = k [substrate][base]

One step reaction, but bimolecular!

The base abstracts a hydrogen on an ADJACENT carbon to leaving group in a single step



These three bonds must be
aligned to allow reaction
in a single step

E2 Reactions

E2 reactions require a strong base

As seen by the rate equation, the properties and concentration of the base will affect the reaction

Similarity to S_N2:
Both are bimolecular and are affected by the substrate and base (or nucleophile)

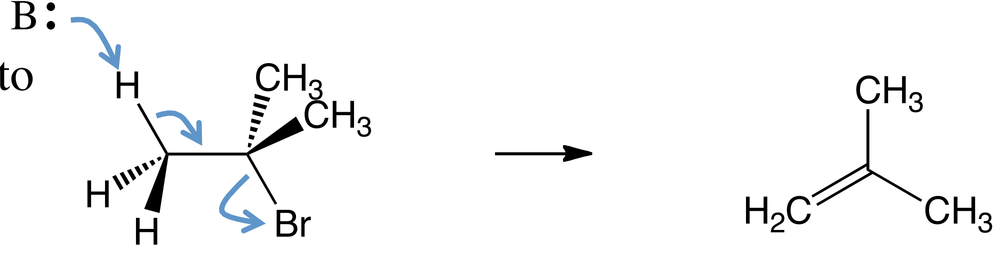
The difference is the reactivity of the substrate

S_N2: $1^\circ > 2^\circ > 3^\circ$
E2: $3^\circ > 2^\circ > 1^\circ$

E2 Reactions

The strong base (which can also react as a nucleophile) has too much steric hindrance to react at a 3° site for a S_N2 mechanism

The 3° halide therefore prefers an E2 mechanism



Too much sterics for approach to 3° carbon

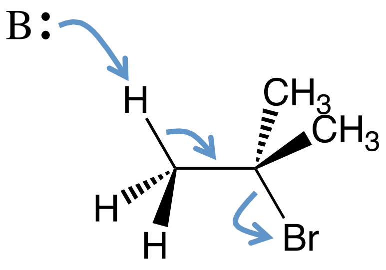
Far easier approach to adjacent hydrogen

In addition, the E2 mechanism also follows Saytzeff's rule with unsymmetrical alkyl halides

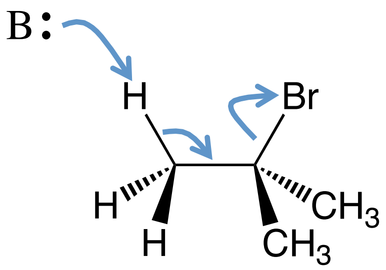
Stereochemistry of E2 Reaction

There are only two possible orientations for the E2 reaction

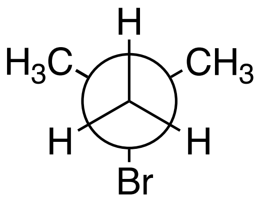
The C-H, C-C and the C-Br bond must be coplanar to allow a concerted elimination
(all bonds being broken or formed in reaction must be in the same plane)

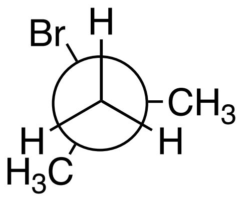


Anti-coplanar



Syn-coplanar

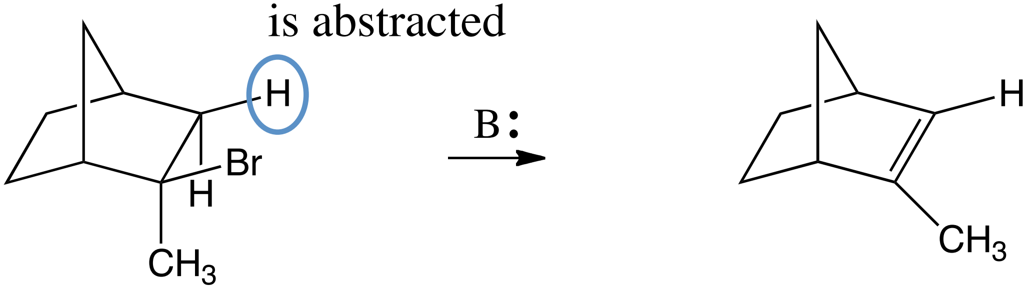




The anti-coplanar arrangement is preferred due to lower non-bonded interactions (sterics), thus E2 reactions proceed with a high stereochemical preference for the anticoplanar

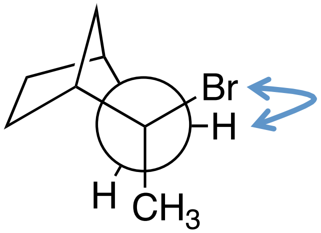
Stereochemistry of E2 Reaction

While the anti-coplanar arrangement is highly favored for acyclic compounds, in some constrained systems it might not be possible to align the leaving group and hydrogen on adjacent carbon in an anti- arrangement



This hydrogen is abstracted

Consider this bicyclo[2.2.1]heptyl compound



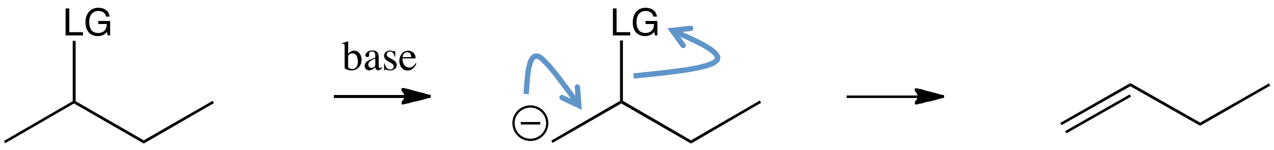
0°, aligned in syn for E2

120°, not aligned for E2

Newman projection

E1cB Eliminations

A different type of elimination involves a base abstracting a proton in the rate determining step and is called E1cB (elimination, unimolecular, conjugate base)



E1cB is also a two-step reaction like E1, but the steps are reversed
(first step is loss of hydrogen and second step is loss of leaving group)

Also notice that the intermediate in the rate determining step forms an anion, not a cation

Stability of anions is opposite that of cations
(methyl anion > 1° anion > 2° anion > 3° anion)

Therefore the regiopreference in a E1cB reaction is often the less substituted alkene

Called the Hofmann product

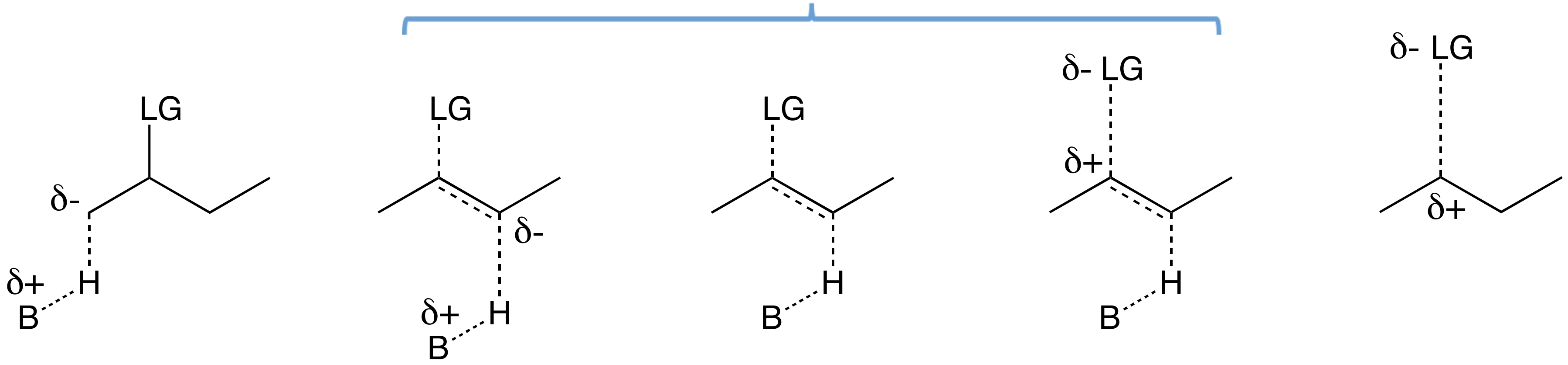
E1cB Eliminations

E1cB eliminations are very rare, but the transition state for a E1cB falls on a continuum for other elimination reactions

E1cB

E2

E1



Only C-H bond is breaking, need to stabilize δ-

C-H bond is mostly breaking, also forming π bond and LG bond is breaking, need to stabilize δ-

Synchronous E2

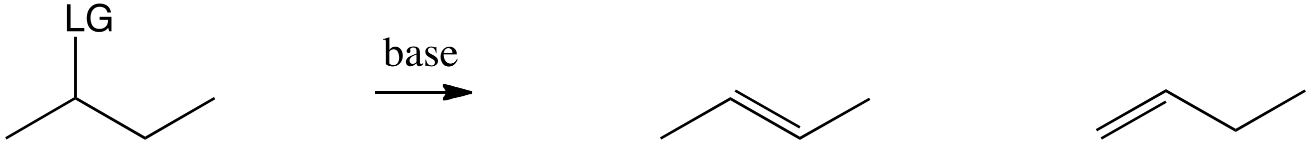
C-LG bond is mostly breaking, less change in C-H bond, need to stabilize δ+

Only C-LG bond is breaking, need to stabilize δ+

Increasing C-LG bond length

Hofmann Eliminations

The more substituted alkene product is therefore called the Saytzeff product
while the less substituted alkene product is called the Hofmann product

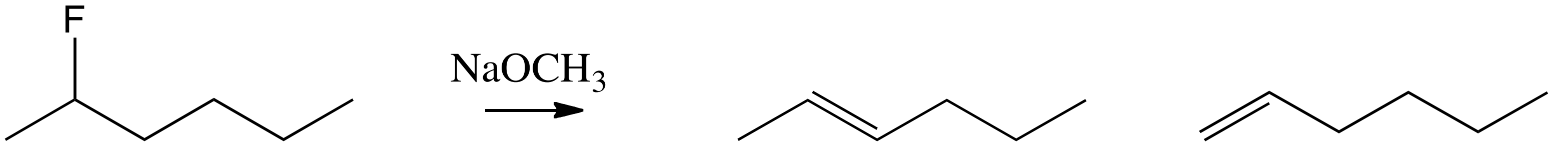


Saytzeff product   Hofmann product

Usually the Saytzeff product is preferred,
but there are some consistent factors which can favor the Hofmann product

-poor leaving groups that have high electronegativity can favor the Hofmann

Classic example is fluorine, very poor leaving group so E2, E1, S_N2 or S_N1 are difficult due to leaving group departing in rate determining step is difficult, but very electronegative so can stabilize negative charge in E1cB like transition state

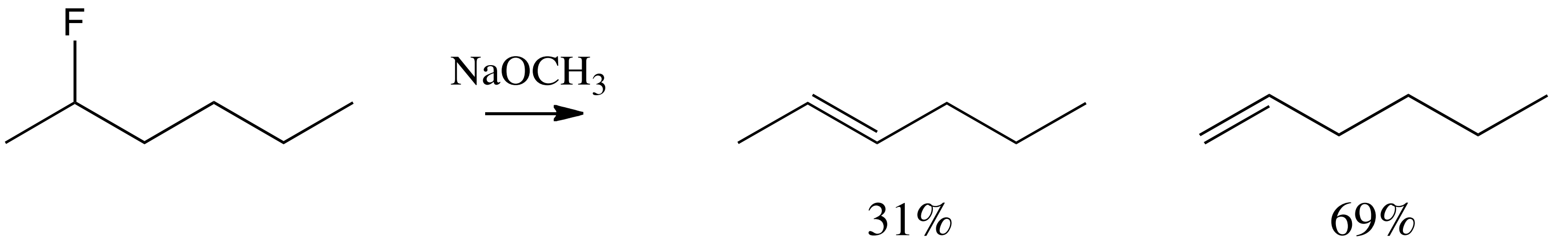


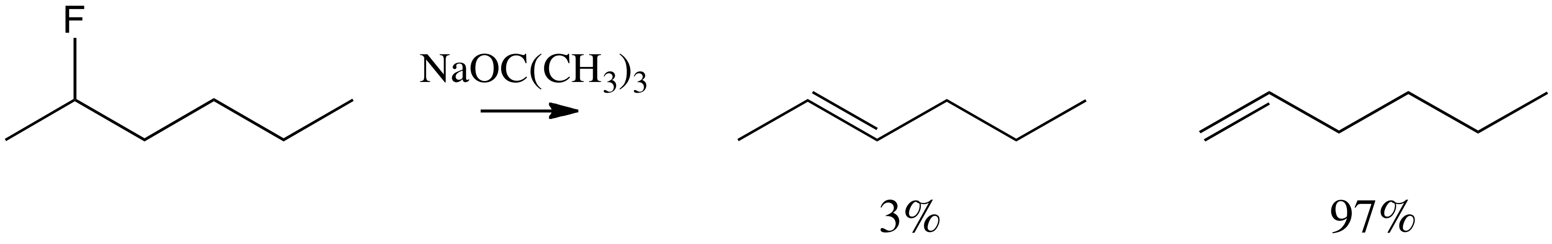
31%   69%

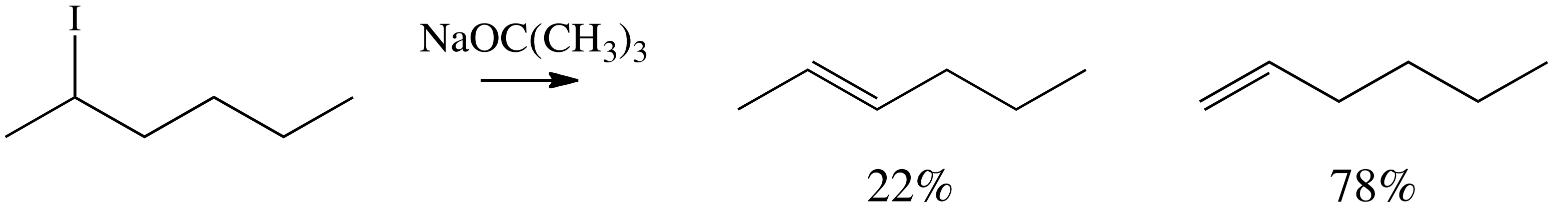
Hofmann Eliminations

Very bulky bases can favor the Hofmann product

As the size of the base increases,
the sterics to approach the hydrogen at the more substituted carbon increases



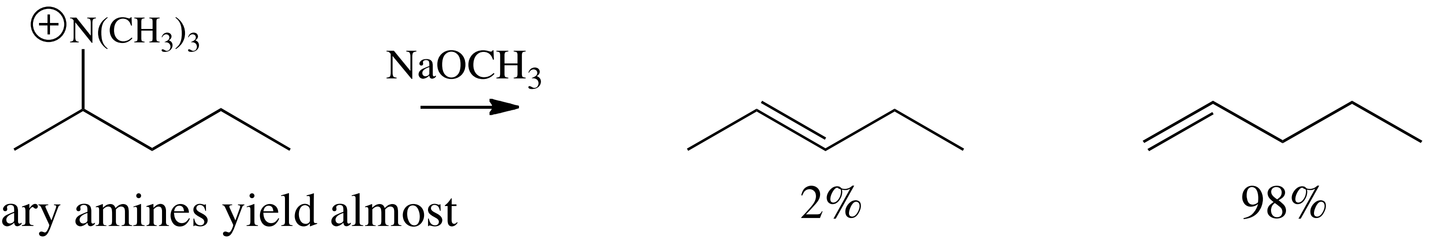




Hofmann Eliminations

In addition to the size of the base,
the size of the leaving group impacts whether Hofmann product is preferred

Very large leaving groups favor the Hofmann product



Quaternary amines yield almost
exclusively Hofmann product

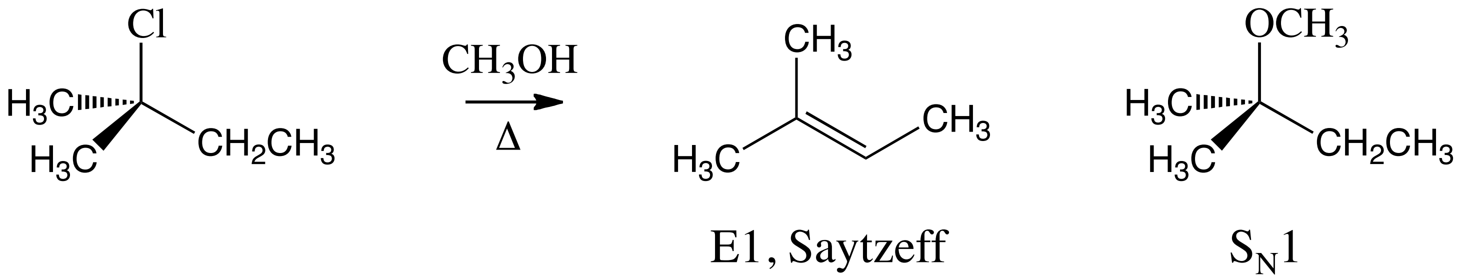
The reason for this preference compared to other E2 reactions
is the bulkiness of the quaternary amine leaving group

E2 reactions must be anticoplanar

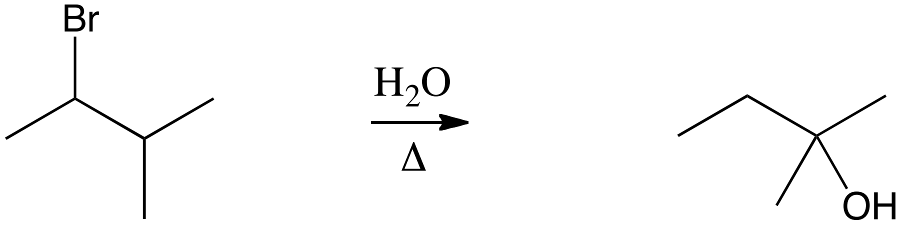
Rearrangements

Have observed carbocation intermediates in three different types of mechanisms:
S_N1, E1 and alkene additions

When these reactions occur at 3° carbons,
the products obtained are predicted by the structure of the starting material



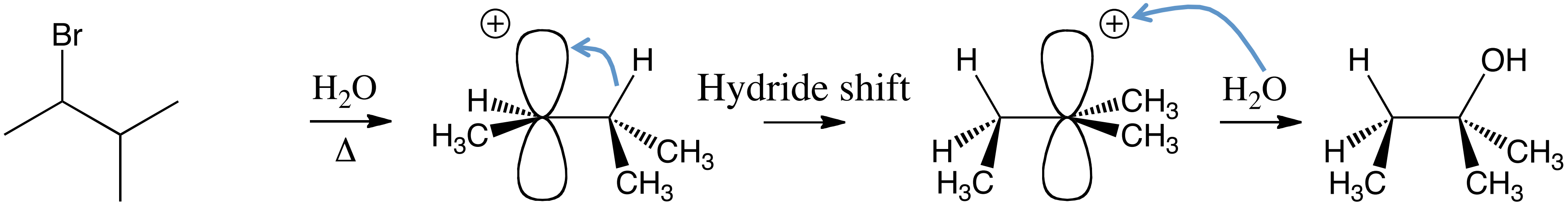
When a carbocation is formed at a 2° or 1° carbon, however,
often the product structure is different than the starting material



Rearrangements

The product has thus undergone a “rearrangement” during the reaction

The mechanism still undergoes a carbocation intermediate



2° cation

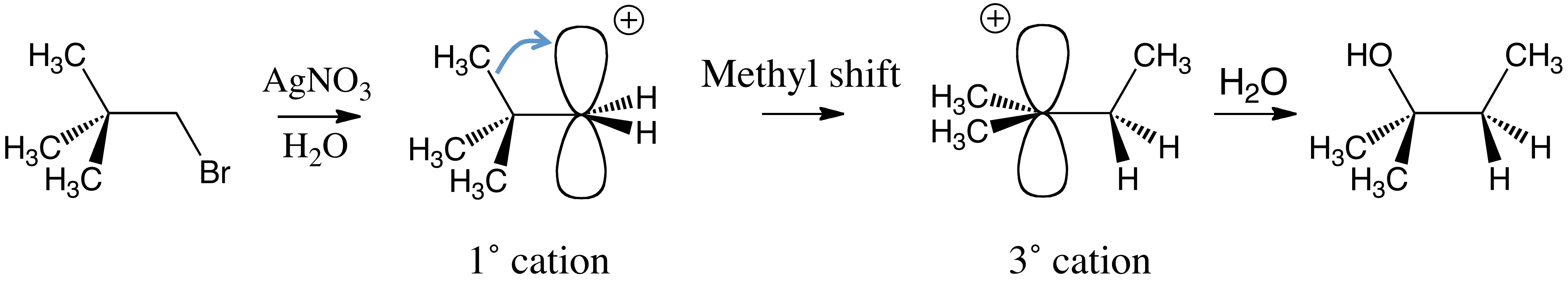
3° cation

The rearrangement is energetic driven by the formation of a more stable intermediate (3° cation versus 2° cation) on the energy diagram

In any reaction that has a cation intermediate, a rearrangement is possible, and energetically favorable, if a more stable cation can be formed after the rearrangement

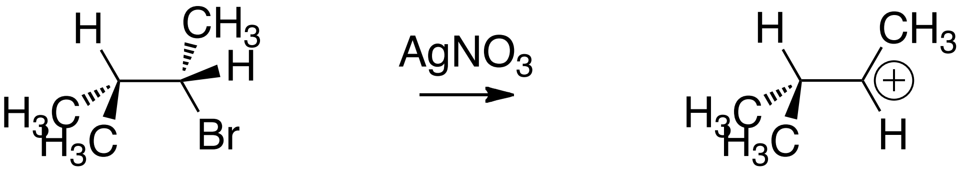
Rearrangements

The rearrangement can involve alkyl shifts in addition to hydride shifts
(alkyl shifts are called Wagner-Meerwein rearrangements)



One way to guarantee cation formation is to react an alkyl halide with $AgNO_3$

Causes the formation of a silver salt (which crystallizes out of solution)



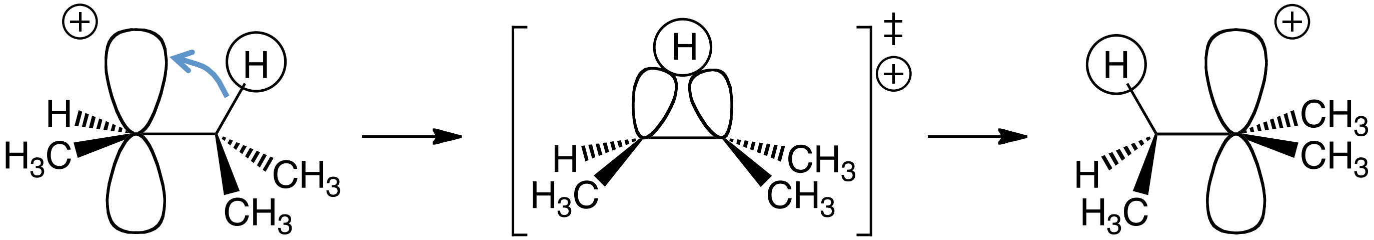
A convenient way to study carbocation reactions and rearrangements
(i.e. S_N1 and E1)

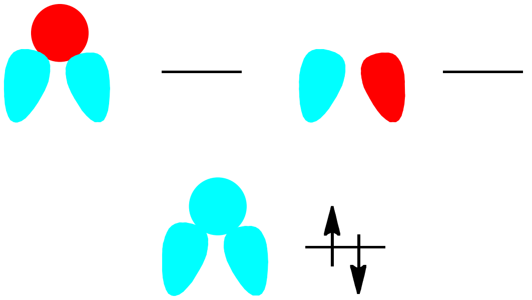
Rearrangements

Rearrangements only occur with cations, not with anions or radicals

Process occurs with an orbital on an adjacent atom interacting
with the empty p orbital of the carbocation

Consider the orbital interactions for the transition state for this process





Antibonding molecular orbital

Bonding molecular orbital

In a cation rearrangement, 2 electrons are involved in a bonding molecular orbital

In a radical or anion rearrangement, additional electrons would be placed in antibonding molecular orbitals (therefore a less stable process)

Comparison of E1 and E2 Reactions

Effect of Substrate

In a E1 reaction a carbocation is formed
Thus a more substituted carbocation is more stable

In a E2 reaction an alkene is formed in the rate determining step
Follows Saytzeff rule where a more substituted alkene is favored

Therefore both E1 and E2 reactions the rate follows the trend:

$3^\circ > 2^\circ > 1^\circ$ (1° usually will not go by E1)

Effect of Base

Single most important factor for eliminations

If the substrate is suitable for an elimination
then a strong base will favor an E2 mechanism

A weak base will favor ionization (E1) first

Therefore:

E2	strong base required
E1	base strength unimportant

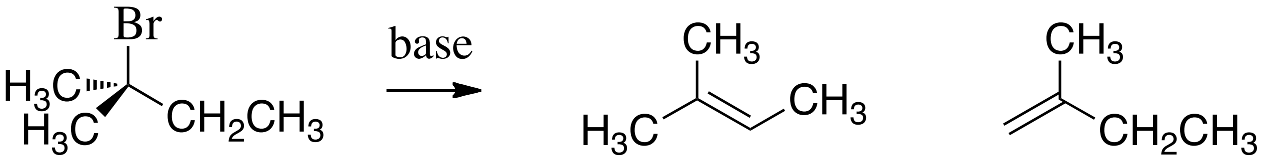
$HO^{\ominus}$ $RO^{\ominus}$ $R\overset{\ominus}{N}H$ $\overset{\ominus}{C}H_3$

Strong bases

Orientation of Eliminations

The product with the more substituted double bond will be favored

Saytzeff rule is followed by both E1 and E2



Saytzeff Hofmann

Hofmann rule is followed only in specific cases
(for example poor leaving group, very steric bases, or steric leaving groups)

Competition Between Substitution and Elimination

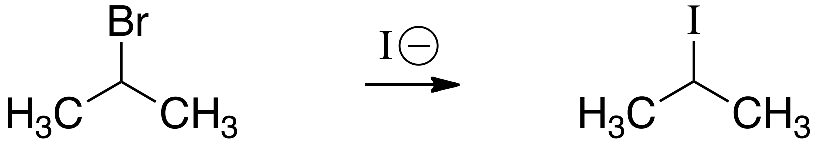
A reaction with a given alkyl halide can follow one of four mechanism
(S_N2, S_N1, E2, E1) yielding different products

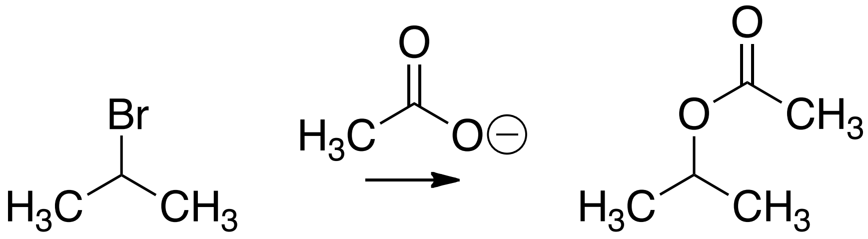
Trends to predict which mechanism will predominate

1) Weakly basic species that are good nucleophiles give predominantly substitution

Examples: halides, RS-, N_3-, RCO_2-

Therefore 1° or 2° halides yield clean S_N2
3° halides give predominantly S_N1 (E1 usually minor pathway)

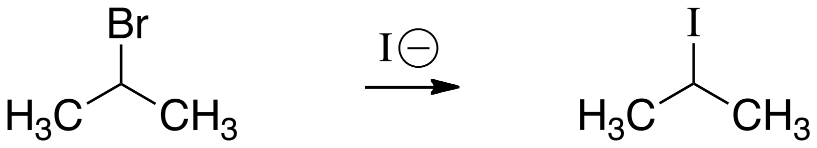


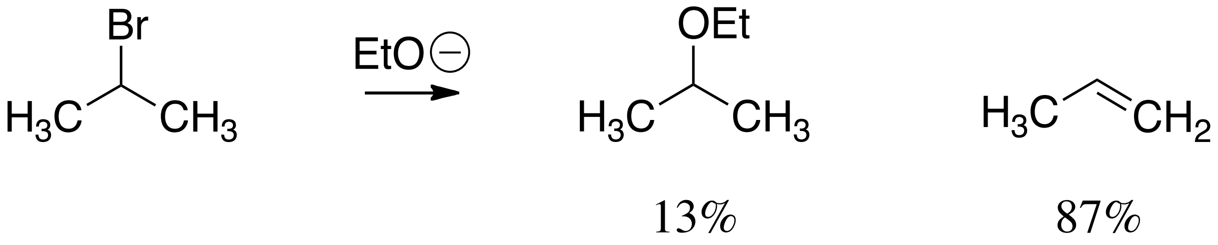


Competition Between Substitution and Elimination

2) Strongly basic nucleophiles give more eliminations

E2 mechanism starts to compete with S_N2 as base strength increases





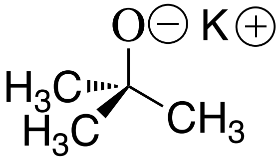
-with methyl halides or 1° halides S_N2 predominates with strong base (nucleophile)
-with 3° halides S_N2 mechanism is impossible and E2 predominates with strong base

Competition Between Substitution and Elimination

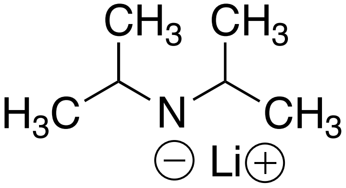
3) Sterically hindered basic nucleophiles favor eliminations

-Just as elimination becomes favored with sterically hindered substrates
E2 becomes favored with sterically hindered bases

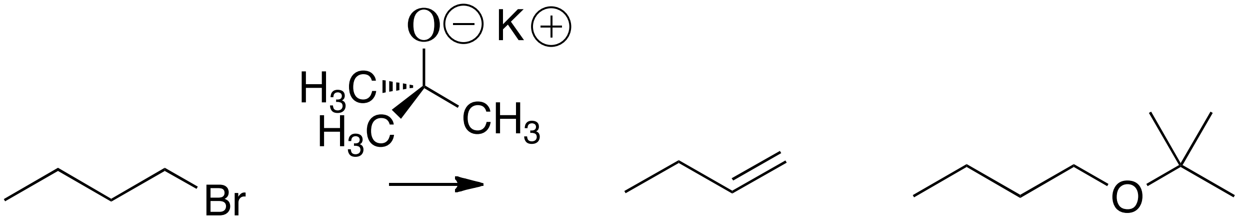
Some common sterically hindered bases



Potassium t-Butoxide



Lithium diisopropylamide
(LDA)



85%

15%

Factors for Substitution versus Elimination

1) Base strength of the nucleophile

Weak	Strong
Halides, RS-, N_3-, NC-, RCO_2-	HO-, RO-, H_2N-
Substitution more likely	Elimination increases

2) Steric hindrance at reacting carbon

Sterically unhindered	Sterically hindered
Methyl, 1°	Branched 1°, 2°, 3°
Substitution predominates	Elimination increases

3) Steric hindrance of strongly basic nucleophile

Sterically unhindered	Sterically hindered
HO-, CH_3O-, H_2N-	$(CH_3)_3CO$-, LDA
Substitution may occur	Elimination favored

Summary of Reactivity of Alkyl Halides

Methyl halide

Reacts only through S_N2 pathway

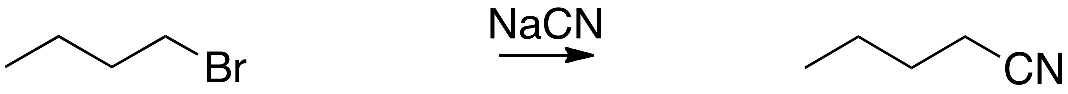
-No other possibilities
No adjacent carbons to form π bond
Methyl cation is too high in energy to go through S_N1 pathway

Primary Alkyl Halides

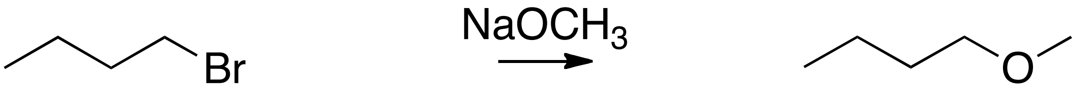
Reactivity of R-X with nucleophiles

Unhindered primary R-X

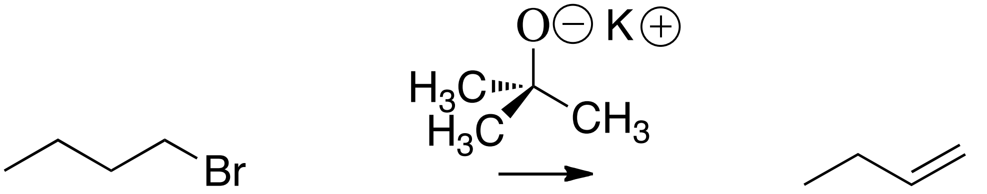
S_N2 with good nucleophiles that are not strongly basic



S_N2 with good nucleophile that are also strongly basic



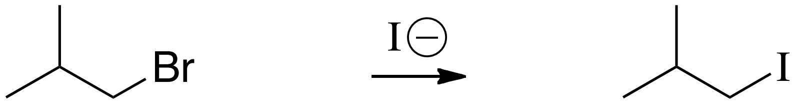
E2 with nucleophiles that are strongly basic and hindered



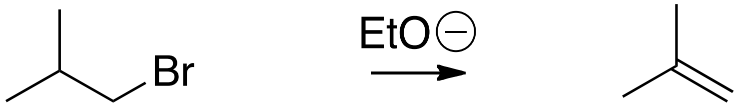
No, or exceedingly slow, reaction with poor nucleophiles

Branched Primary Alkyl Halides

S_N2 with good nucleophiles that are not strongly basic



E2 becomes more prevalent with nucleophiles that are strongly basic

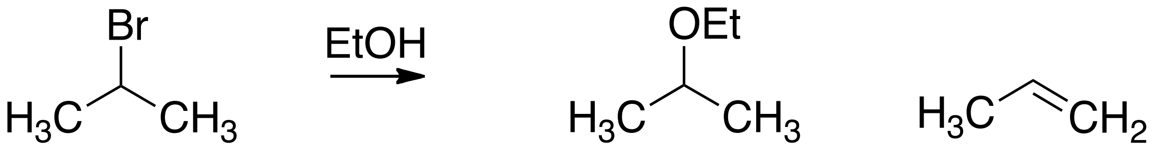


No reaction with poor nucleophiles

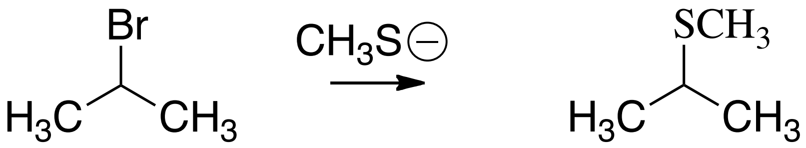
Secondary Alkyl Halides

(hardest to predict – all four mechanisms are possible)

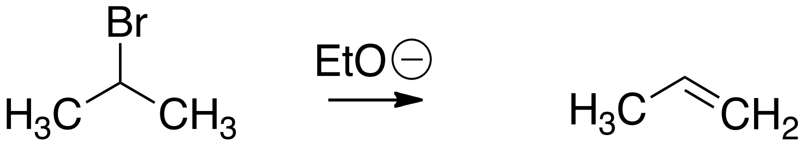
S_N1 or E1 with good leaving group in polar solvent with weak nucleophile



S_N2 with good, weakly basic nucleophiles

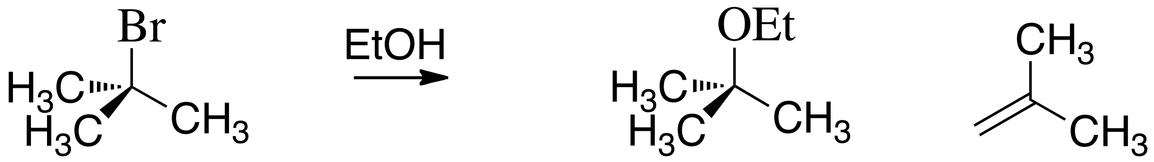


E2 with strongly basic nucleophiles

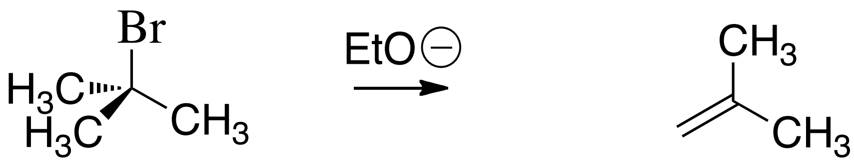


Tertiary Alkyl Halides

S_N1 and E1 with weak bases



E2 with strong base



As base strength increases, rate of E2 increases

Predicted Mechanisms by which Alkyl Halides React with Nucleophiles (or Bases)

Type of Alkyl Halide	Poor NUC (e.g. EtOH)	Good NUC. Weak base (e.g. CH_3SNa)	Good NUC, strong, Unhindered base (e.g. CH_3ONa)	Good NUC, strong, hindered base (e.g. $(CH_3)_3CONa$)
methyl	No reaction	S_N2	S_N2	S_N2
1°				
unhindered	No reaction	S_N2	S_N2	E2
branched	No reaction	S_N2	E2	E2
2°	Slow S_N1, E1	S_N2	S_N2 or E2	E2
3°	S_N1, E1	S_N1, E1	E2	E2

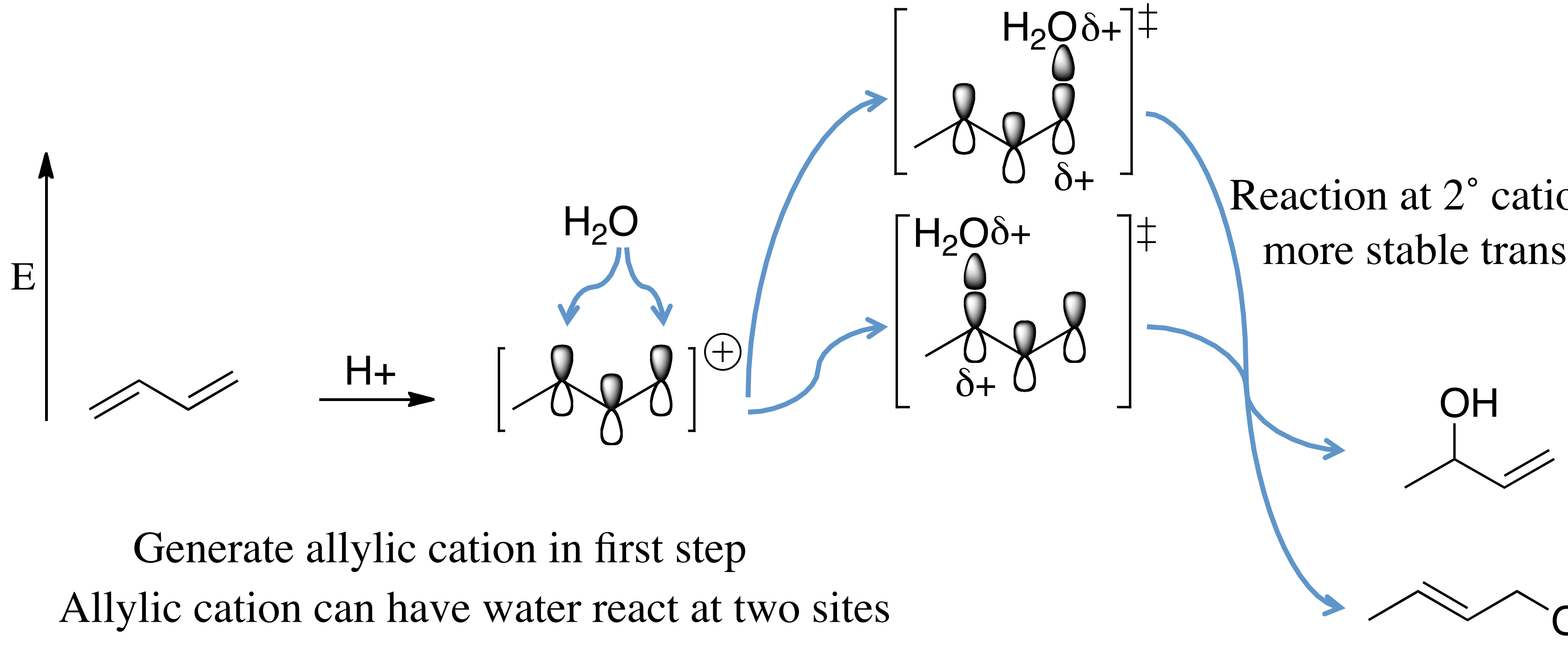
Properties of Each Mechanism

mechanism	stereochemistry	rate	rearrangements
S_N2	Inversion	k[substrate][NUC]	never
S_N1	Racemic, sometimes inversion preference	k[substrate]	Often, if possible
E2	Anti-coplanar Saytzeff rule	k[substrate][base]	never
E1	Saytzeff rule	k[substrate]	Often, if possible

Kinetic versus Thermodynamic Control

What forms faster (kinetic product) and what is more stable (thermodynamic product)
need not be the same

Consider the addition to conjugated dienes, similar to the reaction of H+/H_2O
to an alkene seen earlier and will be studied in more detail later



Reaction at 2° cation site has a
more stable transition state

Generate allylic cation in first step

Allylic cation can have water react at two sites

Reaction at 2° site

Reaction at 1° site

Reaction a 1° site, though,
generates more stable product
(more substituted double bond)

Thus the kinetic product has
water reacting at 2° site

The thermodynamic product has
water reacting at 1° site

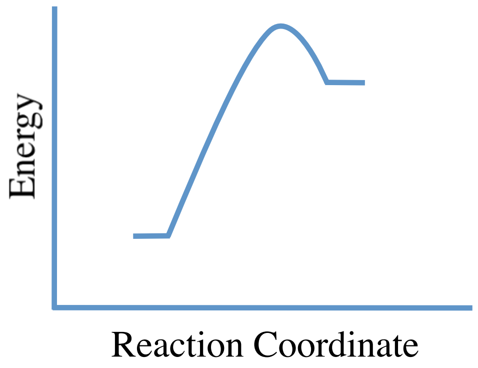
Hammond Postulate

The rate of a reaction is thus dependent upon the energy difference between the starting material and transition state in the rate determining step

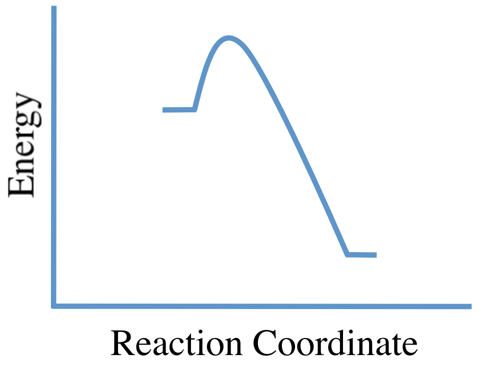
While the structure of the starting material and products can be determined, the structure of the transition state is difficult to determine experimentally because it is at an energy maximum and cannot be isolated

As an aide in predicting rates, a generalization was made that is now referred to as the "Hammond Postulate"

In an ENDOTHERMIC reaction, the transition state is closer to the PRODUCTS in energy and structure. In an EXOTHERMIC reaction, the transition state is closer to the REACTANTS in energy and structure



Endothermic reaction, transition state structure resembles product



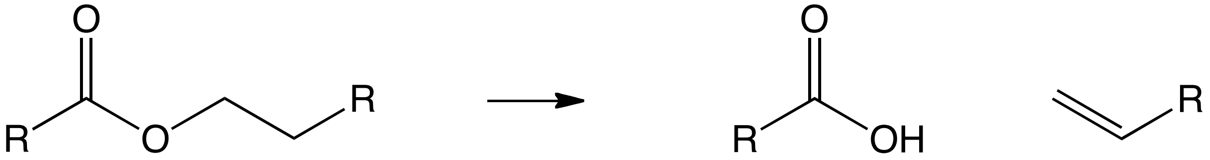
Exothermic reaction, transition state structure resembles starting material

Eliminations Without External Base

Eliminations seen thus far involve the use of a base to abstract a hydrogen,
either initially before leaving group departs (E1cB), while the leaving group is leaving (E2),
or after the leaving group has already left (E1)

There are some reactions that involve an elimination
(groups depart while no groups have added) but do not involve an external base

Esters with β hydrogens

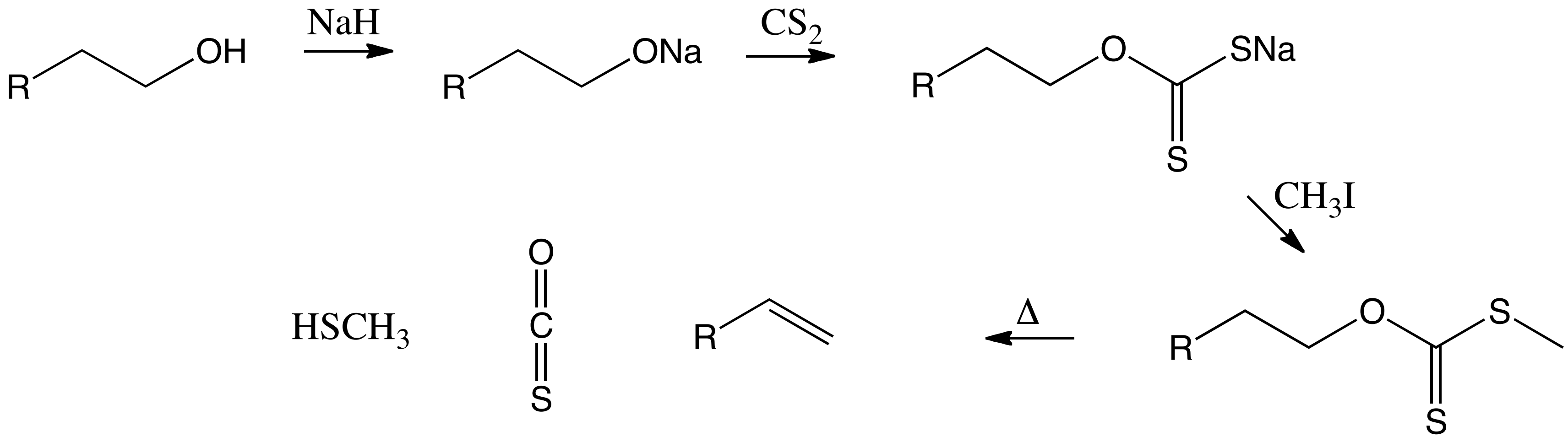


Any ester that contains a hydrogen in the β position will eliminate an alkene thermally
(must occur with a syn elimination from the carbonyl)

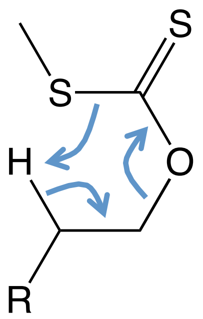
Requires high temperature for elimination (~400-500 ˚C)

Xanthate Esters

In order to allow elimination at a lower temperature, xanthate esters occur at ~200 ˚C



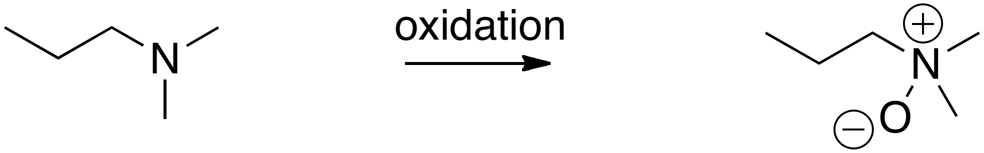
This reaction also occurs through a SYN elimination



Cope Elimination

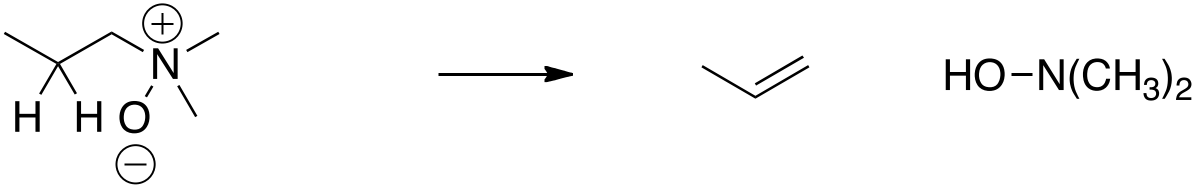
Another method to have an elimination from an amine is the Cope elimination

Instead of an E2 base mechanism, the Cope occurs through an oxidation mechanism
A tertiary amine is oxidized to an amine oxide



(primary amines are oxidized to nitro and secondary amines are oxidized to hydroxylamines)

Amine oxides will eliminate without base



Also occurs with a SYN stereochemistry

Elimination by Loss of Small Molecules

Some eliminations also occur at low temperature through loss of small molecules
(typically the small molecule is a gas which upon loss drives equilibrium)