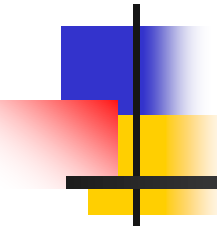


CHEMISTRY 2500

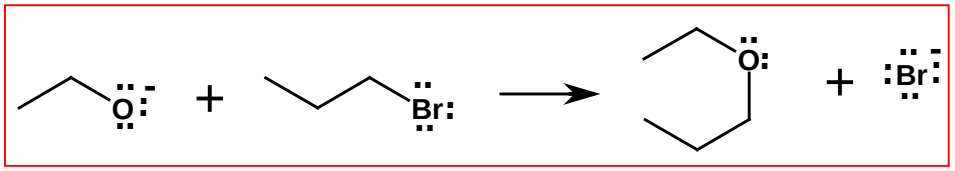
Topic #10: Elimination Reactions (E1 vs. E2 vs. S_N1 vs. S_N2)

Fall 2014

Dr. Susan Findlay

Eliminations Can Interfere with Substitutions

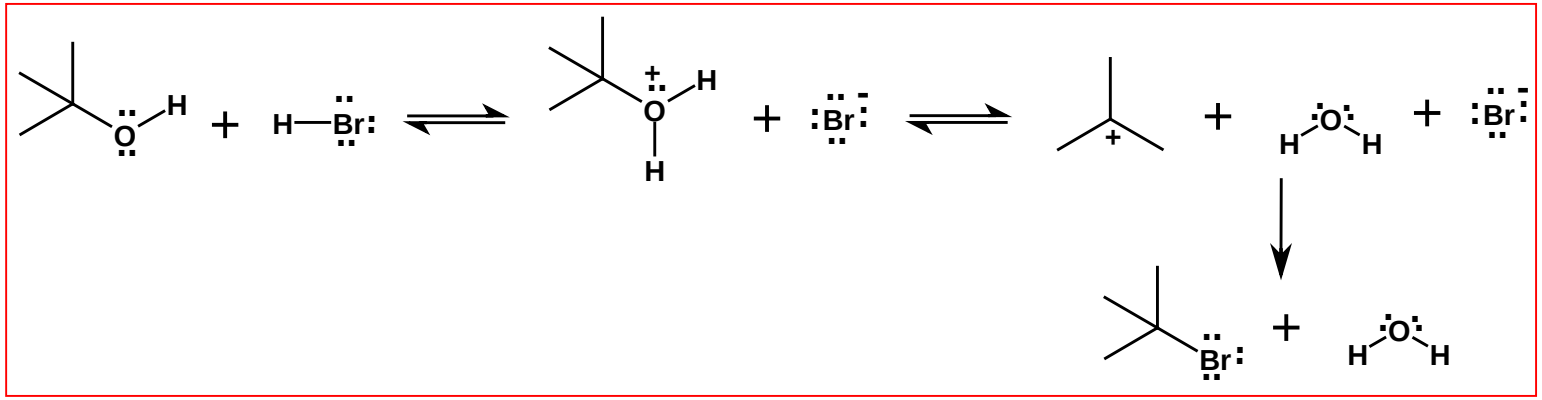
- Consider the following S_N2 reaction:



Ethoxide ($CH_3CH_2O^-$) is used as a nucleophile, but its conjugate acid (ethanol) has a pK_a of ~15 – and a weak acid will have a strong conjugate base! So, why not use ethoxide as a base instead? Does bromopropane have any (weakly) acidic hydrogen atoms?

Eliminations Can Interfere with Substitutions

- Similarly, in the following S_N1 reaction, water (a weak base) is present in the same solution as a carbocation:



What if the acid had been H_2SO_4 instead of HBr? HSO_4^- is not a good nucleophile...

Eliminations Can Interfere with Substitutions

- When considering a substitution reaction, it is therefore important to consider whether or not an elimination reaction might also occur under the same conditions. There are methods to favour one over the other *(either substitution over elimination or vice versa)* but, before we discuss those, we should look in more detail at elimination reactions.

- So, what are the key features of an elimination reaction?
  - Overall, a neutral molecule is "eliminated" from a reactant. *(If the neutral molecule would react with any of the reactants, it may not be in its neutral form. e.g. elimination of HBr in base makes Br^- and protonated base)*
  - A π **bond** is **created** between the two atoms that used to bear each half of the "eliminated" molecule.
  - One reactant must have a good leaving group *(or be able to generate one)*.
  - Another reactant must be a base *(might be a weak one if the leaving group is good enough)*.

Mechanisms of Eliminations (E1 vs. E2)

- Just as there are two major classes of substitution reactions (S_N1 and S_N2), there are two major classes of elimination reactions (E1 and E2):
  - E1 Reactions: In an E1 elimination reaction, only one molecule is involved in the step where the leaving group is lost (the rate-determining step):
  - E2 Reactions: In an E2 elimination reaction, two molecules are involved in the step where the leaving group is lost (the rate-determining step):
- Just as for substitution reactions, which mechanism is favoured is determined by factors such as:
  - Stability of cation formed (if E1); *some solvents help to stabilize*
  - Leaving group ability
  - Strength of base (analogous to nucleophile strength for substitutions)

E1 Reactions (Mechanism)

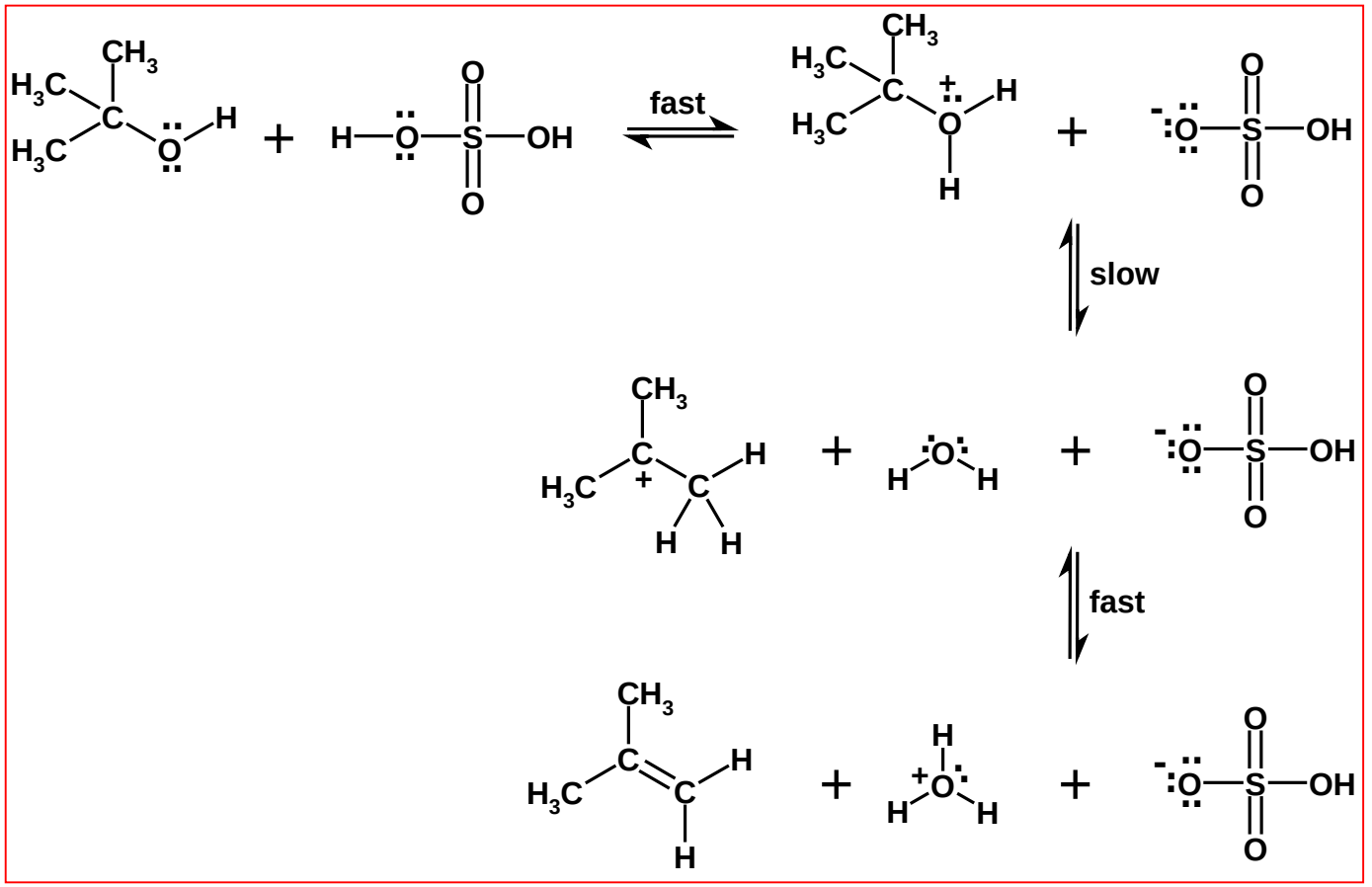
- An E1 elimination reaction will occur when a molecule has a good leaving group attached to a tetrahedral carbon atom that can form a relatively stable carbocation.
- E1 reactions tend not to occur in the presence of a good nucleophile (since that would favour a substitution reaction); however, steric bulk (large substituents) can "block out" a nucleophile, favouring elimination instead.
- The mechanism of an E1 reaction always involves at least two steps:
  - Leaving group leaves
  - Base deprotonates carbocation, forming π bond

  A third step may be required to generate the good leaving group.

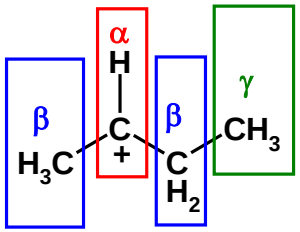
  e.g. protonation of an alcohol to make R-OH_2^+ *or*

  protonation of an amine to make R-NH_3^+

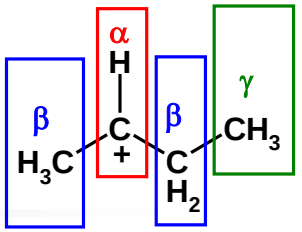
E1 Reactions (Mechanism)



- The acidic hydrogen is referred to as β to the carbocation, or the β-hydrogen:

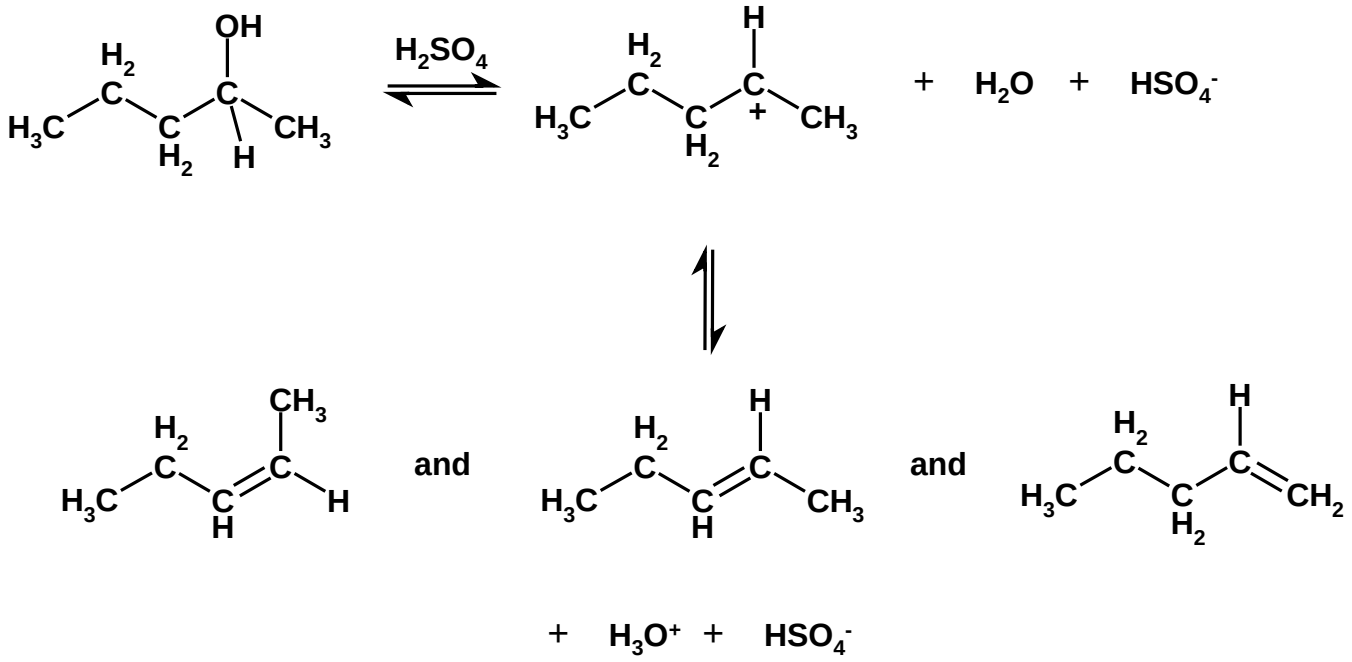


E1 Reactions (Regio- & Stereochem.)

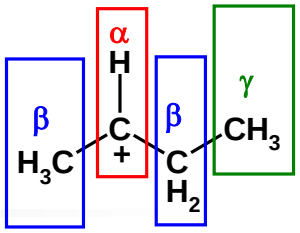


- In the example on the previous page, all of the β-hydrogen atoms were equivalent. If this is not the case, you may see multiple elimination products – one for each type of β-hydrogen.

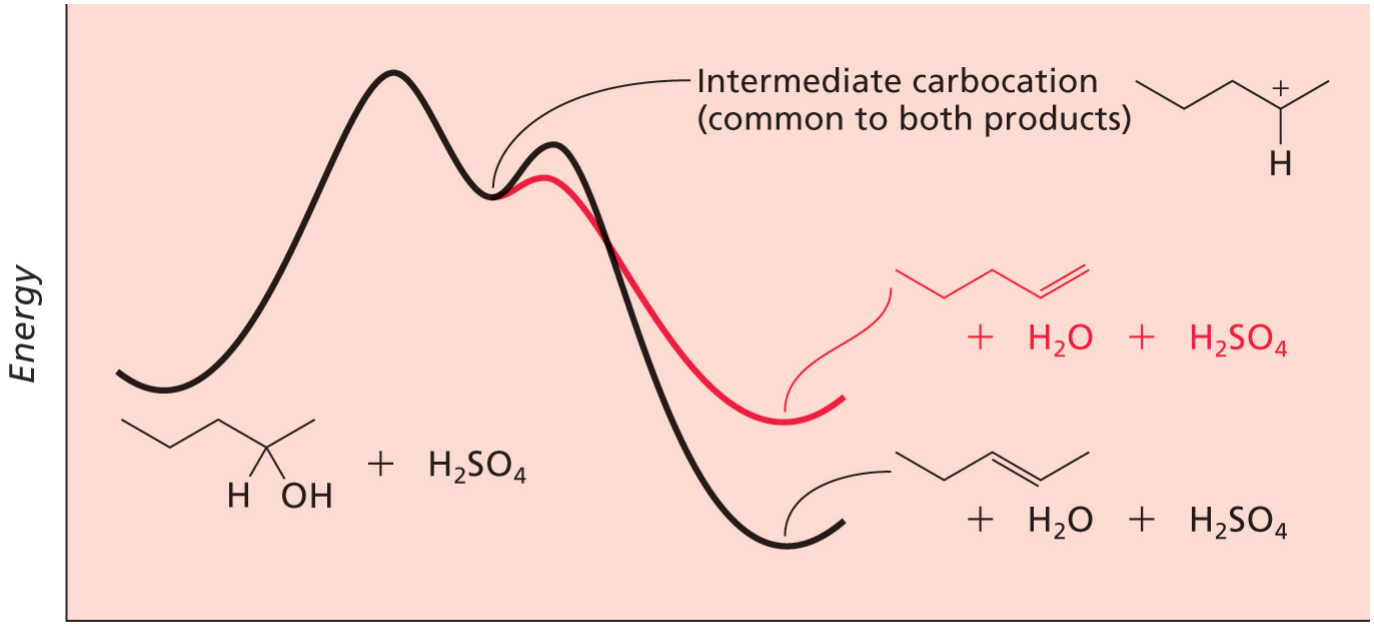
e.g.



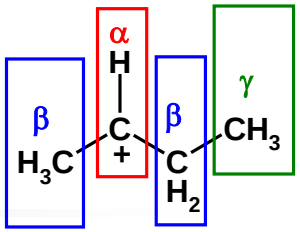
E1 Reactions (Regio- & Stereochem.)



- That's problematic. How can we favour one product over the others?
  - Between 1-pentene and 2-pentene, one product is favoured kinetically (easier to make) and the other is favoured thermodynamically (more stable):



E1 Reactions (Regio- & Stereochem.)

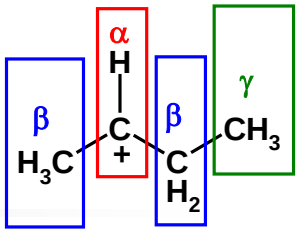


- Why is 1-pentene kinetically favoured (easier to form)?

- Why is 2-pentene thermodynamically favoured (more stable)? What about *cis*- vs. *trans*-2-pentene? Which is more stable?

- Note that not every reaction has one kinetic product and a different thermodynamic product. In many cases, the same product is both! ***Always*** use the definitions; don't assume that thermodynamic = "not kinetic" or that kinetic = "not thermodynamic".

E1 Reactions (Regio- & Stereochem.)

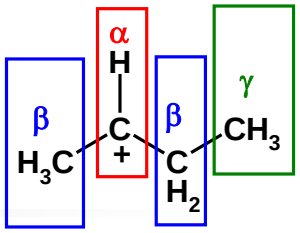


- To favour the kinetic product over the thermodynamic product, we would need to lower the temperature – giving fewer molecules enough energy to overcome the higher activation energy to make 2-pentene. Unfortunately, this would also give fewer molecules enough energy to overcome the activation energy of the FIRST STEP – the rate limiting step. Then the reaction wouldn't go. So, **most E1 reactions <u>cannot</u> be kinetically controlled** since they tend to need to be heated. ☹

- To favour the thermodynamic product over the kinetic product, we would need to raise the temperature – giving more molecules enough energy to overcome the higher activation energy to make 2-pentene AND giving more of the 1-pentene molecules enough energy to do the reverse reactions until they make the more stable 2-pentene. This can be done, so **E1 reactions can be thermodynamically controlled**. ☺

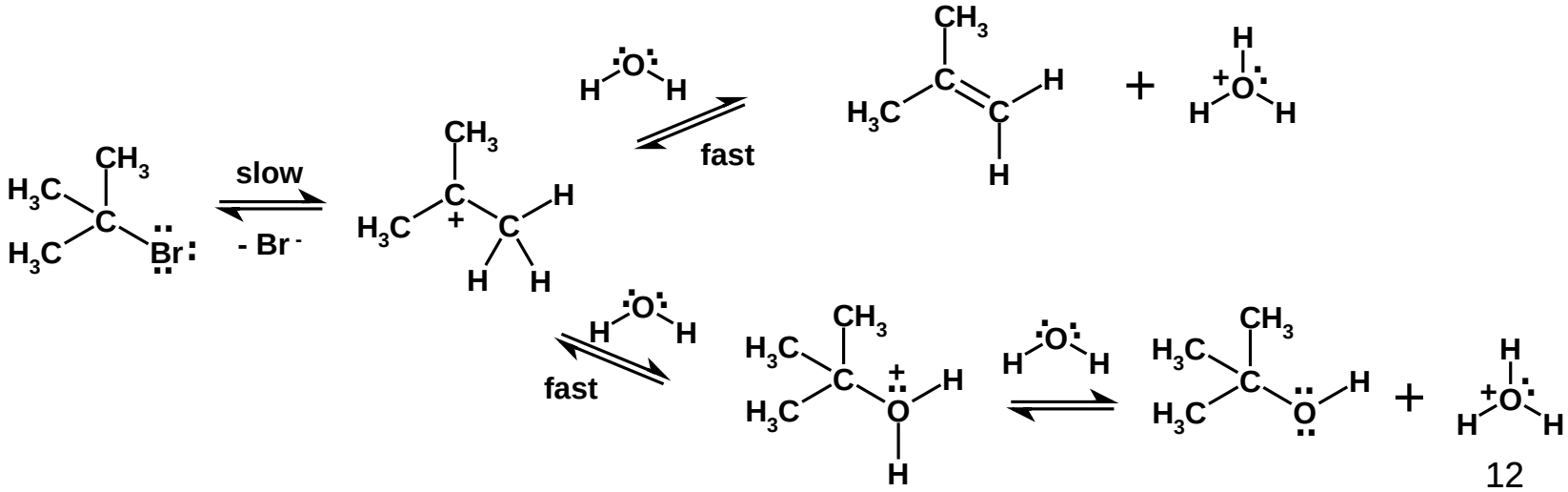
- The thermodynamic product of an elimination reaction is called the **Saytzeff product** (also spelled Zaitsev product).

E1 Reactions

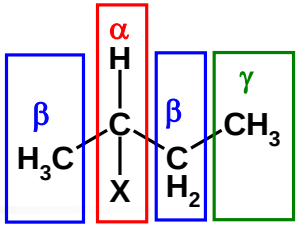


- We can force an alcohol to undergo an E1 reaction by using an acid with a non-nucleophilic conjugate base.

- Alkyl halides can also undergo E1 reactions; however, since the bases used are nucleophilic (H_2O, EtOH, etc.), the S_N1 product tends to be made as well. As such, a mixture will be obtained:

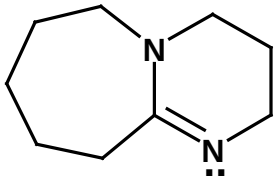


E2 Reactions (Mechanism)

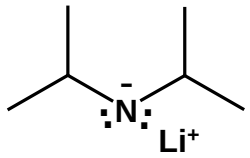


- So, we need a better way to prepare alkenes from alkyl halides. There's no way to do an E1 reaction on an alkyl halide without a nucleophile around, but strong non-nucleophilic bases exist. These can be used to promote E2 elimination reactions.

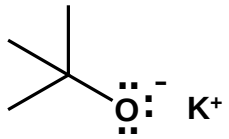
eg.



DBU
(1,8-diazabicyclo[5.4.0]undec-7-ene)



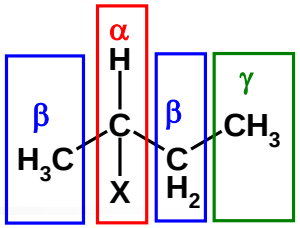
LDA
(lithium diisopropylamide)



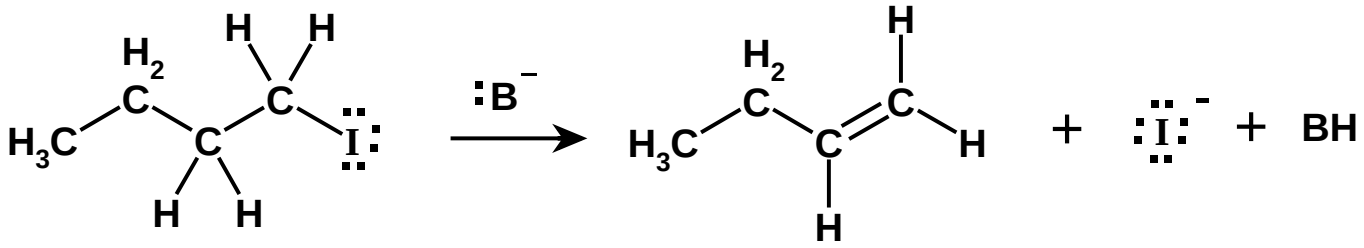
KO*t*Bu
(potassium *tert*-butoxide)

- Why would these bases make lousy nucleophiles?

E2 Reactions (Mechanism)



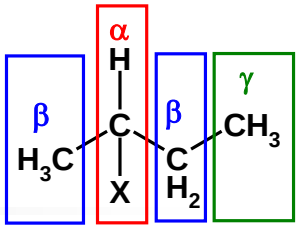
- An E2 elimination reaction will occur when a molecule with a good leaving group is reacted with a strong base (ideally a non-nucleophilic one).
- The mechanism of an E2 reaction usually involves just one step:
  - Base removes β-hydrogen, forming π bond and pushing out leaving group.



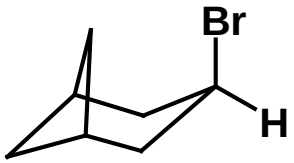
- Usually, the Saytzeff product (more substituted alkene) is the major product. When would the other product form?

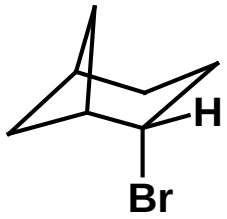
- *Note: Sulfonate esters (R-OMs, R-OTs and R-OTf) undergo E2 reactions under the same conditions as alkyl halides.*

E2 Reactions (Regio- & Stereochem)

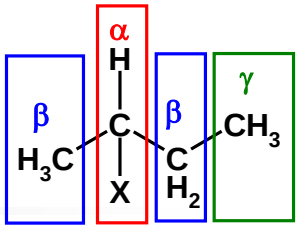


- As in S_N2 reactions, the incoming electrons (on the nucleophile for S_N2; on the base for E2) must attack the molecule from the OPPOSITE side to the leaving group. For an E2 reaction, this is described as "the hydrogen removed must be **anti-periplanar** to the leaving group".
- As such, E2 elimination products are limited to stereochemistry (and regiochemistry) compatible with this requirement.
- Consider elimination reactions for the following compounds:

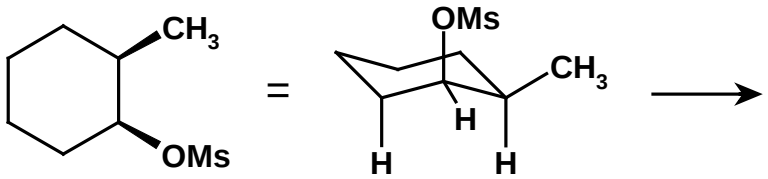


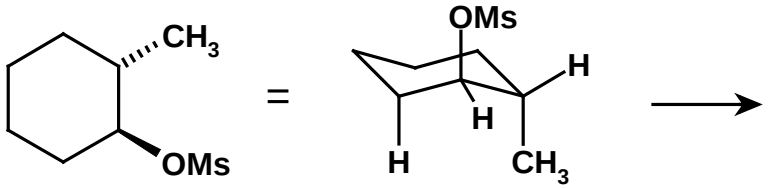


E2 Reactions (Regio- & Stereochem)

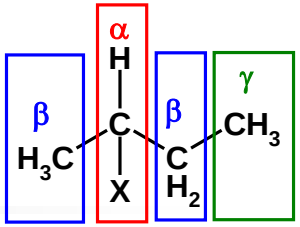


- In each of the structures on the previous page, the leaving group was shown in the _____ position. To perform an E2 reaction in a cyclohexane ring, the leaving group must be _____ and there must be a β-hydrogen anti-periplanar to it (therefore also _____).

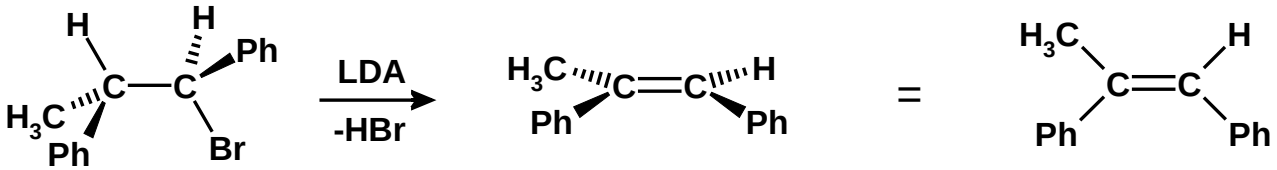


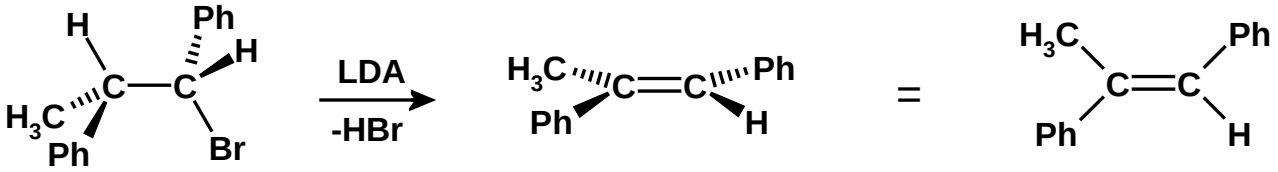


E2 Reactions (Regio- & Stereochem)



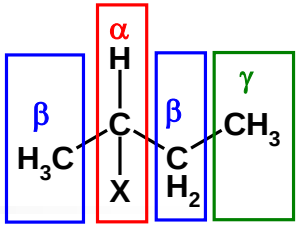
- Even in less rigid systems, there can be stereochemical consequences of an E2 reaction:



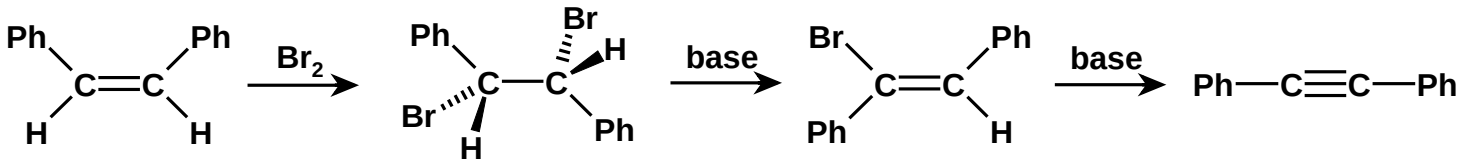


- Here, a pair of _____ produce different products which are stereoisomers. This is a **stereospecific** reaction. The stereochemistry of the products is determined by the stereochemistry of the reactants.
- Would you expect E1 reactions to be stereospecific? Why or why not?

E2 Reactions (Making Alkynes)



- A convenient way to convert an alkene to an alkyne is by adding bromine across the double bond *(see addition reactions; next section)* then doing a pair of E2 reactions to generate a triple bond (i.e. two new π bonds):



- A strong base (e.g. NH_2^-) can also be used to prepare benzyne from bromobenzene; however, the benzyne molecule is HIGHLY reactive and cannot be isolated. It must immediately be reacted to make an isolable product.

E1 vs. E2 vs. S_N1 vs. S_N2

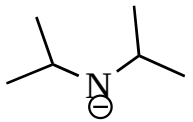
- As a general rule, the type of molecule that will readily undergo S_N1 reactions can also undergo E1 reactions. After all, they both have the same rate-determining step (leaving group loss)! To favour E1 over S_N1 for alcohols, choose an acid with a non-nucleophilic conjugate base. To favour S_N1 over E1, make sure a good nucleophile is available. *(You'll probably still see traces of E1 product.)*

- As a general rule, the type of molecule that will readily undergo S_N2 reactions can also undergo E2 reactions. To favour E2 over S_N2, choose a bulky non-nucleophilic base. To favour S_N2 over E2, choose a weakly basic nucleophile (e.g. a halide).

- Before embarking on a "S_N vs. E" debate, confirm that the compound in question has one or more β-hydrogens! If not, elimination's not even an option...

E1 vs. E2 vs. S_N1 vs. S_N2

	SN1	SN2	E1	E2
Mechanism	2 or more steps involving carbocation intermediate	1 step bimolecular process	2 or more steps involving carbocation intermediate	1 step bimolecular process
Kinetics	First order in substrate	Second order, first in substrate and nucleophile	First order in substrate	Second order, first in substrate and base
Substrate Dependence	Those substrates that form stable carbocations. 3°, allylic, benzylic	Those substrates that are uncluttered at the reaction site: 1°, 2°. Good nucleophiles.	Those substrates that form stable carbocations. 3°, allylic, benzylic	Requires strong base and any substrate with beta proton.
Stereochem	Racemization.	Stereospecific inversion.	Usually mixtures.	Stereospecific involving antiperiplanar relationship of beta-proton and leaving group.
Importance of Base/nucleophile	Not involved in RDS, but less basic form of nucleophile will limit E1.	Reactivity of nucleophile is important since it is involved in RDS.	If a good, non-basic nucleophile is present (halides, bisulfate) then SN1.	Strong, non-nucleophilic bases (KOtBu, LDA) best to limit SN2.
Importance of Leaving group	Involved in RDS so is important.	Involved in RDS so is important.	Involved in RDS so is important.	Involved in RDS so is important.
Competes with..	E1 and E2	E2 when basic nucleohiles employed.	SN1	SN2
Solvent	Polar protic best	Polar aprotic best	Polar protic best	Varies.

	Weak base/ poor Nu	**Weak base/ good Nu**	**Moderate/strong base/good Nu**	**Strong base/ poor Nu**
	H_2O, ROH	Br^-, I^-, H_2S	RS^-, NC^-, RNH_2, NH_3 N_3^- HO^-, RO^-	t-Bu—O^-  LDA
Methyl, CH_3X	NR	S_N2	S_N2	S_N2
1°, RCH_2X	NR	S_N2	S_N2	E2
2°, RCHXR	S_N1 E1	S_N2	S_N2 E2	E2
3°, R_3CX	S_N1 E1	S_N1 E1	E2	E2
1° benzylic	S_N1	S_N2	S_N2	S_N2
2° benzylic	S_N1 E1	S_N2	S_N2 E2	E2
3° benzylic	S_N1 E1	S_N1 E1	E2	E2
1° allylic	S_N1	S_N2	S_N2	S_N2
2° allylic	S_N1 E1	S_N2	S_N2 E2	E2
3° allylic	S_N1 E1	S_N1 E1	E2	E2
Aryl, PhX	NR	NR	NR	E2
Alkenyl, H_2C=CHX	NR	NR	NR	E2