Organic Chemistry
Mechanistic Patterns
(Ogilvie)
Chapter 12

CHEMISTRY 2600

Topic #5: Elimination Reactions (E1 and E2)

Spring 2021

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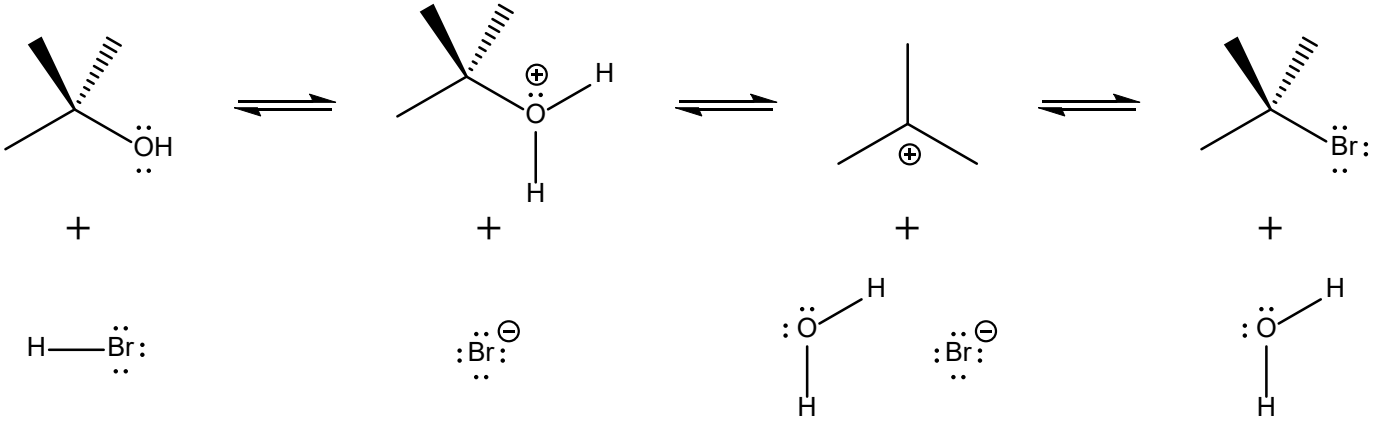
Eliminations Can Interfere with Substitutions

- Consider the following S_N1 reaction. Water (a weak base) is present in the same solution as a carbocation:

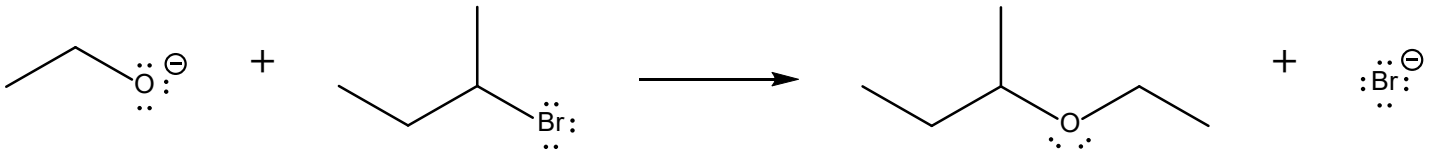


What if the acid had been H_2SO_4 instead of HBr?

HSO_4^- is not a good nucleophile…

Eliminations Can Interfere with Substitutions

- Consider the following plan for an 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!

What if ethoxide acted as a base instead?

Eliminations Can Interfere with Substitutions

- When considering a substitution reaction, we must therefore consider whether or not an elimination reaction might also occur under the same conditions. There are methods to favour either over the other 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. *An elimination reaction is literally the reverse of an addition reaction, and Le Châtelier's principle can determine whether addition or elimination is favoured.*
  - 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). The reaction is therefore **first order**:
  - E2 Reactions: In an E2 elimination reaction, two molecules are involved in the step where the leaving group is lost (the rate-determining step). The reaction is therefore **second order**:
- Just as for substitution reactions, which mechanism is favoured is determined by factors such as:
  - Stability of carbocation intermediate (for E1 mechanism)
  - Strength of base (analogous to nucleophile strength for substitutions)

E1 Reactions (Mechanism)

- An E1 elimination reaction can occur when a molecule has a good leaving group attached to a tetrahedral carbon atom that can form a relatively stable carbocation (and there is a base present).

- E1 reactions are usually performed in the absence of good nucleophiles since the presence of a good nucleophile would lead to competing S_N1 reaction.

- An E1 reaction always involves at least two steps:
  - Leaving group leaves
  - Base deprotonates carbon next to carbocation, forming π bond

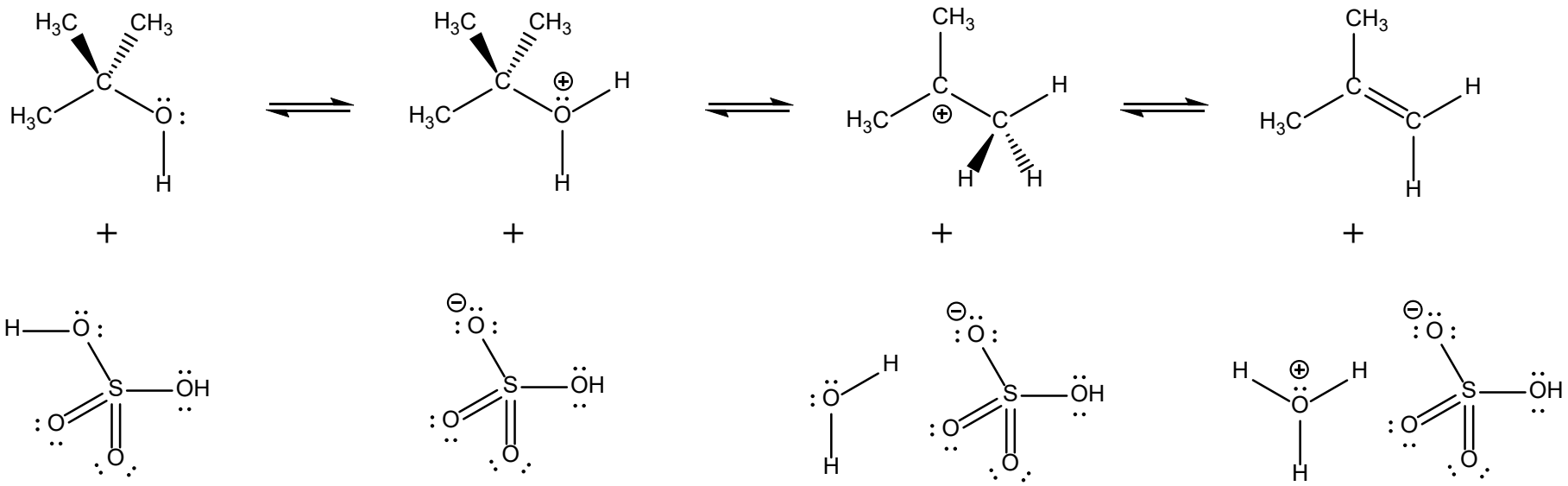
- A third step may be required to generate the good leaving group.

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

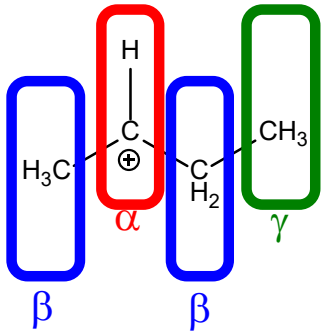
  protonation of an amine to make R-NH_3^+

E1 Reactions (Mechanism)

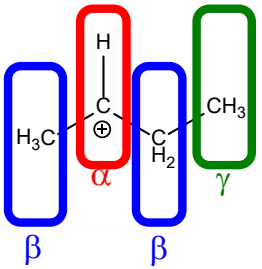
- A mechanism for a typical E1 reaction is shown below:



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

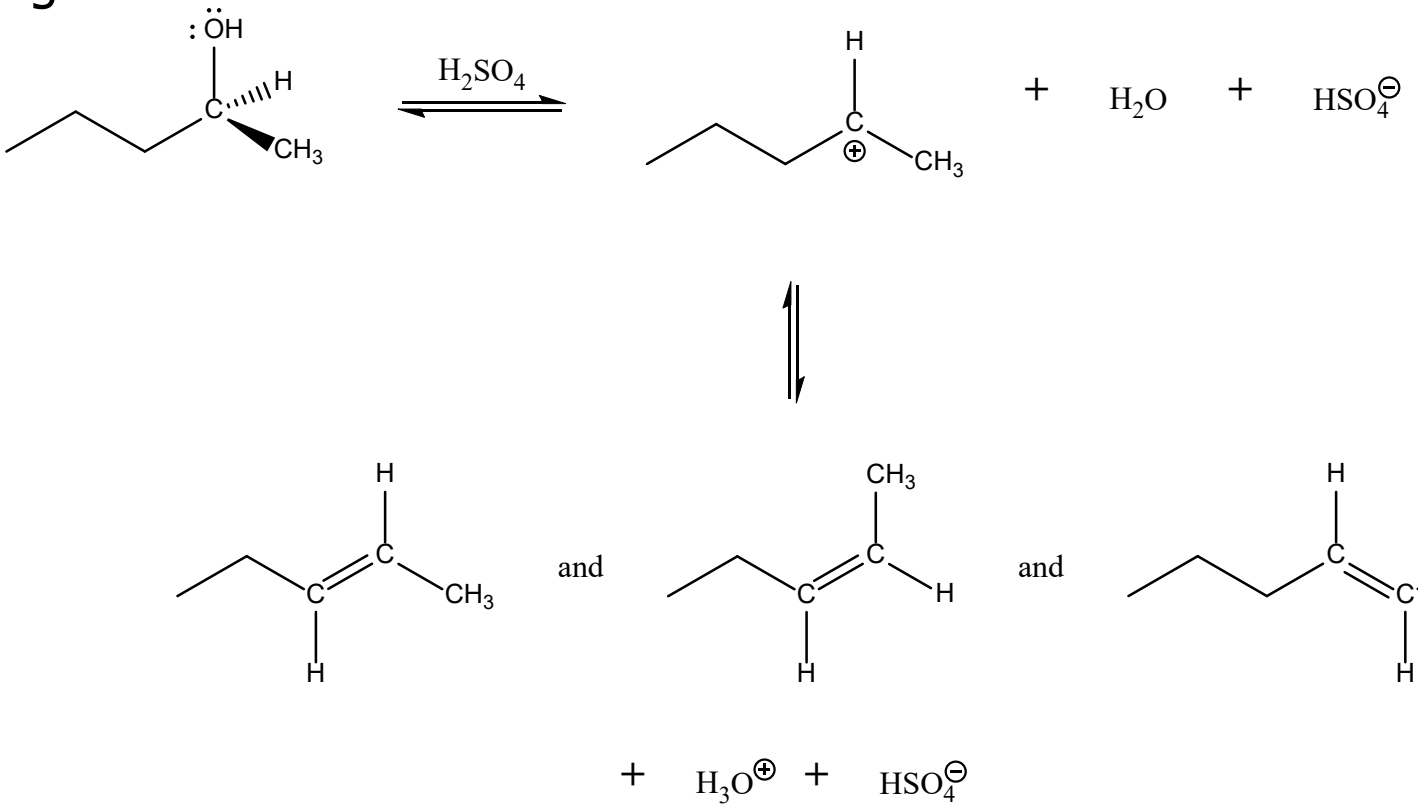


E1 Reactions (Regio- & Stereochem.)

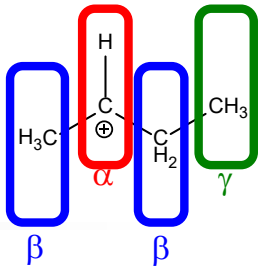


- In the example on the previous page, all of the β-hydrogen atoms were equivalent. If this is not the case, you may see multiple elimination products – one for each type of β-hydrogen.

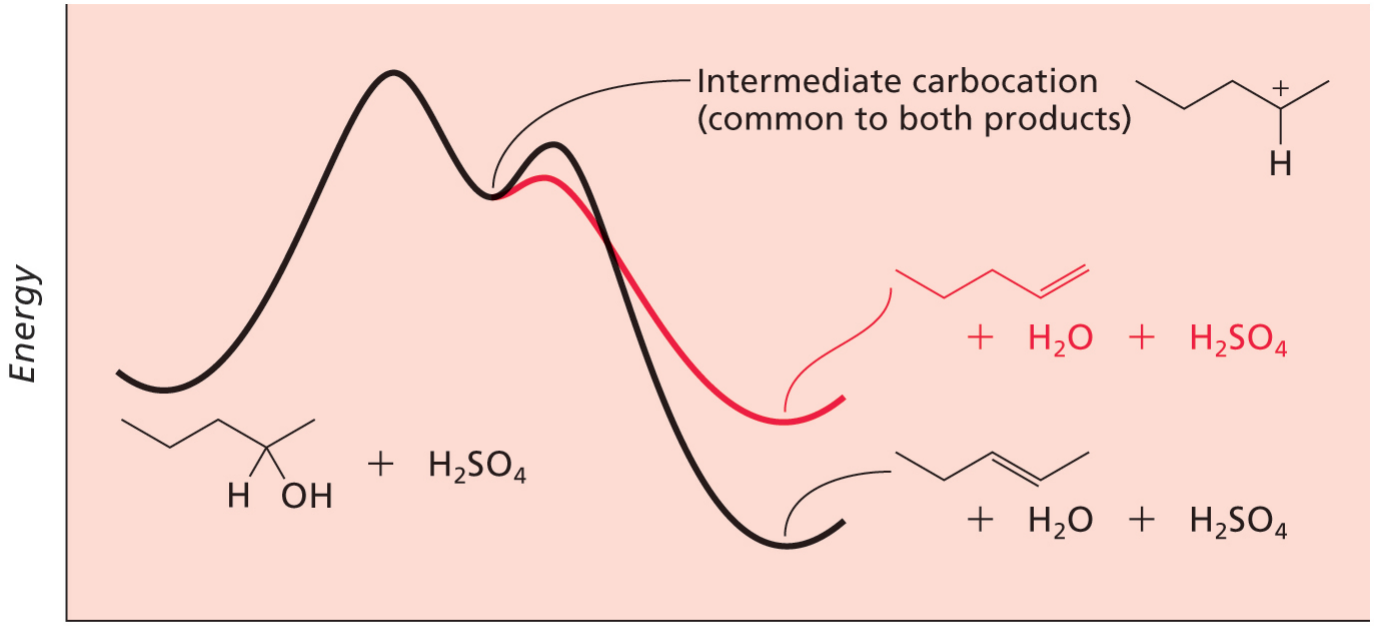
e.g.



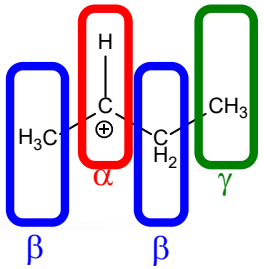
E1 Reactions (Regio- & Stereochem.)



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



E1 Reactions (Regio- & Stereochem.)

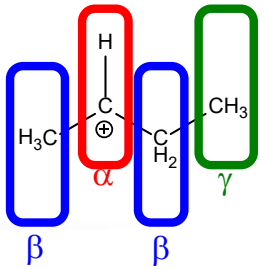


- Why is 1-pentene kinetically favoured (easier to form) when a bulky base is used?

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

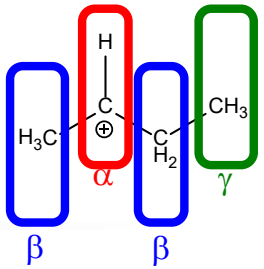


- To favour the kinetic product over the thermodynamic product, we would need to lower the temperature – giving fewer molecules enough energy to overcome the higher activation energy to make 2-pentene. Unfortunately, this would also give fewer molecules enough energy to overcome the activation energy 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. ☹

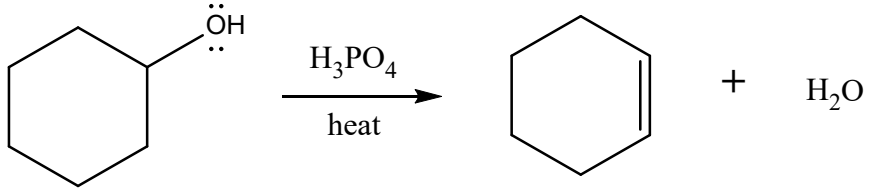
- To favour the thermodynamic product over the kinetic product, we would need to raise the temperature – giving more molecules enough energy to overcome the higher activation energy to make 2-pentene AND giving more of the 1-pentene molecules enough energy to do the reverse reactions until they make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

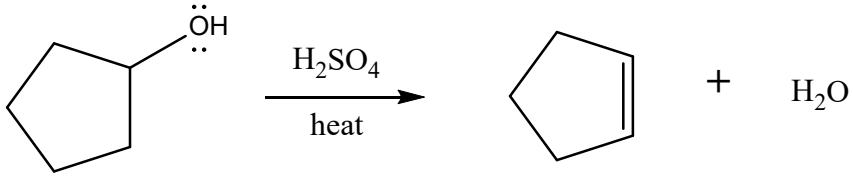
- The thermodynamic product of an elimination reaction is called the **Zaitsev product**.

E1 Reactions



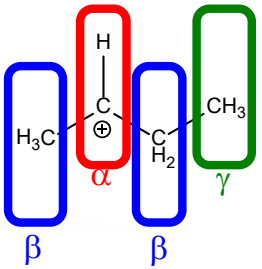
- We can force an alcohol to undergo an E1 reaction by using an acid with a non-nucleophilic conjugate base.





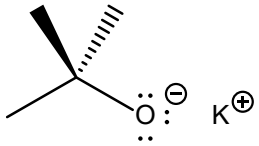
- Alkyl halides can also undergo E1 reactions; however, since the bases typically used are slightly nucleophilic (H_2O, EtOH, etc.), S_N1 reaction tends to compete with the desired E1 reaction, giving a mixture of products.

E2 Reactions (Mechanism)

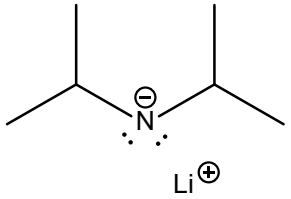


- So, we need a better way to prepare alkenes from alkyl halides. The usual approach is to react the alkyl halide with a strong non-nucleophilic base, promoting elimination via E2 mechanism.

eg.



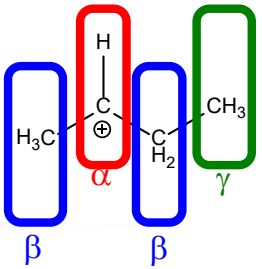
potassium *tert*-butoxide
(KO*t*Bu)



lithium diisopropylamide
(LDA)

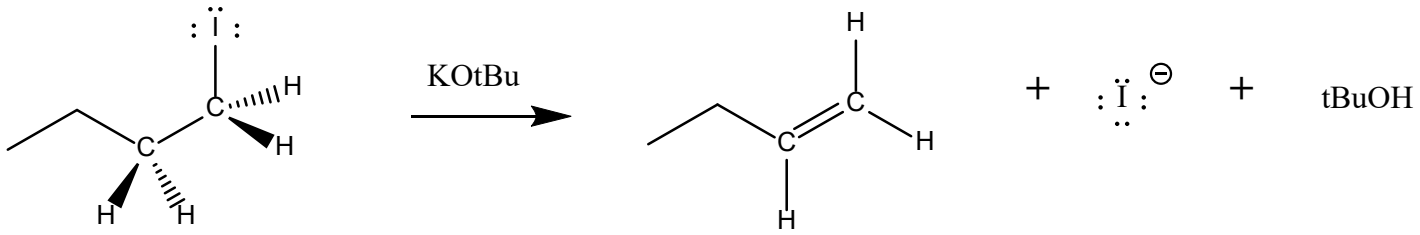
- Why would these bases make lousy nucleophiles?

E2 Reactions (Mechanism)

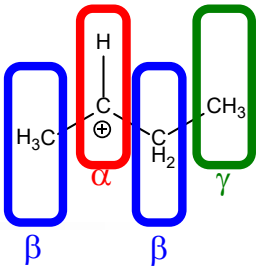


- An E2 elimination reaction can occur when a molecule with a good leaving group is reacted with a strong base (ideally a non-nucleophilic one).

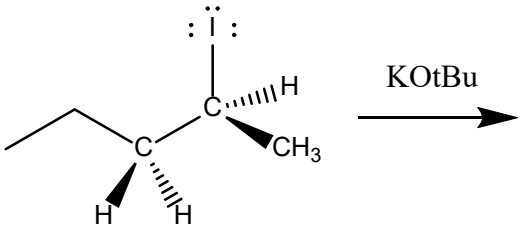
- The mechanism of an E2 reaction usually involves just one step:
  - Base removes β-hydrogen, forming π bond and pushing out leaving group.



E2 Reactions (Mechanism)



- Consider an alkyl halide with two different types of β-hydrogen:

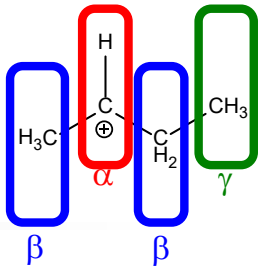


- Usually, the Zaitsev product (more substituted alkene) is the major product.

- The other product (less substituted alkene) is called the Hofmann product. When would the Hofmann 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)

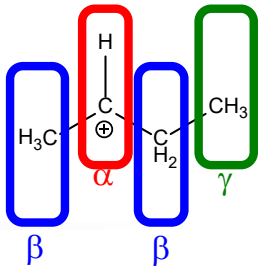


- As in S_N2 reactions, the incoming electrons (on the nucleophile for S_N2; on the base for E2) must attack the molecule from the OPPOSITE side to the leaving group.

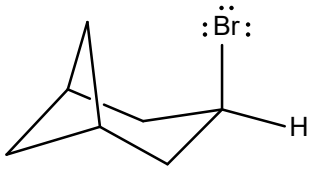
- For an E2 reaction, this is described as "the β-hydrogen removed must be **anti-periplanar** to the leaving group". A 180° dihedral angle is required.

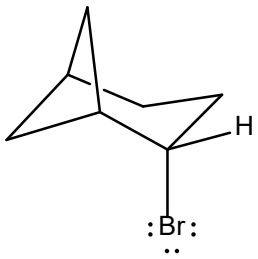
- As such, the products of E2 reactions must have stereochemistry (and regiochemistry) compatible with this requirement.

E2 Reactions (Regio- & Stereochem)

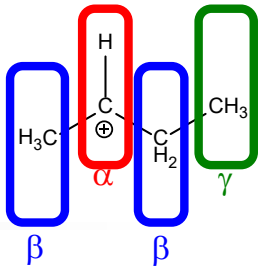


- Consider E2 reactions for the following compounds:

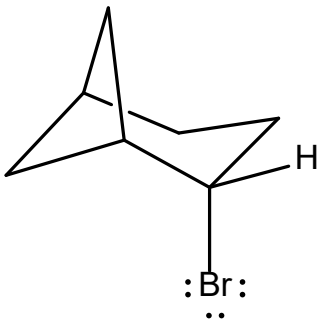


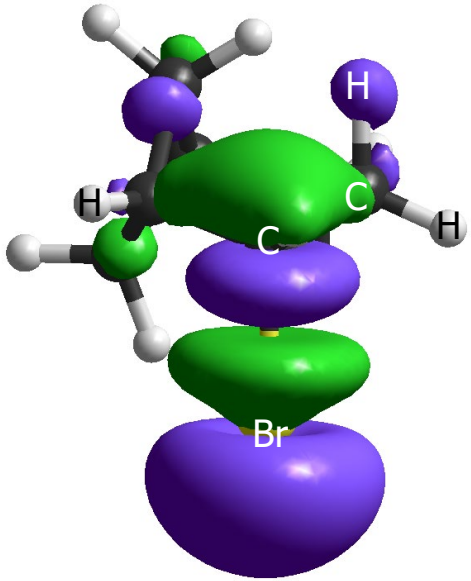


E2 Reactions (Regio- & Stereochem)



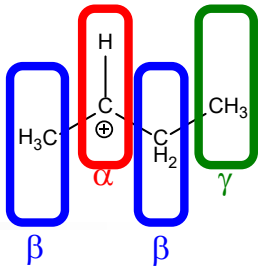
- The reason that the β-hydrogen must be **anti-periplanar** to the leaving group is because of the shape of the substrate's LUMO (the relevant MO because the substrate accepts electrons from the base):





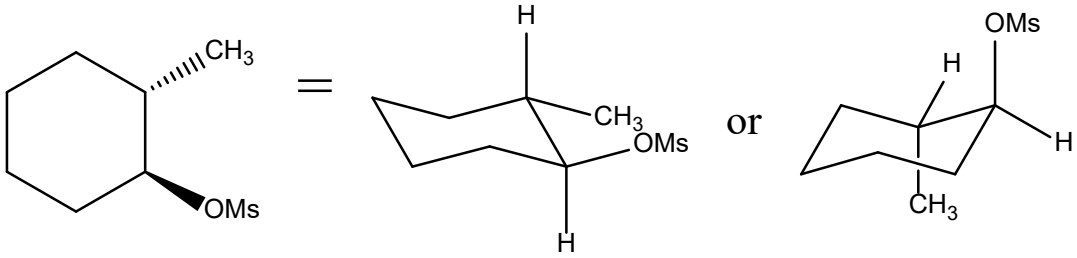
- As shown in the picture above, this MO is antibonding across the C-Br bond. It also has pi symmetry where the new pi bond is going to form. Furthermore, you can see that the LUMO has a lobe on only one of the three β-hydrogen atoms (labeled on the picture) – the one antiperiplanar to the leaving group.

E2 Reactions (Regio- & Stereochem)

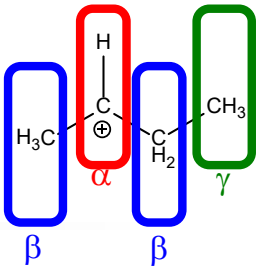


- In each of the structures on page 17, the leaving group was shown in the axial position. To perform an E2 reaction in a cyclohexane ring, the leaving group must be axial, and there must be a β-hydrogen anti-periplanar to it (therefore also axial). This may require a ring flip!

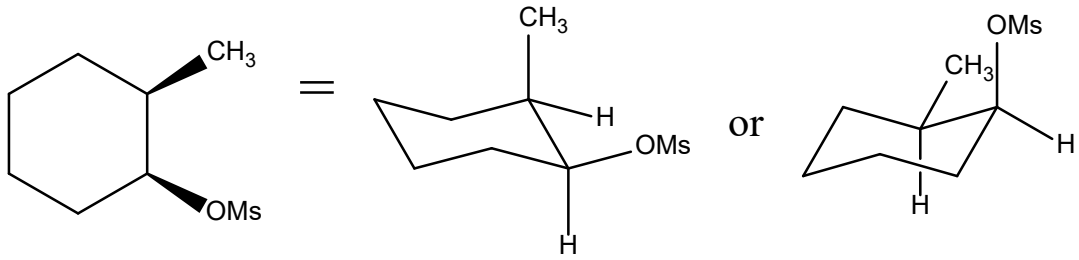
- Consider two isomers. This isomer can only give one elimination product. What is it?



E2 Reactions (Regio- & Stereochem)

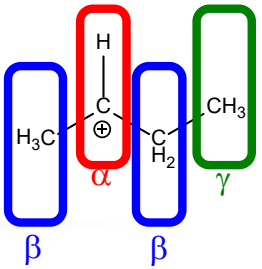


- On the other hand, this isomer can give two different elimination products. What are they?

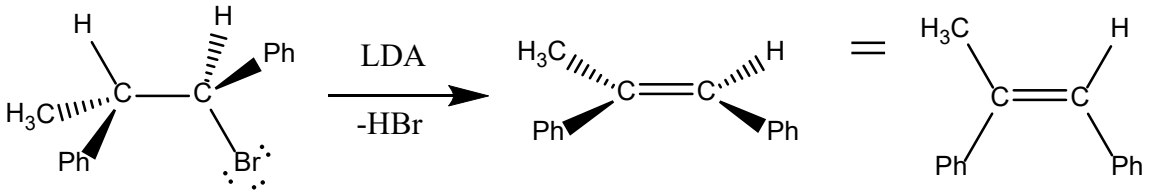


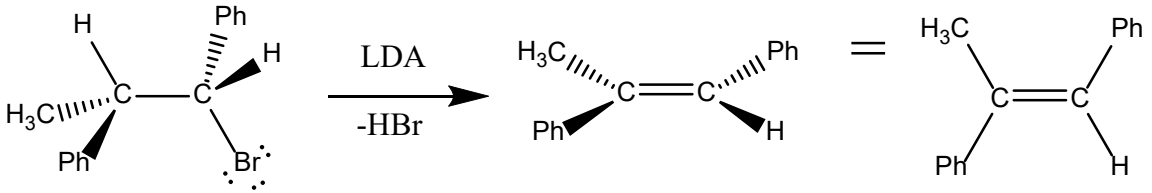
- So, you can see that the stereochemistry of the reactant dictates what products can be formed.

E2 Reactions (Regio- & Stereochem)

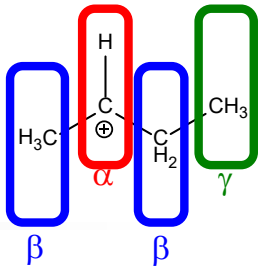


- Even in less rigid systems, requiring the β-hydrogen and leaving group to be antiperiplanar has stereochemical consequences:





E2 Reactions (Regio- & Stereochem)



- E2 reactions are therefore **stereoselective**, strongly favouring production of one stereoisomer over the other. Reaction of one diastereomer of alkyl halide gives the *E*-alkene; reaction of the other diastereomer of alkyl halide gives the *Z*-alkene.

- Would you expect E1 reactions to be similarly stereoselective? Why or why not?

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

- To determine which mechanism(s) are compatible with a particular set of reaction conditions, use the following set of questions to eliminate options.
  - Is there a good leaving group? If not, can one be formed?
    - No? That means no substitution or elimination. Done! ☺
  - Would loss of the leaving group give a relatively stable carbocation?
    - No? That means no S_N1 or E1.
  - Is the electrophilic site accessible?
    - No? That means no S_N2.
  - Is there a good nucleophile?
    - No? That means no S_N2.
  - Is there a strong base?
    - No? That means no E2.
  - Is there a β-hydrogen? *(E2: can be antiperiplanar to leaving group?)*
    - No? That means no E1 or E2.

Whatever you haven't eliminated should be a viable mechanism.

E1 vs. E2 vs. S_N1 vs. S_N2

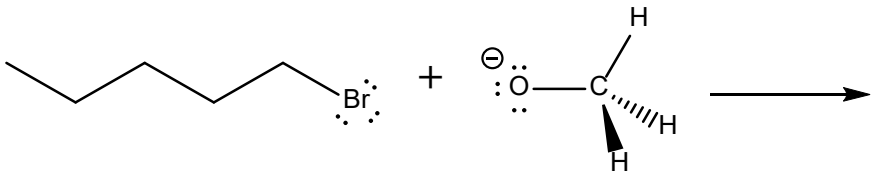
- So, what counts as a "strong" base or "good" nucleophile? Here are a few examples of common reagents and where they fall:
  - Moderate-to-Strong Base/Good Nucleophile (good for E2 and S_N2)
    - ammonia (NH_3), primary amines (RNH_2)
    - cyanide $(N \equiv C^-)$, acetylides $(R - C \equiv C^-)$
    - hydroxide (HO^-), alkoxides (RO^-), thiolates (RS^-)
    - azide (N_3^-)
  - Strong Base/Poor Nucleophile (good for E2, bad for S_N2)
    - *tert*-butoxide $(tBuO^-)$ or lithium diisopropylamide (LDA)
  - Weak Base/Good Nucleophile (bad for E2, good for S_N2)
    - halides (Cl^-, Br^-, I^-)
    - hydrogen sulfide (H_2S), thiols (RSH)
  - Weak base/Poor Nucleophile (bad for E2 or S_N2)
    - water (H_2O), alcohols (ROH)

E1 vs. E2 vs. S_N1 vs. S_N2

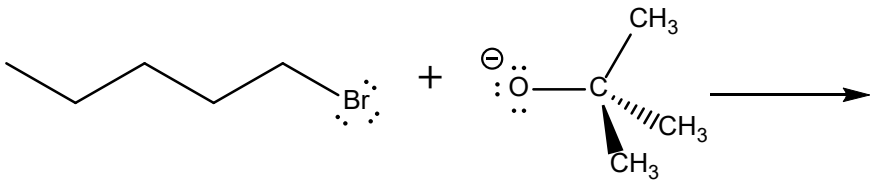
	S_N1	S_N2	E1	E2
Mechanism	2 or more steps; carbocation intermediate	1 step bimolecular process	2 or more steps; carbocation intermediate	1 step bimolecular process
Kinetics	First order in substrate	Second order overall: first in substrate and first in nucleophile	First order in substrate	Second order overall: first in substrate and first in base
Substrate Dependence	Requires substrate that forms stable carbocations: usually 3°, allylic, benzylic	Requires accessible electrophilic site: 1° or 2° without too much bulk nearby	Requires β-hydrogen Requires substrate that forms stable carbocations: usually 3°, allylic, benzylic	Requires β-hydrogen
Stereochemical Implications	Not stereoselective. Racemization at electrophilic site (α-carbon). Carbocation rearrangements possible.	Stereoselective. Inverts stereochemistry of electrophilic site (α-carbon)	Not stereoselective. Carbocation rearrangements possible.	Stereoselective. β-hydrogen and leaving group are oriented in antiperiplanar fashion for reaction to occur.
Importance of Base/nucleophile	Requires a nucleophile, but it's not involved in RDS. Nucleophiles that are not basic are best to limit E1.	Requires a good nucleophile. Nucleophiles that are not basic are best to limit E2.	Requires a base, but it's not involved in RDS. Non-nucleophilic bases are best to limit S_N1.	Requires a strong base. Non-nucleophilic bases (KO*t*Bu, LDA) are best to limit S_N2.
Importance of Leaving group	Involved in RDS so very important.	Involved in RDS so very important.	Involved in RDS so very important.	Involved in RDS so very important.
Solvent	Polar protic usually best	Polar aprotic usually best	Polar protic usually best	Varies.

E1 vs. E2 vs. S_N1 vs. S_N2

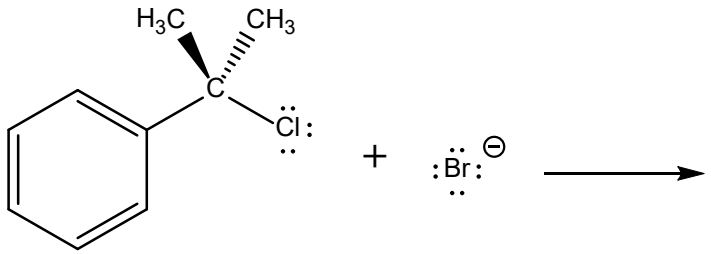
- For each of the following sets of reagents, suggest whether you'd expect to see reaction via S_N1, S_N2, E1 and/or E2. Draw the appropriate product(s).



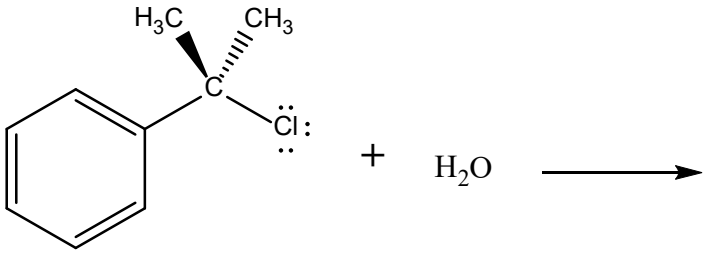
E1 vs. E2 vs. S_N1 vs. S_N2



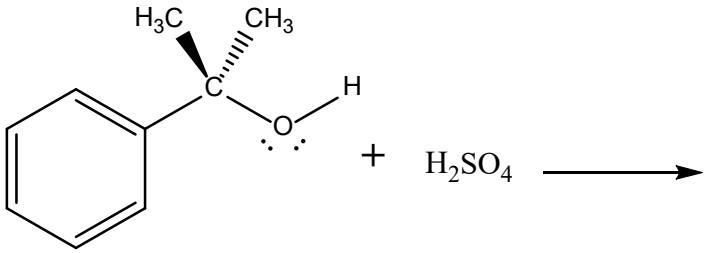
E1 vs. E2 vs. S_N1 vs. S_N2



E1 vs. E2 vs. S_N1 vs. S_N2

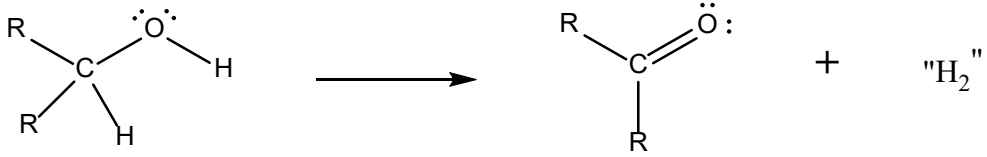


E1 vs. E2 vs. S_N1 vs. S_N2



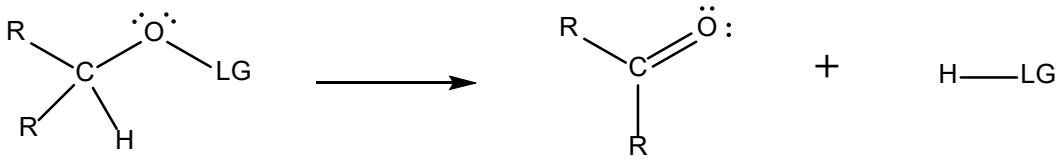
Oxidation Reactions (Alcohol to Carbonyl)

- To convert an alcohol into a ketone or aldehyde, we essentially need to eliminate H_2:



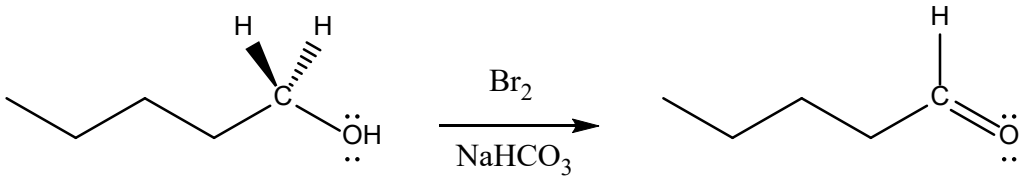
- Of course, H^- would be a horrendous leaving group, so we need to choose one of the two hydrogen atoms to be eliminated and convert that hydrogen atom into a leaving group.

- It is MUCH easier convert the hydrogen atom of the OH into a good leaving group, so that's the usual approach. After this has been done, an elimination reaction gives the desired carbonyl:



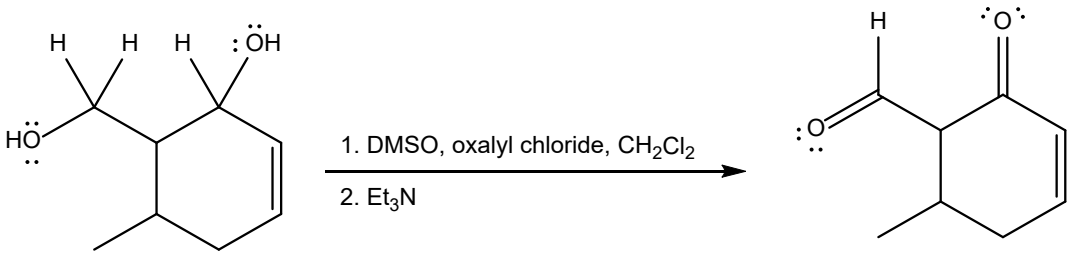
Oxidation Reactions (Alcohol to Carbonyl)

- A reaction that clearly demonstrates this concept is the reaction of a primary alcohol with a halogen in the presence of base:



Oxidation Reactions (Alcohol to Carbonyl)

- Another reaction which accomplishes this is a **Swern oxidation**. This is a multi-step reaction in which:
  - Dimethylsulfoxide [DMSO; $(CH_3)_2SO$] is mixed with oxalyl chloride [$(ClCO)_2$] at low temperature *(usually in CH_2Cl_2 solvent)*
  - The alcohol is then added to the reaction flask and allowed to react.
  - Finally, triethylamine is added and the flask allowed to warm to room temperature.
- Between the DMSO and the Et_3N, this reaction stinks! But it works well and it's very gentle, so it doesn't destroy other functional groups in the molecule. Primary alcohols are oxidized to aldehydes, and secondary alcohols are oxidized to ketones:



Oxidation Reactions (Alcohol to Carbonyl)

- So, how does a Swern oxidation work?
  - Add oxalyl chloride to DMSO:

Oxidation Reactions (Alcohol to Carbonyl)

- Add alcohol:

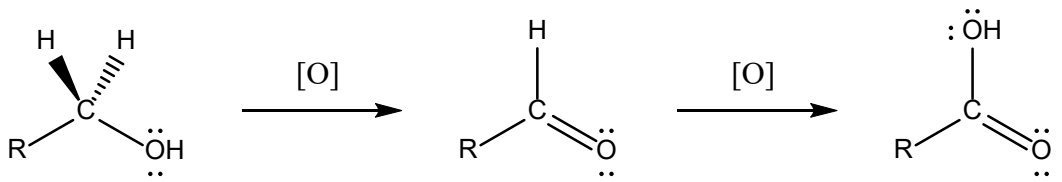
Oxidation Reactions (Alcohol to Carbonyl)

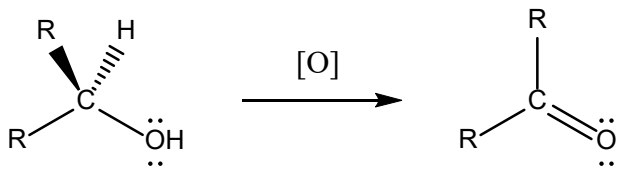
- Add Et_3N:

Oxidation Reactions (Alcohol to Carbonyl)

- Both of these reactions oxidize a primary alcohol to an aldehyde or a secondary alcohol to a ketone. Why can't either of them oxidize a tertiary alcohol?

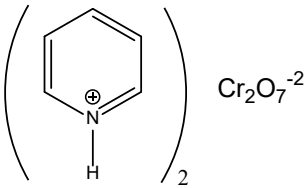
- There are also reactions which can oxidize a primary alcohol (or aldehyde) all the way up to a carboxylic acid:



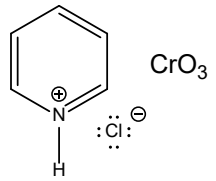


Oxidation Reactions (Alcohol to Carbonyl)

- Many oxidation reactions involve highly oxidized chromium species; however, those are toxic so use them with care…
- To oxidize 1° alcohols to aldehydes (or 2° alcohols to ketones), options include:
  - Br_2 and $NaHCO_3$
  - PDC (pyridinium dichromate) in CH_2Cl_2



  - PCC (pyridinium chlorochromate) in CH_2Cl_2



  - Swern oxidation (DMSO + oxalyl chloride; add alcohol; add Et_3N)
- To oxidize 1° alcohols to carboxylic acids (or 2° alcohols to ketones), options include:
  - Jones oxidation (CrO_3 added to $H_2SO_{4(aq)}$ gives $H_2CrO_{4(aq)}$)

Oxidation Reactions (Alcohol to Carbonyl)

- Draw the organic product for each of the following reactions: