

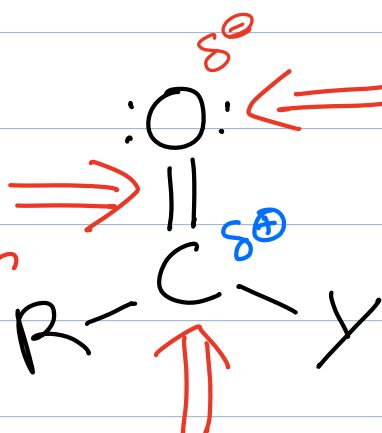
Gleevec – Novartis (\$4.65 Billion in sales in 2015). A kinase inhibitor, that is a first of its kind pill capable of treating certain blood cancers with only limited side effects. It was designed to combat leukemias with the relatively common “Philadelphia chromosome” (BCR-ABL kinase gene fusion)

Carbonyl Death Star

Old
"pi bond"
Kenobi



π bond
breaks
during
reaction



Protons (H^+)
react here

Han
"The
Proton"
Solo



Nucleophiles (δ^-)
react here

"Nuc" Skywalker



" $\text{sp}^3 \text{O}$ "

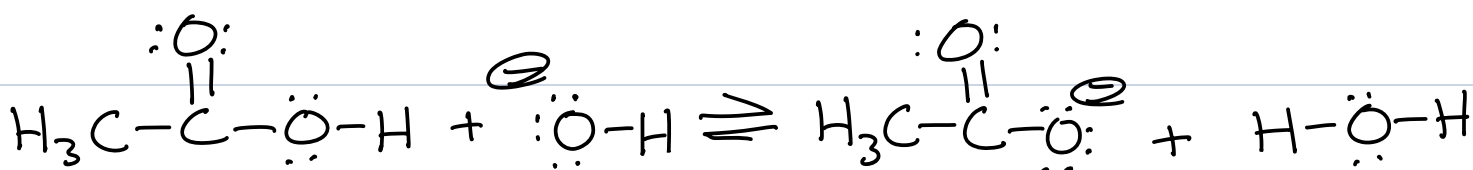
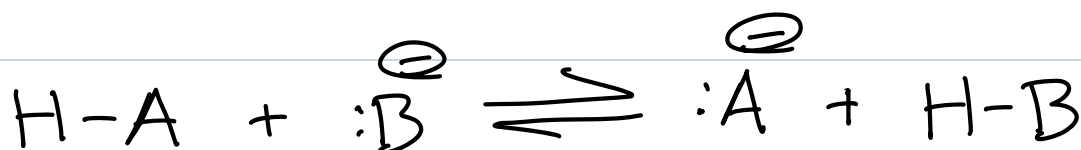


" $\text{S}_\text{N}2/\text{E}2$ "

Equilibrium favors formation of the weaker base and weaker acid

⇓
more stable anion

⇓
higher pKa



pKa = 4.78

⇓

less stable anion

⇓

more stable anion

⇓

weaker base!

pKa = 15.7

⇓

larger pKa so weaker acid

Bottom line → position of equilibrium

favors the side with the more stable anion

Amounts to a thermodynamic driving force (motive) for a reaction

Weaker bases are favored at equilibrium

Compound	Chemical Structure	pK _a
	H-Cl	-7
Carboxylic acids*	$\text{R}-\text{CO}-\text{H}$	3-5
β -Dicarbonyls*	$\text{RC}-\text{CH}_2-\text{CR}'$	10
β -Ketoesters*	$\text{RC}-\text{CH}_2-\text{COR}'$	11
β -Diesters*	$\text{ROC}-\text{CH}_2-\text{COR}'$	13
Water	HOH	15.7
Alcohols	RCH_2OH	15-19
Acid chlorides*	RCH_2-COCl	16
Aldehydes*	RCH_2-CHO	18-20
Ketones*	$\text{RCH}_2-\text{C}(=\text{O})\text{R}'$	18-20
Esters*	$\text{RCH}_2-\text{COOR}'$	23-25
Terminal alkynes	$\text{RC}\equiv\text{C}-\text{H}$	25
LDA	$\text{H}-\text{N}(\text{i-C}_3\text{H}_7)_2$	40
Terminal alkenes	$\text{R}_2\text{C}=\text{C}-\text{H}$	44
Alkanes	$\text{CH}_3\text{CH}_2-\text{H}$	51

Strongest Acid
(Weakest conjugate base)



Weakest Acid
(Strongest conjugate base)

A) Reactions are favored (i.e. have a motive) if they lead to formation of a weaker acid and/or weaker base.

B) Checking pK_a values can predict if a reaction has a motive even if there are other steps besides a proton transfer.

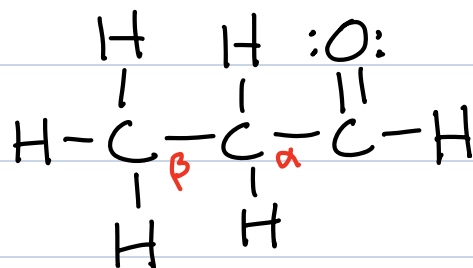
C) Recall that the conjugate base of a stronger acid (lower pK_a) is a weaker base.

D) Check the pK's of the conjugate acid of the bases on either side of the equation. Lower pK_a value corresponds to stronger acid of the conjugate acid, and thus weaker conjugate base. The base with a stronger conjugate acid (lower pK_a value) will be the weaker base and will be favored at equilibrium.

E) Another way to look at it is that the base that is favored at equilibrium is the one that has the more stabilized anion, i.e. the one with the charge spread around more (electronegative) atoms.

F) Above is a pK_a table that we will refer to often.

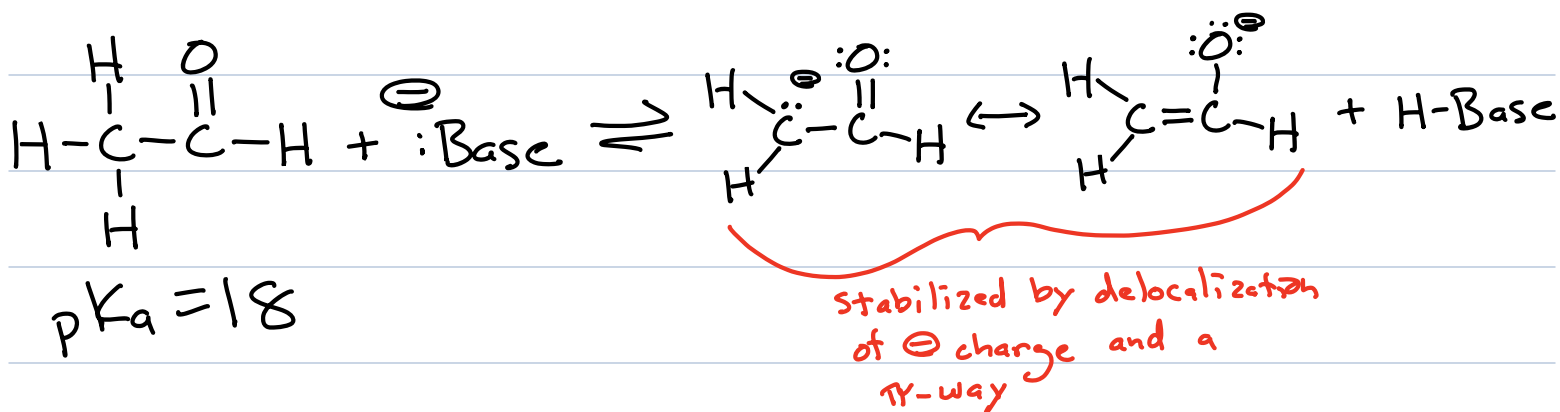
*These have resonance stabilized anions



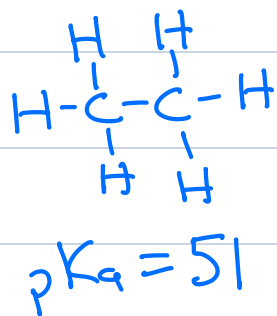
The C atom adjacent to a carbonyl is called the α carbon. The next C atom is called the β carbon.

The H atoms on the α carbon are called α hydrogens

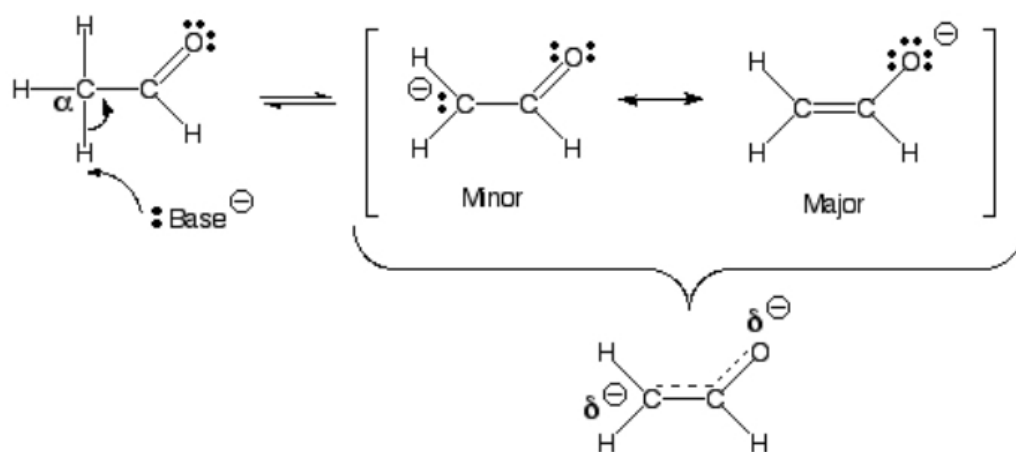
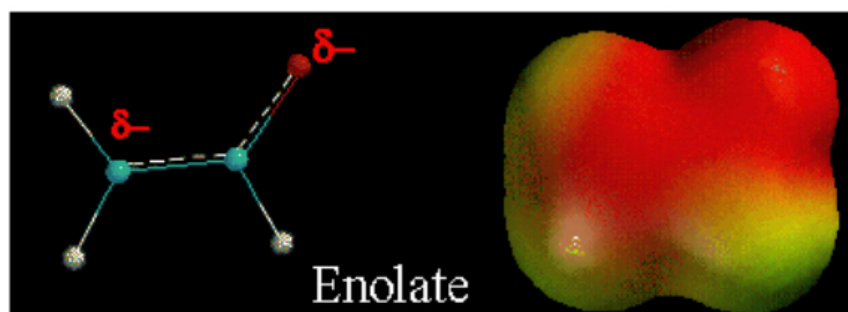
α hydrogens are extremely acidic for a C-H bond



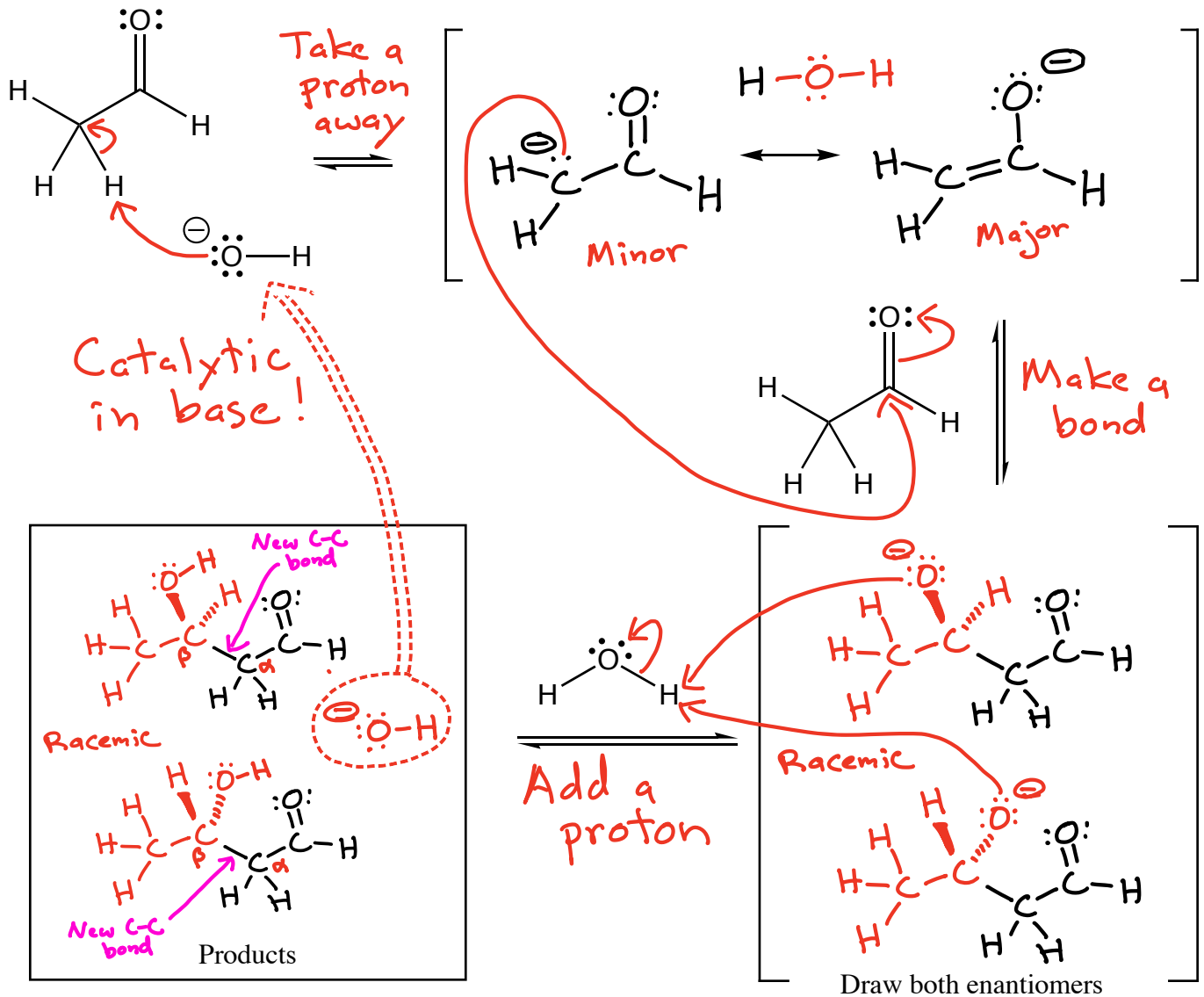
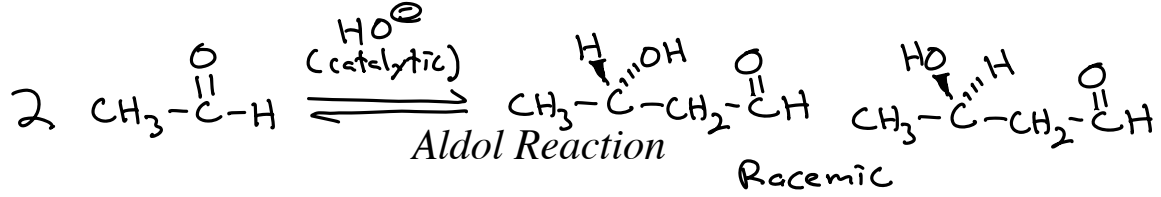
Compare:



Enolates as nucleophiles



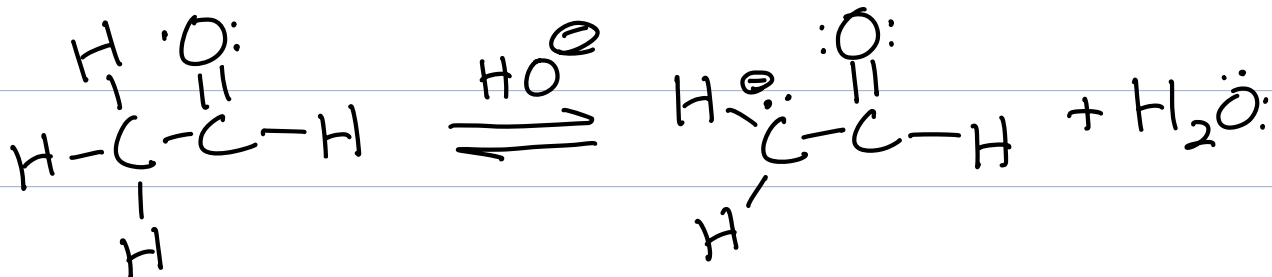
- A) Enolates are resonance stabilized, with a partial negative charge on carbon and oxygen. ✓
- B) Enolates are nucleophiles, so they could react at either the carbon atom or oxygen atom. The partial negative charges give them the **opportunity** to react at either the carbon or oxygen.
- C) Reaction at the carbon atom gives the final product a C=O bond, while reaction at the oxygen atom gives the final product a C=C bond. However, C=O bonds are stronger than C=C bonds, **so the motive is to react at the carbon atom with most electrophiles.**



KRE \rightarrow β -hydroxy aldehyde
with a new C-C
bond between the
aldehyde α and β
carbons

Mechanism
A

Another Movie Rips Off Organic Chemistry



Aldehyde

Enolate

Is Attacked
By Enolate

Attacks
Aldehyde

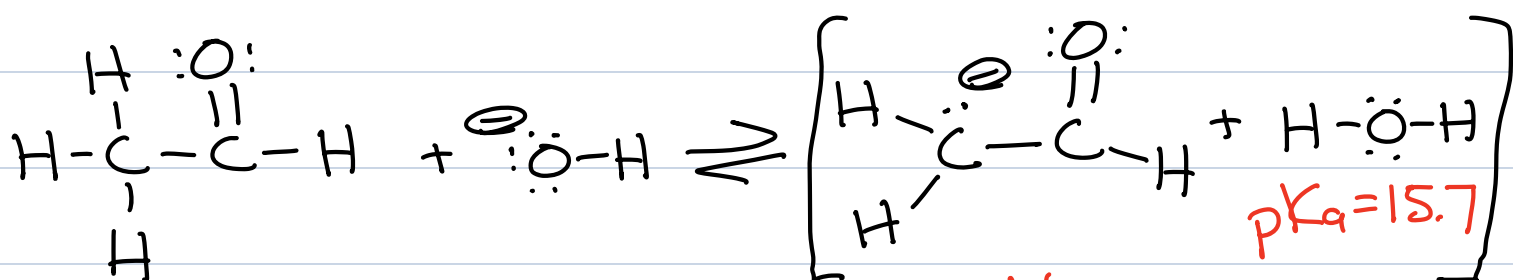
Austin Powers

Dr. Evil



Aldol Reaction Considerations

1) When HO^\ominus is used as the base, equilibrium of the first step favors the aldehyde



$pK_a = 18-20$
weaker base

This side favored at equilibrium

There will be excess aldehyde for the enolate to react with

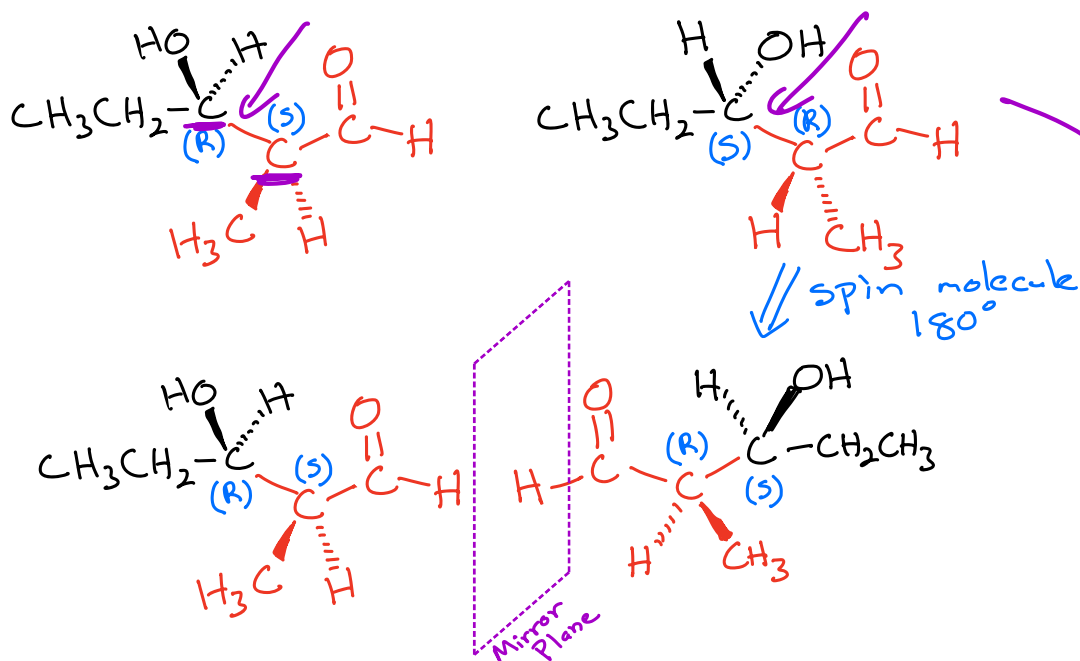
2) Because there is HO^\ominus present at the beginning and end of the reaction there is little driving force (motive) for the aldol reaction \rightarrow the aldol reaction is reversible

3) The aldol reaction is favorable for aldehydes but NOT for ketones

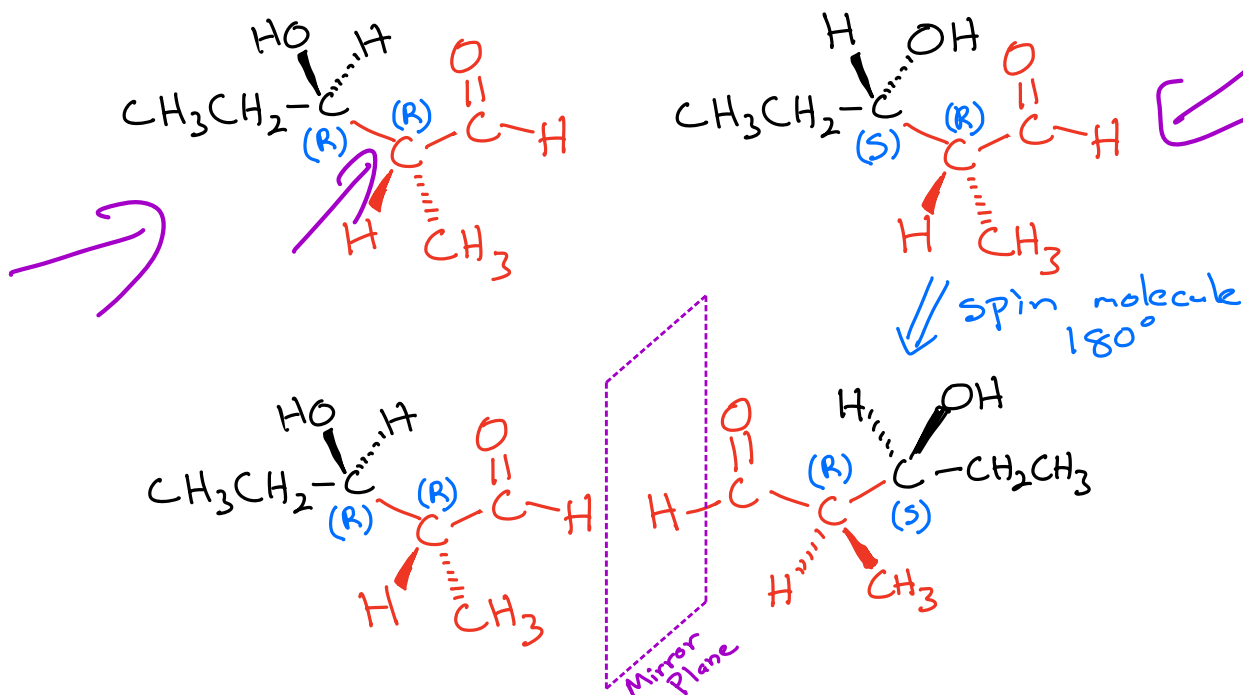
4) The reaction can make two new chiral centers



Enantiomers or Diastereomers?

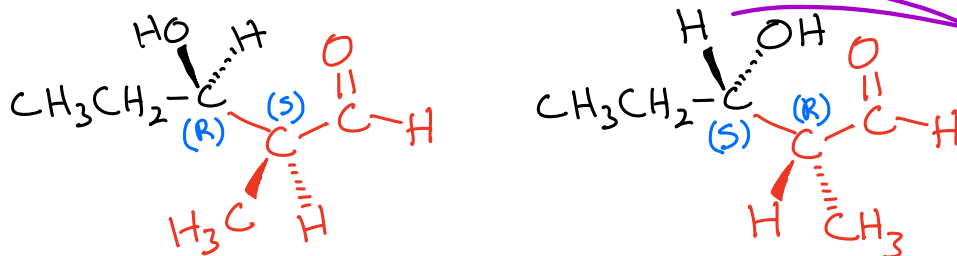


Enantiomers (Section 3.2) Stereoisomers that are nonsuperposable mirror images of each other; refers to a relationship between pairs of objects.

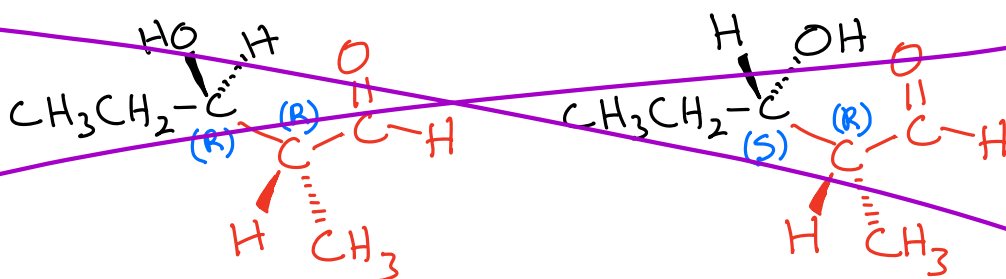


Diastereomers (Section 3.4A) Stereoisomers that are not mirror images of each other; refers to relationships among two or more objects.

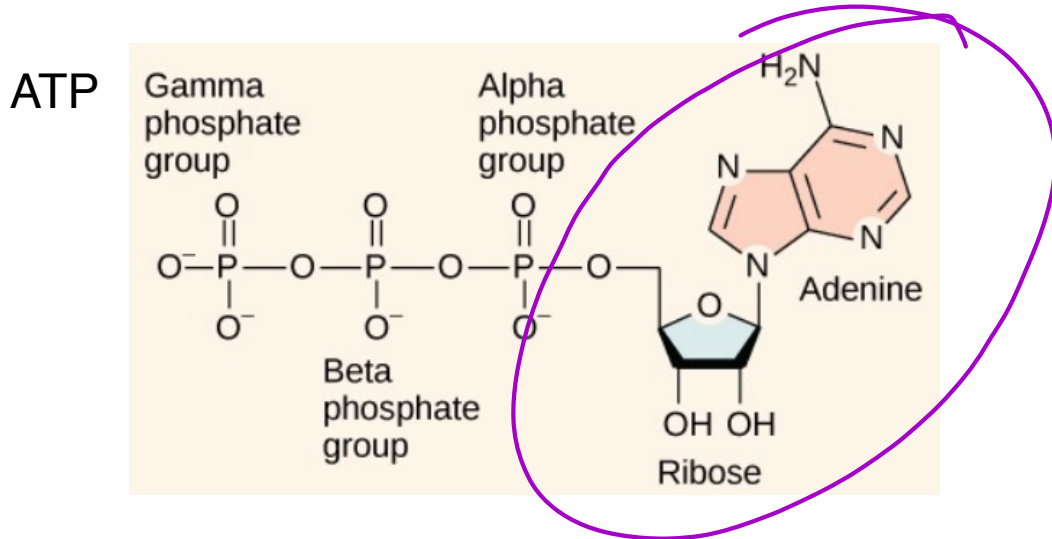
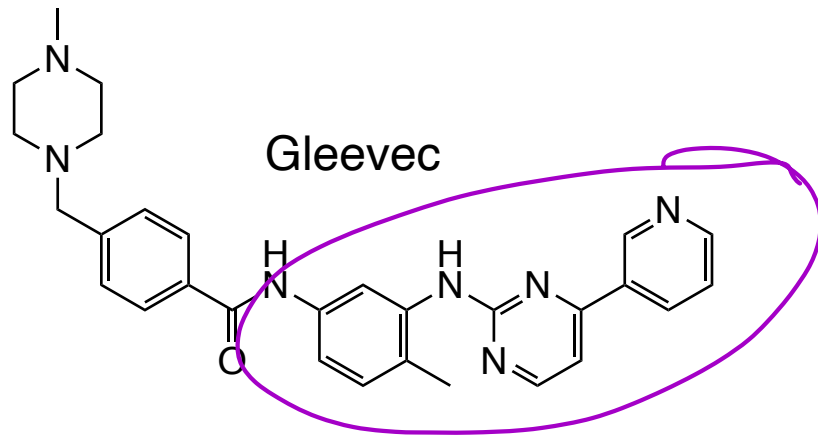
Which pair of molecules could be a racemic mixture?



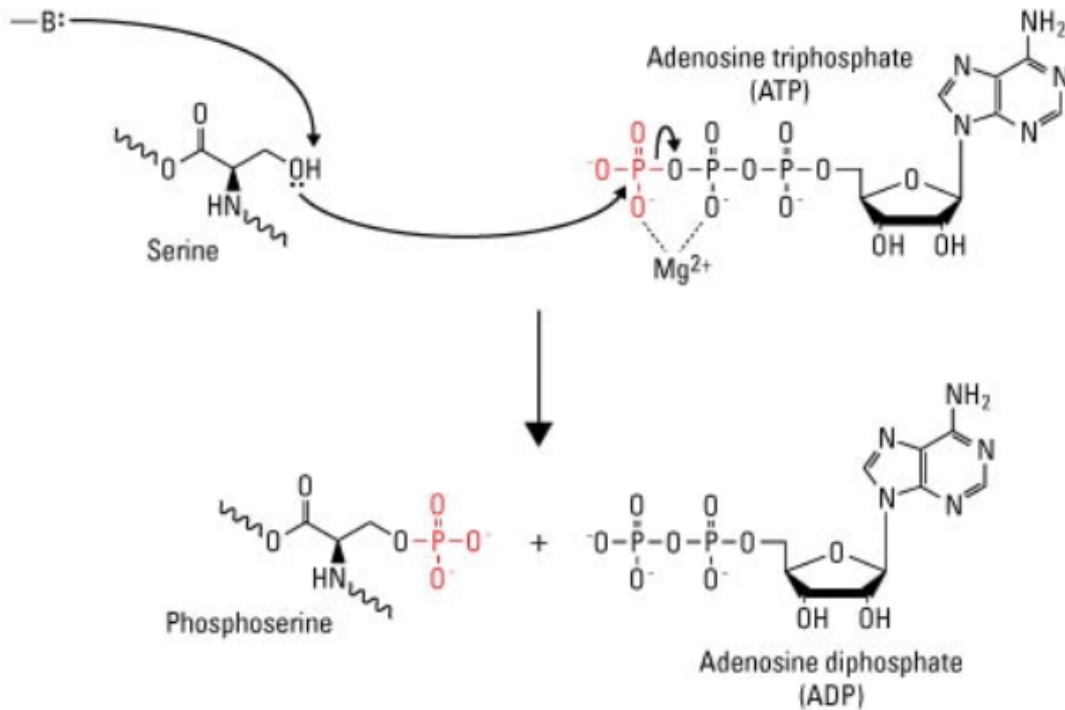
OR



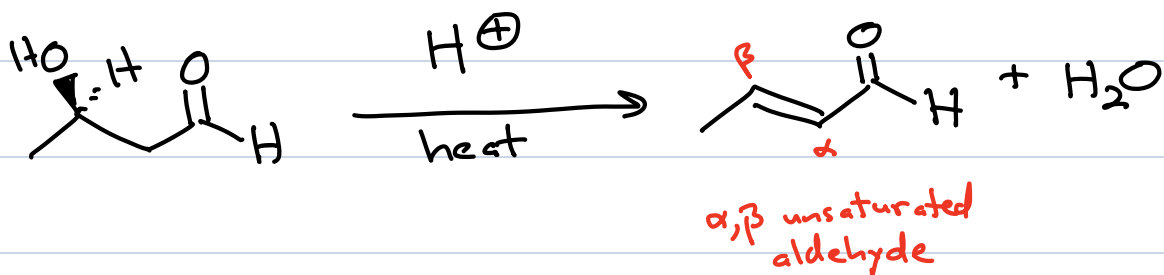
Racemic mixture (Section 3.7C) A mixture of equal amounts of two enantiomers.



How Kinases Work:

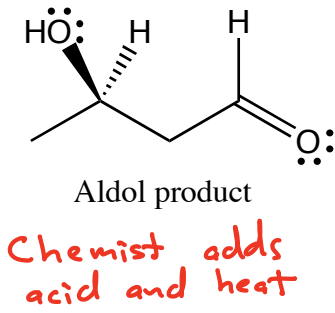


In mild acid with some heating, the aldol product will dehydrate to give an α,β -unsaturated aldehyde.

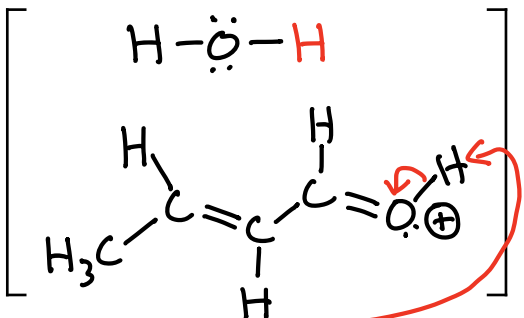
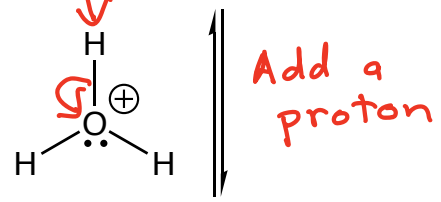
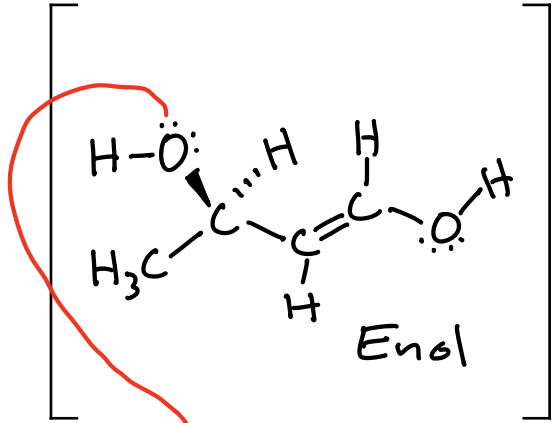


Note: The following mechanism is NOT the simplest you might think of, but it is the one with the lowest energy intermediates (no carbocations, etc.) so this is the correct mechanism

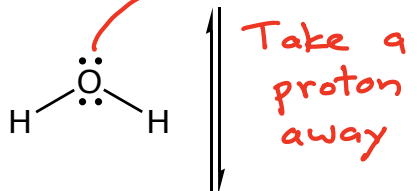
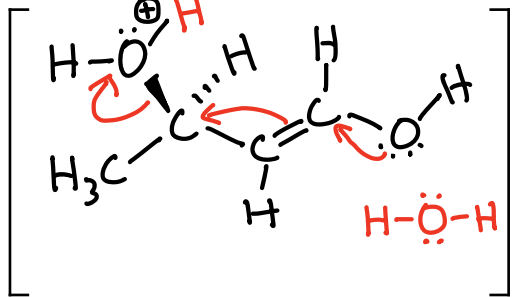
Acid catalyzed dehydration



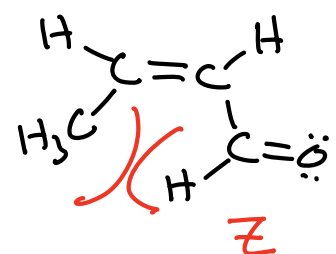
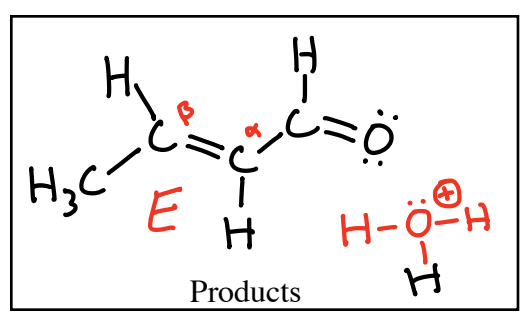
tautomerization



Break a bond



KRE → α,β-unsaturated aldehyde → the C=C is where the new C-C bond is located



THIS IS UNIQUE TO THIS EXAMPLE
 ↓
 USUALLY BOTH E AND Z ARE FORMED

Not much of the Z product is formed because it has significantly more steric strain than E