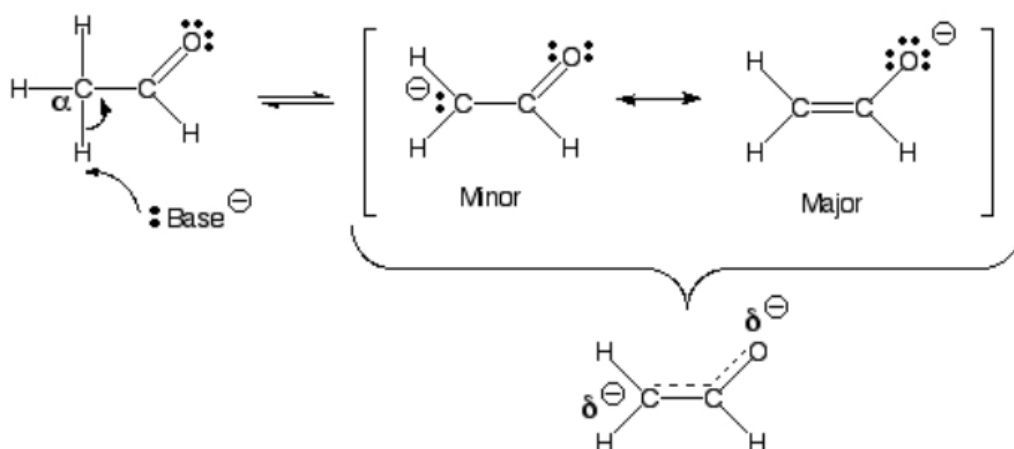
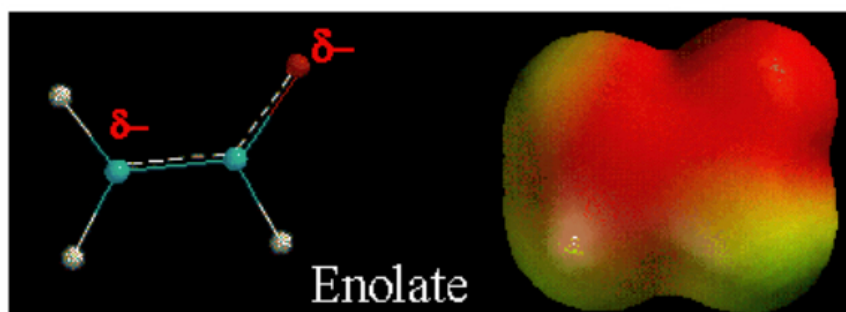


Enolates as nucleophiles

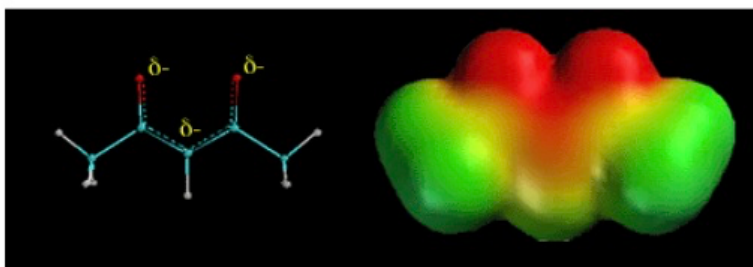
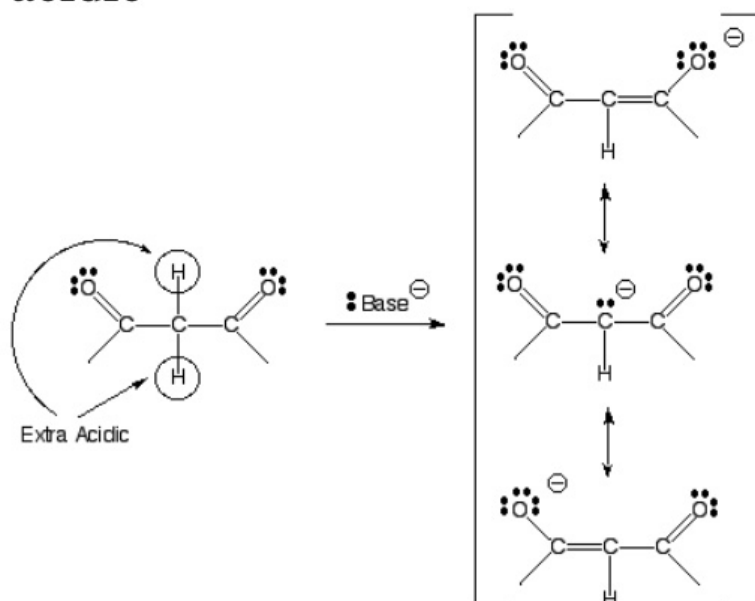


A) Enolates are resonance stabilized, with a partial negative charge on carbon and oxygen.

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.**

Beta-dicarbonyls have alpha-hydrogens that are extra acidic



The C-H hydrogen atoms between two carbonyl groups are even more acidic than normal alpha hydrogens because the resulting anion is double resonance stabilized. The above electrostatic potential surface shows how the negative charge (red color) is spread over all three atoms as predicted by the three resonance contributing structures.

Weaker bases are favored at equilibrium

Compound	Chemical Structure	pK _a
	H-Cl	-7
Carboxylic acids*	$\text{R}-\text{C}(=\text{O})-\text{OH}$	3-5
β-Dicarbonyls*	$\text{RC}(=\text{O})-\text{CH}_2-\text{C}(=\text{O})\text{R}'$	10
β-Ketoesters*	$\text{RC}(=\text{O})-\text{CH}_2-\text{C}(=\text{O})\text{OR}'$	11
β-Diesters*	$\text{ROC}(=\text{O})-\text{CH}_2-\text{C}(=\text{O})\text{OR}'$	13
Water	HOH	15.7
Alcohols	RCH_2OH	15-19
Acid chlorides*	$\text{RCH}_2-\text{C}(=\text{O})\text{Cl}$	16
Aldehydes*	$\text{RCH}_2-\text{C}(=\text{O})\text{H}$	18-20
Ketones*	$\text{RCH}_2-\text{C}(=\text{O})\text{R}'$	18-20
Esters*	$\text{RCH}_2-\text{C}(=\text{O})\text{OR}'$	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.

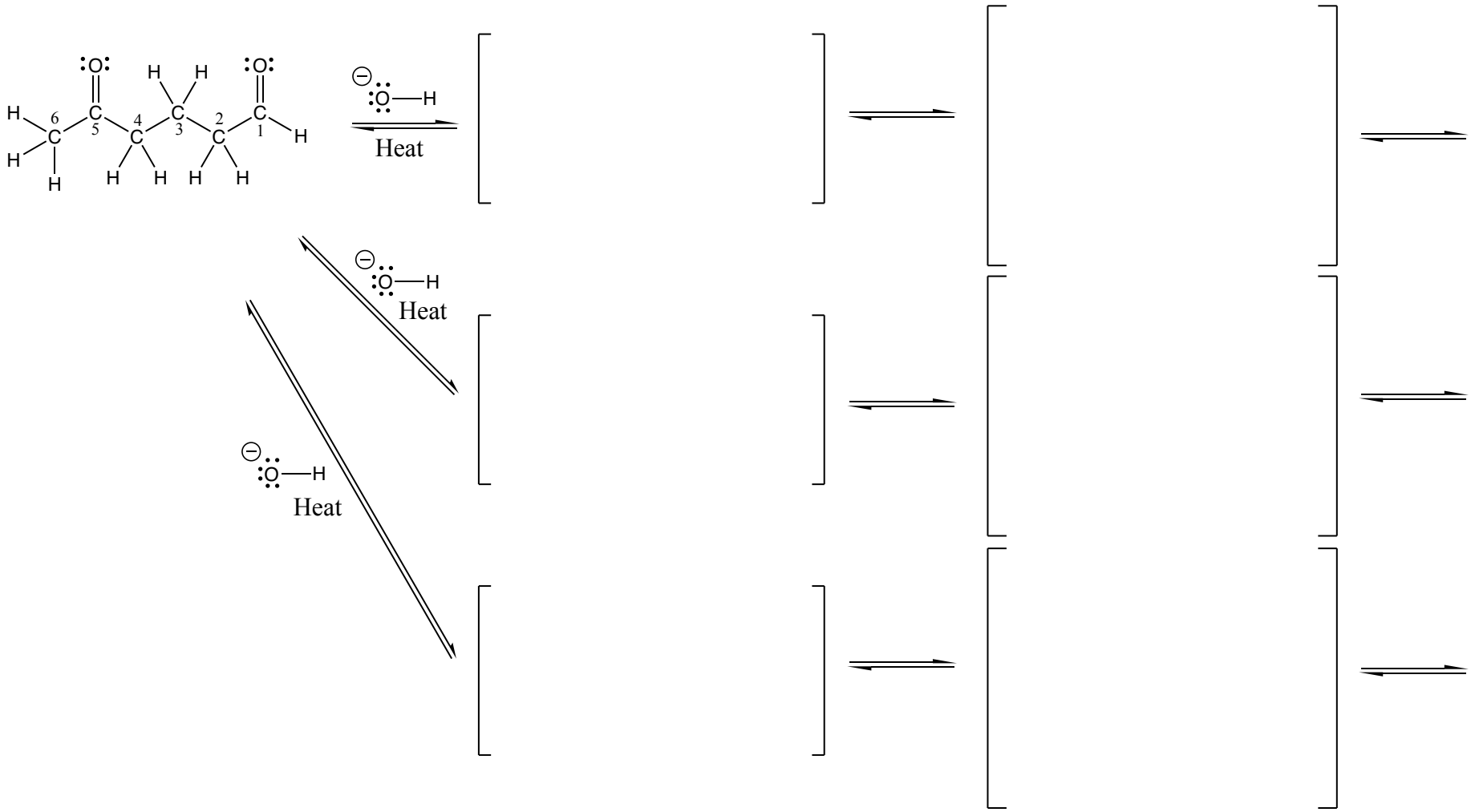
C) Recall that the conjugate base of a stronger acid (lower pK_a) is a weaker base.

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.

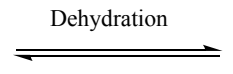
E) Another way to look at it is that the base that is favored at equilibrium is the one that has the more stabilized anion, i.e. the one with the charge spread around more (electronegative) atoms.

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

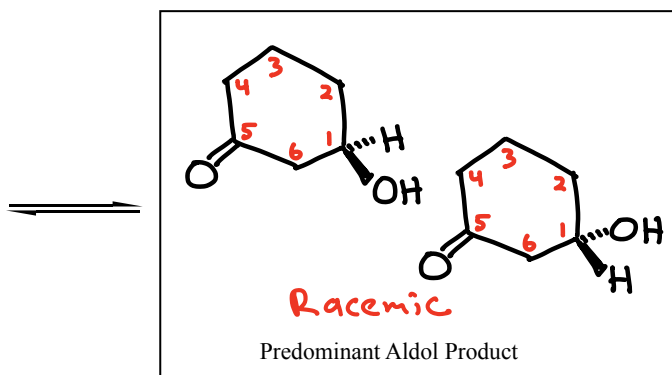
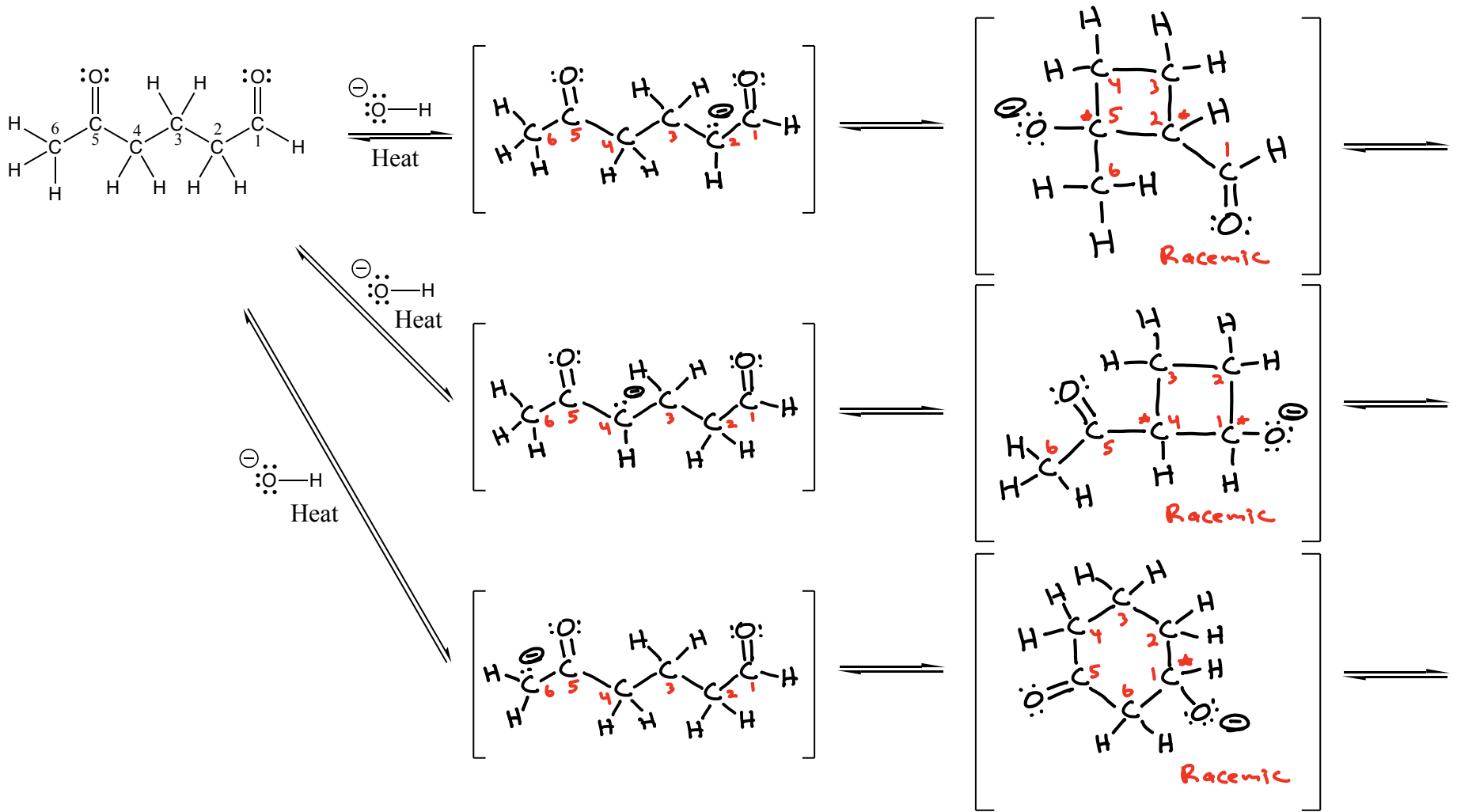
*These have resonance stabilized anions



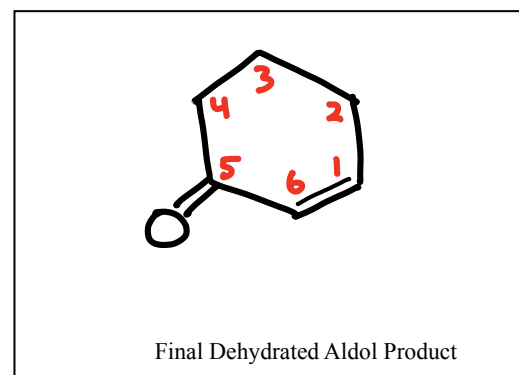
Predominant Aldol Product



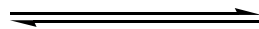
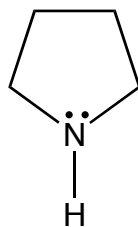
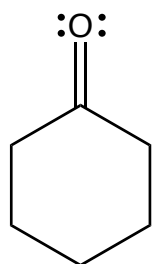
Final Dehydrated Aldol Product



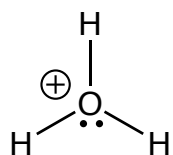
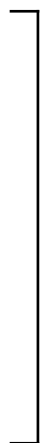
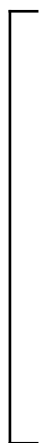
Dehydration



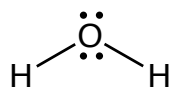
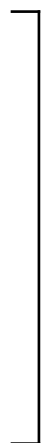
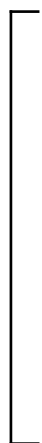
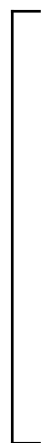
Enamine Formation



proton transfer \rightleftharpoons

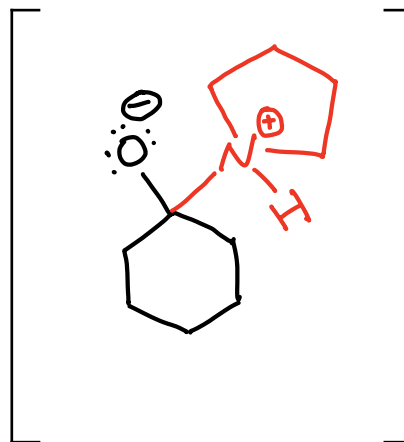
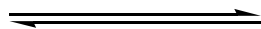
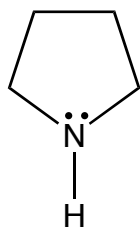
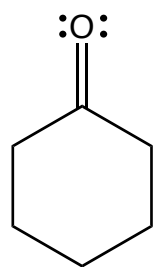


slightly acidic pH

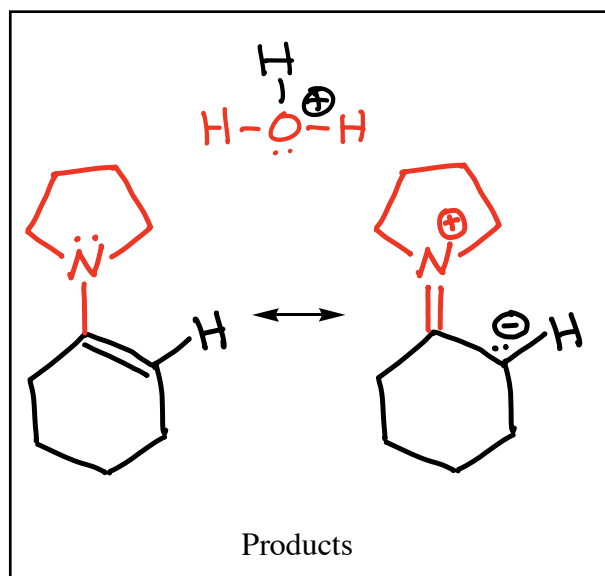
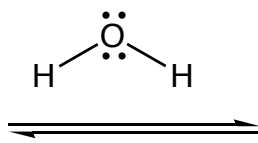
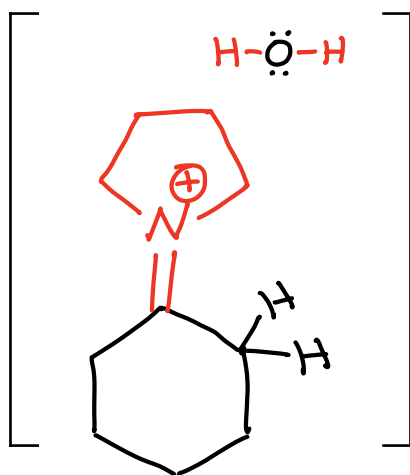
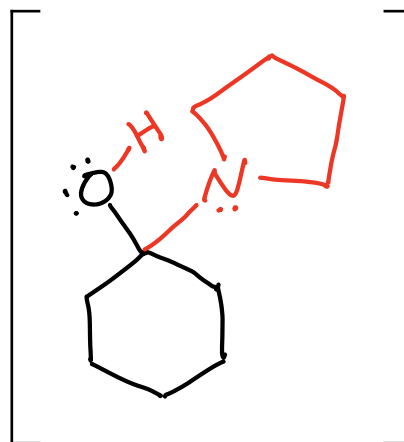
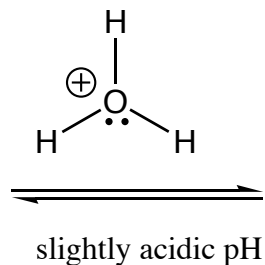
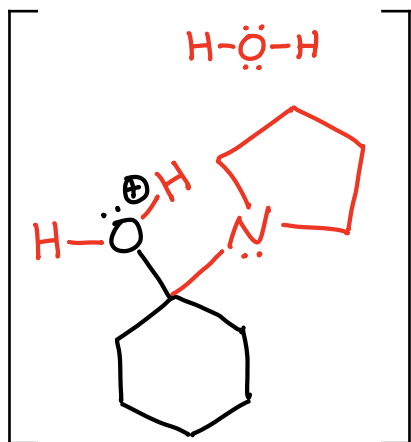


Products

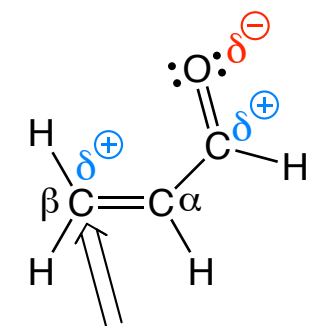
Enamine Formation



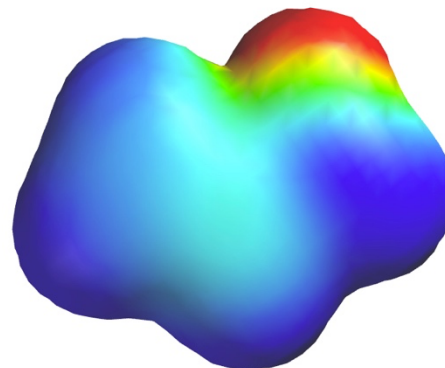
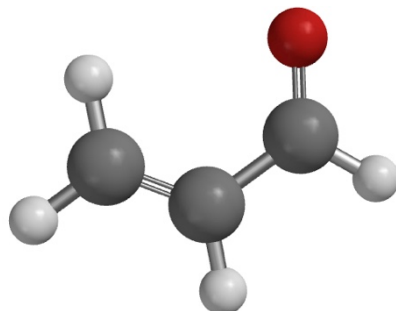
proton transfer \rightleftharpoons



Conjugate Addition



Nucleophiles react here via conjugate addition



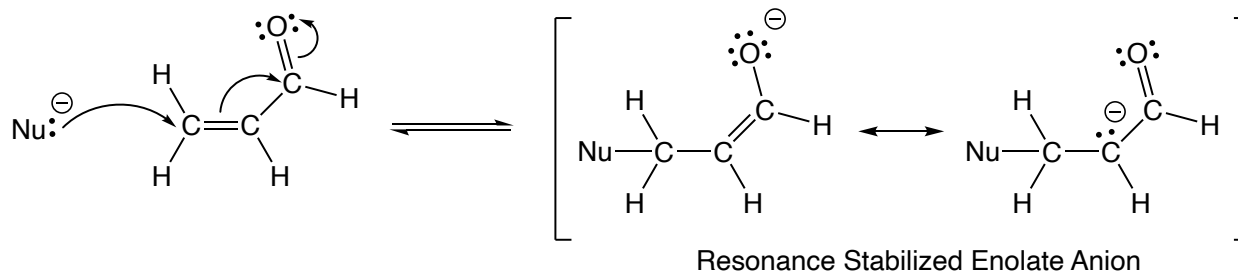
A) Alkenes adjacent to a carbonyl are conjugated and are therefore electrophilic.

B) These species are called α,β unsaturated carbonyl compounds.

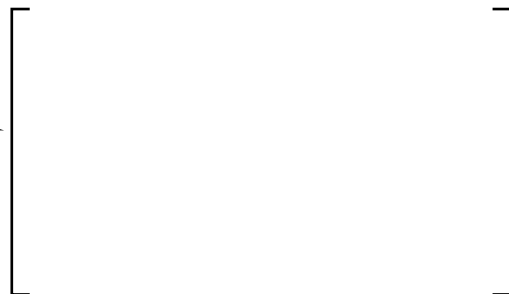
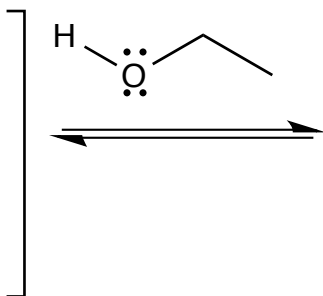
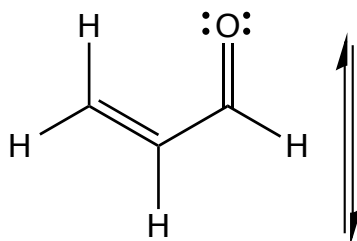
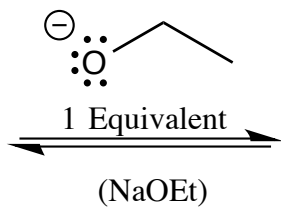
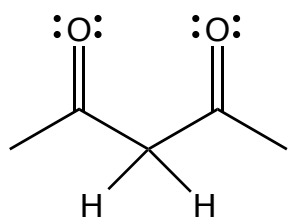
C) α,β unsaturated carbonyl compounds are conjugated, in that the pi electrons of the C=C and C=O bonds can delocalize over all four atoms. This lends some degree of extra stabilization to these species, because [pi electrons prefer to delocalize](#).

D) Nucleophiles can, however, react at the β carbon atom in a process called conjugate addition.

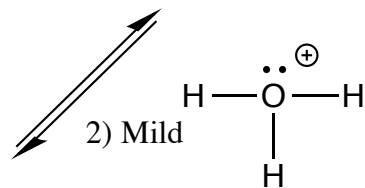
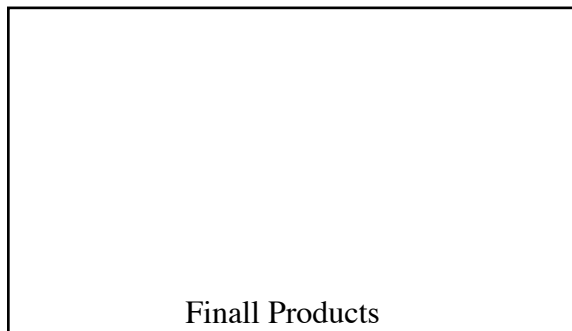
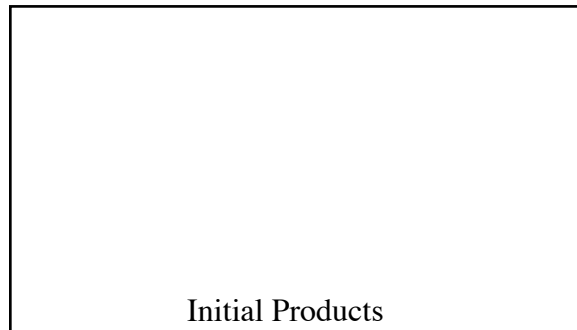
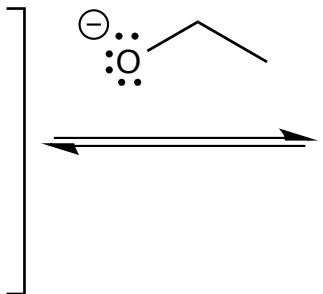
E) Conjugate addition is favorable because the intermediate formed is a resonance stabilized enolate, thus relatively low energy.



Michael Reaction

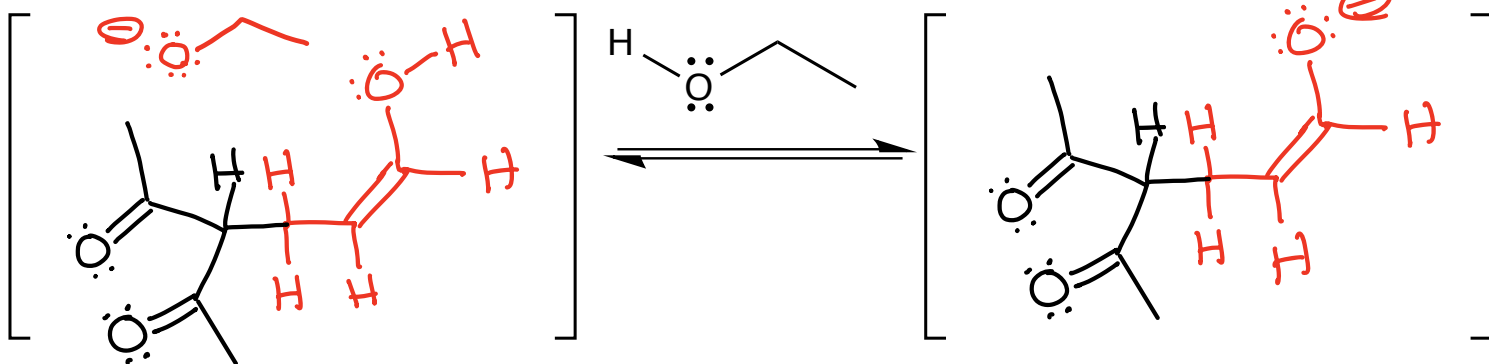
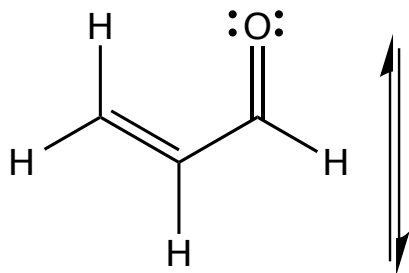
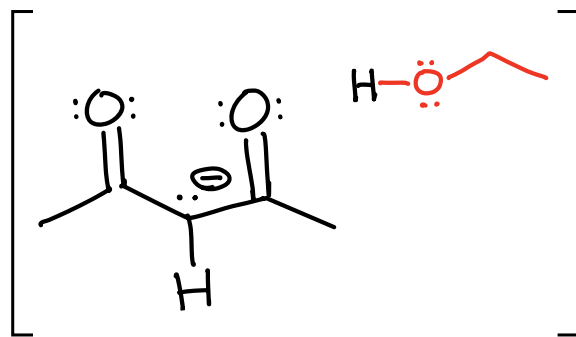
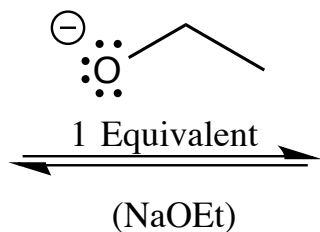
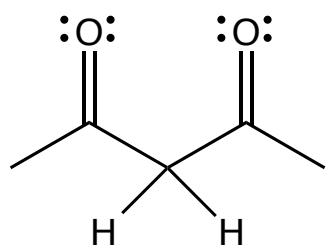


tautomerization \rightleftharpoons

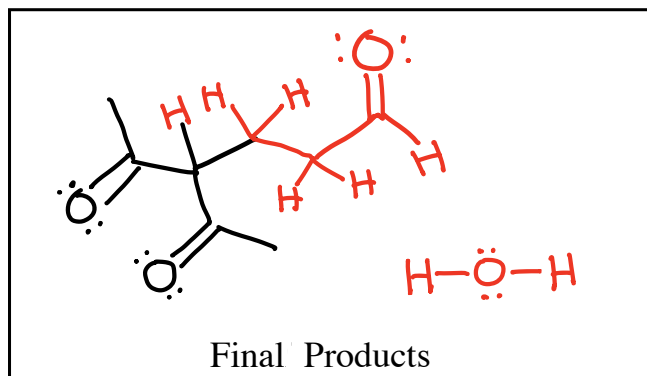
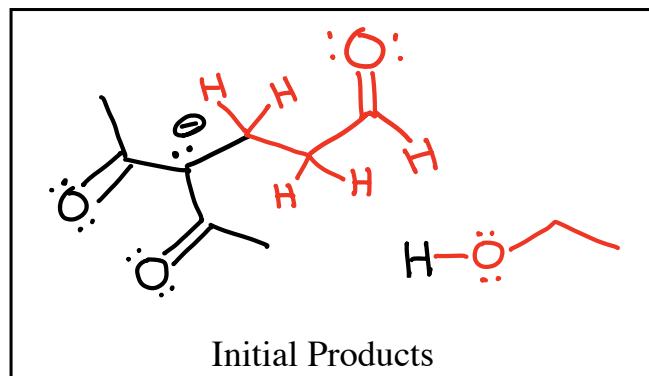
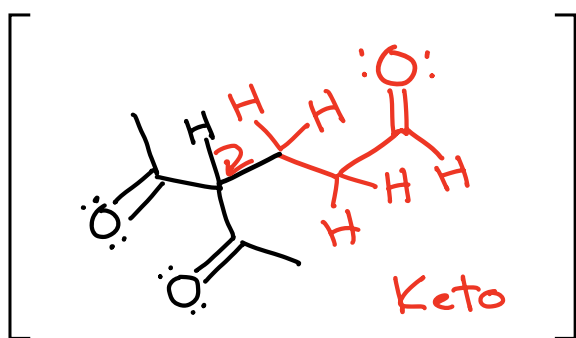


(Chemist opens flask and adds a mild acid)

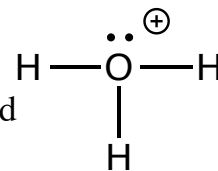
Michael Reaction



tautomerization



2) Mild



(Chemist opens flask and adds a mild acid)

Table 19.1 Combinations of Reagents for Effective Michael Reactions

These Types of α,β -Unsaturated Compounds Are Nucleophile Acceptors in Michael Reactions

These Types of Compounds Provide Effective Nucleophiles for Michael Reactions

