Many molecules required by all growing organisms (both big and small) are ***Biosynthesized*** (i.e. enzymes in the body ~ carry out *Organic chemistry* rxns) using:

Carbonyl ***Condensation*** reactions

Chapter 23

occur in a large number of ***metabolic*** pathways: esp. *Carbohydrates, Lipids, Proteins*, *Nucleic acids* ~ essential for growth and development…

Important ~ general method for making new **C-C** bonds ~ to build larger MOLECULES ☺

Outline

- Administrative
- Background
- Carbonyl condensations: The Aldo reaction
- Dehydration of Aldol products:
  - Synthesis of Enones
- Conjugate Carbonyl Additions:
  - The Michael reaction

Outline

- Background
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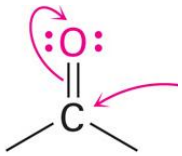
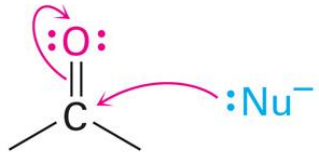
Mini SUMMARY

We've reviewed 3 of 4 general carbonyl-group rxns
That display two types of behavior:



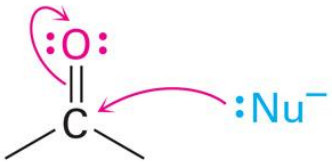
1) Nucleophilic ***addition*** and **2**) acyl ***substitution*** rxns

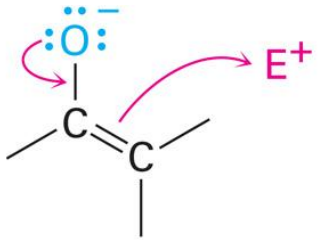


Carbonyl compound behaves as an electrophile when ***e-*** rich reagent (Nu:) adds to it

3) α – ***substitution*** rxns: carbonyl compounds behave as a nucleophile when converted into it's enol or enolate ion (*last lecture*)

4) In this chapter – we'll study briefly how the carbonyl behaves both as an:
a) ***electrophile*** and **b**) ***nucleophile***





a) **Electrophilic carbonyl group reacts with nucleophiles.**

b) **Nucleophilic enolate ion reacts with electrophiles.**

Outline

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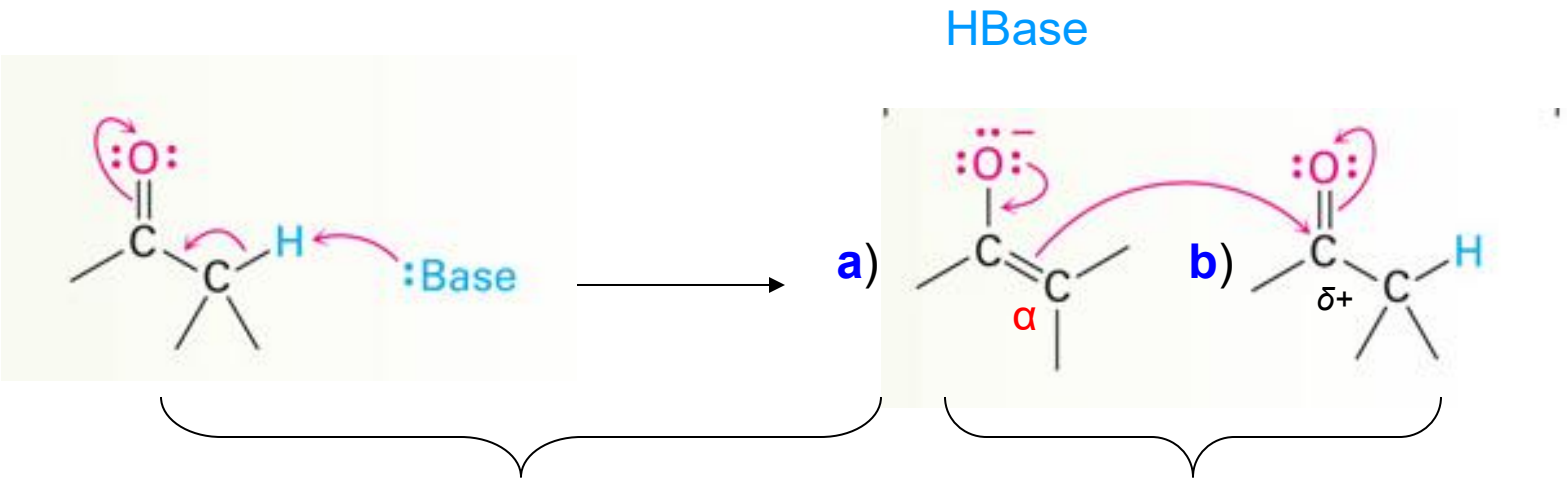
Carbonyl condensations: **The Aldol reaction**

These occur b/w two carbonyl partners and involve a combination of:

1) conversion into **a**) enolate-ion nucleophile – that adds to the…

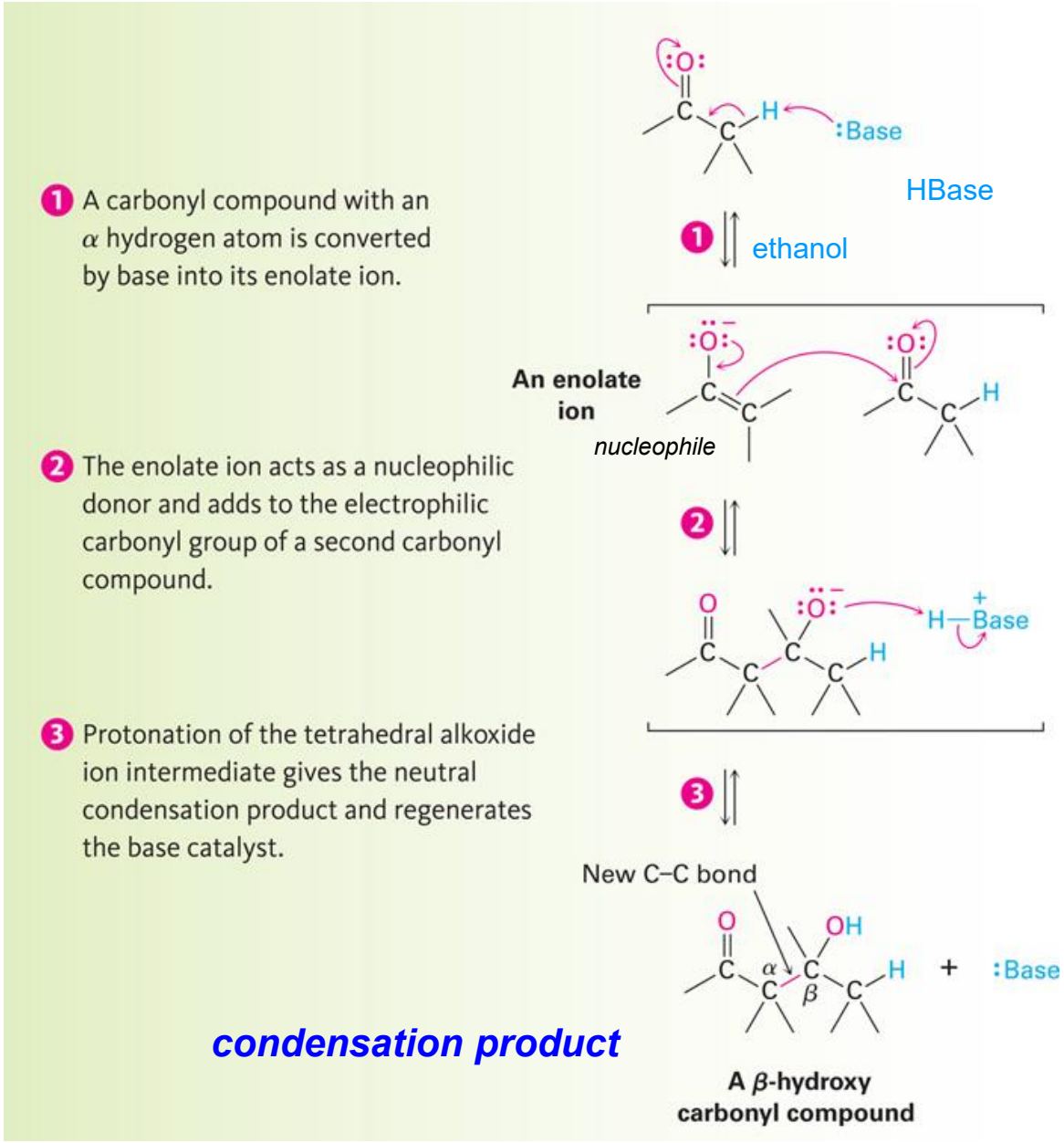
2) electrophillic carbonyl group of b) the second carbonyl partner (~α-substitution step)



(α-substitution step)

Mechanism for carbonyl condensation rxn

You draw ☺



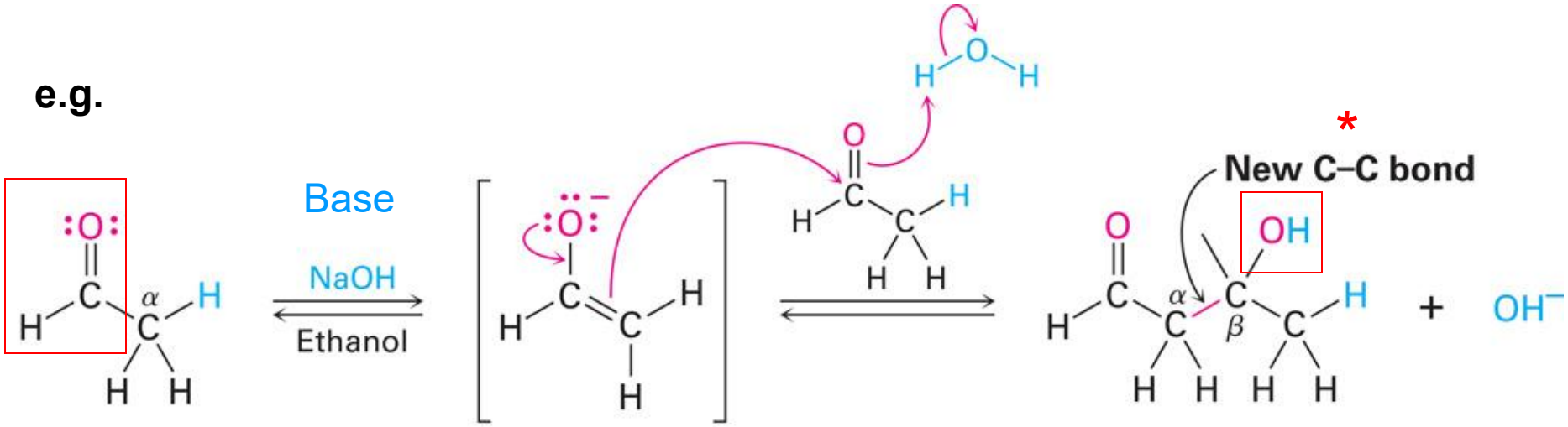
1. A carbonyl compound with an α hydrogen atom is converted by base into its enolate ion.
2. The enolate ion acts as a nucleophilic donor and adds to the electrophilic carbonyl group of a second carbonyl compound.
3. Protonation of the tetrahedral alkoxide ion intermediate gives the neutral condensation product and regenerates the base catalyst.

condensation product

Aldol RXN *Why the Name?* (involves **Ald**ehydes & alcoh**ol**)

The **Aldol** RXN: where Aldehydes/ketones w/ α **H** undergo base cataylzed carbonyl rxn

e.g.



Acetaldehyde **Enolate ion** **3-Hydroxybutanal (aldol–a β-hydroxy carbonyl compound)**

condensation product!

NOTES: RXN in ***equilibrium***

Position of the **Aldol** (aldehydes/alcohol) ***equilibrium*** depends on:
1) reaction conditions
2) substrate structure

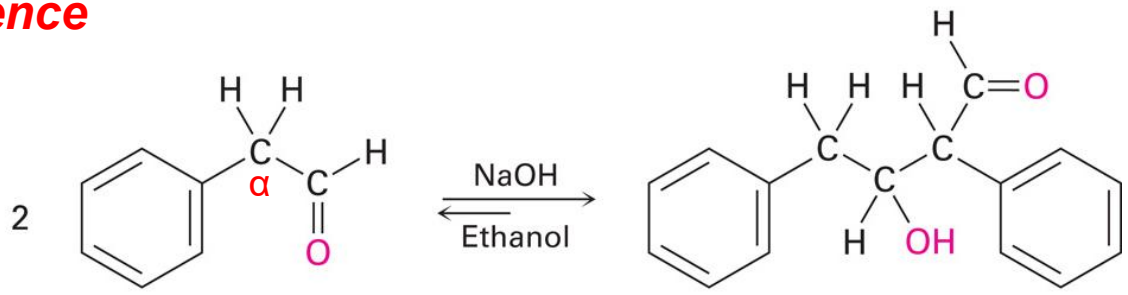
a) *Equilibrium* favors **condensation product** (**2**) for aldehydes w/ no α substituent (**1**)

b) *Equilibrium* favors reactant for di-substituted aldehydes and ketones

Steric factors influence

REACTANT PRODUCT

a) **Aldehydes**



Phenylacetaldehyde **(1)**
(10%)

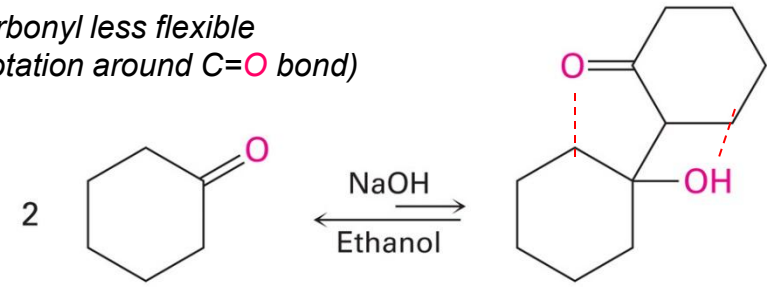
(90%)

condensation product (2)

You draw ☺

carbonyl less flexible
(no free rotation around C=O bond)

b) **Ketones**



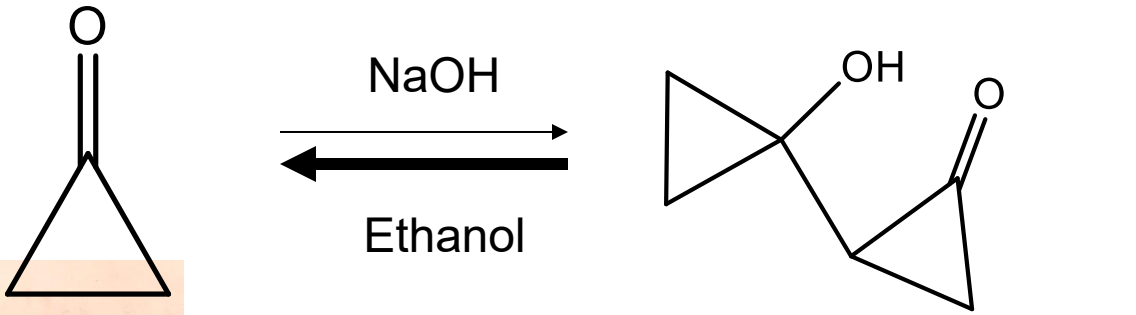
Cyclohexanone
(78%)

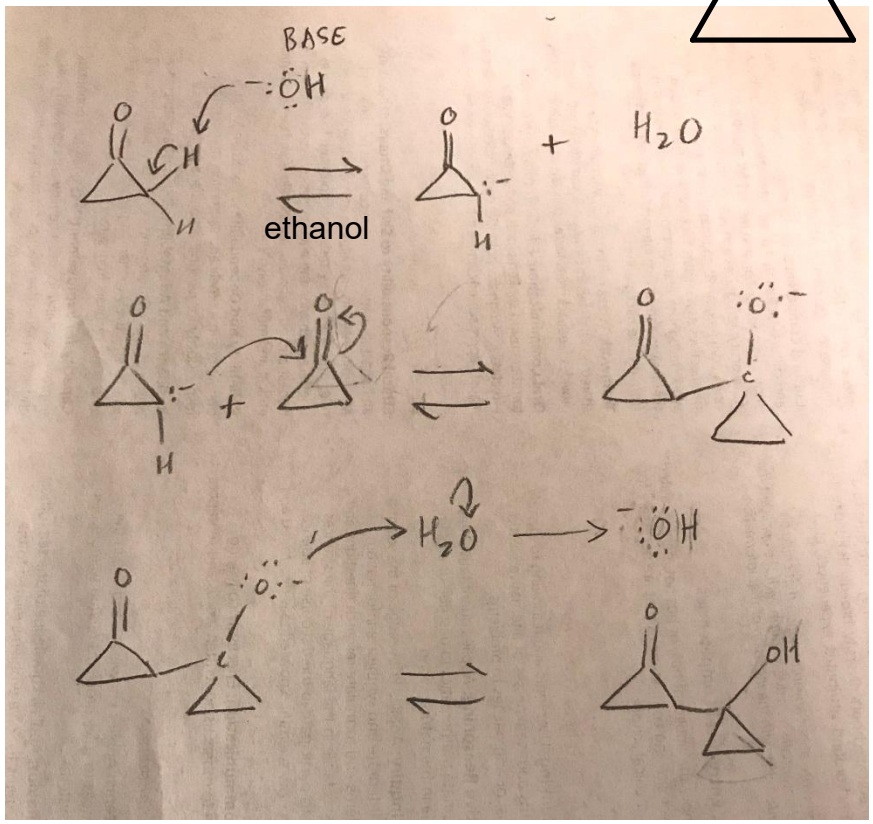
(22%)

Challenge Question

a) What's the expected product of the following Aldol reaction, what reagent(s) is/are needed?
b) What's a plausible mechanism you'd expect and what direction does the *equilibrium* favor?

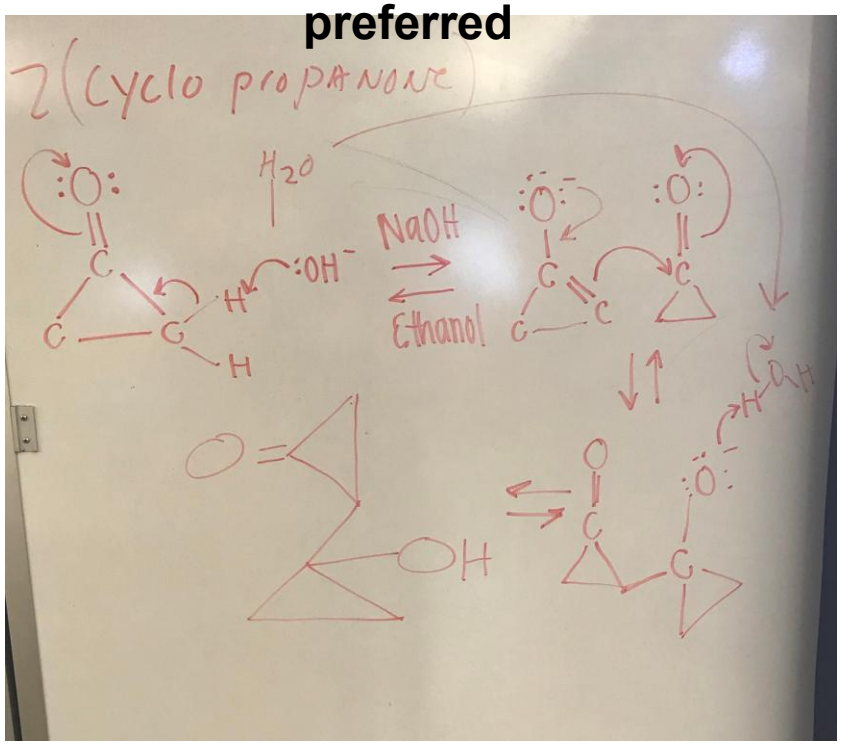
We'll take both proposed mechanisms at this pt.





J. Morris suggests more plausible due to angle strain on ring (3/18)

preferred



L. Persi, R. Torres proposed mechanism (3/18)

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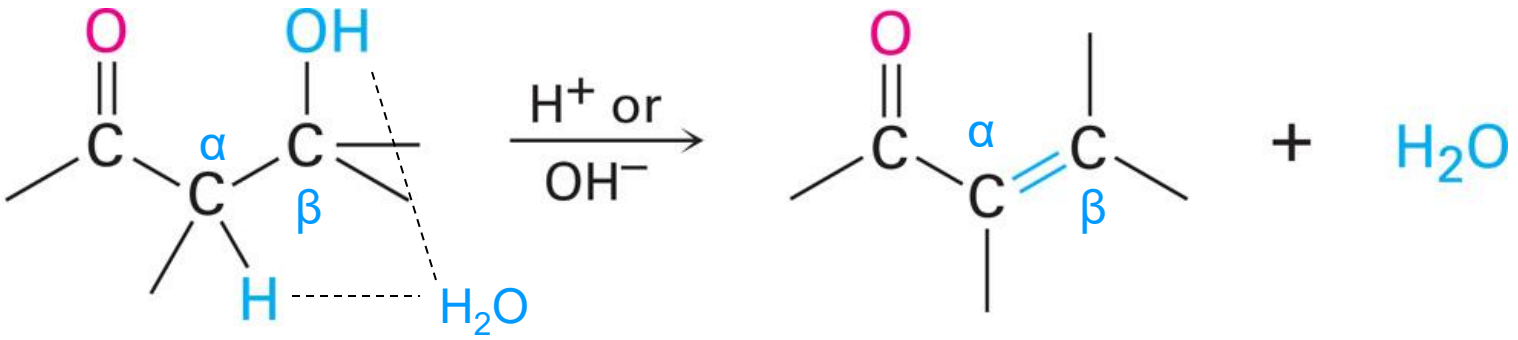
Dehydration of Aldol products: Synthesis of ***Enones***

a) β – hydroxy aldehydes or ketones formed in ALDOL rxns can be dehydrated to yield… **b**) α β unsaturated products or "conjugated" ***enones.***



a) **β-hydroxy ketone or aldehyde**

b) **conjugated enone**

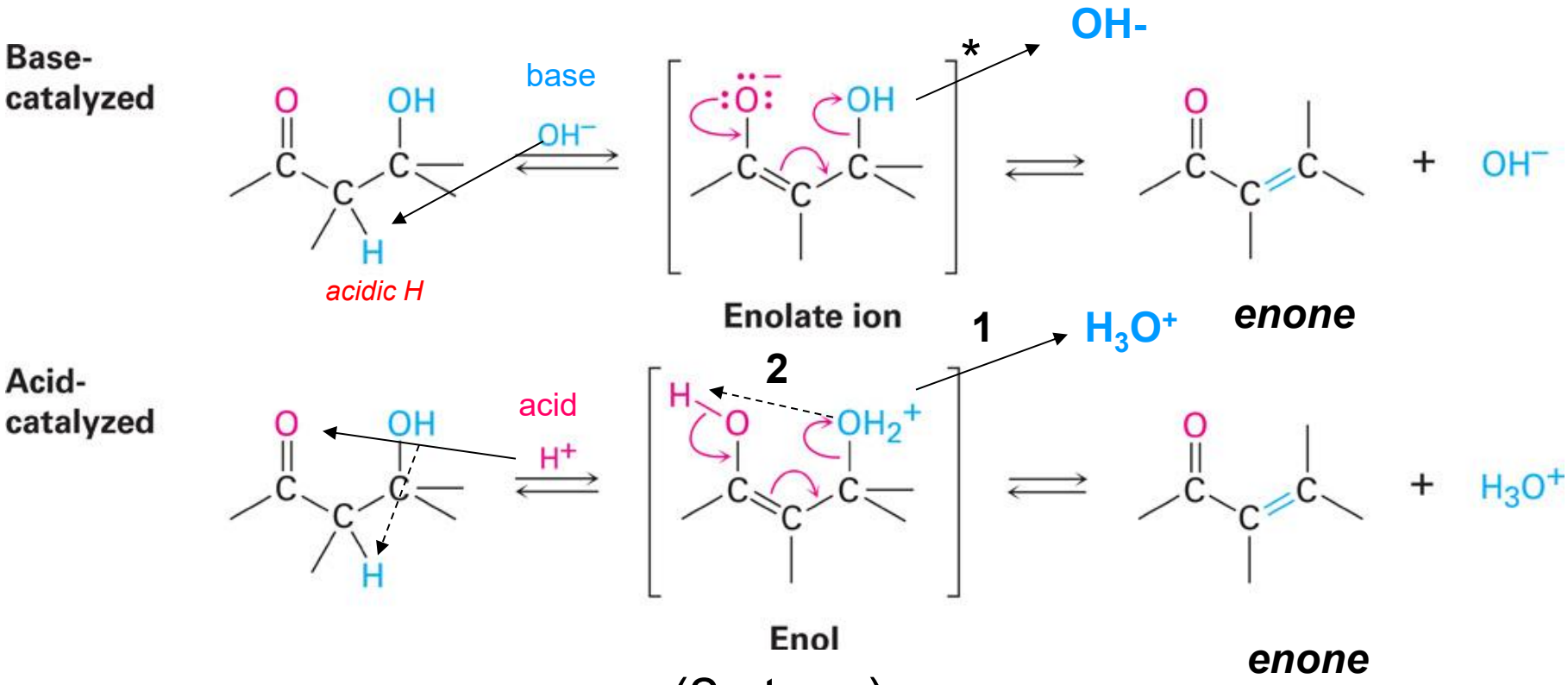
NOTES: this is the origin of "CODENSATION RXN" name (loss of **H2O**)

Most alcohols (in base) don't dehydrate easily b/c **OH** poor leaving group, however ALDO products due b/c of their carbonyl group… → HOW?

Dehydration of Aldol products: Synthesis of ***enones***

TEXTBOOK p.758

(2 steps)
1 not shown

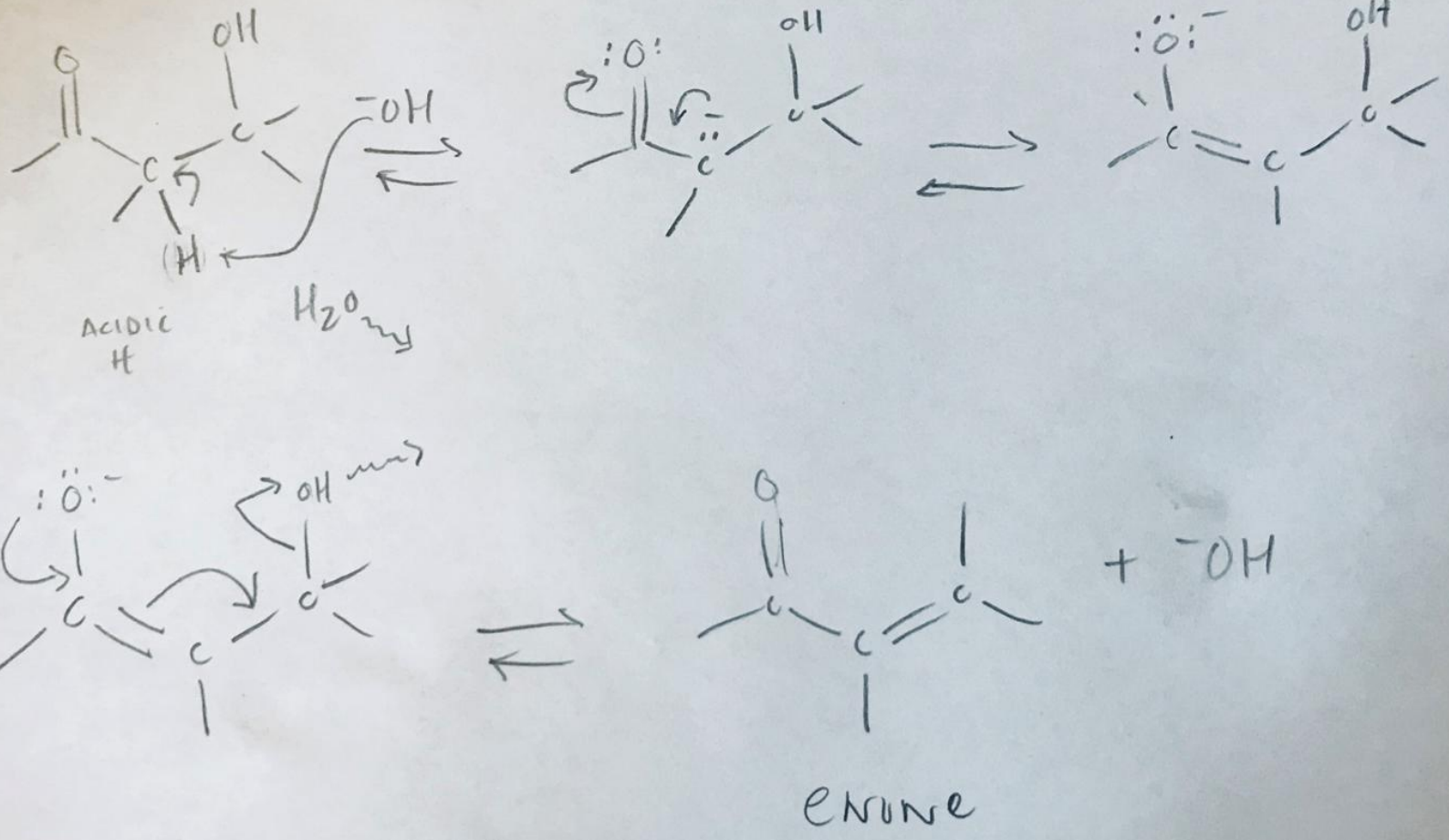


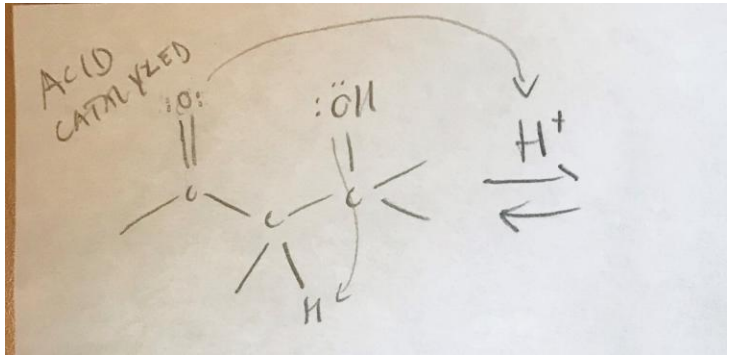
(2 steps)
1 not shown

Notes: More detailed steps – next slides

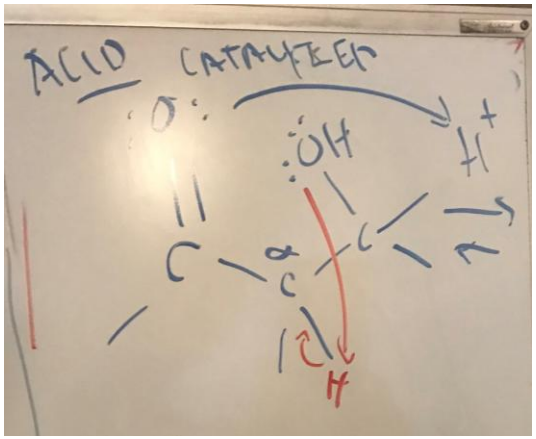
*

BASE CATALYZED

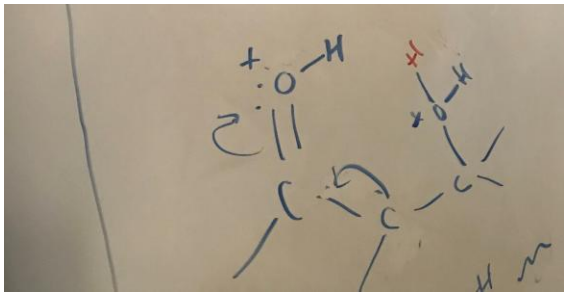




1



2



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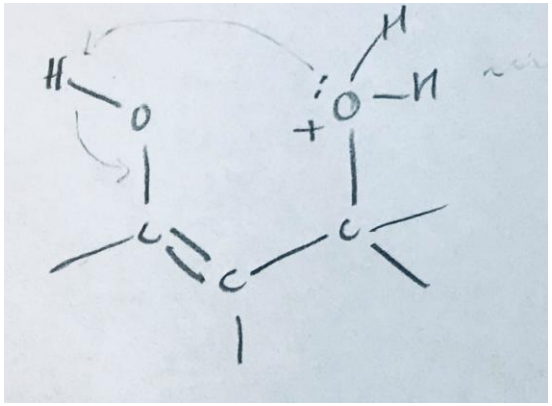

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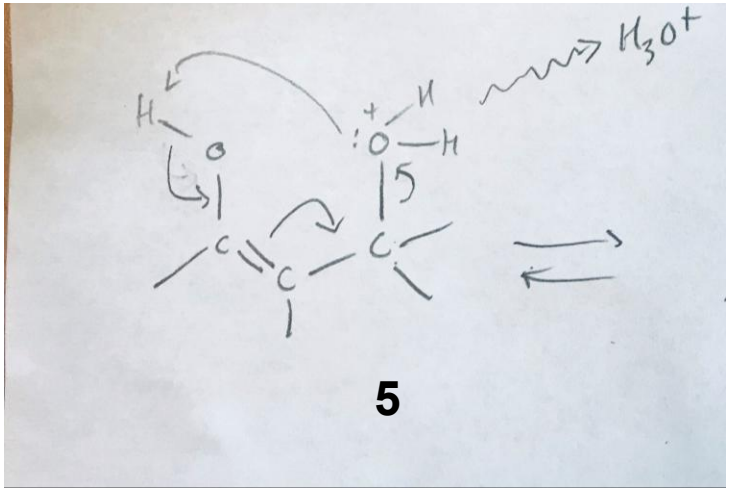

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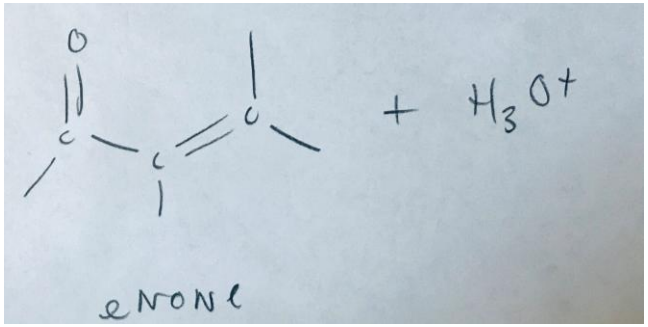
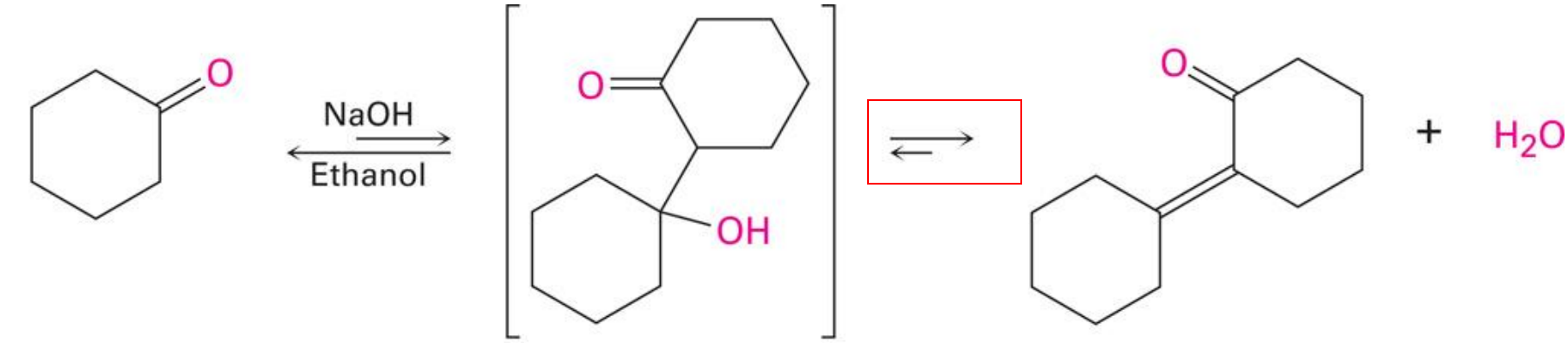


Dehydration of Aldol products: Synthesis of ***enones***

Utility of this RXN is that loss of **H_2O** from RXN mixture (**b**) (i.e. removal of **H_2O**) can **drive** → **a**) ALDOL RXN equilibrium toward product to get 92% yield. ☺



Cyclohexanone

a)

Cyclohexylidenecyclohexanone (92%)

b)

HW 23-3,4

Notes: see previous slide base catalyzed mechanism to remove or p.758 for details

Outline

- Background
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- Conjugate Carbonyl Additions:
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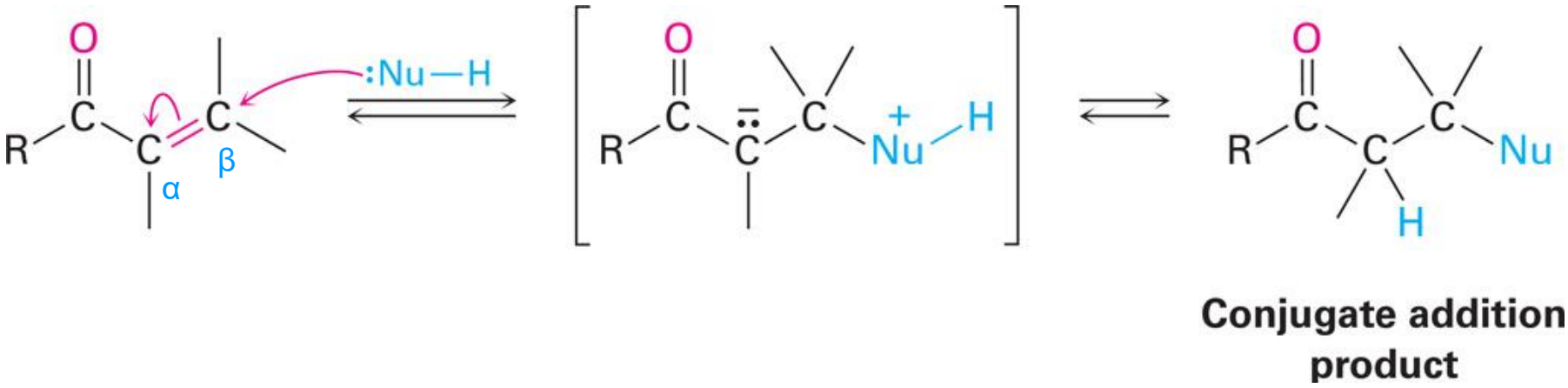
Conjugate Carbonyl Additions:

Recall (Sect 19-13) certain nucleophiles (e.g. amines) react w/ α-β unsaturated ketones
To generate ***conjugate addition products*** vs a direct addition product



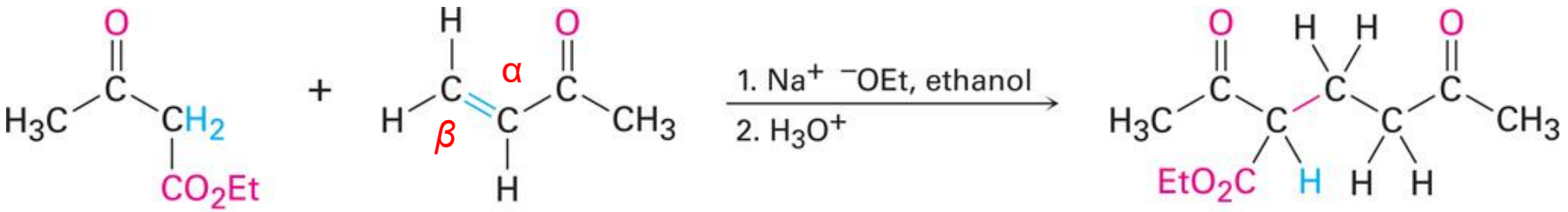
A similar ***conjugate*** addition occurs when a nucelophilic enolated ion reacts w/ a α-β unsaturated carbonyl compound in a process known as….

HW 23-16,17

Conjugate Carbonyl Additions:
The Michael reaction

Involves **a**) stable enolate (derived f/ β Keto ester) or other 1,3 –dicarbonyl compounds that adds to **b**) an unhindered α-β unsaturated ketone (Michael acceptor)

e.g.



Ethyl acetoacetate

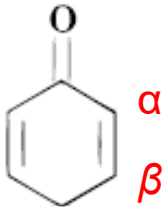
Michael (**donor**)

a)

3-Buten-2-one

Michael (acceptor)

b)



Michael ***acceptor*** α-β unsat. ketone sys.

any *α β* "unsaturated" ketone (carbonyl) system

HW 23-16,17

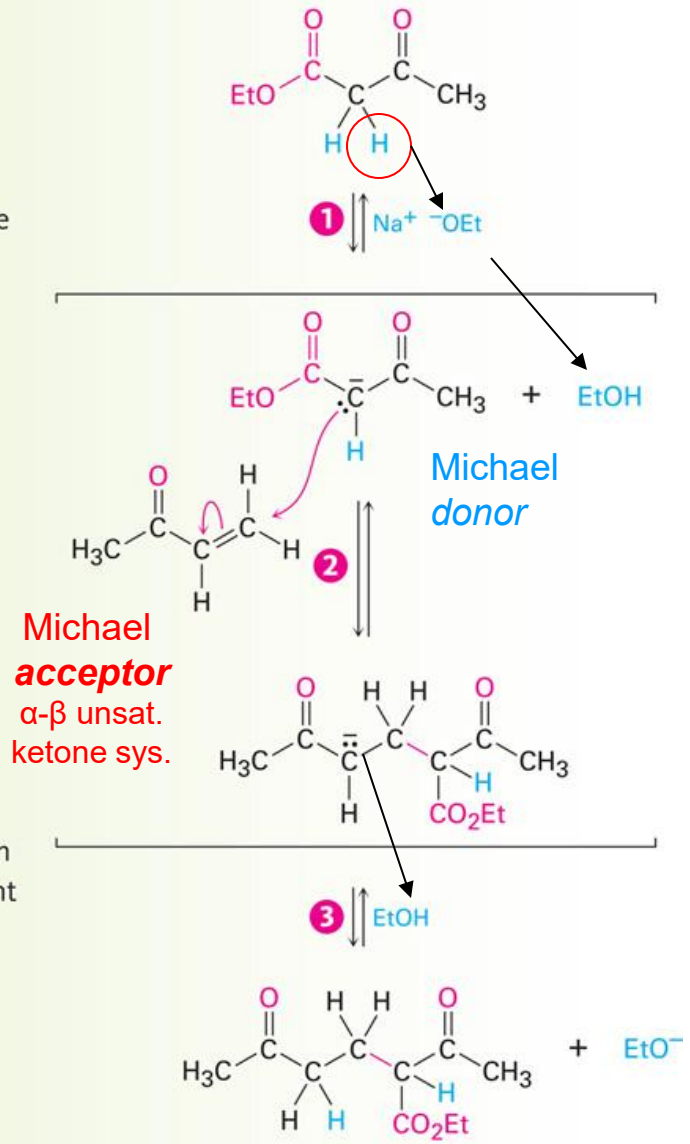
Mechanism for Michael reaction

You draw ☺

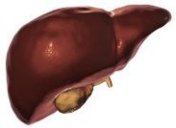
1. The base catalyst removes an acidic alpha proton from the starting β-keto ester to generate a stabilized enolate ion nucleophile.

2. The nucleophile adds to the α,β-unsaturated ketone electrophile in a Michael reaction to generate a new enolate as product.

3. The enolate product abstracts an acidic proton, either from solvent or from starting keto ester, to yield the final addition product.



Michael acceptors & Quinones are converted by detox ***enzymes*** (cytochrome p450) in the **liver** into more toxic intermediates ☹



Michael acceptors & quinones represent a class of ***toxicological intermediates*** which can create hazardous effects *in animals* that include:

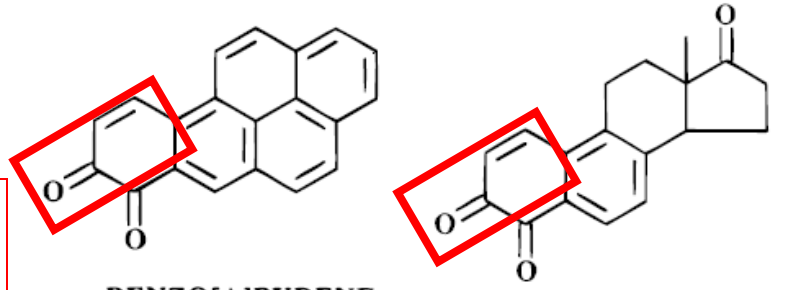
a) acute cytotoxicity, (cell damage)
b) immunotoxicity, (immuno. suppress)
c) carcinogenesis. (tumor growth)

?

(A) BENZENE QUINONES

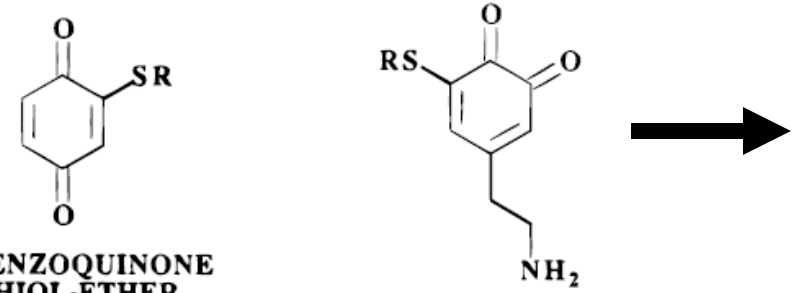
p-BENZOQUINONE *o*-BENZOQUINONE

(B) PAH AND EQUINE ESTROGEN QUINONES



BENZO[A]PYRENE-*o*-QUINONE 4-OHEN-*o*-QUINONE

(C) QUINONE THIOL-ETHERS



p-BENZOQUINONE THIOL-ETHER

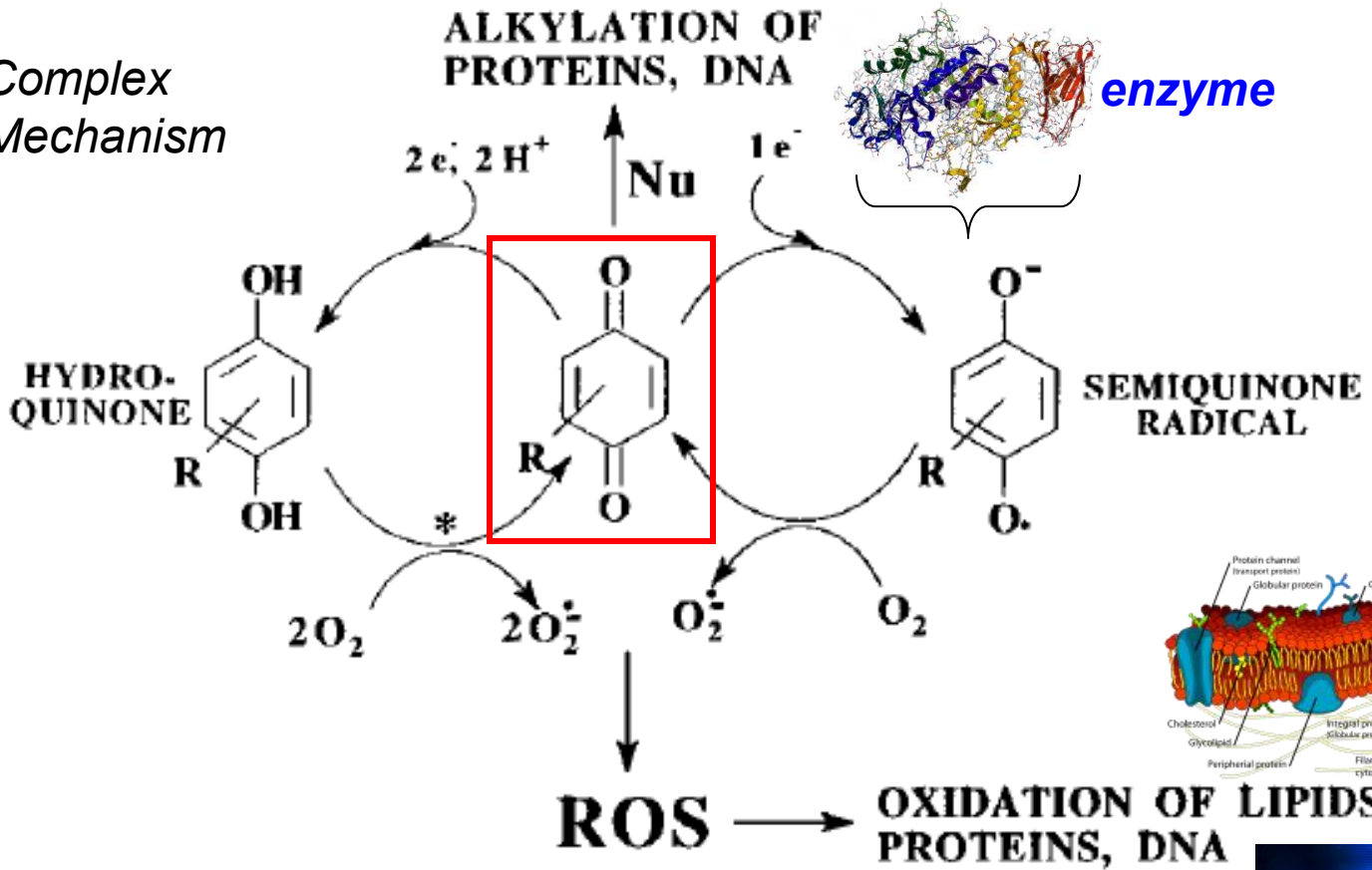
DOPAMINE-o-QUINONE THIOL ETHER

Bolto, J. L., *Chem Res Toxicol.* **2000**,13(3):135-60. https://pubs.acs.org/doi/pdf/10.1021/tx9902082

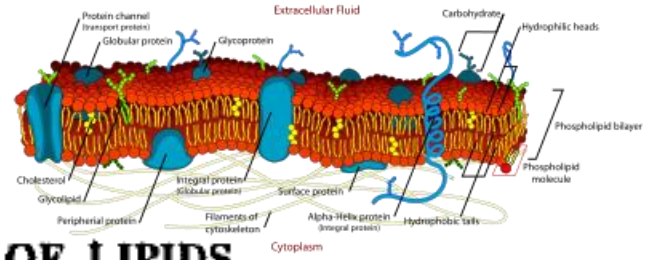
Background

New evidence strongly suggests that the numerous mechanisms of ***Michael acceptor*** and or quinone toxicity (i.e., alkylation & oxidative stress **ROS**) can be correlated with the known *pathology (disease states)* of the parent compound(s).

Complex Mechanism



enzyme



(**R**eactive **O**xygen **S**pecies)

damages/ destroys them ☹

Bolto, J. L., *Chem Res Toxicol.* **2000**,13(3):135-60.

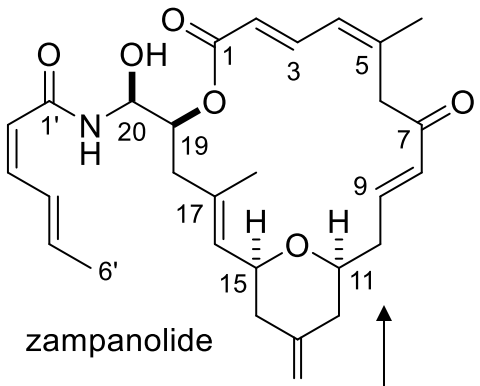
Chem 3900
Worksheet 2
Lecture 14
Chap 23

Challenge Question

Summing it all UP!

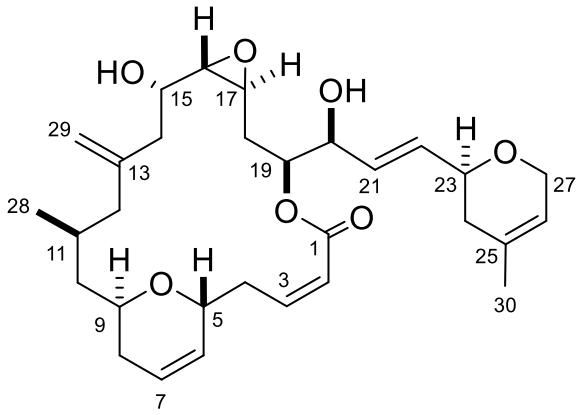
(Medicinal Chemistry & Toxicology)

Identify the compound(s) that may present complications in terms of metabolic induced toxicity by *circling* the structural part(s) of the molecule(s) that can serve as *Michael acceptors*

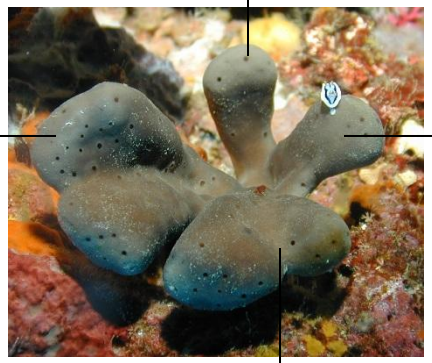


zampanolide

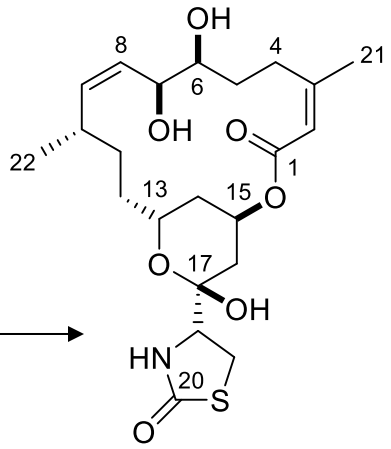
zampanolide (**1**)
IC_{50} = 2.8 nM, Breast (HCC1806) cancer cells
Takahasi-Ruiz, Morris, Johnson et al., **2022** *Molecules*



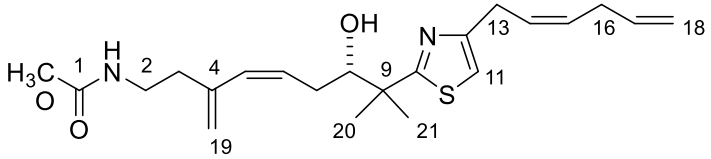
fijianolide B (aka laulimalide) (**2**)
IC_{50} = 3.0 nM Pancreatic (PANC-1) cancer cells
Morris, Persi, Johnson et al., **2022,** *ACS Omega*



C. mycofijiensis: Vanuatu



latrunculol A (**4**)
IC_{50} = 440.0 nM, Colon (HCT-116) cancer cells
Amagata et al., **2008**, *J. Med. Chem.*



mycothiazole (**3**)
IC_{50} = 160.0 pM! Pancreatic (PANC-1) cancer cells
Johnson, Morris, Cook, Persi, Ogarrio, Garcia et al., **2020**, *ACS Med. Chem. Lett.*

Chem 3900
Worksheet 2
Lecture 14
Chap 23

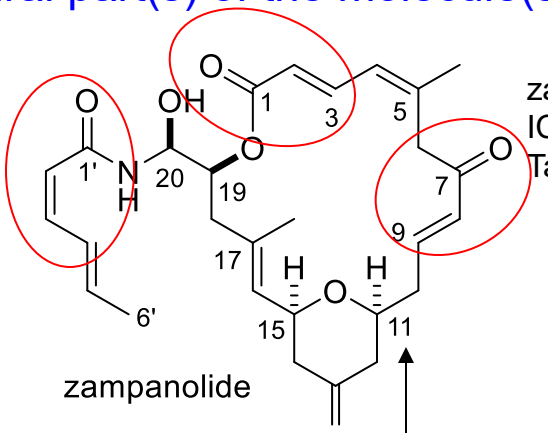
Challenge Question

Summing it all UP!

(Medicinal Chemistry & Toxicology)

Identify the compound(s) that may present complications in terms of metabolic induced toxicity by *circling* the structural part(s) of the molecule(s) that can serve as *Michael acceptors*

These structural features are **Michael acceptors** ☹



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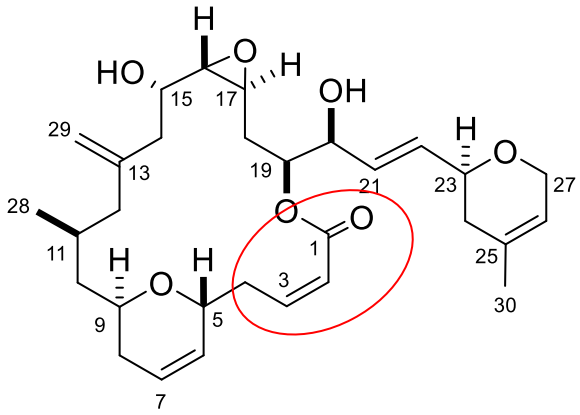

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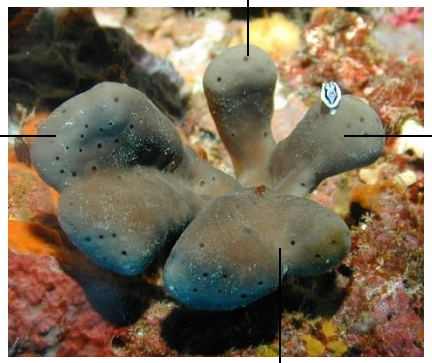

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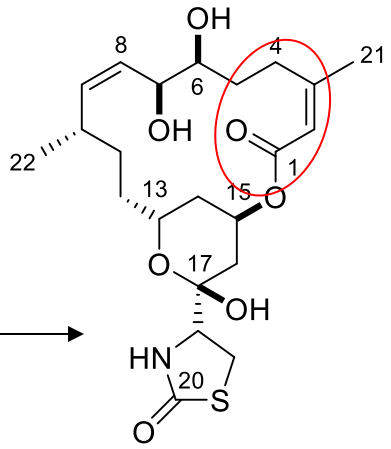
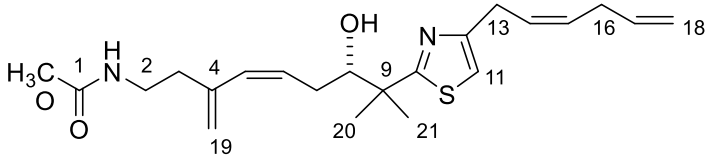


latrunculol A (**4**)
IC_{50} = 440.0 nM, Colon (HCT-116) cancer cells
Amagata et al., **2008**, *J. Med. Chem.*

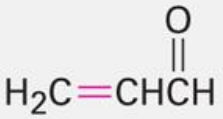
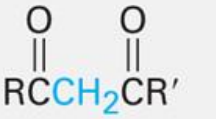
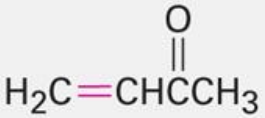
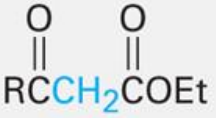
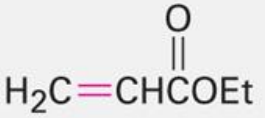
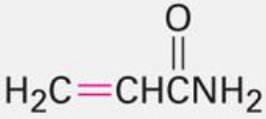
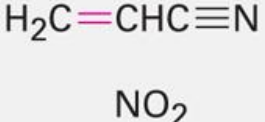
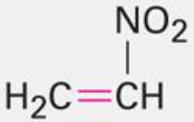


mycothiaozole (**3**)
IC_{50} = 160.0 pM! Pancreatic (PANC-1) cancer cells
Johnson, Morris, Cook, Persi, Ogarrio, Garcia et al., **2020**, *ACS Med. Chem. Lett.*

Michael RXN occurs w/ a wide variety of α-β unsaturated carbonyl compounds

Selected examples are below and important to recognize when moving fwd in Medicinal chemistry and providing **FDA** approved Drugs as therapeutics to treat disease

TABLE 23-1 Some Michael Acceptors and Michael Donors

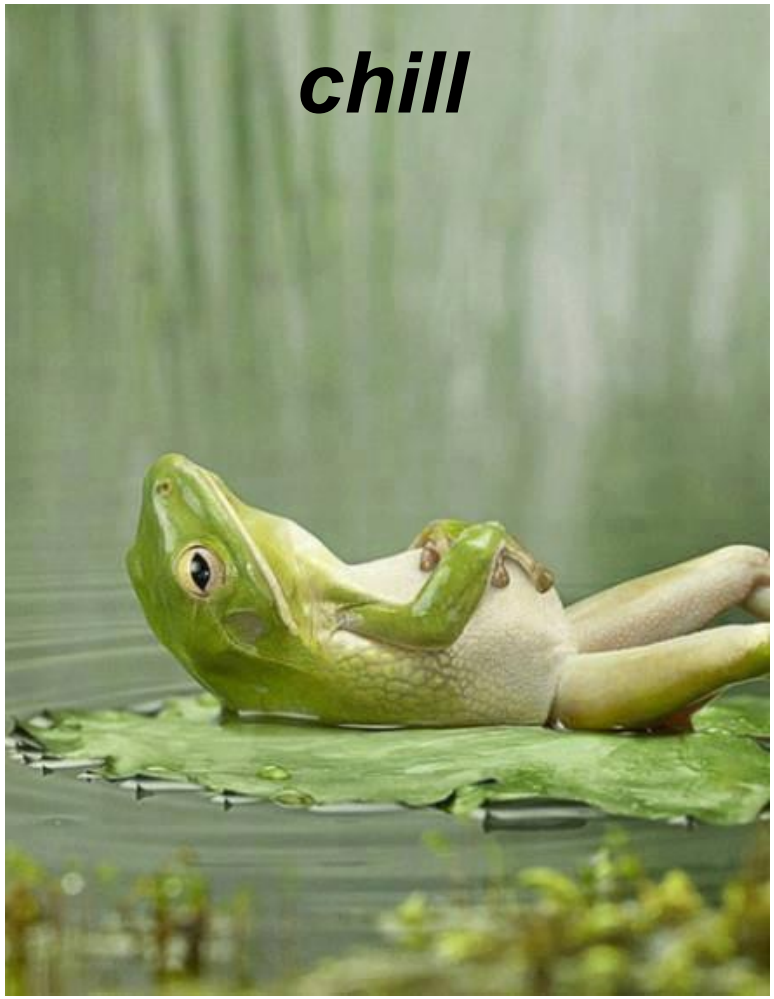
Michael acceptors		Michael donors	
	Propenal		β-Diketone
	3-Buten-2-one		β-Keto ester
	Ethyl propenoate		Diethyl malonate
	Propenamide		β-Keto nitrile
	Propenenitrile		Nitro compound
	Nitroethylene		

b/c scientists may need to modify them
(the ***Michael acceptor*** portion of the compound)
to make the compound safe and non toxic after it's metabolized ☺

HW 23

1, 3, 4, 16, 17

Have a



weekend ☺