CHEM 109
Student Engagement & Assessment

LECTURE TIME

- This Reader = lecture note templates ☺ for max involvement and retention of info!
- iClicker REEF - attendance & participation (**10%**)
  - App only, sorry no clicker remotes
- Processing Time
- Student Talk – group work

DISCUSSIONS

- Worksheets
- Quizzes (**25%**)
- Mechanisms app

EXAMS

2 Midterms (**40%**) and Final Exam (**20%**)

STAY CONNECTED OUT OF THE CLASSROOM

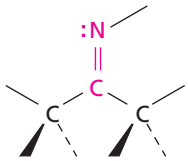
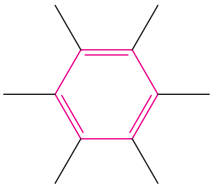
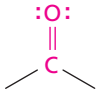
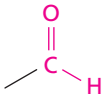
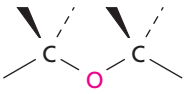
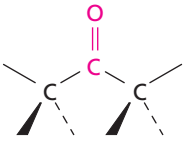
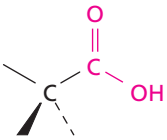
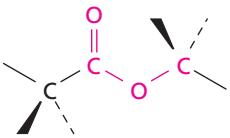
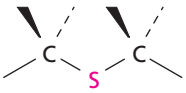
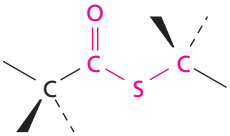
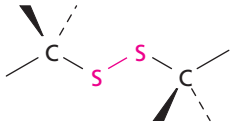
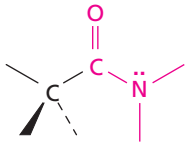
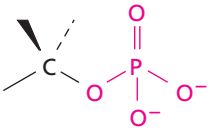
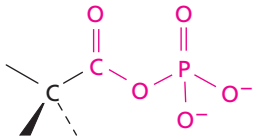
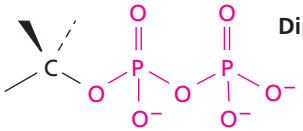
- CHEM 109 Website:
  - **acrochem.sites.ucsc.edu/chem-109**
- Homework - assignments posted in syllabus & online
- Canvas – announcements, grades, surveys
- "Leave it to the Worms" Sustainability Project (**5%**)

Please see syllabus for full course policies, schedule, assignments, etc.

CHEM 109 Functional Group Table

McMurry & Begley's "The Organic Chemistry of Biological Pathways"

Table 1.1 Common Functional Groups in Biological Molecules

Structure*	Name	Structure*	Name
	Alkene (double bond)		Imine (Schiff base)
	Arene (aromatic ring)		Carbonyl group
	Alcohol		Aldehyde
	Ether		Ketone
	Amine		Carboxylic acid
	Thiol		Ester
	Sulfide		Thioester
	Disulfide		Amide
	Monophosphate		Acyl phosphate
	Diphosphate		

* The bonds whose connections aren't specified are assumed to be attached to carbon or hydrogen atoms in the rest of the molecule.

Monophosphate = Phosphoester; Diphosphate = Phosphodiester

CHEM 109, Lecture 1
Structure – Property Relationships
Acid-Base Chemistry

- McMurry & Begley (M&B) Chapter 1.1-1.2 (posted on CHEM 109 website)

Revisiting General Chemistry through Structure – Property Relationships

- *Before class:* brainstorm your current understanding of any or all of the terms below
- *During class:* instructions provided for collaborative activity (concept map)
- *Discussion section:* complete a concept map with any one column of terms below

COLUMN 1	COLUMN 2	COLUMN 3	COLUMN 4
Lewis structure	Intramolecular Forces	Boiling	Polar
Skeletal structure	Ionic Bond	Melting	Non-polar
Hybridization	Covalent Bond	Dissolve	Nucleophile
Molecular Geometry	Intermolecular Forces	Dissociate	Electrophile
Bond Polarity	Hydrogen bond	Salt	Mechanism
Molecular Polarity	London Dispersion	Hydrocarbon	Arrow Pushing
Dipole	Dipole-Dipole	Solubility	Chemical Reaction
Electronegativity	Ion-Dipole	Alcohol	Physical Change

ACID-BASE CHEMISTRY

Rulez to Live By

	Bronsted-Lowry (BL)	Lewis
Acid		
Base		

- **pKa** = - log Ka = **AFFINITY OF AN ACID FOR ITS PROTON**

- Equilibrium (eq≡m) favors the weaker acid

Acid Dissociation Equation: HA →

K_a = pK_a =

What does it mean if $K_a > 1$? If $K_a < 1$? If $K_a = 1$?

ARROW-PUSHING = the language / symbology of this class!

What do arrows push? What are the possible outcomes of arrow pushing?

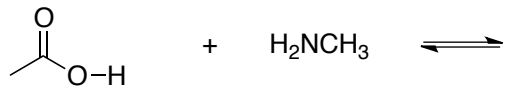
ELECTRON RICH TO **ELECTRON POOR**

Identify the acid, base, conjugate base, conj. acid, and direction of equilibrium (eq≡m)

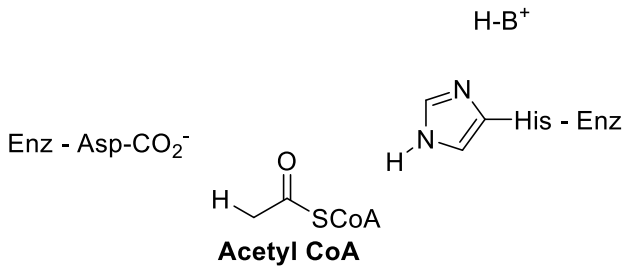
$$H\text{-}Cl + NaOH \longrightarrow NaCl + H_2O$$

Draw proper Lewis structures & mechanism for the reaction above

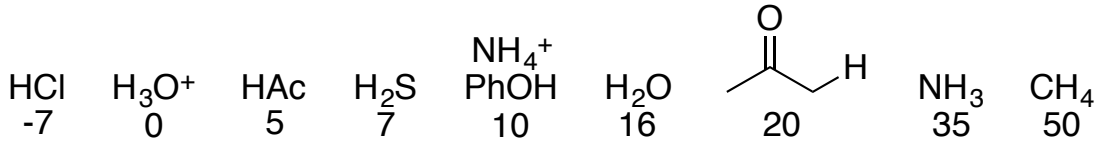
Organic Acid-Base Reactions



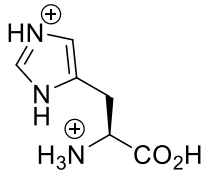
*Amino acid residues = acids & bases in **enzyme active sites**:*



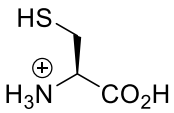
pKa's to Memorize



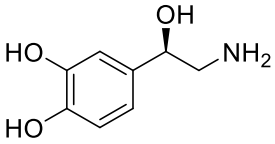
Approximating pKa's: Into which pKa family does each compound belong?



L-Histidine
(fully protonated)



D-Cysteine
(fully protonated)



Norepinephrine

L1 & L2 HW "due" in discussion next week (quiz directly from HW) – assignment online

Next time: Electrophilic Add'n & Substitution Reaction Mechanisms

CHEM 109, Lecture 2

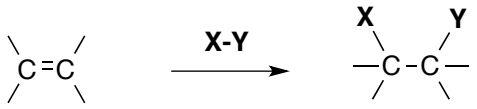
Mechanism Review

1. Electrophilic Addition (E-philic Add'n)
2. Nucleophilic Substitution (S_N1 & S_N2)

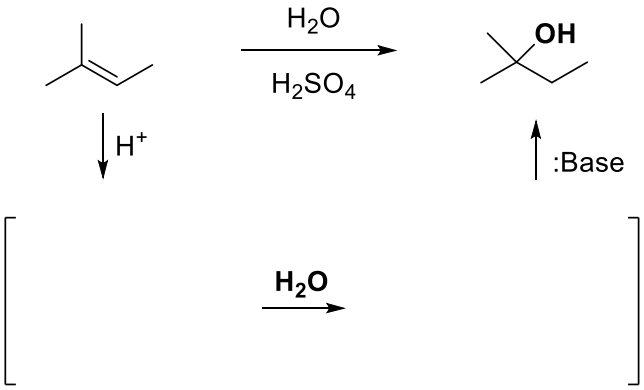
* Given starting materials and either product(s) or name of mechanism, you should be able to complete the mechanism and/or draw the product(s).

MECHANISM REVIEW

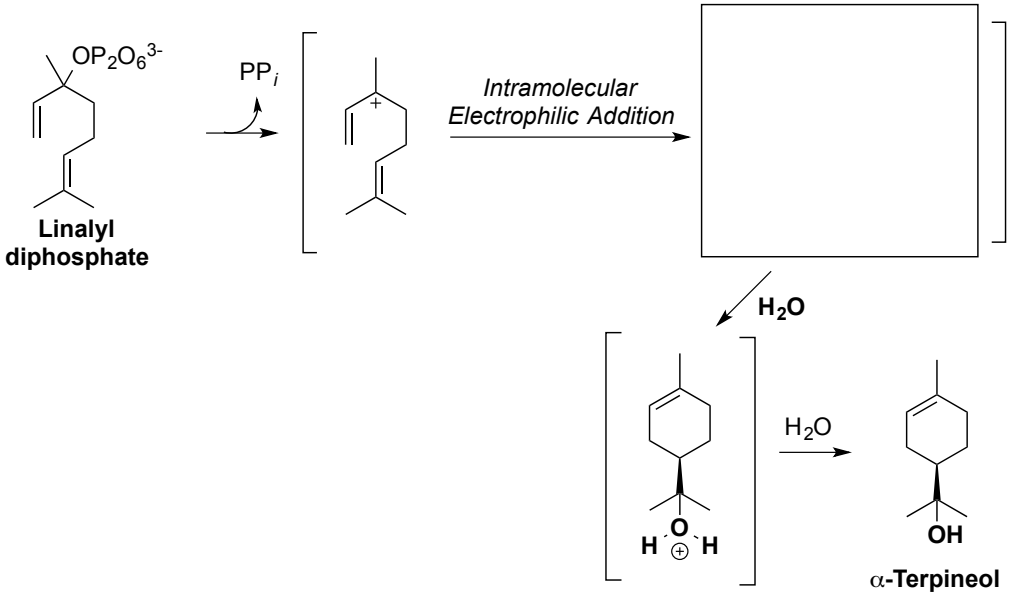
1. Electrophilic Addition to Alkenes



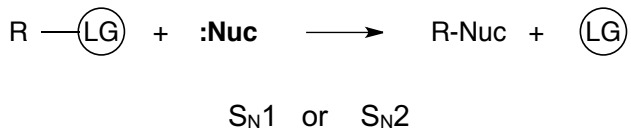
E-philic Add'n in Synthesis: Acid-Catalyzed Hydration of Alkenes



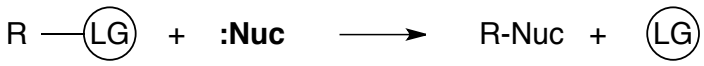
E-philic Add'n in Biology: Biosynthesis of **α-terpineol**, component of pine oil



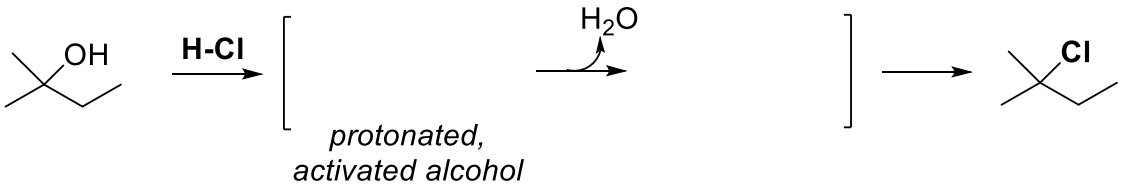
2. Nucleophilic Substitution



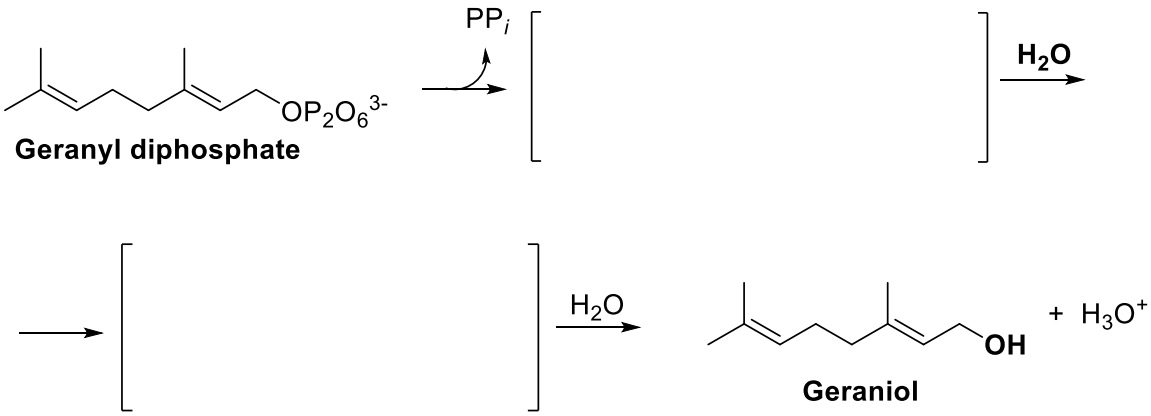
2A. Unimolecular Nucleophilic Substitution (S_N1) Mechanism



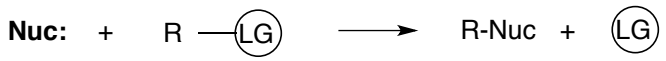
S_N1 *in Synthesis (8L Lab Practical):*



S_N1 *in Biology*: Biosynthesis of geraniol, rose oil component



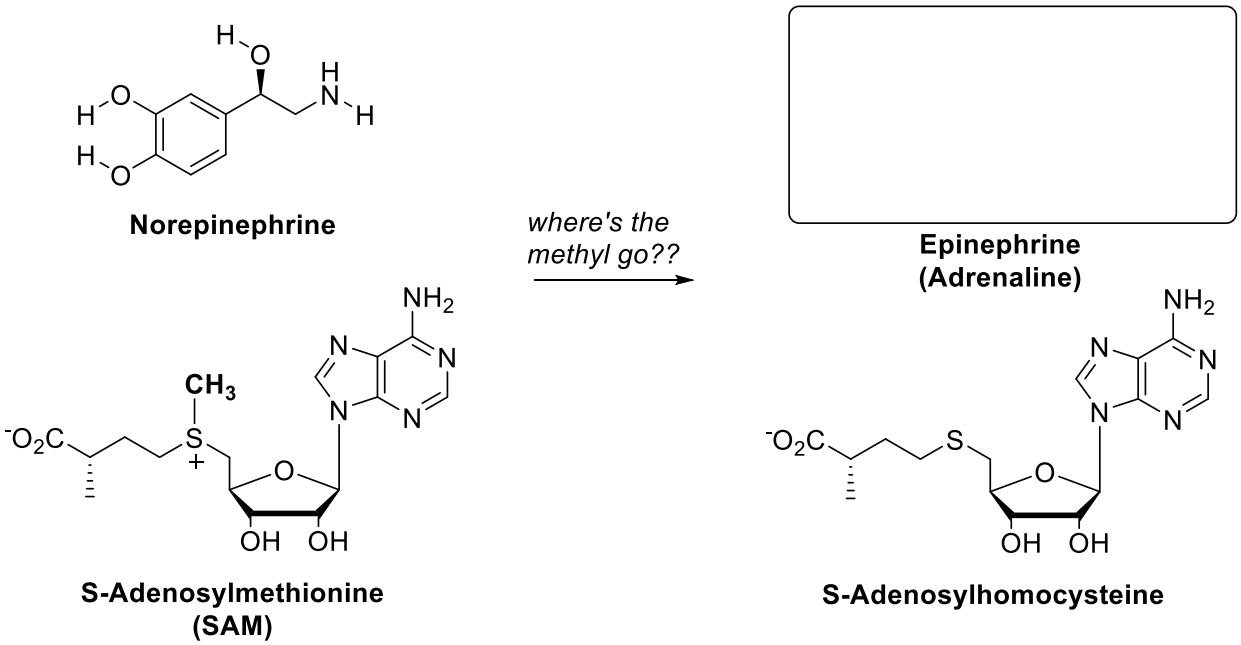
2B. Bimolecular Nucleophilic Substitution (S_N2) Mechanism



S_N2 in Williamson ether synthesis

S_N2 in Biology: **Synthesis of Adrenaline**

Hint: the most basic atom is also the best nucleophile!



Next time…

- Carbonyl Mechanisms: McMurry & Begley (M&B) Chapter 1.5-1.7

Next week in discussion…

- **Open notebook quiz directly from lectures 1 & 2 HW (syllabus)**
  - *Take a few days or at least sleep on it before checking the solutions online!*

CHEM 109, Lecture 3

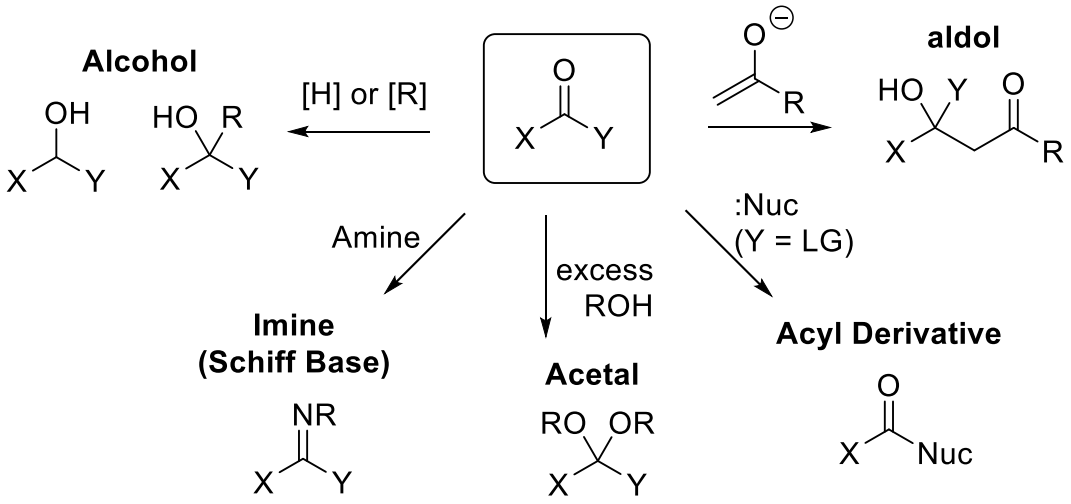
3. Nucleophilic Addition Reactions to Aldehydes & Ketones (**Nuc Add'n**)

A. Alcohol Formation **B.** Imine (Schiff Base) Formation

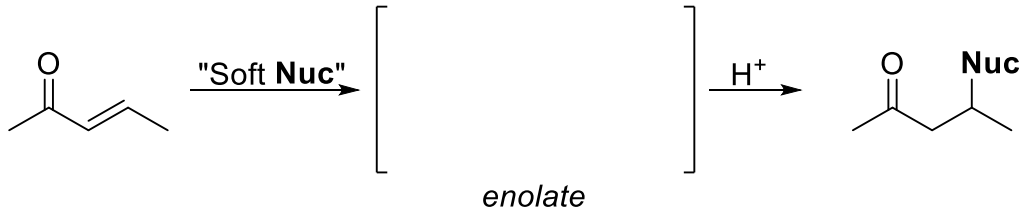
C. Acetal Formation **D.** Conjugate (Michael) Addition

* Given starting materials and either product(s) or name of mechanism, you should be able to complete the mechanism and/or draw the product(s).

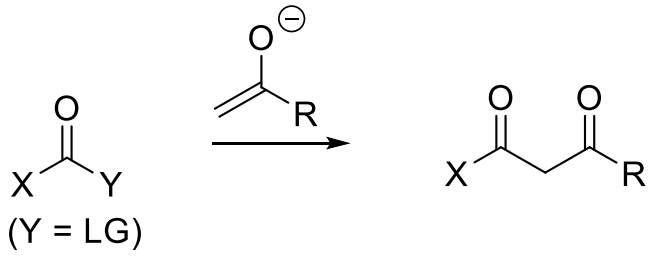
CARBONYL MECHANISM REVIEW



The New Guy: **Michael Addition** (AKA **conjugate addition**, AAKA **1,4-addition**)



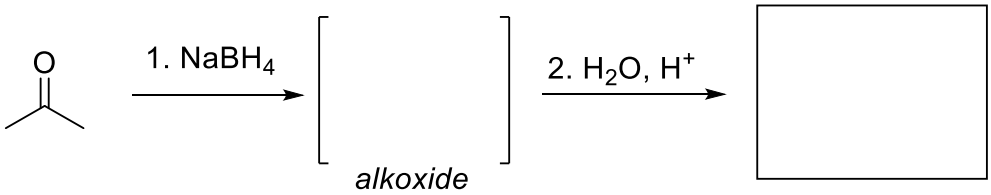
Another new guy: **Claisen** condensation (lecture 4)



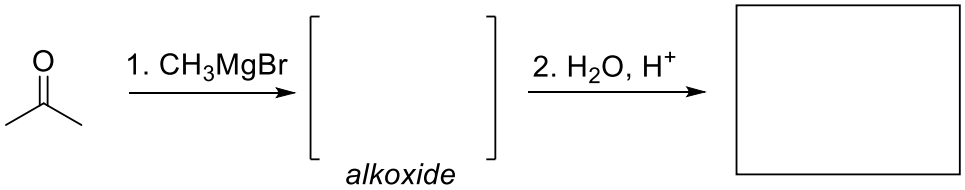
3. Nuc Add'n Rxns to Aldehydes & Ketones

3A. Alcohol Formation…

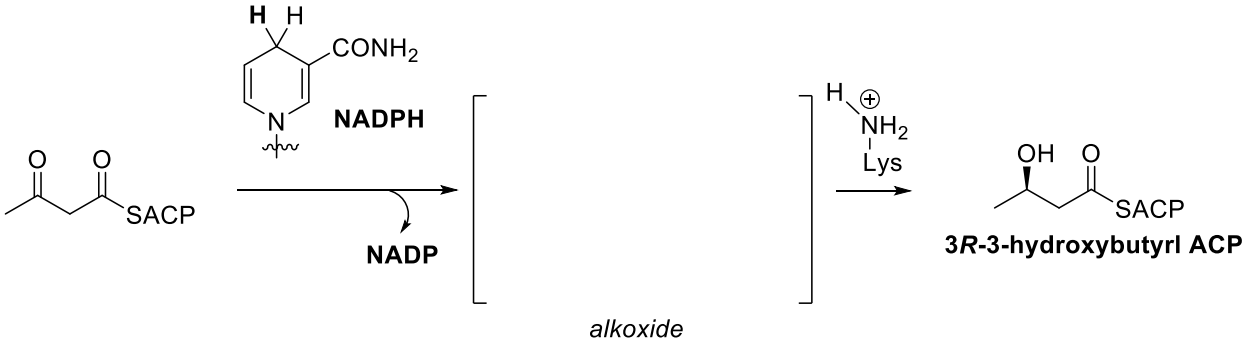
Synthesis: *Sodium borohydride reduction of acetone*



Synthesis: *Grignard addition to acetone*

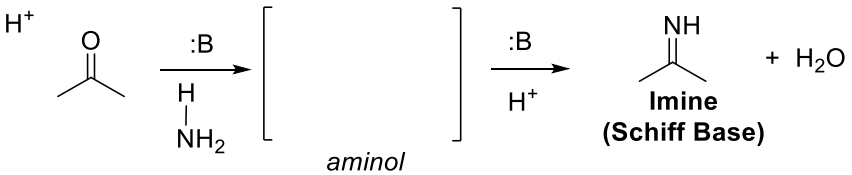


Nuc Add'n in Biology: *Fatty acid synthesis*



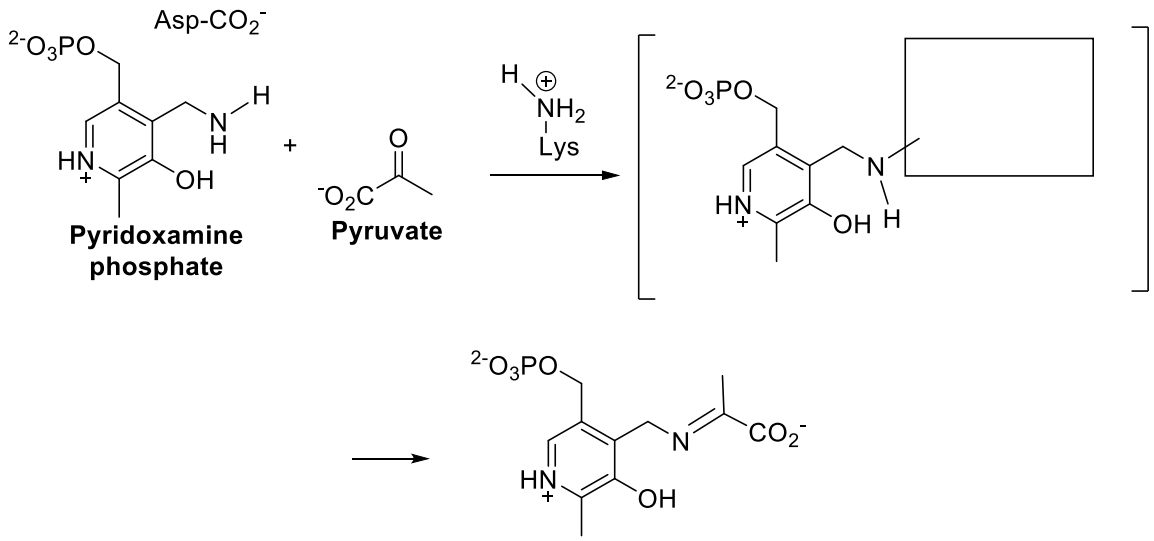
3B. Imine (Schiff Base) Formation

Synthesis: *Treatment of acetone with ammonia*



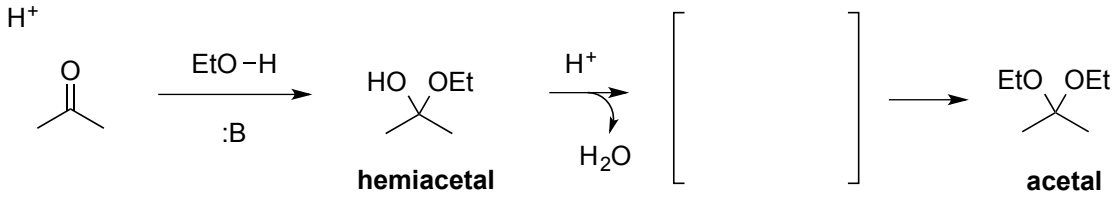
3B. Imine (Schiff Base) Formation (cont'd)

Biosynthesis of Amino Acids:

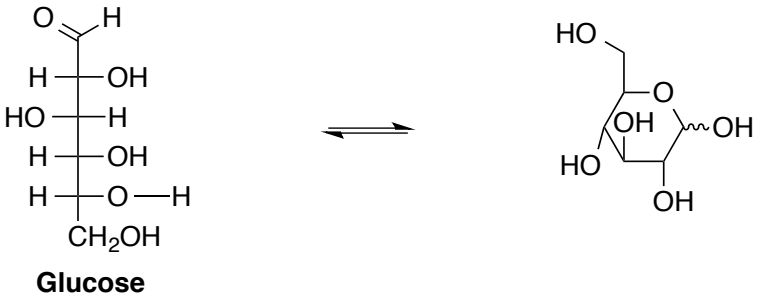


3C. (Hemi)Acetal Formation

Synthesis: *Treatment of acetone with ethanol*

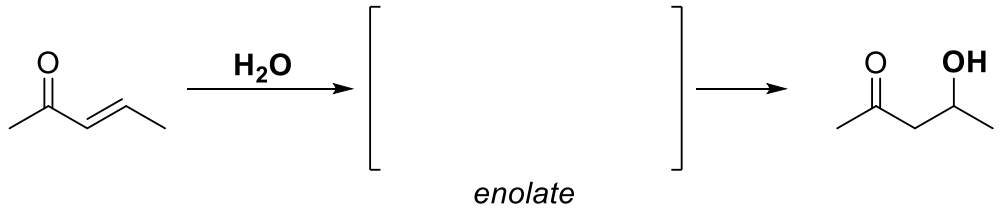


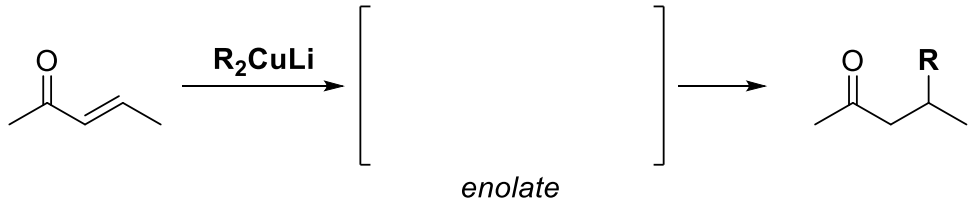
Hemiacetals in Nature: *Carbohydrates*



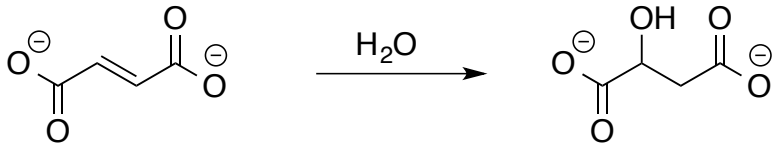
3D. Conjugate 1,4 (Michael) Addition

Synthesis





Biology: *Citric Acid Cycle*



Fumarate **Malate**

Apply the template mechanism from page 1 and keep track of those protons!

Next time…
Nucleophilic Acyl Substitution & Carbonyl Condensation Reactions (aldol & Claisen)

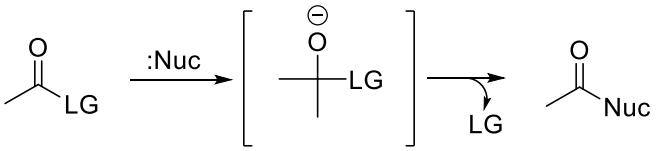
- **M&B Chapter 1.6-1.7**

CHEM 109, Lecture 4

4. Nucleophilic Acyl Substitution (NAS)
5. Carbonyl Condensation
   A. Aldol Condensation B. Claisen Condensation

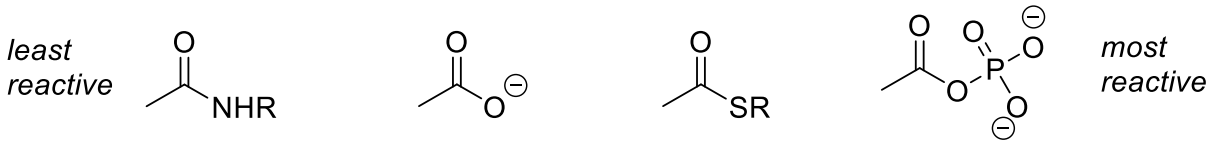
* Given starting materials and either product(s) or name of mechanism, you should be able to complete the mechanism and/or draw the product(s).

4. Nucleophilic Acyl Substitution (NAS)

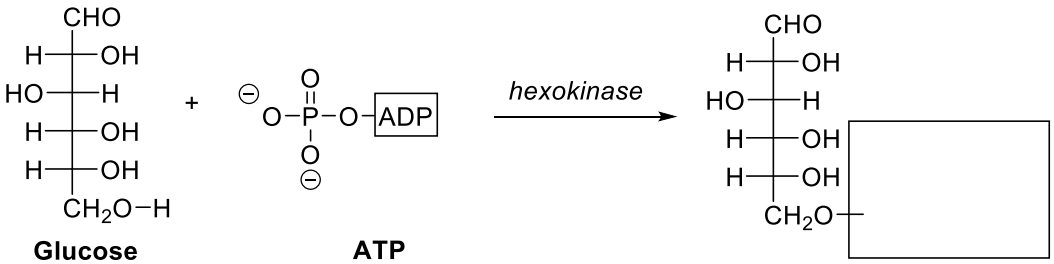


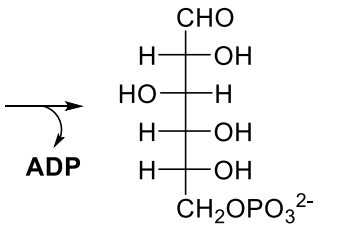
Synthesis: *Fischer Esterification – Fruity Fragrances*

BIOREACTIVITY SERIES toward **NAS**



NAS in Biology: *Glycolysis (first step)*



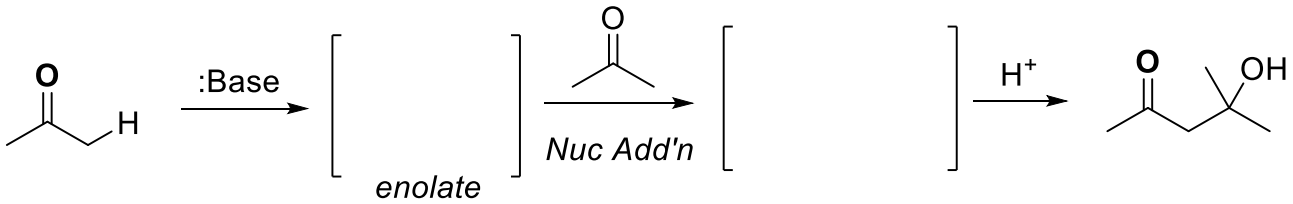


Glucose-6-phosphate

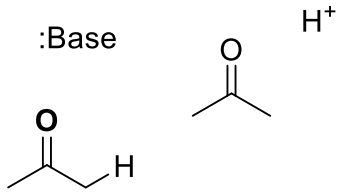
5. Carbonyl Condensation Reactions

Enolate Ions

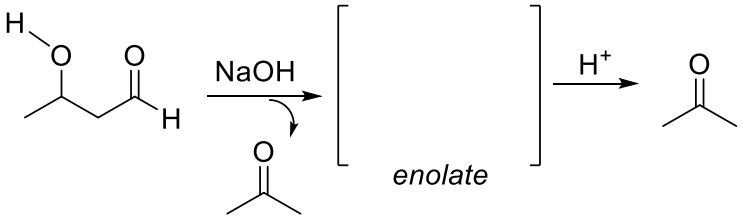
5A. Aldol Condensation



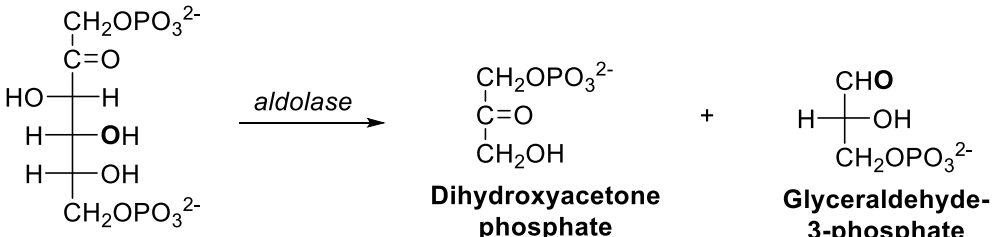
Draw that mechanism in one step:



Retro-aldol Reaction



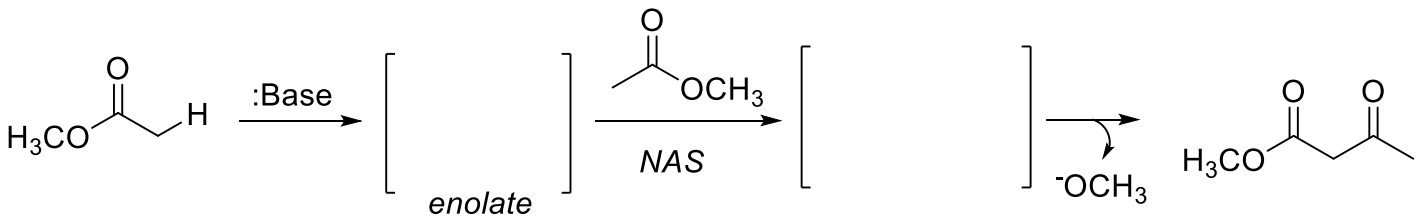
Retro-aldol: *Glycolysis*



Fructose-1,6-bisphosphate (F1,6P) **Dihydroxyacetone phosphate (DHAP)** **Glyceraldehyde-3-phosphate (GAP)**

Re-draw F1,6P below and propose a one-step mechanism…

5B. Claisen Condensation



Draw that mechanism in two steps!

Claisen Condensation in Biology: *Lipid Biosynthesis*

Retro-Claisen Reaction:

Carbonyl Reaction Overview

Nucleophilic Addition
to Aldehydes & Ketones

Nucleophilic Acyl Substitution (NAS)
with Esters, Thioesters, Carboxylic Acids, Amides

Aldol Condensation

Claisen Condensation

Next time…Elimination, Redox, pKa and Amino Acids

CHEM 109, Lecture 5

Mechanism Review

6. Elimination Reactions
7. Oxidation & Reduction Reactions

Polyprotic Acids & pKa

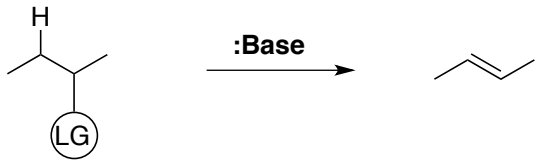
- Relationship between (pKa of acid) and (pH of solution)
- Titration of amino acids

**** Know the full structures & abbreviations of the 20 common amino acids (p 7) ****

---

6. Elimination Reactions

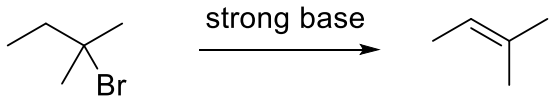
What is eliminated?



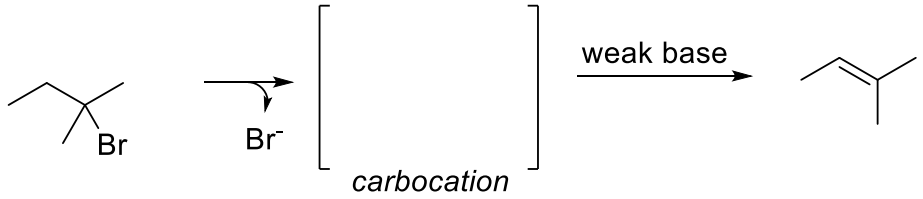
E2 **E1** **E1cB**

Elimination *in synthesis…*

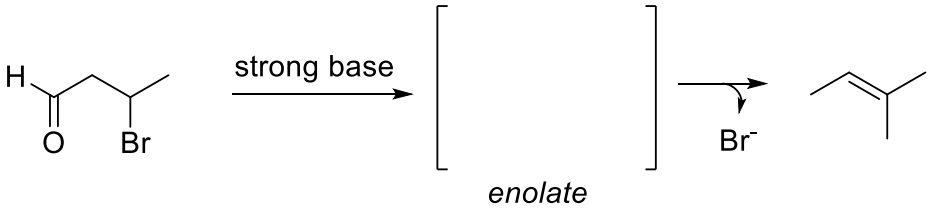
E2



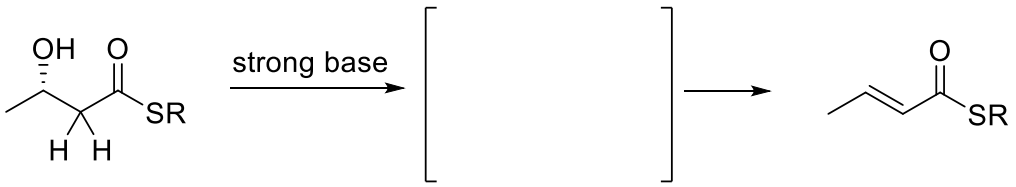
E1



E1cB

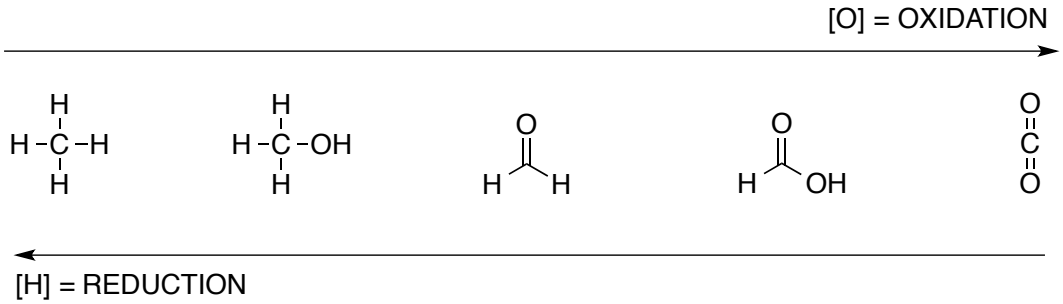


Elimination in Biology – *Fatty Acid Synthesis*

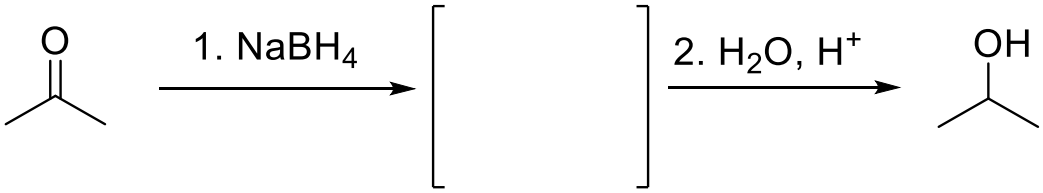


-Hydroxy thioester

7. Oxidation and Reduction (Redox) Reactions

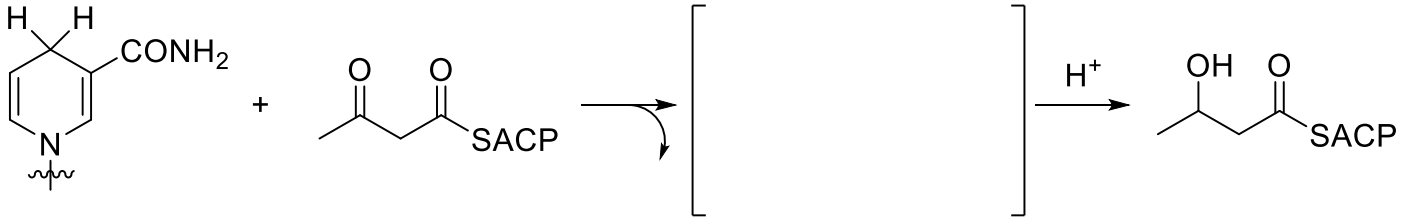


Reduction in Synthesis

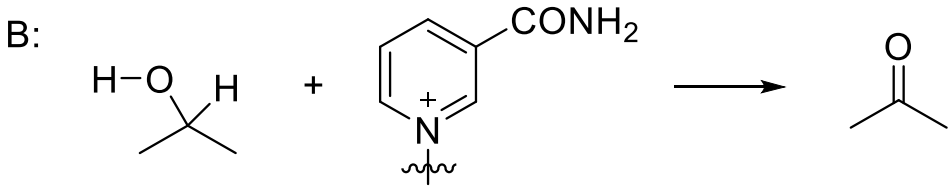


Redox in Biology…

REDUCING AGENTS: NADH & NADPH



OXIDIZING AGENTS: NAD^+ & $NADP^+$



Polyprotic Acids & pKa

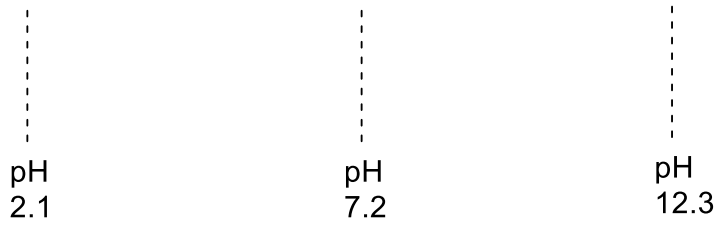
How does an acid's pKa relate to the pH of a solution of that acid?

$HA \rightarrow H^+ + A^-$

$$pH = pKa + \log \frac{[A-]}{[HA]}$$

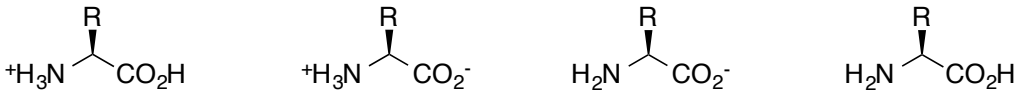
pH < pKa pH = pKa pH > pKa

Titration of Phosphoric Acid (pKa_1 2.1; pKa_2 7.2; pKa_3 12.3)

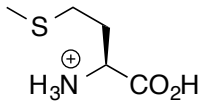


What's the charge of the *dominant* ionic phosphate species at pH 1? pH 5? pH 7.4? pH 13?

Amino Acids – which one looks weird to you?



Titration of a L-Methionine, a neutral amino acid



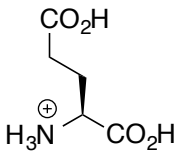
L-Methionine
(fully protonated)

	pH < 2.28	2.28 < pH < 9.21	pH > 9.21
Charge:			

pI = Isoelectric point – pH at which the molecule is neutral (not necessary neutral @ pH 7)

- Calculate by taking the average of the 2 pKa's on either side of neutral molecule

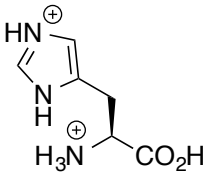
Titration of L-Glutamic Acid, an acidic amino acid



L-Glutamic Acid
(fully protonated)

	pH < 2.10	2.10 < pH < 4.07	4.07 < pH < 9.47	pH > 9.47
Charge:				

Titration of L-Histidine, an interesting basic amino acid

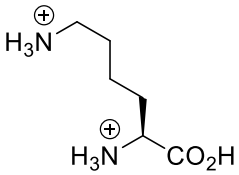


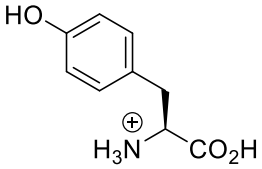
L-Histidine
(fully protonated)

	pH < 1.77	1.77 < pH < 6.10	6.10 < pH < 9.18	pH > 9.18
Charge:				

pH of solution vs. charge of amino acids…

	pH 1	pH 3	pH 5	pH 7	pH 9	pH 11
Met						
Glu						
His						
Lys						
Tyr						





Next time…Biosynthesis of select amino acids

The 20 Common Amino Acids – pKa's and Isoelectric Points (pI)

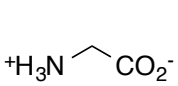
Name	pKa_1	pKa_2	pKa_R	pI
Alanine	2.34	9.69	-	6.01
Arginine	2.17	9.04	12.48	10.76
Asparagine	2.02	8.80	-	5.41
Aspartic Acid	1.88	9.60	3.65	2.77
Cysteine	1.96	10.28	8.18	5.04
Glutamic Acid	2.19	9.67	4.25	3.22
Glutamine	2.17	9.13	-	5.65
Glycine	2.34	9.60	-	5.97
Histidine	1.82	9.17	6.00	7.59
Leucine	2.36	9.60	-	5.98
Isoleucine	2.36	9.60	-	5.98
Lysine	2.18	8.95	10.53	9.74
Methionine	2.28	9.21	-	5.74
Phenylalanine	1.83	9.13	-	5.48
Proline	1.99	10.60	-	6.30
Serine	2.21	9.15	-	5.68
Threonine	2.09	9.10	-	5.60
Tryptophan	2.83	9.39	-	5.89
Tyrosine	2.20	9.11	10.07	5.66
Valine	2.32	9.62	-	5.96

* You do not need to memorize these pKa's. You should know how to use them when given. *

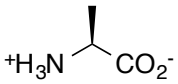
* Learn the name, structure, and abbreviations for all of the amino acids below *

NEUTRAL AMINO ACIDS

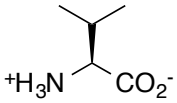
NON-POLAR AMINO ACIDS



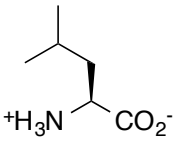
L-Glycine (Gly, G)



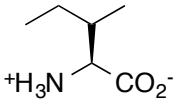
L-Alanine (Ala, A)



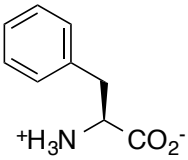
L-Valine (Val, V)



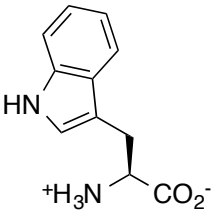
L-Leucine (Leu, L)



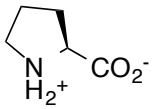
L-Isoleucine (Ile, I)



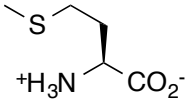
L-Phenylalanine (Phe, F)



L-Tryptophan (Trp, W)

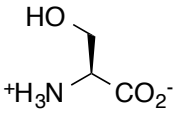


L-Proline (Pro, P)

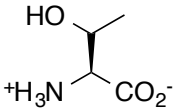


L-Methionine (Met, M)

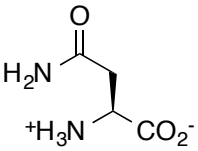
POLAR AMINO ACIDS



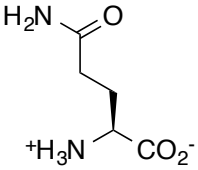
L-Serine (Ser, S)



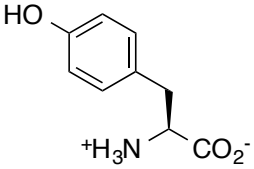
L-Threonine (Thr, T)



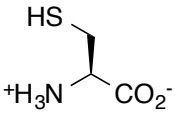
L-Asparagine (Asn, N)



L-Glutamine (Gln, Q)

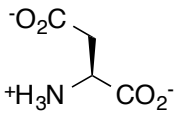


L-Tyrosine* (Tyr, Y)

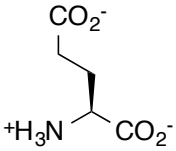


D-Cysteine* (Cys, C)

ACIDIC AMINO ACIDS

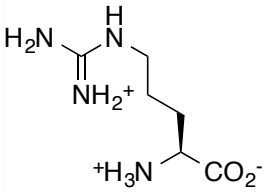


L-Aspartic Acid (Asp, D)

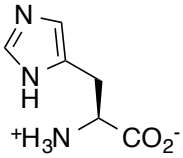


L-Glutamic Acid (Glu, E)

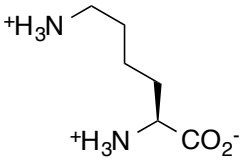
BASIC AMINO ACIDS



L-Arginine (Arg, R)



L-Histidine (His, H)



L-Lysine (Lys, K)

CHEM 109, Lecture 6

Amino Acid Synthesis

- Organic Synthesis – Reductive Amination
- Biosynthesis of Asparagine and Proline – not in the textbook, use lecture notes

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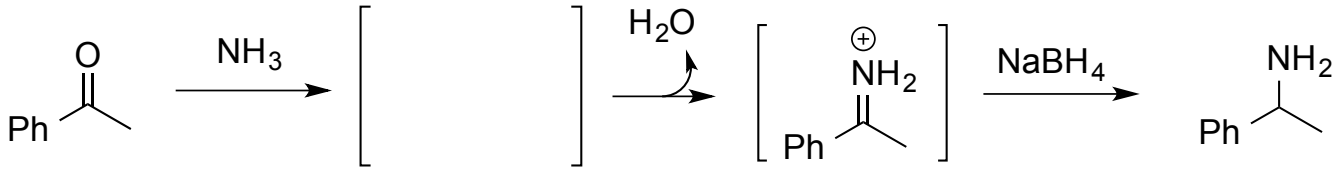
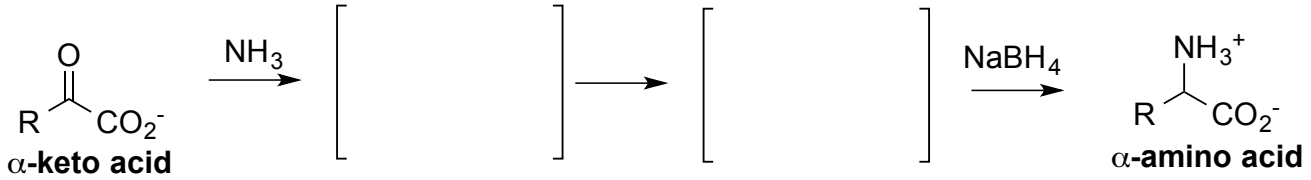
Mechanisms to Know for AA Synthesis

- **Reductive Amination**

Add arrows to complete this mechanism, adding acids (H^+) and bases (:B) when needed

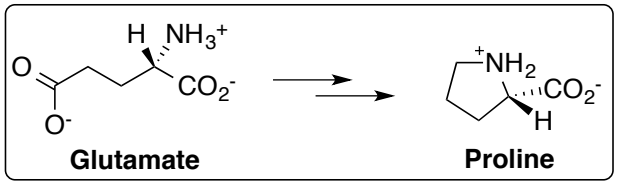


Applied to racemic amino acid synthesis:



- **Nucleophilic Acyl Substitution (NAS)**

Biosynthesis of Proline

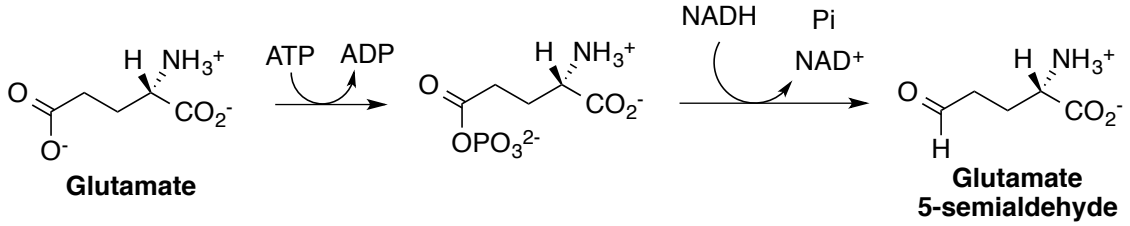


Each step takes place in the active site of an enzyme, which contains all the acids (H⁺**) and bases (**:B**) necessary to complete each transformation (more on that later). Until then, feel free to use **H⁺** and **:B** as needed.**

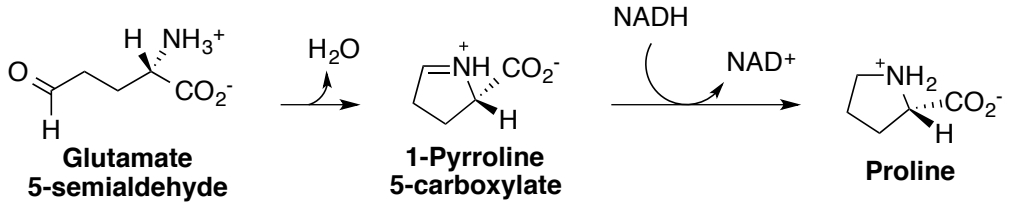
Always consider physiological pH when drawing intermediates and products.

- **Nitrogen** is usually protonated (+), sometimes neutral, NEVER (-)
- **Carboxylic acids** should be deprotonated (-), sometimes protonated / neutral
- **Phosphates** have 2 (-) oxygen atoms per P
- **Alcohols** should always be protonated / neutral

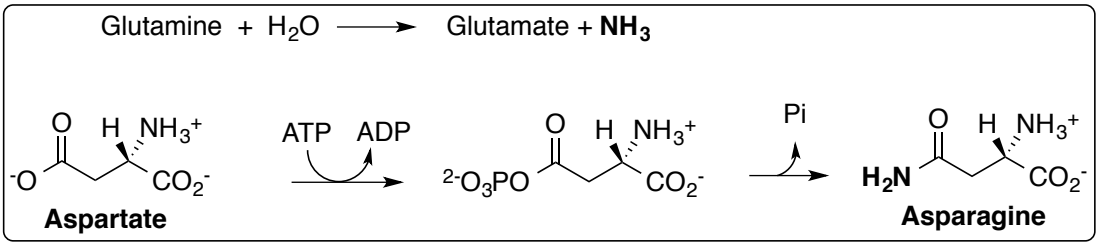
Formation and NADH Reduction of Phosphoester



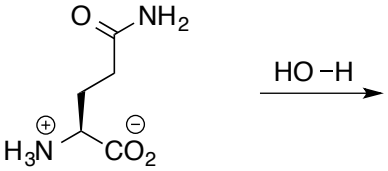
Intramolecular Reductive Amination



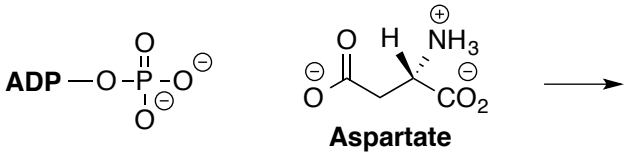
Biosynthesis of Asparagine



Hydrolysis of Glutamine

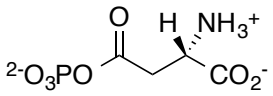


Phosphate Transfers with ATP



Amide Formation

Mixed Anhydride



$H_2N—H$
(from glutamine hydrolysis)

Exam 1 Overview
Anything in the lecture notes or HW is fair game!

- Know functional group structure & name – "**FG Table**" on 109 website

- Structure – Property Relationships

    - Link term to definition or figure / scenario
    - Ex. What happens structurally when ethanol boils?
    - Ex. What happens when NaCl dissolves? When sugar dissolves?

- Acid-Base Chemistry
    - Know the **pKa's from lecture 1**, use to predict pKa of new molecule
    - Draw products of acid-base reaction, predict direction of equilibrium

Be ready to draw any the following **mechanisms** given starting materials *and* either the name of mechanism *or* the product(s). **Formal charges** must be clearly represented, where appropriate. The **exact start and end point of arrows** is important! Know **what arrows mean**: bonds broken / formed.

- Electrophilic Addition to Alkenes

- S_N1 & S_N2

- Nucleophilic Addition to Aldehydes & Ketones

- Nucleophilic Acyl Substitution (NAS)

- Aldol & Claisen Condensation Reactions (forward and reverse)

- E1, E2, & E1cB

- Reduction with NADH & Oxidation with NAD+

    - Be able to draw the core structure of NADH if given NAD^+ & vice versa

- Polyprotic acids: given pKa's, draw all ionic forms over given pH range

Exam 2 material begins with…

- Amino Acid Synthesis

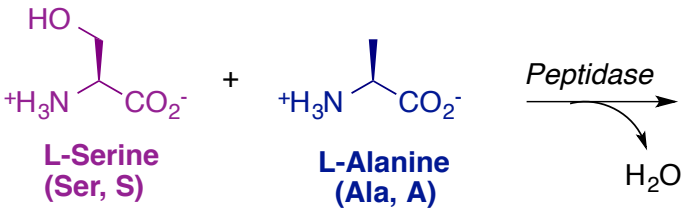
    - Similar or identical to examples in today's notes or HW

CHEM 109, Lecture 7

Peptides

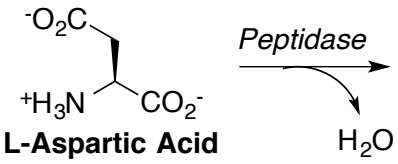
Enzymes – Nature's Reaction Factories!

PEPTIDES



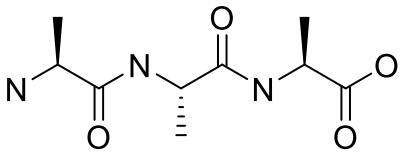
Ser-Ala Dipeptide

Ser-Ala Dipeptide +



Ser-Ala-Asp Tripeptide

Tripeptide template: [(Nitrogen) – (Carbon w Side Chain) – (Carbonyl)]…



Primary (1°) Structure →

Secondary (2°) Structure →

Tertiary (3°) Structure →

Quaternary (4°) Structure →

Enzymes

E or **Enz** = Enzyme; **S** = Substrate (Reactant); **P** = Product

Reactions Mechanisms & the Active Site

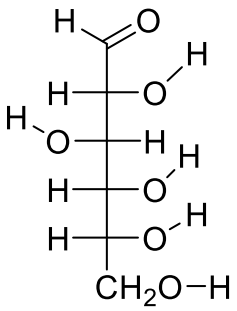
- Reactants = **Substrates**

- Reagents = **Cofactors** - small organic molecules; not catalysts / not regenerated
  - Ex. Glycolysis requires NAD^+

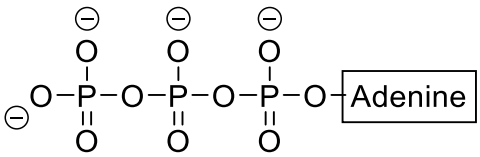
- **Amino acid residues** = side chains off enzyme's peptide backbone
  - Acids
  - Bases
  - Covalently bind substrate

- **Stabilizing Factors** hold substrates and cofactors in place *via* IMF's!!

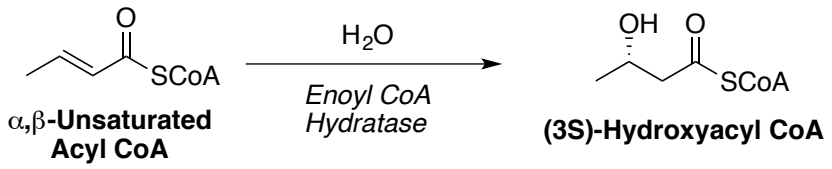
H-bonding

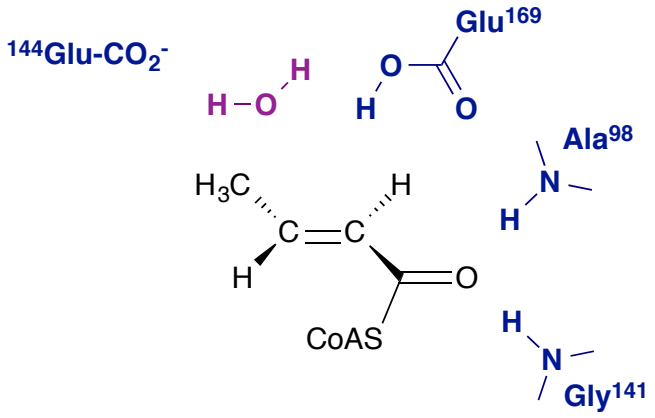


Ion-Dipole

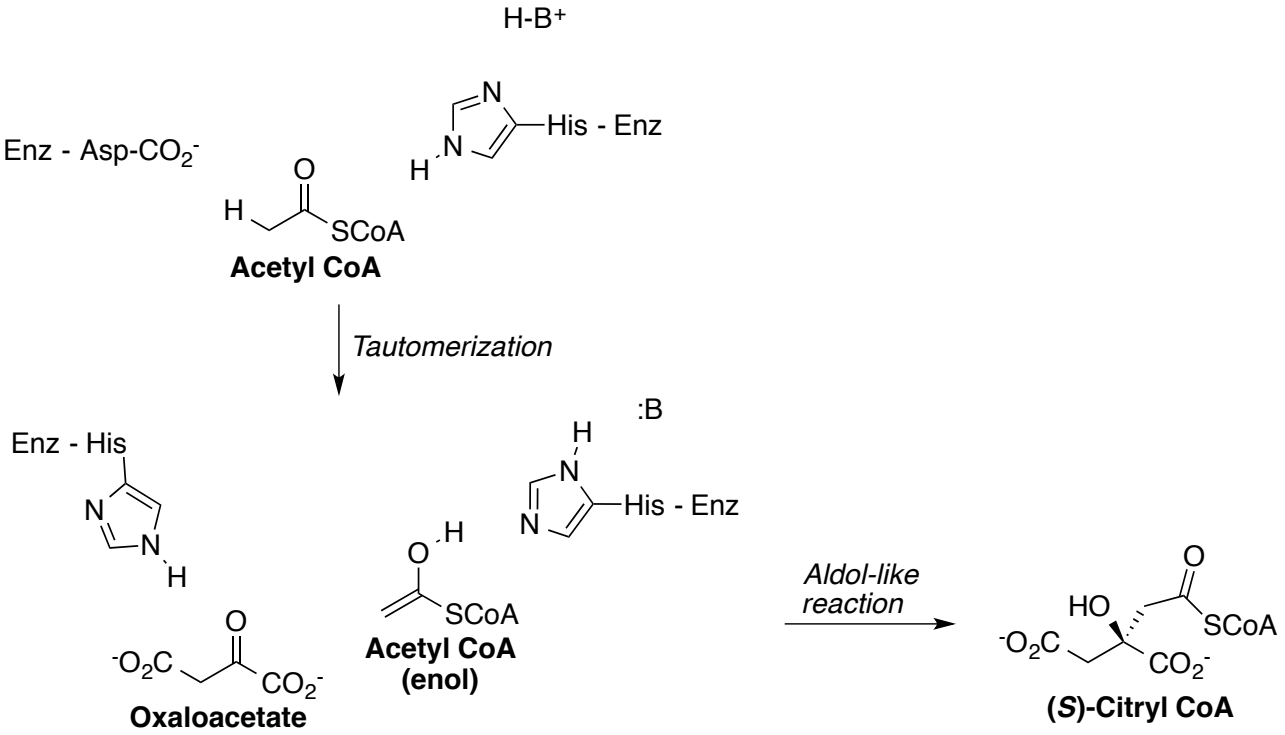


Active Site Example: Conjugate Addition of Water

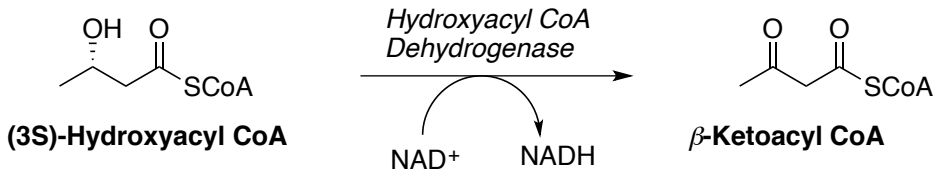


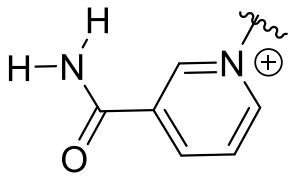


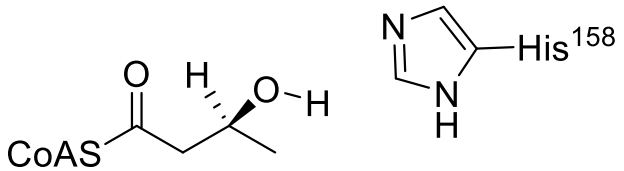
Active Site Example: Citrate Synthase (Citric Acid Cycle)



Active Site Example: Oxidation of an Alcohol







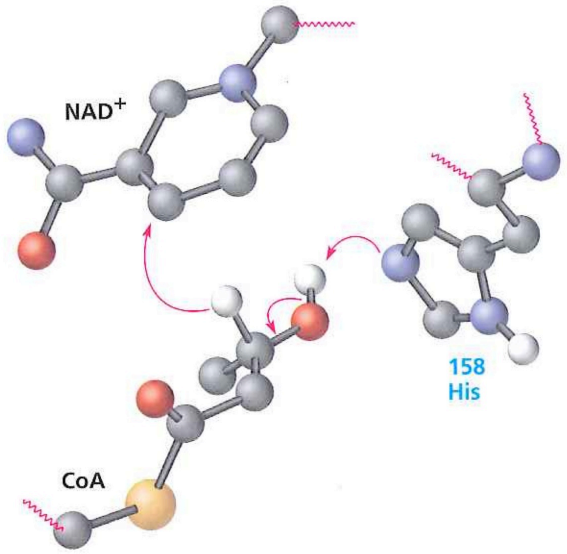


FIGURE 3.9 X-ray crystal structure of the enzyme–substrate complex from hydroxyacyl CoA dehydrogenase. His-158 deprotonates the hydroxyl group, and the adjacent hydride ion is transferred to NAD^+.

Next time…Carbohydrates & Polysaccharides

CHEM 109, Lecture 8

Monosaccharide Nomenclature
- Fischer projections (no rotation) and
- Hemiacetals: Ring-closing of D-monosaccharides

Disaccharides: Formation & Hydrolysis
Polysaccharides & Digestions

CARBOHYDRATES

Monosaccharide Classification

Prefix: *aldo-* or *keto-* for aldehyde or ketone, respectively

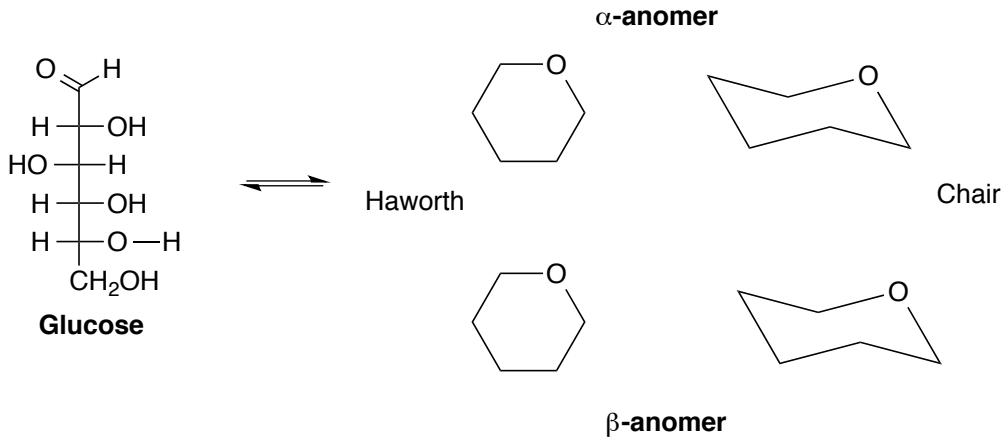
Infix: *-tri-, -tetr-, -pent-, -hex-, -hept-*, etc. for the number of carbons

Suffix: *-ose* for sugars!

Examples (more in Lecture 7 HW):

D-aldotriose L-ketopentose

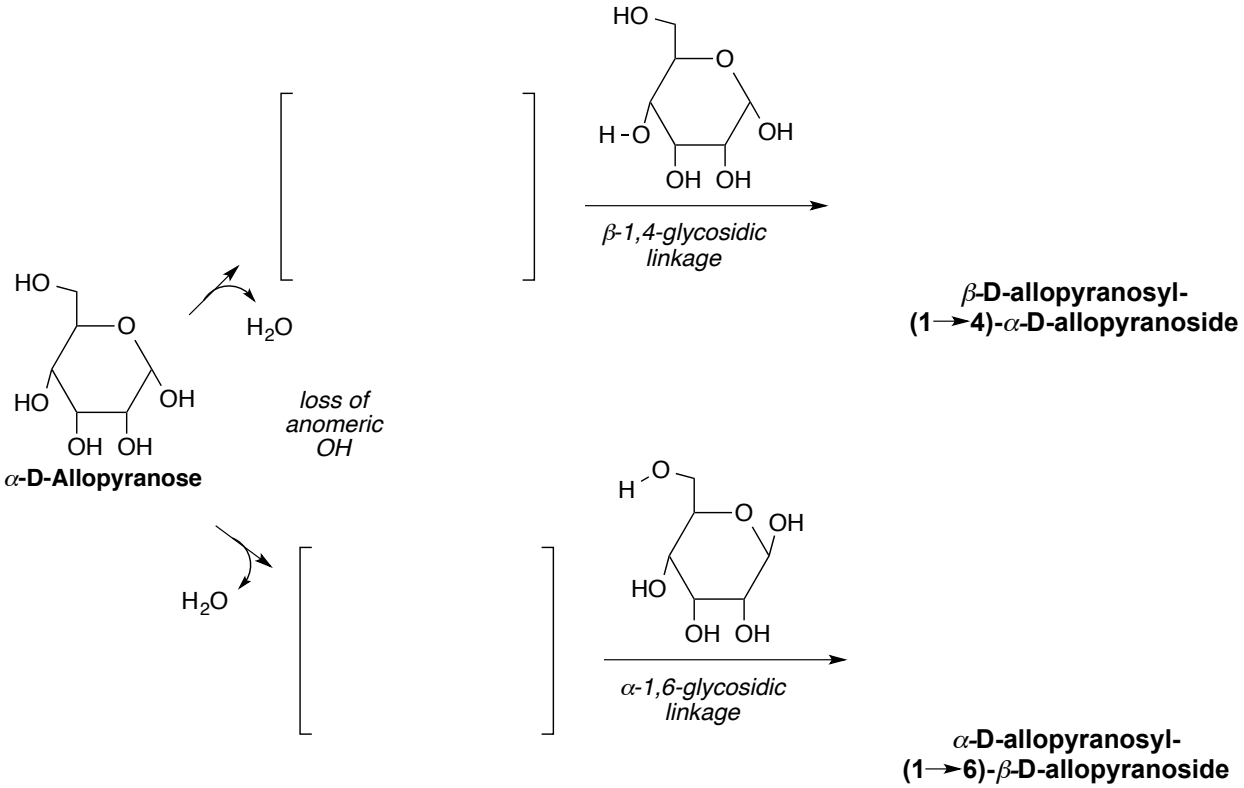
Equilibrium between open and closed sugars:



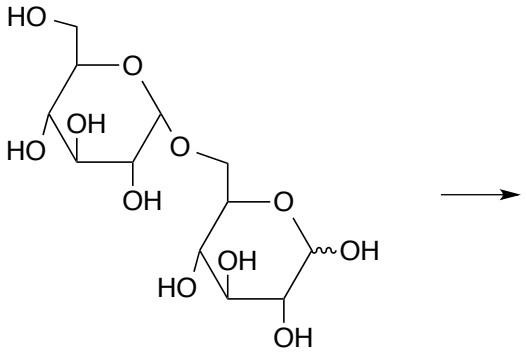
Draw the C2-epimer of glucose in open and closed form (Haworth & chair):

Lots more practice in the homework!

Formation of Disaccharides (Glycosidic Linkage)



Hydrolysis of Disaccharides



Isomaltose
One of the many products of carmelization of glucose

Complex Carbohydrates: Ex. Starch

Polysaccharides

Amylose (20% of starch) Amylopectin (80% of starch)

Carbon Cycle:

ANIMALS

PLANTS

When you eat…

STARCH → *Random Hydrolysis*

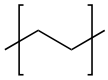
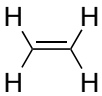
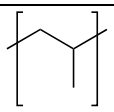
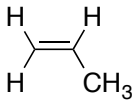
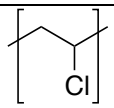
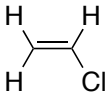
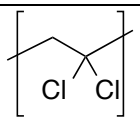
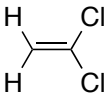
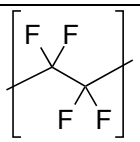
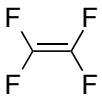
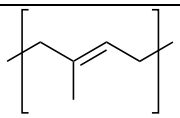
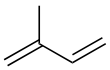
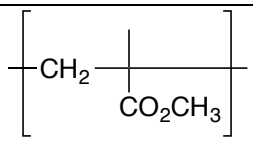
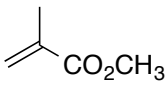
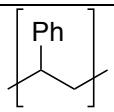
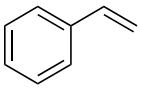
↓

Intestinal Hydrolysis → **Maltose, Maltotriose, limit dextrins**

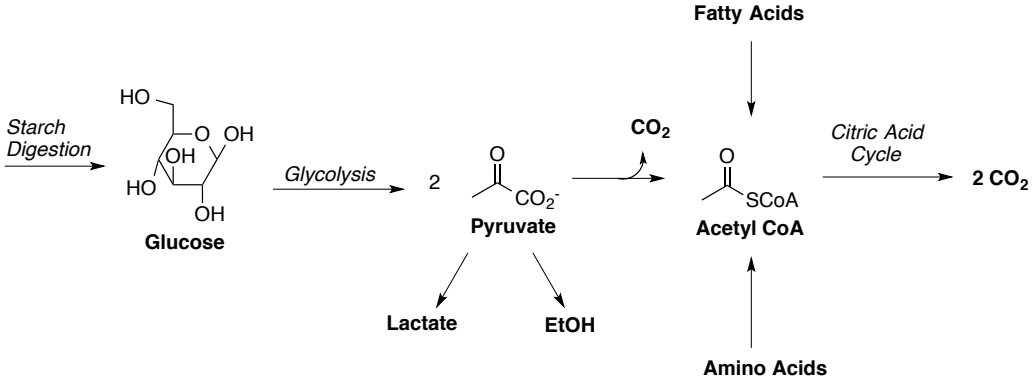
↓ *Glycosidases*

Glucose → glucose in bloodstream

Plastics: Synthetic Polymers

Name	Repeating Unit	Monomer	Applications
High-density polyethylene (**HDPE**)			Milk jugs, insulation, pipes
Low-density polyethylene (**LDPE**)			Packaging film, insulation, flexible bottles
Polypropylene (**PP**)			Appliances, car parts
Poly(vinylchloride) (PVC or **V**)			Pipes, floor covering
Poly(vinylidene chloride) (Saran)			Packaging film
Polytetrafluoroethylene (PTFE or Teflon)			Nonstick coating, stopcocks
cis-1,4-polyisoprene			Tires, shoes, sports equipment
Poly (methyl methacrylate) (PMMA)			Display signs, plexiglass, dentures
Polystyrene (**PS**)			Packaging, drinking cups

Metabolism Overview (Big picture)



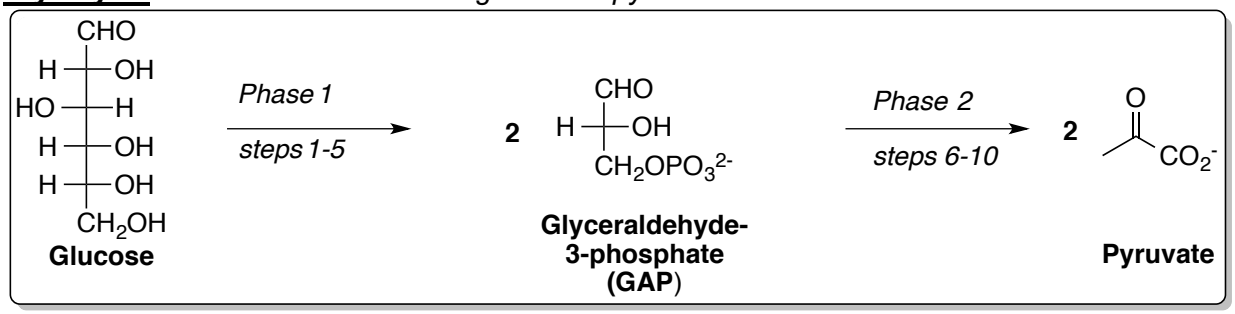
Next time…Glycolysis – McMurry 29.5

CHEM 109, Lecture 9

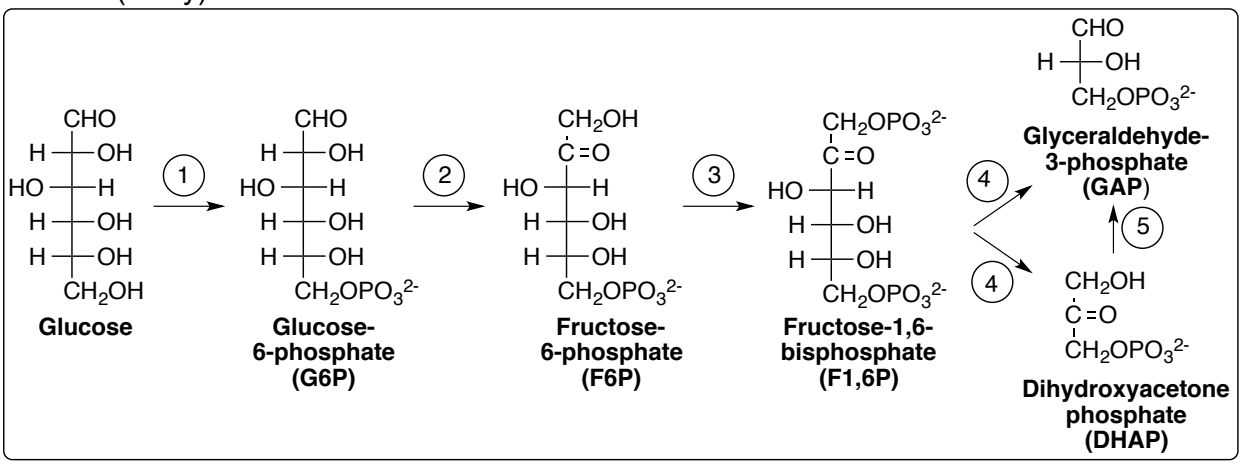
Glycolysis

– Active site examples – types of binding, roles of co-factors & AA residues

Glycolysis - *Know the structures of glucose & pyruvate.*



Phase 1 (today)

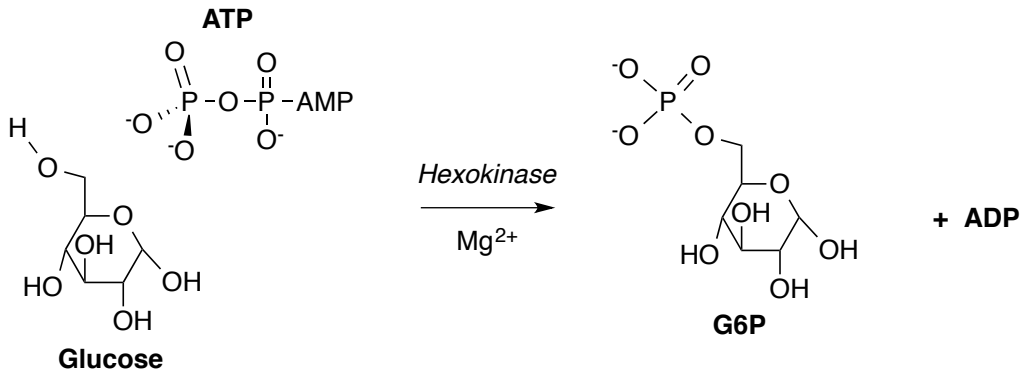


Mechanism Overview in Phase 1 of Glycolysis

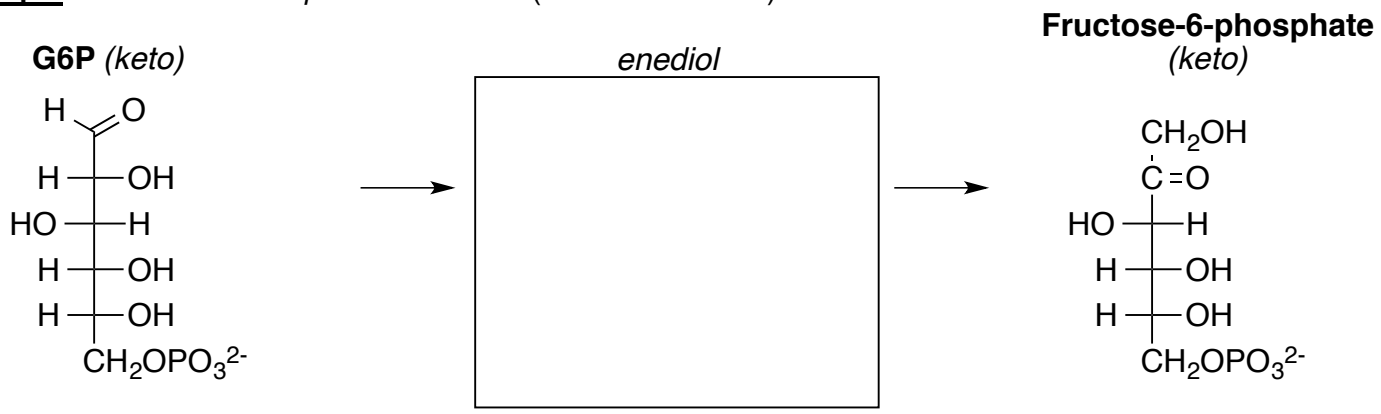
- Nucleophilic Acyl Substitution
- Tautomerization

- Nucleophilic Addition with Dehydration
- Retro-aldol

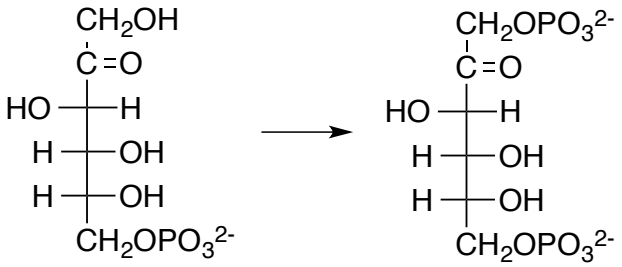
Step 1 – *Hexokinase* active site



Step 2 – *Glucose-6-Phosphate Isomerase* (Tautomerizations)

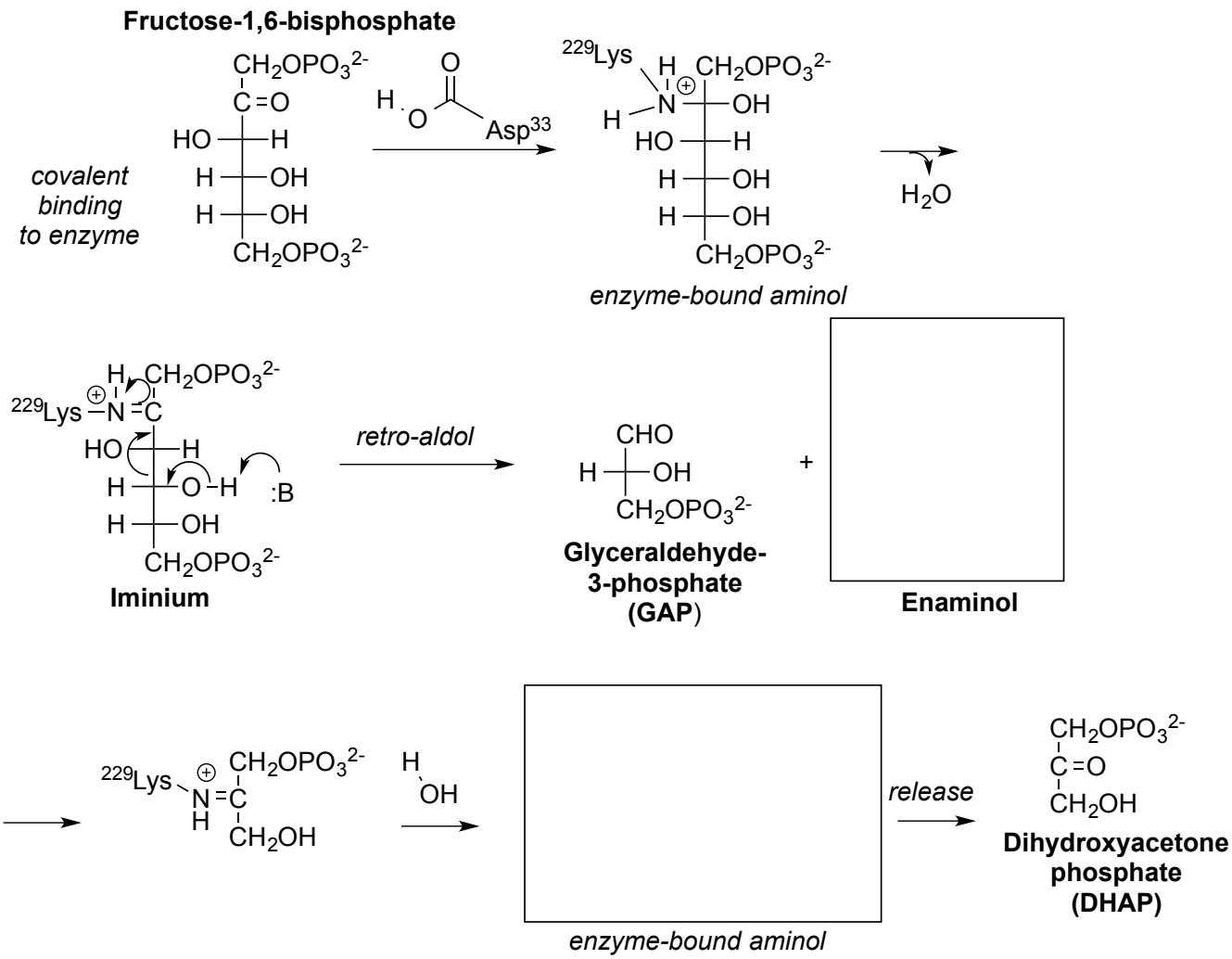


Step 3 – *Phosphofructokinase* (nearly identical to step 1 - try on your own)



<u>Step 4</u> – *Aldolase* (see HW #1.10 for simpler – not real - version)

1. Covalent binding of **F-1,6-BP** to active site *via* **iminium** bond to a lysine residue
2. Retro-aldol to form **GAP** & **enaminol**
3. Release of **DHAP** from lysine residue



<u>Step 5</u> – *Triose Phosphate Isomerase*

Next time…Phase 2 – Profit!

CHEM 109, Lecture 10

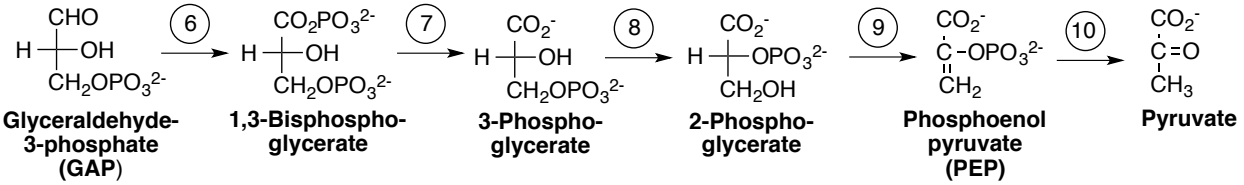
Glycolysis Phase 2

Decarboxylation Overview

Lecture 10 HW = re-print lecture blanks, fill in missing intermediates and mechanisms – these notes are your answer key (check webcast too)

Last time…Phase 1 left us with 2 x GAP

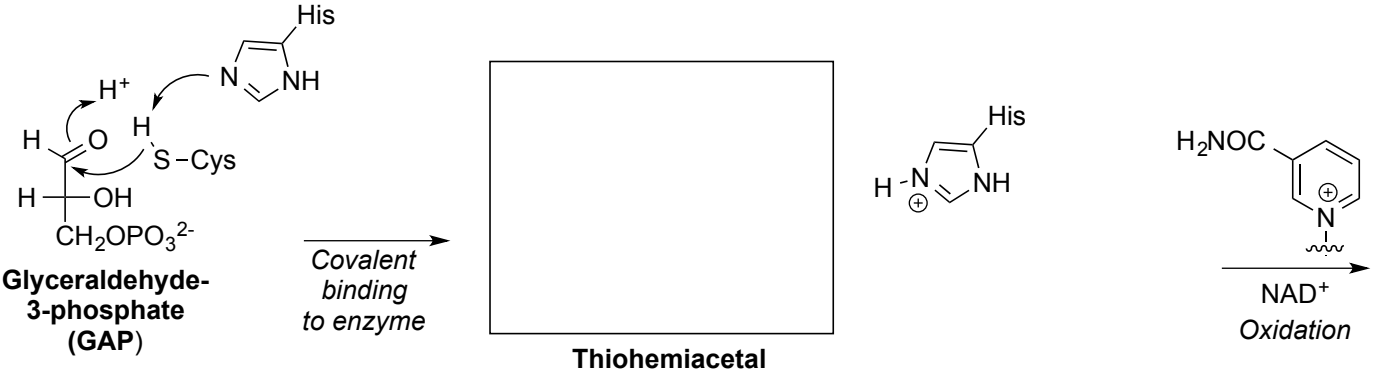
This time…Phase 2 – Profit!

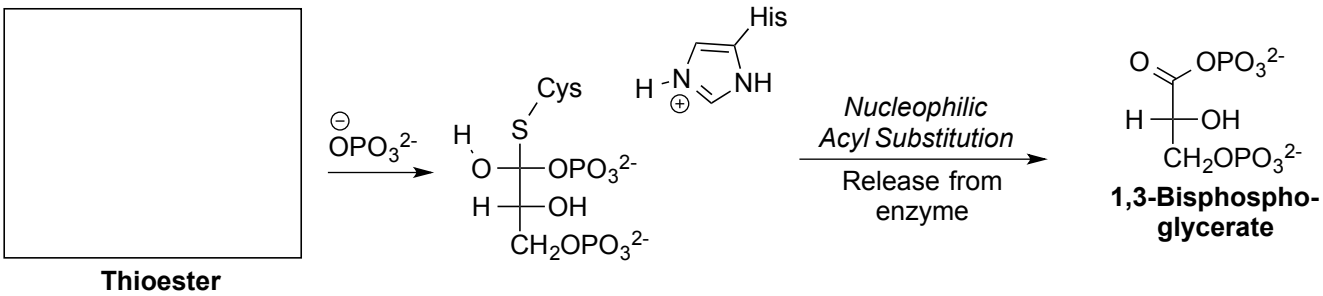


Hemiacetal **Thiohemiacetal** **Ester** **Thioester**

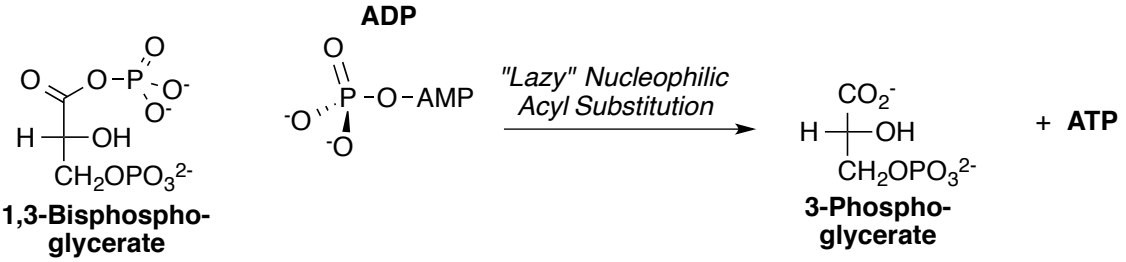
Step 6 – *GAP Dehydrogenase*

1. Covalent binding of **GAP** to active site *via* **thiohemiacetal** bond with cysteine residue
2. Oxidation to **thioester** via NAD^+
3. Phosphorylation
4. Release product from active site

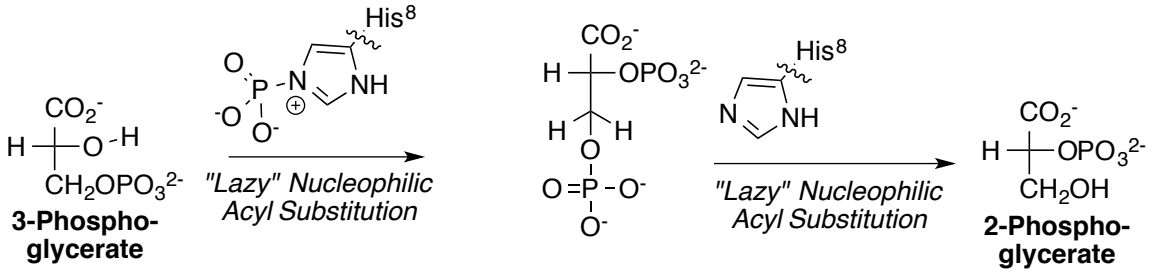




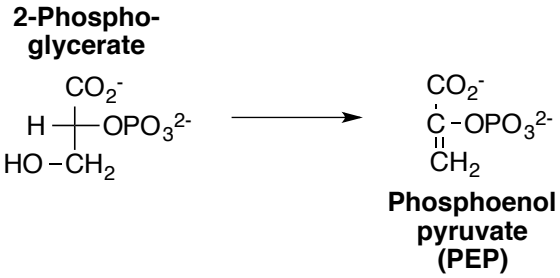
Step 7 – *Phosphoglycerate kinase*



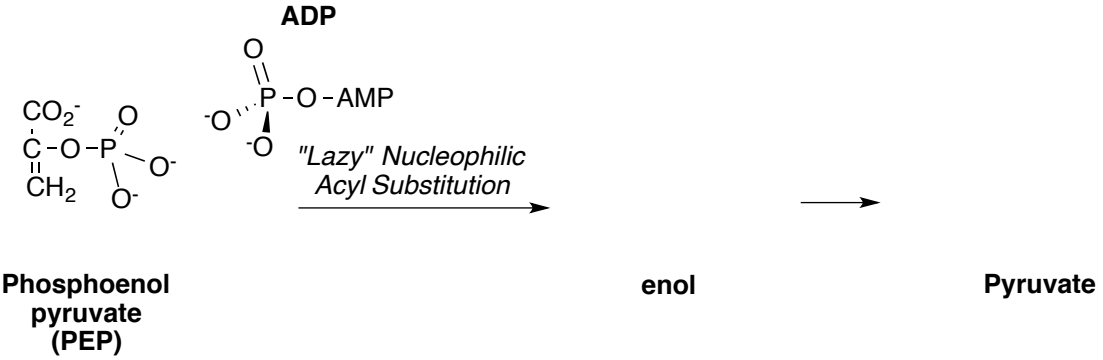
Step 8 – *Phosphoglycerate mutase*



Step 9 – *Enolase*

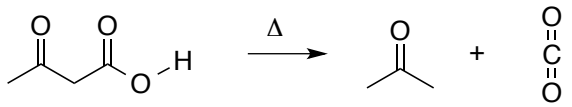


Step 10 – *Pyruvate kinase*

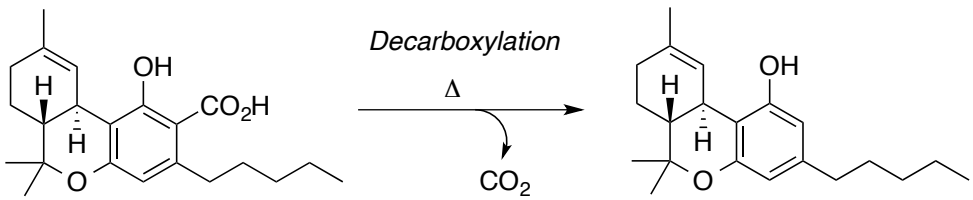


Preview to fates of Pyruvate…

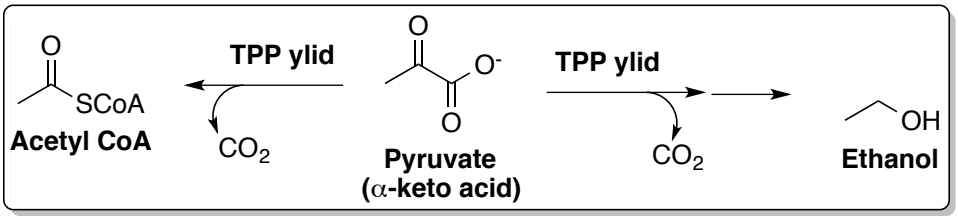
<u>Decarboxylation</u> → loss of CO_2



β-keto acid



Tetrahydrocannabinolic acid (THCA) **Tetrahydrocannabinol (THC)**



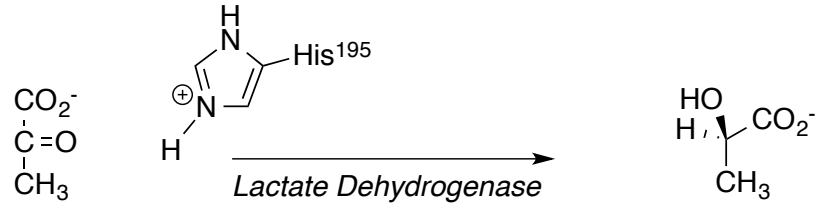
Fates of Pyruvate

- Anaerobic metabolism
  1. Lactate – enantioselective NADH reduction
  2. Ethanol & CO_2 (yeast) – TPP ylide binding
- Aerobic metabolism (mammals)
  3. Acetyl CoA – TPP ylide binding & lipoamide transfer

Why aerobic vs. anaerobic?

Glucose → Pyruvate
2 ADP → 2 ATP
2 NAD^+ → 2 NADH

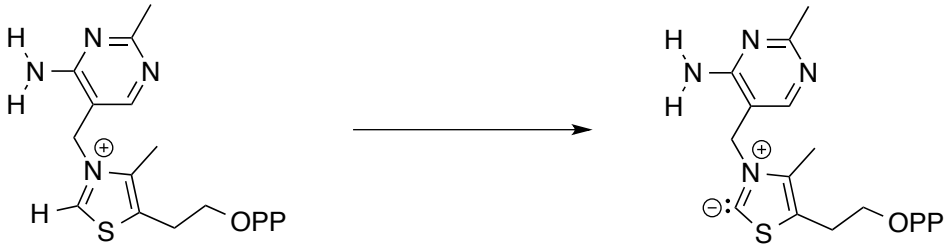
1. Anaerobic Metabolism in Mammals



Pyruvate **(*S*)-Lactate**

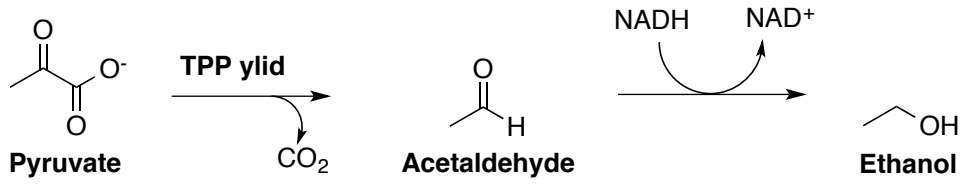
Other fates of pyruvate (#2-3) involve decarboxylation (-CO_2)

TPP – the decarboxylation cofactor



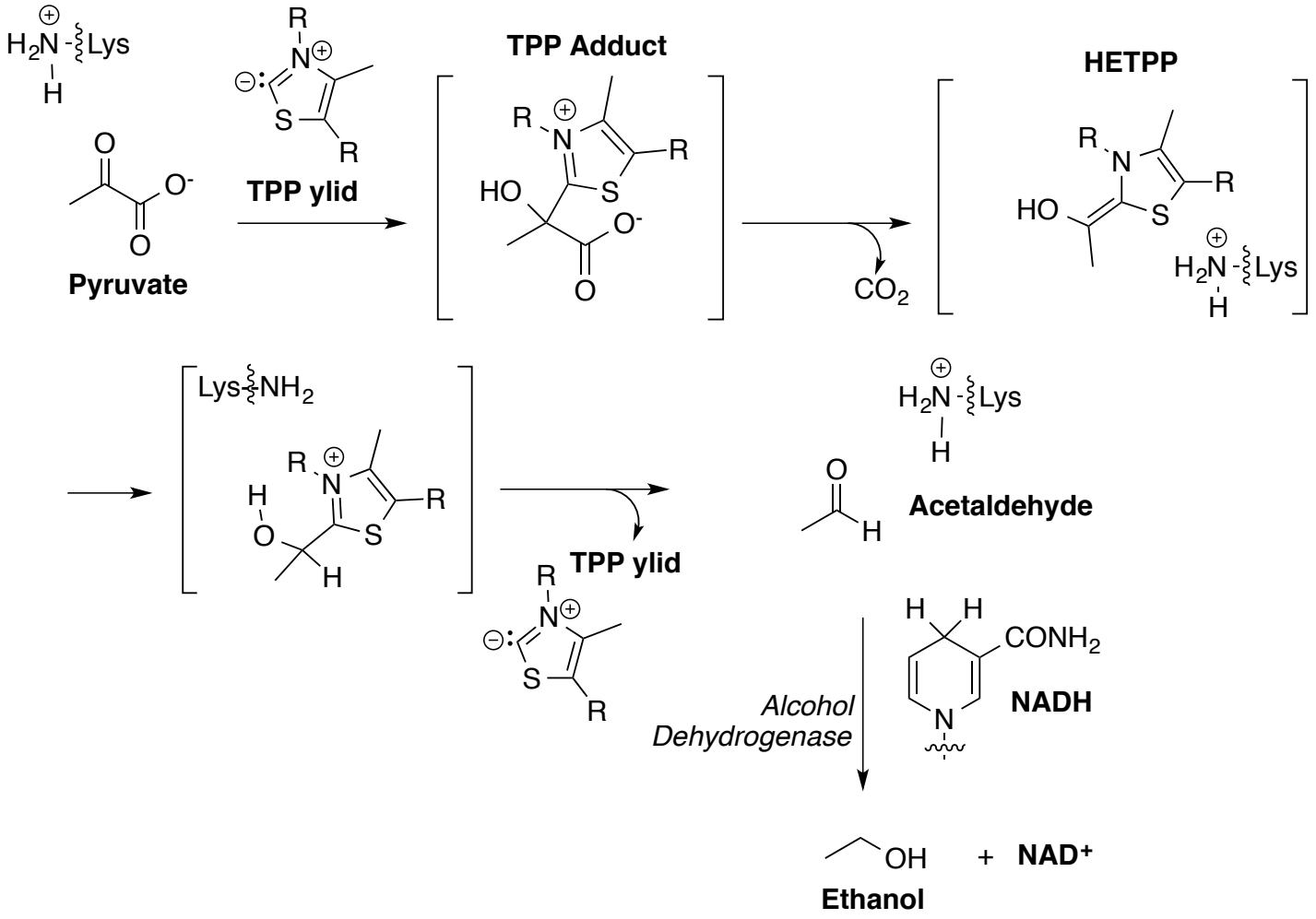
Thiamin diphosphate (TPP) **TPP ylide**

2. Yeast anaerobic metabolism (fermentation)

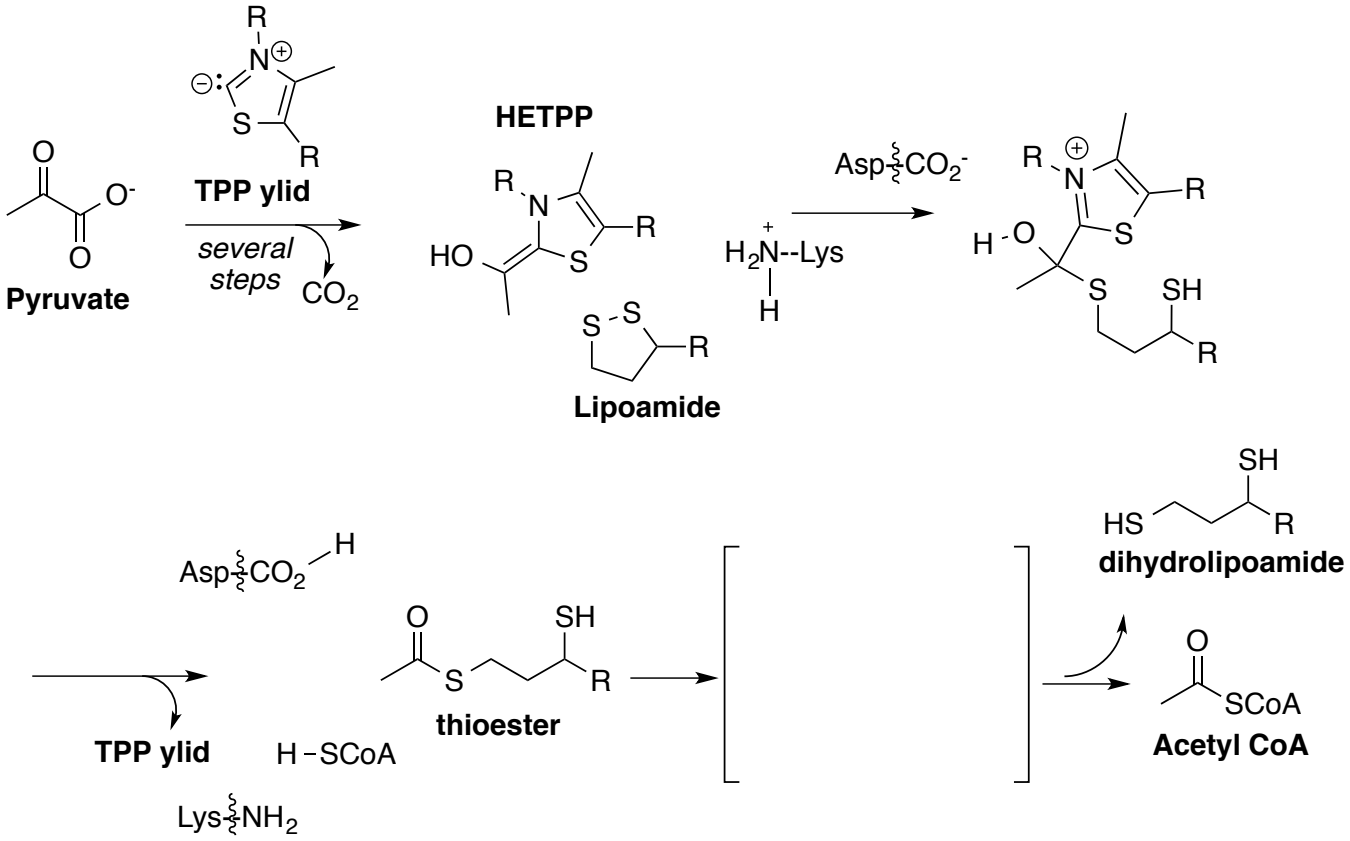


a. Addition of **TPP ylid** to ketone
b. Decarboxylation
c. Protonation of **enaminol**
d. **Acetaldehyde** formation & release of **TPP ylid**
e. Reduction with **NADH**

Fermentation, add the arrows…



3. Aerobic Metabolism (mammals) – Pyruvate Dehydrogenase Complex



Reaction Overview

Lecture	Process / Chemistry	Mechanism
7 – Peptides & Carbohydrate Nomenclature		
8 – Disaccharides		
9 – Glycolysis #1		
10 – Glycolysis #2		
11 – Fates of Pyruvate		
12 - Lipids		

Active Site Recap

Acids

Bases

Reducing Agent

Oxidizing Agent

Decarboxylation

Phosphate Transfer

Acyl Transfer

Covalent Binding to Enzyme

Stabilizing Factors (Place-Holders)

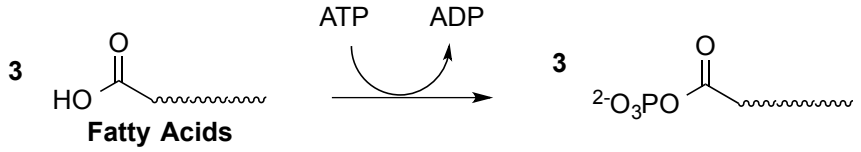
CHEM 109, Lecture 12

Lipids
- Classification
- Mevalonate Pathway to Isopentenyl Diphosphate (IPP)
- Conversion of IPP to Terpenoids
  - Carbocation Rearrangements (RRGT): Hydride & Methyl Shifts

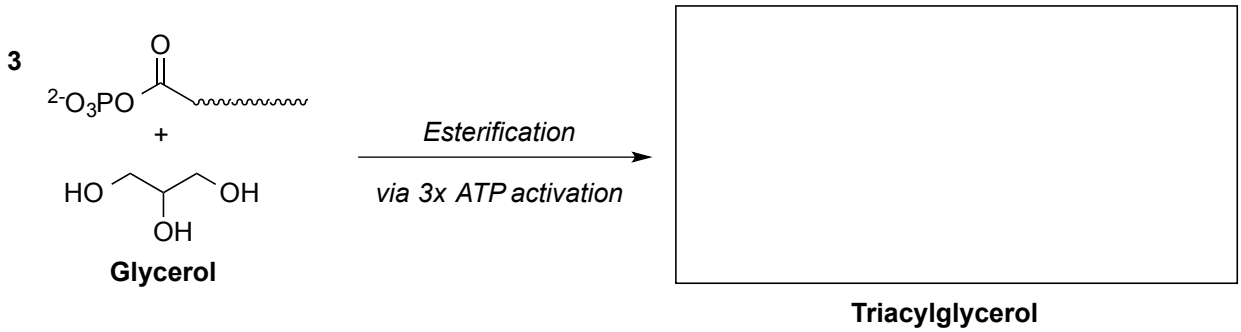
General Lipid Classifications
- Fatty acids, triacylglycerols, and terpenes
  - Be able to identify and/or construct these given the components

Fatty Acids & Triacylglycerols

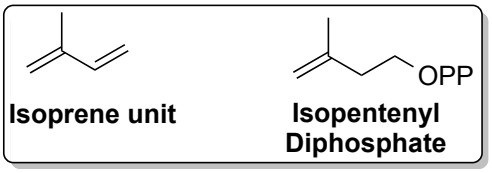
- ATP Activation



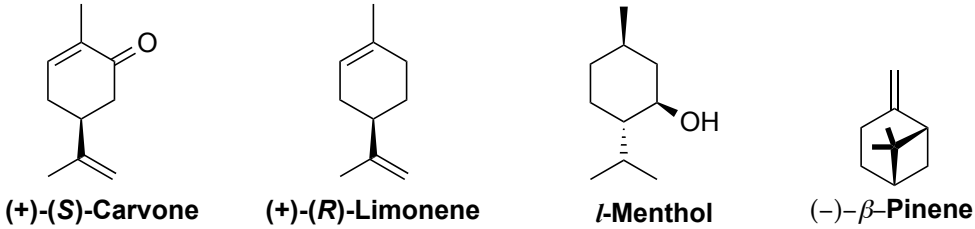
- Esterification



Terpenes & Terpenoids

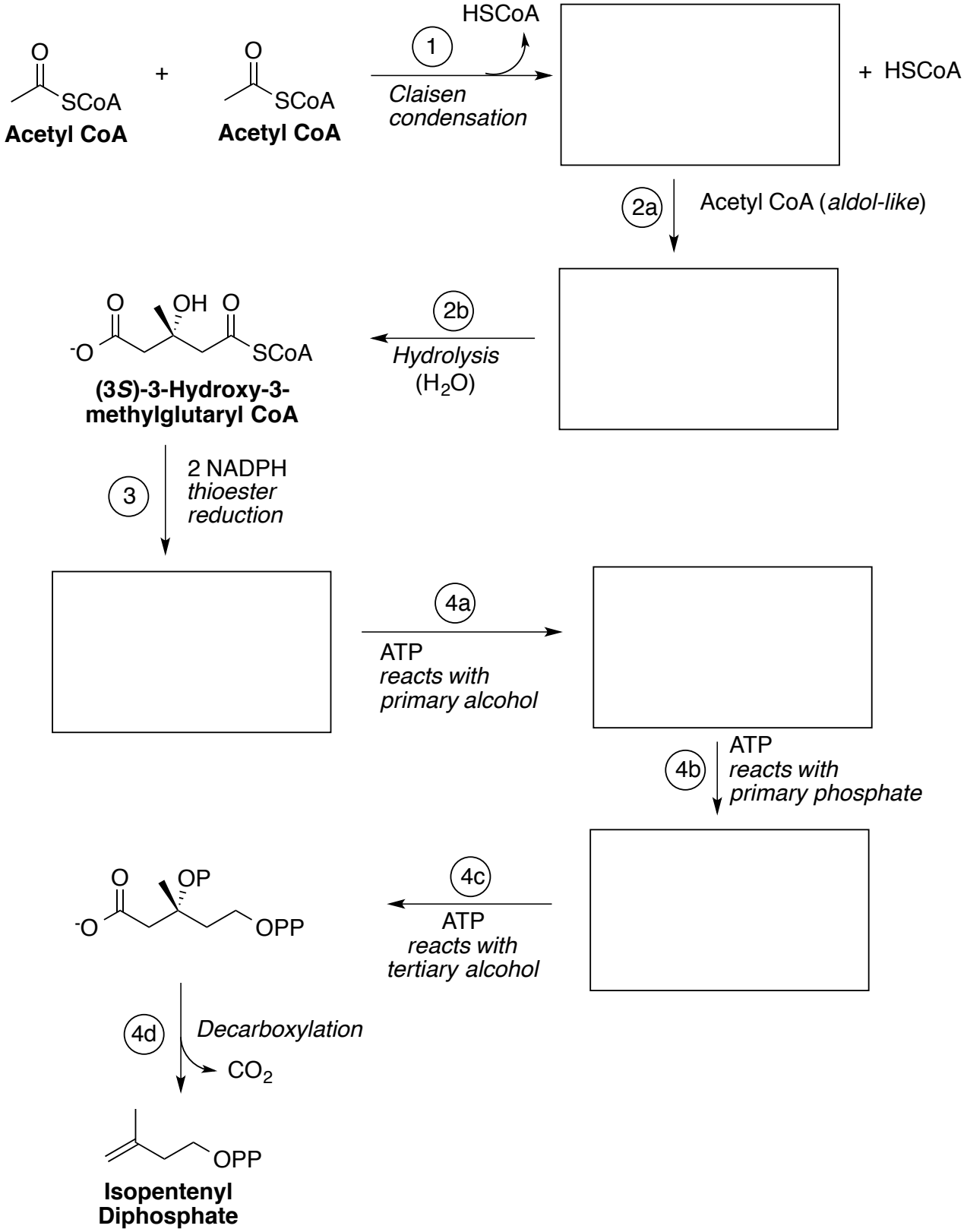


some monoterpenoids:

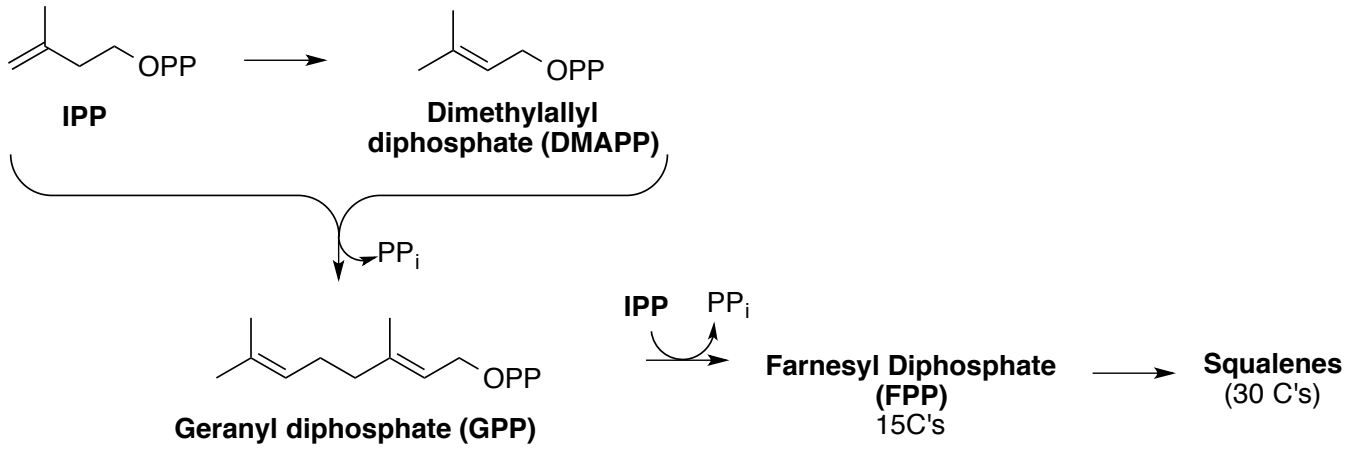


Mevalonate Pathway to Isopentenyl Diphosphate (IPP)

Fill in the boxes! Test your knowledge of reaction names, co-factors, etc.

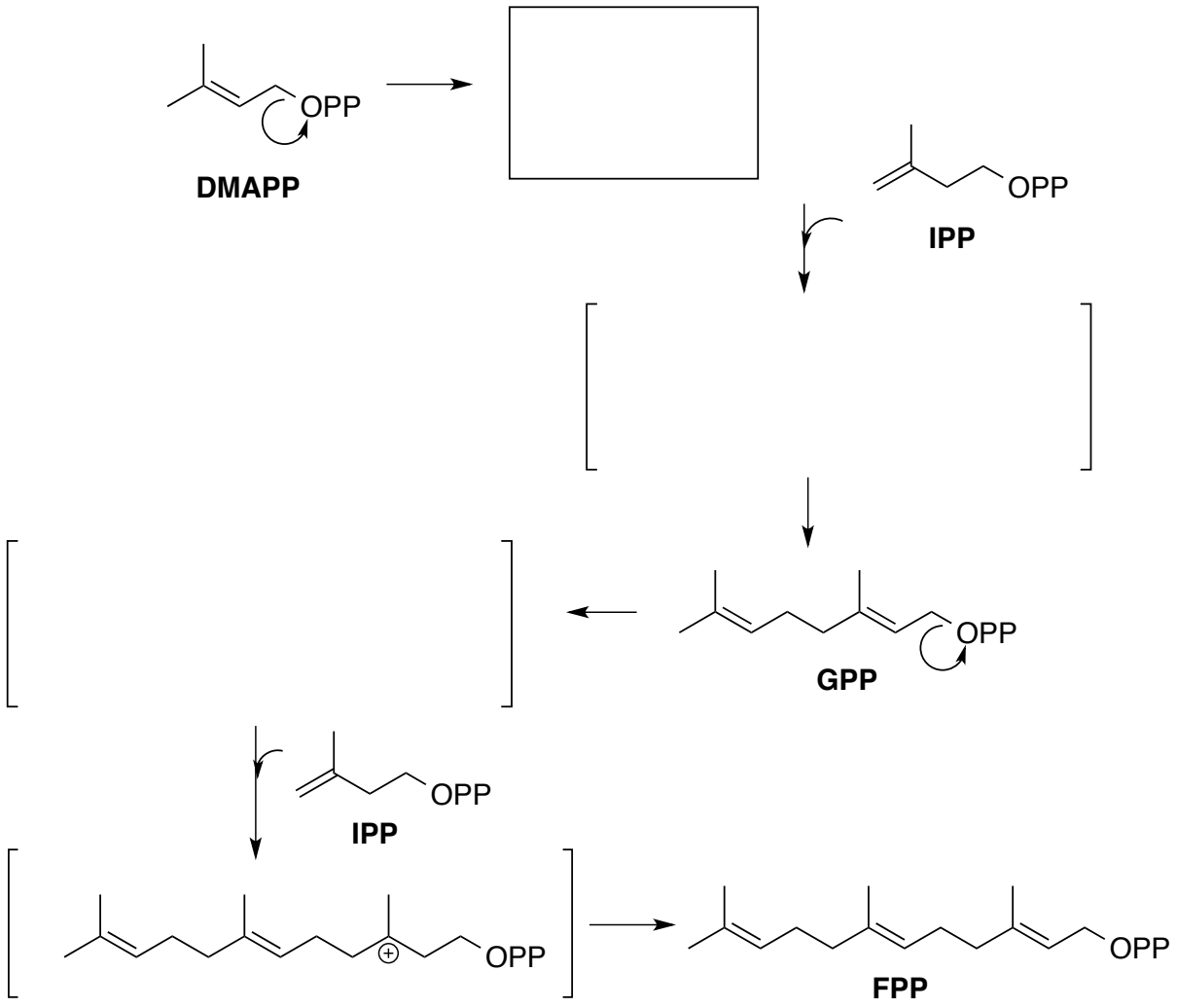


The IPP Building Block – process overview



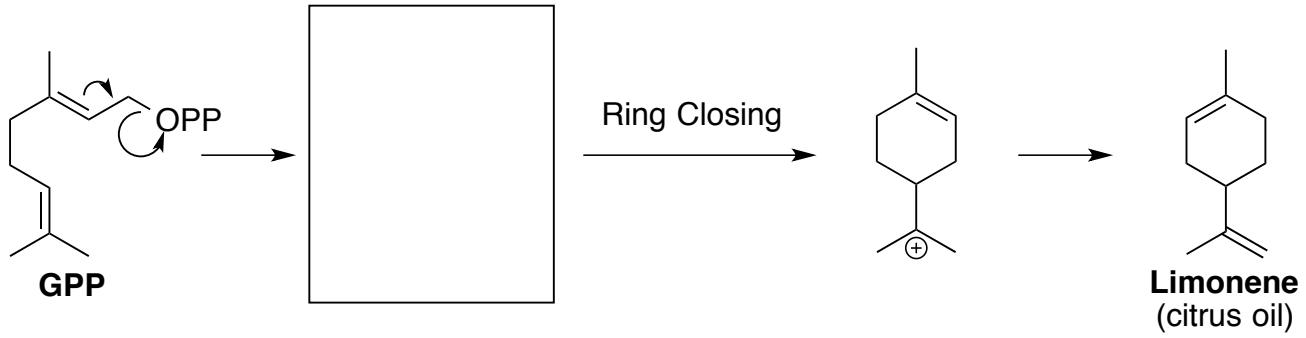
Geranyl Diphosphate (GPP) & Farnesyl Diphosphate (FPP):
Mono- and Sesquiterpenoid Scaffolds

Add or follow arrows, fill in the boxes…



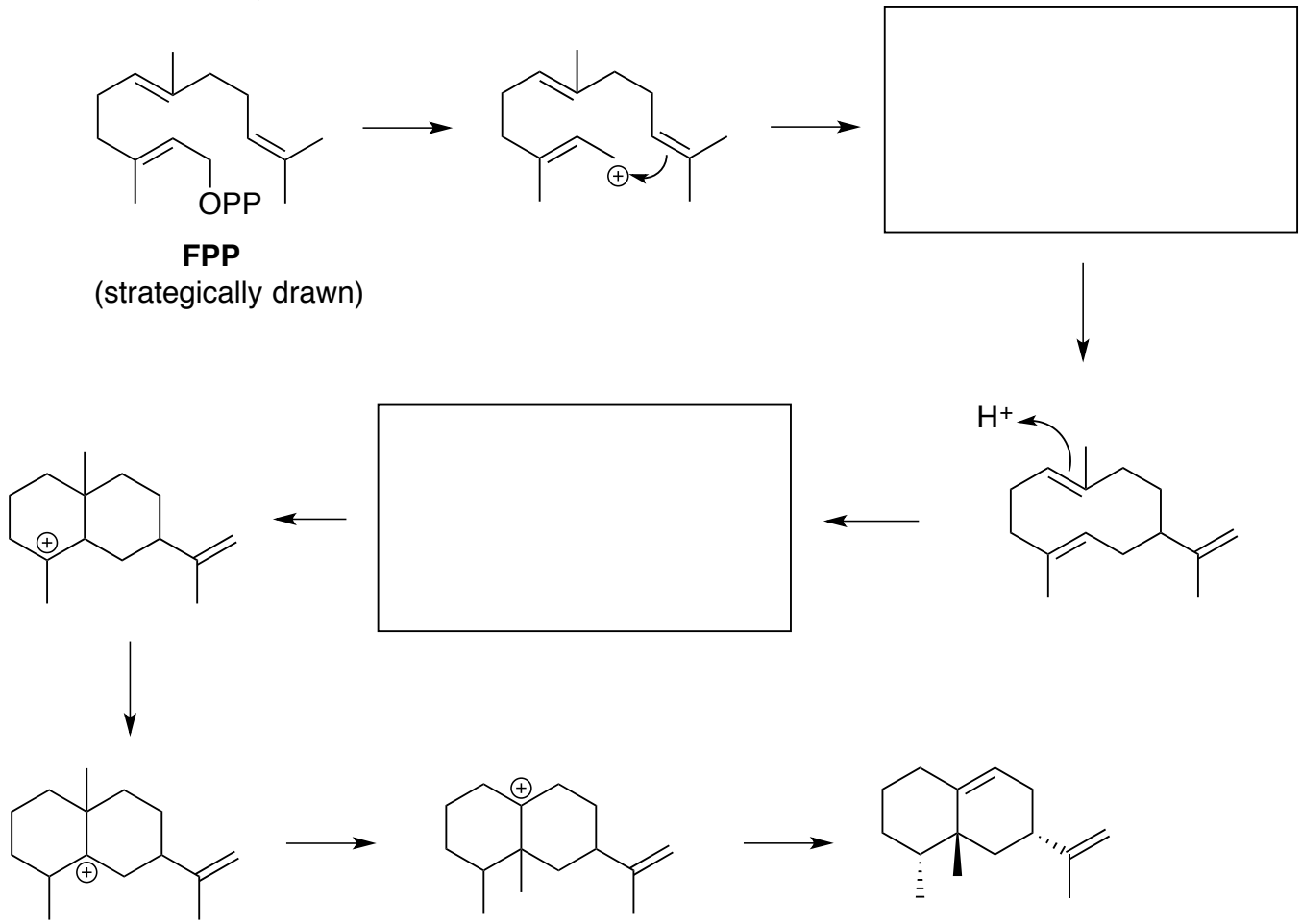
Monoterpenoids: Biosynthesis of Citrus Oil from GPP *via* C⁺ Rearrangements

Add or follow arrows, fill in the boxes…



Sesquiterpenoids: Biosynthesis of a Tobacco Component *via* C⁺ Rearrangements

Add or follow arrows, fill in the boxes…



***epi*-Aristolochene**
(stereochem incorporated along the way, not shown until now!)

And thus concludes Exam 2 material (Lectures 6-12)!