Bio-Organic Mechanism Game – Simplistic biochemical structures and simplistic organic reaction mechanisms are used to explain common biochemical transformations. Simplified biochemical molecules are presented first.

Many biomolecules have a somewhat complex structure that makes it difficult to write out step by step mechanisms. However, if we simplify those structures to the essential parts necessary to explain the mechanistic chemistry of each step, it becomes much easier to consider each step through an important cycle. I have proposed possible simplified structures that are used in the later examples of biochem cycles and problems. The usual strategy in biochem cycles is to just write names, or perhaps, names and a structure. Occasionally a few mechanistic steps are suggested, but almost never is a detailed sequence of mechanistic steps provided. Since it is hard to find such detailed mechanistic steps anywhere (sometimes they are not known) our proposed steps are, of necessity, somewhat speculative. In this book we are not looking for perfection, which is not possible, but for sound organic logic that is consistent with the biochemical examples presented below. There is great satisfaction in blending organic knowledge with real life reactions that help explain how life works. In working through some of the problems, you may develop an alternative mechanism that is just as good, or even better than the one I have proposed. If you do, I hope you will share it with me and if an improved version of this book ever gets written I can include it the next edition (and give you credit). It is almost certain that I have made some errors and I would appreciate it if you would let me know about them.

Biomolecules and our simplified representation.

1. ATP – adenosine triphosphate – phosphorylation, energy source

![ATP simplified and actual structure](image)

2. NAD⁺ and NADP⁺ - nicotinamide adenine dinucleotide (hydride acceptor)

![NAD⁺ and NADP⁺ simplified and actual structure](image)
3. NADH and NADPH - nicotinamide adenine dinucleotide (hydride donor)

![Diagram of NADH and NADPH]

4. Vitamin B-6 – pyridoxal phosphate (amino acid metabolism, transamination with \(\alpha\)-ketoacids, decarboxylation, removal of some amino acid side chains, epimerizations)

![Diagram of Vitamin B-6]

5. TPP – Thiamine diphosphate (decarboxylation and enamine chemistry with proton or carbohydrates)

![Diagram of TPP]
6. Coenzyme A (acyl transfer)

Thiol esters form here.

This is an acetyl group

All of this is "Co-A"

actual structure of acetyl Co-A

7. FAD / FADH₂ – Flavin adenine dinucleotide (oxidation – reduction) – used to deliver hydride to C=C or take hydride from CH-CH (fatty acid metabolism, etc.)
Hydride transfer reduces FAD to FADH\textsubscript{2} which can be oxidized to FAD.

8. THF – tetrahydrofolate (transfer of one carbon units) –recycles cysteine to methionine and other 1C metabolic functions, many variations

Tetrahydrofolate (THF)
one carbon transfers as "CH\textsubscript{3}", "CH\textsubscript{2}".

One glutamate is shown, but several can be attached.
9. SAM = S-adenosylmethionine (methyl transfer agent). The methyl group (CH₃) attached to the methionine sulfur atom in SAM is chemically reactive. This allows donation of this group to an acceptor substrate in transmethylation reactions. More than 40 metabolic reactions involve the transfer of a methyl group from SAM to various substrates, such as nucleic acids, proteins, lipids and secondary metabolites. SAM can be made from methionine and N⁵-methyl THF (just above).
10. Cytochrom P-450 enzymes are oxidizing agents in the body. They can convert inert alkane sp\(^3\) C-H bonds into C-OH bonds and they can make epoxide groups at alkenes and aromatic pi bonds.

Oxidations in the body often use cytochrom P-450 enzymes.

![Heme structure](image)

heme, protoporphyrin IX, found in cytochrom P-450 oxidative enzymes

This is the structure that we will use.

11. Halogenase Enzymes (related to cytochrom P-450 enzymes, can have imidazole ligands from histidine amino acids

Halogenations in the body often iron halogen bonds.

![Halogenation structure](image)

This is the structure that we will use.

Biochemical Reaction Mechanism Examples

Mechanism arrows used in the “Bio-Org Game” are meant to suggest how the electrons move over a single transformation, and are not necessarily meant to imply that all of the electrons and atoms transfer in one huge “domino” cascade. Organic mechanisms are often multistep transformations, but it’s harder to pin down biochemical transformations. The symbolism used in these examples represents a concise way to show electron movement involving making and breaking bonds. Lone pairs are rarely drawn (or used). They are included on the generic base (B:) used to show proton transfers. A generic acid (H-B\(^+\)) is used to provide a proton. Very occasionally a pair of electrons is used when it provides some special effect (enamine reaction,
resonance stabilization in acetal formation or breakdown). Multiple resonance structures are not drawn. Only very occasionally is an intermediate drawn, when confusion arises from too many arrows going in too many different directions. **Do not** confuse these examples for real mechanisms! They are designed to show the essential how changes might occur in complex biochemical reactions. Also, at physiological pH (≈7) a few organic groups are ionized (RCO₂H is anionic as RCO₂−, and RNH₂ is cationic as RNH₃⁺). They are drawn in their neutral forms in this game. The initial examples of biochemical transformations can serve as foundational reactions in endless biochemical sequences or cycles. Knowing how these reactions work can provide insight into many biochemical aspects of anabolism and catabolism and can help improve your organic “mechanistic” logic. First, bare-bones examples are provided to show the essence of each type of reaction. The problems that follow use several “typical” types of biochemical transformations in made-up sequences and many real biochemical cycles in which to practice. With such practice using these simple model reactions you can learn to recognize where (when) and how similar transformations might be occurring in real biochemical reactions that are presented without any mechanistic detail in a book or article. Nature uses simple strategies applied to limited classes of molecules (carbohydrates, lipids, fats, steroids, amino acids, nucleic acids, neurotransmitters, alkaloids, terpenoids and more) having enormous variation of patterns. It’s amazing what you can speculate upon using these few reactions.

**An example of mechanistic simplification.**

An “organic” arrow pushing mechanism, showing keto → enol tautomerization in acid, is shown without simplification, having all of the normal mechanistic details (lone pairs, formal charge, resonance, etc.). We won’t do it this way in the Bio-Org game.

![Keto / enol tautomerization mechanism](image)

A complete organic mechanism shows lone pairs, each individual step and resonance structures.

The same mechanism in the Bio-Organic Mechanism Game is shown in the first “biochem” example, using the simplified mechanistic conventions of this game.

1. **Keto / enol tautomerization (two proton transfers and a shift of pi electrons).**

![Keto / enol tautomerization](image)
Quite often in biochemistry the acid and base functions are a cooperative action in the active site of an enzyme, much in the manner used in this Game. This avoids the necessity of very strong acid or very strong base, often used by chemists in their reactions. Such conditions are not tolerated by living organisms. We arbitrarily use neutral base, B: and cationic acid H-B⁺.

2. Carbonyl hydration – a regioselective addition reaction of H₂O to a carbonyl group. This also requires some proton transfers. A carbonyl hydrate can be dehydrated via an elimination reaction which also requires some proton transfers. These steps are very similar to hemiacetal/hemiketal reactions (Example 6), but use H-O-H instead of R-O-H. The carbonyl hydrate can be used to oxidize an aldehyde (example 8) or allow a reverse aldol reaction (example 3).

3. Aldol reactions make a new carbon-carbon bond, forming a β-hydroxycarbonyl compound. A carbonyl Cα position becomes the nucleophile (as enol or enolate) and reacts with a separate electrophilic carbonyl carbon. Reverse aldol reactions cleave the Cα-Cβ bond, leaving the electrons on a Cα position and forming a C=O at the Cβ-OH position. The aldol product can proceed on an additional step as shown in Example 5 (reverse Michael → α,β-unsaturated carbonyl compounds)
4. Claisen reactions make a new carbon-carbon bond, forming \( \beta \)-ketocarbonyl compounds. A carbonyl \( C_\alpha \) position becomes the nucleophile (as enol or enolate) and reacts with a separate electrophilic carbonyl carbon (similar to Example 3, except carbonyl substitution occurs instead of carbonyl addition). Ester groups are common in organic chemistry and thiol ester groups (acetyl Co-A) are common in biochemistry. Reverse Claisen reactions cleave the \( C_\alpha-C_\beta \) bond leaving the electrons on the \( C_\alpha \) position and forming a carboxyl at the \( C_\beta=O \) position. The tetrahedral intermediate is omitted in the Bio-Organic Game.
5. Reverse Michael reaction (elimination = dehydration) eliminates \( \text{H}_2\text{O} \) between the \( \text{C}_\alpha-\text{C}_\beta \) bonds (E1cB mechanism). Dehydration carries the aldol (Example 3) one step farther along, forming \( \alpha,\beta \)-unsaturated carbonyl compounds. Michael reaction (addition / hydration) is the reverse reaction and adds the elements of water across the \( \text{C}_\alpha=\text{C}_\beta \), a resonance extension of the \( \text{C}=\text{O} \). We have taken liberties with the name “Michael”. It is probably better to describe these reactions as conjugate addition and reverse conjugate addition. A close variation of this reaction eliminates alcohols instead of water. Other possibilities also exist.

6. Hemiacetal (or hemiketal) formation is an addition reaction to a carbonyl by alcohol, similar to carbonyl hydration and dehydration, Example 2. The reverse reaction reforms the carbonyl group and alcohol in an elimination reaction., A second alcohol can react with the hemiacetal/ketal and undergo an \( S_N1 \) reaction with the OH to form an acetal or ketal (Example 7, just below). The example shown here is an intramolecular reaction and typically forms rings of 5 or 6 atoms.
7. Acetal (or ketal) formation from a hemiacetal (or hemiketal). The “OH” becomes a water molecule leaving group that is replaced by an “OR” in an \( S_N1 \) reaction, producing an ether linkage. In the reverse reaction (acetal or ketal forming a hemiacetal or hemiketal) an alcohol leaving group is replaced by a water molecule in an \( S_N1 \) reaction. These are reversible reactions that require acid catalysis. Because arrows are used in both directions on the same bonds, we show the intermediate in this example. These reactions often occur when one sugar molecule “OH” connects to another sugar molecule at its hemiacetal site (such as galactose + glucose = lactose). Such linkages can go on for hundreds of sugar molecules (glycogen in animals and cellulose in plants).

8. a. Oxidation of \( \text{CH(OH)} \) to \( \text{C}=\text{O} \) (\( 1^\circ \text{ROH} \rightarrow \text{aldehyde}, 2^\circ \text{ROH} \rightarrow \text{ketone}, \text{hydrated aldehyde} \rightarrow \text{carboxylic acid} \)) with an equivalent of \( \text{NAD}^+ \). \( \text{NAD}^+ \) accepts a hydride via conjugate addition, quenching the positive charge on the nitrogen and forms \( \text{NADH} \). A base removes a proton from the adjacent oxygen atom allowing an elimination reaction to produce the \( \text{C}=\text{O} \) (or in Example 9, a \( \text{C}=\text{N} \)).
b. Reduction of C=O to CH(OH) with an NADH equivalent is the opposite of the above reaction. NADH is a hydride donor that becomes aromatic (forms NAD⁺) with the transfer of the nucleophilic hydride to the electrophilic C=O. A nearby acid protonates the oxygen completing the addition reaction.

9. a. Oxidation of an amine, CH(NHR), to imine (C=N-R) with an NAD⁺ equivalent that is reduced to NADH, followed by hydrolysis to a C=O. This is the opposite of 9b, below. The first step is similar to reaction 8a above with an alcohol. Overall, this is a transformation of an amine into a carbonyl group and a primary amine.
b. Formation of an imine, C=N-R, from a C=O, followed by reduction to CH(NHR) (an amine) with an NADH equivalent that is oxidized to NAD⁺. This is the opposite of 9a, above. The second step is similar to reaction 8b above with an alcohol. Overall, this is a transformation of a carbonyl group into an amine.

10. Decarboxylation of a β-ketocarboxylic acid, forming an enol, which tautomerizes to a keto group.
11. Decarboxylation of an $\alpha$-ketocarboxylic acid with TPP (thiamine diphosphate). Also includes both “TPP ylid” and “TPP enamine” chemistry. The enamine can be protonated to form an aldehyde or it can react with another carbonyl compound to make a new carbon-carbon bond (a larger carbohydrate in this game) The TPP ylid is also regenerated, which can react again or protonate to make TPP. See another reaction of $\alpha$-ketocarboxylic acids with Vit B-6 in Example 13.

TPP reaction with an a-ketoacid, decarboxylation and formation of enamine.

![Diagram](https://example.com/diagram.png)

Reaction of enamine nucleophile with a carbonyl electrophile followed by an E2-like reaction to form a new (larger) carbohydrate.

![Diagram](https://example.com/diagram.png)
12. a. Phosphorylation of an OH with an ATP equivalent (making an inorganic phosphate ester).

Complexing with Mg\(^{2+}\) can make one phosphorous atom more electrophilic and the other one a better leaving group. The Mg\(^{2+}\) is not required to show this reaction. Mg\(^{2+}\) is not used in the other reactions below, but it could be.

b. Dephosphorylation of an inorganic phosphate ester to an alcohol and phosphate.

c. An elimination reaction of a phosphate leaving group to make an alkene (pi bond). Could actually be E1 or E2.
d. acyl phosphate (inorganic anhydride) and formation of a thiol ester (like acetyl Co-A)

ADP leaving group

\[
\begin{align*}
\text{acyl-like substitution reaction} & : B \\
\text{organic-inorganic anhydride} & : B \\
\text{very reactive thiol ester (acetyl Co-A)} & : B
\end{align*}
\]

13. Vit B-6 reactions – 1. imine formation with \(\alpha\)-keto acid and the amino version of Vit B-6 (similar to Example 9b), 2. tautomerization (Example 1) and 3. imine hydrolysis to amino acid and the aldehyde version of Vit B-6 (similar to Example 9a).
Similar to Example 1.

Keto/enol tautomerization, makes imine on the other side.

Similar to Example 9a.

Hydrolysis of imine

Vitamin B-6 (aldehyde version)

α-amino acid

Addition of water
Three additional vit B6 reactions from aromatic imine

1. Decarboxylation

\[
\begin{align*}
\text{Decarboxylation} & \quad \text{Decarboxylation} \\
\end{align*}
\]
2. Elimination of side R group, like serine or threonine.

3. Epimerize a proton at the Cα position of an amino acid.
14. FAD / FADH₂ reduction of C=O to CH-CH or the reverse reaction oxidation of CH-CH to a C=O, FAD can be recharged with NADH.

Simplified mechanism of action for reduction of C=O by FADH₂ → FAD and mechanism for reforming FADH₂ from NADH.
15. Cytochrom P-450 oxidation of \(\text{sp}^3\) C-H bonds to make \(\text{sp}^3\) C-OH groups

The free radical-like oxygen atom abstracts a hydrogen atom from a C-H bond in the enzyme cavity, forming an O-H bond and a carbon free radical.

The carbon free radical abstracts hydroxyl (OH) from iron, making an C-OH bond where a C-H bond had been. The iron is reduced back at Fe\(^{+3}\) to begin the process all over again.

16. Cytochrom P-450 oxidation of C=C pi bonds (alkenes and aromatics) to make epoxides, which can be opened to diols.

The free radical-like oxygen atom adds to a C=C bond (alkene or aromatic) in the enzyme cavity, forming a O-C bond and a carbon free radical.

The carbon free radical abstracts the oxygen atom from the iron, making an epoxide ring. The iron is reduced back at Fe\(^{+3}\) to begin the process all over again. Reactive epoxides can be opened up to diols (more water soluble).


Sulfoxides, further oxidation is possible, all the way to sulfate, \(\text{SO}_4^{2-}\)

N-oxides, further oxidation is possible, all the way to nitrate, \(\text{NO}_3^{-}\)
18. Halogenation of sp\textsuperscript{3} C-H bonds to make C-X groups (X = Cl, Br, I) using halogenase enzymes.

![Reaction Diagram]

The free radical-like oxygen atom abstracts a hydrogen atom from a C-H bond in the enzyme cavity, forming an O-H bond and a carbon free radical.

The carbon free radical abstracts a halogen (Cl or Br) forming an unusual halogenated bioorganic molecule.

19. Halogenations of aromatic rings using X-OH to make sp\textsuperscript{2} C-X bonds (like thyroxine).

Iodide is stored in the thyroid gland. Iodoperoxidase enzyme makes it electrophilic (instead of nucleophilic iodide). It could react as hypoiouso acid, or the oxygen could be made into an even better leaving group if it was a phosphate (using ATP).

![Speculative Mechanism Diagram]

Speculative mechanism for iodinating tyrosine and formation of thyroxine from two tyrosines.

**Tyrosine**

**Diiodotyrosine - makes thyroxine**
20. S-adenosyl methionine (SAM-e) to methylate biomolecules.

21. Anti-oxidation reactions using vit E (fat soluble), vit C (water soluble), (also possible are glutathione, resveratrol and other bio-antioxidants).
3 types of problems are possible

1. Fill in the missing mechanistic details.
2. State what transformation occurred (and provide the missing mechanistic details).
3. Given the term, draw the step (and provide the missing mechanistic details).

Summary of Biochemical Topics having examples provided above:

1. Keto/enol tautomerization (proton transfer, resonance, proton transfer).
2. Carbonyl hydration (addition reaction of H₂O to a C=O) / carbonyl hydrate dehydration (elimination reaction forms a C=O and H₂O).
4. Claisen (makes a β-keto ester). Reverse Claisen (makes two esters). Often occurs using thiol esters in biochemistry (such as acetyl Co-A).
5. Reverse Michael reaction (elimination / dehydration) of β-hydroxy carbonyl compounds, an elimination reaction forms α,β-unsaturated carbonyl compounds and carries an aldol reaction one step farther. Michael reaction (addition / hydration) adds a nucleophile at the beta carbon of an α,β-unsaturated carbonyl compound (usually OH in this game) and adds a proton at the alpha carbon.
6. Hemiacetal (or hemiketal) formation (an addition reaction) of an alcohol to a C=O, forms an ether and an alcohol group on the same carbon. The reverse reaction reforms the carbonyl and alcohol from an elimination reaction. Typical ring sizes in the intramolecular reaction are 5-6 atoms. These transformations are very similar to carbonyl hydration / dehydration, presented in example 2 above.
7. Acetal (or Ketal) formation from a hemiacetal (or hemiketal) makes a water molecule leaving group that is replaced by an alcohol in an S₈₁ reaction, producing a second ether linkage. In the reverse reaction (acetal or ketal forming a hemiacetal or hemiketal) an alcohol leaving group is replaced by a water molecule in an S₈₁ reaction. Both are reversible reactions. Because arrows are used in both directions on the same bonds, we show the intermediate in this reaction.
8. a. Oxidation of CH(OH) to C=O with an NAD⁺ equivalent, which is reduced to NADH (opposite of 8b, below).
b. Reduction of C=O to CH(OH) with an NADH equivalent, which is oxidized to NAD\(^+\) (opposite of 8a, above).

9. a. Oxidation of an amine, CH(NHR), to C=N-R (an imine) with an NAD\(^+\) equivalent which forms NADH, followed by imine hydrolysis to a C=O (opposite of 9b, below).
   b. Formation of an imine, C=N-R, from a C=O, followed by reduction to CH(NHR) (an amine) with an NADH equivalent which forms NAD\(^+\) (opposite of 9a, above).

10. Decarboxylation of a \(\beta\)-ketocarboxylic acid, liberates CO\(_2\) and forms an enol which tautomerizes to a keto group.

11. Decarboxylation of an \(\alpha\)-ketocarboxylic acid with TPP (thiamine pyrophosphate = diphosphate). The “TPP ylid” adds to an \(\alpha\)-keto group, liberates CO\(_2\) and becomes a “TPP enamine”, which can protonate or react with a C=O of another carbohydrate.

12. a. Phosphorylation of an OH with an ATP equivalent (making a phosphate ester) – common in enzyme signaling
   b. Dephosphorylation of a phosphate ester to an alcohol and phosphate – common in enzyme signaling
   c. Making an alcohol OH into a phosphate ester makes it a better leaving group. An elimination (E1 or E2) or substitution (S\(_N\)2) reaction with a phosphate leaving group is possible.
   d. Formation of acyl phosphates (mixed anhydrides) also allows for exothermic carbonyl substitution reactions (can make thiol esters).

13. Vit B-6 reactions – Many reactions are possible. The only example shown is 1. imine formation with an \(\alpha\)-keto acid and the primary amine version of Vit B-6, 2. tautomerization to a different imine, and 3. imine hydrolysis to an amino acid and the aldehyde version of Vit B-6. The imine complex also allows for the loss of various groups on amino acids (the acid part, CO\(_2\)H, an alpha C-H proton, and certain amino acid side groups, -CH\(_2\)OH in serine, and -CH\(_2\)CH\(_2\)OH in threonine). Imines are also seen in Example 9 and \(\alpha\)-keto acids in Example 11.

14. FAD / FADH\(_2\) reduction of C=C to CH-CH or the reverse reaction oxidation of CH-CH to a C=C, FAD can be recharged with NADH.

15. Cytochrom P-450 oxidation of sp\(^3\) C-H bonds to make sp\(^3\) C-OH groups.

16. Cytochrom P-450 oxidation of C=C pi bonds (alkenes and aromatics) to make epoxides, which can be opened to diols.


18. Halogenation of sp\(^3\) C-H bonds to make C-X groups (X = Cl, Br, I) using Fe halogenase enzymes.

19. Halogenations of aromatic rings using X-OH to make sp\(^2\) C-X bonds (X = Cl, Br, I) (thyroxine).

20. S-adenosyl methionine (SAM-e) to methylate biomolecules.

Many of the steps of biochemical cycles can be explained with the above reactions.

Problem – Use $\text{B-H}^+ / \text{B}$ and any necessary cofactors to accomplish the following transformations using simplistic mechanisms (you do not need to show lone pairs of electrons and you can combine multiple steps using several arrows).

1. Reverse aldol reaction, then do a forward aldol reaction.

2. Hemiacetal formation, then reverse that reaction. Go back to a carbonyl and an alcohol.

3. Reverse Michael (dehydration) reaction, then forward Michael (hydration) reaction.

4. Keto/enol tautomerization to form an aldehyde, then carbonyl hydration reaction (twice).

5. Keto/enol tautomerization to form a new ketone, then hemiacetal formation reaction (twice).
6. Keto/enol tautomerization to form a beta keto acid → Decarboxylation → Keto/enol tautomerization to form an aldehyde

7. Keto/enol tautomerization to form an alpha keto acid → Reaction with TPP ylid → Decarboxylation to TPP enamine

8. Reverse Claisen (acyl substitution reaction) → Forward Claisen (acyl substitution reaction)

9. NADH reduction (addition reaction) → NAD\(^+\) oxidation to an aldehyde (elimination reaction)
10. Acetal formation (2 steps)

intermediate

overall = $S_N 1$

11. Acetal hydrolysis to hemiacetal (2 steps)

intermediate

overall = $S_N 1$

12. Vit B-6 imine formation (2 steps)

hydrolysis of imine to amino acid and the aldehyde version of Vit B-6 (2 steps)

13. Keto/enol tautomeration to new imine

14. Imine formation (2 steps)

NADH reduction to an amine
15. 

\[
\begin{align*}
R & \quad \text{NAD}^+ \\
\text{oxidation to an imine} & \quad \text{imine hydrolysis to an aldehyde} \\
(\text{elimination reaction}) & \quad (2 \text{ steps}) \\
& \quad (\text{addition and elimination reactions})
\end{align*}
\]

16. 

\[
\begin{align*}
\text{phosphorylation of 3\textsuperscript{o} alcohol with ATP} & \quad \text{formation of mixed anhydride} \\
& \quad (\text{acyl-like substitution reaction}) \\
\end{align*}
\]

17. 

\[
\begin{align*}
\text{elimination reaction to form an alkene alcohol (show as an E2 reaction)} & \quad \text{Claisen condensation} \\
& \quad (\text{acyl-like substitution reaction})
\end{align*}
\]

18. 

\[
\begin{align*}
\text{hydrolysis of phosphate ester to di-alcohol} & \quad \text{Claisen condensation} \\
& \quad (\text{acyl-like substitution reaction})
\end{align*}
\]

19. 

\[
\begin{align*}
\text{formation of mixed anhydride} & \quad \text{Claisen condensation} \\
& \quad (\text{acyl-like substitution reaction})
\end{align*}
\]
21. NADH reduction of keto group (addition reaction)

22. reverse Michael reaction (elimination reaction)

23. NADH hydride reduction of the conjugated C=C by a Michael reaction (addition reaction)
Methylates choline, norepinephrine, DNA (epigenetics)

Biotin (carboxylations)

Lipoic acid (acyl transfer)

**Possible reactions**

- Aldol
- Hemi-acetal formation
- Acetal formation
- Michael reaction
- Carbonyl hydration reaction
- Tautomeric changes (keto $\rightarrow$ enol and/or enol $\rightarrow$ keto) (enamine chem.?)

**Additional possibilities??**

- Enamine chemistry
- Imine chemistry
- Amine oxidation to carbonyl
- Phosphate ester / anhydride synthesis and hydrolysis (tyrosine, serine, ATP, throxine, etc.)

Lipid chemistry – glycerol esters, ethers, phosphates, carbohydrates
Problem - What kind of reaction occurred in each part? Use a simplistic mechanism to show how the reaction could have proceeded. The following problems are more limited questions from the original “carbohydrate game” and do not include many of the biochemical “co-factors”.

1. [Reaction Mechanism]

2. [Reaction Mechanism]

3. [Reaction Mechanism]

4. [Reaction Mechanism]

5. [Reaction Mechanism]

6. [Reaction Mechanism]

7. [Reaction Mechanism]

8. [Reaction Mechanism]

9. [Reaction Mechanism]

10. [Reaction Mechanism]

11. [Reaction Mechanism]

12. [Reaction Mechanism] (2 steps)
Problem – Use B-H⁺ / B: to accomplish the following transformation using simplistic mechanisms (you do not need to show lone pairs of electrons and you can combine multiple steps using several arrows).
dehydration (reverse Michael) → hydration (Michael)

keto/enol tautomerization (form an aldehyde) (2 steps) → reverse aldol

keto/enol tautomerization (form a ketone) (2 steps) → reverse aldol to form a 3 carbon ketone and 4 carbon aldehyde

hydration of carbonyl → dehydration of carbonyl hydrate
A few possible answers

reverse aldol

forward aldol (reverse steps)

hemiacetal formation (6 atom ring)

reverse reaction back to carbonyl & alcohol

dehydration (reverse Michael)

hydration (Michael)

keto/enol tautomerization (form an aldehyde)

keto/enol tautomerization (form a new ketone)

hydration of carbonyl

reverse reaction dehydration of diol
Problem - State what type of transformation occurred and show a simplistic arrow pushing mechanism for how it occurred, adding in any B: and/or B-H⁻ that is necessary. (an older problem set)

a. 

\[
\begin{align*}
\text{H}_2\text{O} & \xrightarrow{\text{H}_2\text{O}} \text{H}_2\text{O} \\
\text{O} & \xrightarrow{\text{O}} \text{O} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH}
\end{align*}
\]

b. 

\[
\begin{align*}
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH}
\end{align*}
\]

c. 

\[
\begin{align*}
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH}
\end{align*}
\]

d. 

\[
\begin{align*}
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH}
\end{align*}
\]

e. 

\[
\begin{align*}
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH}
\end{align*}
\]

f. 

\[
\begin{align*}
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH}
\end{align*}
\]

g. 

\[
\begin{align*}
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH}
\end{align*}
\]

h. 

\[
\begin{align*}
\text{R} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH}
\end{align*}
\]

i. 

\[
\begin{align*}
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH} \\
\text{OH} & \xrightarrow{\text{OH}} \text{OH}
\end{align*}
\]
Partial Answers
a. H\_2\text{O}H \xrightarrow{\text{reverse Michael}} \text{tautomeration} \xrightarrow{} \text{reverse aldol}

b. OH\_2\text{O}H \xrightarrow{\text{Michael}} \text{hemi-acetal formation}

c. OH\_2\text{O}H \xrightarrow{\text{tautomeration}} \text{tautomeration}

d. OH\_2\text{O}H \xrightarrow{\text{reverse Michael}} \text{dehydration} \xrightarrow{} \text{tautomeration}

e. OH\_2\text{O}H \xrightarrow{\text{aldol}} \text{reverse aldol}

f. OH\_2\text{O}H \xrightarrow{\text{hemi-acetal formation}} \text{acetal formation (2 steps)} \xrightarrow{} \text{acetal formation (2 steps)}

g. OH\_2\text{O}H \xrightarrow{\text{hemi-acetal formation}} \text{acetal formation (2 steps)} \xrightarrow{} \text{acetal formation (2 steps)}

h. R\_2\text{O}H \xrightarrow{\text{reverse acetal formation (2 steps)}} \text{reverse hemi-acetal formation}

i. OH\_2\text{O}H \xrightarrow{\text{reverse aldol}} \text{carbonyl hydration} \xrightarrow{} \text{carbonyl dehydration}