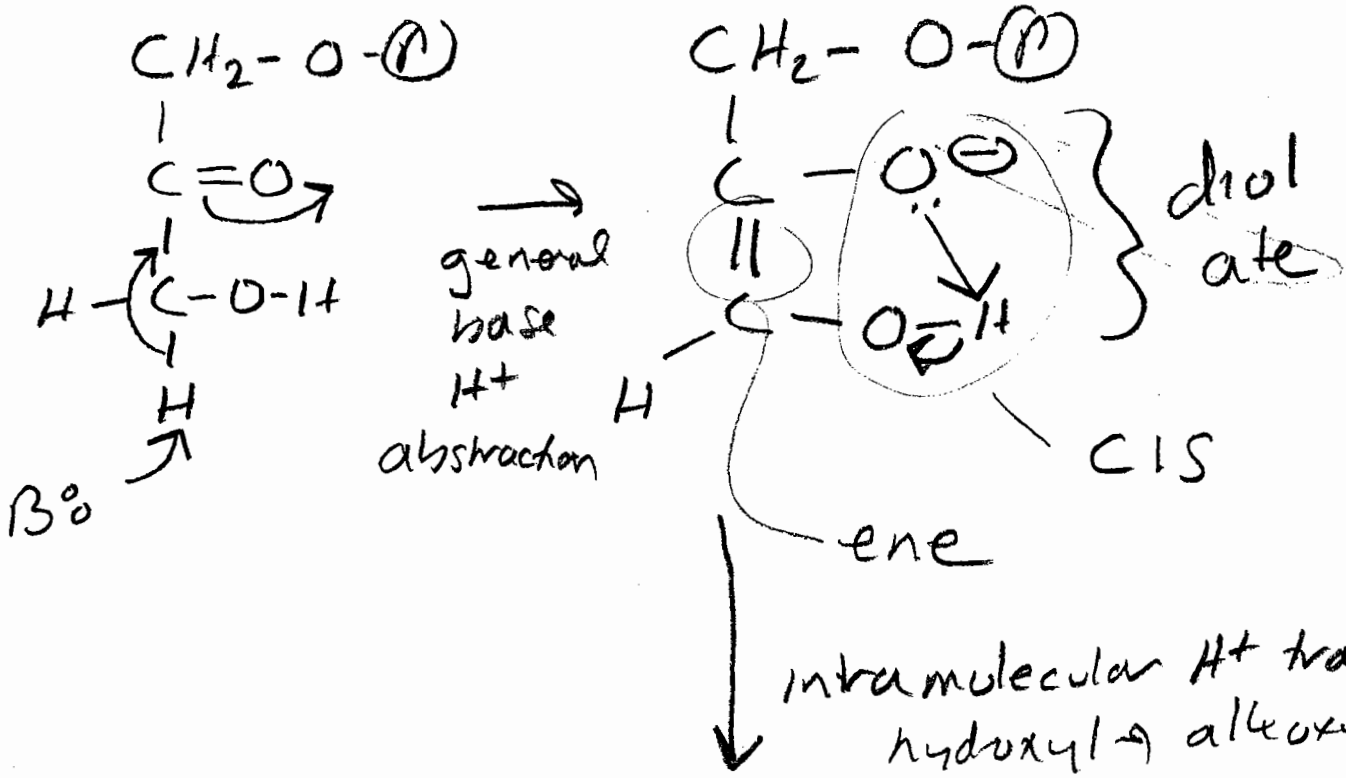
Reaction mechanisms in glycolysis/ citric acid cycle

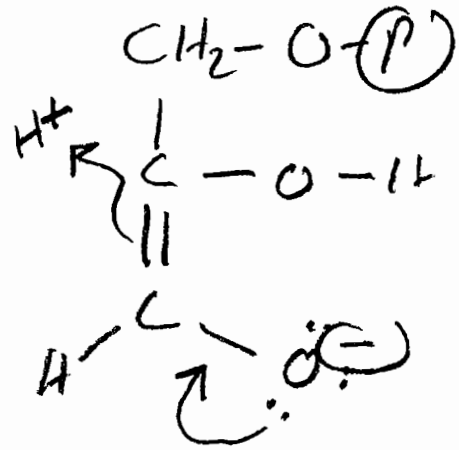
Objective: To understand the chemistry/logic of common metabolic transformations

- -kinase — P_i transfer to/from ATP/ADP
- -mutase — phosphoenzyme & diphosphorylated substrate intermediate
- -isomerase — general acid/base with cis-ene-diolate intermediate; aldo ⟷ keto sugar
- aldolase — C–C bond cleavage to keto & aldo sugars; reverse is aldol condensation
- dehydrogenase — hydride transfer to/from NAD^+
- enolase — general acid/base dehydration

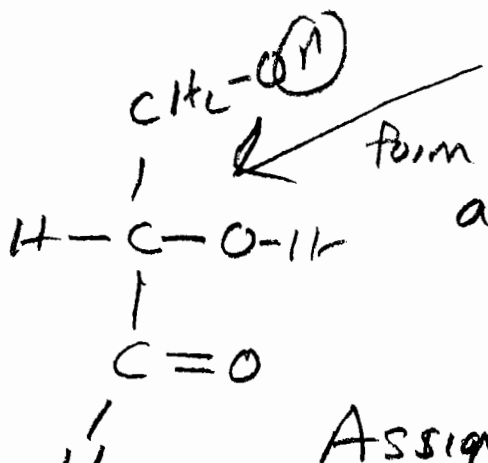
The Illustrious Isomerase

- Cis-ene-diolate is the key
- general acid-base chemistry





Still a cis-ene-diolate

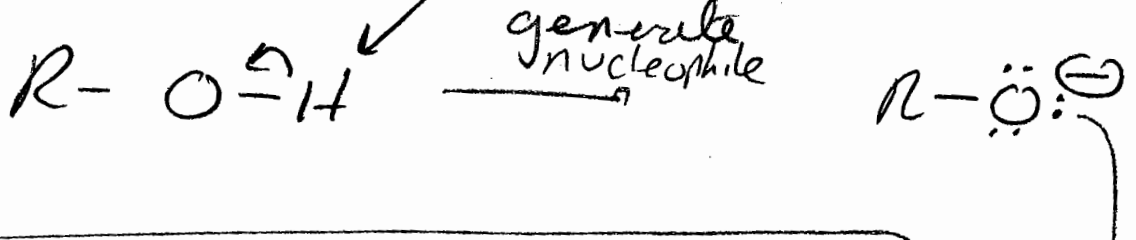


form aldehyde carbonyl, reprotonate ene at C2

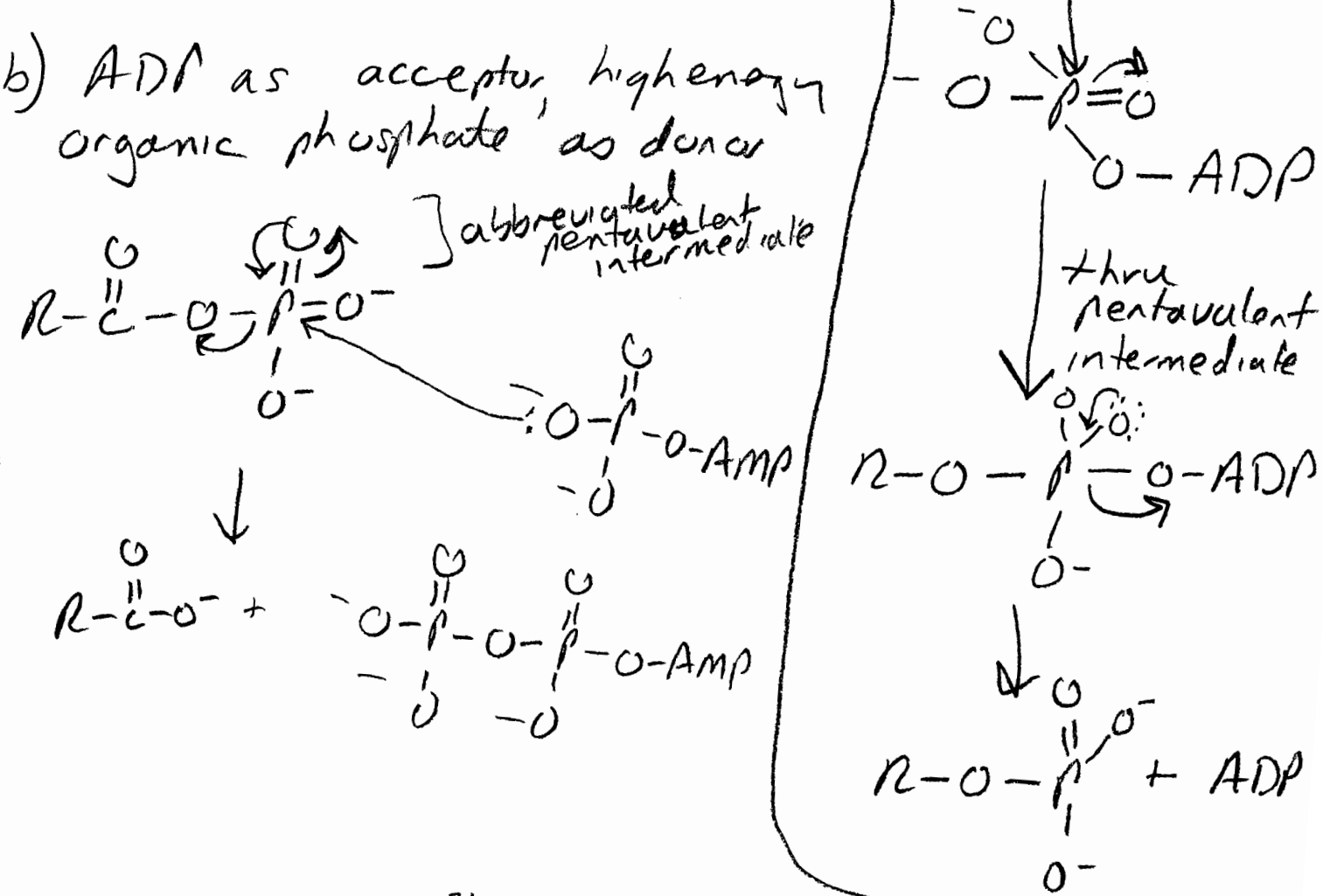
Assignment: Practice drawing this reaction going from aldehyde to ketone

The cunning kinase

a) ATP as phosphoryl donor, alcohol as acceptor



b) ADP as acceptor, high energy organic phosphate as donor

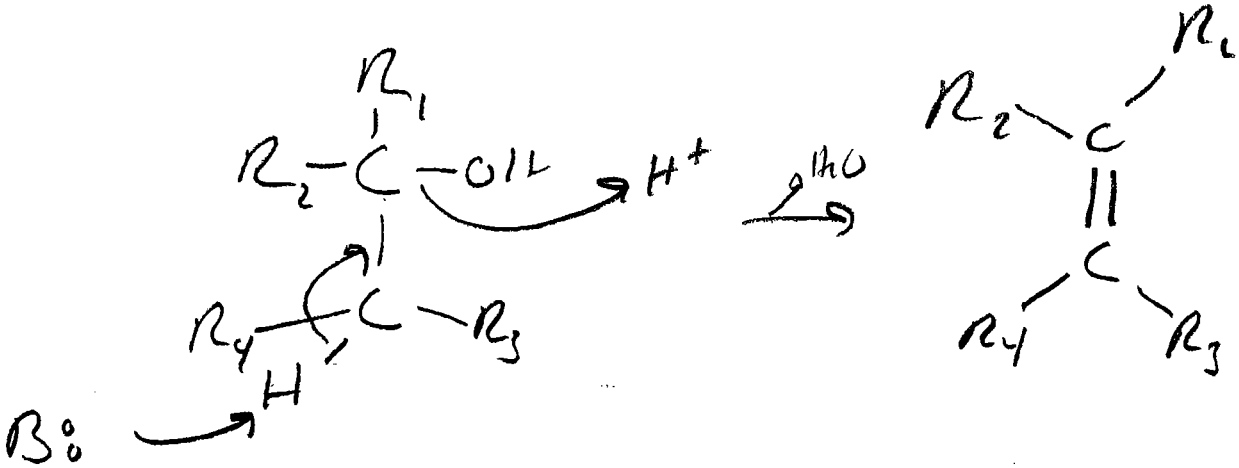


why is Mg^{2+} required for these reactions?

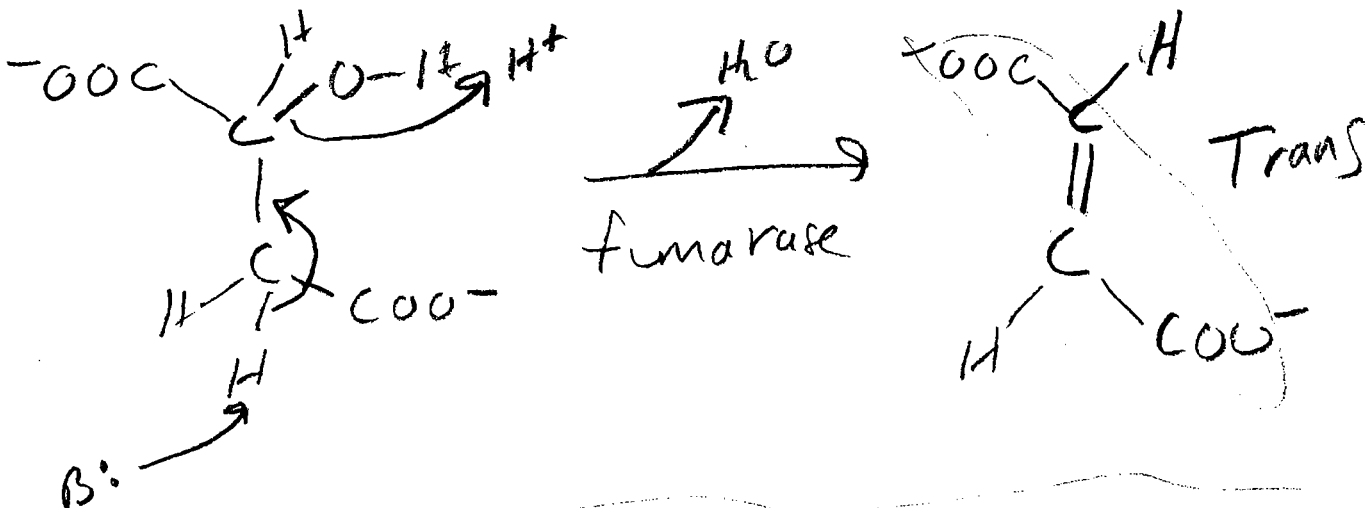
Remember the rules that make some organic phosphates high energy (acyl phosphates, guanidinium, enol)

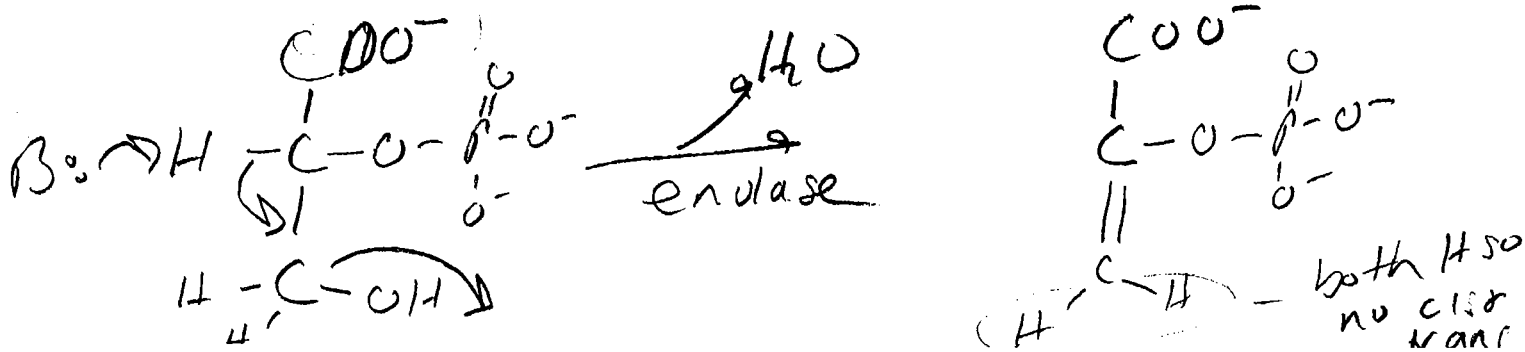
Enolase

dehydration strategy:



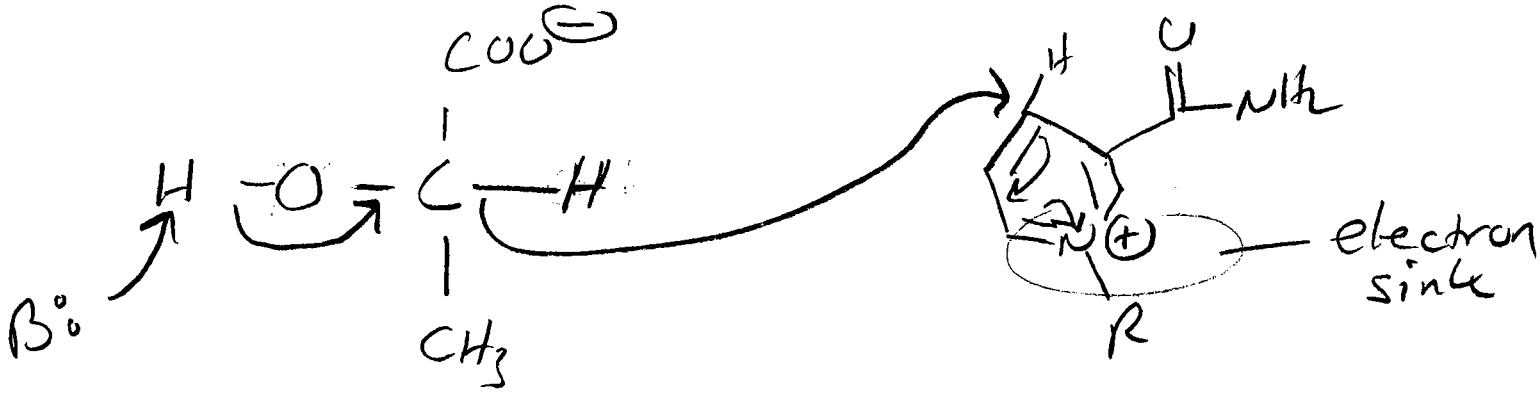
Stereochemistry can be important here. With 2-phosphoglycerate, product is achiral. But with fumarase, only *trans*-double bond is substrate/product



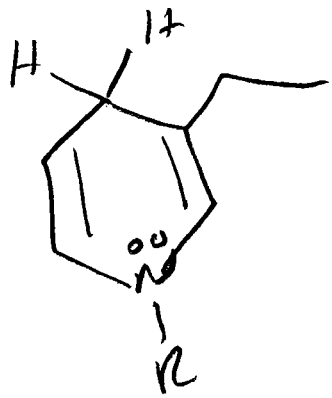


Dehydrogenase : hydride transfer

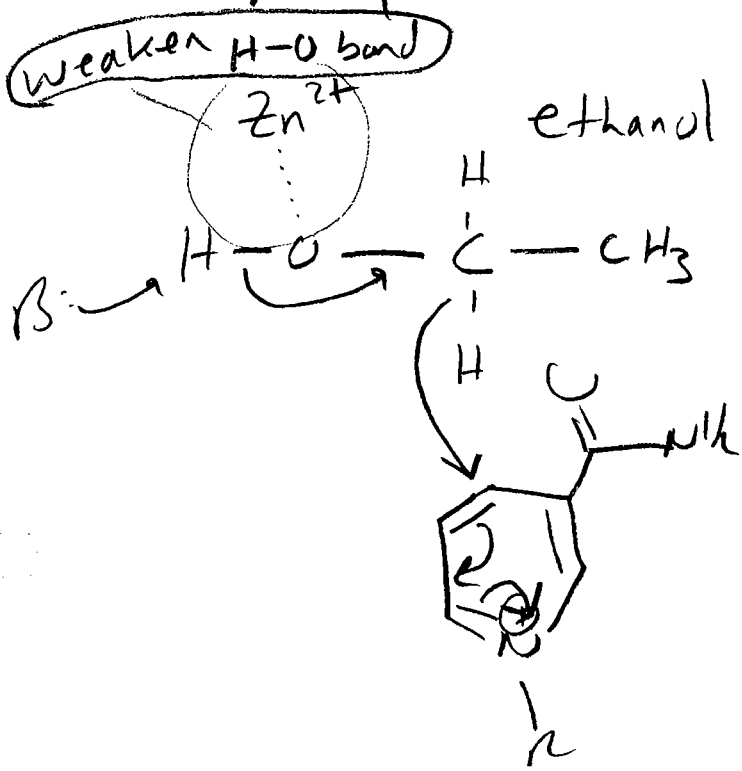
→ e.g., alcohol dehydrogenase

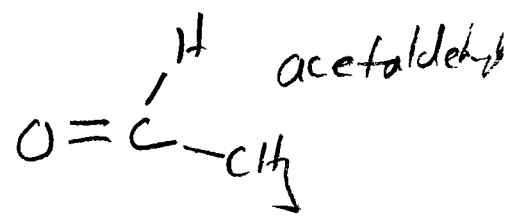


L- lactate



May be facilitated by zinc:





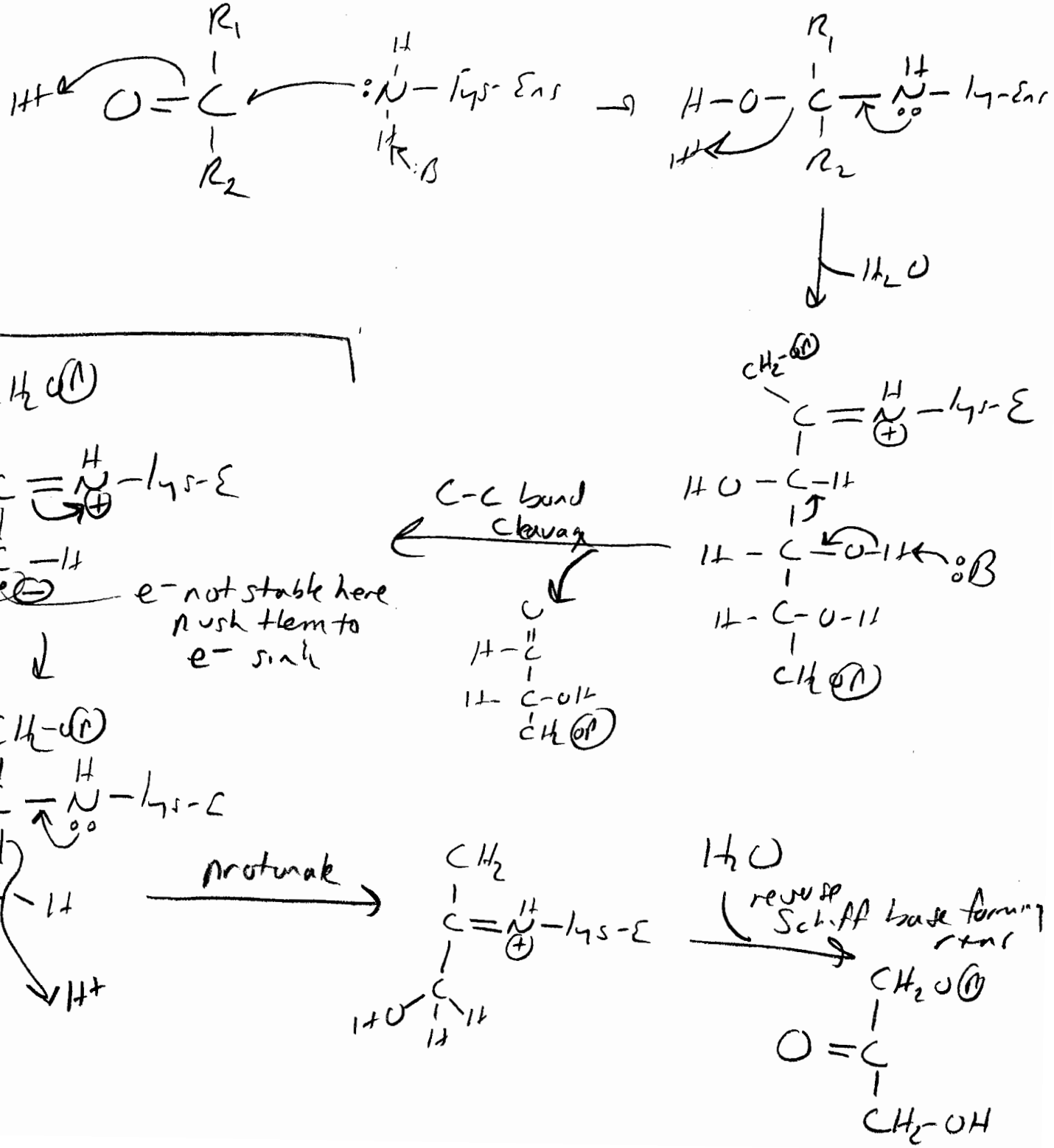
acetaldehyde

Assignment- practice these mechanisms in reverse direction

Aldolase

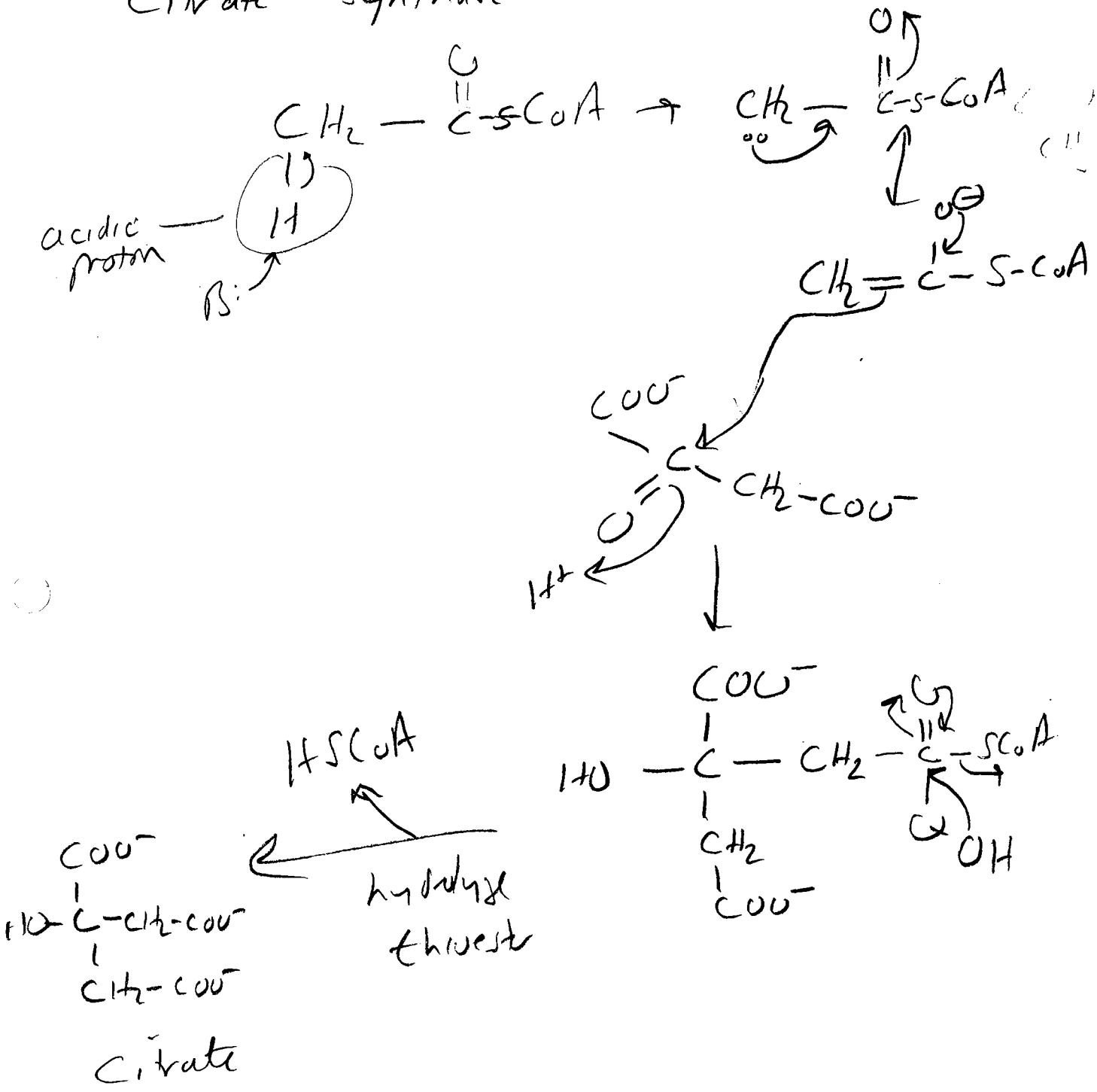
- Schiff base
- reverse of aldol condensation

1) Form Schiff base with ketone



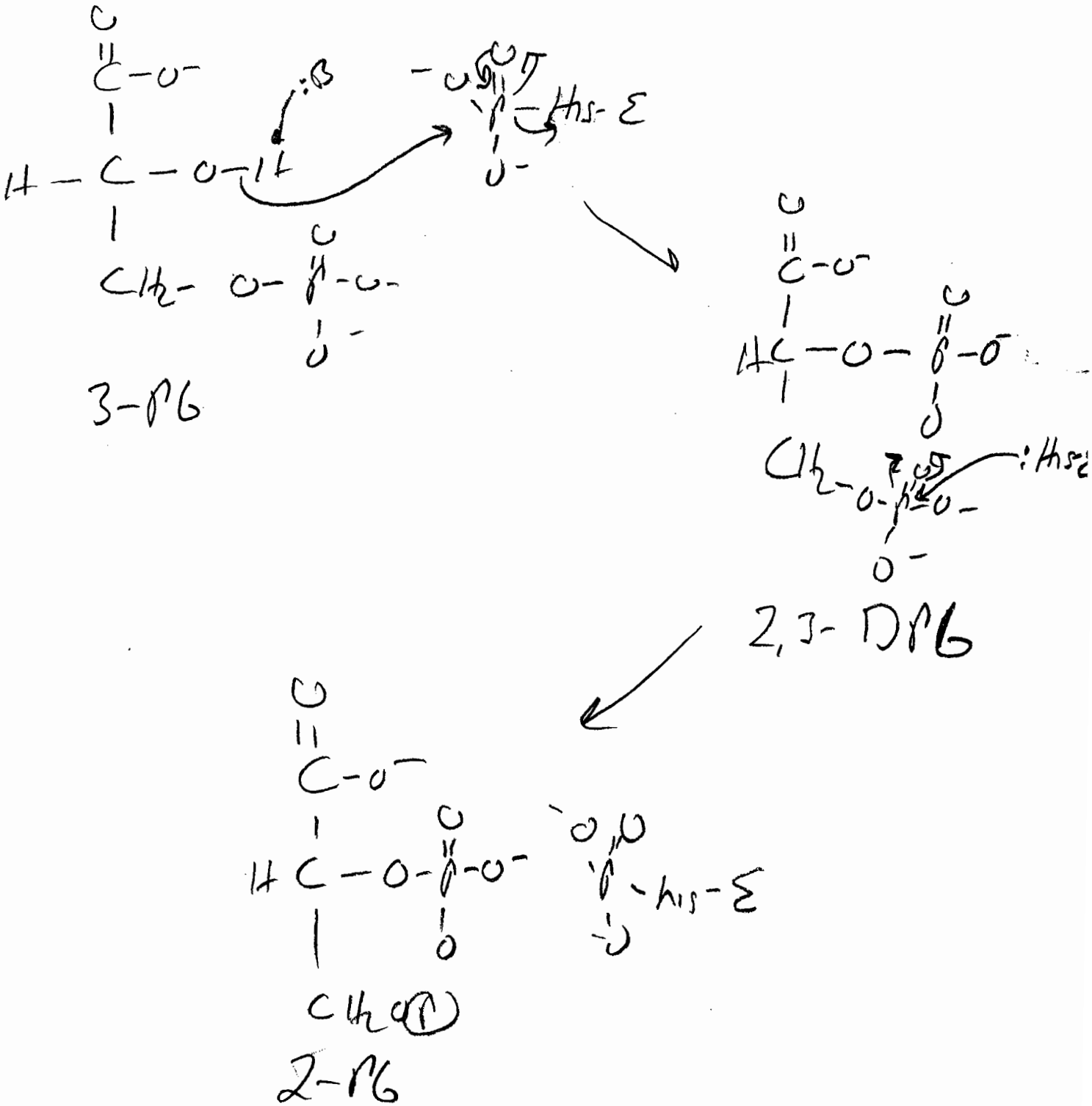
Claisen condensation

Citrate synthase



Mutase

intramolecular phosphoryl group transfer

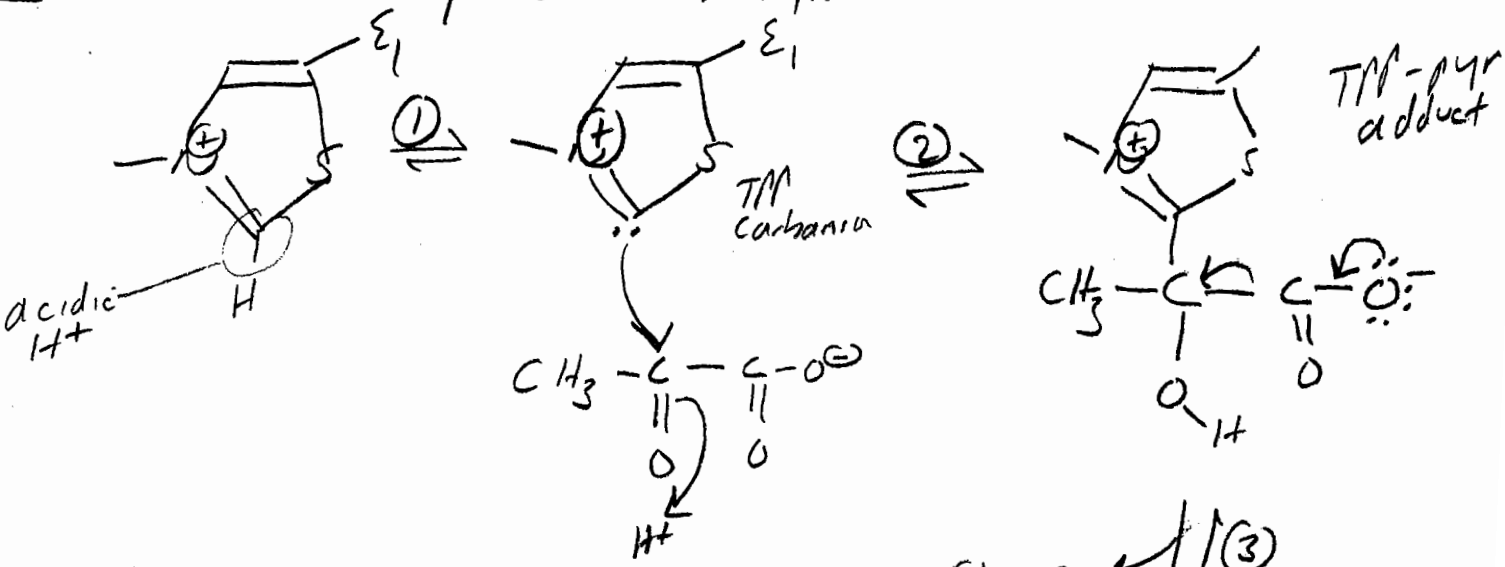


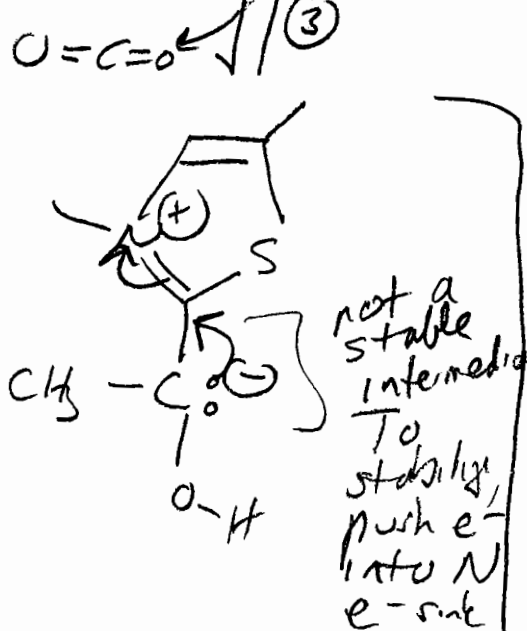
Mechanism of α-keto acid oxidative decarboxylation: pyruvate & α-KG dehydrogenases

- These dehydrogenases are more complicated than standard hydride transfer

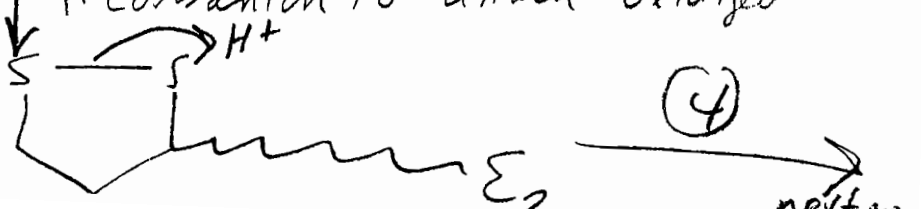
PDH rxn

I Start w/ decarboxylation on TPP:

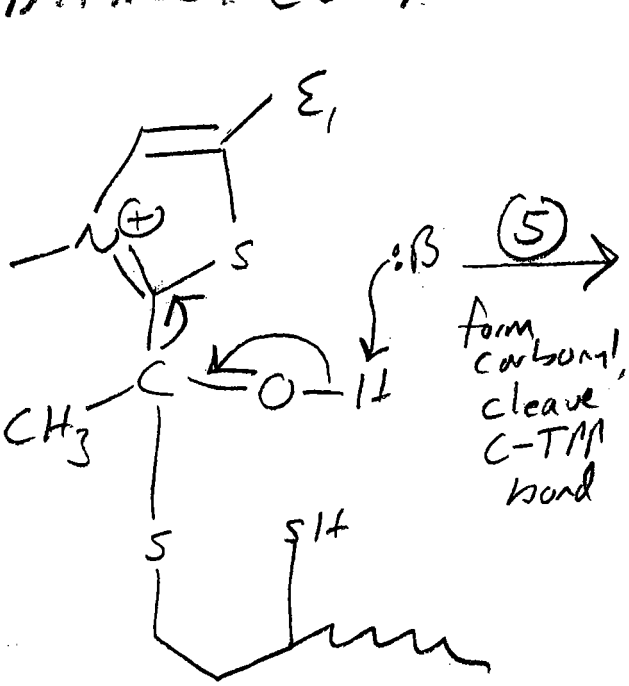


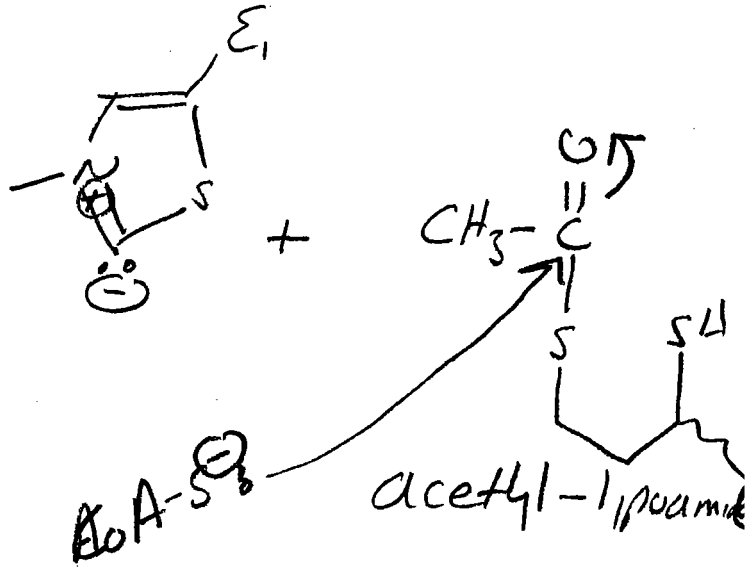


II Use TPP-hydroxyethyl carbanion to attack oxidized lipoamide

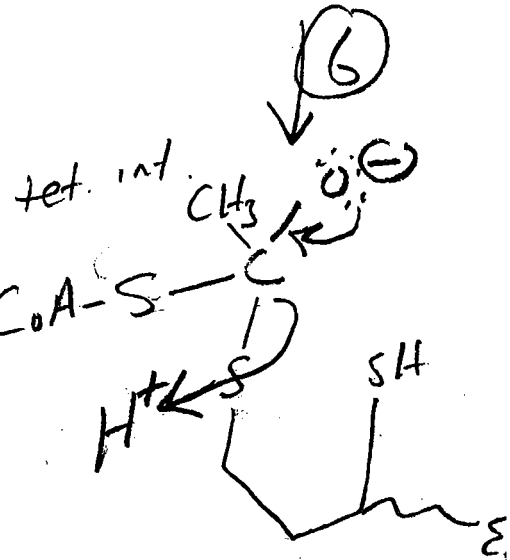


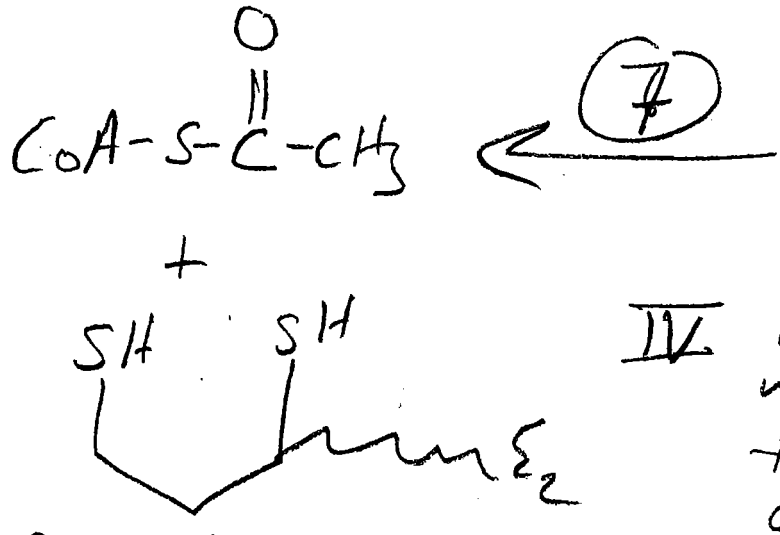
PDH mech (cont)





III / CoA comes in, attacks acetyl-lipoamide





IV oxidize lipoamide w/ FAD (don't need to know mechanism of this)