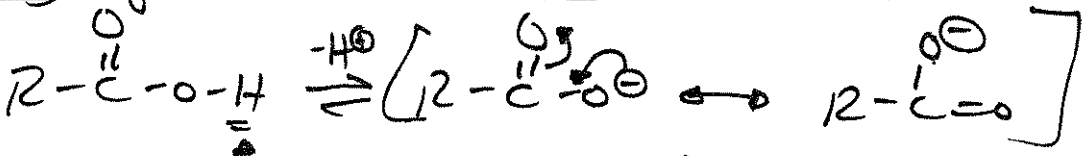
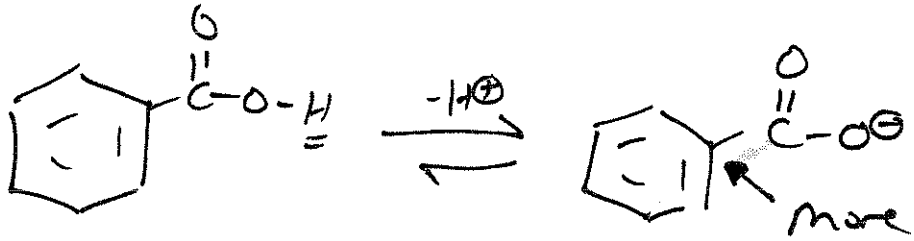
Chapter 16 — Structural Effects in Acidity + Basicity Revisited

Acidity of Aromatic Carboxylic Acids



(Review)

acidic because conj. base stabilized by resonance

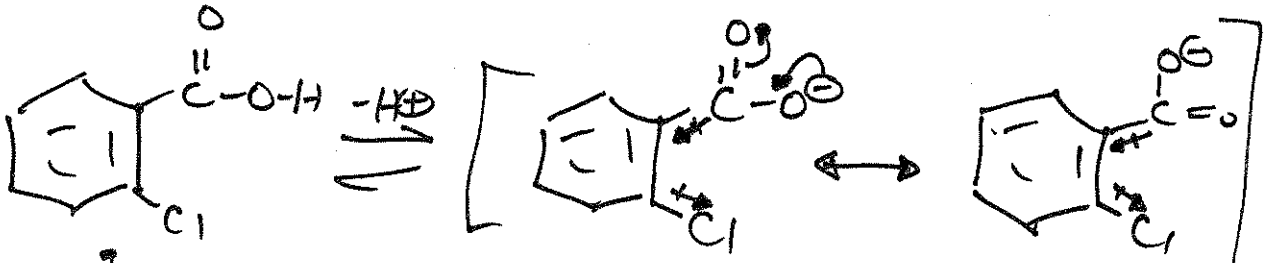


benzoic acid

more electronegative than R (alkyl)

- benzoic acid is more acidic than alkyl carboxylic acids

* If another electronegative group is added onto the ring, get even more acidic carboxylic acids

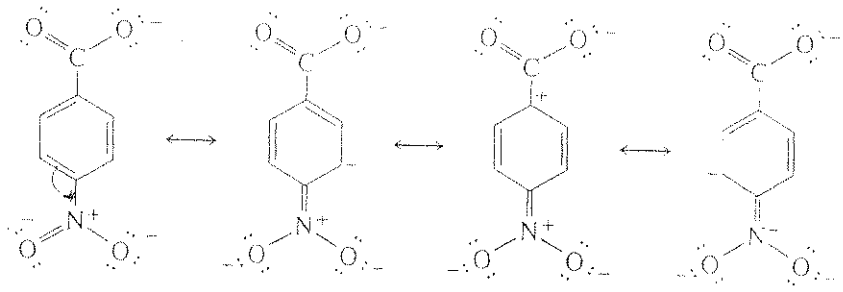


(o-chlorobenzoic acid - more acidic than benzoic acid)

- With some substituted benzoic acid derivatives, the position of the substituent makes a difference (o, m or p)

ortho meta para

ex: nitro group: $-NO_2$ (from text p 655)

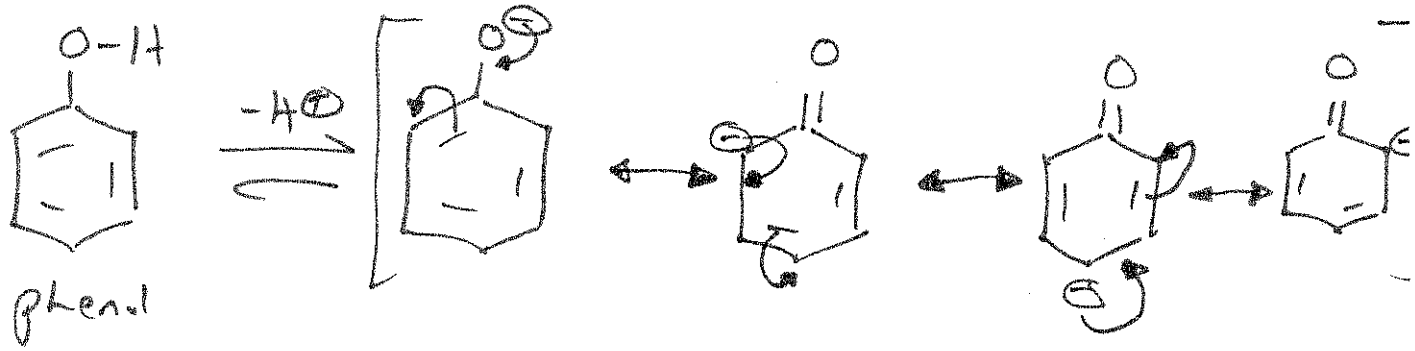


this resonance contributor puts a positive charge on the carbon atom to which the carboxylate group is bound

- NO_2 group in ortho + para position stabilize anion more than in meta position

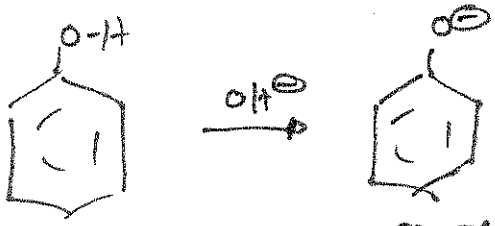
Phenol Acidity

- (Benzoic acid more acidic than phenol)



phenol

- phenol -O-H proton relatively acidic because conj. base stabilized by resonance (+ inductive effect of electronegative carbon in ring)
- Could separate a water insoluble phenolic cmpd from an organic solution by EXTRACTING with a basic soln (aqueous) to form a water soluble salt.

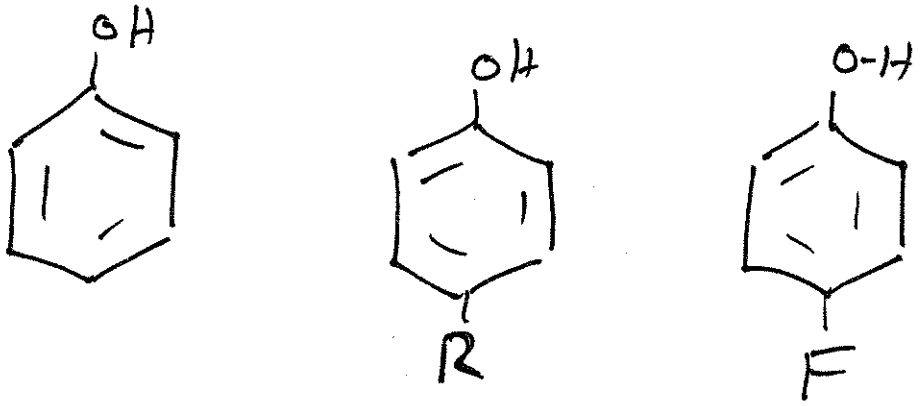


less water soluble

more water soluble

- Acidity of Phenols also effected by substitutions on the ring

⊛ Rank the acidity of the following phenols from MOST acidic to LEAST acidic.



- R → alkyl groups :- electron donating
  - makes phenol derivative slightly less acidic than phenol itself
- electronegative groups → like F (very electronegative), Br, I, NO_2 etc.
  - makes phenol derivative more acidic than phenol itself

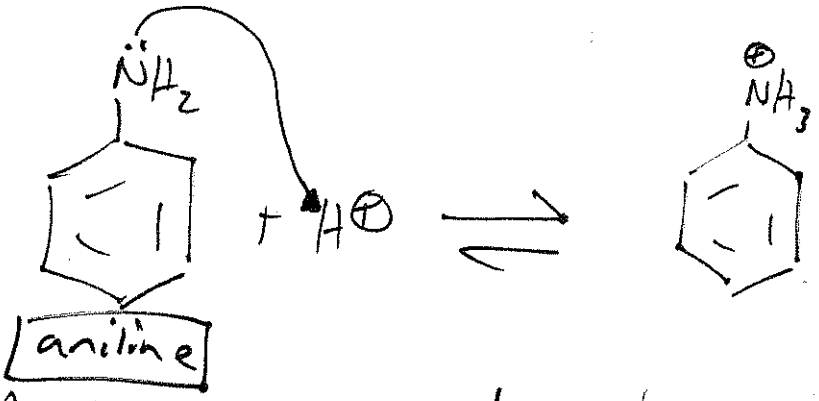
Aromatic Amines

Remember alkyl amine basicity Trend?

$R_2NH > RNH_2 > R_3N > NH_3$

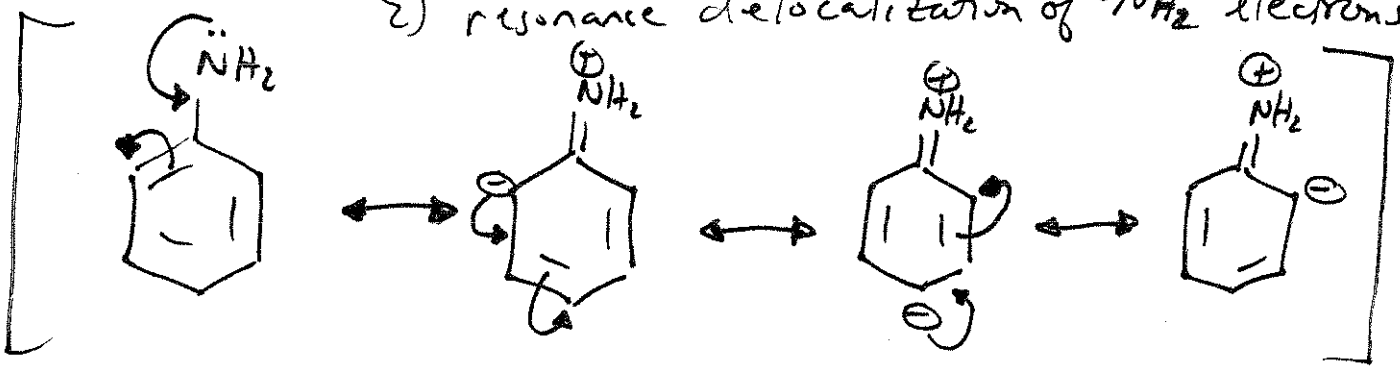
most basic — least basic

- Are aryl amines more or less basic than alkyl amines?



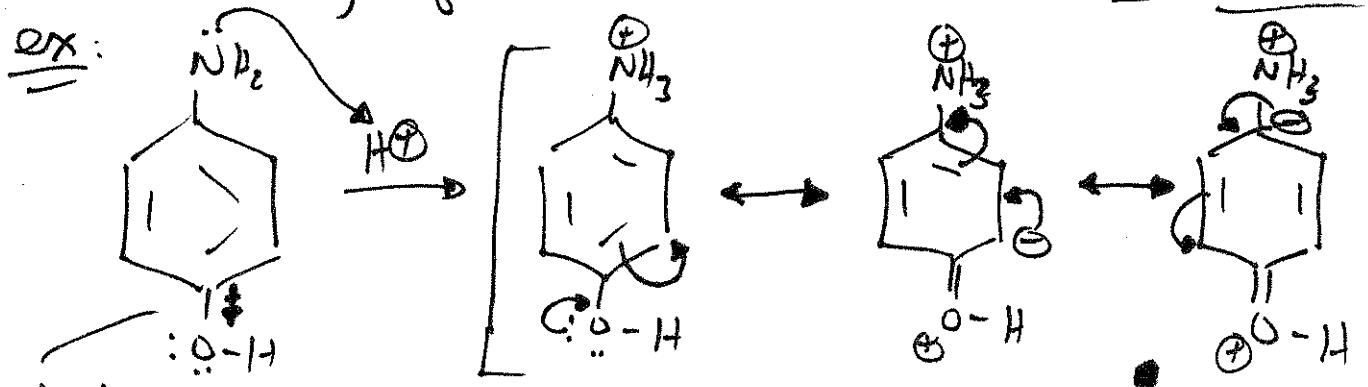
vs $R\text{-}\ddot{N}H_2 + H^{\oplus} \rightleftharpoons R\text{-}\overset{\oplus}{N}H_3$

- Aryl amines are <u>less</u> basic than alkyl amines because 1) electronegativity of ring attached to NH_2
  2) resonance delocalization of $-\ddot{N}H_2$ electrons



- Do you think ring substituents effect the basicity of aniline derivatives? <u>Sure does</u>!!

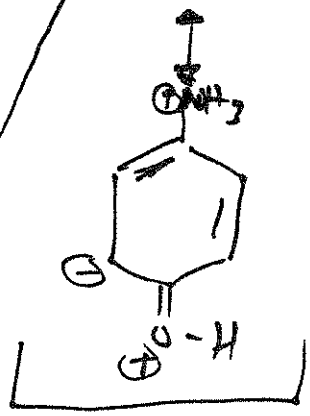
ex:



inductive effect, but also has <u>resonance</u> effect on protonated aniline derivative

- makes -OH substituted aniline a <u>STRONGER</u> base than aniline (e^- density higher close to $\overset{\oplus}{N}H_3$ of protonated aniline der.)

(Stabilizes ⊕ charge on $-\overset{\oplus}{N}H_3$)



(*) The larger the distance between the 2 carboxylic acid groups (in diprotic acids) the smaller the pKa difference between the two acidic groups.

What is the pKa?

→ It is the pH where the concentrations of an acid / conj. base pair are equal.

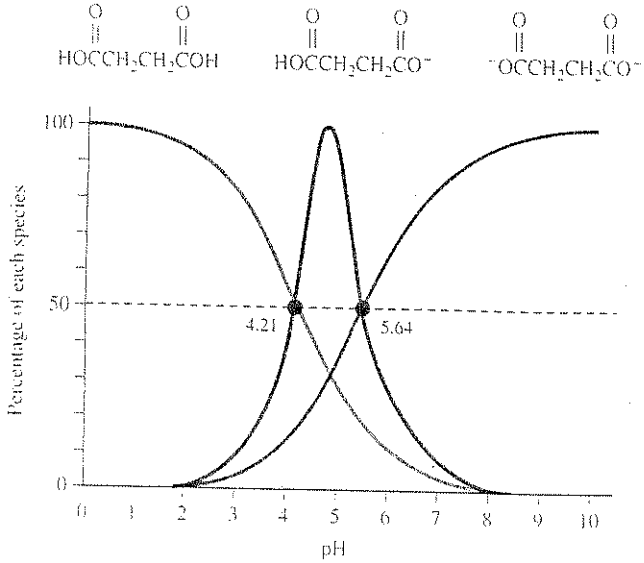
Henderson - Hasselbach Equation

If $[A^-] = [HA]$
Then $\frac{[A^-]}{[HA]} = 1$

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

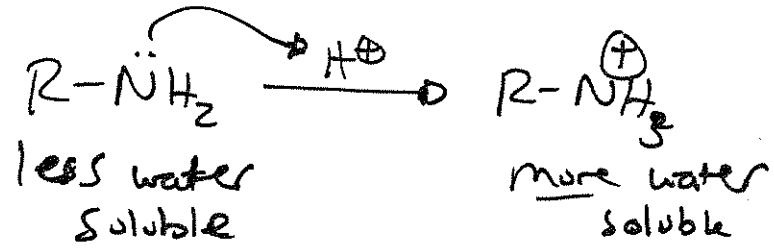
$\log 1 = 0$
Then $pH = pK_a$

Fig 16.1 p 663 →



- In polyprotic acids at different pH's will have different amounts of totally protonated, or mono or di anion.

- Can separate amines from other nonbasic compounds with acid protonation → makes a water soluble salt that can be extracted from an organic solvent



Acidity & Basicity in Polyfunctional Compounds

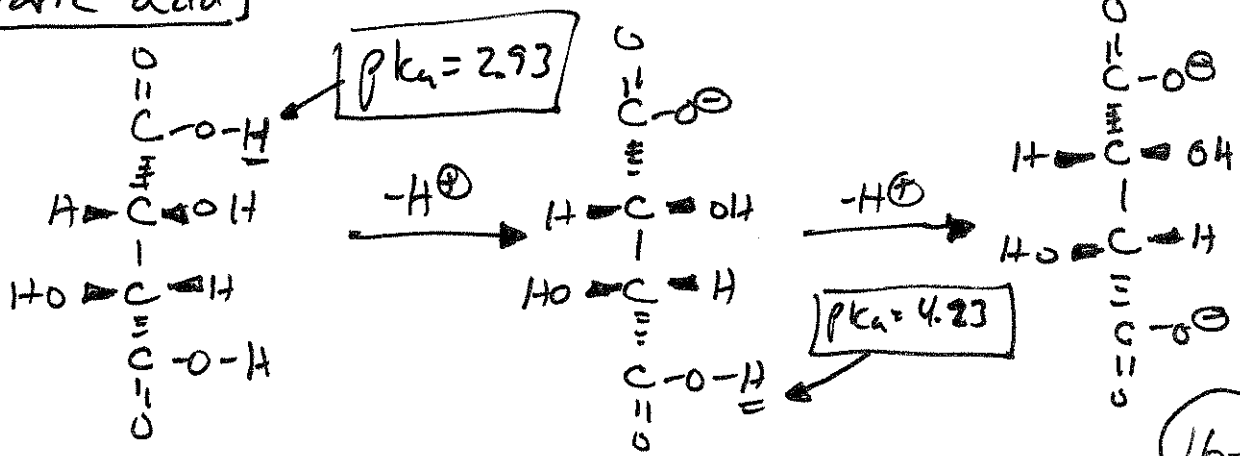
- Polyprotic acids have 2 or more pKa's

ex: triprotic acid
- → 1st is more acidic - lower pka → easier to remove
- → 2nd is less acidic - higher pka → harder to remove
- → 3rd is even less acidic - highest pka → hardest to remove

Why??

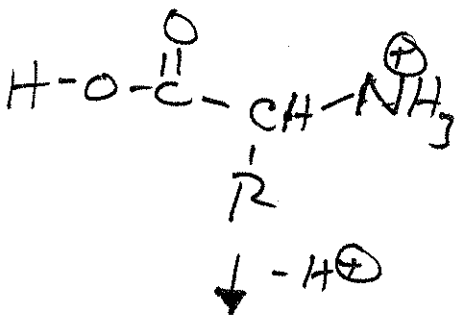
- Once the 1st proton is removed have an anion (neg. charge) its harder to remove another H⊕ from a cmpd with a negative charge.
- 1st proton approx 10 times easier to remove than 2nd proton

ex: tartaric acid



Amino Acids + Peptides as Polyprotic Acids

Amino acid structure ⟹ at **low pH**

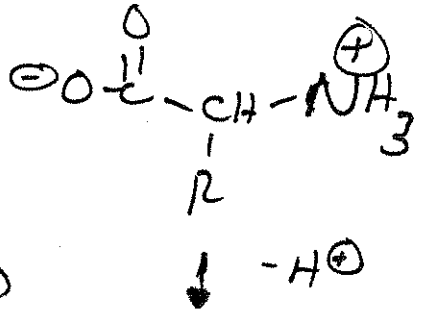


(where R = various substituents)

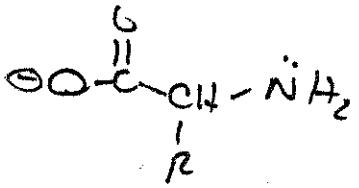
- High water solubility because charged

intermediate pH

(zwitterion)
+ charges cancel, so net charge = 0 (zero)



high pH



pI = Isoelectric Point

→ pH where the amino acid exists mainly as a zwitterion

- At the pI the amino acid will have no net movement in an electric field because the cmpd has no net charge.

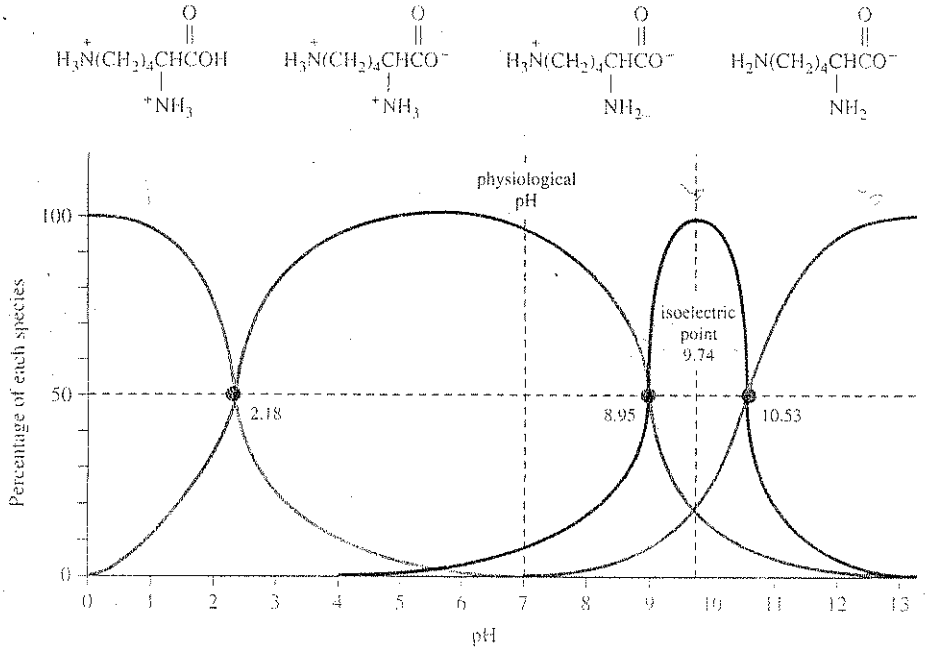
* Can determine pI by taking the average of the two pka's on an amino acid

$$pI = \frac{1}{2}(pK_{a_1} + pK_{a_2})$$

- Amino acids with additional amino or CO_2H groups have 3 pKas

→ pI is average of pKas where amino acid goes from +1 → 0 & 0 → -1

Figure 16.3
The relative amounts of the different acid–base forms of lysine as pH varies.



⊛ at physiological pH lysine has a net (+1) charge

Carbon Acids

Carbanions - carbon atom that has a VERY reactive nonbonding pair of electrons (strong nucleophile or strong base)

- We have seen already:

$$R-C\equiv C-H \xrightarrow{NaNH_2} R-C\equiv C^{\ominus}\,Na^{\oplus} + NH_3$$

↑ sp hybridized; more electronegative; easier to pull $H^{\oplus}$ off

Grignard & organo lithium reagents

ex: $R\text{-}MgBr \equiv R:^{\ominus}$ ← carbanion → very reactive

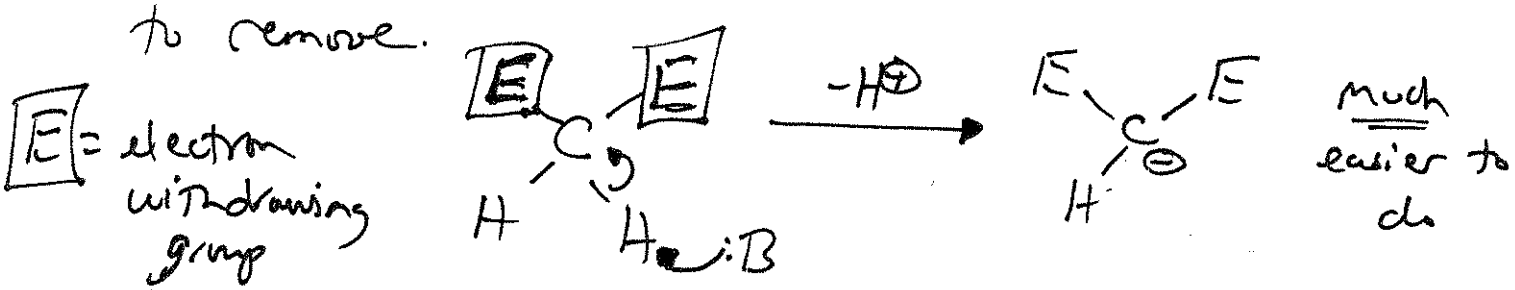
- sp^3 hybridized carbons without electron withdrawing groups near are very difficult to deprotonate

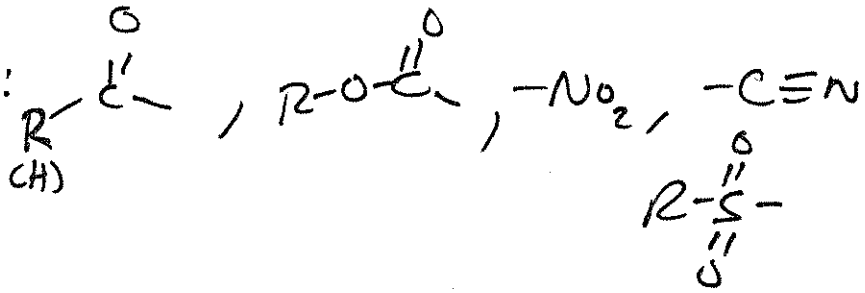
  Why? → no stabilization of e^- density

  ex: $R\text{-}CH_3 \xrightarrow{-H^{\oplus}} R\text{-}\overline{C}H_2$ very difficult to do (i.e. doesn't happen)

  ↑ very high pKa

- But, if a sp^3 hybridized carbon has electron withdrawing groups α to it, the proton is easier to remove.



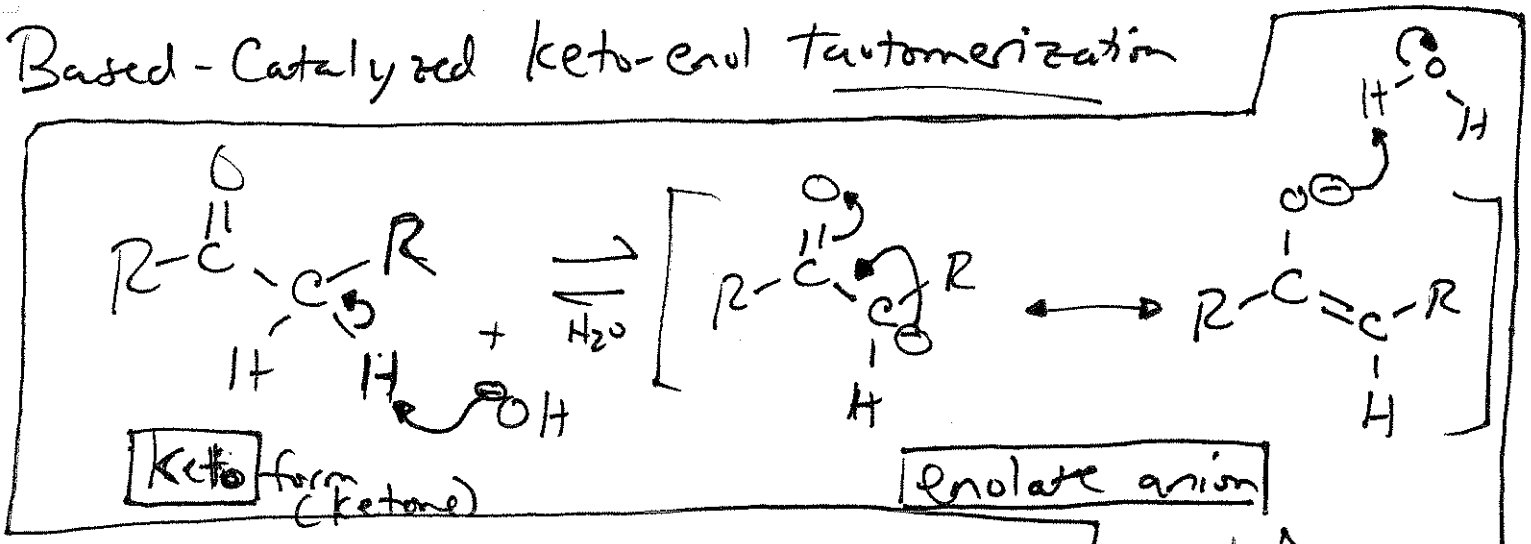
E = groups like: 

→ These groups have an inductive effect ± resonance effect to help stabilize anion formed, therefore the proton is easier to pull off (lower pKa)

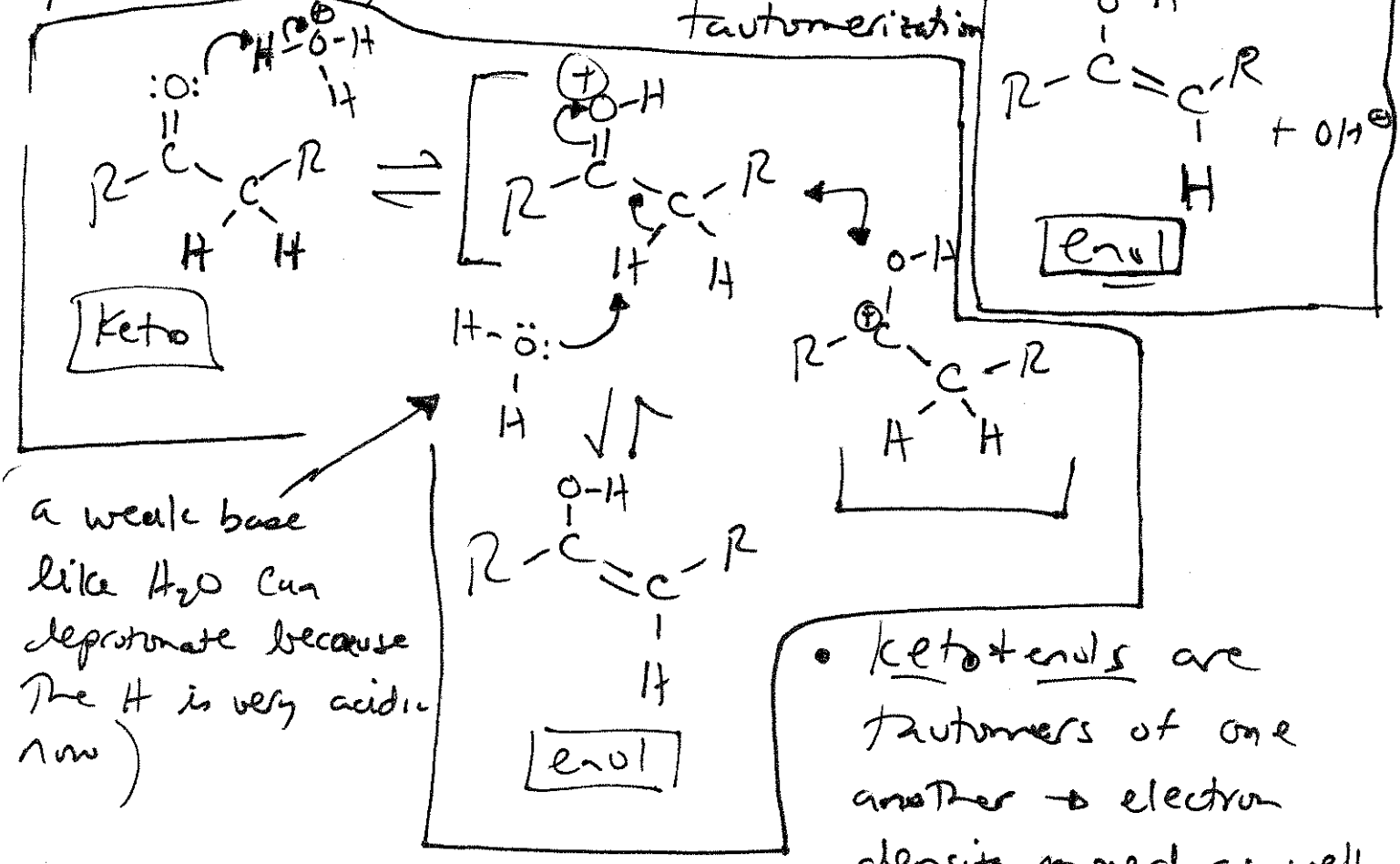
Enols and Enolates

(we've seen before)

- Based-Catalyzed keto-enol tautomerization



- Acid-Catalyzed keto-enol tautomerization



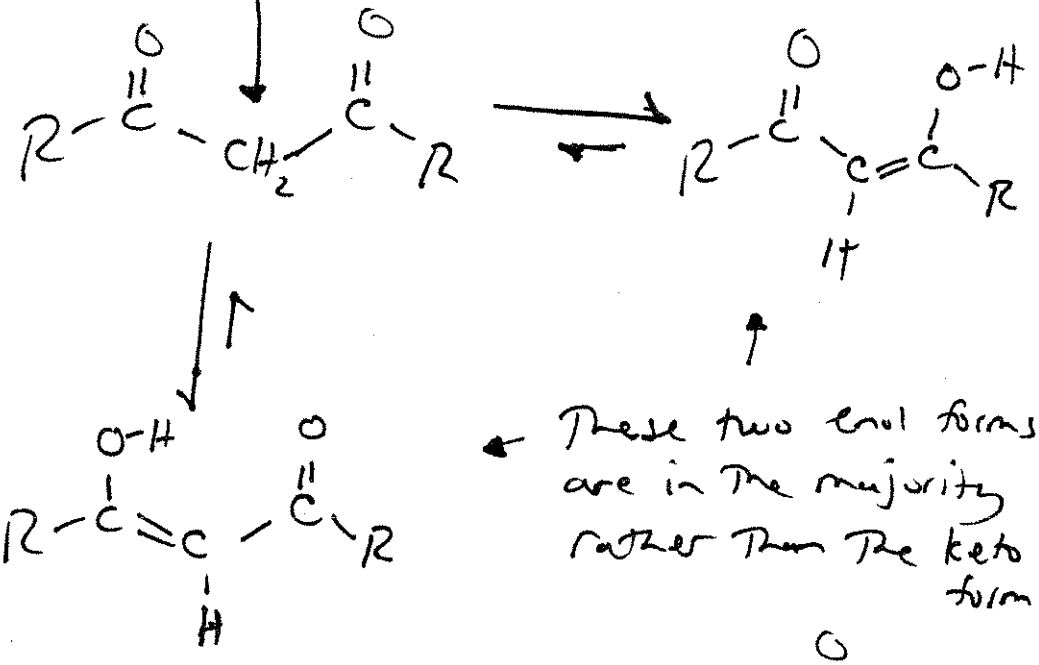
a weak base like H_2O can deprotonate because the H is very acidic now)

- keto + enols are tautomers of one another → electron density moved as well as a proton

Active Methylene Compounds

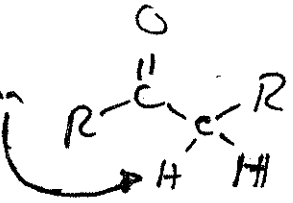
- methylene between two electron withdrawing groups

ex:



← These two enol forms are in the majority rather than the keto form

- Active methylene H's are more acidic than



Why?

→ Because enolate electron density can be delocalized into 2 electron withdrawing groups

- other functional groups besides ketones + aldehydes can also produce active methylene groups

($-NO_2$ > $-\overset{O}{\overset{\|}{C}}-R$(H) > $-C\equiv N$ > $-\overset{O}{\overset{\|}{C}}-OR$)

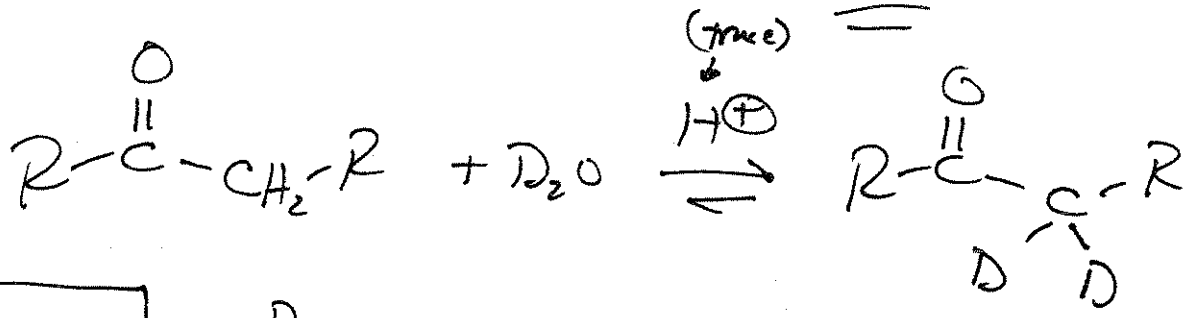
ex: $-NO_2$, $-C\equiv N$, esters

($-NO_2$ more effective than $-\overset{O}{\overset{\|}{C}}-R$ group)

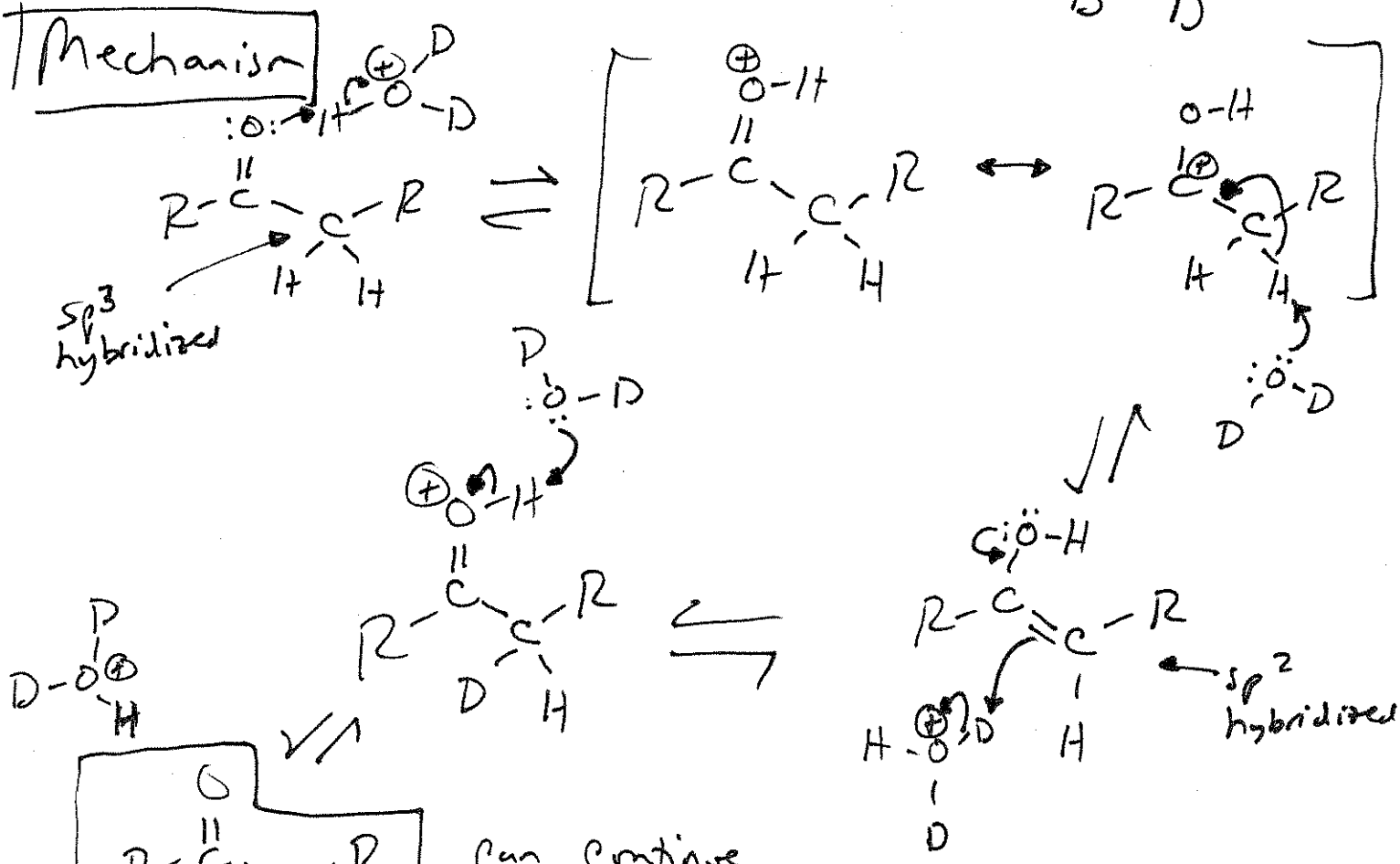
(but esters not as good at stabilizing anion as ketones + aldehydes are through resonance)

Enols and Enolates as Intermediates in the Exchange of Protons in Carbon Acids

- Detection of Proton Exchange with Deuterium
  - → normally can't tell enolization is occurring (in H_2O, H^+) but one can use D_2O, H^+



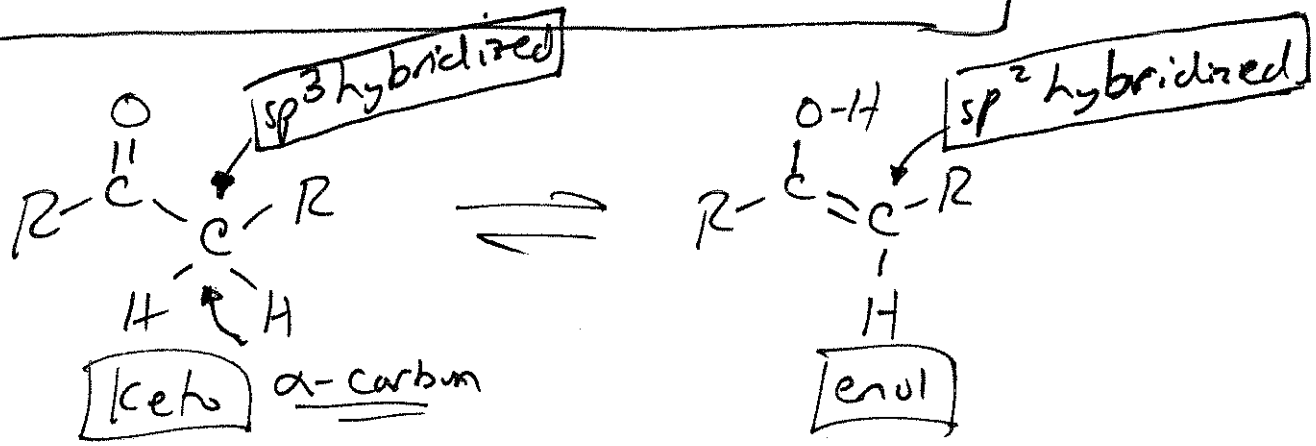
Mechanism



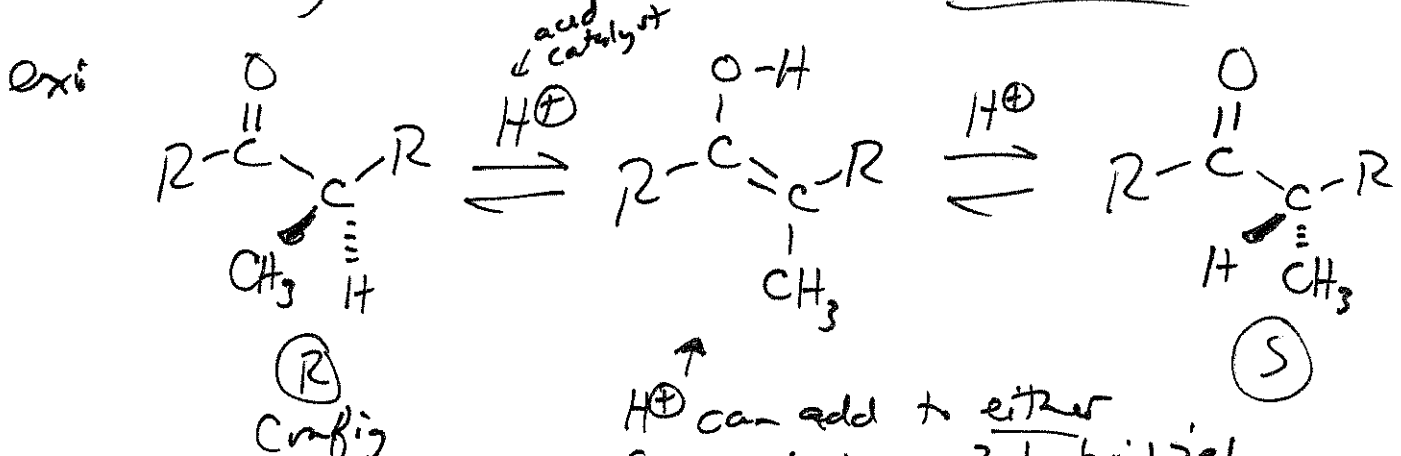
Can continue again

- Can use deuterium exchange to detect all sorts of exchangeable protons by ^1H-NMR (proton signal diminishes as exchange occurs) + by mass spectrometry (deuterium = 2 ; H = 1)

Racemization of Carbonyl Compounds with Stereocenters at The α-Carbon



- if have chiral center at α-carbon, that chirality is lost during tautomerization

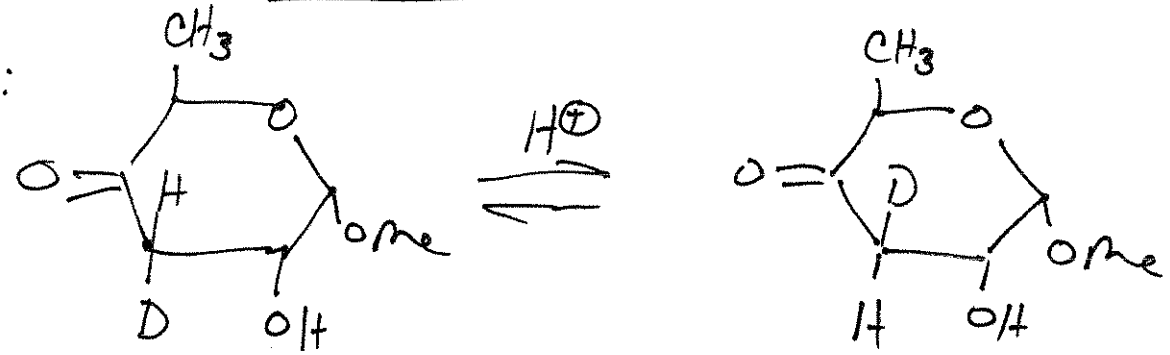


H^+ can add to either face of the sp^2 hybridized C atom → gives 50% (R) + 50% (S) configuration

- over time get racemic mixture

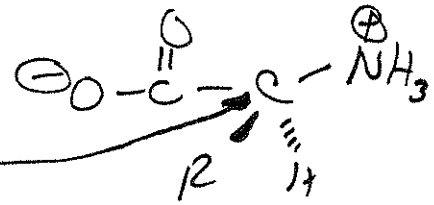
- If you have a cmpd with 2 or more stereocenters the process whereby one stereocenter undergoes inversion of config. by tautomerization is called **epimerization**

eg:



Racemization of Amino Acids (Fossil Dating Technique)

- Amino acids naturally have an (S) configuration at this stereocenter



→ after any living thing dies the amino acids racemize to the unnatural amino acids (R) config); the rate of this conversion varies – depends on temp. environment, tissue type

→ In stable life structures (shells, bones, teeth) in stable environments can tell approx. how long ago something died by ratio of natural vs unnatural amino acids.

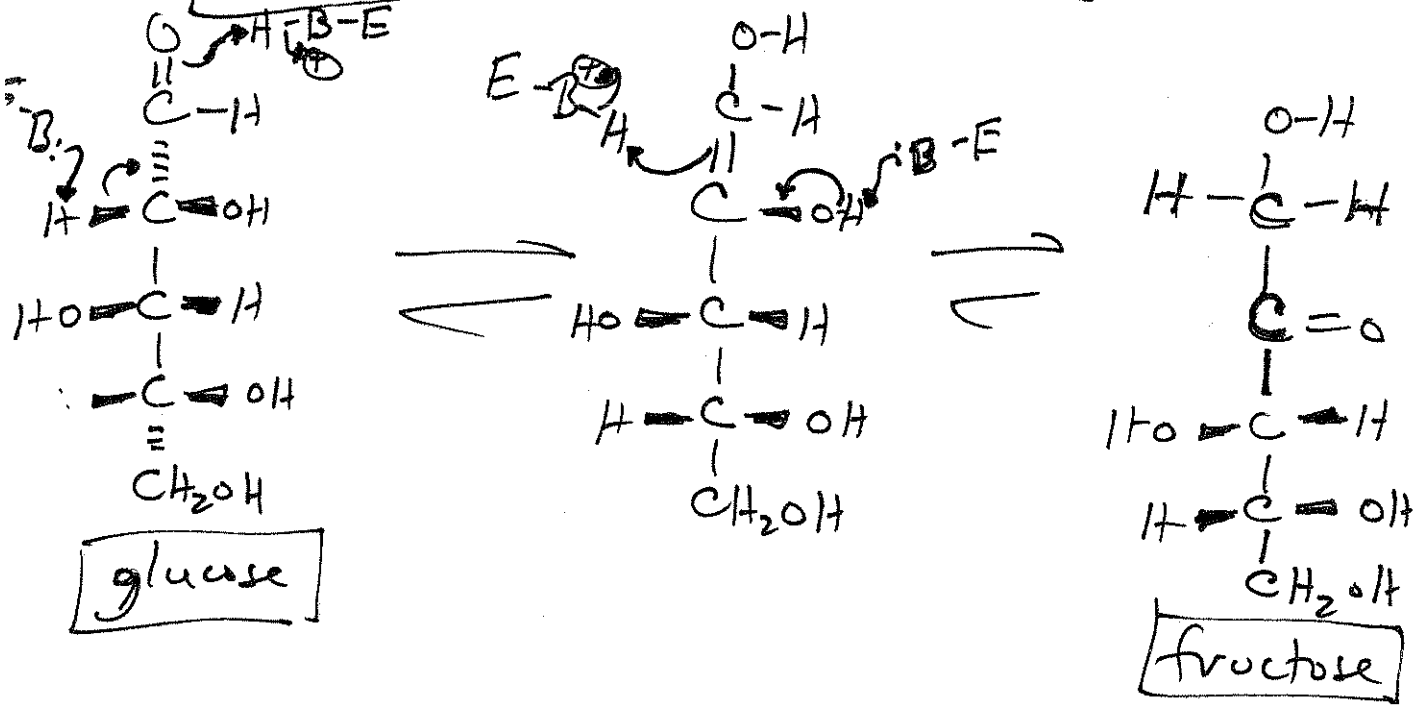
Biological Importance of Enolization Rxns

- Enzyme catalyzed enolizations are important in many biological processes

E = enzyme

ex in book → one step in glycolysis

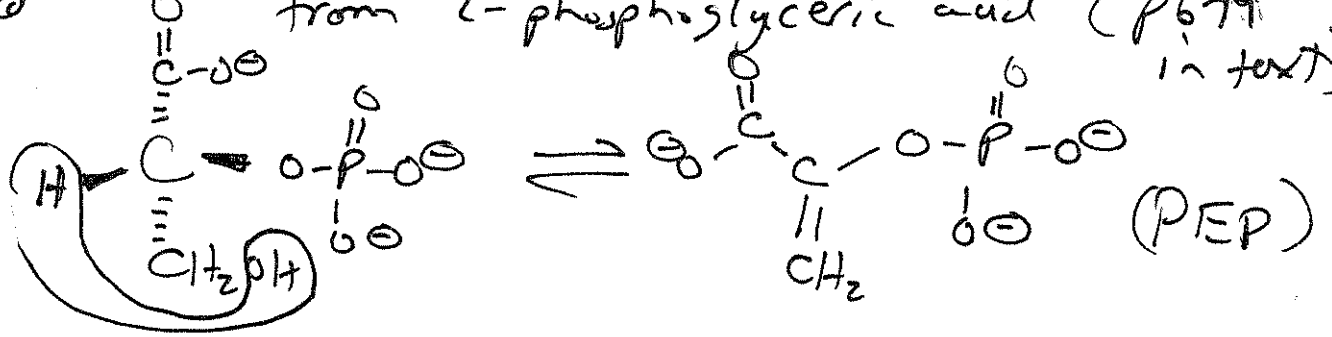
Conversion of glucose to fructose



glucose → fructose

- Another enol in glycosis → phosphoenol pyruvate (PEP) formation

Catalyzed by an enzyme



from 2-phosphoglyceric acid (p679 in text)

(PEP)

- net loss of H_2O involves an enolate intermediate