



Bio-110

Ex. 5

Acid Base reactions

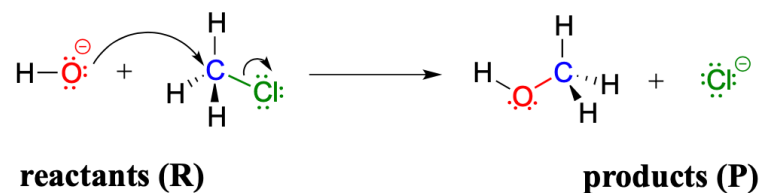
Discussion

Reaction Mechanisms in organic chemistry

- How reactions take place ?
- Which bonds break ?
- Which bonds form ?
- Why do they break or form ?
- Which order ?
- Which intermediate species ?



Reaction mechanism

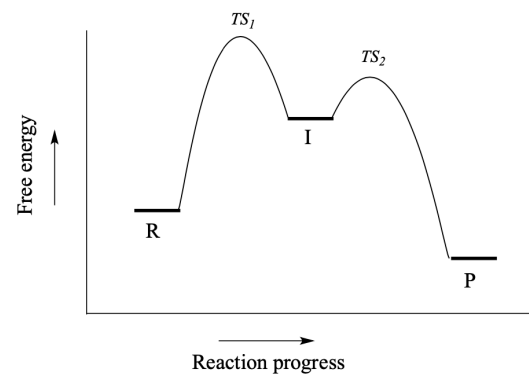
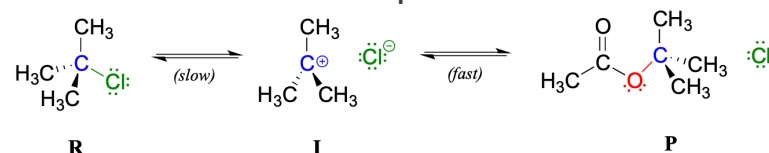


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Remember (!): curly arrows = movement of 2 electrons

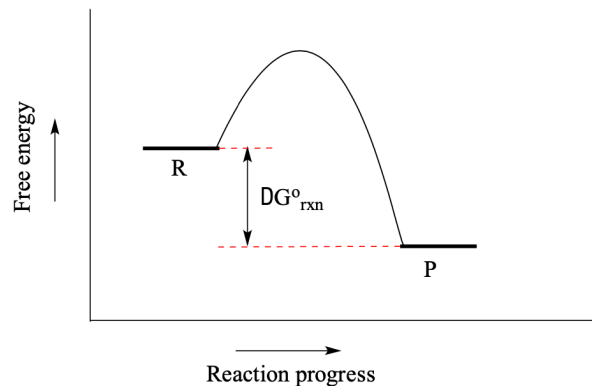
Multistep Reaction:



Thermodynamics Vs Kinetics

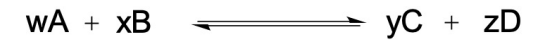
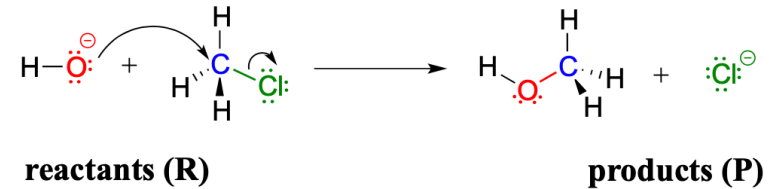
Thermodynamics

Difference in energy between reactants (R) and products (P): whether the reaction as a whole is uphill (**Endergonic**) or downhill (**Exergonic**).

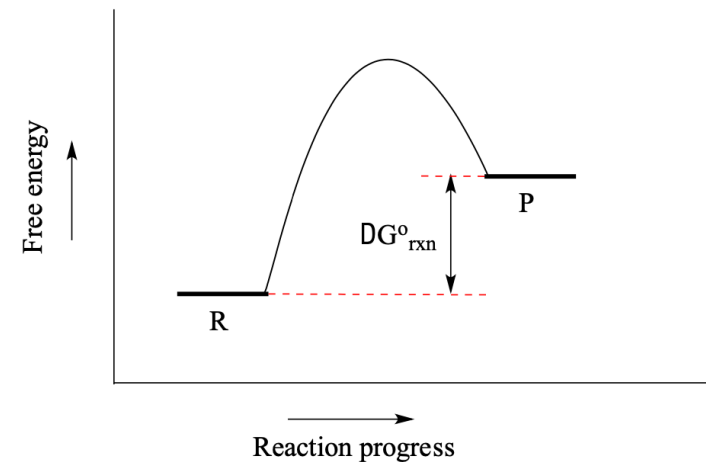


Exergonic

- Gibbs free-energy change is negative
- Energy releasing
- Thermodynamically favorable
- $K_{eq} > 1$



$$K_{eq} = \frac{[products]}{[reactants]} = \frac{[C]^y [D]^z}{[A]^w [B]^x}$$



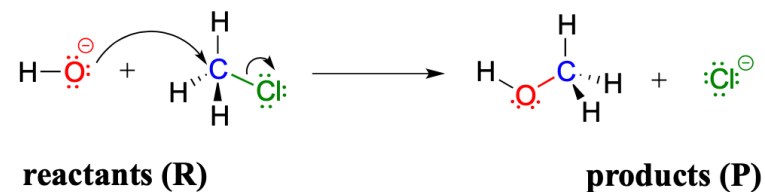
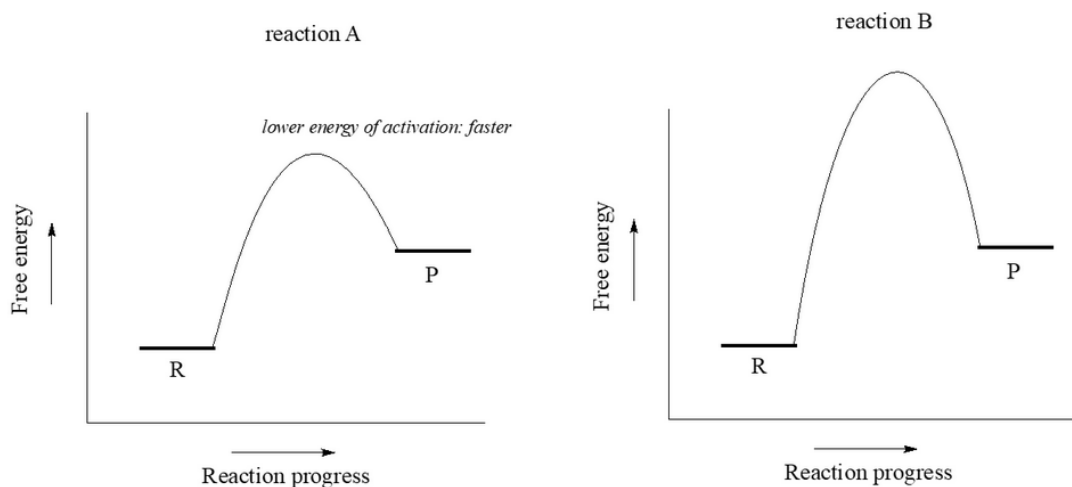
Endergonic

- Gibbs free-energy change is positive
- Energy absorbing
- Thermodynamically unfavorable
- $0 < K_{eq} < 1$

Thermodynamics Vs Kinetics

Kinetics

How fast does a reaction (and steps of reactions) take place. The higher the activation energy the slower the reaction.



In multi-step reactions the slowest step (highest activation barrier) is referred to as **rate-determining** step determining the speed of the reaction.

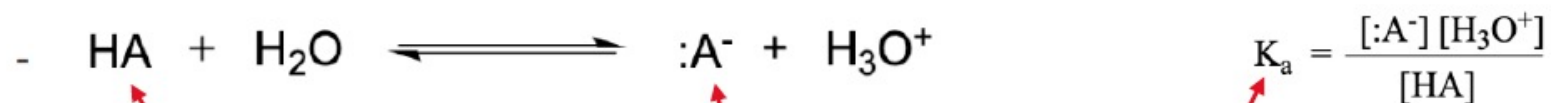
Acid base reactions

One of many types of reactions we will look at in this course:

Organic reactivity, Acid-base
Nucleophilic substitutions
Phosphate transfer reactions
Addition reactions
Nucleophilic -acyl substitutions
Reactions in alpha-carbons
Electrophilic reactions
Redox reactions

Acid base reactions

To judge how strong an acid is we consider the stability of the conjugate base!



Acid	Conjugate Base	Acidity (pKa)
Low Stability	High Stability	Strong Acidity (low pKa)
High Stability	Low Stability	Weak Acidity (high pKa)

Acid base reactions

To judge how strong an acid is we consider the stability of the conjugate base!

Factors to consider for the stability for the conjugate base:

1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms?
3. **Size:** Can the charge be localized over a larger/smaller space? (size of atom)
4. **Resonance effect:** Does the conjugate base have resonance structures that stabilize them?
5. **Inductive effect:** Do we have electron withdrawing or donating groups that stabilize/destabilize the compound.
6. **Hybridization and Energies** of occupied molecular orbitals. (For us acidity: $sp > sp^2 > sp^3$)

Electronegativity

Electronegativity: Are negative charges on electronegative atoms?

Electronegativity Trend

1A

2A

1

H

1.00797

3

Li

6.941

4

Be

9.0122

11

Na

22.9898

12

Mg

24.305

19

K

39.098

20

Ca

40.08

37

Rb

85.47

38

Sr

87.62

55

Cs

132.905

56

Ba

137.53

87

Fr

(223)

88

Ra

226.0254

21

Sc

44.956

22

Ti

47.90

39

Y

88.905

40

Zr

91.22

57

La

138.91

58

Ce

140.12

89

Ac

(227)

23

V

50.942

24

Cr

51.996

41

Nb

92.906

42

Mo

95.94

72

Hf

178.49

73

Ta

180.948

104

Rf

(257)

25

Mn

54.9380

26

Fe

55.847

43

Tc

(99)

44

Ru

101.07

74

W

183.85

75

Re

186.2

105

Ha

(260)

27

Co

58.9332

28

Ni

58.70

45

Rh

102.905

46

Pd

106.4

76

Os

190.2

77

Ir

192.2

106

Bo

(263)

29

Cu

63.54

30

Zn

65.38

47

Ag

107.868

48

Cd

112.41

78

Pt

195.09

79

Au

196.967

107

Hs

(264)

31

Ga

69.72

32

Ge

72.59

49

In

114.82

50

Sn

118.69

81

Tl

204.37

82

Pb

207.19

108

Uu

(269)

33

As

74.9216

34

Se

78.96

51

Sb

121.75

52

Te

127.60

83

Bi

208.980

84

Po

(210)

109

Uuh

(270)

35

Br

79.904

36

Kr

83.80

53

I

126.9045

54

Xe

131.30

85

At

(210)

86

Rn

(222)

5

B

10.811

6

C

12.01115

13

Al

26.9815

14

Si

28.086

31

Al

26.9815

32

Si

28.086

49

In

114.82

50

Sn

118.69

81

Tl

204.37

82

Pb

207.19

108

Uu

(269)

7

N

14.0067

8

O

15.9994

15

P

30.9738

16

S

32.064

33

As

74.9216

34

Se

78.96

51

Sb

121.75

52

Te

127.60

83

Bi

208.980

84

Po

(210)

109

Uuh

(270)

9

F

18.9984

10

Ne

20.179

17

Cl

35.453

18

Ar

39.948

35

Br

79.904

36

Kr

83.80

53

I

126.9045

54

Xe

131.30

85

At

(210)

86

Rn

(222)

2

He

4.0026

Directions of increasing electronegativity

0

collegearcade

To remember:
Electronegativity trend: $F > O > N > C$

Atom Size

Size: Can the charge be localized over a larger/smaller space?

Atomic Size

1	2																	18	19
3	4																	19	20
5	6																	21	22
7	8																	23	24
9	10																	25	26
11	12																	27	28
13	14																	29	30
15	16																	31	32
17	18																	33	34
19	20																	35	36
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535	536																	551	

Size and Electronegativity

Size: Can the charge be localized over a larger/smaller space?

Table 2.2 The pK_a Values of Some Simple Acids

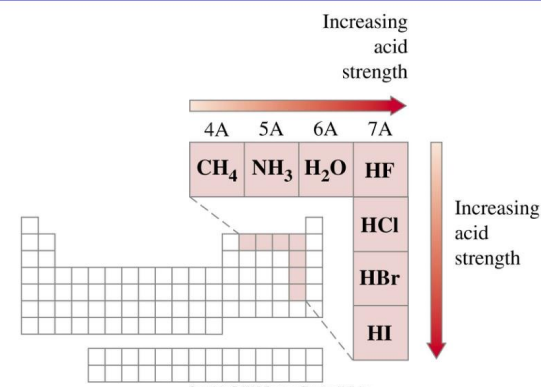
CH_4	NH_3	H_2O	HF
$pK_a = 60$	$pK_a = 36$	$pK_a = 15.7$	$pK_a = 3.2$
		H_2S	HCl
		$pK_a = 7.0$	$pK_a = -7$
			HBr
			$pK_a = -9$
			HI
			$pK_a = -10$

To remember:
Size trend: $\text{I} > \text{Br} > \text{Cl} > \text{F}$

The bigger the atom the more stable the negative charge of the conjugate base the more acidic the acid.

13

Periodic Trends in Acid Strength



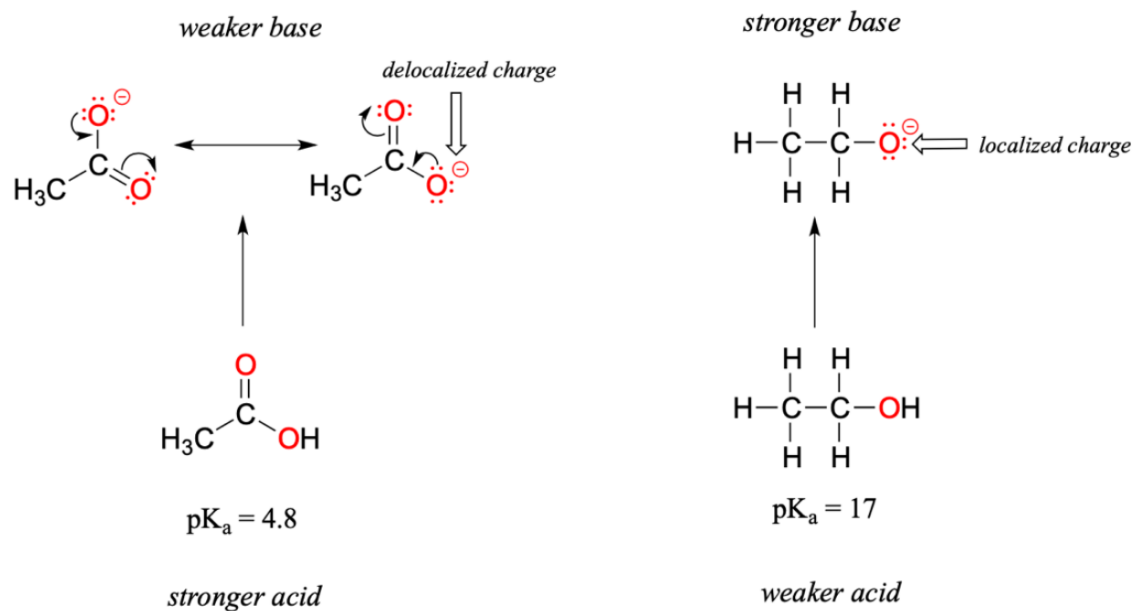
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General Chemistry 4th edition, Hill, Petrucci, McCreary, Perry

Chapter Fifteen

Resonance effect

Does the conjugate base have resonance structures that stabilize them?



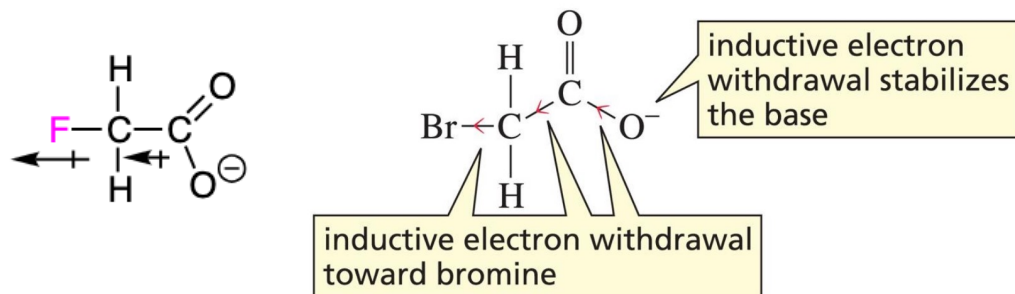
- Resonance structures stabilize the charge in the conjugate base.

- The more and energetically favoured resonance structures the more stabilized the conjugate base the stronger the acid.

Got to lecture 1 (slides 86-88) if you are unsure about resonance structures. They will stay important throughout the course!

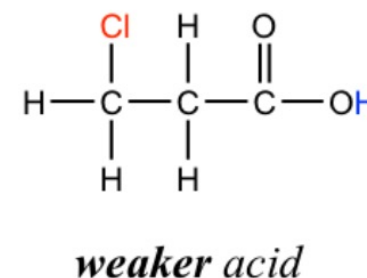
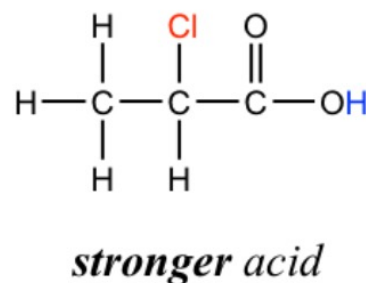
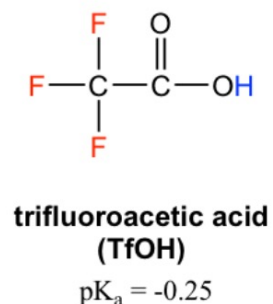
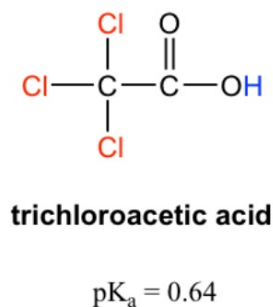
Inductive effect

Do we have electron withdrawing (or donating) groups that stabilize/destabilize the compound.



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- Effect over one or several bonds
- Dependent on electronegativity of the withdrawing group (size does not matter).
 - The more electronegative the bigger the effect
- Dependent on the distance (#bonds) to the
 - The further away the smaller the effect.



Acid base reactions

To judge how strong an acid is we consider the stability of the conjugate base!

Factors to consider for the stability for the conjugate base:

1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms?
3. **Size:** Can the charge be localized over a larger/smaller space? (size of atom)
4. **Resonance effect:** Does the conjugate base have resonance structures that stabilize them?
5. **Inductive effect:** Do we have electron withdrawing or donating groups that stabilize/destabilize the compound.
6. **Hybridization and Energies** of occupied molecular orbitals. (For us acidity: $sp > sp^2 > sp^3$)

5.1 Organic reactivity

a)

- Is the overall reaction endergonic or exergonic in the forward (A to D) direction?

Endergonic (D is higher in energy than A)

- How many steps does the reaction mechanism have?

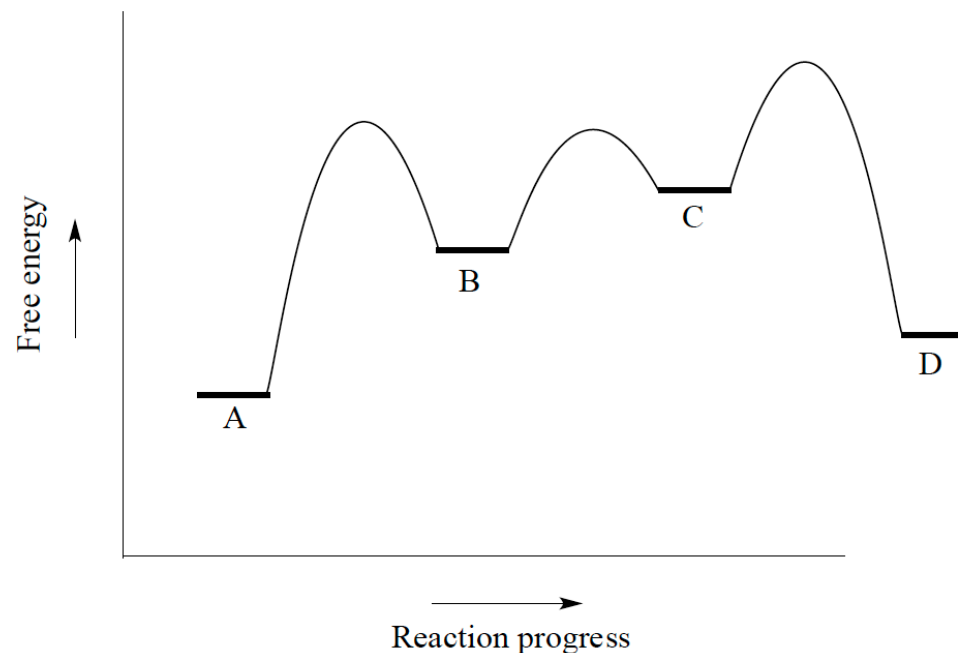
3 steps

- How many intermediates does the reaction mechanism have?

Two intermediates (B and C)

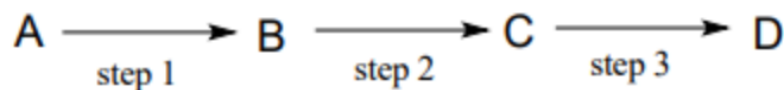
- Which one is the rate-determining step of the forward reaction? Step 1
- What is the fastest reaction step, considering both the forward and reverse directions?

C to B in the reverse direction (activation energy from C to middle transition state is lowest of the six possible activation energies).

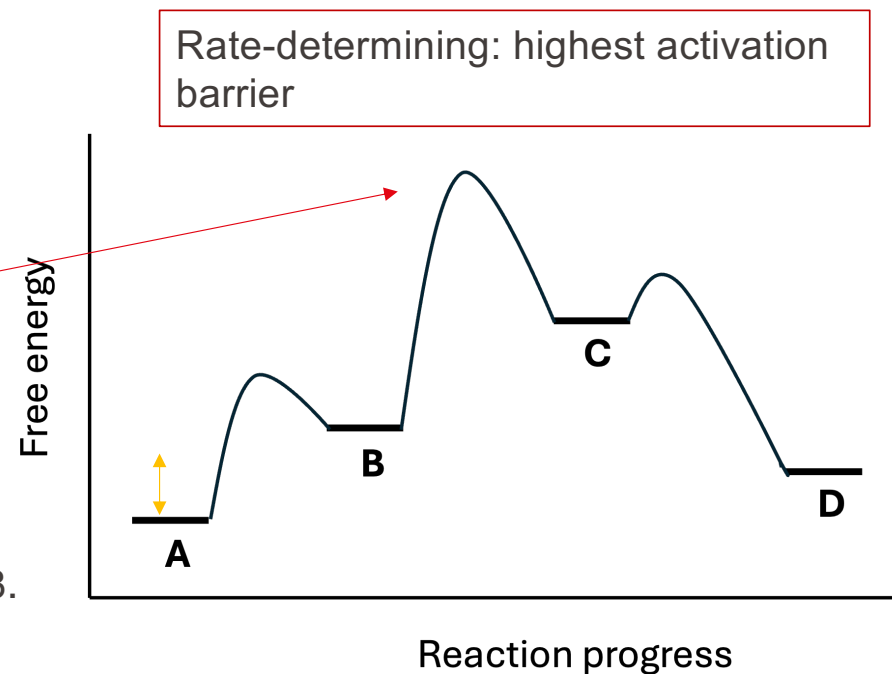


5.1 Organic reactivity

b)



Step 2 is the rate-determining step,
C is the least stable species,
B is higher energy than D,
and the overall reaction has an equilibrium constant $K_{eq} = 0.33$.

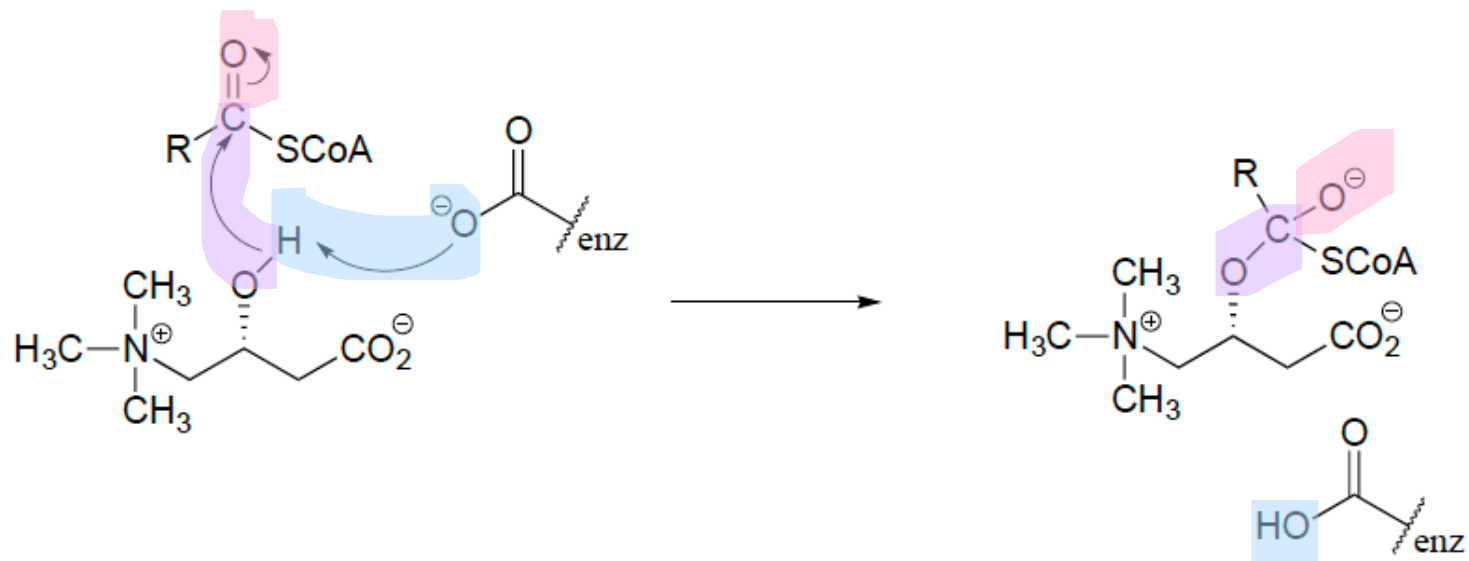
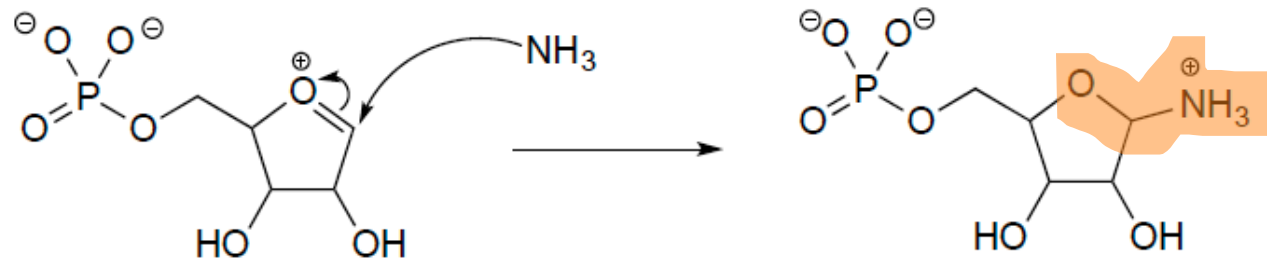


Draw a diagram that corresponds to all of this information.

$K_{eq} = 0.33$ therefore it is an endergonic forward reaction (D is higher than A)

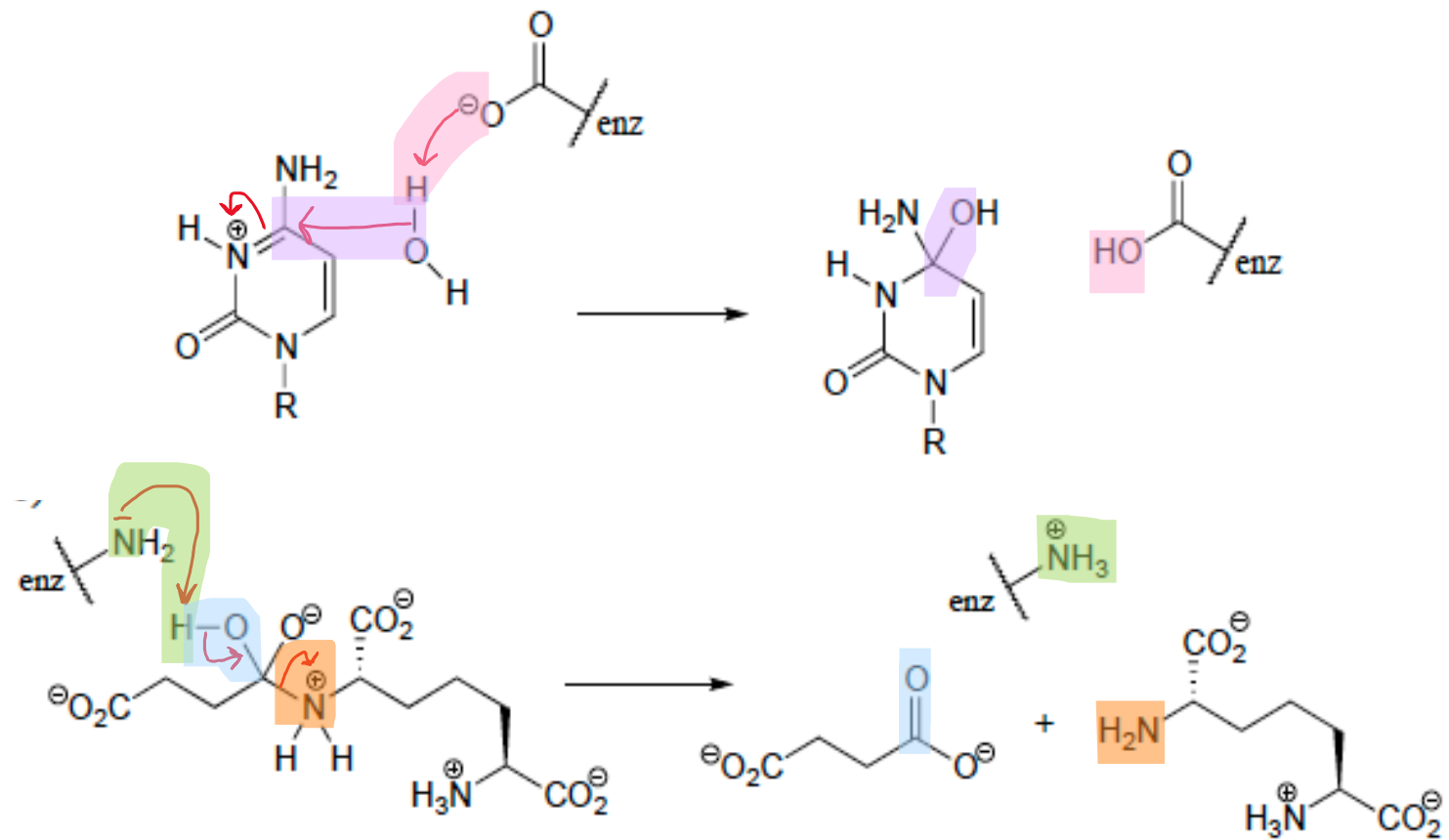
5.1 Organic reactivity

c)



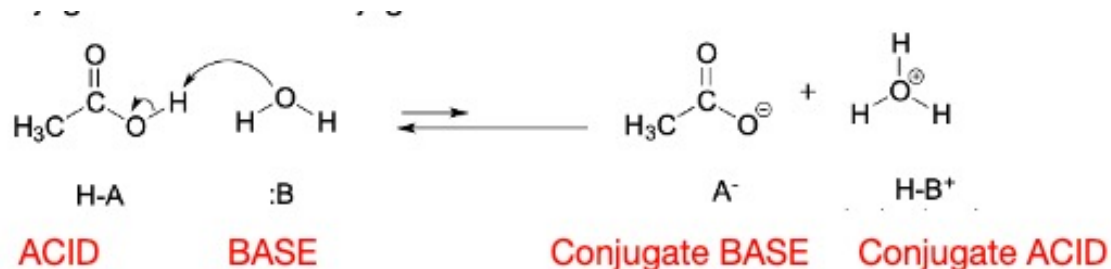
5.1 Organic reactivity

d)



5.2 Acidity and Basicity – Definition and important concepts

a) and b)



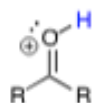
A strong acid has a weak conjugate base that can stabilize the accepted electrons (negative charge well) and a low pKa.

- b) Remind yourself of the relationship between strong acids, weak bases and pKa and answer following questions as true (T) or false (F)

An acid base reaction will be favored when a weaker base and a weaker acid combine to form a stronger acid and stronger base.	T F
Generally, strong acids have weak conjugate bases	T F
Strong acid have high pKa values	T F
A weak base is less stable than a strong base	T F

5.2 Acidity and Basicity – Definition and important concepts

c)



protonated ketone

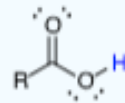
pKa

< 0



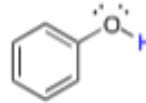
protonated alcohol

< 0



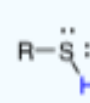
carboxylic acid

5



phenol

10



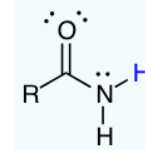
thiol

10



alcohol

15



amide

20

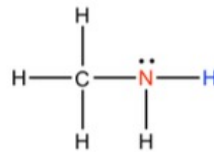
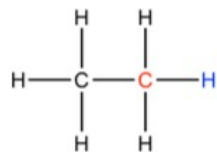
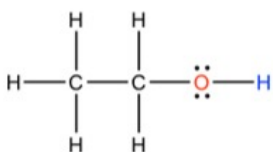
5.2 Acidity and Basicity – Definition and important concepts

d)



Assessing acidity and basicity

Classify the compounds according to their acidity



Electronegativity: 1.

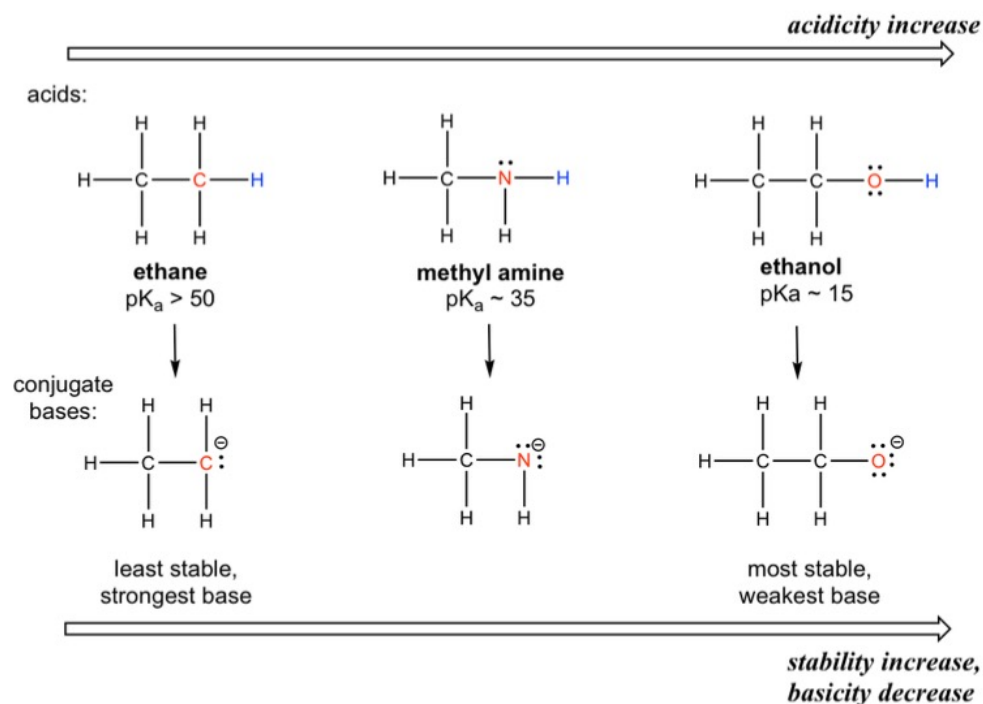
3.

2.

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Assessing acidity and basicity

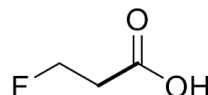
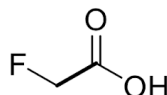
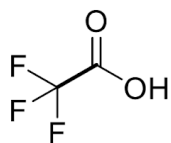
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Assessing acidity and basicity

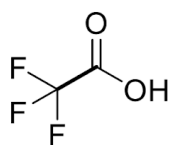
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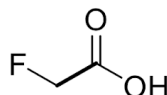
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Assessing acidity and basicity

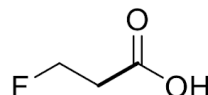
Classify the compounds according to their acidity



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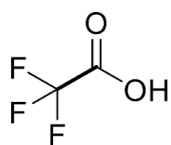
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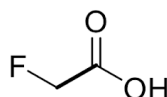
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Assessing acidity and basicity

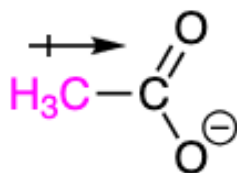
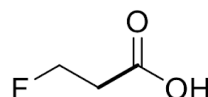
Classify the compounds according to their acidity



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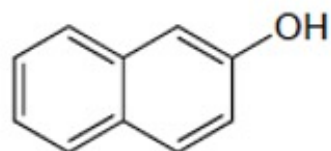
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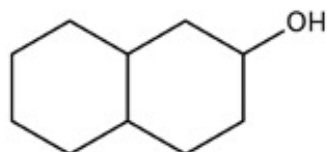
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Assessing acidity and basicity

Classify the compounds according to their acidity



2-naphthol

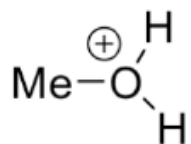


Decahydro-2-naphthol

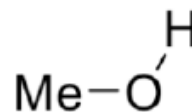
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Assessing acidity and basicity

Classify the compounds according to their acidity



Methyloxonium

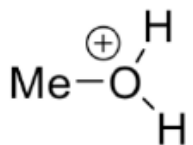


Methanol

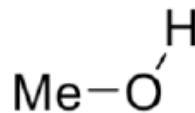
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Assessing acidity and basicity

Classify the compounds according to their acidity




Methyloxonium



Methanol

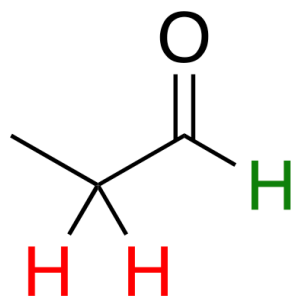
More acidic



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Assessing acidity and basicity

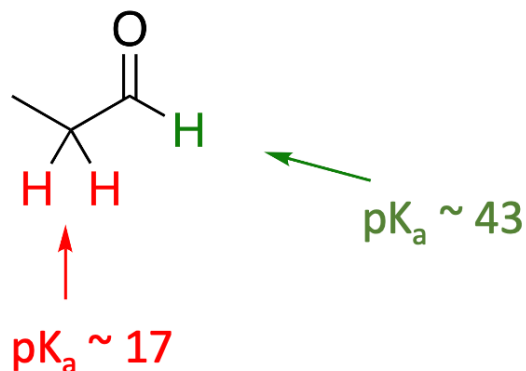
Classify the compounds according to their acidity



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Assessing acidity and basicity

Classify the compounds according to their acidity



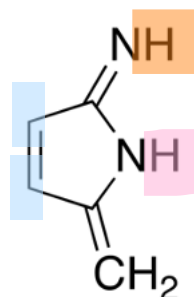
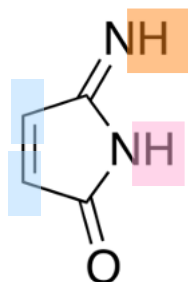
H: can be stabilized by resonance structure

H: Can't be stabilized by resonance

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Assessing acidity and basicity

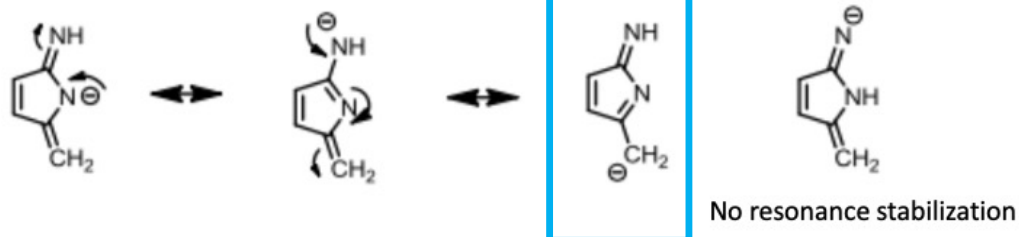
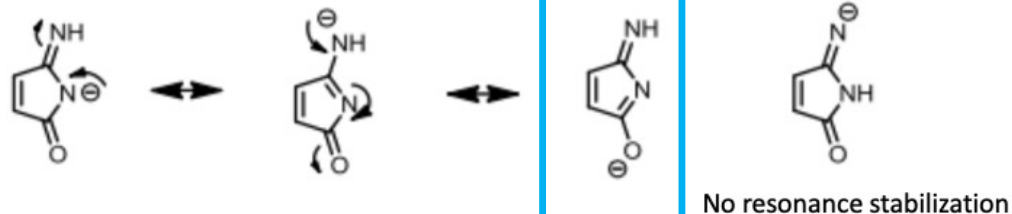
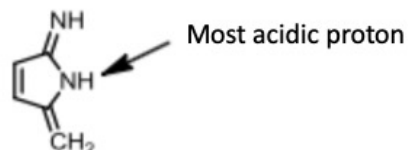
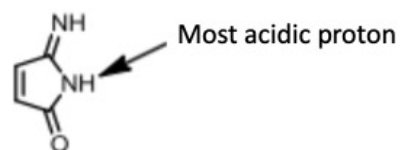
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Assessing acidity and basicity

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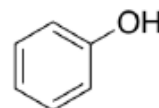
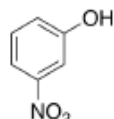
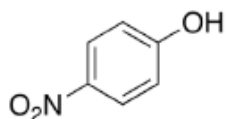
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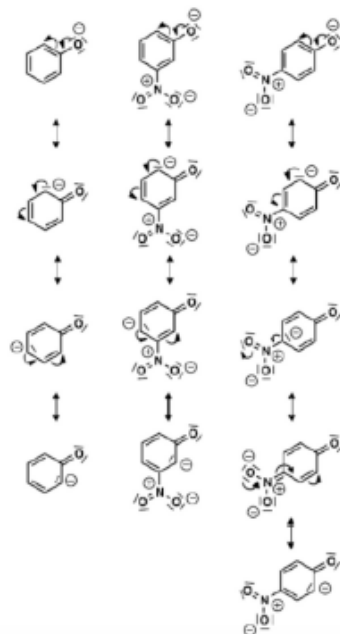
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Assessing acidity and basicity

Classify the compounds according to their acidity



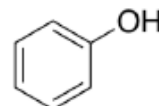
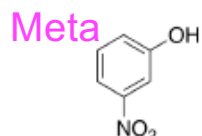
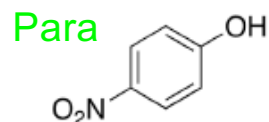
Most acidic



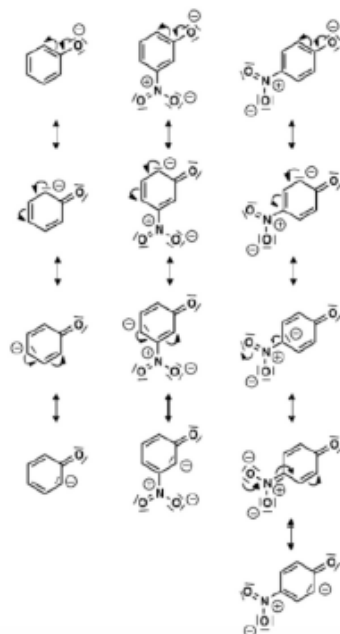
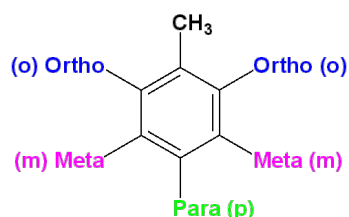
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Assessing acidity and basicity

Classify the compounds according to their acidity



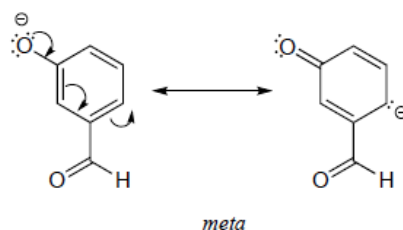
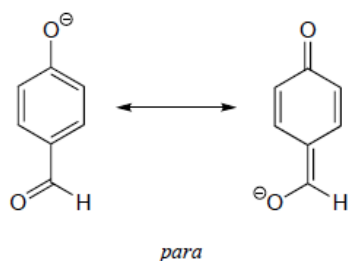
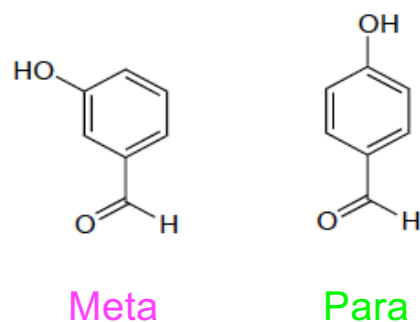
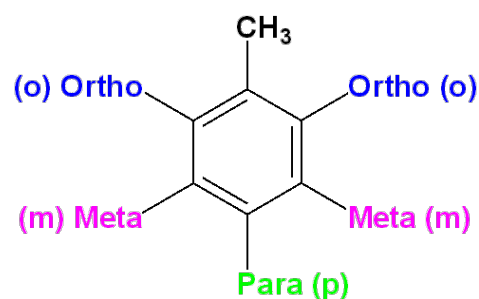
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Assessing acidity and basicity

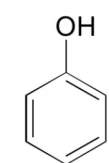
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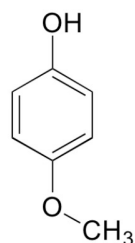
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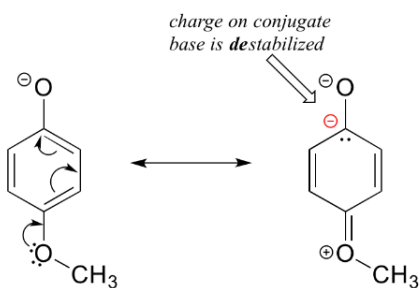
Classify the compounds according to their acidity



$pK_a = 10$



$pK_a = 10.6$



Donating by resonance

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5.4 Calculations

Weak acid



Conjugate base



a) What is the pH of an aqueous buffer solution that is 30 mM in acetic acid and 40 mM in sodium acetate? The pKa of acetic acid is 4.8. (Tip: use Henderson-Hasselbalch equation introduced in the lecture).

Henderson-Hasselbalch equation :

$$pH = pKa + \log\left(\frac{\text{conc.conjugate base}}{\text{conc conjugate weak acid}}\right)$$

The ratio of base to acid is 40mM/30mM, or 1.33.

Therefore, substituting these values and the pKa results in

$$\begin{aligned} pH &= 4.8 + \log(40\text{mM}/30\text{mM}) \\ &= 4.8 + \log 1.33 \\ &= 4.8 + 0.125 \\ &= 4.9 \end{aligned}$$

5.4 Calculations

b) What is the ratio of acetate ion to neutral acetic acid when a small amount of acetic acid ($pK_a = 4.8$) is dissolved in a buffer of pH 2.8? pH 3.8? pH 4.8? pH 5.8? pH 6.8?

We again use the Henderson-Hasselbalch equation and let the base to acid ratio

be X.

For pH = 2.8:

$$2.8 = 4.8 + \log X$$

$$X = 0.01 \text{ to } 1$$

pH 3.8, the ratio is 0.10 to 1

pH 4.8, the ratio is 1.0 to 1

pH 5.8, the ratio is 10 to 1

pH 6.8, the ratio is 100 to 1

5.4 Calculations

c) What is the approximate net charge on a tetrapeptide Cys-Asp-Lys-Glu in pH 7 buffer?

We must consider the protonation state/charge of all ionizable groups on the peptide - including the terminal amino and carboxylic acid groups - at pH 7.

terminal amino: +1

Cys: thiol, 0

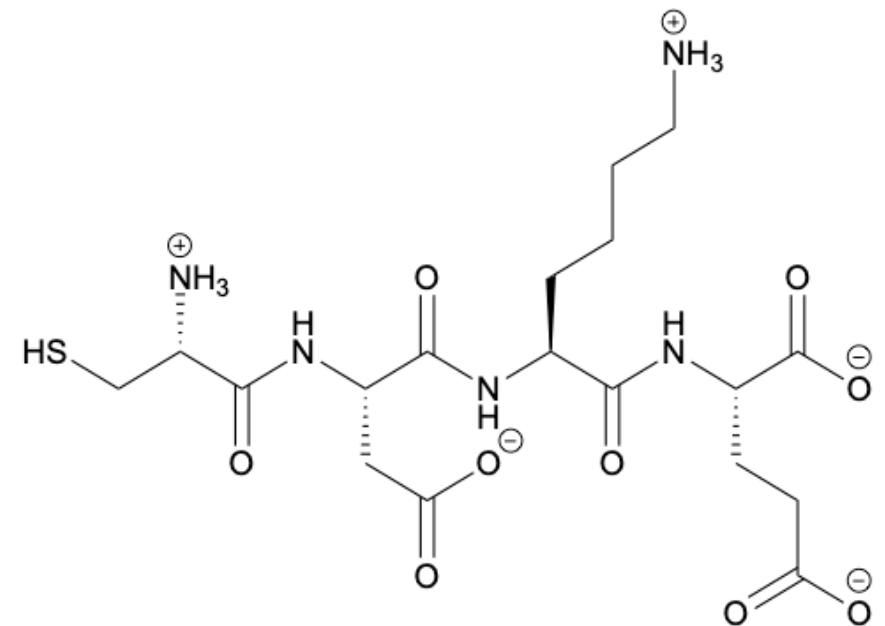
Asp: carboxylate, -1

Lys: ammonium, +1

Glu: carboxylate, -1

terminal carboxylate: -1

Net charge is therefore approximately -1.



Cys-Asp-Lys-Glu