EPFL

# Bio-110

## Ex. 5

## Acid Base reactions

Discussion

28.03.2025

École
polytechnique
fédérale
de Lausanne

# Reaction Mechanisms in organic chemistry

-How reactions take place ?

-Which bonds break ?

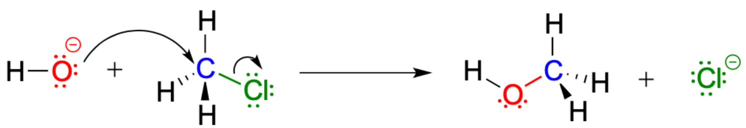
-Which bonds form ?

-Why do they break or form ?

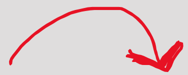
-Which order ?

-Which intermediate species ?

**Reaction mechanism**

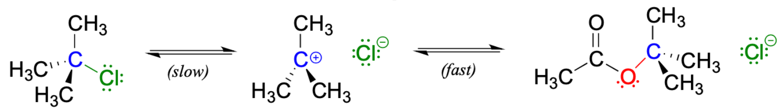



**reactants (R)** **products (P)**

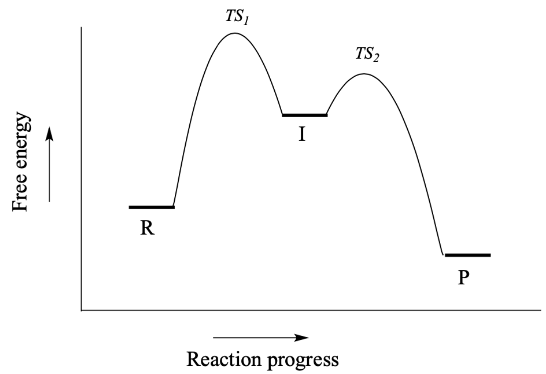


**Remember (!): curly arrows = movement of 2 electrons**

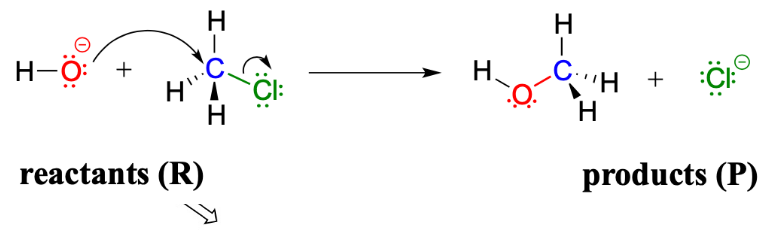
Multistep Reaction:




R I P



# Thermodynamics Vs Kinetics

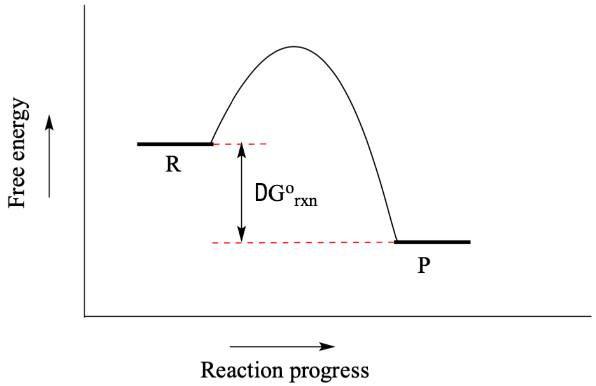



$$wA + xB \rightleftharpoons yC + zD$$

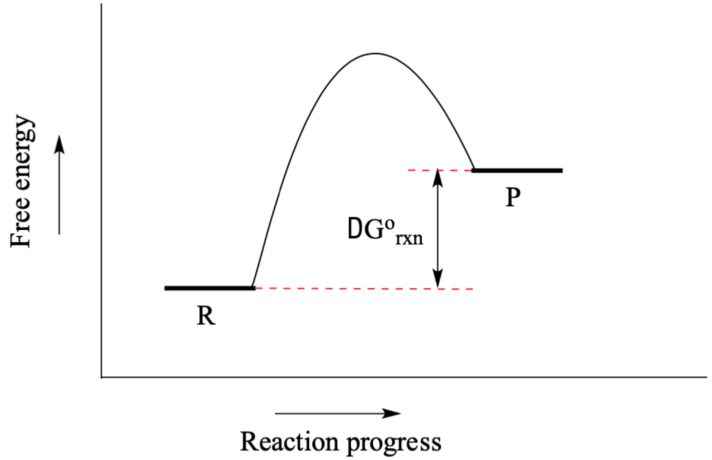
$$K_{eq} = \frac{[products]}{[reactants]} = \frac{[C]^y [D]^z}{[A]^w [B]^x}$$

## Thermodynamics

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

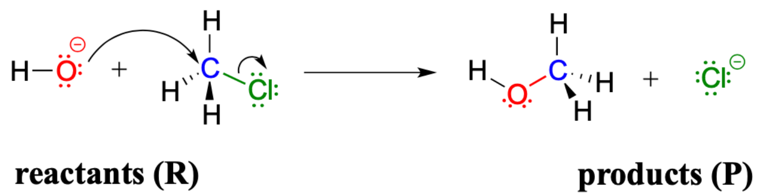



**Exergonic**
- Gibbs free-energy change is negative
- Energy releasing
- Thermodynamically favorable
- $K_{eq} > 1$



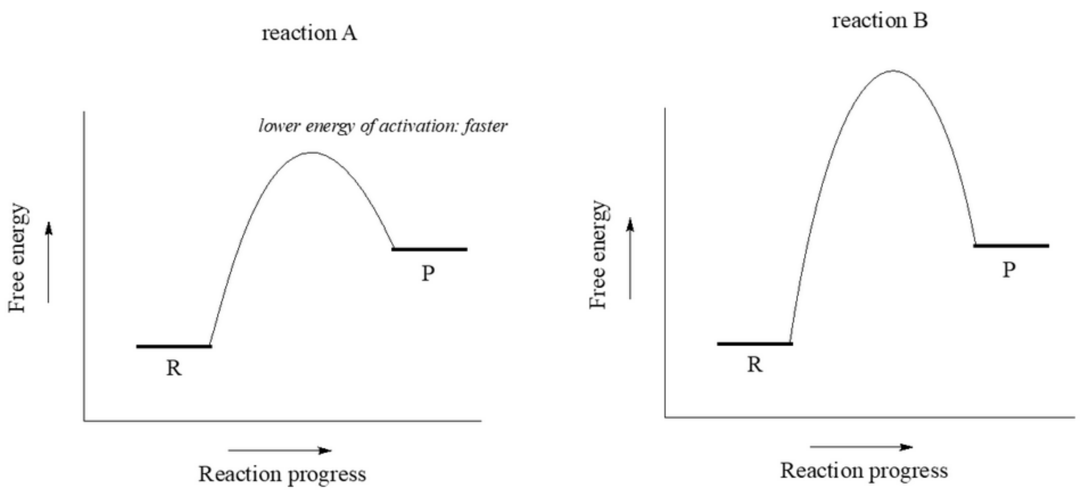

**Endergonic**
- Gibbs free-energy change is positive
- Energy absorbing
- Thermodynamically unfavorable
- $0 < K_{eq} < 1$

## 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!**

- $$HA + H_2O \rightleftharpoons :A^- + H_3O^+ \qquad K_a = \frac{[:A^-][H_3O^+]}{[HA]}$$

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

# Acid base reactions

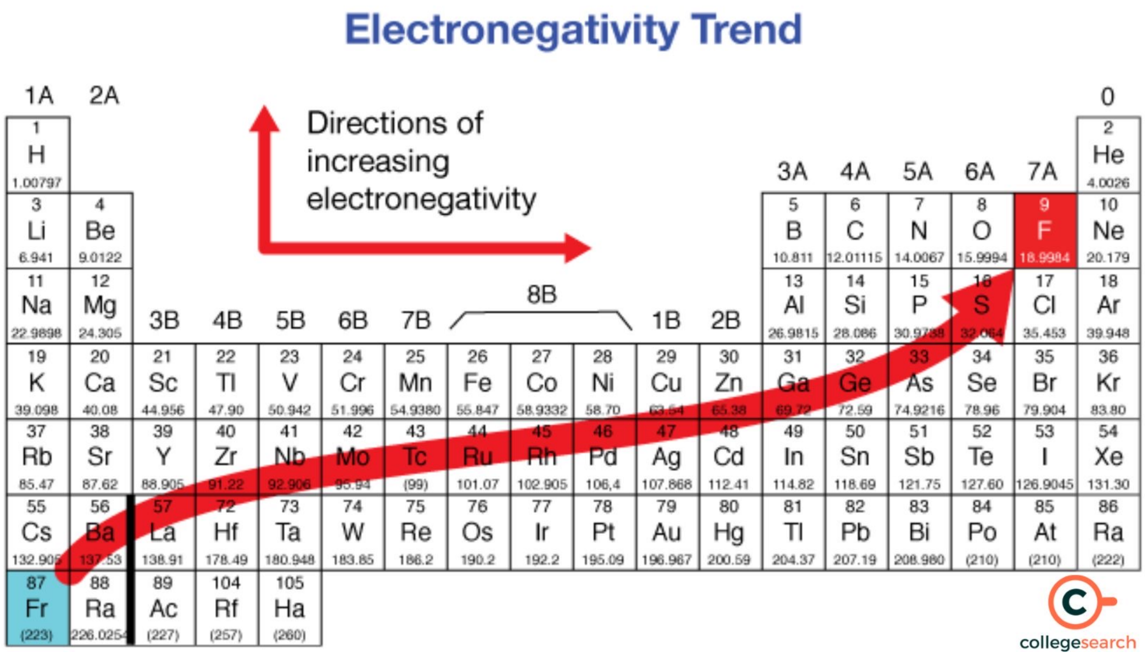
**To judge how strong an acid is we consider the stability of the conjugate base!**

**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 chare 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

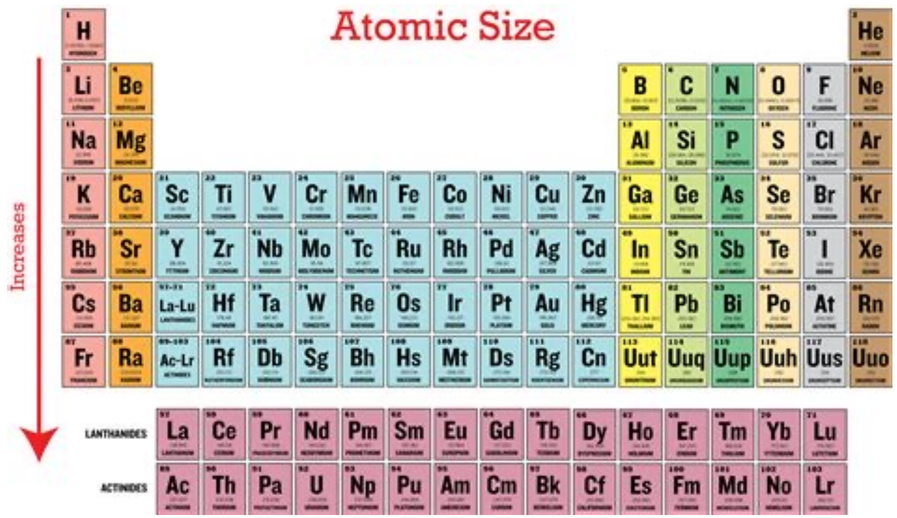
**Electronegativity**: Are negative charges on electronegative atoms?

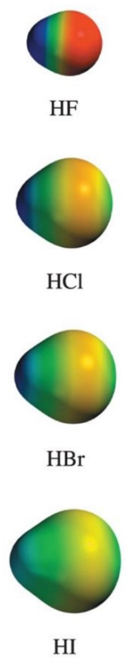



**To remember:**
Electronegativity trend: F > O > N > C

# Atom Size

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




To remember:
Size trend: I > Br > Cl > F

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

# Size and Electronegativity

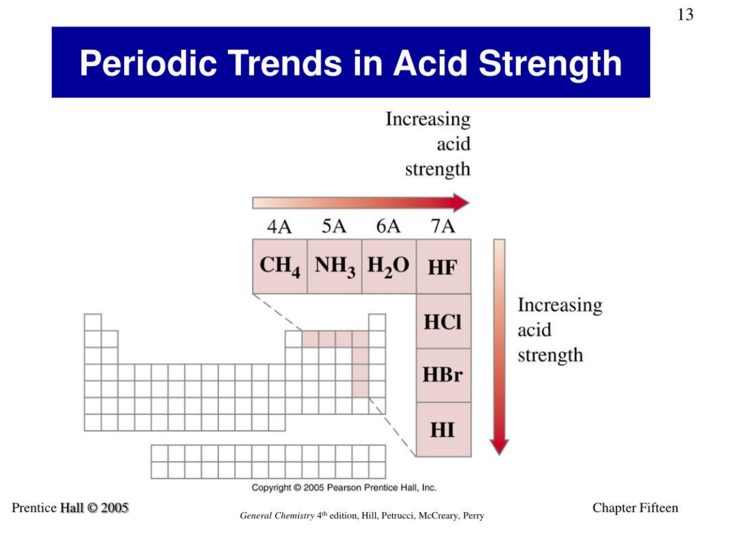
**Size:** Can the chare be localized over a larger/smaller space?

To remember:
Size trend: I > Br > Cl > F

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

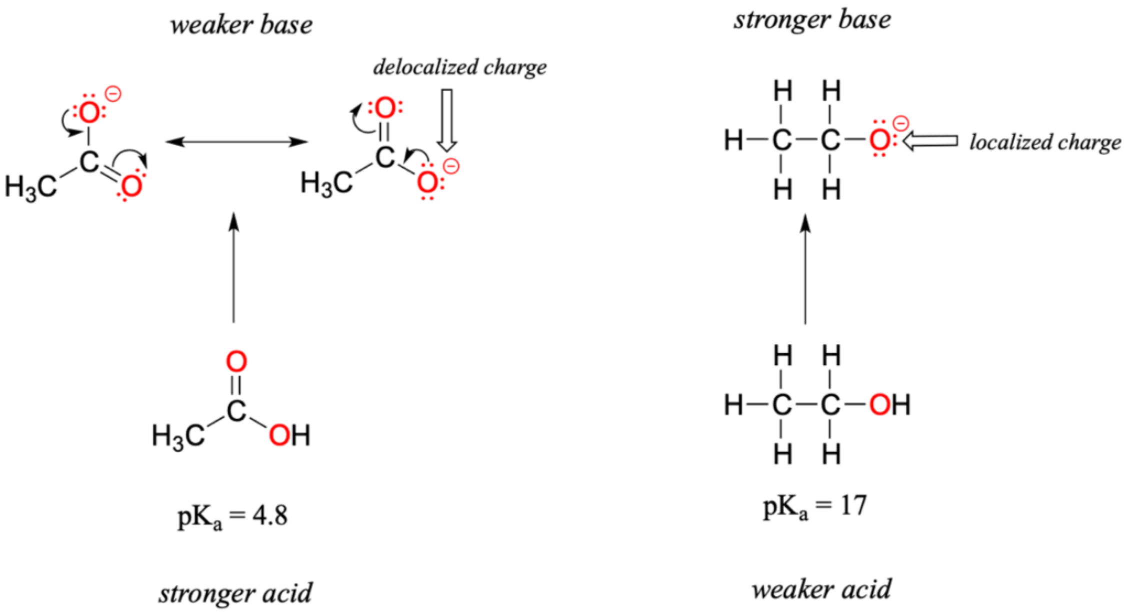
**Table 2.2** The p$K_a$ Values of Some Simple Acids

| | | | |
|---|---|---|---|
| $CH_4$ | $NH_3$ | $H_2O$ | HF |
| p$K_a$ = 60 | p$K_a$ = 36 | p$K_a$ = 15.7 | p$K_a$ = 3.2 |
| | | $H_2S$ | HCl |
| | | p$K_a$ = 7.0 | p$K_a$ = −7 |
| | | | HBr |
| | | | p$K_a$ = −9 |
| | | | HI |
| | | | p$K_a$ = −10 |



# Resonance effect

Does the conjugate base have resonance structures that stabilize them?



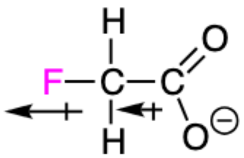

- Resonance structures stabilize the charge in the conjugate base.

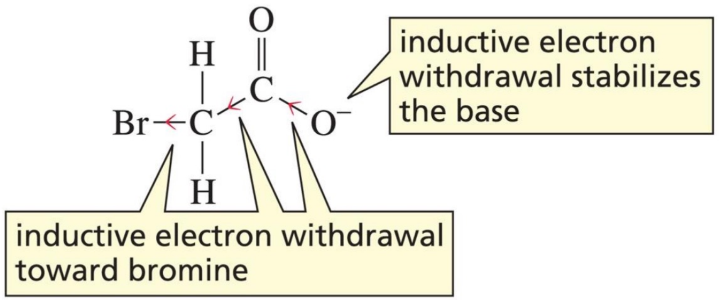
- The more and energetically favoured resonance structures the more stabilized the conjugate base the stronger the acid.

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

# Inductive effect

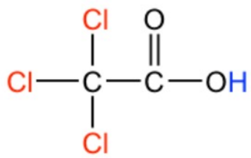
Do we have electron withdrawing (or donating) groups that stabilize/destabilize the compound.





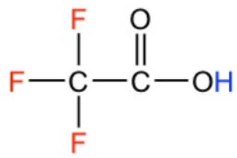



- Effect over one or several bonds
- Dependent on electronegativity of the withdrawing group (size does not matter).
  - The more electronegative the bigger the effect
- Dependent on the distance (#bonds) to the
  - The further away the smaller the effect.



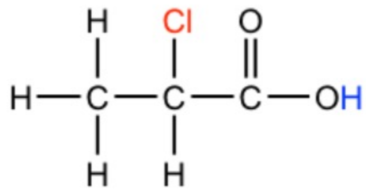
**trichloroacetic acid**

$pK_a = 0.64$

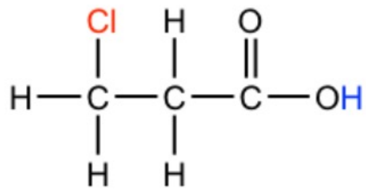


**trifluoroacetic acid (TfOH)**

$pK_a = -0.25$



***stronger*** *acid*



***weaker*** *acid*

# 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 chare 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

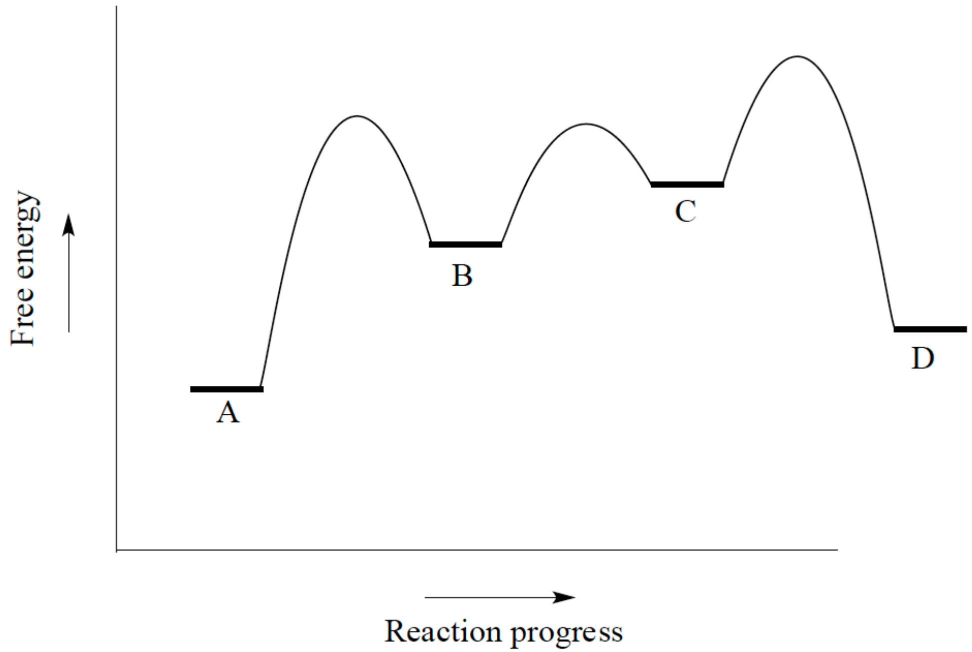
## a)

- 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?

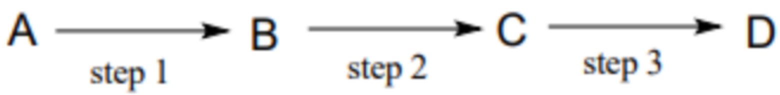
  Two intermediates (B and C)
- Which one is the rate-determining step of the forward reaction? Step 1
- What is the fastest reaction step, considering both the forward and reverse directions?

  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

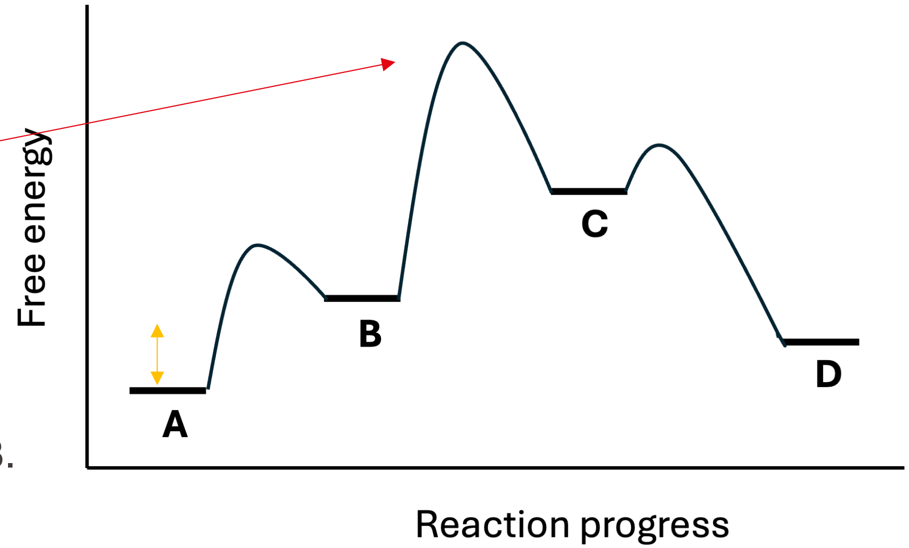
## b)




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 Keq = 0.33.

Draw a diagram that corresponds to all of this information.

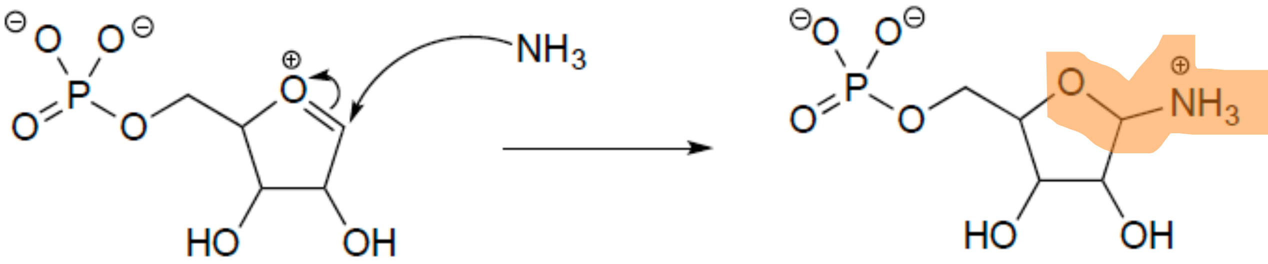
Rate-determining: highest activation barrier

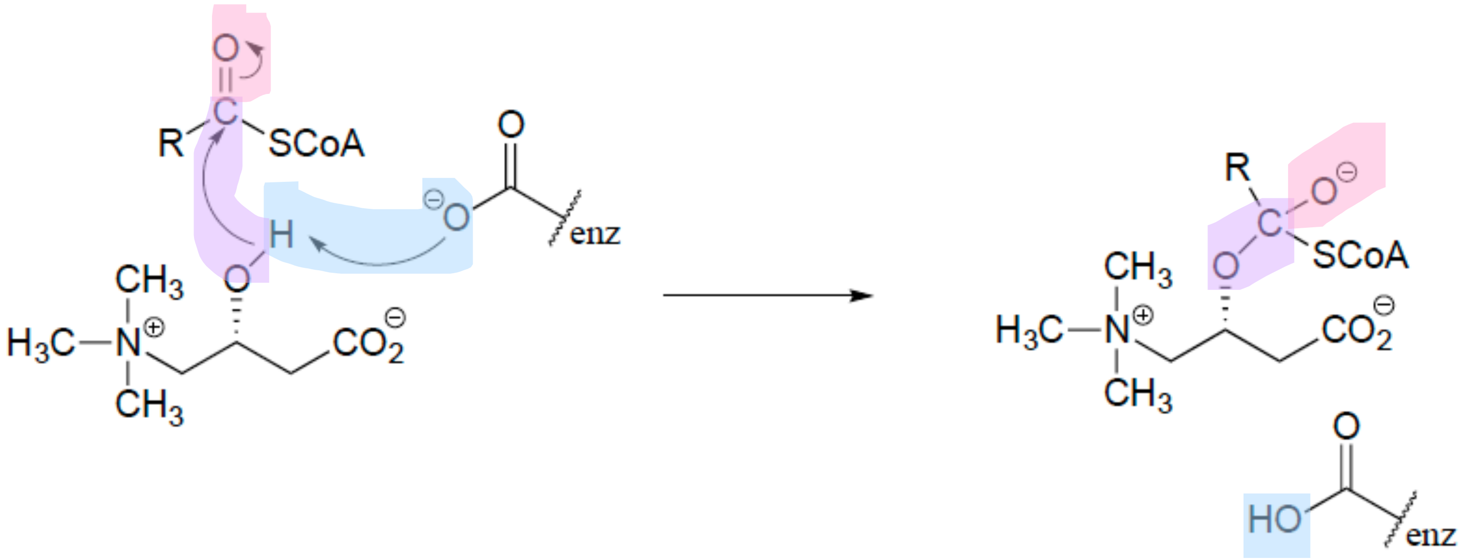



Keq = 0.33 therefore it is an endergonic forward reaction (D is higher than A)

# 5.1 Organic reactivity

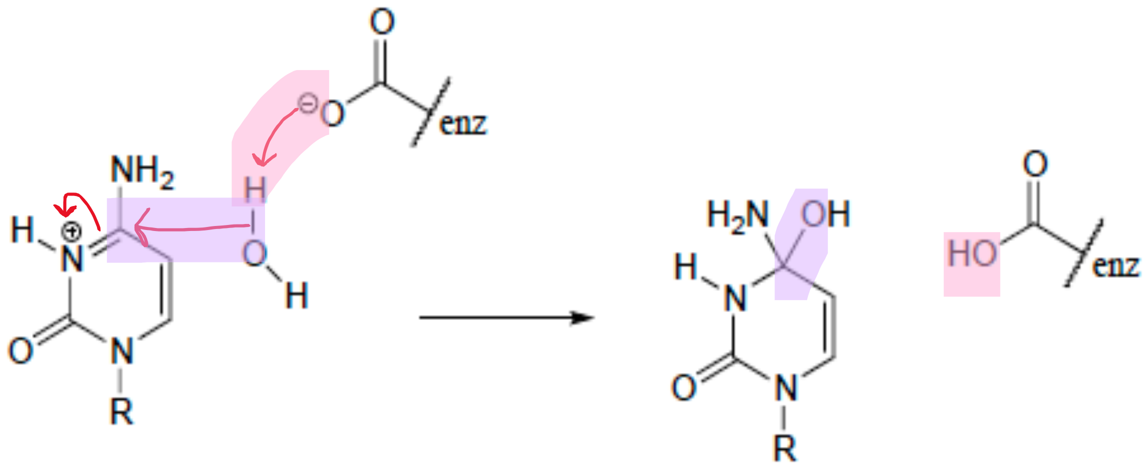
## c)

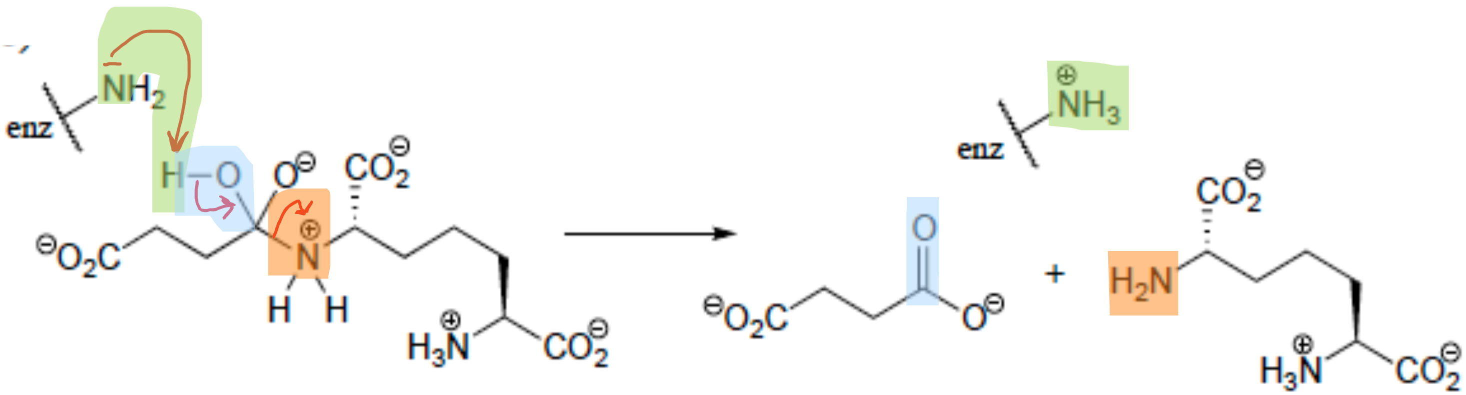


# 5.1 Organic reactivity

## d)



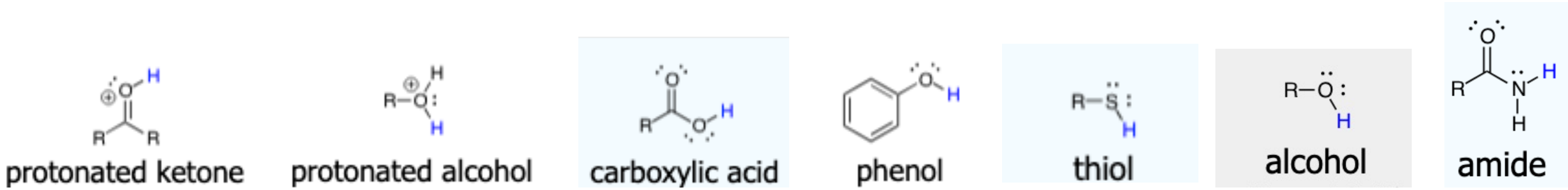
# 5.2 Acidity and Basicity – Definition and important conepts a) and b)


*A strong acid has a weak conjugate base that can stabalize 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** |

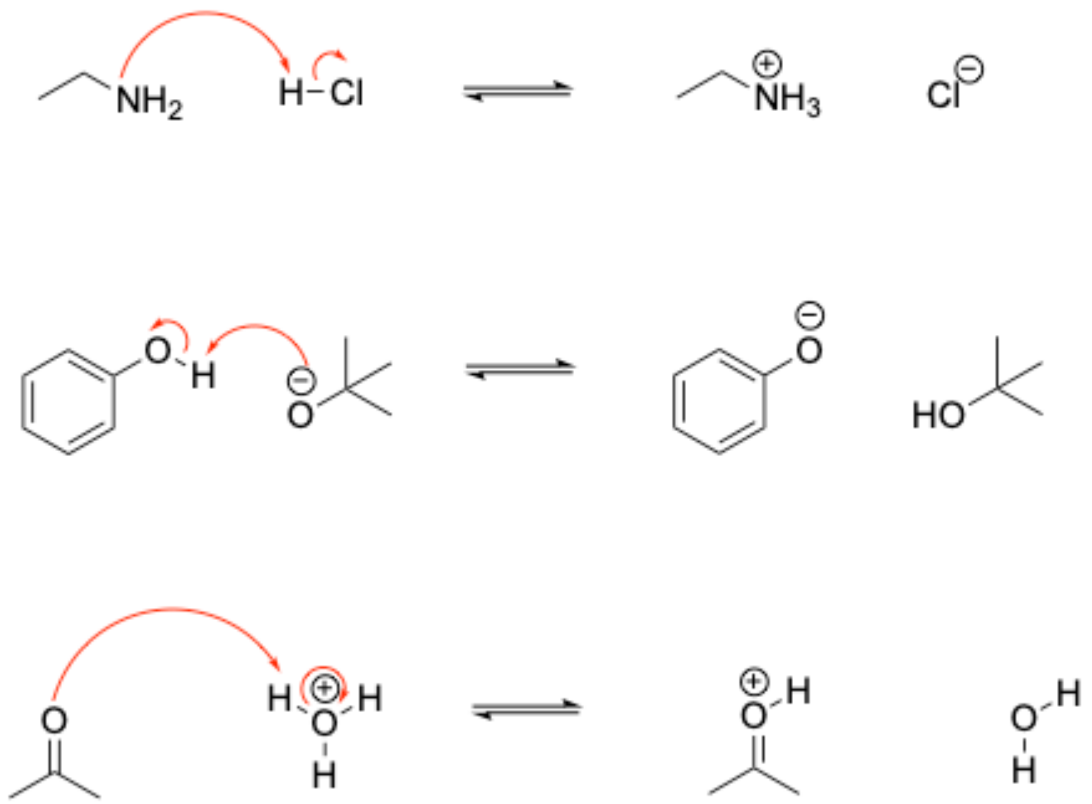
# 5.2 Acidity and Basicity – Definition and important conepts c)




| pKa | < 0 | < 0 | 5 | 10 | 10 | 15 | 20 |
|---|---|---|---|---|---|---|---|

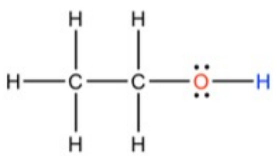
# 5.2 Acidity and Basicity – Definition and important conepts

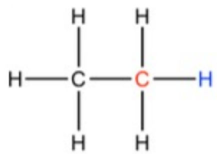
**d)**

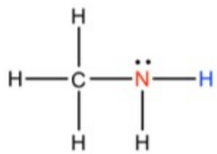


# Assessing acidity and basicity

## Classify the compounds according to their acidity





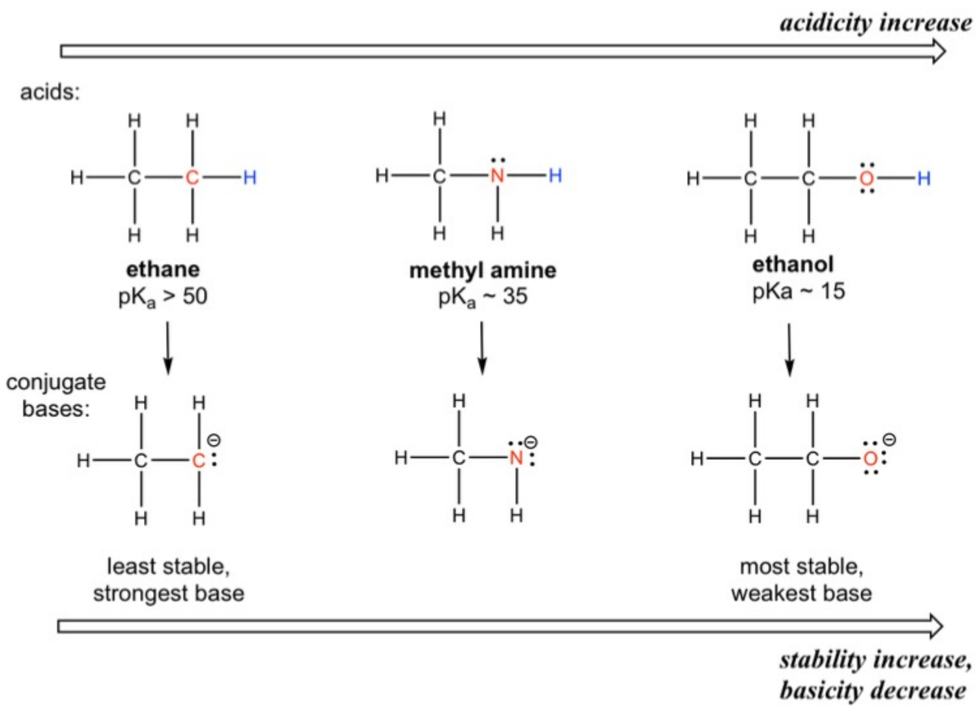


Electronegativity: 1. 3. 2.

1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms? The other way around?
3. **Size:** Can a charge be delocalized over a larger/smaller space?
4. **Resonance Structures:** Do the acid or conjugate base have resonance structures that stabilize them?
5. **Electron withdrawing or donating groups:** Do they stabilize or destabilize the compound?
6. **Energies of occupied molecular orbitals:** Are they relatively high/low?

# Assessing acidity and basicity

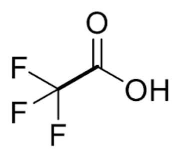
## Classify the compounds according to their acidity

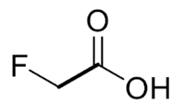


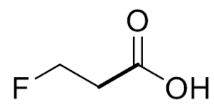

1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms? The other way around?
3. **Size:** Can a charge be delocalized over a larger/smaller space?
4. **Resonance Structures:** Do the acid or conjugate base have resonance structures that stabilize them?
5. **Electron withdrawing or donating groups:** Do they stabilize or destabilize the compound?
6. **Energies of occupied molecular orbitals:** Are they relatively high/low?

# Assessing acidity and basicity

## Classify the compounds according to their acidity



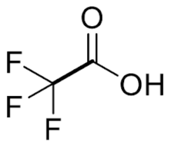




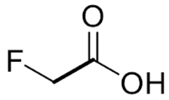
1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms? The other way around?
3. **Size:** Can a charge be delocalized over a larger/smaller space?
4. **Resonance Structures:** Do the acid or conjugate base have resonance structures that stabilize them?
5. **Electron withdrawing or donating groups:** Do they stabilize or destabilize the compound?
6. **Energies of occupied molecular orbitals:** Are they relatively high/low?

# Assessing acidity and basicity

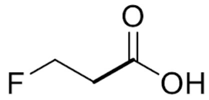
## Classify the compounds according to their acidity




>



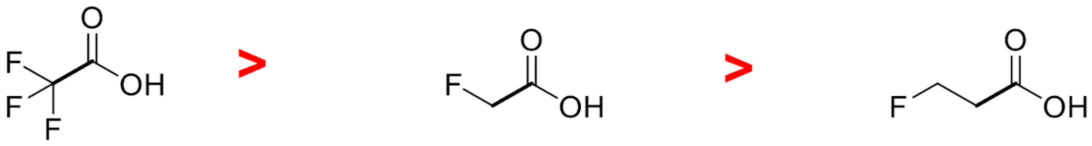

>

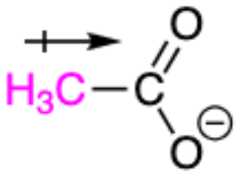



1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms? The other way around?
3. **Size:** Can a charge be delocalized over a larger/smaller space?
4. **Resonance Structures:** Do the acid or conjugate base have resonance structures that stabilize them?
5. **Electron withdrawing or donating groups:** Do they stabilize or destabilize the compound?
6. **Energies of occupied molecular orbitals:** Are they relatively high/low?

# Assessing acidity and basicity

## Classify the compounds according to their acidity

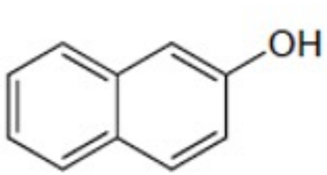


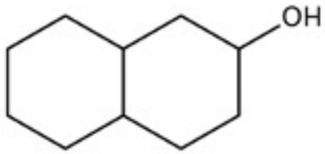

1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms? The other way around?
3. **Size:** Can a charge be delocalized over a larger/smaller space?
4. **Resonance Structures:** Do the acid or conjugate base have resonance structures that stabilize them?
5. **Electron withdrawing or donating groups:** Do they stabilize or destabilize the compound?
6. **Energies of occupied molecular orbitals:** Are they relatively high/low?

# Assessing acidity and basicity

## Classify the compounds according to their acidity




**2-naphthol**

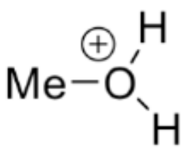



**Decahydro-2-naphthol**

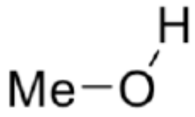
1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms? The other way around?
3. **Size:** Can a charge be delocalized over a larger/smaller space?
4. **Resonance Structures:** Do the acid or conjugate base have resonance structures that stabilize them?
5. **Electron withdrawing or donating groups:** Do they stabilize or destabilize the compound?
6. **Energies of occupied molecular orbitals:** Are they relatively high/low?

# Assessing acidity and basicity

## Classify the compounds according to their acidity



Methyloxonium



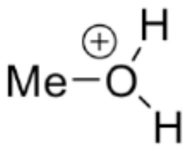
Methanol

1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms? The other way around?
3. **Size:** Can a charge be delocalized over a larger/smaller space?
4. **Resonance Structures:** Do the acid or conjugate base have resonance structures that stabilize them?
5. **Electron withdrawing or donating groups:** Do they stabilize or destabilize the compound?
6. **Energies of occupied molecular orbitals:** Are they relatively high/low?

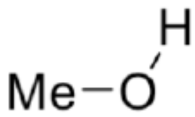
EPFL

# Assessing acidity and basicity

## Classify the compounds according to their acidity




Methyloxonium



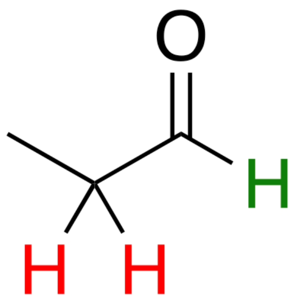

Methanol

More acidic

1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms? The other way around?
3. **Size:** Can a charge be delocalized over a larger/smaller space?
4. **Resonance Structures:** Do the acid or conjugate base have resonance structures that stabilize them?
5. **Electron withdrawing or donating groups:** Do they stabilize or destabilize the compound?
6. **Energies of occupied molecular orbitals:** Are they relatively high/low?

# Assessing acidity and basicity

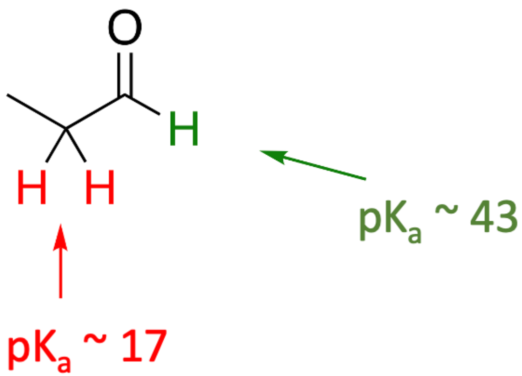
## Classify the compounds according to their acidity




1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms? The other way around?
3. **Size:** Can a charge be delocalized over a larger/smaller space?
4. **Resonance Structures:** Do the acid or conjugate base have resonance structures that stabilize them?
5. **Electron withdrawing or donating groups:** Do they stabilize or destabilize the compound?
6. **Energies of occupied molecular orbitals:** Are they relatively high/low?

# Assessing acidity and basicity

## Classify the compounds according to their acidity




H: can be stabilized by resonance structure

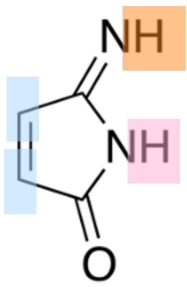
H: Can't be stabilized by resonance

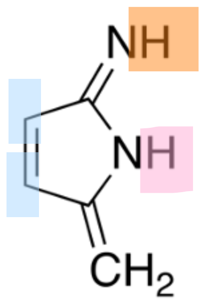
1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms? The other way around?
3. **Size:** Can a charge be delocalized over a larger/smaller space?
4. **Resonance Structures:** Do the acid or conjugate base have resonance structures that stabilize them?
5. **Electron withdrawing or donating groups:** Do they stabilize or destabilize the compound?
6. **Energies of occupied molecular orbitals:** Are they relatively high/low?

EPFL

# Assessing acidity and basicity

## Classify the compounds according to their acidity



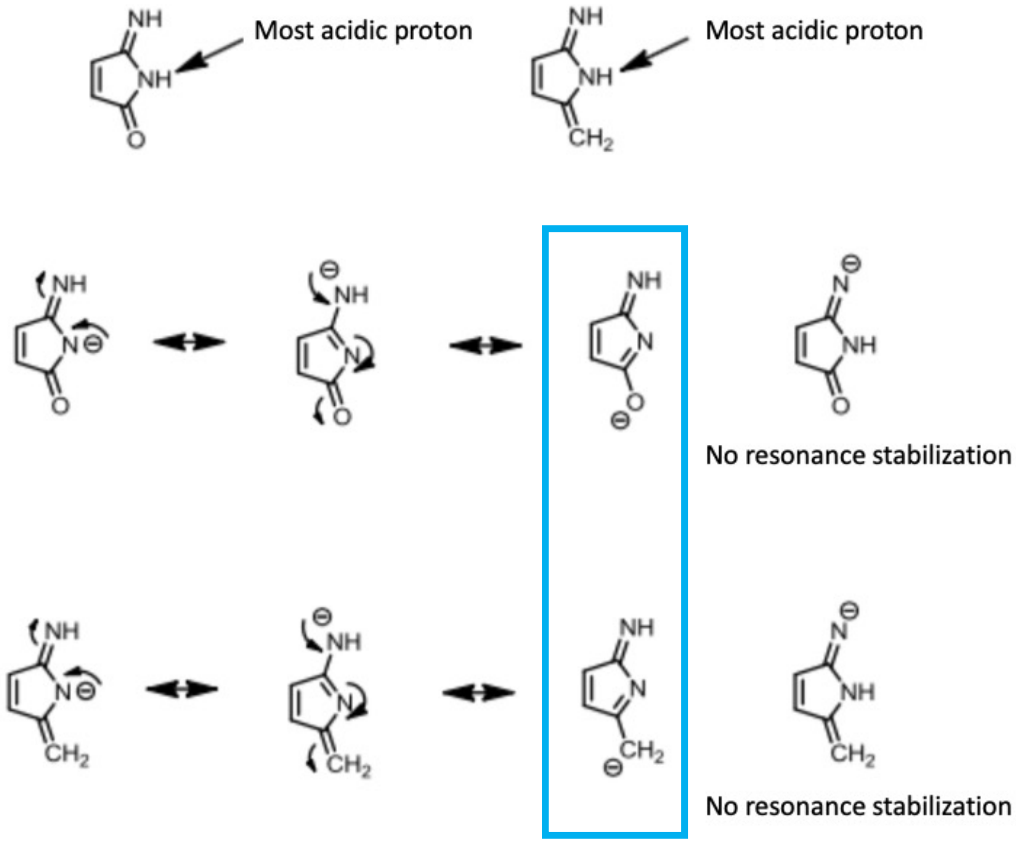




1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms? The other way around?
3. **Size:** Can a charge be delocalized over a larger/smaller space?
4. **Resonance Structures:** Do the acid or conjugate base have resonance structures that stabilize them?
5. **Electron withdrawing or donating groups:** Do they stabilize or destabilize the compound?
6. **Energies of occupied molecular orbitals:** Are they relatively high/low?

EPFL

# Assessing acidity and basicity

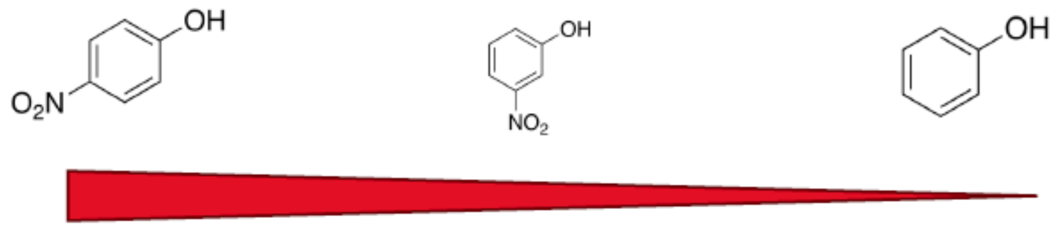
## Classify the compounds according to their acidity



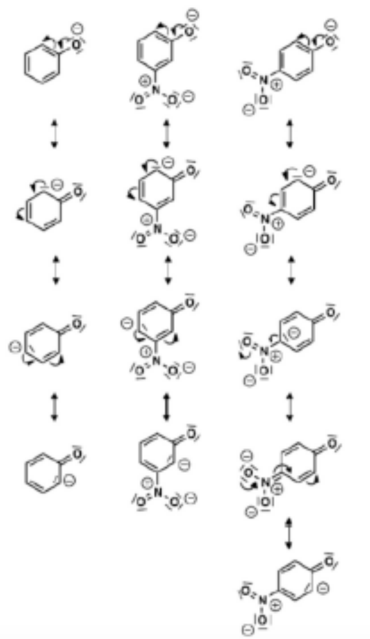

1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms? The other way around?
3. **Size:** Can a charge be delocalized over a larger/smaller space?
4. **Resonance Structures:** Do the acid or conjugate base have resonance structures that stabilize them?
5. **Electron withdrawing or donating groups:** Do they stabilize or destabilize the compound?
6. **Energies of occupied molecular orbitals:** Are they relatively high/low?

# Assessing acidity and basicity

## Classify the compounds according to their acidity




Most acidic

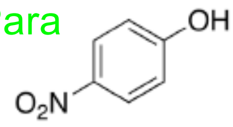


1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms? The other way around?
3. **Size:** Can a charge be delocalized over a larger/smaller space?
4. **Resonance Structures:** Do the acid or conjugate base have resonance structures that stabilize them?
5. **Electron withdrawing or donating groups:** Do they stabilize or destabilize the compound?
6. **Energies of occupied molecular orbitals:** Are they relatively high/low?

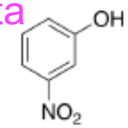
# Assessing acidity and basicity

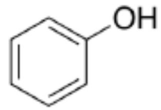
## Classify the compounds according to their acidity

Para

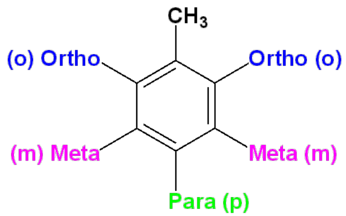


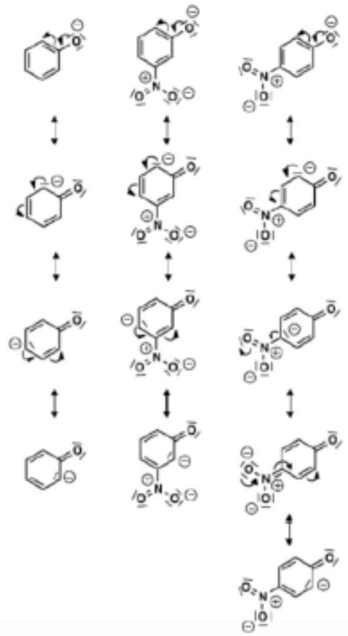

Meta




Most acidic



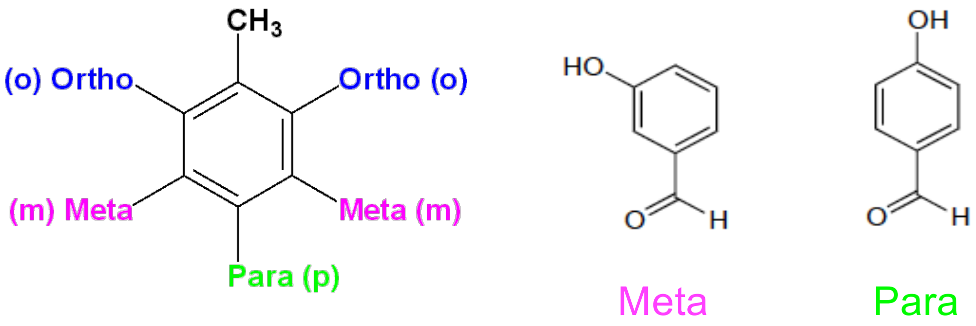



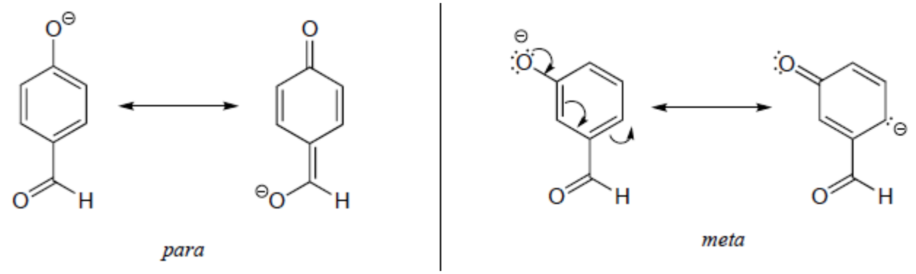
1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms? The other way around?
3. **Size:** Can a charge be delocalized over a larger/smaller space?
4. **Resonance Structures:** Do the acid or conjugate base have resonance structures that stabilize them?
5. **Electron withdrawing or donating groups:** Do they stabilize or destabilize the compound?
6. **Energies of occupied molecular orbitals:** Are they relatively high/low?

EPFL

# Assessing acidity and basicity

## Classify the compounds according to their acidity

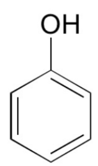


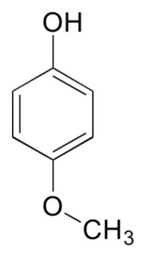

1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms? The other way around?
3. **Size:** Can a charge be delocalized over a larger/smaller space?
4. **Resonance Structures:** Do the acid or conjugate base have resonance structures that stabilize them?
5. **Electron withdrawing or donating groups:** Do they stabilize or destabilize the compound?
6. **Energies of occupied molecular orbitals:** Are they relatively high/low?

# Assessing acidity and basicity

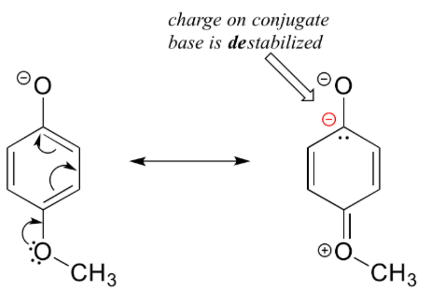
## Classify the compounds according to their acidity




$pK_a = 10$




$pK_a = 10.6$




**Donating by resonance**

1. **Charge:** Is the compound more or less stable with a charge?
2. **Electronegativity:** Are negative charges on electronegative atoms? The other way around?
3. **Size:** Can a charge be delocalized over a larger/smaller space?
4. **Resonance Structures:** Do the acid or conjugate base have resonance structures that stabilize them?
5. **Electron withdrawing or donating groups:** Do they stabilize or destabilize the compound?
6. **Energies of occupied molecular orbitals:** Are they relatively high/low?

## 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 :

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

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

Therefore, substituting these values and the *pKa* results in

*pH* =4.8+log(40mM/30mM)

=4.8+log1.33

=4.8+0.125

=4.9

## 5.4 Calculations

b) What is the ratio of acetate ion to neutral acetic acid when a small amount of acetic acid (pKa = 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 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

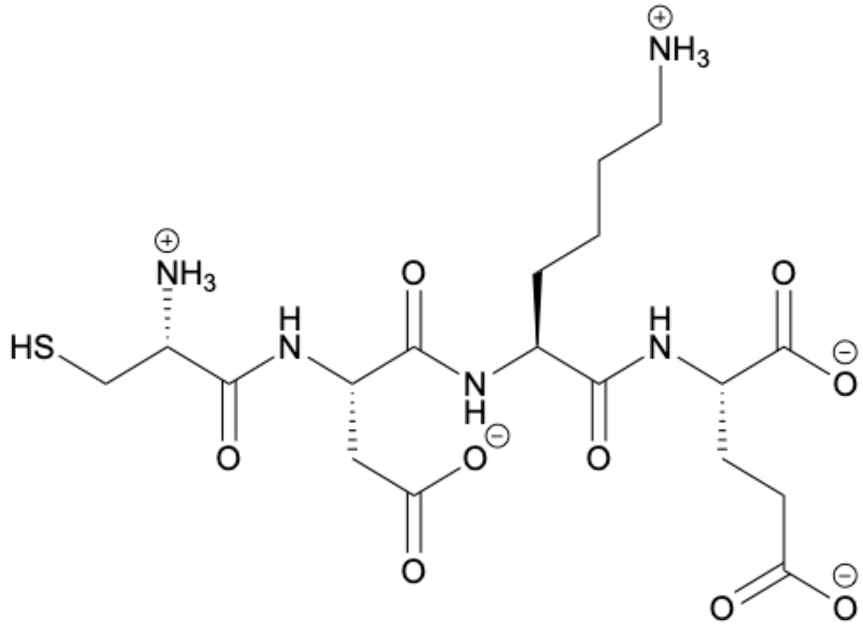
Asp: carboxylate, -1

Lys: ammonium, +1

Glu: carboxylate, -1

terminal carboxylate: -1

Net charge is therefore approximately -1.




Cys-Asp-Lys-Glu