Bioorganic Chemistry

Lecture 5

^{13}C-NMR spectroscopy

- Remember ^{12}C does not have a nuclear magnetic moment and is not NMR active

-However ^{13}C is NMR active

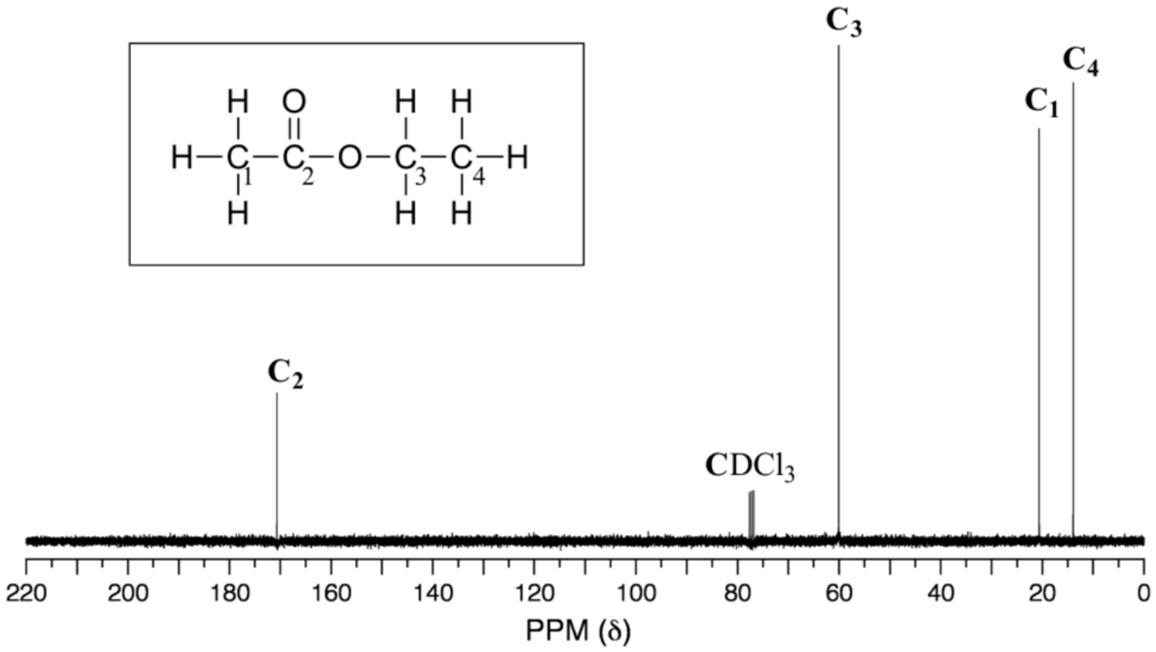
-Many things are common between ^{13}C and ^{1}H NMR spectroscopy but many aren’t:
    -NMR signals much weaker
    -More sample required
    -More complex experiments
    -Area under the peak is not as informative as for ^{1}H

-Generally ^{13}C don’t couple and to avoid complexity in the interpretation of the data ^{1}H-^{13}C coupling is turned off

-The peak you see labeled as $CDCl_3$ is deuterated chloroform included in the solvent

^{13}C-NMR spectroscopy

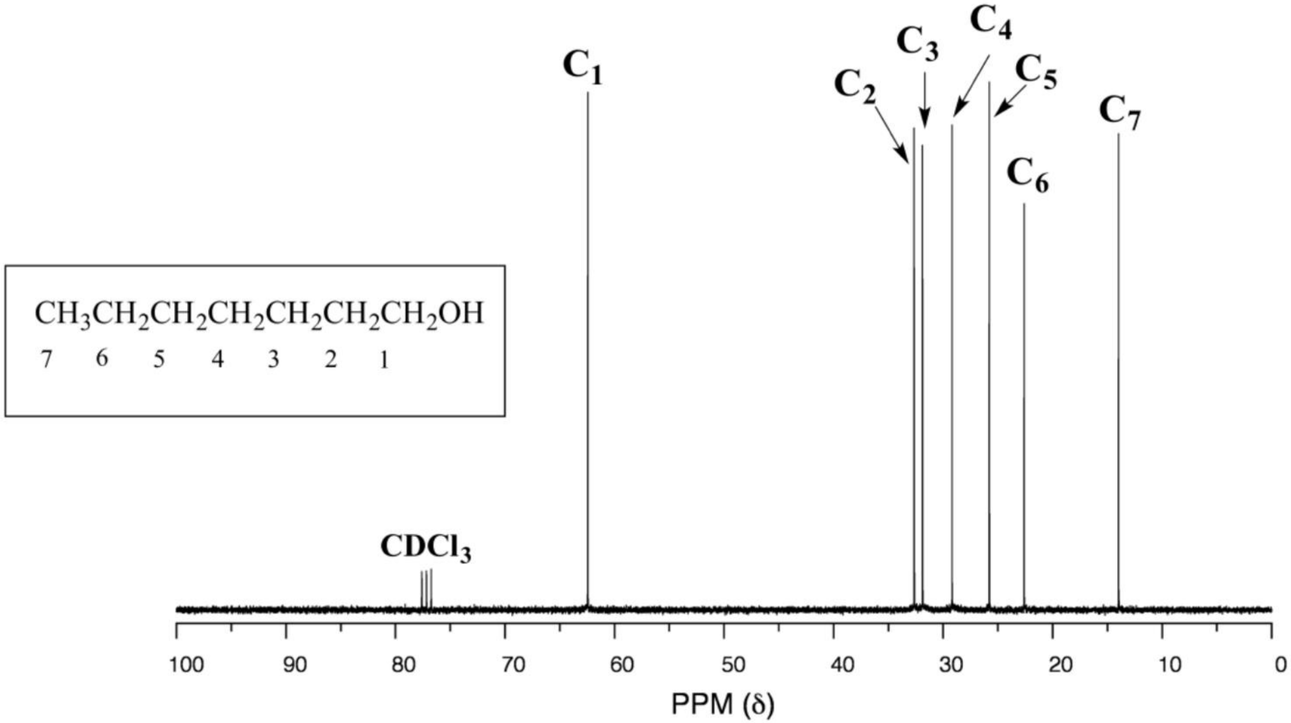
-let’s look an example



-Carbon peaks almost never overlap making the interpretation of the data easier

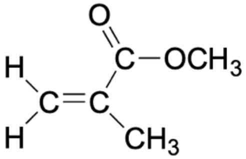
^{13}C-NMR spectroscopy

-let’s look an example

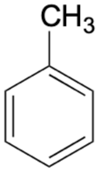


Let's discuss

Which spectrum belongs to which molecule ?

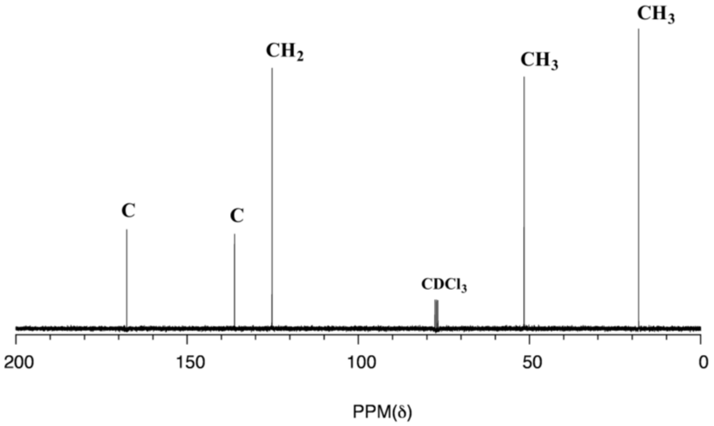


methyl methacrylate

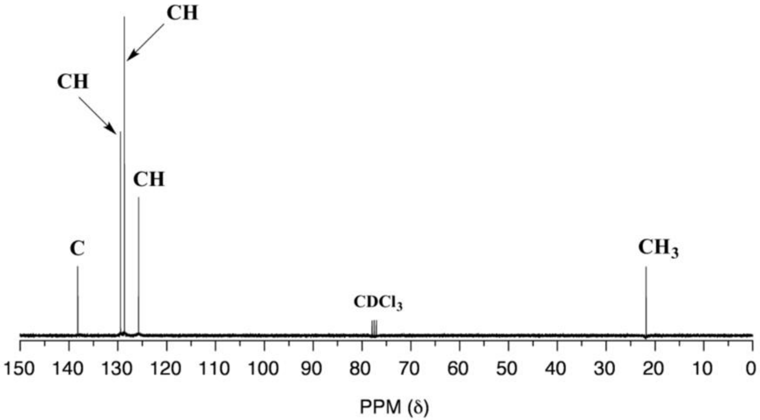


toluene

Spectrum A:

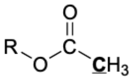
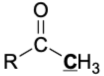
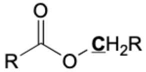
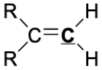
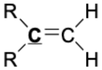
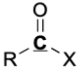
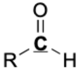
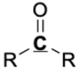


Spetrum B:



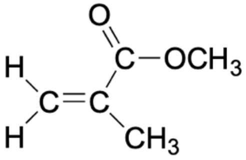
Let’s discuss

If I would give you this information would it become easier ?

Carbon type	**Chemical shift (ppm)**
$R\underline{\mathbf{C}}H_3$	13 - 16
$R\underline{\mathbf{C}}H_2R$	16 - 25
$R_3\underline{\mathbf{C}}H$	25 - 35
	18 - 22
	28 - 32
$R\underline{\mathbf{C}}H_2NHR$	35 - 45
$R\underline{\mathbf{C}}H_2OH$	50 - 65
$R{-}C{\equiv}\underline{\mathbf{C}}{-}R$	65 - 70
$RO\underline{\mathbf{C}}H_2R$	50 - 75
	50 - 75
	115 - 120
	125 - 140
aromatic carbon	125 - 150
 (carboxylic acid derivatives)	165 - 185
	190 - 200
	200 - 220

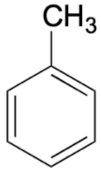
Let's discuss

Which spectrum belongs to which molecule ?



methyl methacrylate

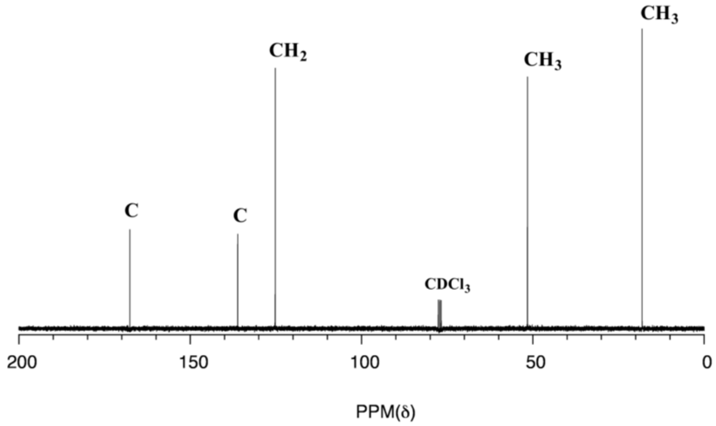
a



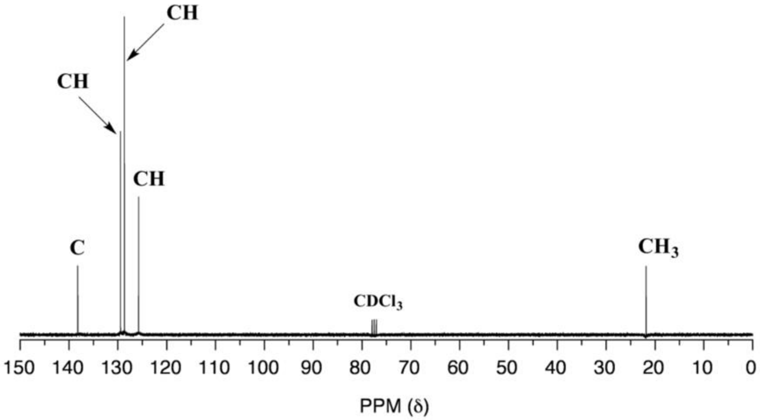
toluene

b

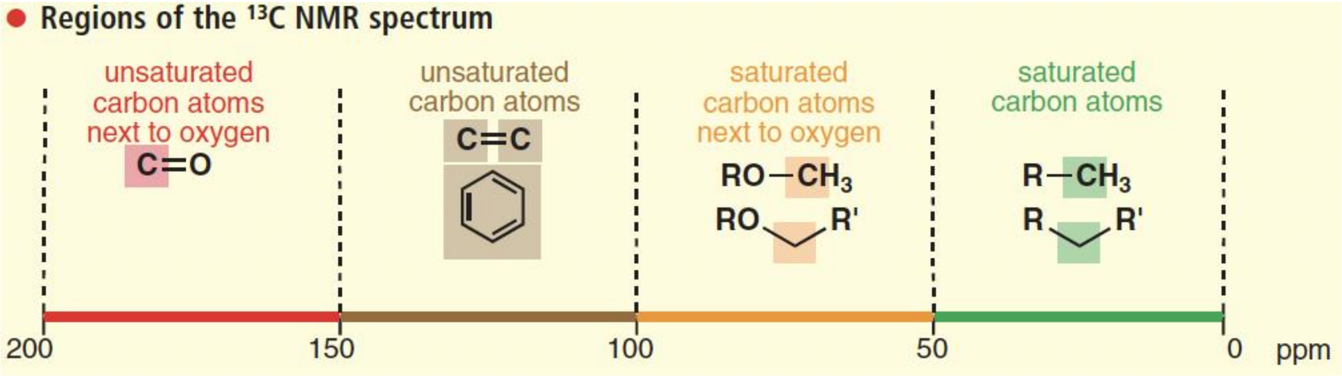
Spectrum A:



Spetrum B:



^{13}C-NMR



Regions of the ^{13}C NMR spectrum

unsaturated carbon atoms next to oxygen

C=O

unsaturated carbon atoms

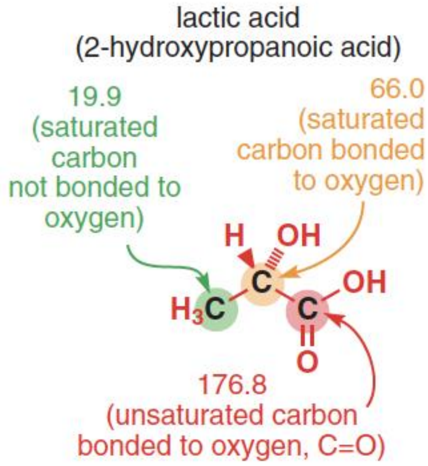
C=C

saturated carbon atoms next to oxygen

RO—CH_3

saturated carbon atoms

R—CH_3

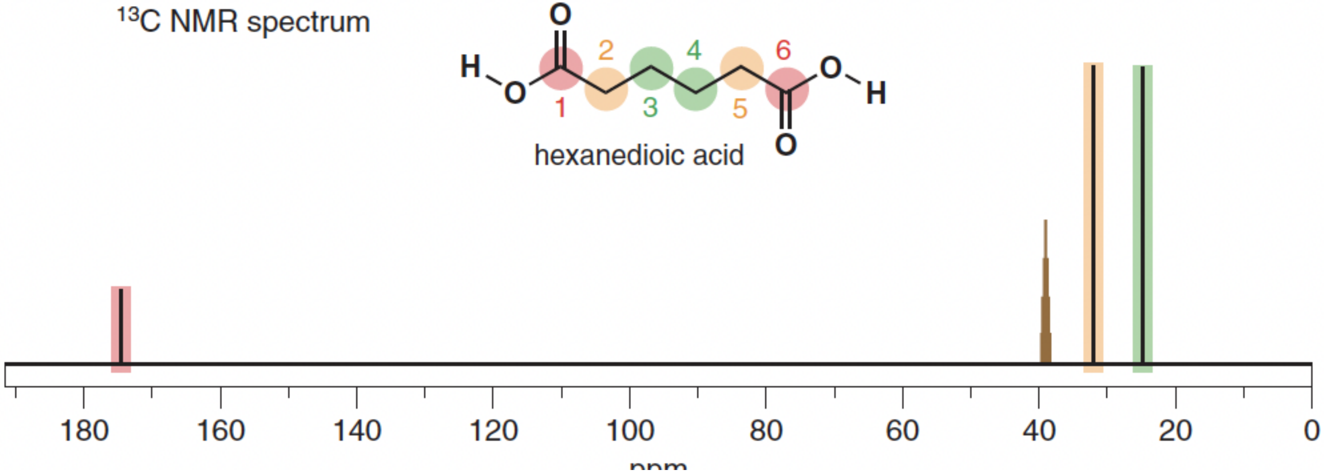


lactic acid
(2-hydroxypropanoic acid)

19.9
(saturated carbon not bonded to oxygen)

66.0
(saturated carbon bonded to oxygen)

176.8
(unsaturated carbon bonded to oxygen, C=O)



^{13}C NMR spectrum

hexanedioic acid

Solving unknown structures

- you are given a vial of an unknown sample – you are the first one to analyze it !!!!!

Step 1 – Use MS and combustion analysis to determine the molecular formula

Combustion analysis – will tell us the mass % of each element; the mass of O gest combusted

working example -> 52% of C; 38.3% Cl; 9.7% H

Next – we need to know its molecular mass - How to do it ?

Molecular ion peak in mass spec tells us that the molar mass 92 g/mole

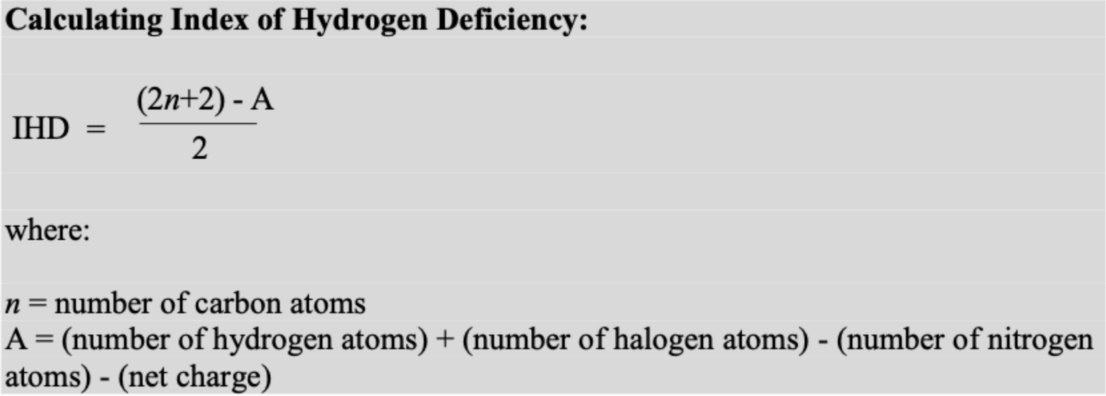
Moles of C -> 0.52* 92g = 47.8 g -> 1 mole of compound X has 4 moles of carbon
Analogously -> 9 moles of H and 1 Cl

The formula is C_4H_9Cl

Solving unknown structures

Step 2 – Calculating Index of Hydrogen Deficiency

-Will tell us the how many hydrogen bonds an/or ring structures our molecule has
Simple idea – presence of a double bond or a ring means that two fewer hydrogen atoms can be part of the compound



Calculating Index of Hydrogen Deficiency:

$$\text{IHD} = \frac{(2n+2) - \text{A}}{2}$$

where:

n = number of carbon atoms
A = (number of hydrogen atoms) + (number of halogen atoms) - (number of nitrogen atoms) - (net charge)

Examples:
C_6H_{14} -> IHD = 0 -> no double bonds or rings
C_6H_{12} -> IHD = 1 -> one double bond or ring like cyclohexane or 2-hexene
C_6H_6 -> IHD = 4 -> three double bonds and one ring benzene

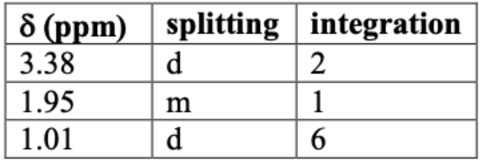
- For our molecule C_4H_9Cl -> IHD = 0 -> no double bonds or rings

Solving unknown structures

Step 3 – Use available spectroscopy data to identify discrete parts of the structure

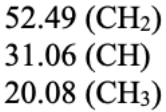
-In this case we will just use NMR data (C_4H_9Cl)

^{1}H-NMR



δ (ppm)	splitting	integration
3.38	d	2
1.95	m	1
1.01	d	6

^{13}C-NMR

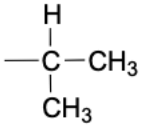


52.49 (CH_2)
31.06 (CH)
20.08 (CH_3)

-only 3 signals in each NMR spectrum -> tell us that two carbons are chemically equivalent

-1.01 ppm in the proton spectrum corresponds to six protons strongly suggests that the molecule has two equivalent methyl (CH_3) groups

-Since this signal is a doublet there must be a CH carbon bound to each of these two methyl groups



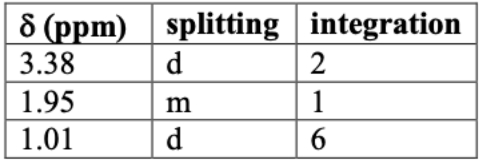
$-\overset{\displaystyle H}{\underset{\displaystyle CH_3}{C}}-CH_3$

Solving unknown structures

Step 3 – Use available spectroscopy data to identify discrete parts of the structure

-In this case we will just use NMR data (C_4H_9Cl)

^{1}H-NMR



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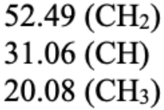
^{13}C-NMR



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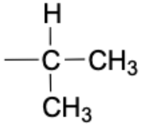
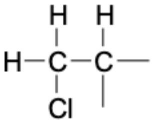


- 1H-NMR signal at 3.38 ppm must be for protons bound to the carbon which is bound to the chlorine (electromagnetic atom which dishields)

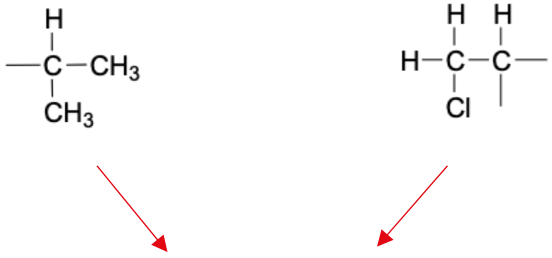
-The signal is for 2 protons and is a doublet meaning there is a single non-equivalent proton on an adjacent carbon

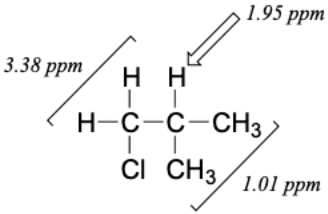


Solving unknown structures

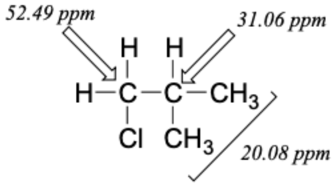
Step 4 – Put the pieces of the puzzle together

-In this case we will just use NMR data (C_4H_9Cl)





^{1}H-NMR assignments



^{13}C-NMR assignments

Key concepts

-Identify groups of chemically equivalent protons and carbons in a structure

- Understand how to look at an NMR spectrum including meaning of the ppm label and chemical shift

-Predict trends in chemical shift

-Understand how to use proton peak integration values to determine how many protons a peak is worth

-Interpret splitting in NMR spectrum

-Understand ^{13}C NMR spectra

-Match structures to ^{1}H and ^{13}C spectra

-Capable of solving an unknown structure from multiple experimental data sources

Questions ?

Next lecture

Organic Reactivity (Chapter 6)

Now we start with organic chemistry

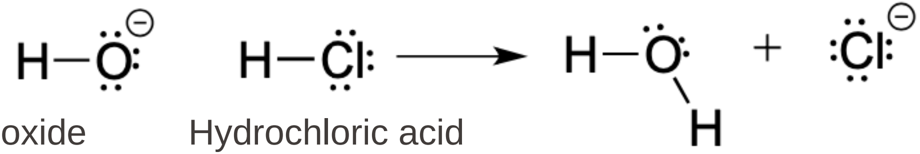
What has happened until now in bio-organic chemistry

Structure → **Experimental techniques** → **Chemical reactions**

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

Reaction mechanism

Let's look at a simple reaction – acid-base (proton transfer) reaction

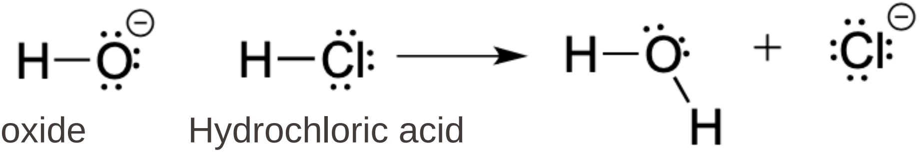


Hydroxide

Hydrochloric acid

What is there to know in simple chemical reactions

-Let’s look at a simple reaction – acid-base (proton transfer) reaction

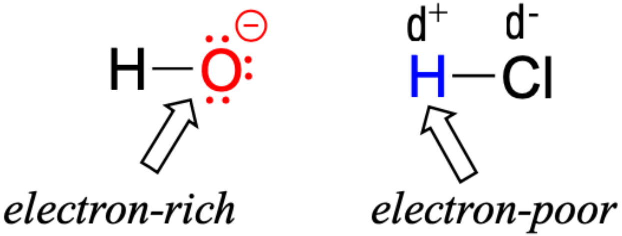


Hydroxide Hydrochloric acid Water chloride

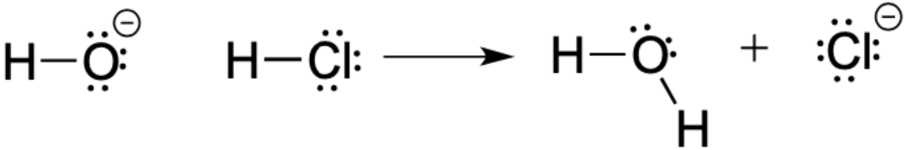
Reactants **Products**

-A proton is transferred from HCl (acid) to the hydroxide ion the base

-To understand such reaction mechanism we need to think in terms of **electron density**



What is there to know in simple chemical reactions



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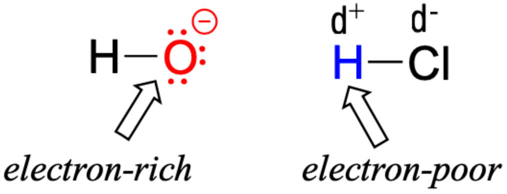


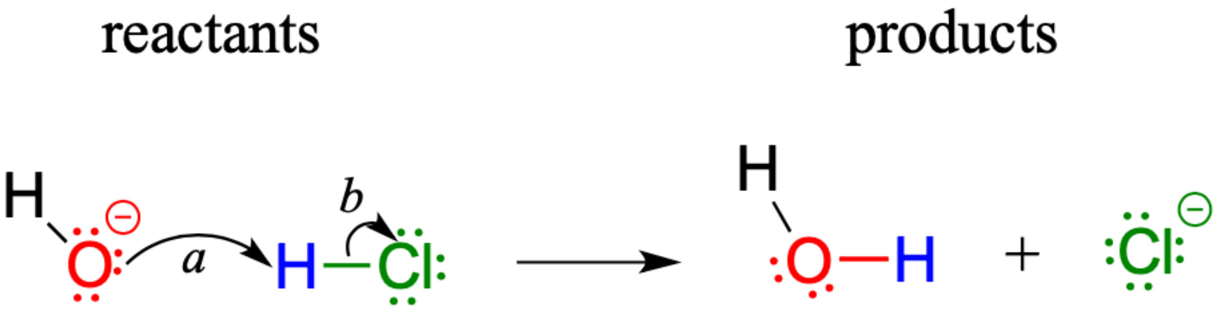
- The bond breaking and forming events, **electron movement**, is based on electron density

High electron density
(O has a negative charge)

Low electron density
(Cl is very electronegative)

- Electron rich groups are attracted to electron poor reagents

What is there to know in simple chemical reactions



-We will use curved arrows in mechanism drawings to show electron movement where bonds are broken and formed

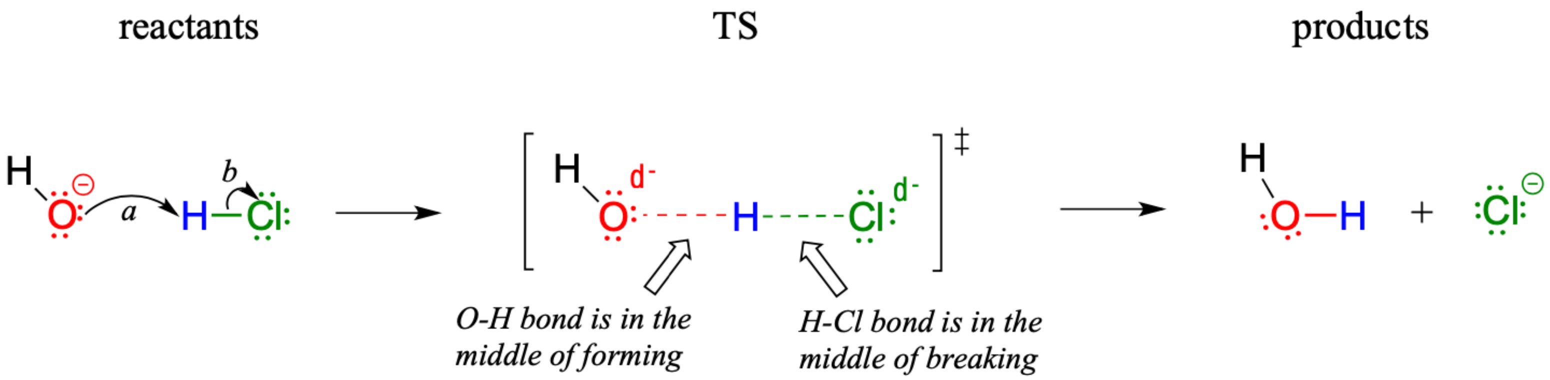
a – originates at one of the lone pairs on hydroxide oxygen and points to the H symbol in hydrochloric acid

b- originates at the middle of the hydrogen-chlorine bond and points to the Cl symbol indicating that the bond is breaking

-These steps are occurring simultaneously

-An arrow always indicates the movement of two electrons

What species are formed in the process of a chemical reaction



O-H bond is in the middle of forming

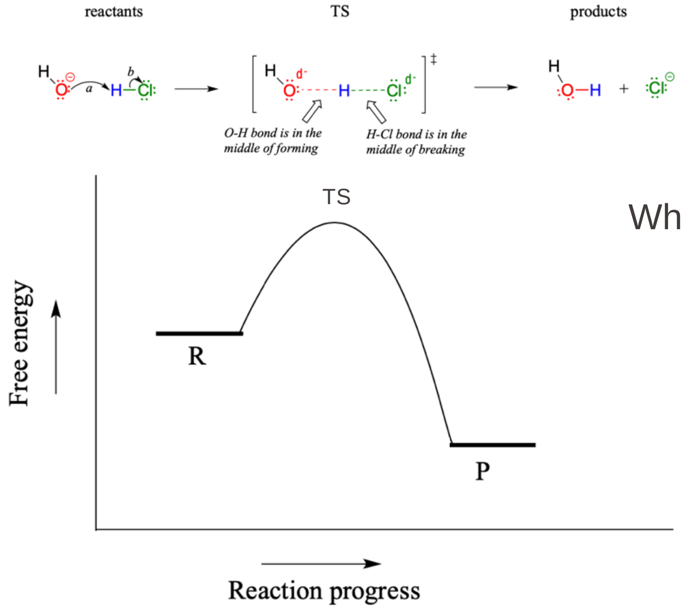
H-Cl bond is in the middle of breaking

-Transition state of a chemical step indicates the highest energy of a chemical step

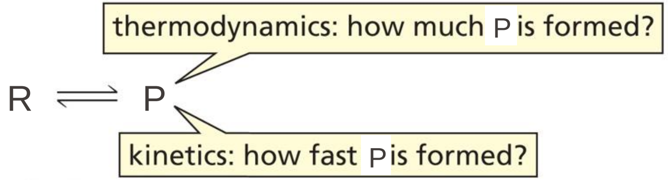
-Notice the format in which the transition state molecule us described

Remembering general chemistry

The reaction coordinate diagram (free energy surface along the reaction pathway)



What can we derive from the reaction coordinate diagram?



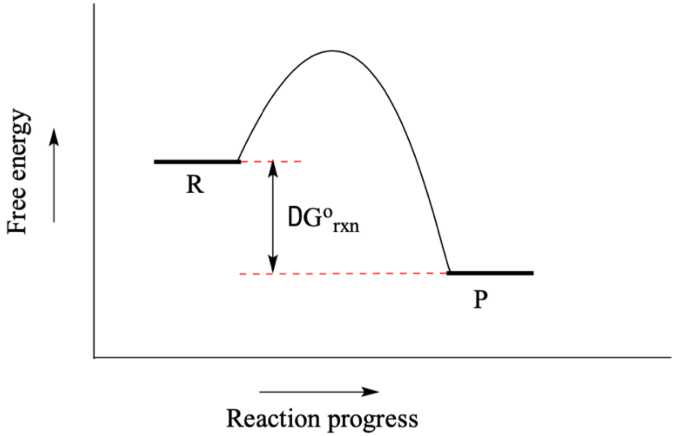
thermodynamics: how much P is formed?

$R \rightleftharpoons P$

kinetics: how fast P is formed?

Reaction Thermodynamics

Change in free energy



-Standard Gibbs free-energy change (ΔG) tells us the difference between the energy of reactants and products

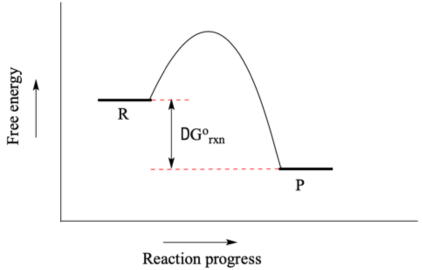
-Enthalpy change (ΔH^0) – heat released or absorbed by the reaction

-Entropy change (ΔS^0) – change in disorder from reactants to products

$$\Delta G = \Delta H^o - T\Delta S^o$$

Reaction Thermodynamics

Chemical equilibria



this means that w molecules of compound A react with x molecules of compound B)

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

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

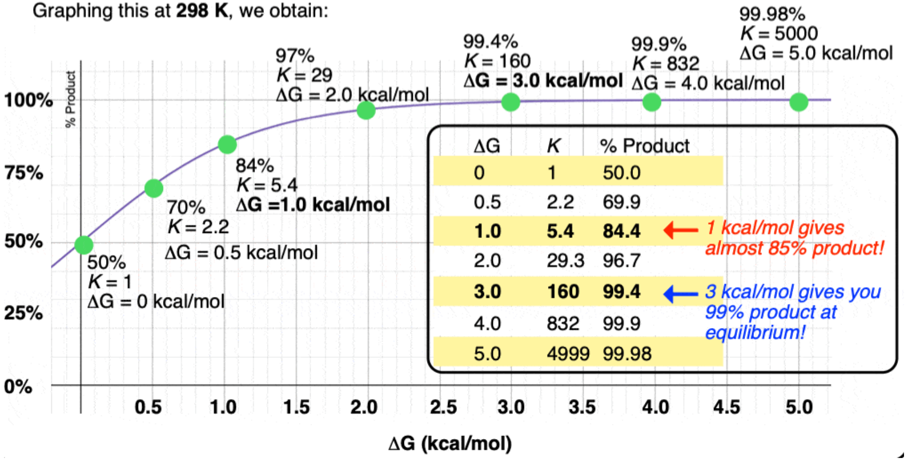
Equilibrium constant (K_{eq}) – relative concentration of reactants and products

$$\Delta G^\circ = -RT\ \ln K_{eq}$$

$$\boxed{K = e^{(-\Delta G/RT)}}$$ or, rearranged $$\boxed{\Delta G = -RT\ \ln K}$$

where R is the gas constant (0.0019872 kcal K^{-1} mol $^{-1}$) note: 1 kcal/mol = 4.184 kJ/mol
and T is temperature (in Kelvin)

Graphing this at **298 K**, we obtain:



ΔG	K	% Product
0	1	50.0
0.5	2.2	69.9
1.0	**5.4**	**84.4**
2.0	29.3	96.7
3.0	**160**	**99.4**
4.0	832	99.9
5.0	4999	99.98

1 kcal/mol gives almost 85% product!

3 kcal/mol gives you 99% product at equilibrium!

Graph: https://www.masterorganicchemistry.com/2023/08/02/equilibrium-constant-delta-g-calculations-organic-chemistry/, 20.03.2025.

Let’s discuss

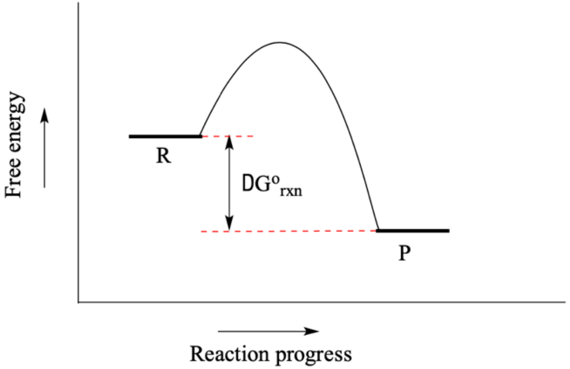
What happens to the equilibrium constant when the temperature is changed?

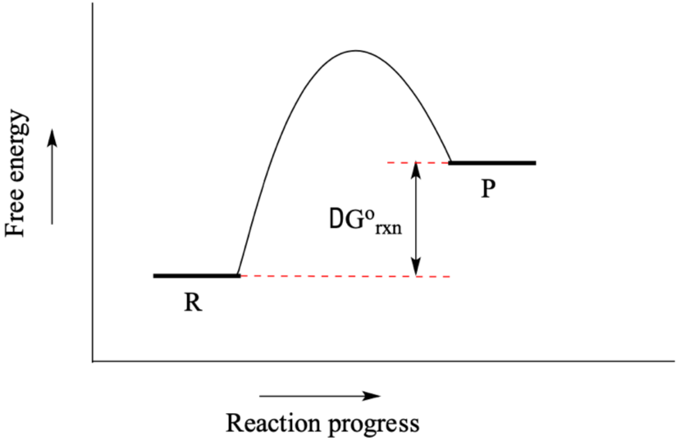
$$K = e^{(-\Delta G/RT)}$$

Graph: https://www.masterorganicchemistry.com/2023/08/02/equilibrium-constant-delta-g-calculations-organic-chemistry/, 20.03.2025.

Reaction Thermodynamics

Reaction classification

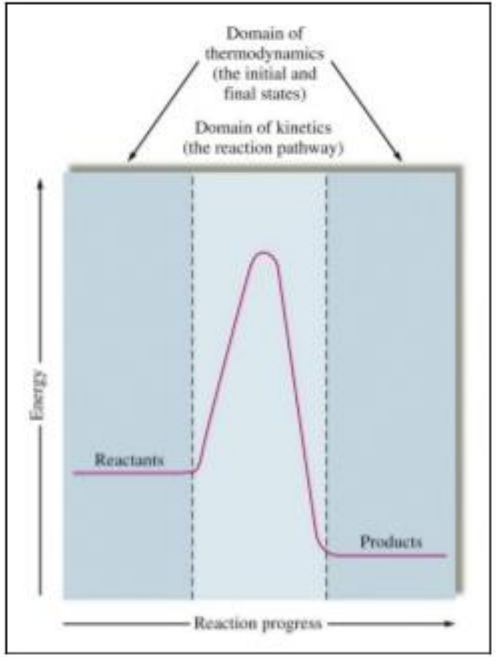




Exergonic
-Gibbs free-energy change is negative
-Energy releasing
-Thermodynamically favorable
-$K_{eq} > 1$

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

Thermodynamics Vs Kinetics

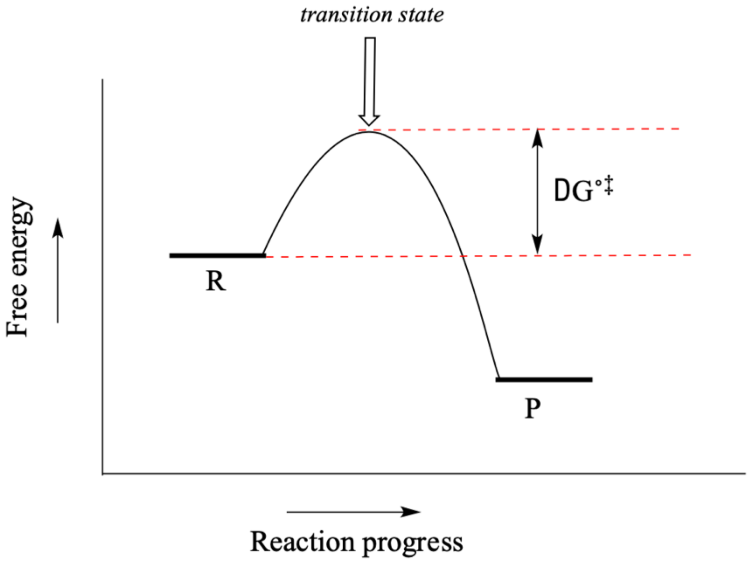


-Thermodynamics has no concept of time simply of energy

-Thermodynamics does not consider the existence of a pathway only considers initial state and final state

Reaction Kinetics

Activation energy



The free energy of activation ΔG‡ is the energy barrier of the reaction:

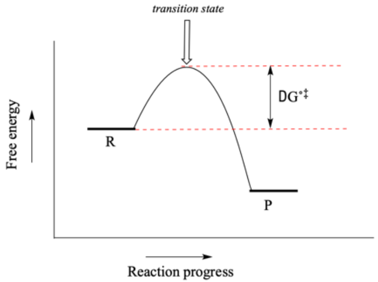
$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

$$\Delta H^{\ddagger} = (\text{enthalpy of the transition state}) - (\text{enthalpy of the reactants})$$

$$\Delta S^{\ddagger} = (\text{entropy of the transition state}) - (\text{entropy of the reactants})$$

Chemical Reactivity

Rate of a Reaction



$$\text{rate of a reaction} = \left(\begin{array}{c}\text{number of collisions}\\ \text{per unit of time}\end{array}\right) \times \left(\begin{array}{c}\text{fraction with}\\ \text{sufficient energy}\end{array}\right) \times \left(\begin{array}{c}\text{fraction with}\\ \text{proper orientation}\end{array}\right)$$

First order kinetics: A -> B

$$\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = -k[\mathrm{A}]$$

Reaction Rate

Rate constant

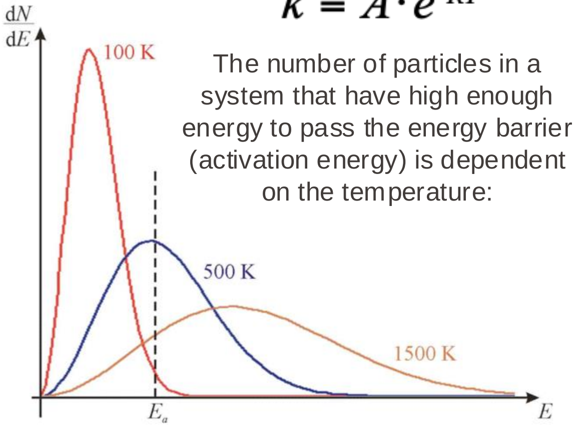
Second order kinetics A + B -> C

$$\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathrm{B}]}{\mathrm{d}t} = -k \cdot [\mathrm{A}] \cdot [\mathrm{B}]$$

Arrhenius:

$$k = A \cdot e^{\frac{-E_a}{RT}}$$

The number of particles in a system that have high enough energy to pass the energy barrier (activation energy) is dependent on the temperature:

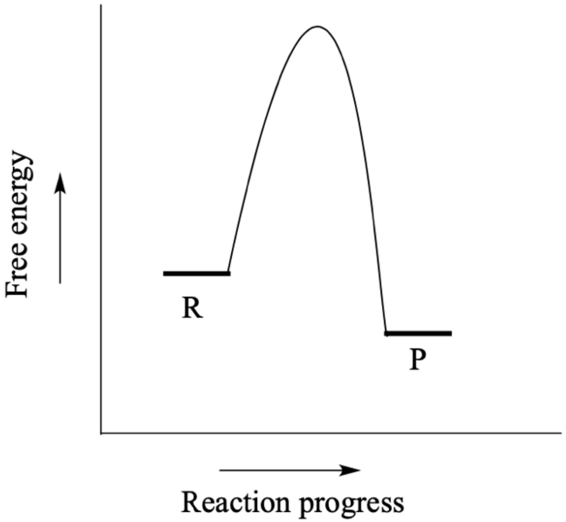


Le Chatelier:

- Increasing the concentration increases the rate.
- Increasing the temperature increases the rate.
- The rate can also be increased by a catalyst.

Catalysis

R -> P

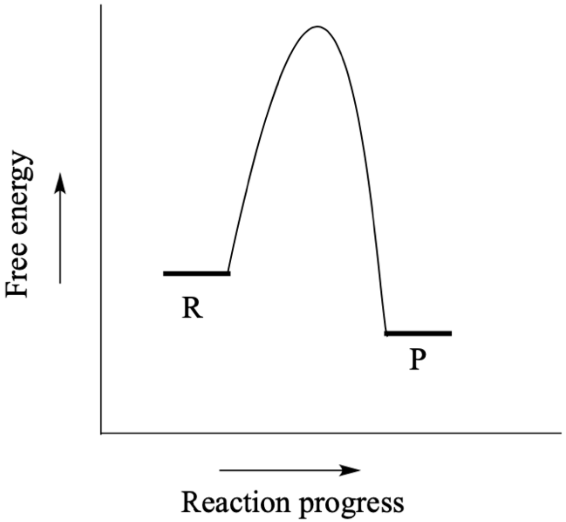


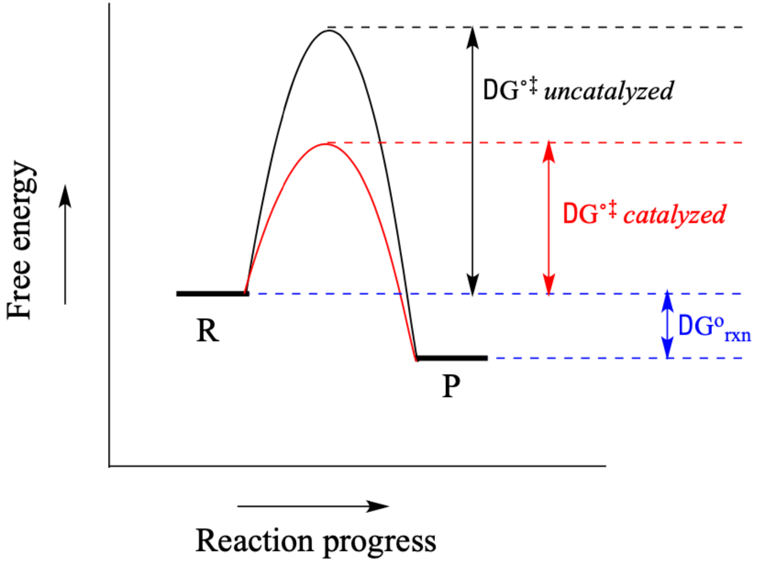
How can we accelerate such reaction ?

-Exergonic reaction
-High activation energy
-Favorable but slow

Catalysis

R -> P

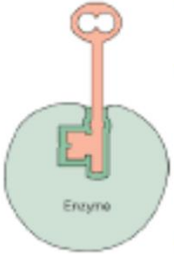




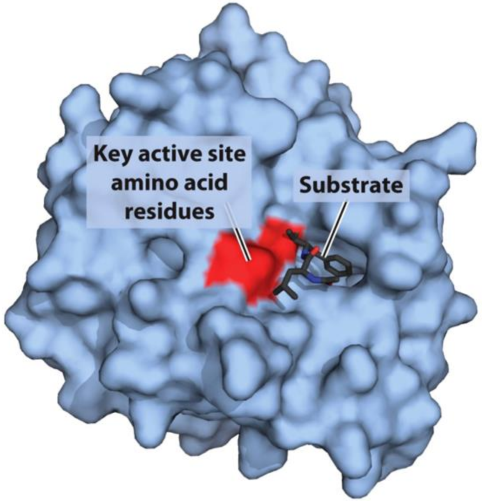
-Exergonic reaction
-High activation energy
-Favorable but slow

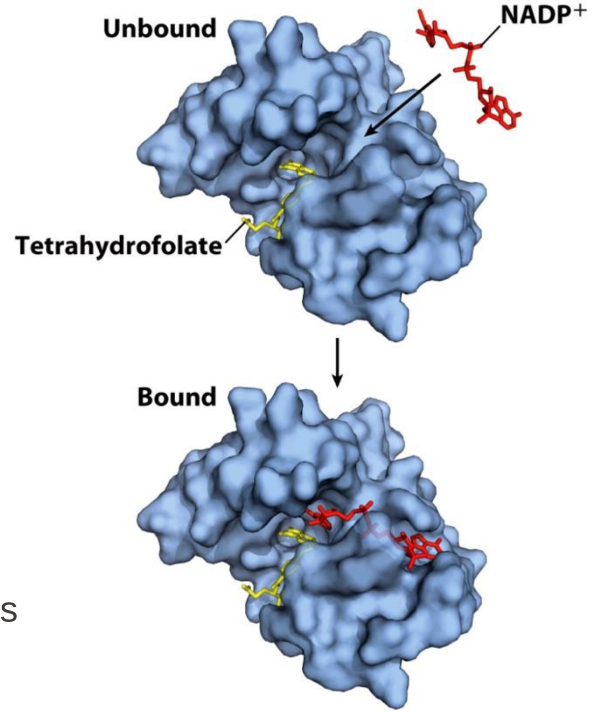
-Catalyst accelerates the reaction by stabilizing the transition state
-Catalysts increase the reaction rate but do not get consumed
-Do not affect the equilibrium constant
-Affect the kinetics but not the thermodynamics

Nature makes some of the best catalysts



- Binding of two molecules reduces the Gibbs Energy (Binding energy)
- Lock and key model (Fischer, 1894) was proposed to explain the specificity of enzyme with substrate
- It cannot explain how an enzyme reduces energy barrier
- Key is not the substrate, but the transition state : Transition state stabilization explains both specificity and catalysis (Pauling, 1946)



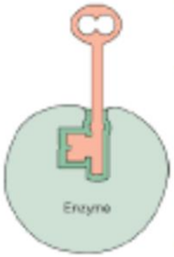


-Positioning of two reacting molecules close to each other in the active site as opposed to random collisions in solution

-Binding substrates in the proper configuration for the reaction

-Increasing reactivity of the the substrates by enhancing acidity, nucleophilicity, electrophilicity

Nature makes some of the best catalysts



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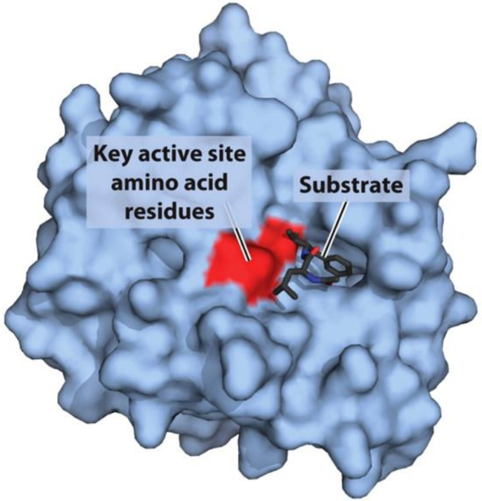
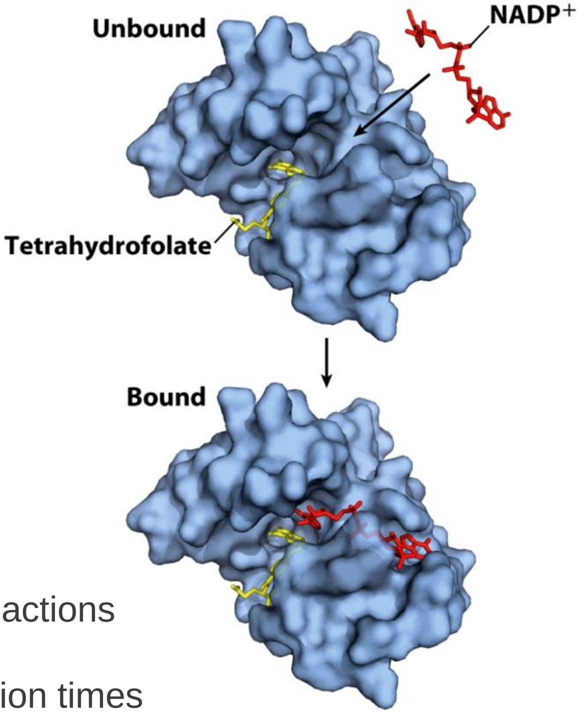




-Stabilizing the transition states of the slower, rate determining steps of the reactions

-Typical enzymes will speed up a reaction by anywhere from a million to a billion times

-The most efficient enzyme currently known to scientists accelerates its reaction by a factor of about 10^{17} over the uncatalyzed reaction

Differences between laboratory and biological reactions

Catalyst – bio-reactions use enzymes chemists often metals, acids or bases as catalysts

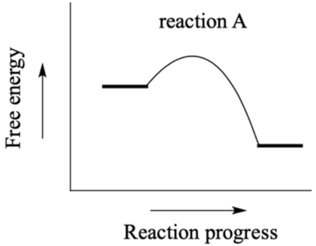
Solvent – bio-reactions in water, chemical reactions varying from apolar (e.g.hexane) to polar (e.g. methanol)

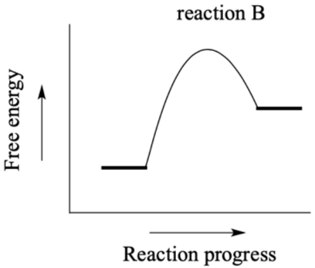
Reactant mixture – bio-reactions done at μM levels with complex media (many proteins and other biomolecules) while chemical reactions are generally carried with purified molecules at very high concentrations

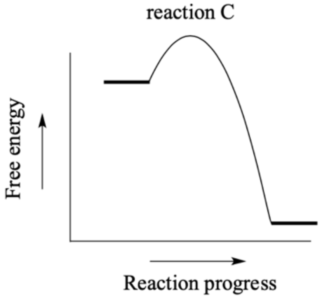
Temperature – Bio-reactions run at a very narrow range of temperature (in humans around 37 ^{0}C) while chemical reactions on large range of temperatures

pH – Bio-reactions take place at around pH around 7 while chemical reactions over a wide range

Let’s discuss







-Which diagram describes a reaction with K_{eq} <1 ?

-Which diagram describes the fastest reaction ?

-Which diagram describe the reaction with highest value of K_{eq} ?

Key concepts

-Interpreting and using the **curved arrow** drawing convention for showing **two-electron movement**

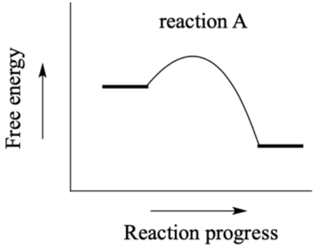
-Given a reaction coordinate diagram for a hypothetical reaction, you should be able to recognize whether the reaction is **endergonic or exergonic**, and whether the **equilibrium constant is greater than or less than 1**.

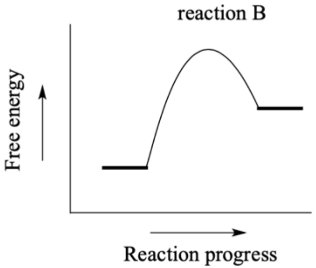
-Explain the role of a **catalyst** in a reaction.

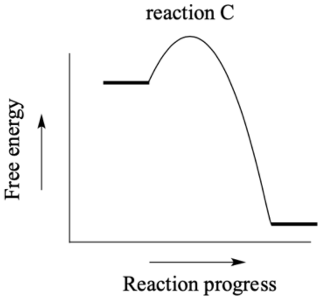
-Major differences between a **typical biological reaction and a typical laboratory reaction**.

Questions ?

How to predict reactivity

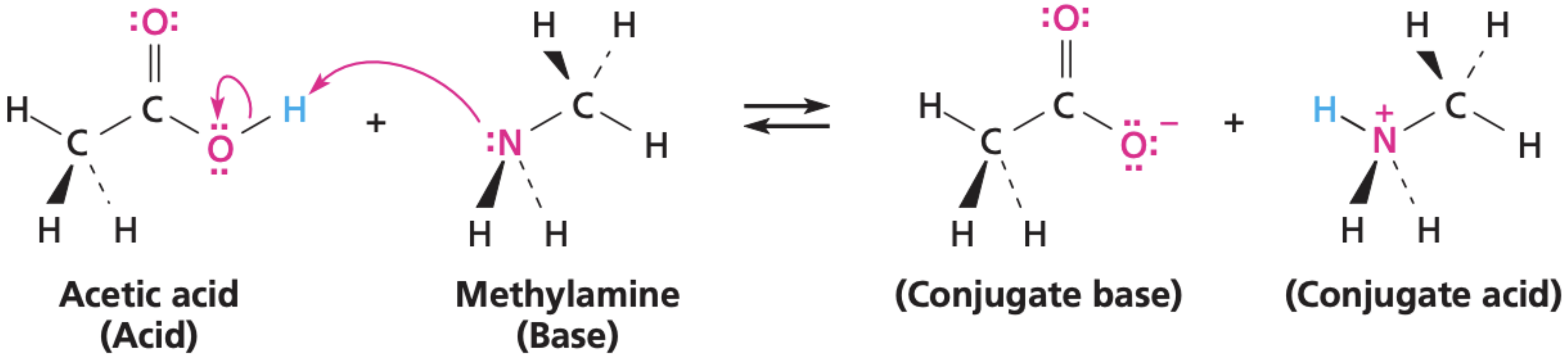




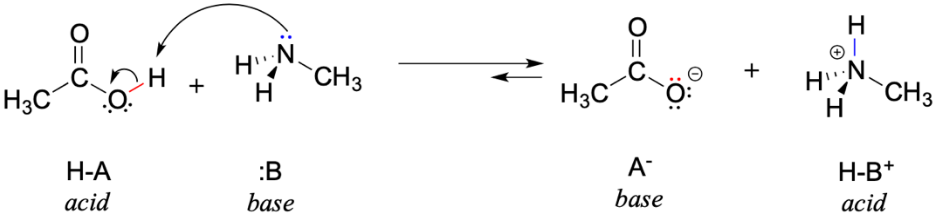


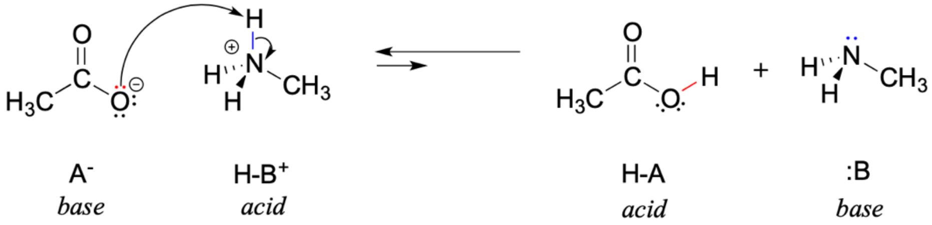
Brønsted-Lowry Acids and Bases

Acid = Proton Donor
Base = Proton Acceptor



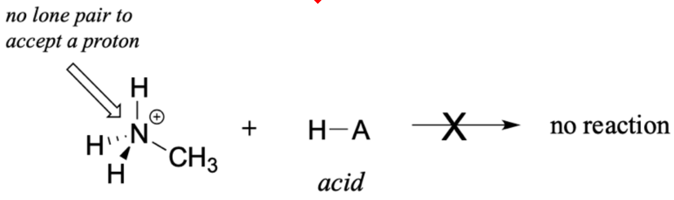
Brønsted-Lowry Acids and Bases



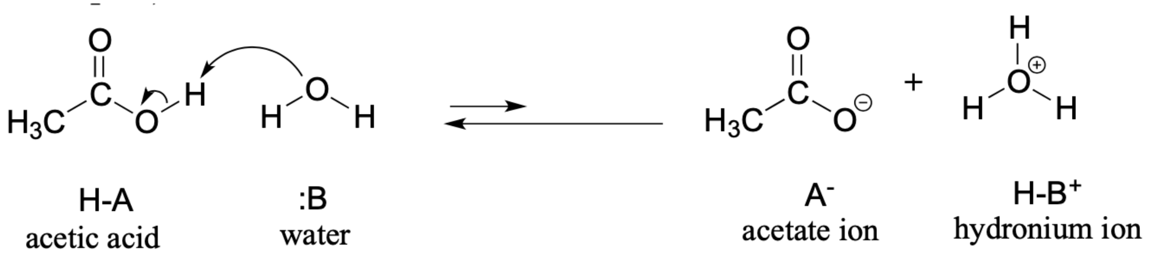


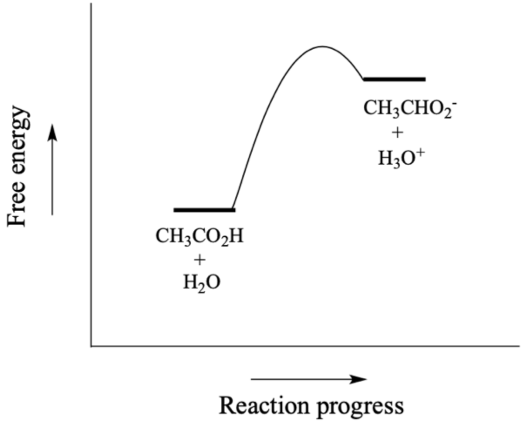
What makes a compound acidic (likely to donate electrons) or basic (likely to accept electrons)?

In order to act as a base, a molecule must have a reactive pair of electrons



Defining the acidity constant





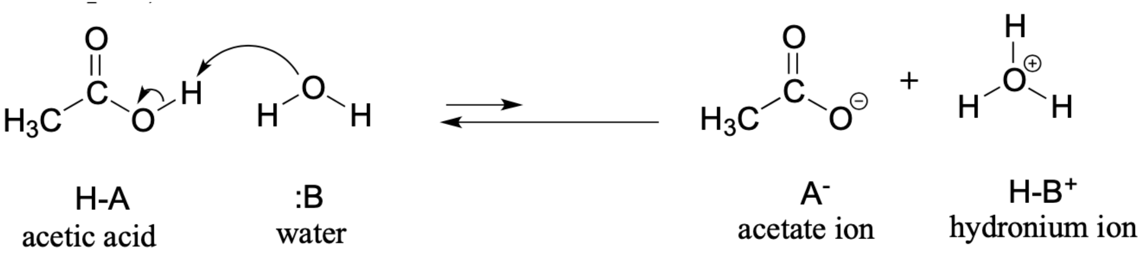
-the capacity to donate a proton to a base – is quantified by a number called the acidity constant, abbreviated **K_a**.

-In this case acetic acid is a weak acid and is thermodynamically unfavorable

$$K_{eq} = \frac{[\text{products}]}{[\text{reactants}]} = \frac{[CH_3COO^-]\,[H_3O^+]}{[CH_3COOH]\,[H_2O]} \longrightarrow K_a = K_{eq}[H_2O] = \frac{[CH_3COO^-]\,[H_3O^+]}{[CH_3COOH]}$$

- Water concentration is so high that it barely changes as such can be considered a constant

Defining the acidity constant



$$K_a = K_{eq}[H_2O] = \frac{[CH_3COO^-]\,[H_3O^+]}{[CH_3COOH]}$$

-In general terms

$$HA + H_2O \rightleftharpoons :A^- + H_3O^+ \qquad HB^+ + H_2O \rightleftharpoons :B + H_3O^+$$

$$K_a = \frac{[:A^-]\,[H_3O^+]}{[HA]} \quad \textit{or} \quad K_a = \frac{[:B]\,[H_3O^+]}{[HB^+]}$$

K_a acetic acid = 1.75×10^{-5}

Much < 1 indicating that the reactants are in greater quantity

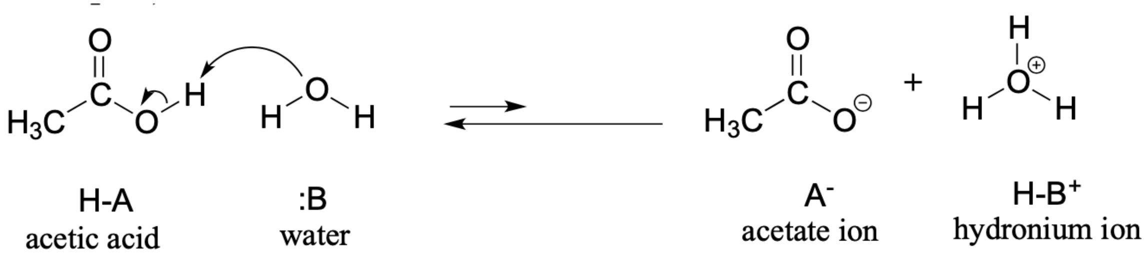
Weak acid

K_a sulfuric acid = 10^9

Much > 1 indicating that the products are in greater quantity

Strong acid

Defining the acidity constant



K_a acetic acid = 1.75×10^{-5}

Much < 1 indicating that the reactants are in greater quantity

Weak acid

$$K_a = K_{eq}[H_2O] = \frac{[CH_3COO^-]\,[H_3O^+]}{[CH_3COOH]}$$

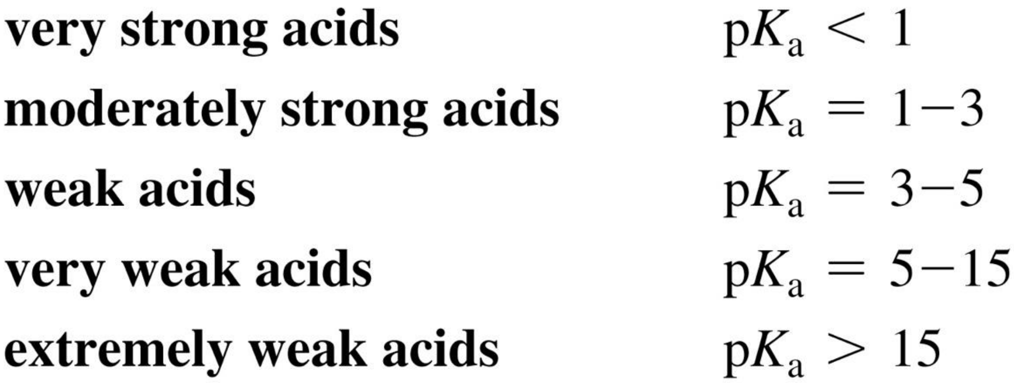
$$pKa = -\log Ka \qquad Ka = 10^{-pKa}$$

K_a acetic acid = 1.75×10^{-5} => pKa = 4.8

K_a sulfuric acid = 10^9 => pKa = -10

The lower the pKa the stronger the acid

Acid strength



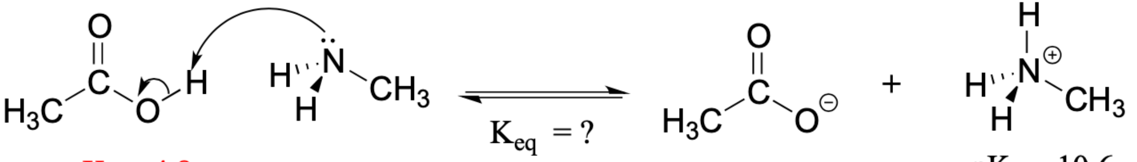
very strong acids	$pK_a < 1$
moderately strong acids	$pK_a = 1-3$
weak acids	$pK_a = 3-5$
very weak acids	$pK_a = 5-15$
extremely weak acids	$pK_a > 15$

$$pKa = -\log Ka$$

The stronger the acid, the higher the K_a.

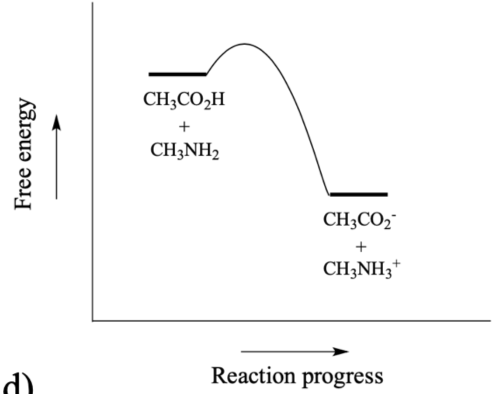
The stronger the acid, the lower the pK_a.

Using pKa values to predict reaction equilibrium



$pK_a = 4.8$
(stronger acid)

$pK_a = 10.6$



$$K_{eq} = 10^{\Delta pKa}$$

ΔpKa = (pKa of product acid minus pKa of reactant acid)

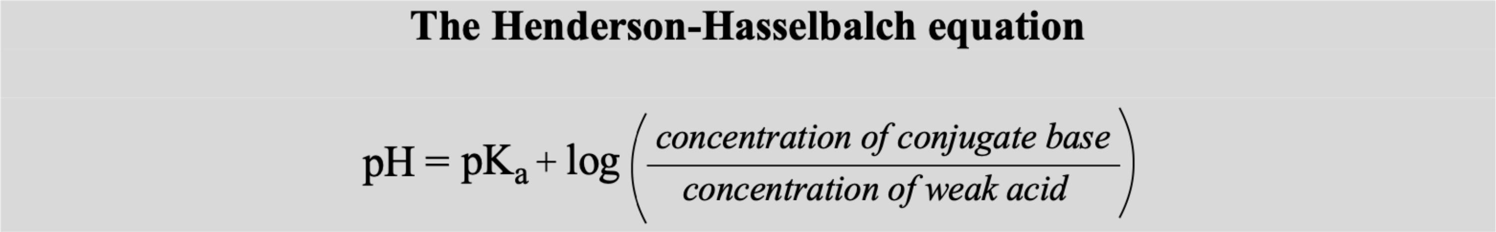
-First you look up the pKa values of both acids (reactants and products)
-We already have a notion that pKa of acetic acid is 5 and ammonium is about 10
-acetic acid has a lower pKa so it wants to donate its proton more than ammonium

$$K_{eq} = 10^{\Delta pKa} = 10^{(10.6 - 4.8)} = 10^{5.8} = 6.3 \text{ x } 10^5$$

reaction goes from left to right

-> The equilibrium favors formation of the weaker acid (weaker ≡ more stable ≡ less reactive)

Organic molecules in buffered solution
Henderson-Hasselbalch equation



The Henderson-Hasselbalch equation

$$\mathrm{pH} = \mathrm{p}K_a + \log\left(\frac{\textit{concentration of conjugate base}}{\textit{concentration of weak acid}}\right)$$

-if our buffer is an equimolar solution of a weak acid and its conjugate base the pH of the buffer will be equal to the pKa of the acid (log of 1 is 0)

- if there is more acid the pH of the buffer is lower than the pKa of the acid

-The Henderson-Hasselbalch equation is useful to try to figure out the protonation state of different functional groups at pH 7

Organic molecules in buffered solution
Henderson-Hasselbalch equation

The Henderson-Hasselbalch equation

$$pH = pK_a + \log\left(\frac{\textit{concentration of conjugate base}}{\textit{concentration of weak acid}}\right)$$

Lets think about aspartate side chain

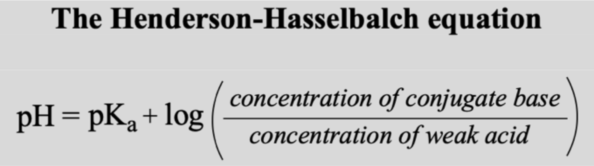
pKa = 5

pH = 7

With this amount of information you should be able to tell me which species does the carboxylic acid is more present at pH=7?

Give it a try !!!!!

Organic molecules in buffered solution
Henderson-Hasselbalch equation



The Henderson-Hasselbalch equation

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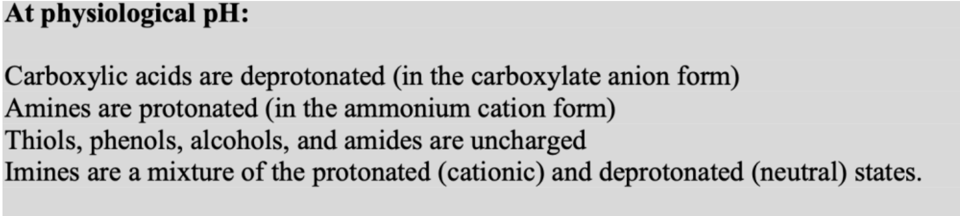
Doing calculations for other groups :



At physiological pH:

Carboxylic acids are deprotonated (in the carboxylate anion form)
Amines are protonated (in the ammonium cation form)
Thiols, phenols, alcohols, and amides are uncharged
Imines are a mixture of the protonated (cationic) and deprotonated (neutral) states.

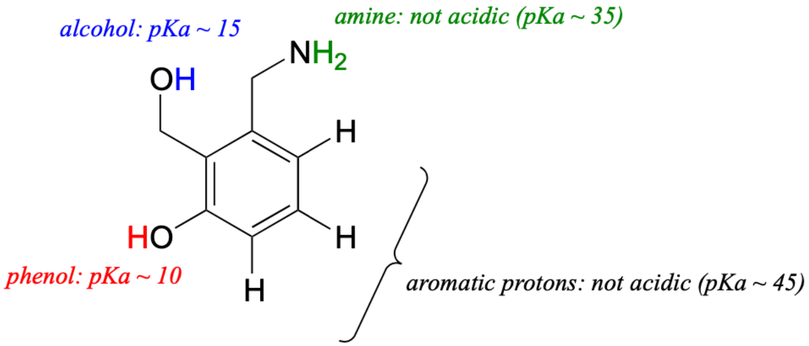
Acidity of different groups

(weaker ≡ more stable ≡ less reactive)

The **key idea** to remember is this: **The weaker (more stable) the conjugated base the stronger the acid.**

→

Hydroxide ion is a stronger base than ammonia (NH_3), because ammonium ion (NH_4+, pKa = 9.2) is a stronger acid than water (pKa = 15.7)



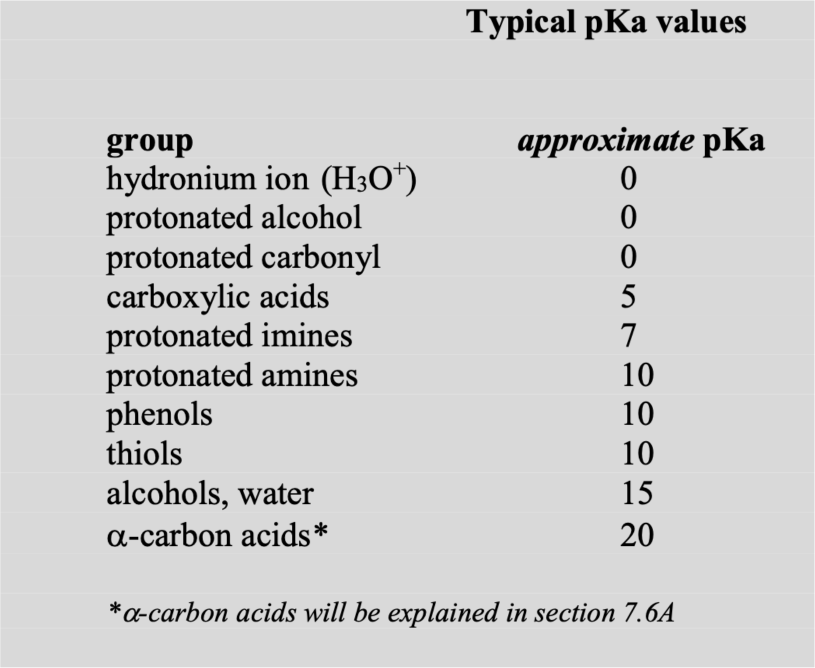
-aromatic, amines are not acidic

-phenol proton more acidic than alcohol

-phenol proton will donated to form the phenolate anion

Acidity of different groups

-pKa values of common compounds and functional groups on a numerical scale of about –10 (for a very strong acid) to 50 (for a compound that is not acidic at all)



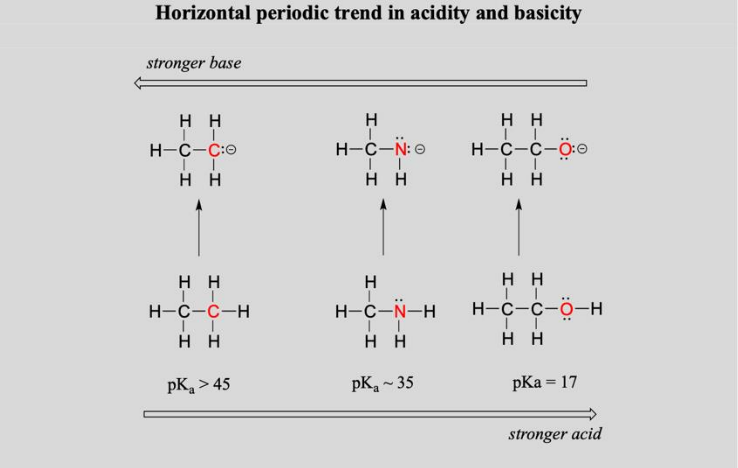
Typical pKa values

group	***approximate* pKa**
hydronium ion (H_3O^+)	0
protonated alcohol	0
protonated carbonyl	0
carboxylic acids	5
protonated imines	7
protonated amines	10
phenols	10
thiols	10
alcohols, water	15
α-carbon acids*	20

******α-carbon acids will be explained in section 7.6A*

Structural effects on acidity and basicity

Electronegativity affects pK_a values



relative electronegativities: C < N < O < F

most electronegative

When atoms are the same size, the strongest acid has its hydrogen attached to the most electronegative atom.

relative acidities: $CH_4 < NH_3 < H_2O < HF$

strongest acid

-> Stable bases are weak bases

Structural effects on acidity and basicity

Some pK_a values

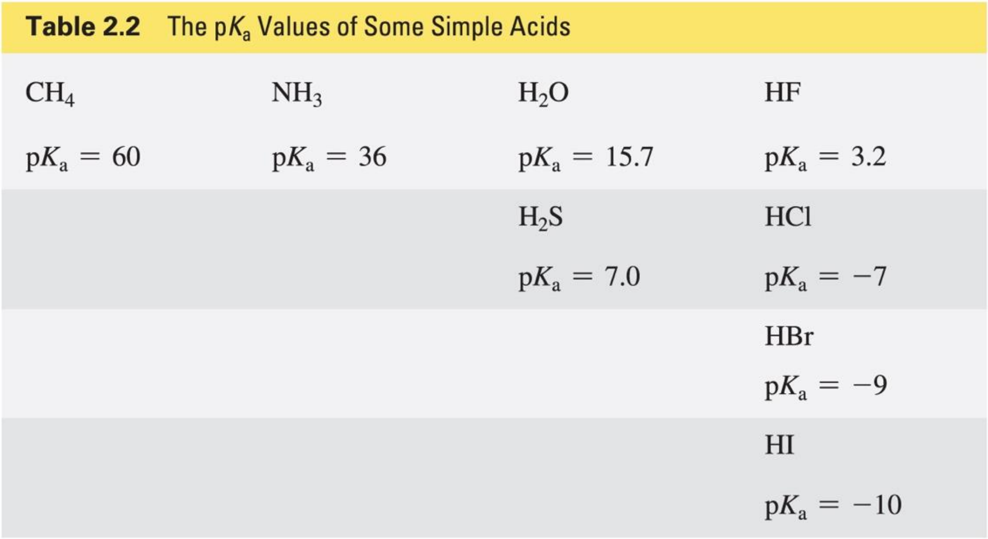


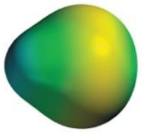
Table 2.2 The pK_a Values of Some Simple Acids

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

HF

HCl

HBr



HI

-> Vertical trend not following electronegativity!?

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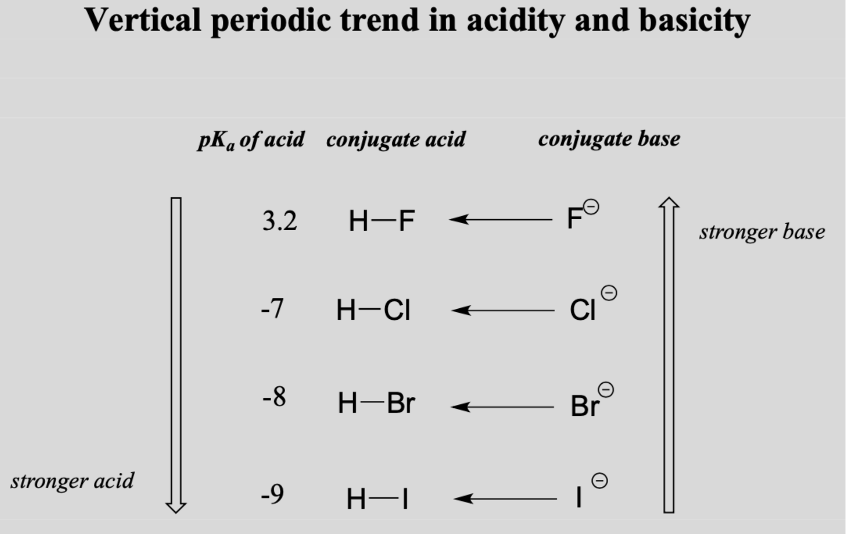
Structural effects on acidity and basicity

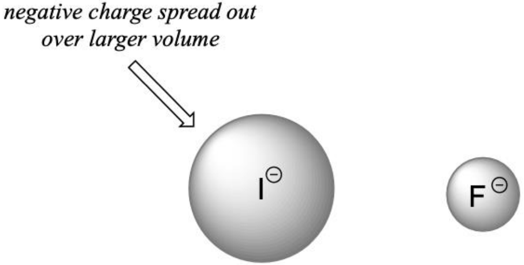
Atom radius affects pK_a values



Vertical periodic trend in acidity and basicity

pK_a of acid	*conjugate acid*	*conjugate base*
3.2	H—F	$F^\ominus$
-7	H—Cl	$Cl^\ominus$
-8	H—Br	$Br^\ominus$
-9	H—I	$I^\ominus$

Electrostatic charges whether positive or negative, are more stable when they are spread out over a larger area.



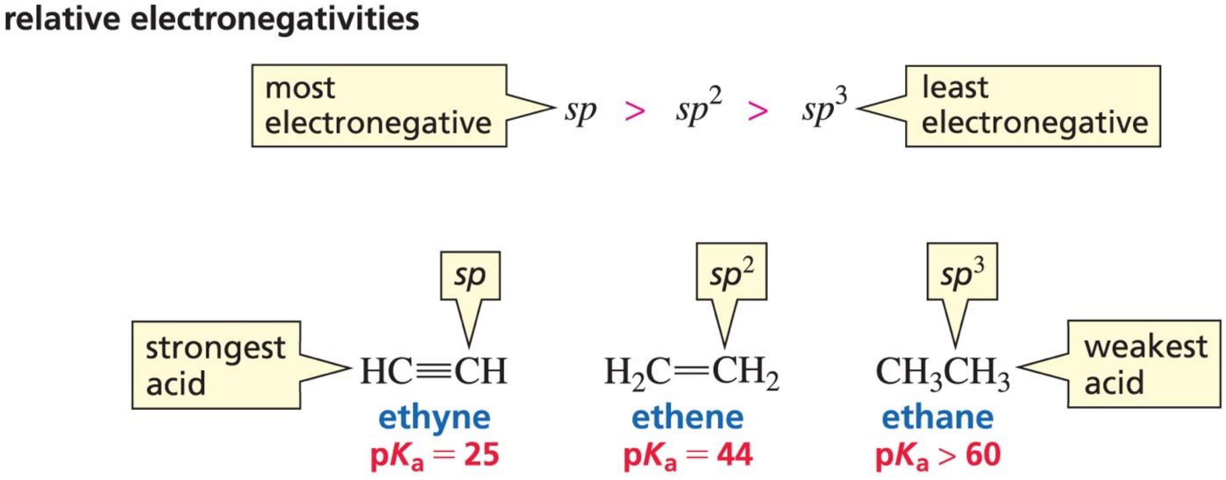
Thinking about driving forces for a reaction: $HCl + F^- \rightarrow HF + Cl^-$

HCl pKa = -7
HF pka = 3.2

The equilibrium lies on the side of the product
-We are going from a less stable ion to a more stable one
-H-F bond is more energetic (stronger than HCl)

Structural effects on acidity and basicity

Hybridization Affects pK$_a$ values through electronegativity



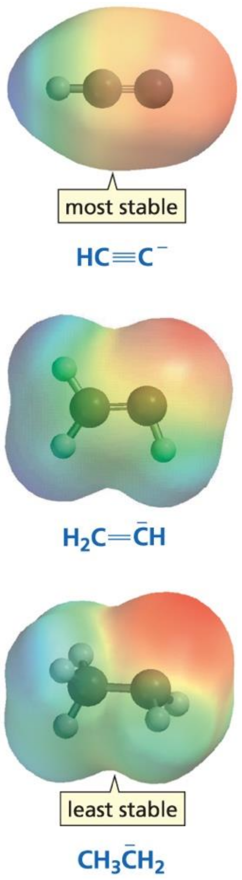
relative electronegativities

most electronegative → $sp > sp^2 > sp^3$ ← least electronegative

strongest acid → $HC{\equiv}CH$ (*sp*) **ethyne** p$K_a = 25$

$H_2C{=}CH_2$ (*sp*^{2}) **ethene** p$K_a = 44$

CH_3CH_3 (*sp*^{3}) **ethane** p$K_a > 60$ ← weakest acid



most stable

$HC{\equiv}C^-$

$H_2C{=}\bar{C}H$

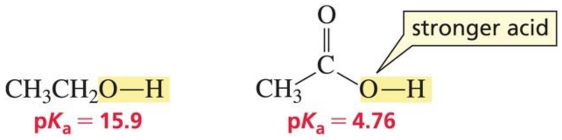
least stable

$CH_3\bar{C}H_2$

Structural effects on acidity and basicity

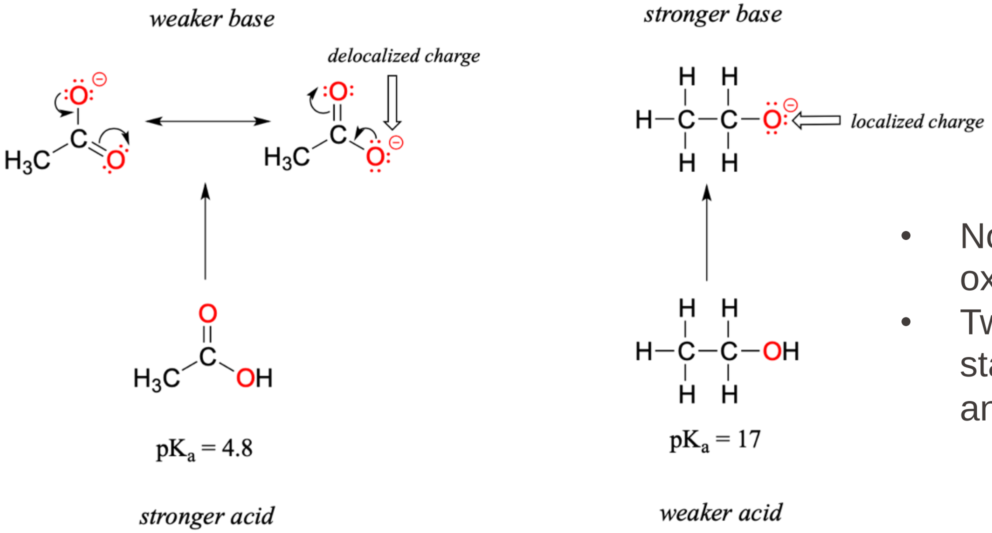
Resonance Stabilization

Why is a Carboxylic Acid a stronger acid than an alcohol?



$CH_3CH_2O{-}H$ $pK_a = 15.9$

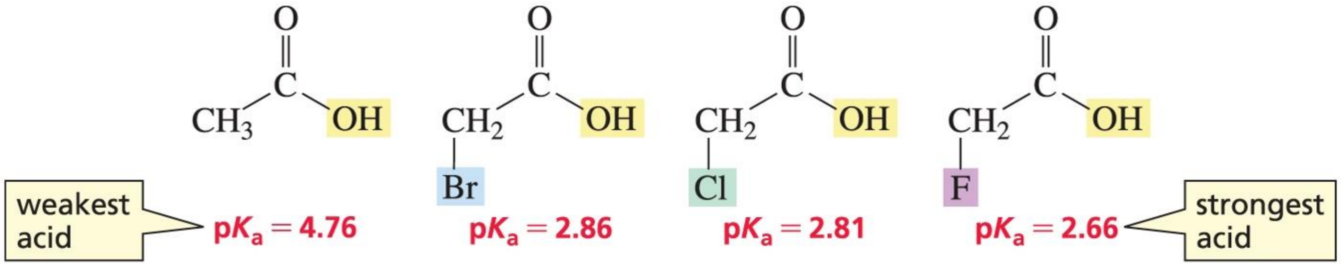
$CH_3C(=O){-}O{-}H$ $pK_a = 4.76$

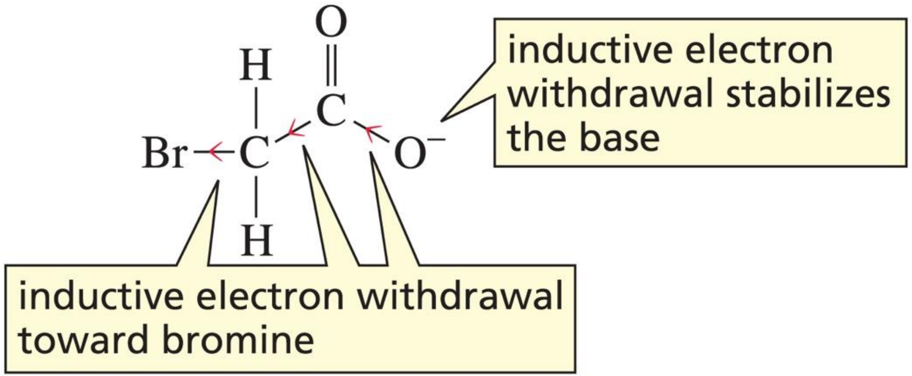


- No periodic trends evoked because is oxygen in both molecules
- Two resonance contributors justify the stability, weaker (more stable) base, and stronger acid

Structural effects on acidity and basicity

Inductive electron withdrawal

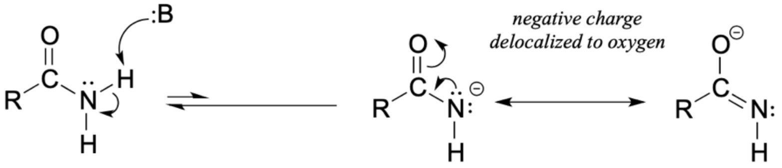




Acid-base properties of nitrogen-containing groups

-Amide nitrogens are not basic and act like weak acids

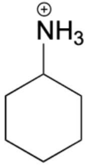
amide can act as a weak acid



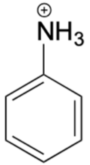
negative charge delocalized to oxygen

$pK_a \sim 20$

-Anilines substantially less basic tan an amine



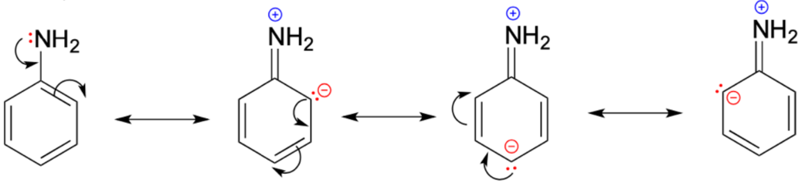
protonated amine
$pK_a \sim 10$



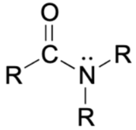
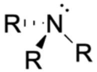
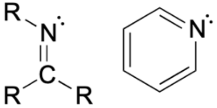
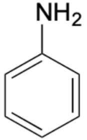
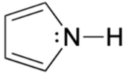
anilinium
(protonated aniline)
$pK_a \sim 5$

-same ides as before of stabilization by resonance

lone pair is stabilized by resonance

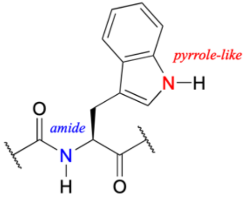


Acid-base properties of nitrogen-containing groups

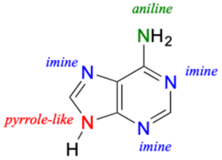
nitrogen group	**structure**	**pKa of conjugate acid**
amide		NA (amide nitrogens are not basic)
amine		~ 10
imine		~ 5 - 7
aniline		~ 5
pyrrole		~ 0

-Spend some time looking at the explanations in the book for each of these groups

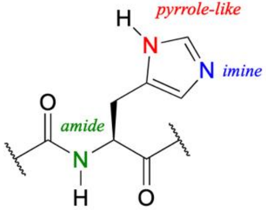
Some examples found in biological molecules



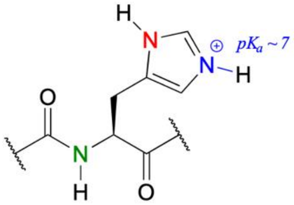
tryptophan



adenine

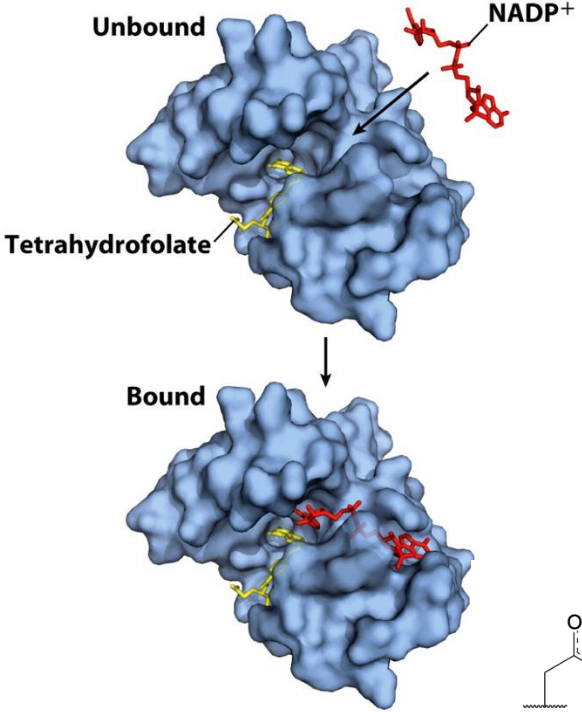


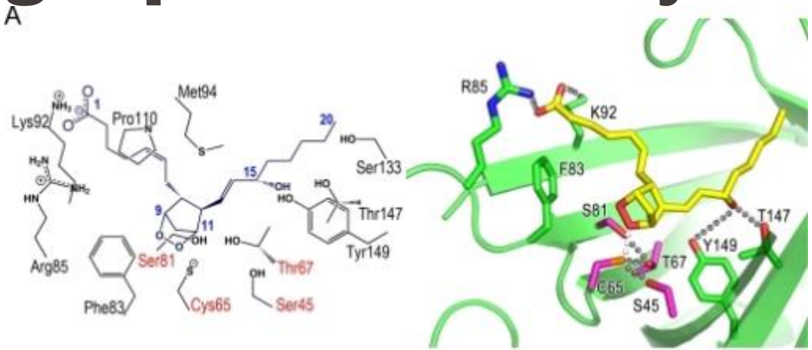
histidine (deprotonated)



histidinium (protonated)

Acidic and basic groups are affected by the environment

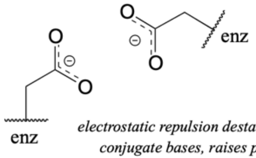




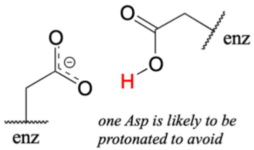
-Microenvironments inside of proteins chance properties of protonatable groups

-pKa of residues in solution and residues in proteins are very different

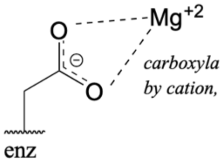
-Example aspartate has a pKa =3.9 which means at pH= 7 is in its deprotonated form



electrostatic repulsion destabilizes conjugate bases, raises pK_a



one Asp is likely to be protonated to avoid negative-negative repulsion



carboxylate state stabilized by cation, pK_a lowered

Key concepts

-Bronsted-Lowry definition of acidity

-K_a and pK_a and how it relates to the strength of the acid

-Strong acid will have a weak conjugated basis; strong base a weak conjugated basis

-Henderson-Hasselbalch equation

-Periodic trends, inductive effects and resonance delocalization

-Basicity of nitrogen containing groups

-α-carbons on a carbonyl compound and its acidity

Questions ?

Lewis Acids and Bases

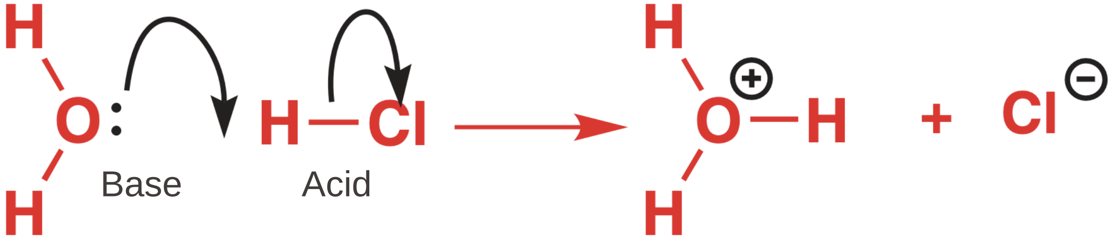
- Book p. 337
- Clayden p. 180 ff.

Resonance Stabilization

From Lecture

Lewis (1924)
Acid = Electron-pair Acceptor
Base = Electron-pair Donor

Brønsted Lowry (1923)
Acid = Proton Donor
Base = Proton Acceptor

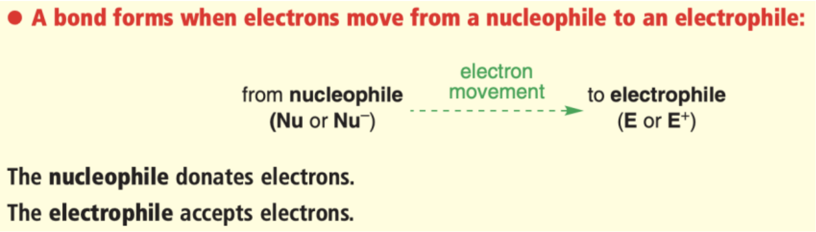


$H_2O + HCl \rightarrow H_3O^+ + Cl^-$

→ All Brønsted acids are also Lewis acids, but not all Lewis acids (only protic ones) are also Bronsted acids

Reaction Mechanisms

Reactions happen when electrons flow between molecules

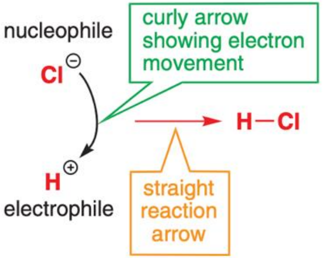


- **A bond forms when electrons move from a nucleophile to an electrophile:**

from **nucleophile** (**Nu** or **Nu**$^-$) → to **electrophile** (**E** or **E**$^+$)

The **nucleophile** donates electrons.

The **electrophile** accepts electrons.



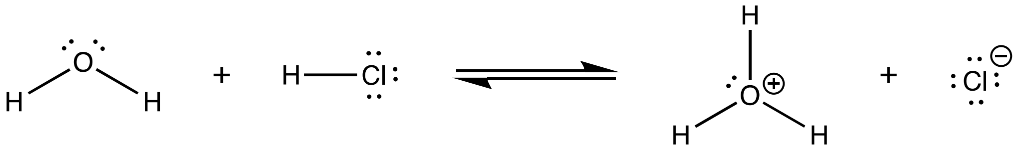
Confusion alarm – this is now an example from the book and not our reaction

Highly recommended! →

- Book p. 307 ff.
- Clayden p. 107 ff.

Reaction Mechanisms

Let’s look at the reaction of hydrochloric acid with water



What are we looking at? Brønsted acid-base **reaction** between **water** (H_2O: Lewis base) and **hydrogen chloride** (HCl: Lewis acid).

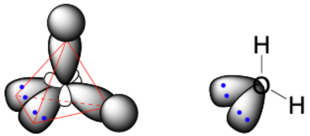
Electron acceptor (Lewis),
proton donor (Bronsted)

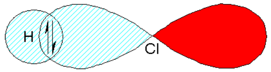
Electron donor (Lewis),
proton acceptor (Bronsted)

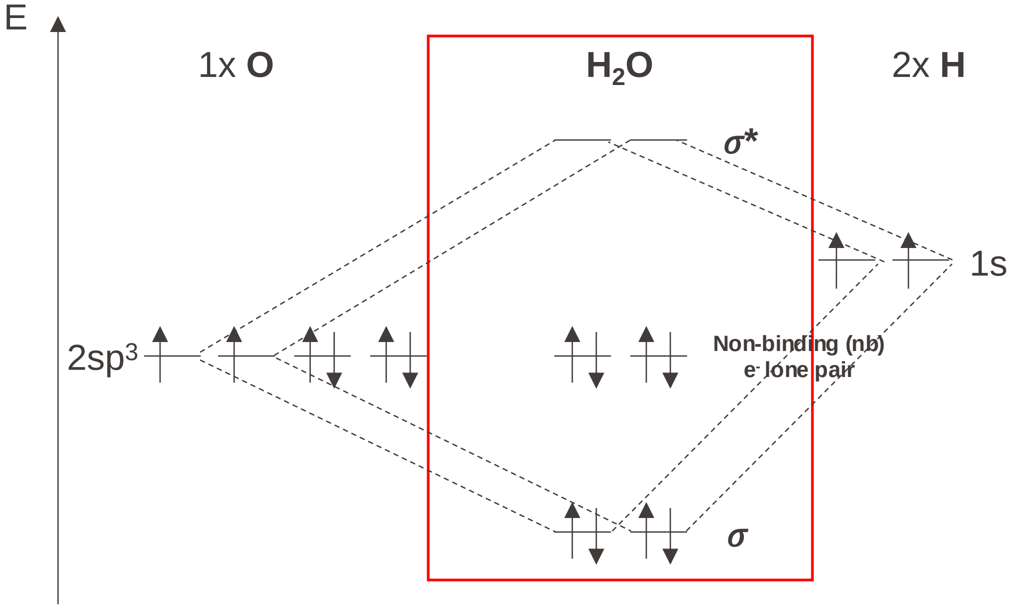
Reaction Mechanisms

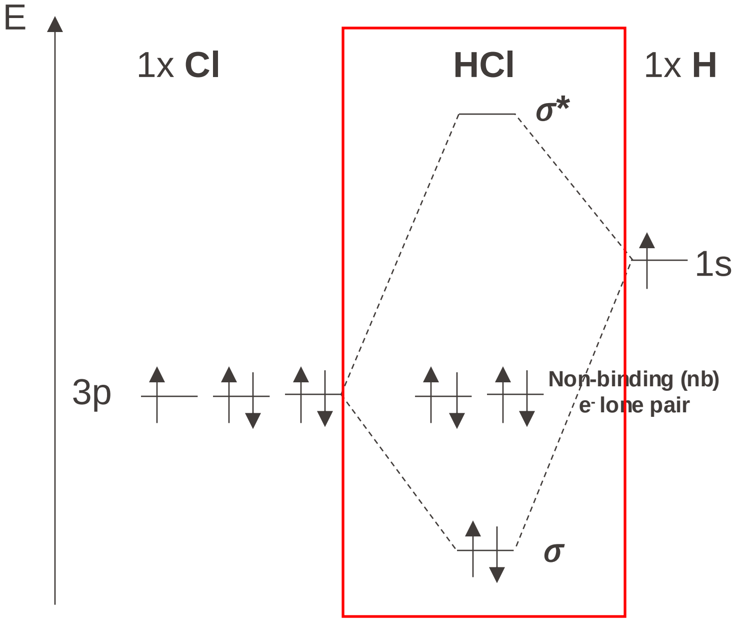
Not exam relevant

Electron arrow ”pushing”



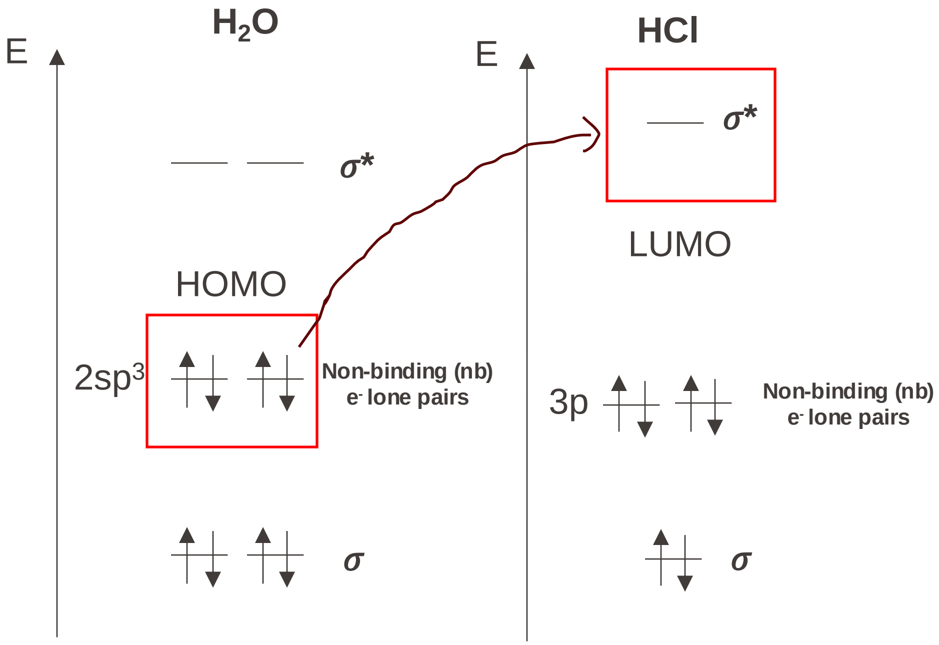






Reaction Mechanisms

Electron arrow ”pushing”



H_2O

E

σ*

HOMO

$2sp^3$

Non-binding (nb)
e^- lone pairs

σ

HCl

E

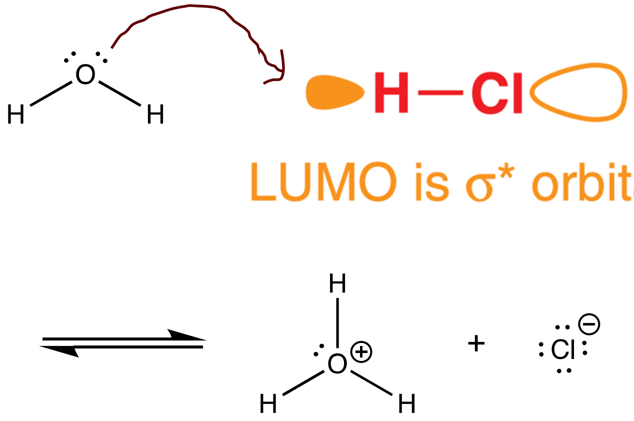
σ*

LUMO

3p

Non-binding (nb)
e^- lone pairs

σ



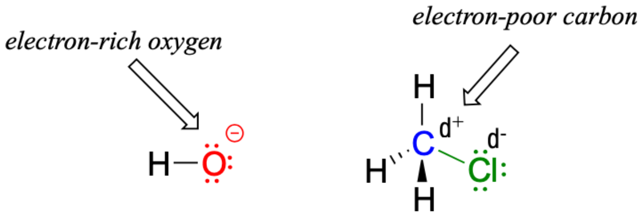
LUMO is σ* orbital

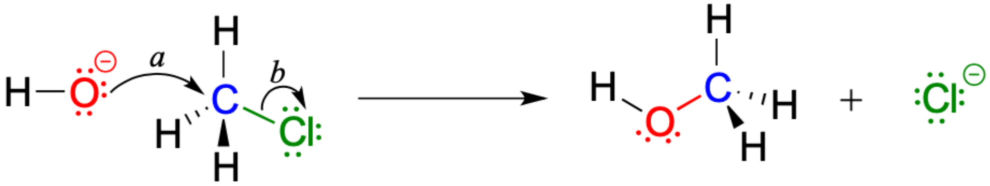
Looking at other types of reactions

One step nucleophilic substitution reaction

- Reaction where bonds of a carbon atom are rearranged

Electron distribution guides reaction steps





Cloromethane

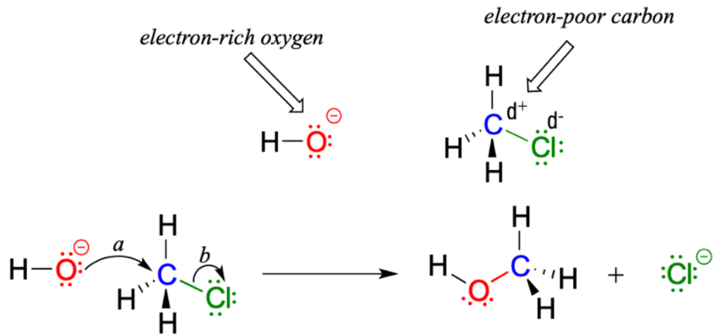
-Hydroxide is expected to to act as a base and attack a hydrogen
-Electronegativity of the chlorine makes the carbon-chlorine bond polar

-(**a**) lone pair of electrons filling up the sp3 orbital on chloromethane
-(**b**) two electrons in the carbon-chloride bond and become a lone pair

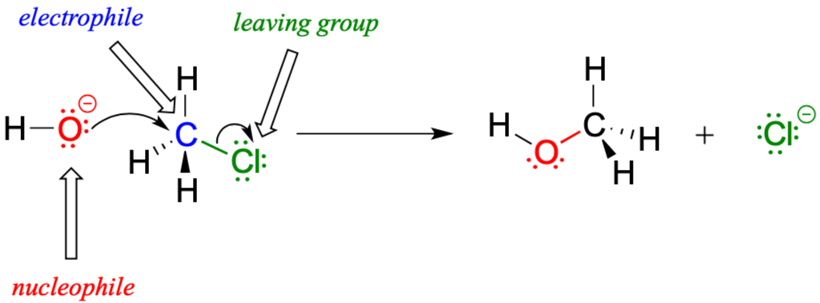
Looking at other types of reactions

One step nucleophilic substitution reaction

-A few terms to keep in mind and understand



Cloromethane



-**Nucleophilic** - ”nucleus-loving” the

-The oxygen is a **nucleophile –** an electron-rich species attracted to the electron-poor nucleus of the carbon atom “attacking” with a lone pair to form a new covalent bond

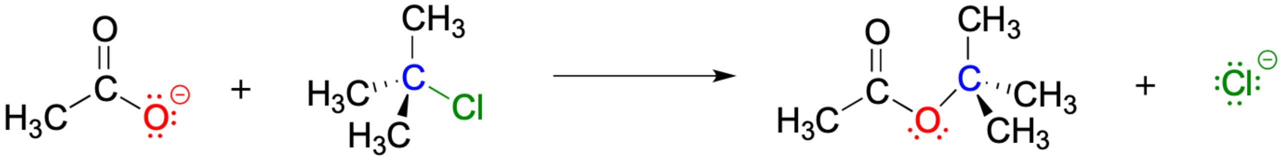
-The carbon in methyl chloride is electron-poor nucleus and is referred as **electrophile**

-chloride behaves as the leaving group of the reaction

Looking at other types of reactions

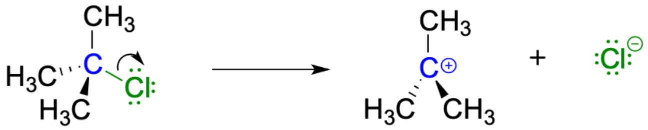
Two step nucleophilic substitution reaction

-Reactions also describe the order in which the events occur



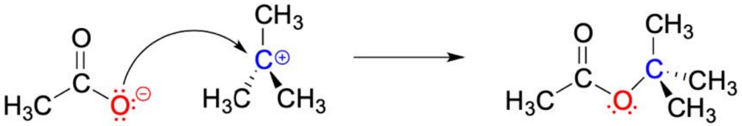
Acetate ion 2-chloro-2-methylpropane

Step 1: loss of leaving group (slow)



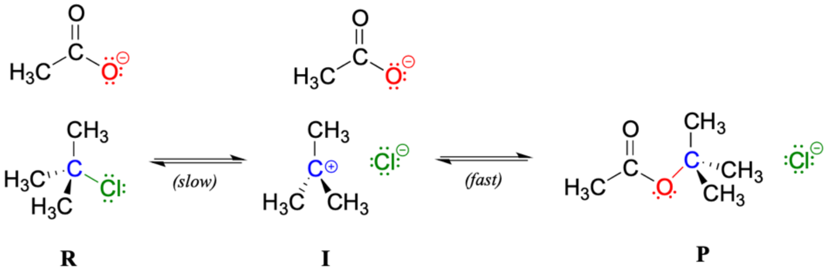
carbocation intermediate

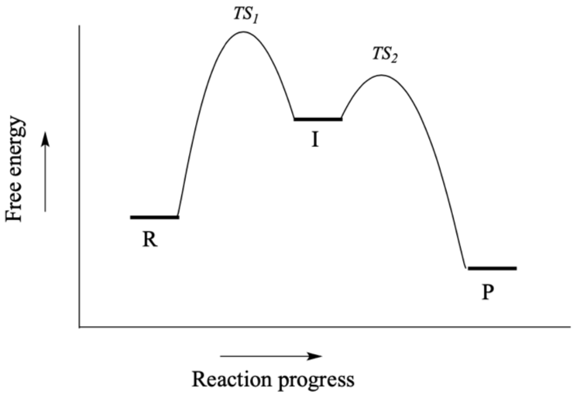
Step 2: nucleophilic attack (fast)



- -the carbocation is a **reaction intermediate**

Two step reactions





-Notice that the activation energy of the first step is higher and as such is slower (bond breaking step)

-The slowest step is referred to as **rate-determining** step determining the speed of the reaction

Key concepts

-Recognize three reaction mechanism types: an acid-base reaction, a one-step nucleophilic substitution, and a two-step nucleophilic substitution.

-Identify a **nucleophile, electrophile**, and in many cases a **leaving group**.

-Recognize one or more reaction intermediates given the reaction.

-Identify the point(s) on the diagram corresponding to **transition state(s) and reaction intermediate(s)**. In a multi-step reaction diagram, you should be able to identify the **rate determining step**.

Questions ?

Next lecture

Nucleophilic substitution (Chapter 8)

Reaction Model

What is formed?

When is it formed?

How can a chemist ‘push’ it?

Type	Mechanism	Transition State or Intermediate	Control	Stereo-selectivity	Stereo-specificity (Educts)	Substrate	Attacking Group	Leaving Group	Solvent	…
Substitutions	S_n1	intermediate (IM): carbenium ion (positive charge is typically solvated)	kinetic, 1st Order	both stereoisomers (racemization)	n.a.	typically tertiary substrates, electron donators stabilize the neg. charge	irrelevant	The more stable the solvated Y^-, the better (weak bases)	polar-protic, to stabilize the leaving group and intermediate, e.g.: H_2O, Alcohols, Carboxylic acids	
	S_n2	transition state (TS): partial X-C and C-Y bonds (negative charge is distributed over all 3 atoms)	kinetic, 2nd Order	one stereoisomer (inversion)	n.a.	typically primary substrates, electron acceptors stabilize the neg. charge	strong nucleophile	The more stable the solvated Y^-, the better (weak bases)	polar-aprotic, to not stabilize the nucleophile, e.g.: DMF, DMSO, HMPT, Acetone	

→ From the Reaction Model, all other columns can be derived … which is what we will do now ☺

Book p. 388 ff.
Clayden p. 328 ff.