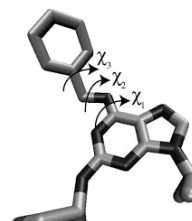
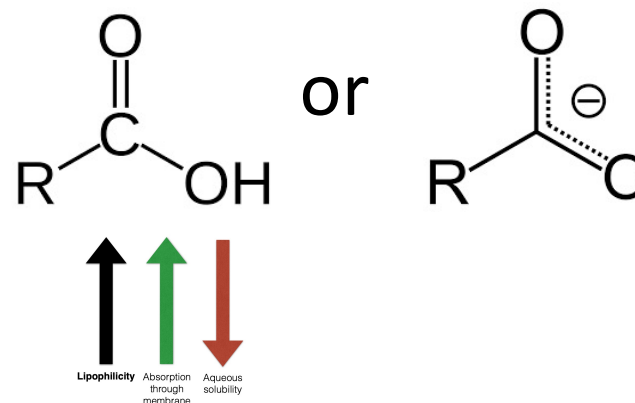


Drug Ionization, pKa vs pH Membrane Permeability

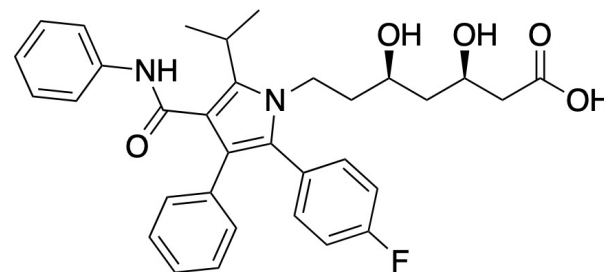
Henderson–Hasselbalch equation

Drug Physico-Chemical Properties

- **Ionization** (pH, pKa)
- **Lipophilicity** (logP)
- **Solubility in water** ($\log S_0$)
- **Stability.** Metabolic stability in human liver microsomes
- **Size** (MW, Da, number of atoms)
- **Flexibility**



Lipitor Atorvastatin



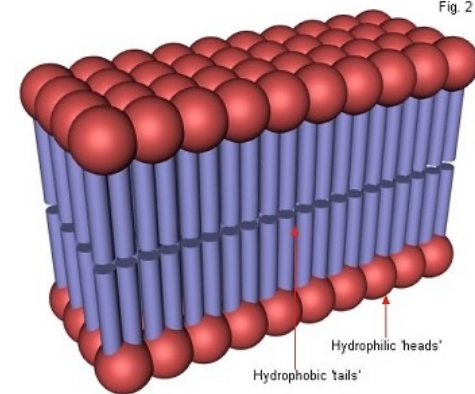
Which groups are charged at pH = 7.4?

What is LogD?

Is it going to be water soluble? What about the GI environment?

Opposite requirements: Drugs may need to be **neutral** to permeate and **charged** to act

- Solubility and absorption of a drug are highly variable and require opposite properties
- It depends on the chemical nature of the drug, pH, concentrations
- Dissolution, absorption and distribution depend on the charge of the drug
- In most cases the *neutral form* of a drug can *passively permeate* the membrane
- Every exposed charge matters (rather than the mean). Zwitterions do not help
- Active transport may change things : hijacking the bio-traffic

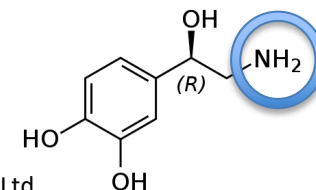
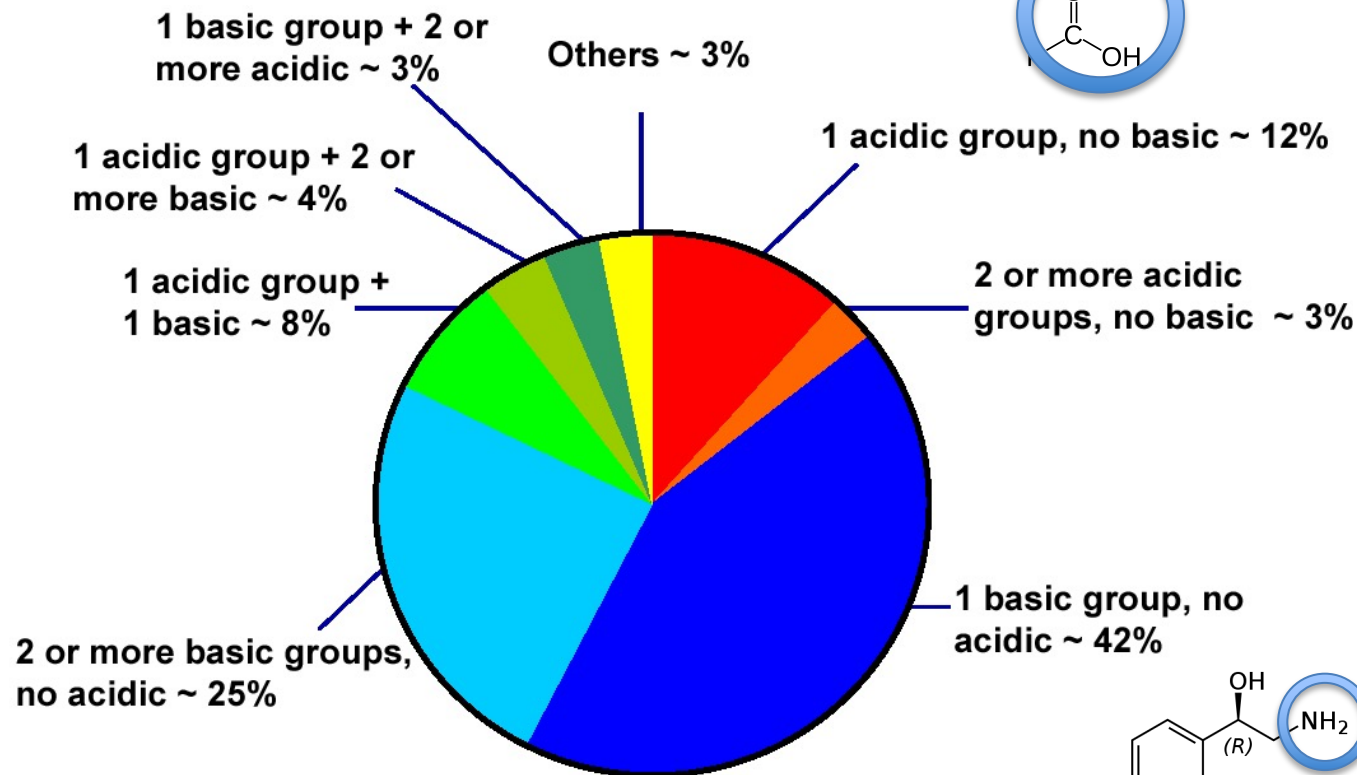
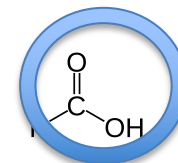


Most drugs have ionizable groups



- From about 55K drugs in WDI, 63% (~32K) are ionizable.
- 2/3rds have one or more basic group.

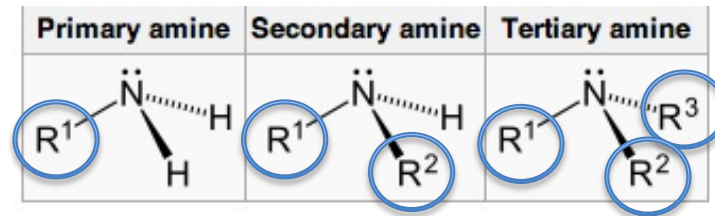
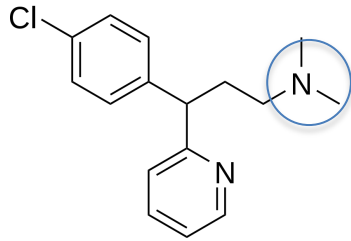
E.g.: Carboxylic acid



E.g.: Amine

From: Tim Mitchell and Ryszard Koblecki, Millennium Pharmaceuticals Ltd.

Amines in Drugs: Examples



Lone pair or H⁺ depending on the pH

Amines become additionally protonated and positively charged at **pH** less than **pK_a** of that amine
pK_a is **pH** at which 50% are protonated and 50% deprotonated

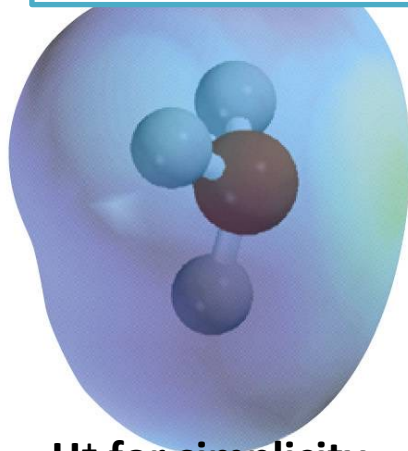
- Chlorpheniramine : an antihistamine.
- Chlorpromazine : a tranquillizer
- Ephedrine and phenylephrine :decongestants.
- Amphetamine, methamphetamine, and methcathinone : psycho-stimulant amines
- Amitriptyline, imipramine, lofepramine and clomipramine : tert. amines, tricyclic antidepressants (TCA) ad.
- Nortriptyline, desipramine, and amoxapine : secondary amines, tricyclic antidepressants

Most atoms stay covalently bonded, but hydrogen is an exception

Hydrogen ions jump:

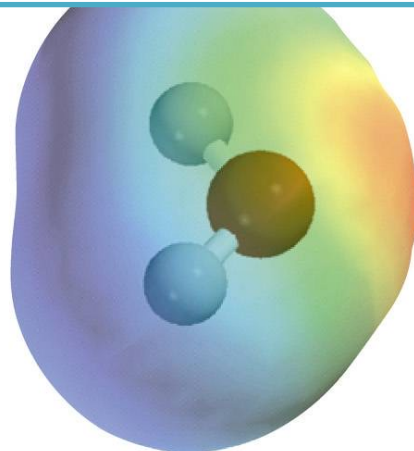
- Between water molecules
- Between drugs and water molecules
- Between both and acids/bases in solution

Dissociation of water : $2\text{H}_2\text{O} \rightarrow [\text{OH}^-] + [\text{H}_3\text{O}^+]$

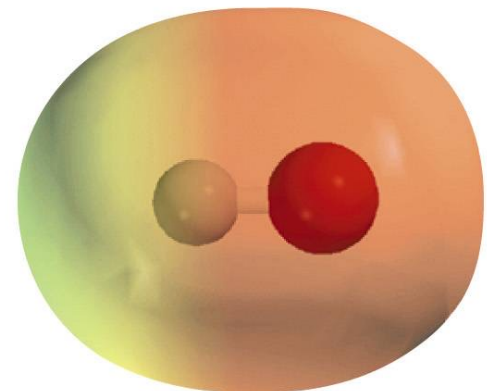


H^+ for simplicity

H_3O^+



H_2O



HO^-

Log-measure is convenient for a large range of concentrations, pH and pK_a

**Hydroxonium
molarities range from
1 to 10^{-14} M**

Use the “p” (power) operator: $p \Rightarrow -\log_{10}$

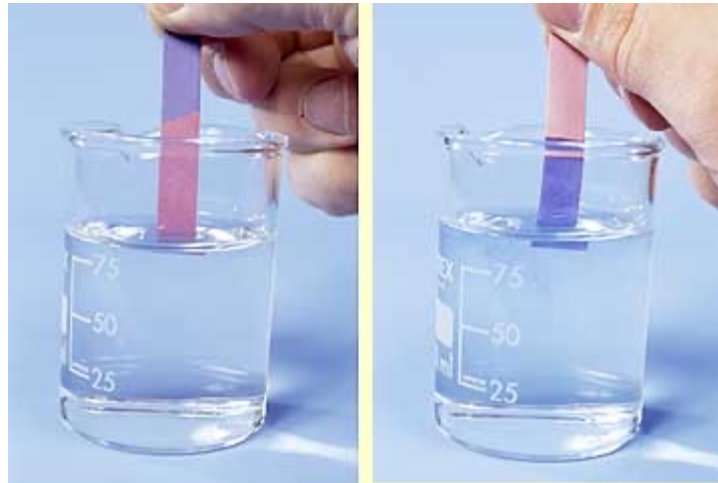
$$pH = -\log_{10}[H_3^+O]$$

pH

- **pH** (**p**ower of **H**ydrogen ion) is a measure of $[\text{H}_3\text{O}^+]$ molarity.
- $\text{pH} \equiv -\log_{10}[a_{\text{H}^+}]$,
- a_{H^+} is *activity* of water (“effective concentration”)
- $a_{\text{H}^+} \approx [\text{H}^+]$, i.e. molarity of hydroxonium ions, in $\text{M}=\text{mol/L}$
- **Example**: lemonade has $[\text{H}^+] \sim 0.005\text{M}$,
 $\text{pH} \approx -\log_{10}(0.005) \approx 2.3$

Acidity, Body and Drugs

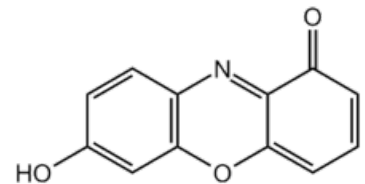
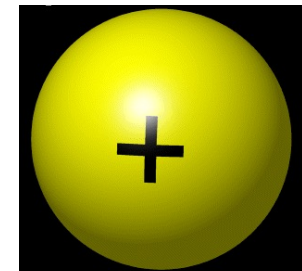
- Litmus test (**pH** indicator)
- **pH** is a log-measure of proton (or H_3O^+) *concentration*



below pH 4.5
4.5



above pH 8.3
8.3

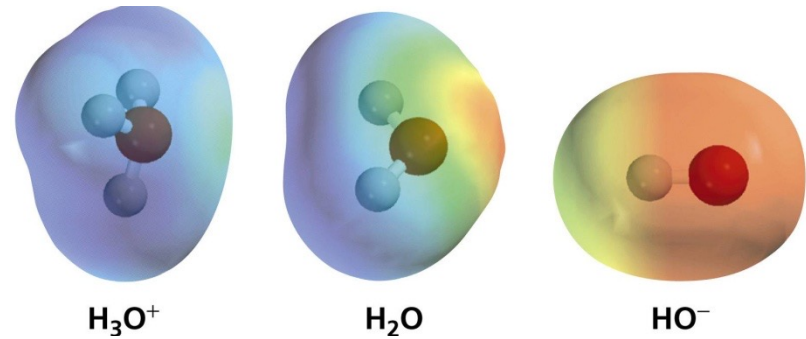


Litmus is a water-soluble mixture of different dyes extracted from [lichens](#).
Chemical structure of 7-hydroxyphenoxazone, the chromophore of litmus components



Lichens: Fungus + Alga or cyanobacterium

Self-ionization of water



- $2\text{H}_2\text{O} \rightarrow [\text{OH}^-] + [\text{H}_3\text{O}^+]$
- $K_w = [\text{H}_3\text{O}^+][\text{OH}^-]$, dissociation constant via molarities of two ions.
- Warning! K_w is NOT a standard equilibrium constant, since the $[\text{H}_2\text{O}]^2$ is omitted.
- Water molarity will also be omitted in K_a later
- $K_w = 10^{-14} \text{ (mol/L)}^2$

$$[\text{H}_3\text{O}^+]_{\text{pure } w} = 10^{-7} \text{ M} \quad \text{pH} = 7$$

- Low pH : many free protons/ H_3O^+
- High pH : few free protons/ H_3O^+

Acid-Base Imbalances

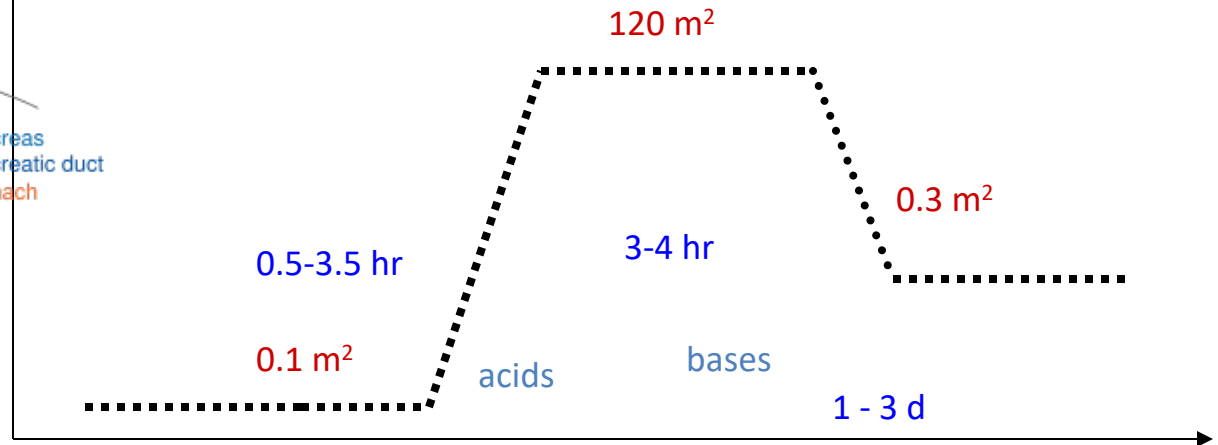
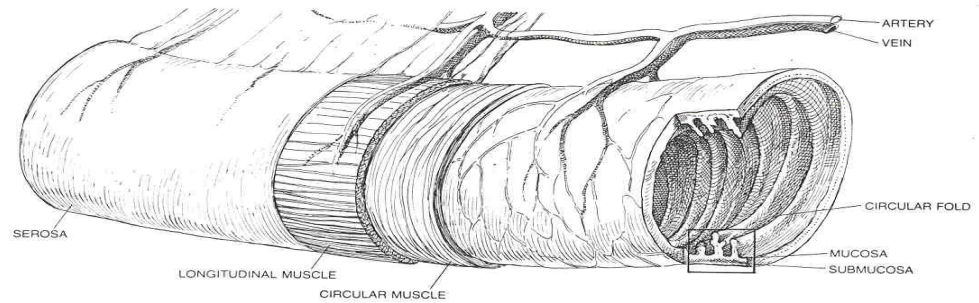
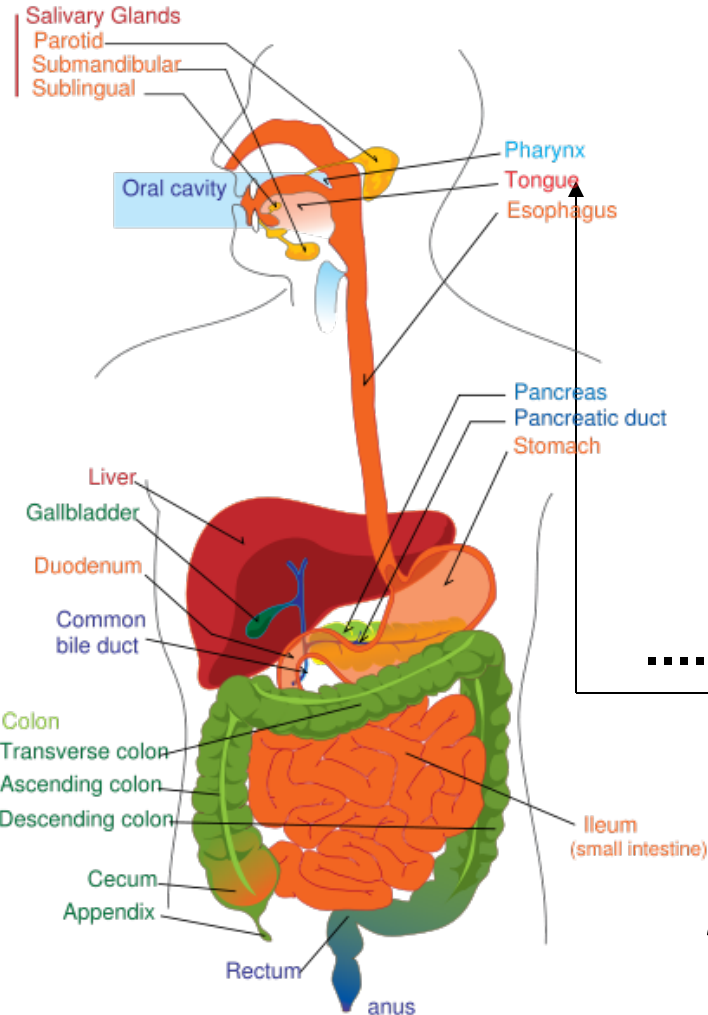
- Blood *plasma* is slightly alkaline or basic at pH=**7.4**
- Body compartments and cell compartments may have different pH values
- Plasma Acidosis
 - High blood $[H^+]$
 - Low blood pH, <7.35
- Plasma Alkalosis
 - Low blood $[H^+]$
 - High blood pH, >7.45

Site	Nominal pH
Aqueous humour	7.21
Blood, arterial	7.40
Blood, venous	7.39
Blood, maternal umbilical	7.25
Cerebrospinal fluid	7.35
Duodenum	5.5
Faeces ^b	7.15
Ileum, distal	8.0
Intestine, microsurface	5.3
Lacrimal fluid (tears)	7.4
Milk, breast	7.0
Muscle, skeletal ^c	6.0
Nasal secretions	6.0
Prostatic fluid	6.45
Saliva	6.4
Semen	7.2
Stomach	1.5
Sweat	5.4
Urine, female	5.8
Urine, male	5.7
Vaginal secretions, premenopause	4.5
Vaginal secretions, postmenopause	7.0

^a Reproduced from D. W. Newton and R. B. Kluza, *Drug Intell. Clin. Pharm.*, 12, 547 (1978).

^b Value for normal soft, formed stools, hard stools tend to be more alkaline, whereas watery, unformed stools are acidic.

Absorption in GI tract, from pH of 1.4 to 8

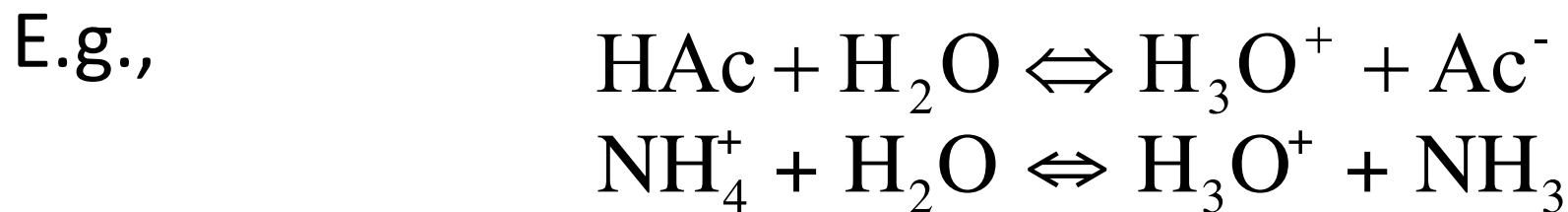


pH

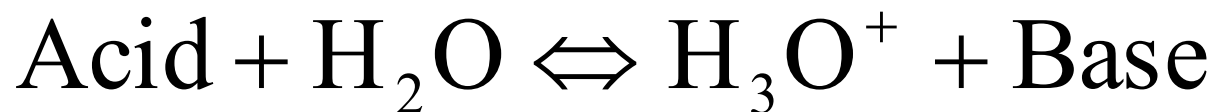
	Stomach	Jejunum	Ileum	Colon	
	1.4-2.1	4.4 - 6.6	6.8 - 8.0	5 - 8	fasted state
	3 - 7	5.2 - 6.2	6.8 - 8.0	5 - 8	fed state

Acids and Bases, K_a and pK_a

We'll consider only *Bronsted* equilibria.



or, more generally,



which has the *acidity constant* K_a

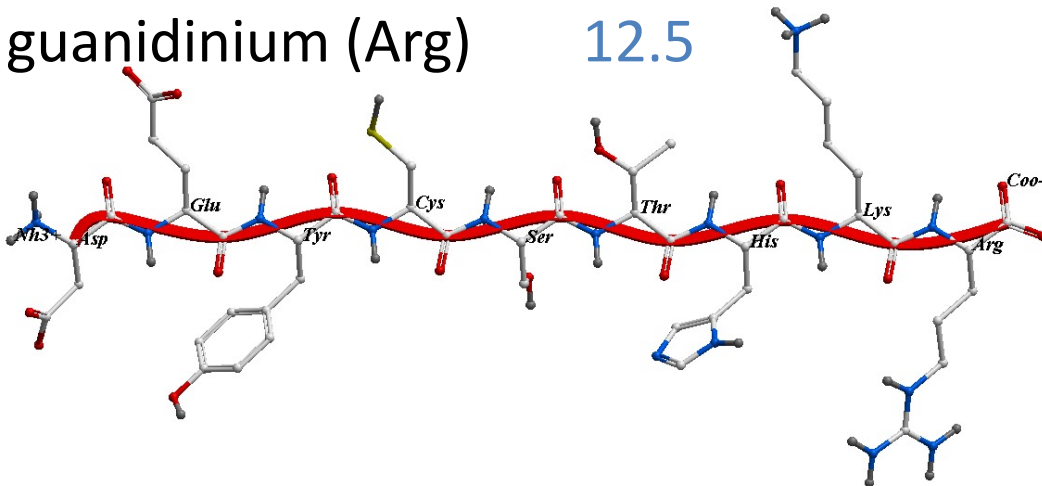
($[\text{H}_2\text{O}]$ is omitted, as in K_w)

$$K_a = \frac{a(\text{H}_3\text{O}^+)a(\text{Base})}{a(\text{Acid})}$$

$$pK_a = -\log_{10} K_a$$

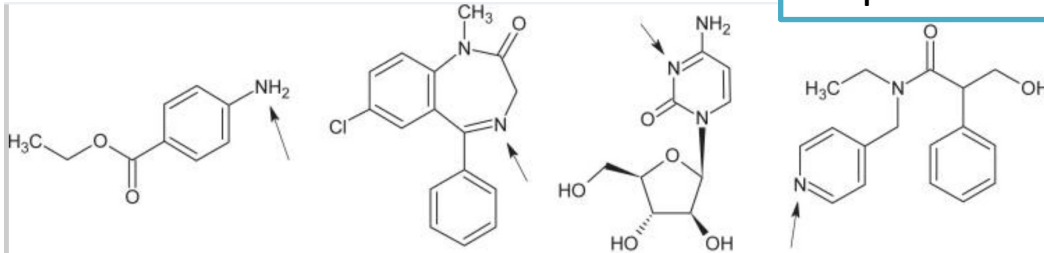
pKa of some functional groups

phosphates (DNA)	1.5, 6.5
carboxylates (Asp, Glu, C-ter)	3.5-5
phenols (Tyr)	9.5-11
sulfhydryls (Cys)	8.4 (charged near metals)
hydroxyls (Ser, Thr)	13.5
amines	2.5-11
imidazole (His)	6-7
amino (Lys, N-term)	10.5
guanidinium (Arg)	12.5

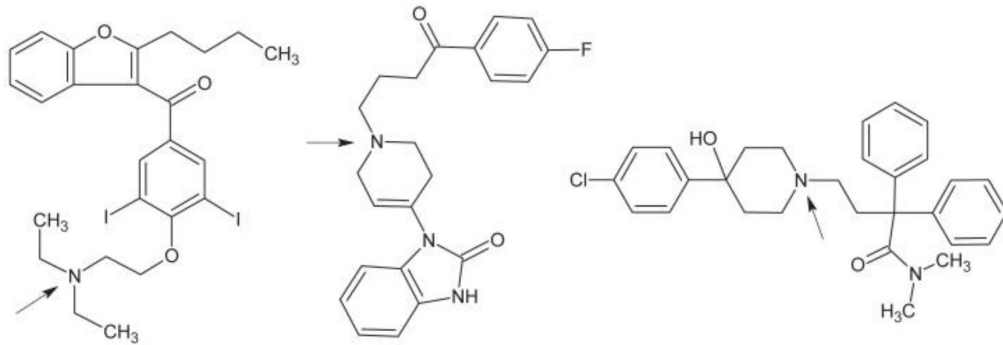


Range of pK_as for drugs with amines

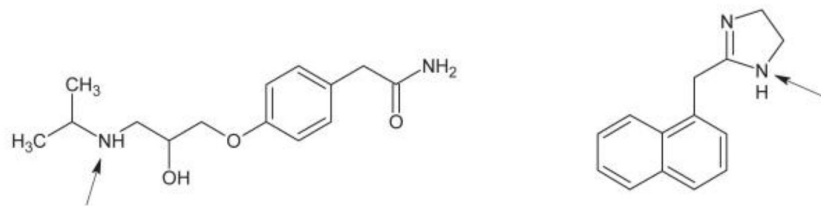
Tropicamide (5.3)



Benzocaine (2.5) Diazepam (3.4) Cytarabine (4.3)

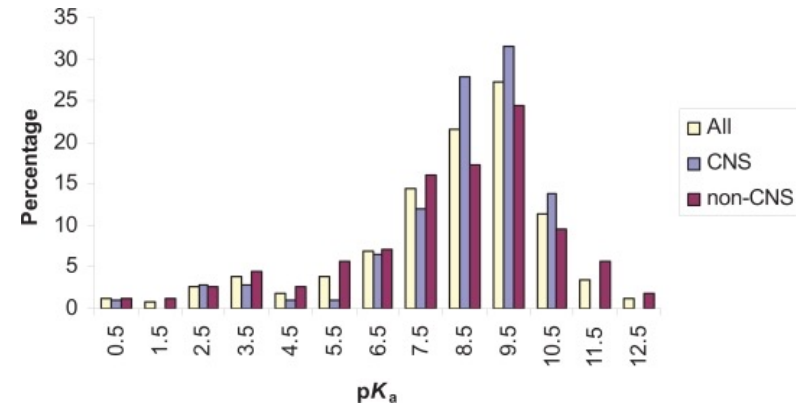


Amiodarone (6.6) Droperidol (7.6) Loperamide (8.6)

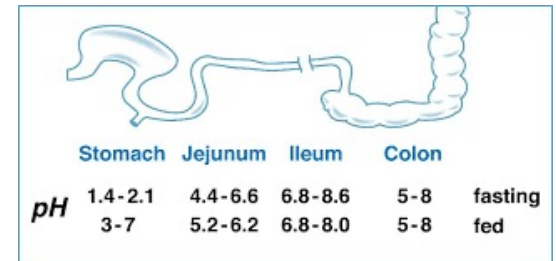


Atenolol (8.6)

Naphazoline (10.9)



Single basic group: pK_a distribution



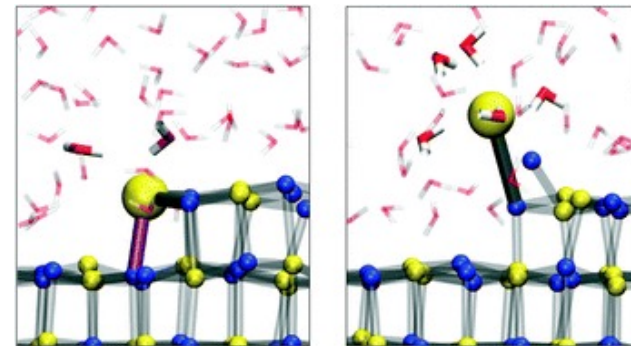
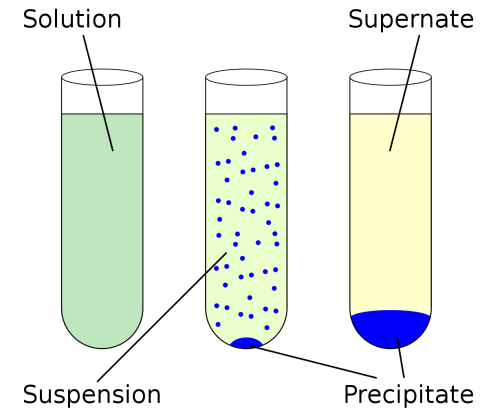
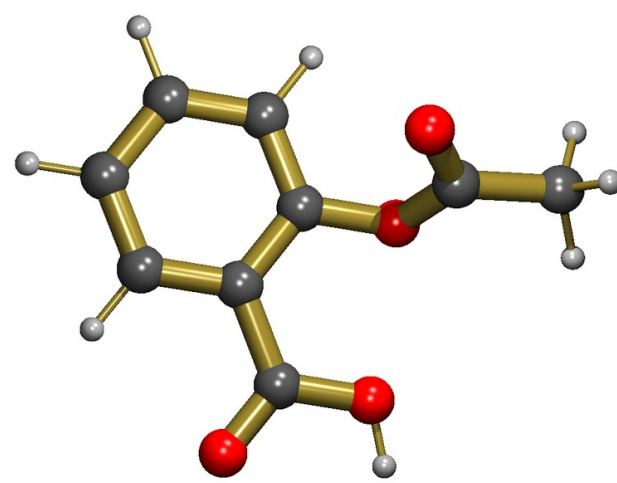
Credit:

Manallack DT. The pK(a) Distribution of Drugs: Application to Drug Discovery. *Perspect Medicin Chem.* 2007;1:25-38. Published 2007 Sep 17.

Groups are shown by arrows, pK_a values in parentheses

Solubility

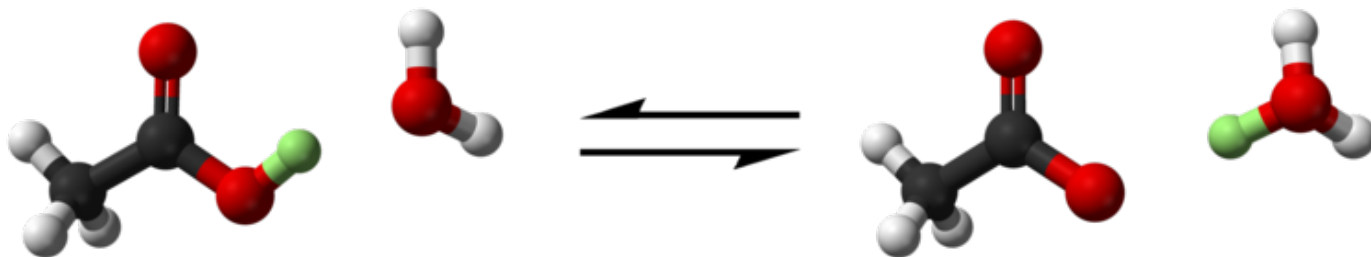
- $S = [\textit{concentration of a saturated solution}]$
- Units: g/dL, g/L, mol/L
- *Like dissolves like*
- Polar solutes dissolve in polar solvents.
- Nonpolar solutes dissolve in nonpolar solvents.
- Need to predict or measure pKa (s) since charged groups help water solubility and conflict with fat solubility.



From: LM Liu, A. Laio and A. Michaelides *Phys. Chem. Chem. Phys.*, 2011, 13, 13162

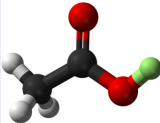
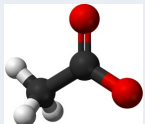
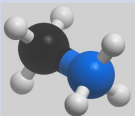
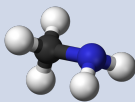
Drug Solubility depends on pH, pK_a s

- For each drug, water and fat solubility vary.
- Relative solubilities depend on
 - Chemical structure of the drug
 - pH of the solution
 - pK_a values of the drug groups
- Solubility percentages depend on **ionization ratios**

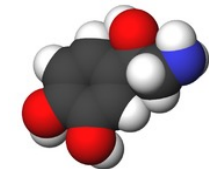


Acetic-acid-dissociation

Solubility, pH and pKa diagram

Drug pKa	Solution pH	
	<7 (Acidic solution)	>7 (Basic solution)
<7 (Acidic drug, charge is -1 or 0)	pKa > pH Un-ionized, Fat soluble 	pKa < pH (-) Ionized, Water soluble 
>7 (Basic drug, charge is 0 or +1)	pKa > pH (+) Ionized, Water soluble 	pKa < pH (0) Un-ionized, Fat soluble 

Caution: In most information sources and databases the drug groups ionized at pH=7.4 groups will still be shown as neutral.



Norepinephrine in its unnatural neutral form

Henderson-Hasselbalch equation: calculating charged fraction

- The difference between the pH of the solution and the pK_a of the drug is the common logarithm of the ratio of ionized to unionized forms of the drug.
- For *acidic drugs*

$$\text{Log}(\text{Ionized}/\text{Unionized}) = \text{pH} - \text{p}K_a, \text{ or}$$

$$[I]/[U] = 10^{(\text{pH}-\text{p}K_a)}$$

Derivation:

$$K_a = [\text{H}^+][\text{A}^-]/[\text{HA}]$$

$$-\log K_a = -\log([\text{H}^+][\text{A}^-]/[\text{HA}])$$

$$-\log K_a = -\log[\text{H}^+] - \log([\text{A}^-]/[\text{HA}])$$

$$\text{p}K_a = \text{pH} - \log([\text{A}^-]/[\text{HA}])$$

$$\log([\text{A}^-]/[\text{HA}]) = \text{pH} - \text{p}K_a$$

H.H.: a quantitative evaluation of charged/un-charged ratio

- Most drugs are weak acids or weak bases
- It is not all or nothing, there are always several species at different concentrations
- For drugs with multiple acidic or basic groups there is a cross-dependence

$$\log\left(\frac{[A^-]}{[HA]}\right) = pH - pKa$$

$$\log\left(\frac{[B]}{[BH^+]}\right) = pH - pKa$$