

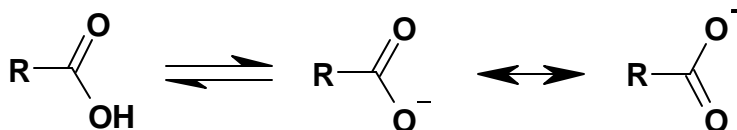
## Physicochemical Properties of Drugs

### Objectives:

At the end of the next hour:

- The student should be able to calculate the degree of ionization for an acidic or basic drug using an approximate method of calculation that does not require the use of calculators or computers.

Example: (Acetic Acid, pKa ~5)



Ionized species is stabilized by resonance.

If pKa ~5 then acetic acid will be 50% ionized at pH~5. When the pH is lowered by one pH unit, the hydrogen ion concentration is increased by 10 fold resulting in a shift of equilibrium toward the unionized species. The shift follows the laws of mass action and results in ~90% unionized at pH~4.

To calculate an approximate the degree of ionization just subtract the pka from the pH, round off to the nearest integer to determine how many 9s to use. Next determine which is the major species, and write down that many nines with a decimal point after the second nine.

For example to determine the degree of ionization of acetic acid in the stomach at pH~1: pKa - pH = 4, therefore acetic acid is 99.99% unionized in the stomach.

- The student should know the approximate pKa values for the following chemicals which illustrate most of the important concepts of acid-base chemistry (inductive electron withdrawing, resonance, and loss of aromaticity) in drugs:

Compound	pKa	Compound	pKa	Comparison Principle
acetic acid (sp <sup>2</sup> )	~5	trifluoroacetic A.	~0	Inductive e <sup>-</sup> withdraw
ethanol (sp <sup>3</sup> )	~15	phenol (sp <sup>2</sup> )	~10	Resonance e <sup>-</sup> withdraw
methylamine (sp <sup>3</sup> )	~10*	aniline (sp <sup>2</sup> )	~5*	Resonance e <sup>-</sup> withdraw
ethylamine (sp <sup>3</sup> )	~10*	acetamide (sp <sup>2</sup> )	~0*	Resonance e <sup>-</sup> withdraw
pyridine (sp <sup>2</sup> )	~5*	pyrimidine (sp <sup>2</sup> )	~0*	Inductive e <sup>-</sup> withdraw
pyrole (sp <sup>2</sup> ) -> (sp <sup>3</sup> )	~0*	imidazole (sp <sup>2</sup> )	7*,13	Loss of aromaticity
pyrrolidine (sp <sup>3</sup> )	~10*	benzoic acid (sp <sup>2</sup> )	~4	

\*These are the approximate pKa's of the conjugate acid of the base. Most these pKa values have been rounded off to the nearest 5.

3. The student should be able to rank the following functional groups on the basis of their lipophilic ( $\pi$ ), electronic ( $\sigma$ ), and steric (MR) properties:

Physicochemical Parameters

By Type

Subst. Group	$\pi$	$\sigma_{para}$	MR
-H	0.00	0.00	1.03
-CH <sub>3</sub>	0.56	-0.17	5.65
-CH <sub>2</sub> CH <sub>3</sub>	1.02	-0.15	10.30
-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	1.55	-0.13	14.96
-C(CH <sub>3</sub> ) <sub>2</sub>	1.53	-0.15	14.96
-OCH <sub>3</sub>	-0.02	-0.27	7.87
-NH <sub>2</sub>	-1.23	-0.66	5.42
-F	0.14	0.06	0.92
-Cl	0.71	0.23	6.03
-Br	0.86	0.23	8.88
-I	1.12	0.18	13.94
-CF <sub>3</sub>	0.88	0.54	5.02
-OH	-0.67	-0.37	2.85
-COCH <sub>3</sub>	-0.55	0.50	11.18
-NHCOCH <sub>3</sub>	-0.97	0.00	14.93
-NO <sub>2</sub>	-0.80	0.78	7.36
-CN	-0.57	0.66	6.33

By Lipophilicity

Subst. Group	$\pi$	$\sigma_{para}$	MR
-NH <sub>2</sub>	-1.23	-0.66	5.42
-NHCOCH <sub>3</sub>	-0.97	0.00	14.93
-NO <sub>2</sub>	-0.80	0.78	7.36
-OH	-0.67	-0.37	2.85
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By Electronic

Subst. Group	$\pi$	$\sigma_{para}$	MR
-NH <sub>2</sub>	-1.23	-0.66	5.42
-OH	-0.67	-0.37	2.85
-OCH <sub>3</sub>	-0.02	-0.27	7.87
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-NO <sub>2</sub>	-0.80	0.78	7.36

By Size

Subst. Group	$\pi$	$\sigma_{para}$	MR
-F	0.14	0.06	0.92
-H	0.00	0.00	1.03
-OH	-0.67	-0.37	2.85
-CF <sub>3</sub>	0.88	0.54	5.02
-NH <sub>2</sub>	-1.23	-0.66	5.42
-CH <sub>3</sub>	0.56	-0.17	5.65
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## Lipophilic (p)

$$\pi = \Delta \log P \text{ going from the (Parent - H) to the (Parent - R).}$$
$$\log P = \log [\text{Octanol}]/[\text{Water}]$$

## Electronic (s)

$\sigma$  = Hammett electronic sigma constant (sigma constant)

Specifically the substituent constant for *meta*- and for *para*-substituents in benzene derivatives as defined by Hammett on the basis of the ionization constant of a substituted benzoic acid in water at 25 °C, i.e.  $\log (K_a/K_{a0})$ , where  $K_a$  is the ionization constant of a *m*- or *p*-substituted benzoic acid and  $K_{a0}$  that of benzoic acid itself.

A large positive  $\sigma$ -value implies high electron-withdrawing power by inductive and/or resonance effect, relative to H; a large negative  $\sigma$ -value implies high electron-donating power relative to H.

## Molar Refractivity (MR) –

[http://www.pharmacy.umaryland.edu/~alex/www\\_alex/lectures/qsar.html](http://www.pharmacy.umaryland.edu/~alex/www_alex/lectures/qsar.html)

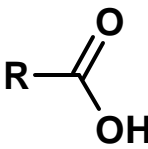
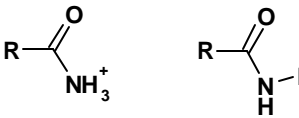
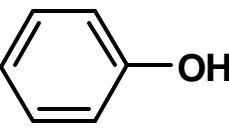
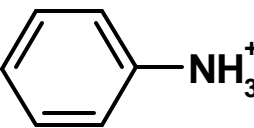
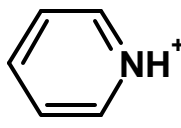
The molar refractivity is the molar volume corrected by the refractive index. It represents size and polarizability of a fragment or molecule.

Originally proposed by Pauling and Pressman as a parameter for the correlation of dispersion forces involved in the binding of haptens to antibodies. Now determined from the refractive index,  $n$ , the molecular weight, MW and the density of a crystal,  $d$ .

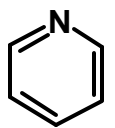
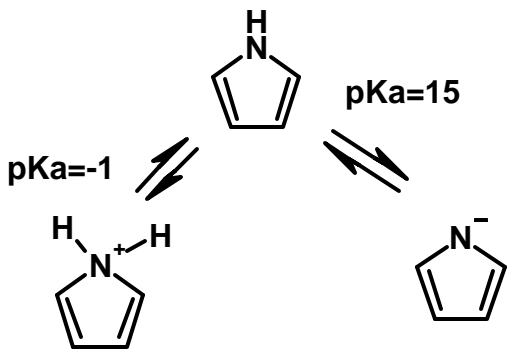
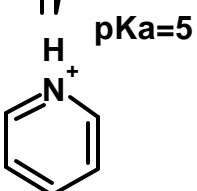
$$MR = \frac{(n^2 - 1)}{(n^2 + 1)} \cdot \frac{MW}{d}$$

Since refractive index doesn't change much for organic molecules, the term is dominated by the MW and density. Larger MW, larger the steric effect and greater the density, the smaller the steric effect (the molecules tend to pack better). A smaller MR for the same MW indicates stronger interactions in the crystal (larger density indicates that the packing is better due to stronger interactions).

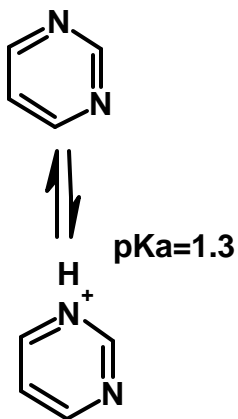
**Review of Acid-Base Properties:**

Acid or Conjugate Acid	Carboxylic Acid 	Amine $R-NH_3^+$	Amide 
pka	4.5	10	0.3 and 16
Acid or Conjugate Acid	Phenol 	Aniline 	Pyridine 
pka	10	4.6	5

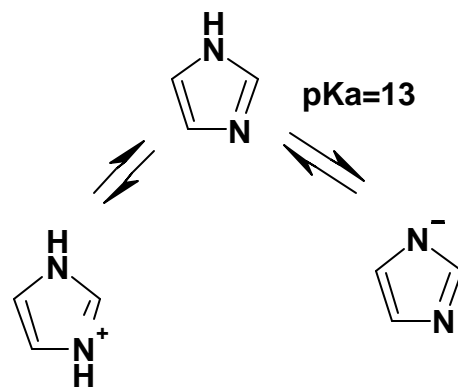
**Aromaticity greatly effects the acid-base properties of heterocycles:**

Uncharged in blood At pH = 7.4		
charged in stomach at pH 1.0	$\rightleftharpoons$ 	
Protonation of pyridine does not effect aromaticity.		The pyrrole ring would be neutral in any biological system. This is because protonation of pyrrole (left most structure) requires that 2 electrons be removed from the $\pi$ -system which destroys aromaticity

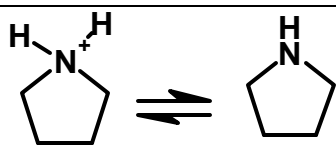
Pyrimidine would always be neutral in a bio-system



However, the lone pair electrons are available for H-bonds as in DNA.

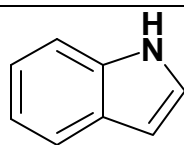


Imidazole ( $\text{pKa}=7$ ) retains aromaticity when protonated (left-most struc). Thus, the  $\text{pKa}$  of the conjugate acid is more basic than pyrole.

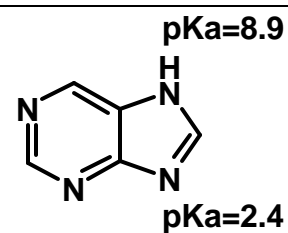


$\text{pKa} = 10$

Pyrolidine acts like a normal tertiary amine



Indole would also remain neutral in a bio-system

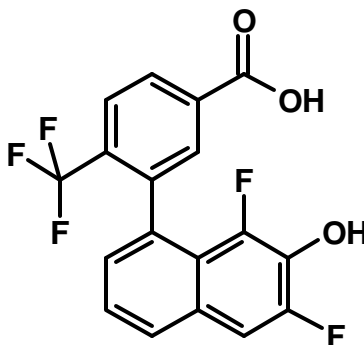


Purine is more acidic and less basic than imidazole

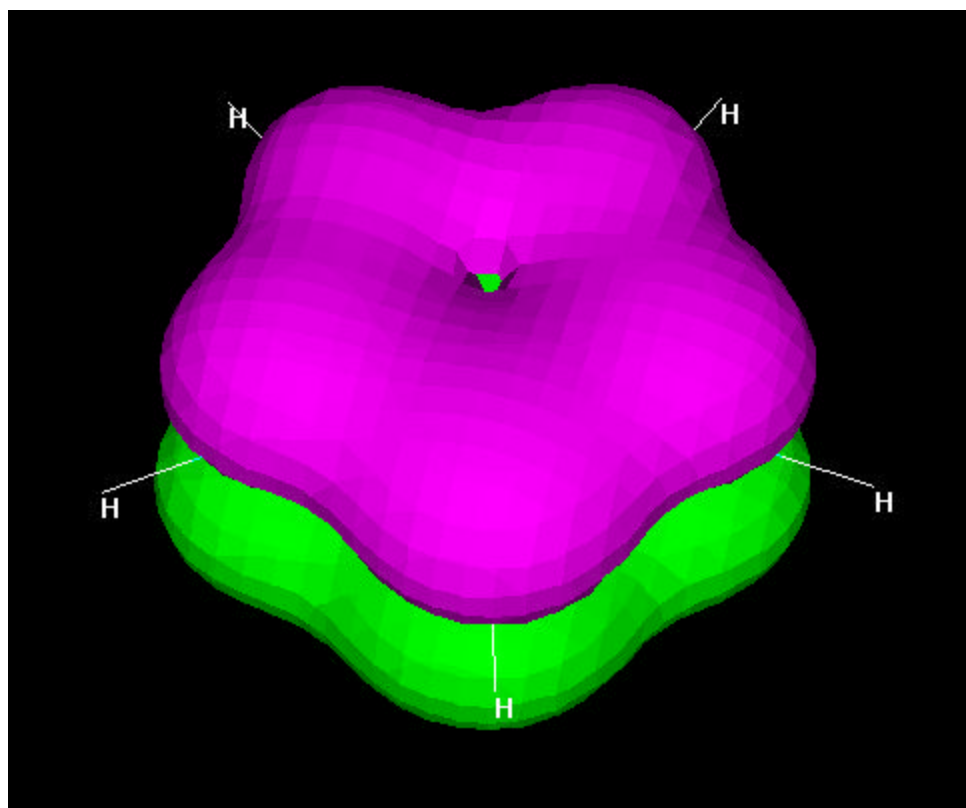
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-NO <sub>2</sub>	-0.80	0.78	7.36
-CN	-0.57	0.66	6.33

4. You are a chemist working at King Konglomerate in New Jersey. Your lead structure (a weak acid), shown below, sticks too tightly to a plasma carrier protein and does not penetrate to its cellular receptor. Use the table of physicochemical properties shown above to select a substitution at the position para to the carboxylic acid, that will decrease lipophilicity and increase the pK<sub>a</sub> of the phenolic hydroxyl compared to the trifluoromethyl substitution.

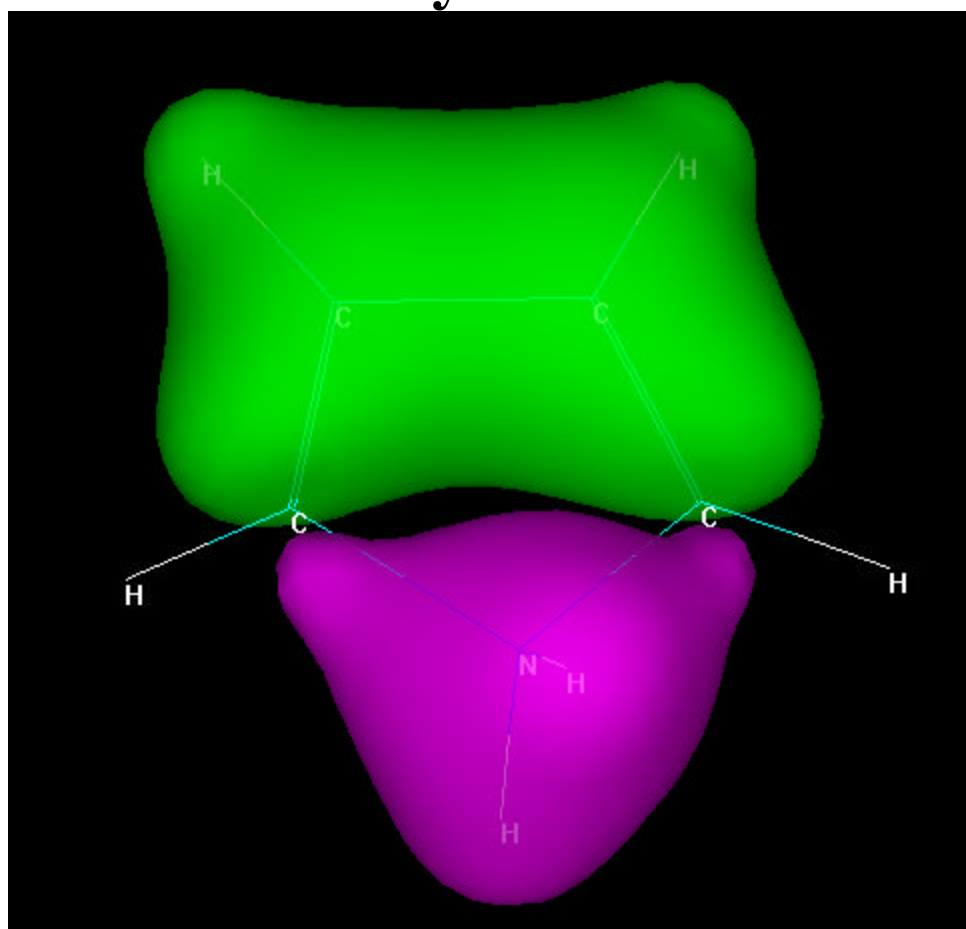


- A. ethyl (-CH<sub>2</sub>CH<sub>3</sub>)  
 B. cyano (-CN)  
 C. methoxy (-OCH<sub>3</sub>)  
 D. iodo (-I)  
 E. nitro (-NO<sub>2</sub>)
5. Assume that the pK<sub>a</sub> of the phenolic hydroxyl group in the parent molecule is 4. At the current pH, the phenolic hydroxy group is 99% unionized and the carboxylic acid is 50% ionized. What is the pK<sub>a</sub> of the carboxylic acid?
- A. 0  
 B. 1  
 C. 2  
 D. 3  
 E. 4



**Neutral**

## **Pyrrole**



**Cation (-12)**

