How to Understand Aqueous Ionization and Its Influence on Key Physical Properties of Drugs

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Simulations Plus, Inc.

Drug Discovery Chemistry

San Diego, 2018

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Part I

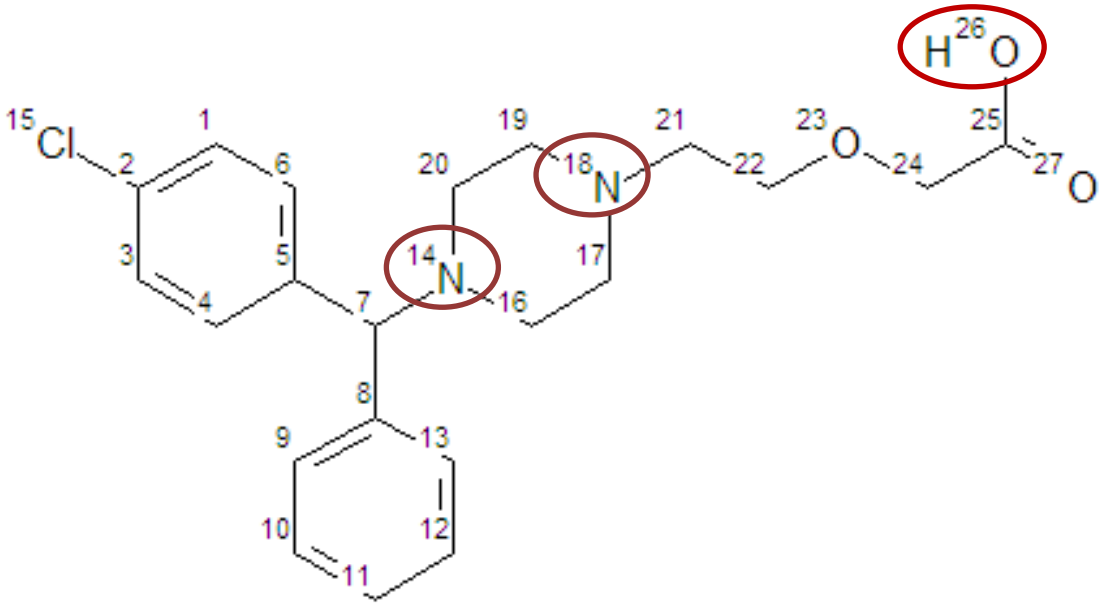
“You Must Unlearn What You Have Learned”:

Clearing Up Myths About Aqueous Ionization of Drugs

"No! No different. Only different in your mind… You must unlearn what you have learned."

Master Yoda to Luke Skywalker in the swamps of Dagobah.

Myth #1: <u>apparent</u> pK_a can always be "assigned" to functional groups



2.10
3.01
8.17

Marosi A, Kovacs Z, Beni S, Kokosi J and Noszal B. European Journal of Pharmaceutical Sciences, 37: 321-328, 2009.

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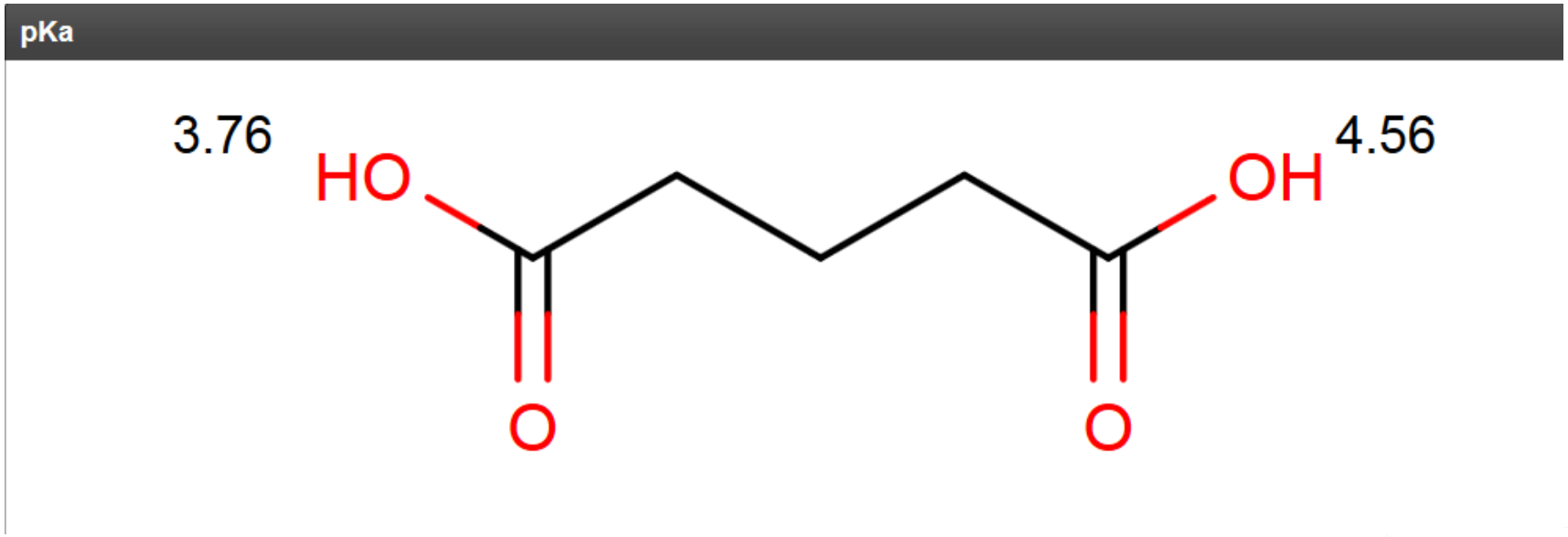
Glutaric acid example

Measured apparent pK_a: 5.42
4.35

German,W. & Vogel,A.,
J.Am.Chem.Soc., 58, 1546 (1936)

How one popular program predicts and reports pK_a for glutaric acid:



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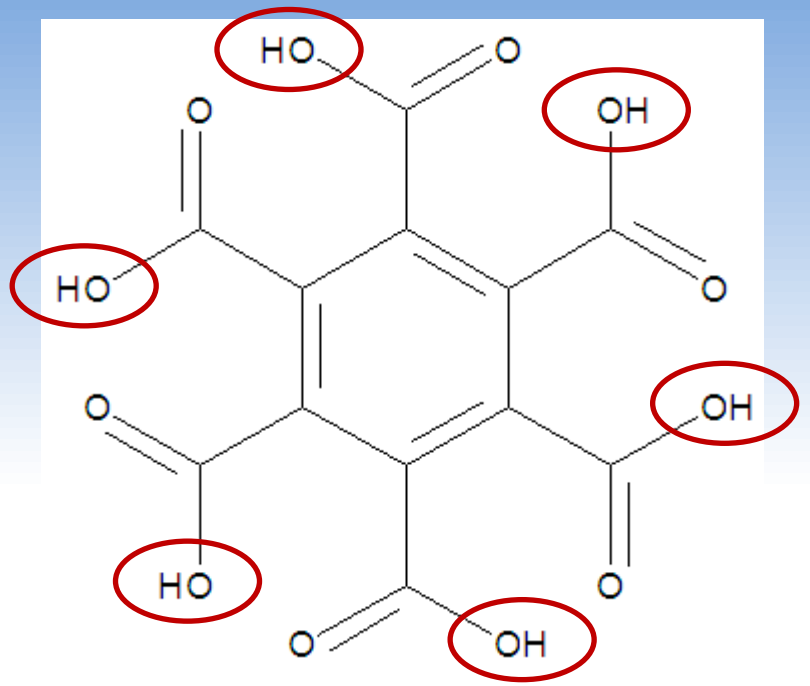
Futility of “assignments” – another example

Apparent pK_a

1.40
2.19
3.31
4.78
5.89
6.96

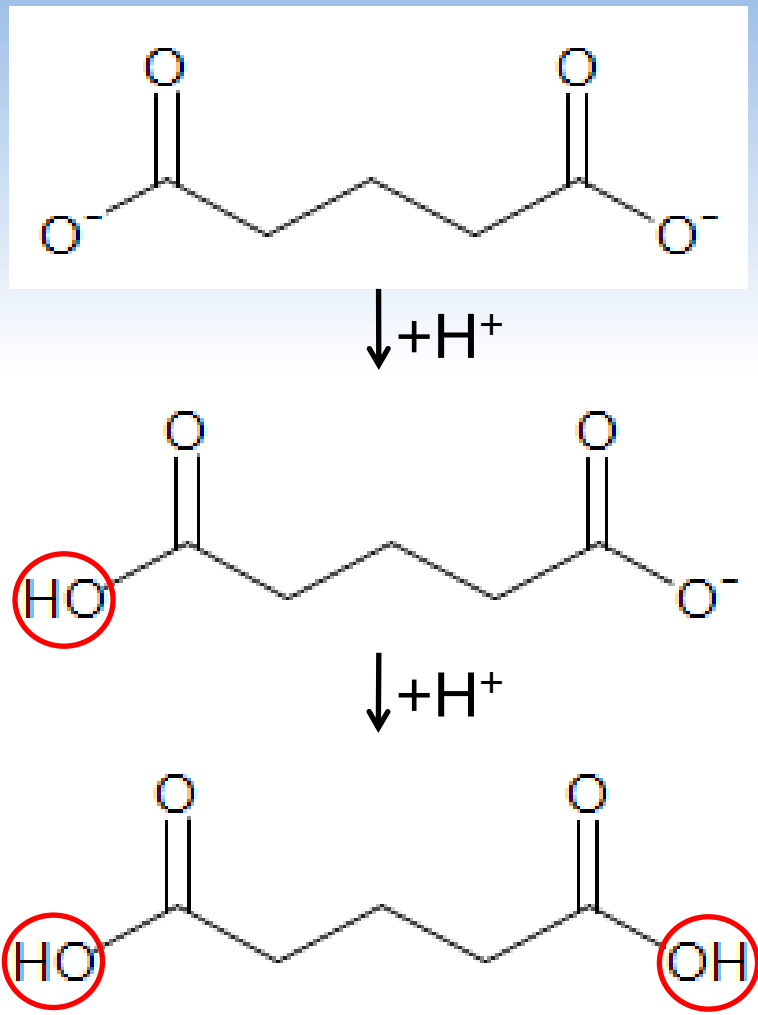


“Assign”? How?

Maxwell W & Partington J. *Trans Farad Soc*. **31**, 922 (1935)

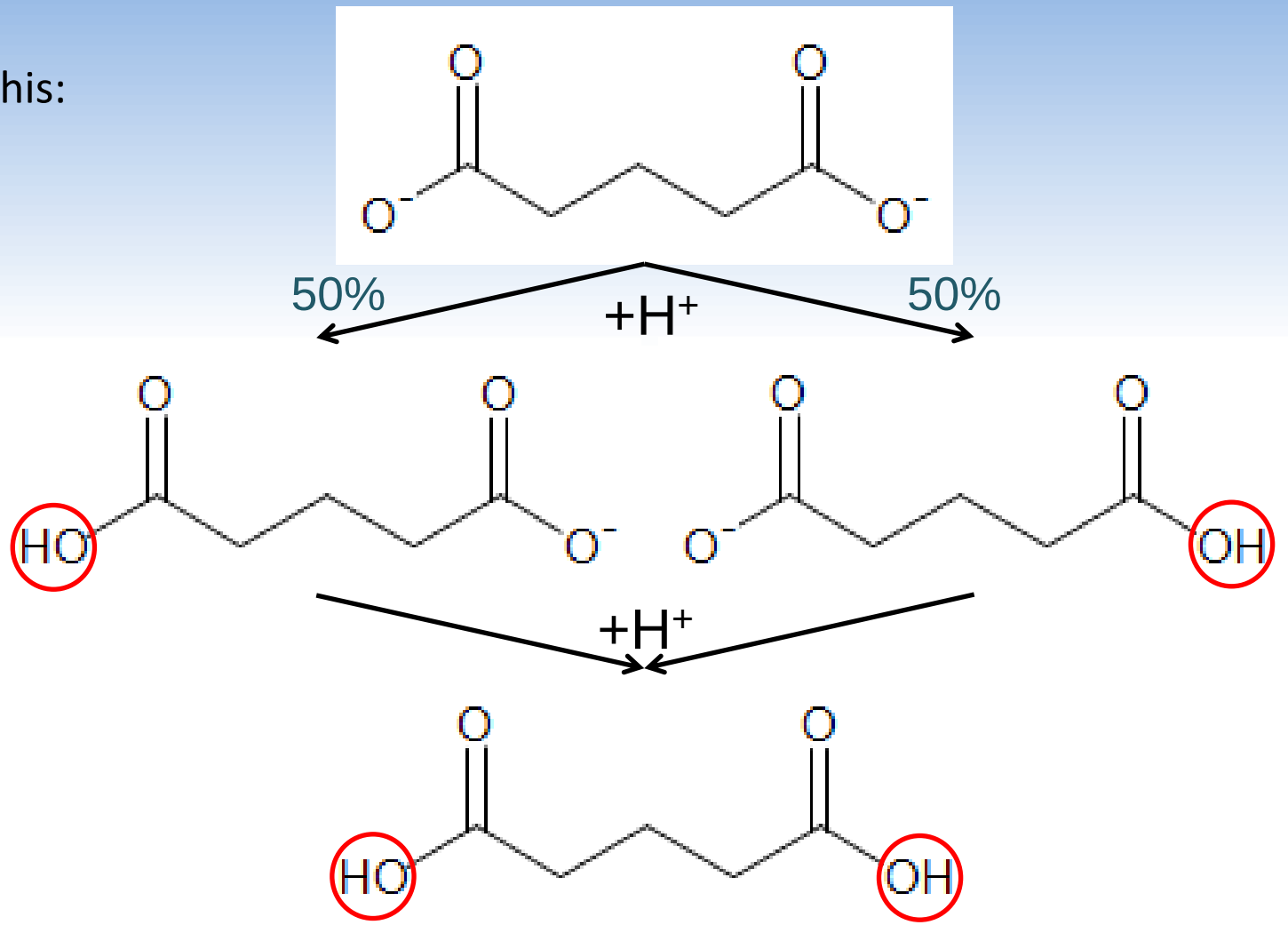
How do polyprotic molecules protonate?

Like this? :

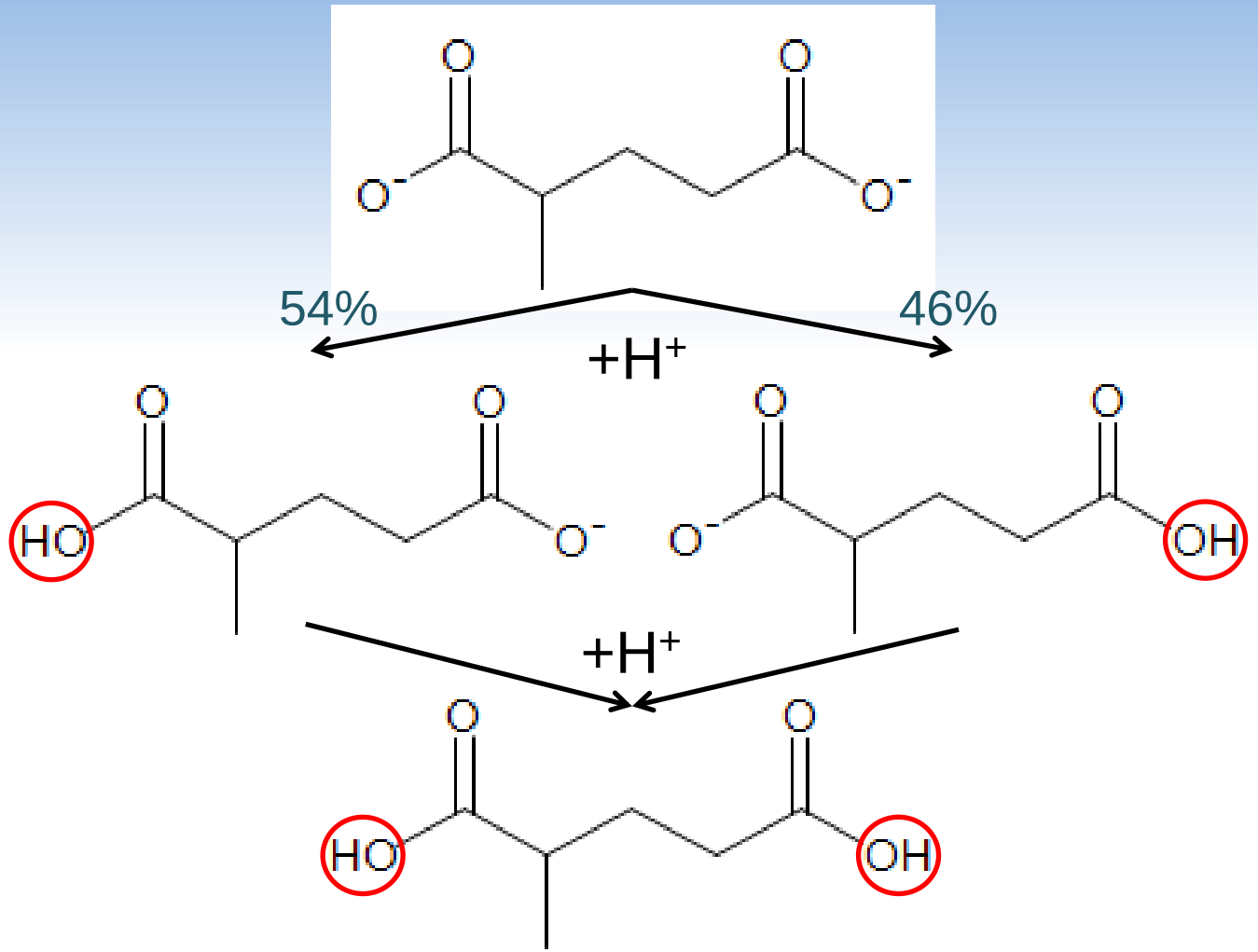


How do polyprotic molecules protonate?

No! Like this:



How do polyprotic molecules protonate?



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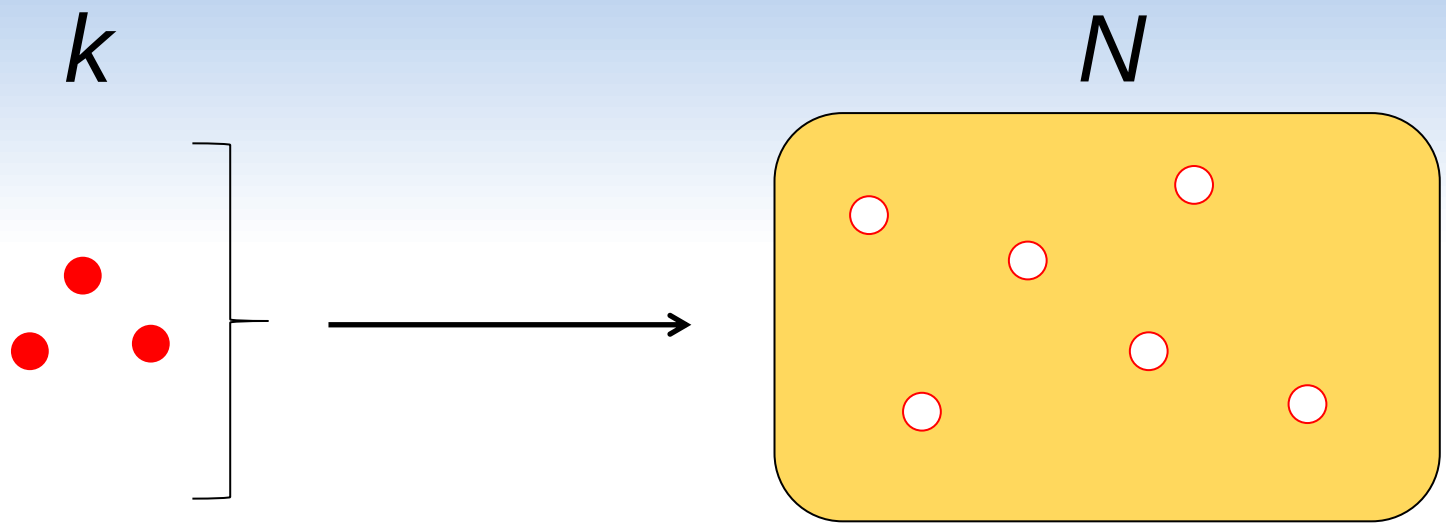
It‘s a simple combinatorial problem

Distribute k protons among N sites; $0 \leq k \leq N$



$$\binom{N}{k}$$ distinct combinations

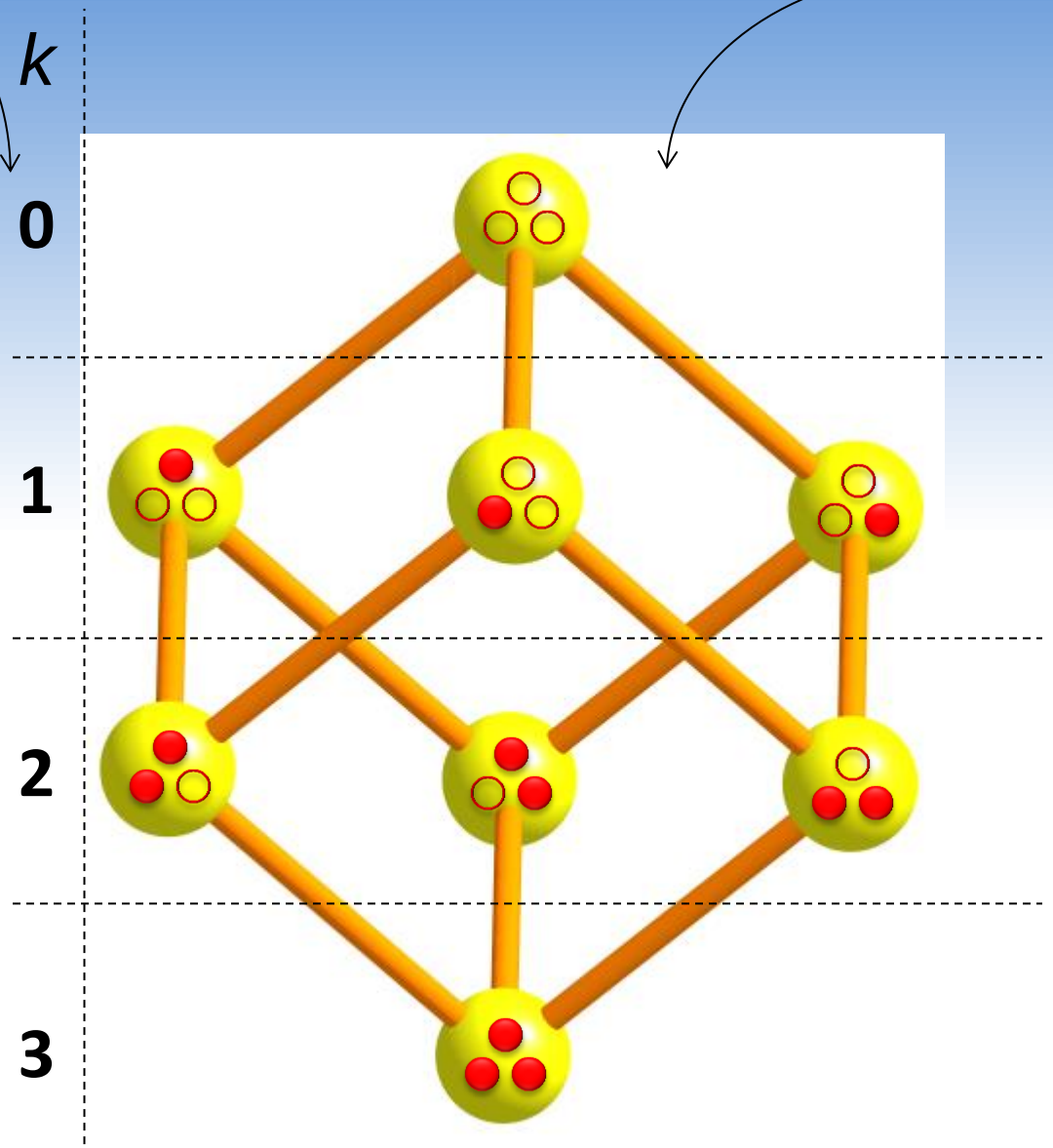
N=3

Macrostates:

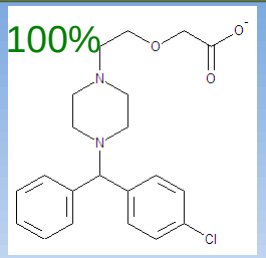
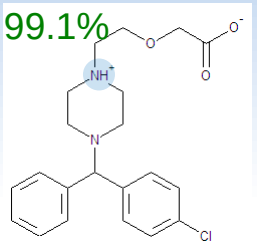
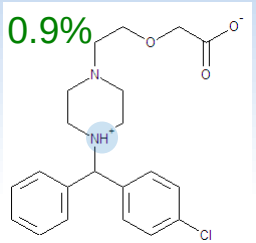
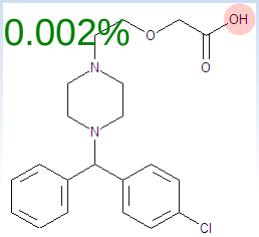
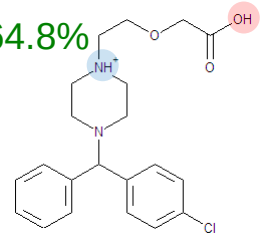
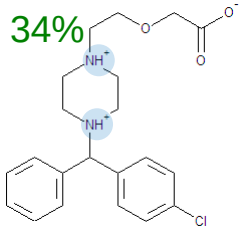
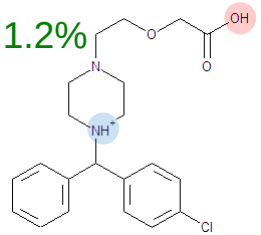
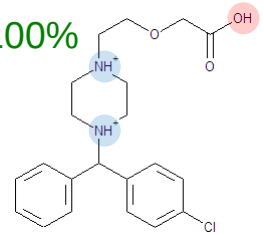
knowing there are *k* protons somewhere

Microstates:

knowing where the *k* protons exactly are



Cetirizine, N=3

Macrostates		Microstates
0	Cet^-	
1	$HCet^0$	  
2	H_2Cet^+	  
3	H_3Cet^{++}	

Marosi, A.; Kovacs, Z.; Beni, S.; Kokosi, J.; Noszal, B.
Eur. J. Pharm. Sci. 2009***, 37,*** 321-328.

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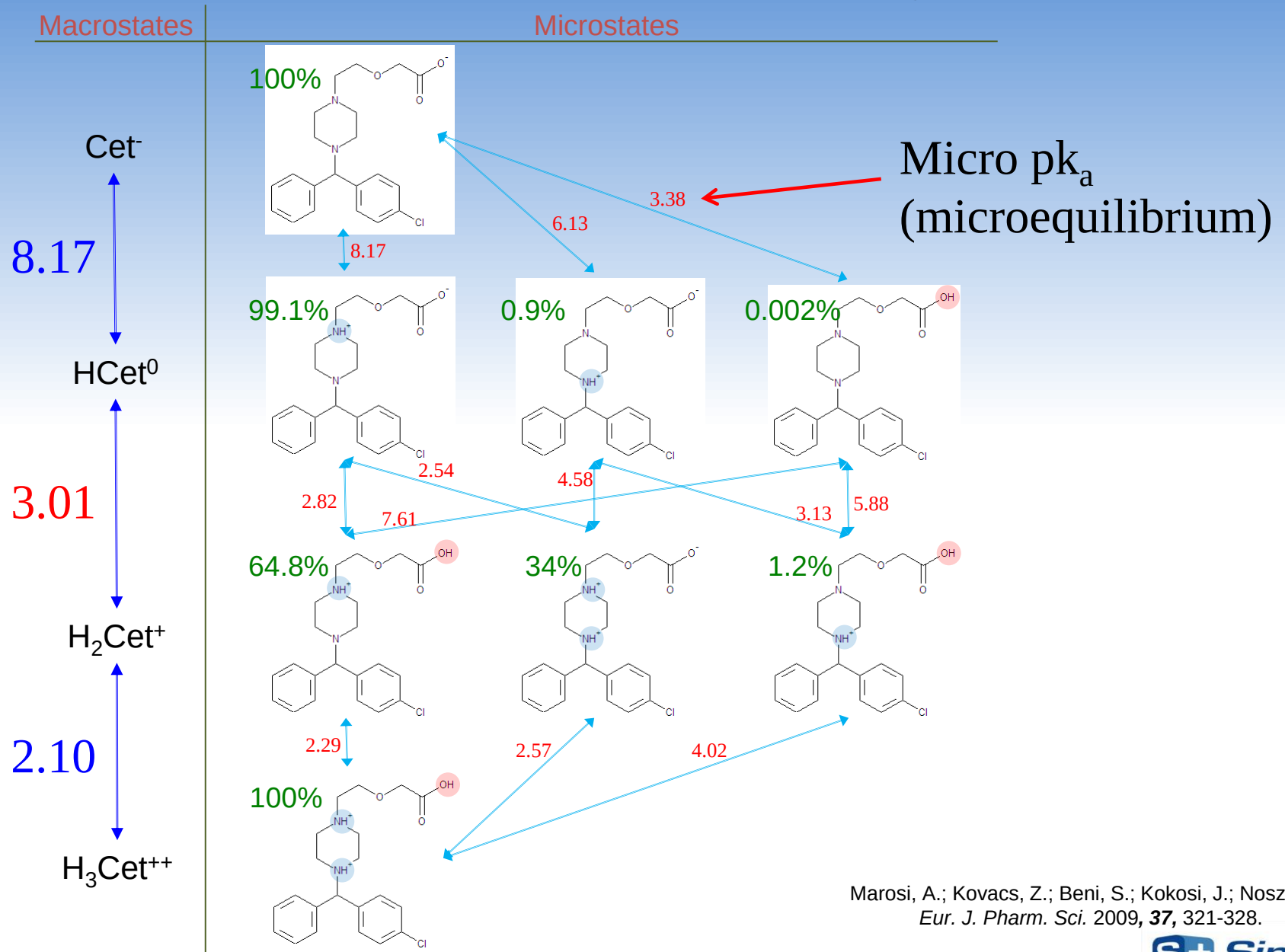
Cetirizine, N=3, with pK_a



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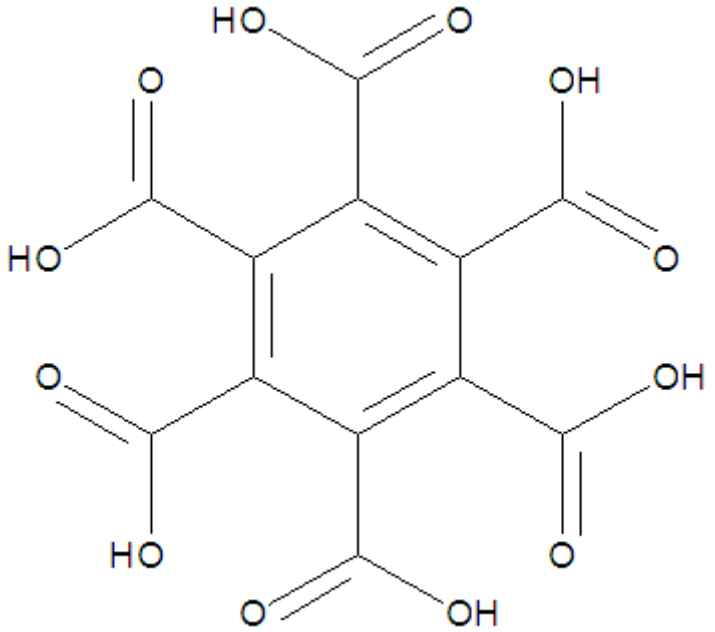
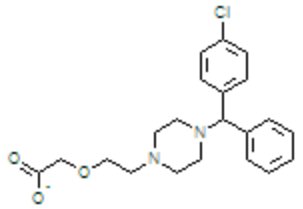
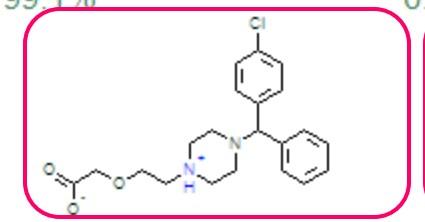
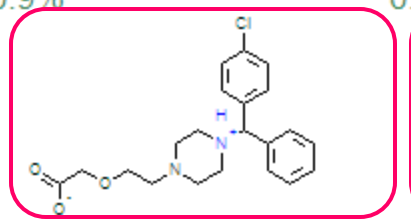
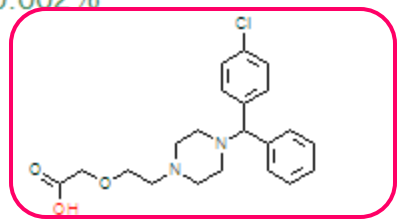
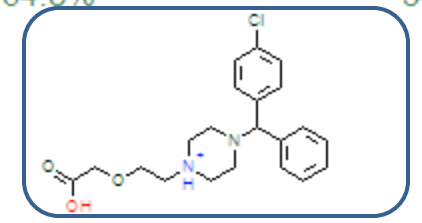
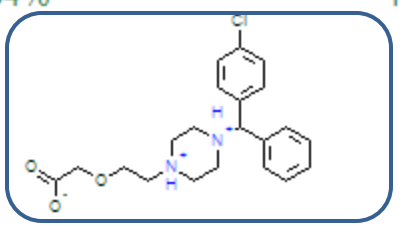
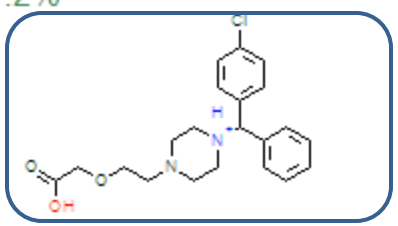
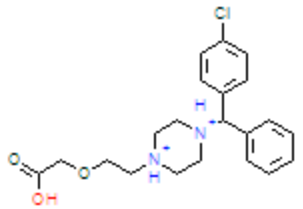
Mellitic Acid, N=6

pK_a	Macrostates	Microstates
	M^{-6}	100.0%
6.66	⇅	
	HM^{-5}	16.7% 16.7% 16.7% 16.7% 16.7% 16.7%
5.37	⇅	
	H_2M^{-4}	11.4% 11.4% 11.4% 7.4% 7.4% 7.4% 7.4% 7.4% 7.4% 3.5% 3.5% 3.5% 3.5% 3.5% 3.5%
4.13	⇅	
	H_3M^{-3}	8.7% 8.7% 6.0% 6.0% 6.0% 6.0% 6.0% 6.0% 6.0% 6.0% 6.0% 6.0% 6.0% 6.0% 1.8% 1.8% 1.8% 1.8% 1.8% 1.8%
2.97	⇅	
	H_4M^{-2}	10.6% 10.6% 10.6% 7.7% 7.7% 7.7% 7.7% 7.7% 7.7% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6%
2.03	⇅	
	H_5M^{-}	16.7% 16.7% 16.7% 16.7% 16.7% 16.7%
1.56	⇅	
	H_6M	100.0%

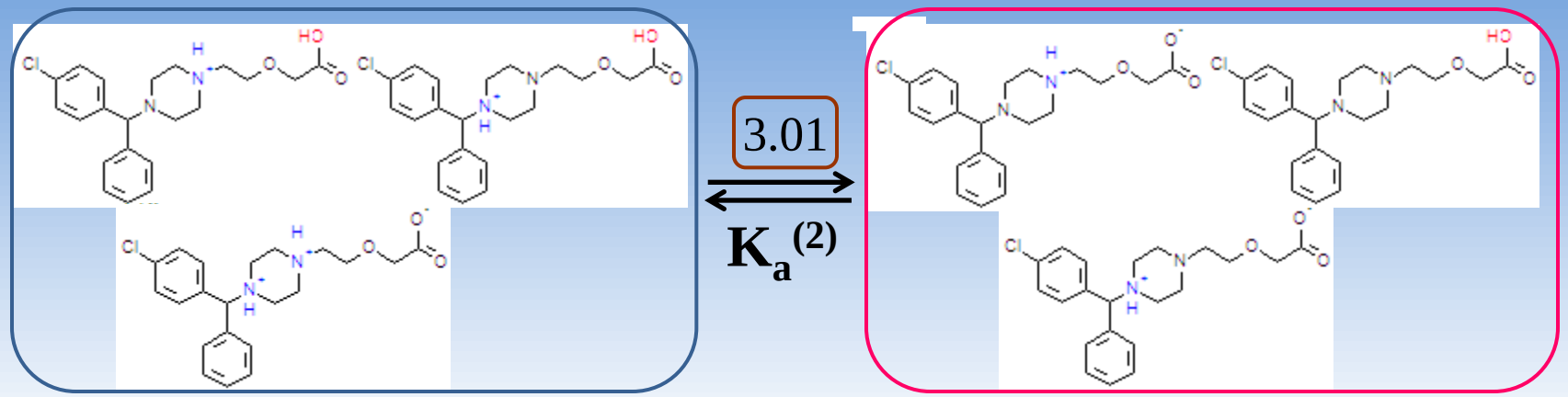


A microscopic/thermodynamic view of cetirizine ionization

pKa Table for Cetirizine.mol
1 acidic atoms: 26(-OH)
2 basic atoms: 14(>N-)18(>N-)
Aliphatic -OH groups were ignored
Aliphatic amides were ignored
Carbon protonation was ignored

pK_a	Macrostates	Microstates
	M^-	100.0% 
8.17		
	HM	99.1%  0.9%  0.002% 
3.01		
	H_2M^+	64.8%  34%  1.2% 
2.10		
	H_3M^{+2}	100.0% 

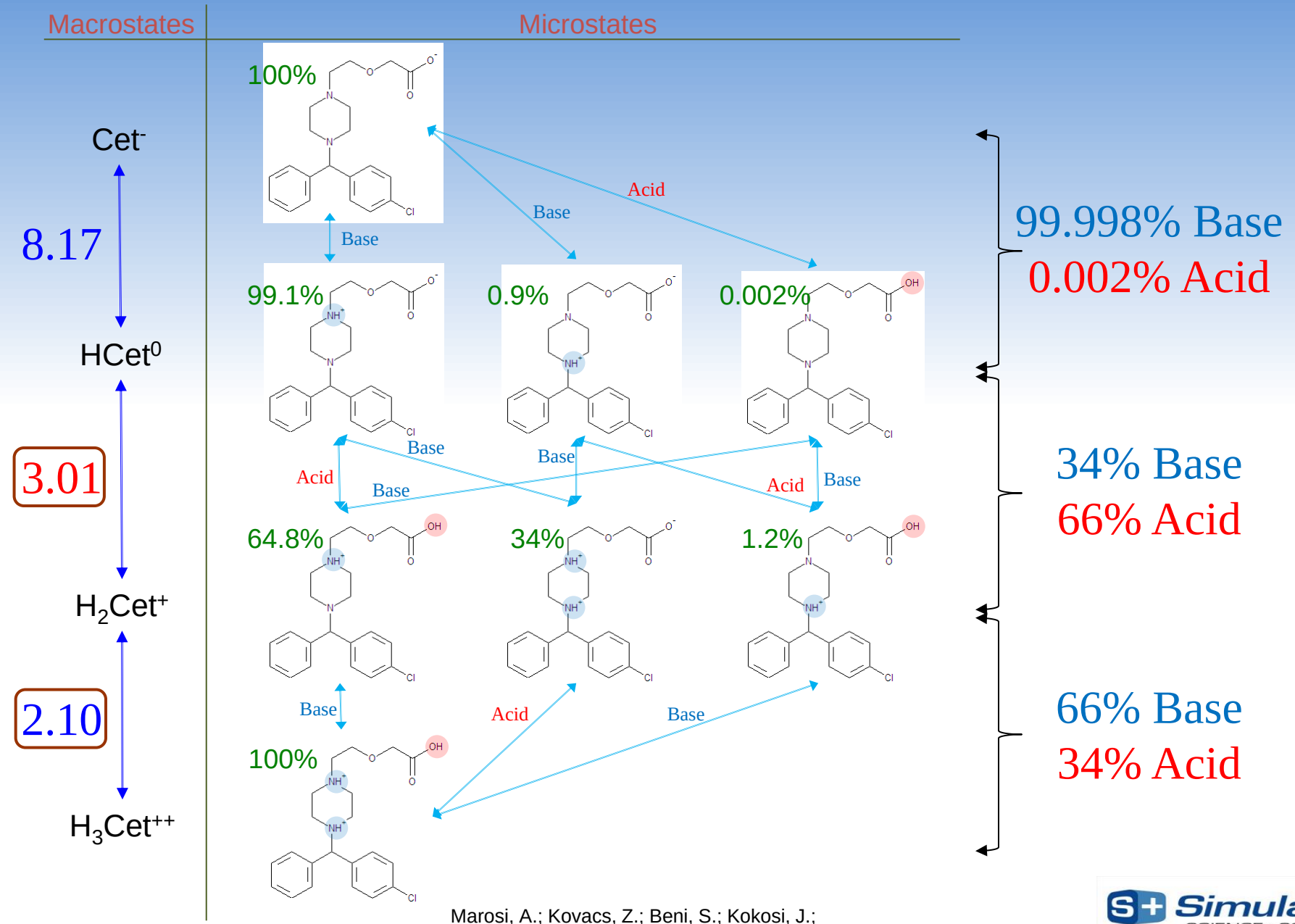
Apparent pK_a is NOT a property of a single ionizable group



H_2M^+ $\quad$ HM

$$K_a^{(2)} = \frac{\left[\left[\text{ionized}\right] + \left[\text{neutral}\right] + \left[\text{zwitterion}\right]\right][H^+]}{\left[\text{cation}\right] + \left[\text{neutral}\right] + \left[\text{zwitterion}\right]}$$

Myth #2: <u>apparent</u> pK_a can always be "labeled" as either acidic, or basic



Marosi, A.; Kovacs, Z.; Beni, S.; Kokosi, J.; Noszal, B. *Eur. J. Pharm. Sci.* 2009, ***37,*** 321-328.

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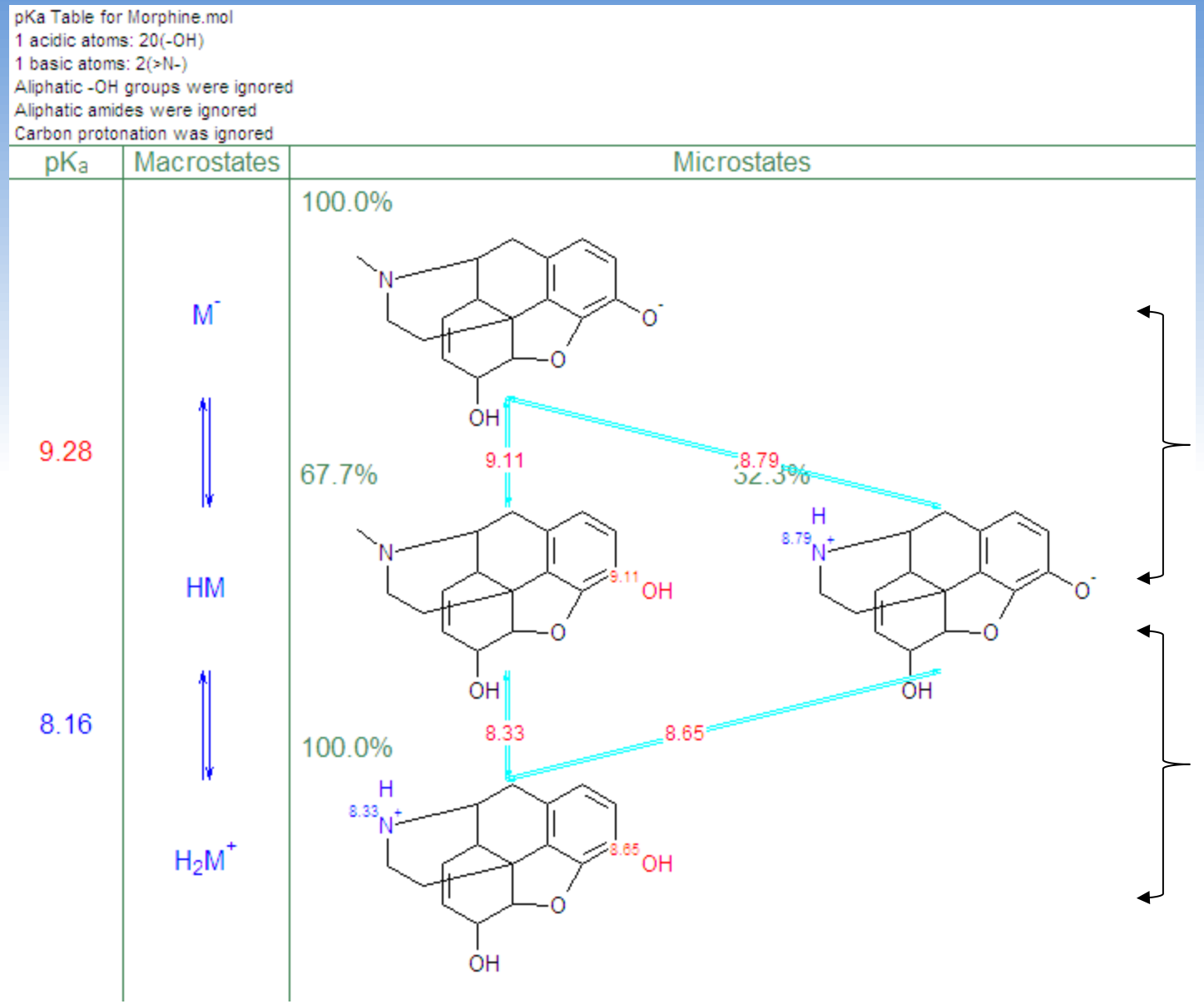
Apparent and microscopic pK_a for morphine



[Experimental data from Mazák K, Noszál B. Poster presented at the LogP2009 Symposium, Zürich, Switzerland, 2009]

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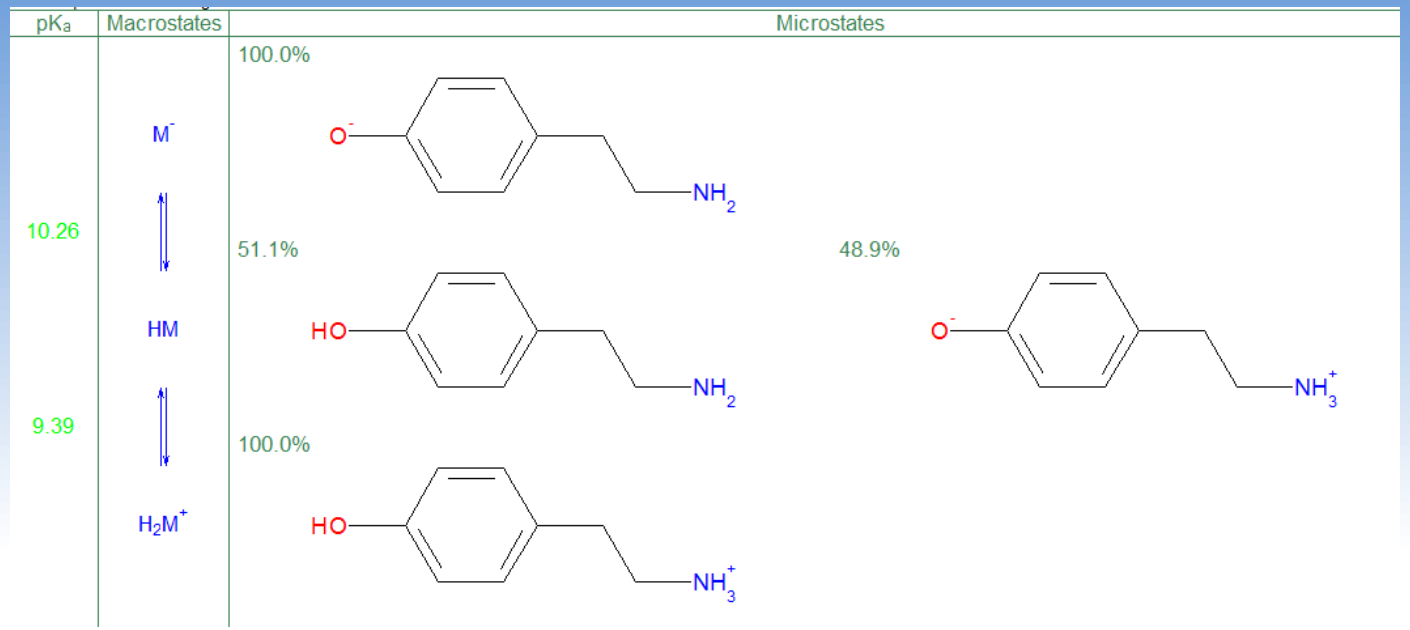
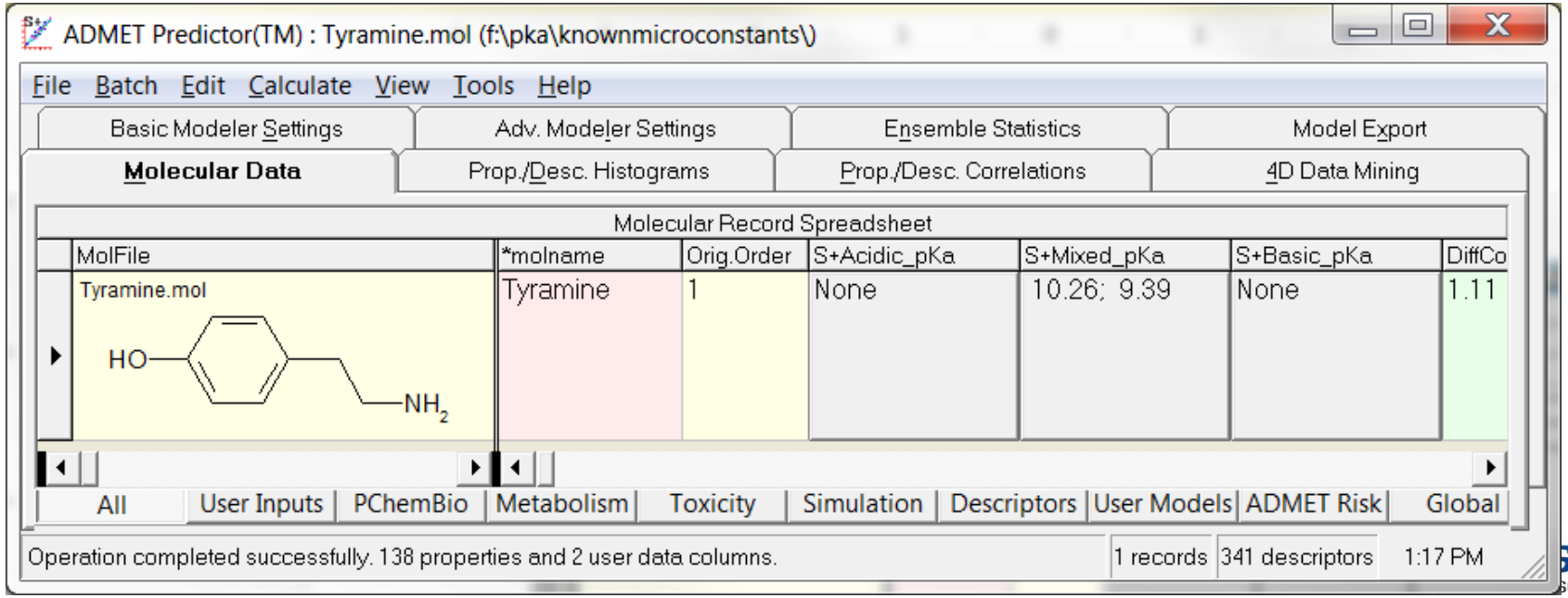
What is mixed pK_a?



49% Base
51% Acid

51% Base
49% Acid



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I'M
51% SWEETHEART
AND
49% BITCH
SO DON'T PUSH IT!!!

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Part II

“It’s either salty, or it’s free”:

Understanding the pH Dependence of Aqueous Solubility

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Example: solubility of a free monoprotic base

At high pH...

$B_{(s)} <=> B_{(aq)}$ $\qquad \frac{[B_{(aq)}]}{a_{B_{(s)}}} = K_{(s-aq)}$

Intrinsic solubility of B

$$IS_B \equiv [B_{(aq)}] = K_{(s-aq)} a_{B_{(s)}} = const$$

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Ionization of a free monoprotic base

At any pH...

$$BH^+_{(aq)} <=> B_{(aq)} + H^+_{(aq)}$$

$$\frac{[B_{(aq)}][H^+_{(aq)}]}{[BH^+_{(aq)}]} = K_a$$

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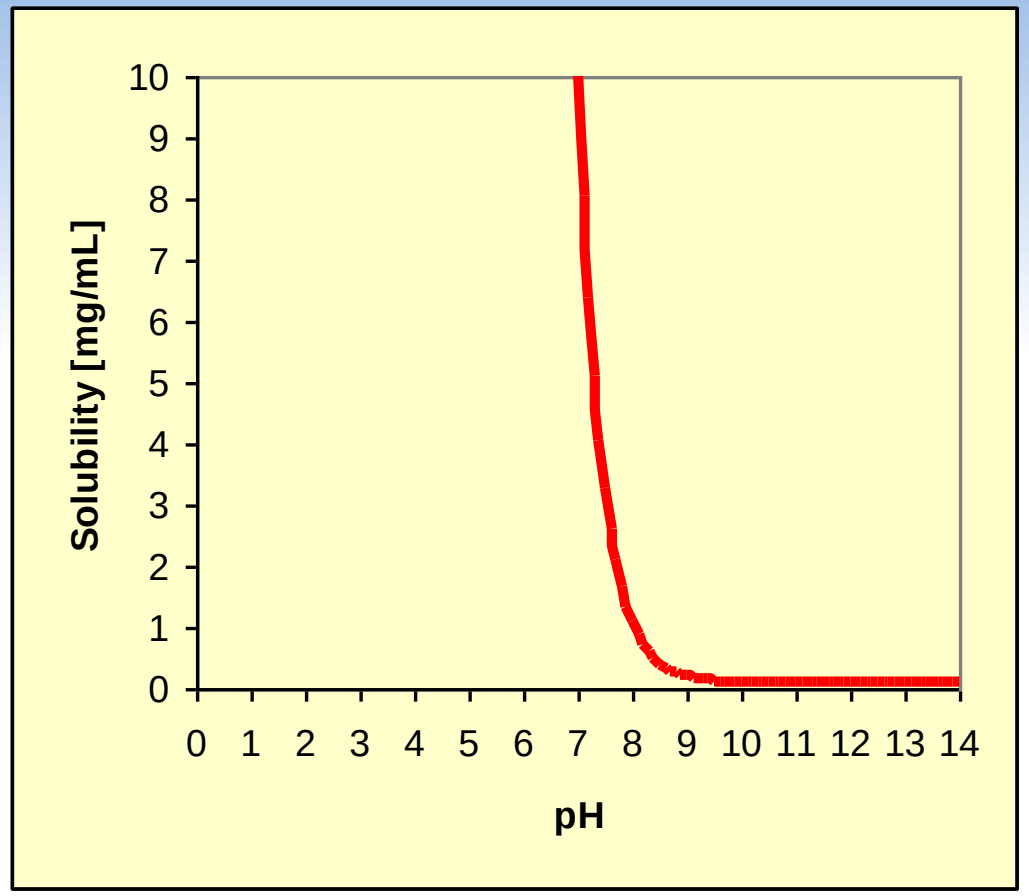
Free: Solubility profile of a free monoprotic base

Apparent solubility of B

$$S_B(pH) = [B_{(aq)}] + [BH^+_{(aq)}]$$

$$S_B(pH) = IS_B\left(1 + 10^{pK_a - pH}\right)$$

“Acid catastrophe”



A base with intrinsic solubility of 0.1 mg/mL and pK_a = 9 would at pH = 1 be soluble at amazing 10^7 mg/mL ...

10 *kilograms* per mL?

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Salty: Counterions to the rescue

At low pH a different solid-liquid equilibrium is reached:

$$BHX_{(s)} \Longleftrightarrow BH^{+}_{(aq)} + X^{-}_{(aq)}$$

$$[BH^{+}_{(aq)}][X^{-}_{(aq)}] = K_{sp}$$

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Complete solubility profile of a monoprotic base

Free base region:

$$S_B(pH) = IS_B\left(1+10^{pK_a-pH}\right)$$

Source of trouble if many Xs compete…

Salt region:

$$S_B(pH, K_{sp}, [X^-]) = \frac{K_{sp}}{[X^-]}\left(1+10^{pH-pK_a}\right)$$

Source of the common ion effect!

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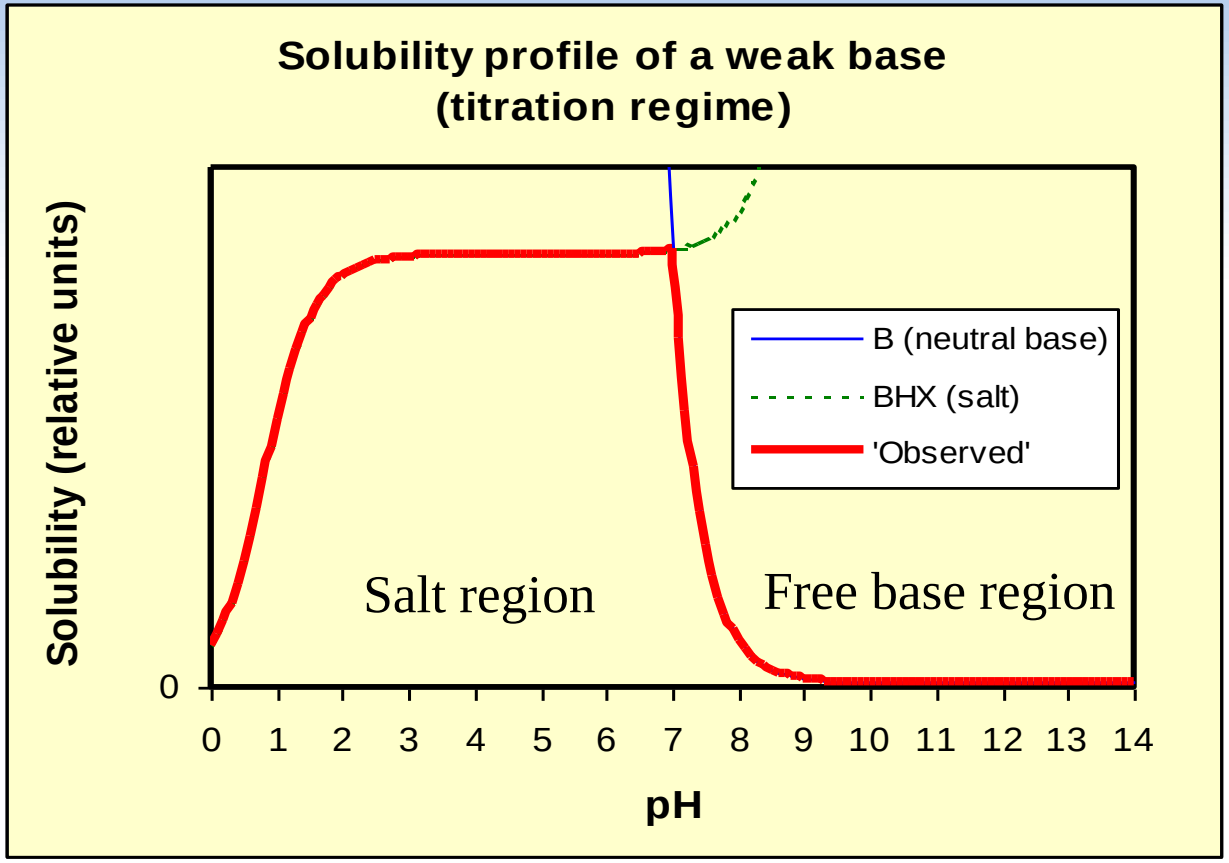
Complete "*in vitro*" solubility profile of a monoprotic base



Titration regime requires

$[BH^+] + [H^+] = [X^-]$

at all times.

Hence, $[X^-]$ goes up with decreasing pH.

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Parameters to be defined or predicted

$$IS_B, pK_a, K_{sp}, X, [X^-]$$

1) Standarize counterion to approximate *in vivo* conditions

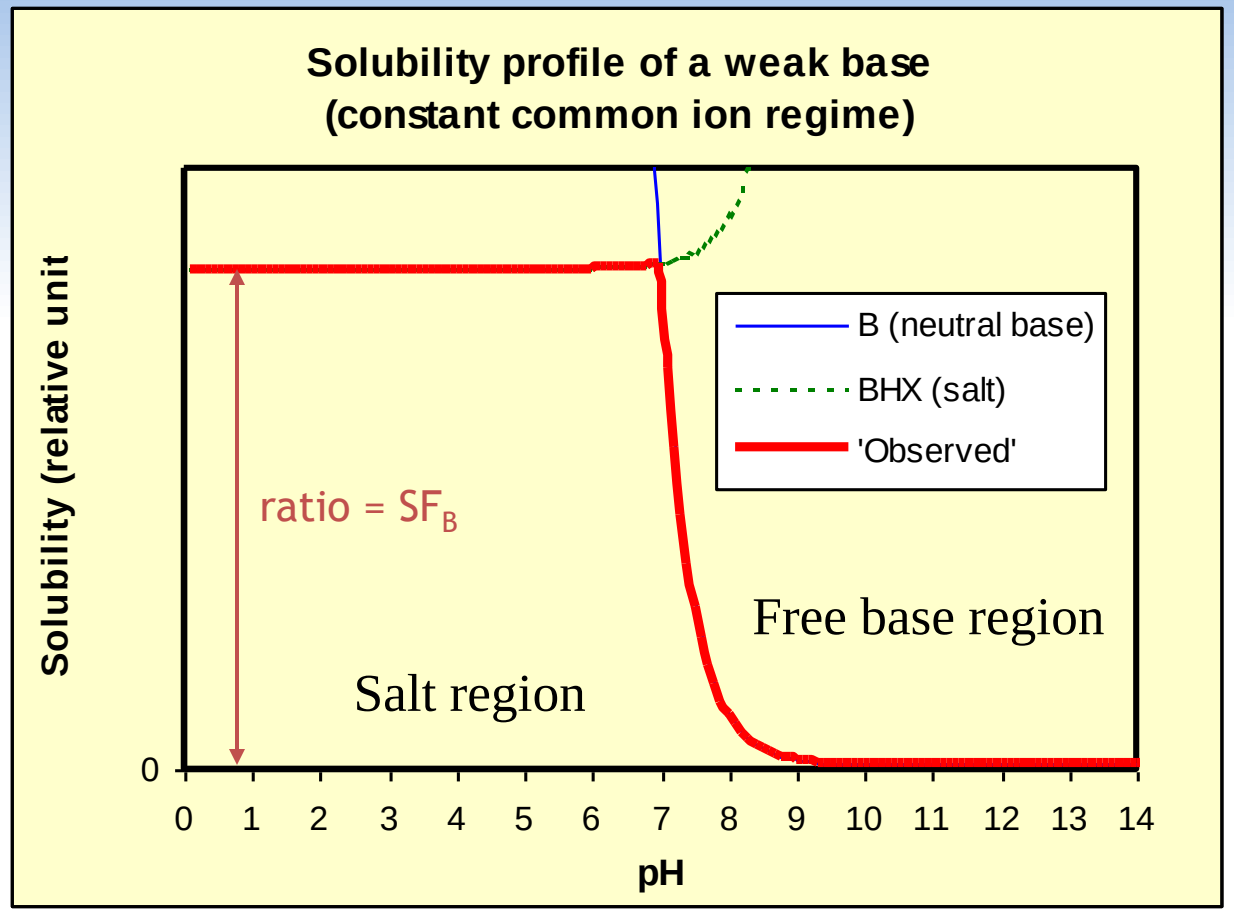
X = Cl, $[X^-]$ = 0.14 M

Johnson LR; "Fluid and Electrolyte Absorption" in Johnson LR (Ed.) *Gastrointestinal Physiology*; Mosby, St. Louis, 1989

2) Define *Solubility Factor*:

$$SF_B \equiv \frac{K_{sp}}{[X^-]} \Big/ IS_B$$

Complete "*in vivo*" solubility profile of a monoprotic base



Constant common ion regime requires

$[X^-]$ = const

at all times

Best if standardized to X^- = Cl^- and

$[Cl^-]$ = 0.14 M

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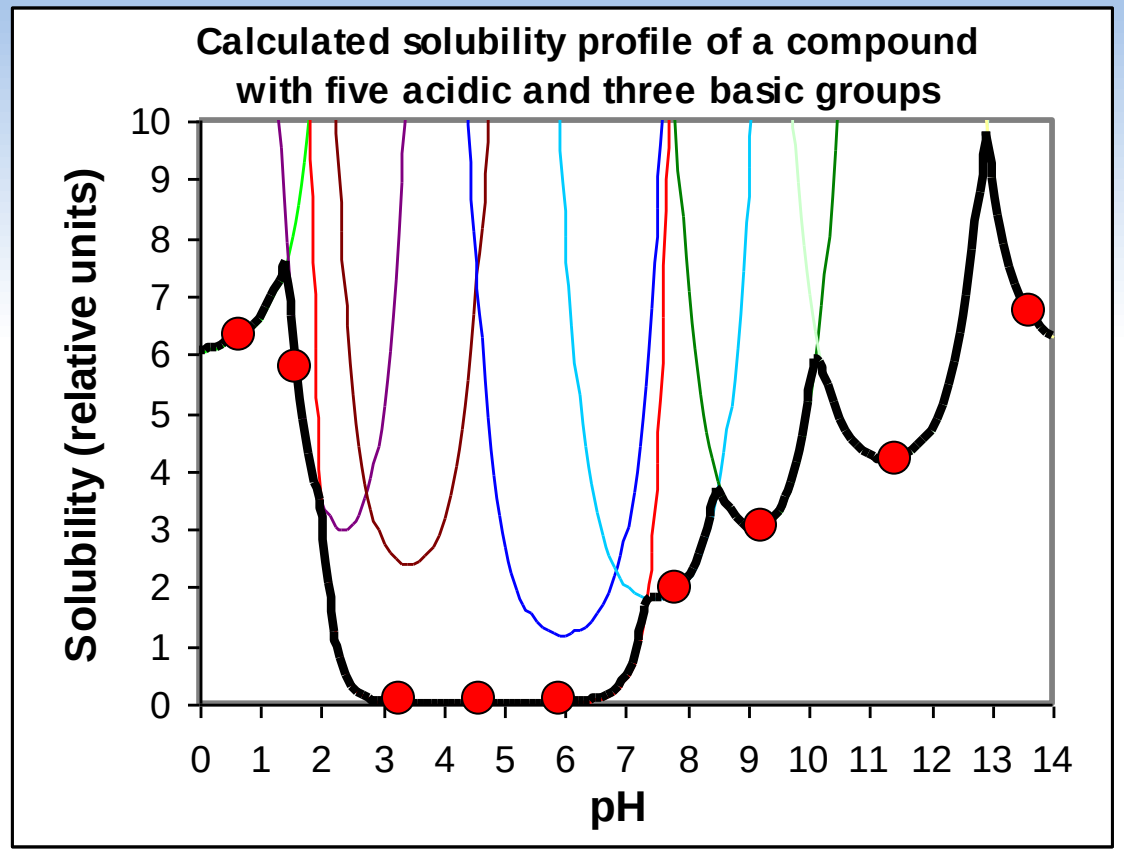
Solubility profiles of polyprotic compounds



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Part III

“*Et vincere nemo dividat*”:

Understanding the pH Dependence of Partitioning

Example: partition of a monoprotic base

At any pH...

$B_{(aq)} \Longleftrightarrow B_{(oct)}$ $\qquad \frac{[B_{(oct)}]}{[B_{(aq)}]} = P^N$

$BH^+_{(aq)} \Longleftrightarrow BH^+_{(oct)}$ $\qquad \frac{[BH^+_{(oct)}]}{[BH^+_{(aq)}]} = P^C$

Electroneutrality requires counterion partition

$BH^+_{(aq)} + X^-_{(aq)} \Leftrightarrow BH^+_{(oct)} + X^-_{(oct)}$ $\qquad \frac{[BH^+_{(oct)}][X^-_{(oct)}]}{[BH^+_{(aq)}][X^-_{(aq)}]} = \Pi_1$

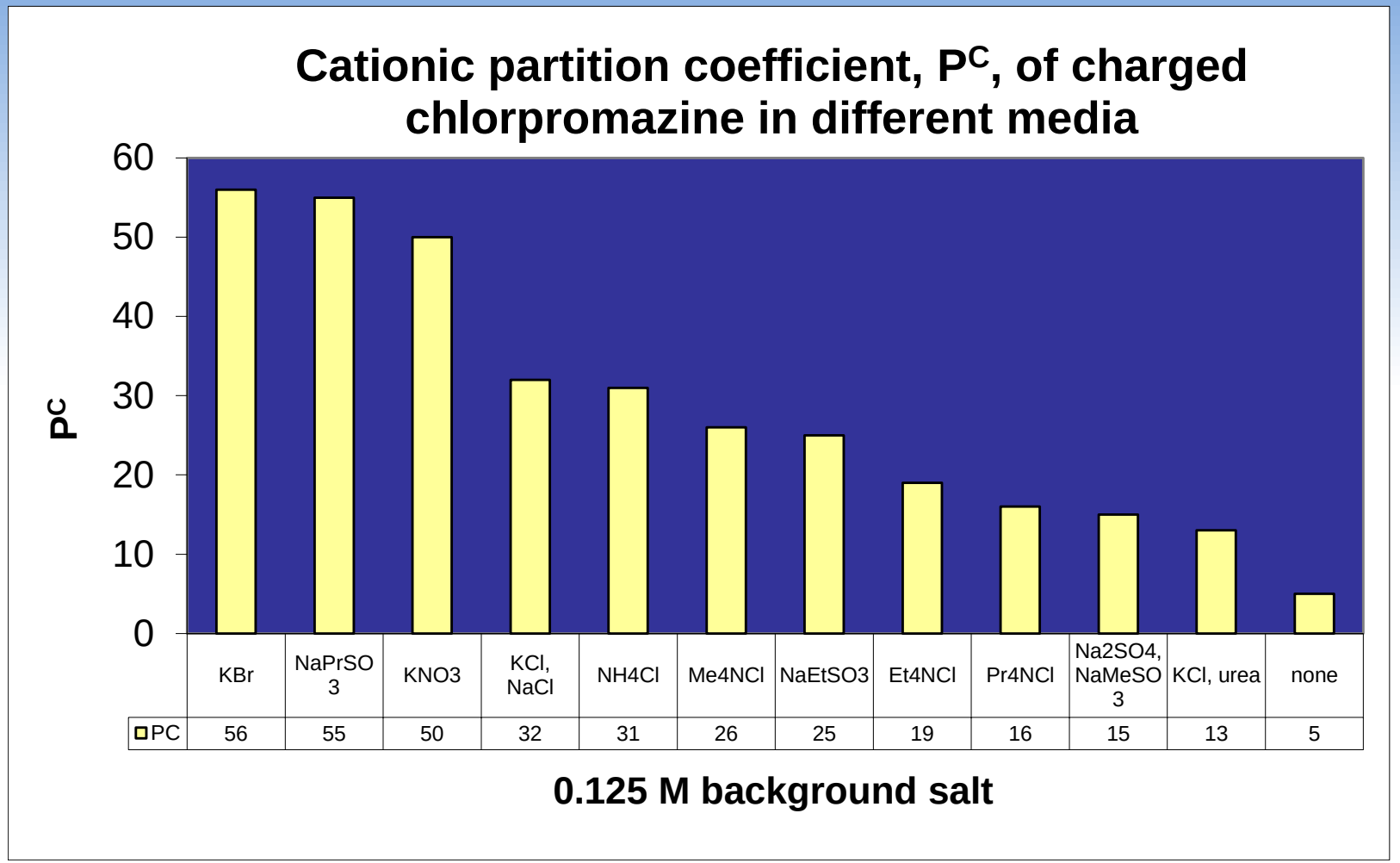
Not so fast...

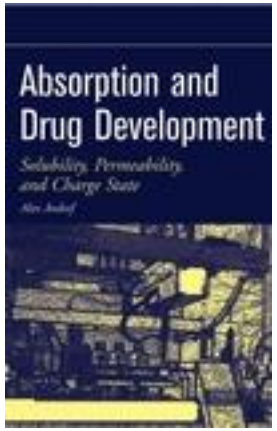
OR

Are we forgetting something?

$BH^+_{(aq)} + X^-_{(aq)} \Leftrightarrow BH^+X^-_{(oct)}$ $\qquad \frac{[BH^+X^-_{(oct)}]}{[BH^+_{(aq)}][X^-_{(aq)}]} = \Pi_2$

Partition of charged species into octanol depends on the ionic environment of aqueous phase





Avdeef, A.; *Absorption and Drug Development*; Wiley-Interscience, Hoboken, NJ; 2003

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Complete distribution profile of a monoprotic base

Don't forget ionization... $\frac{[B_{(aq)}][H^+_{(aq)}]}{[BH^+_{(aq)}]} = K_a$

At all pH:

$$D(pH, X) = \frac{P^N + P^C(X) \cdot 10^{pK_a - pH}}{1 + 10^{pK_a - pH}}$$

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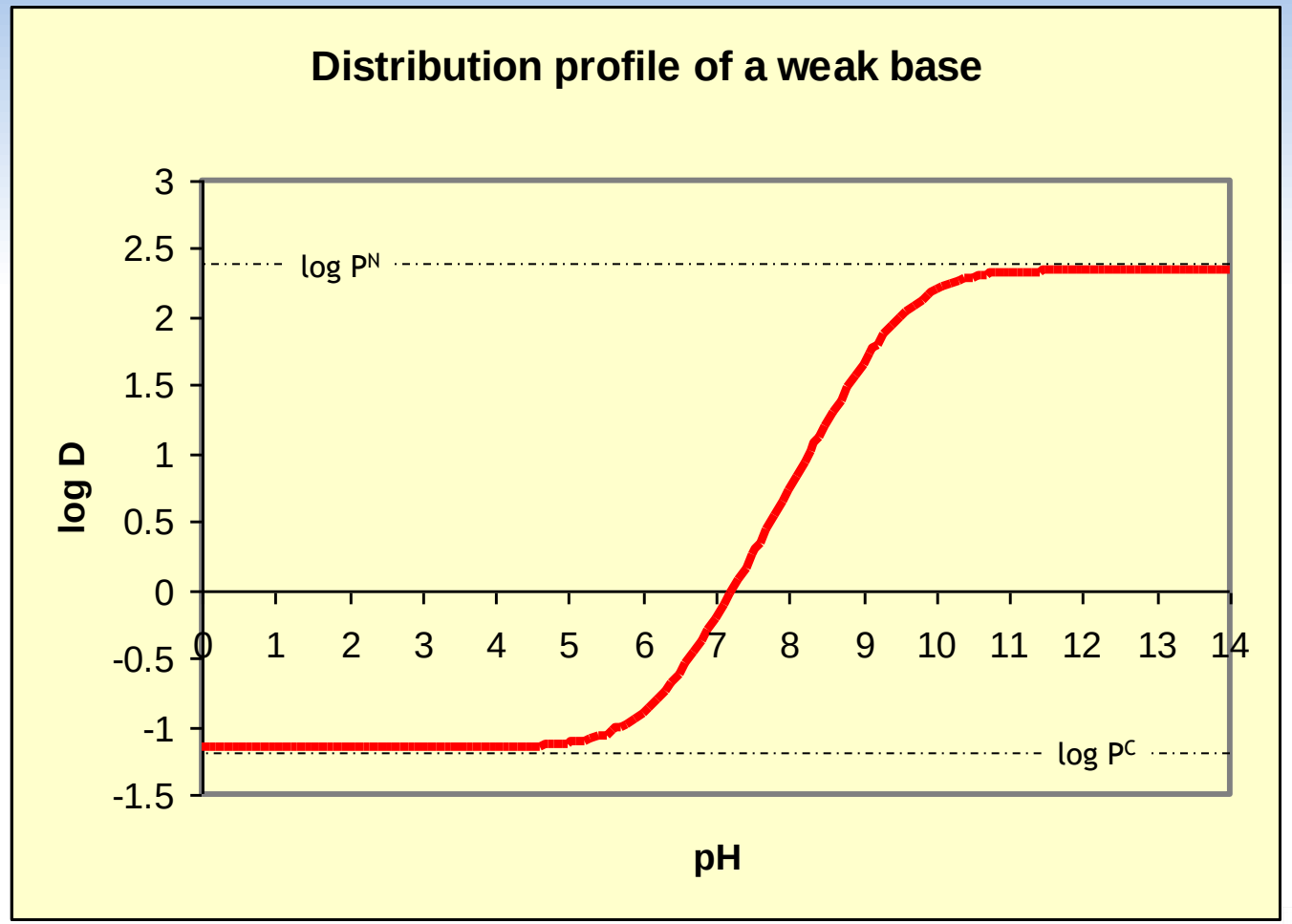
Complete distribution profile of a monoprotic base



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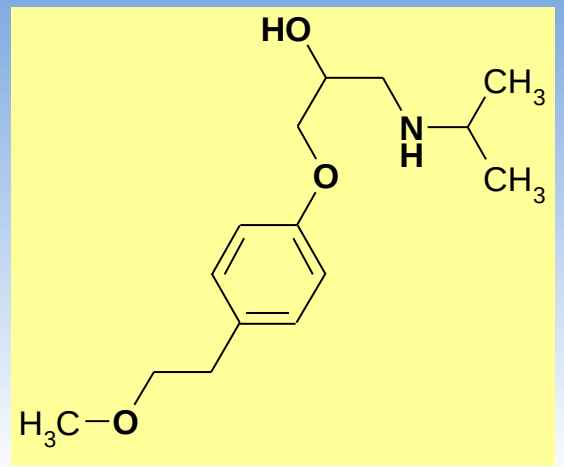
Distribution profiles of polyprotic compounds

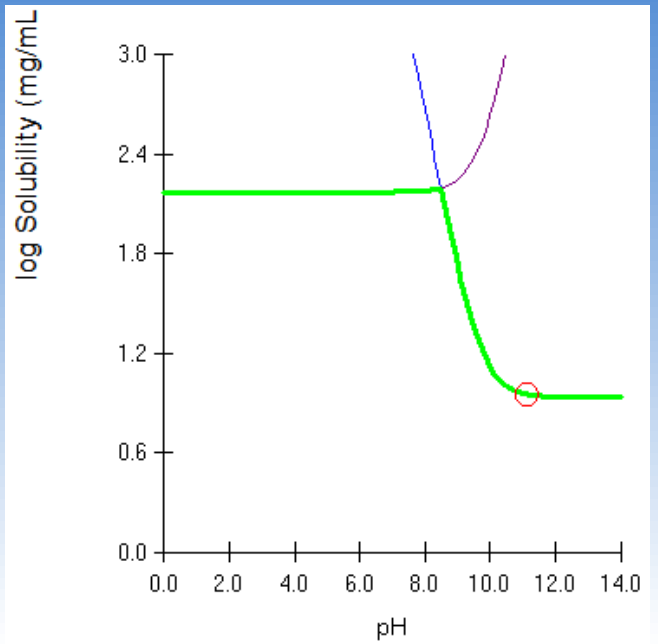
$$D(pH, X) = f_N(pH)P^N + \sum_{i=1}^{n} f_i(pH)P^i(X)$$

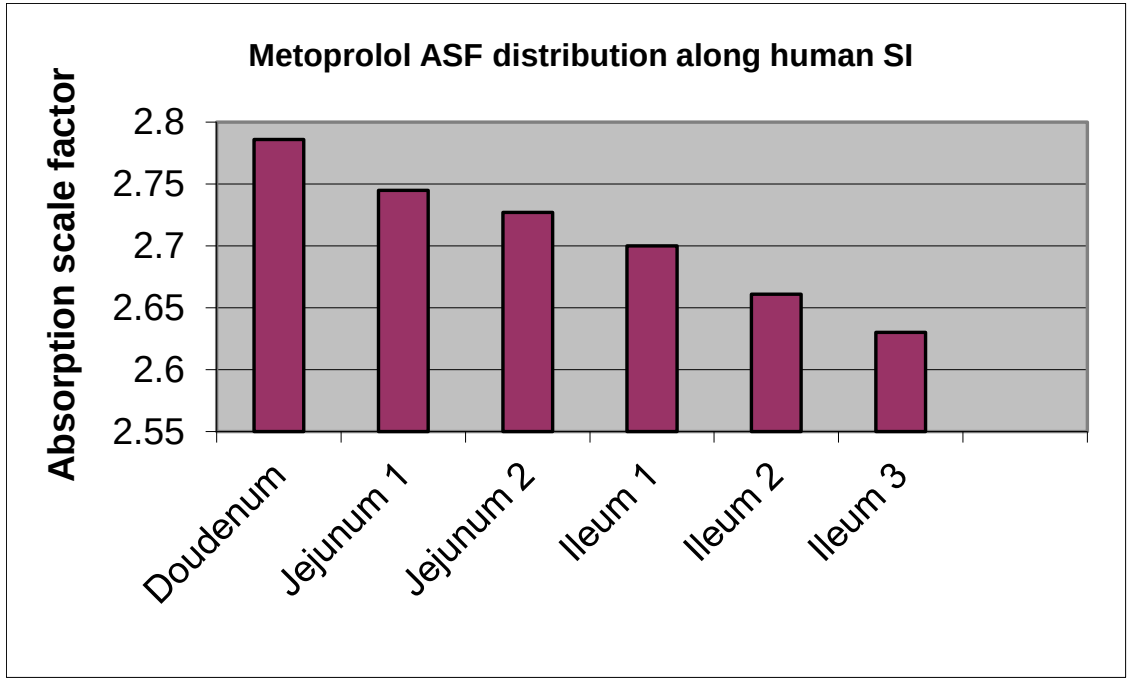
- f_N = molar fraction of neutral species
- P^N = partition coefficient of neutral species
- f_i = molar fraction of ionized species *i*
- P^i = partition coefficient of ionized species *i*
- X = counterion

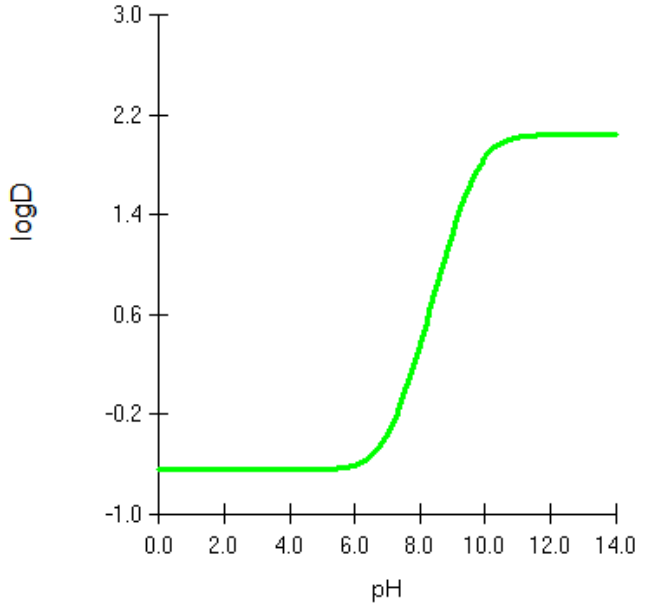
Metoprolol Profiles (base)



pK_a = 9.72
logP = 2.04
logD(7.4) = -0.12
S(11.1) = 9.0 mg/mL
S(7.4) = 149 mg/mL







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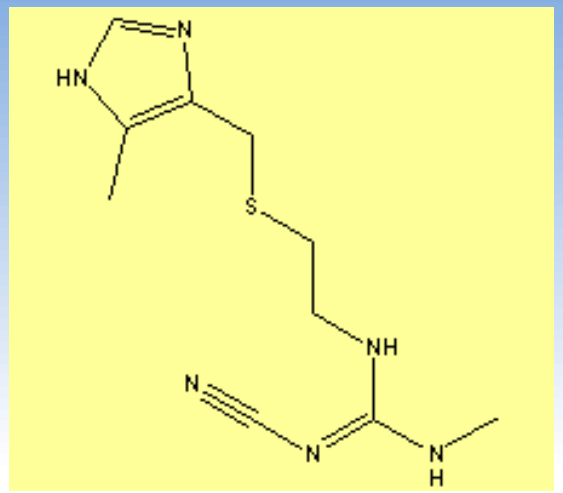
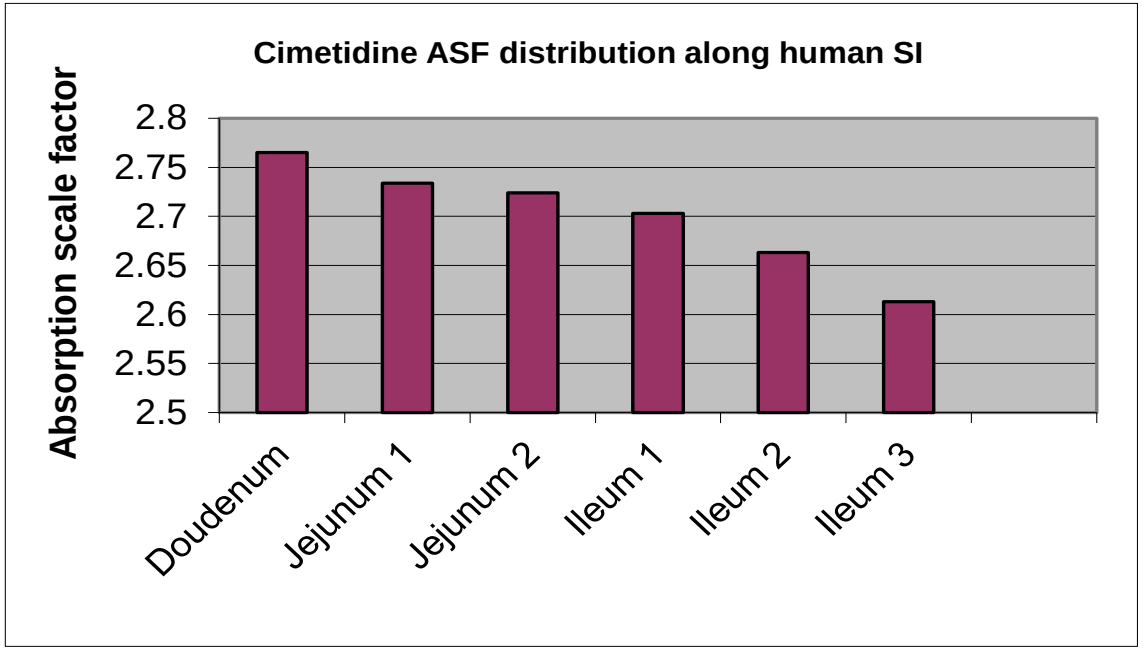
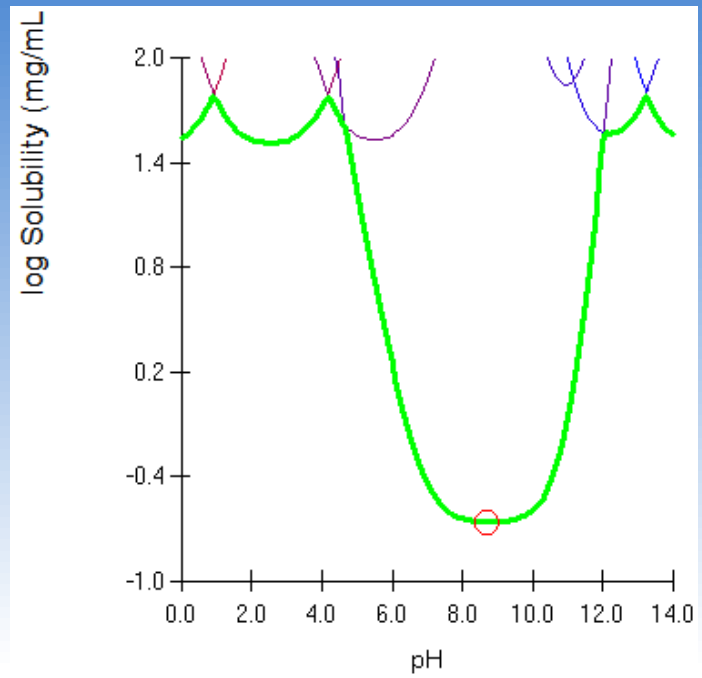
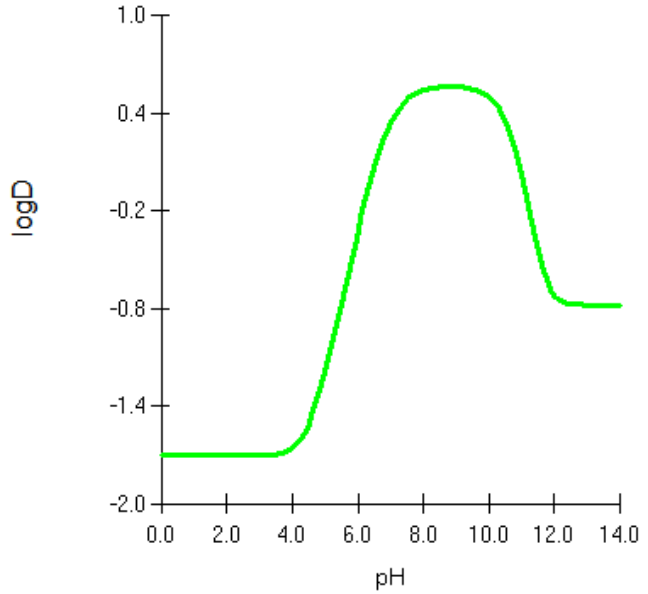
Cimetidine Profiles (ampholyte)



pK_a = 11.16
pK_a = 10.75
pK_a = 6.85
pK_a = 4.16
pK_a = 0.93
logP = 0.57
logD(7.4) = 0.46
S(8.69) = 0.22 mg/mL
S(7.4) = 0.28 mg/mL







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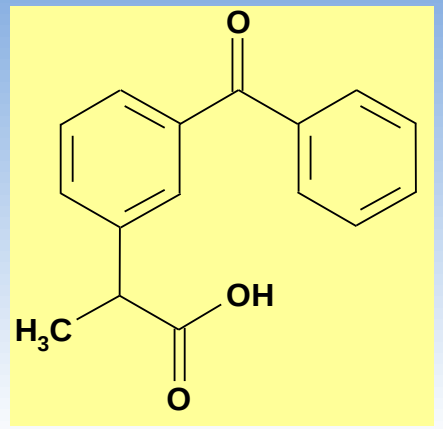
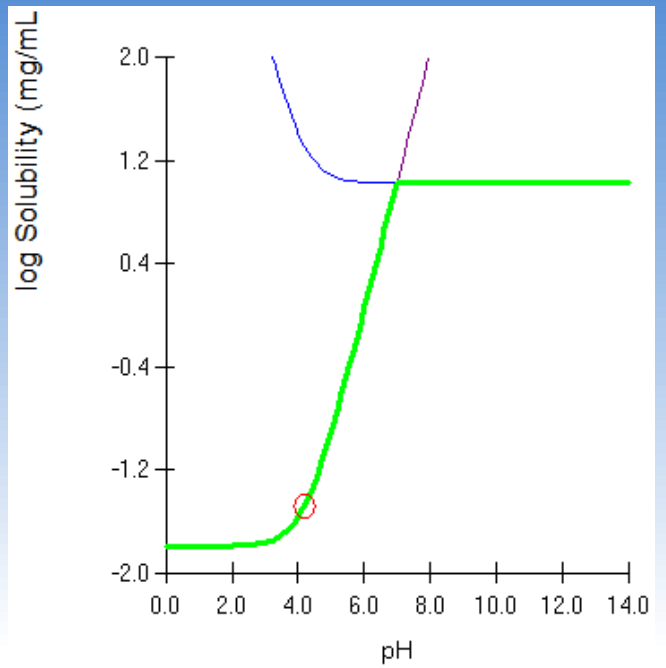
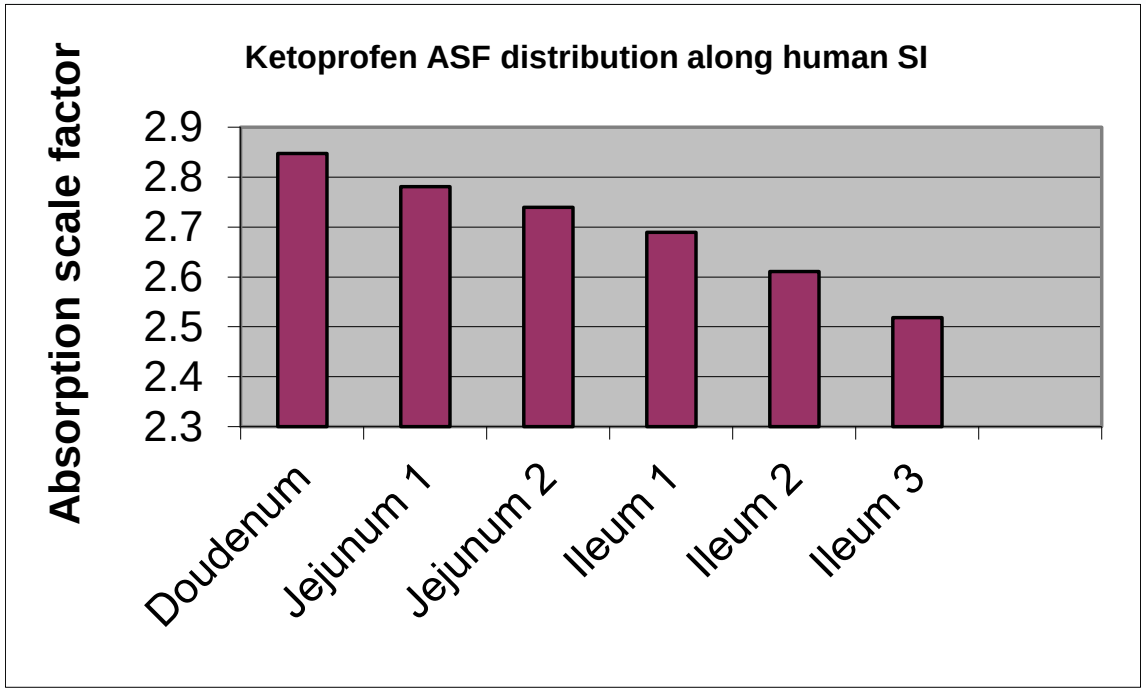
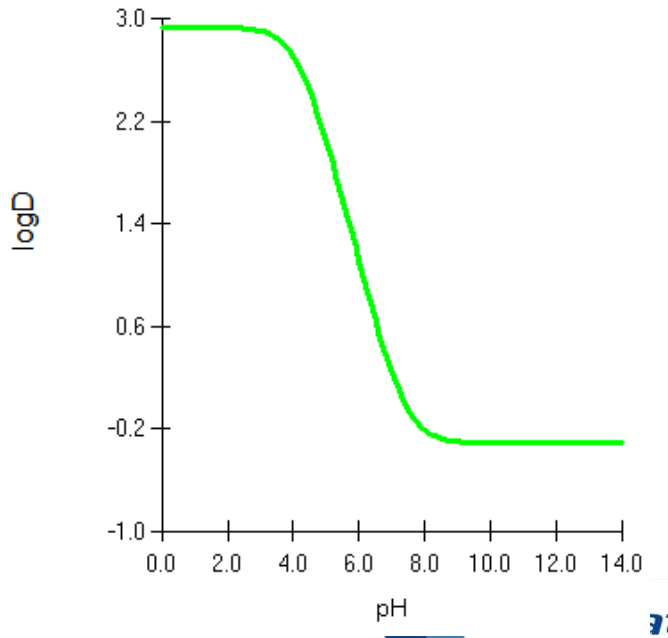
Ketoprofen Profiles (acid)



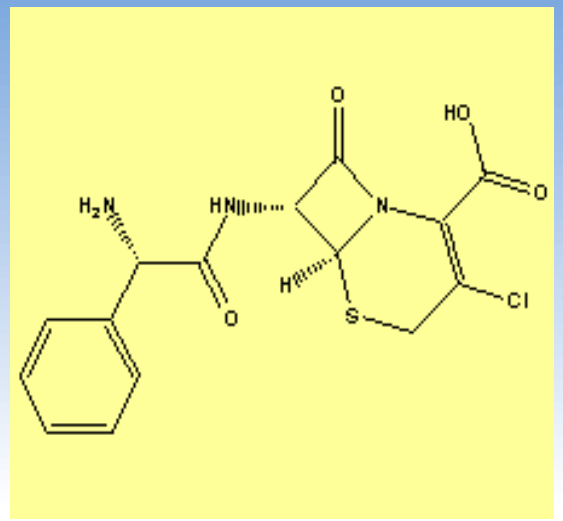
pK_a = 4.17
logP = 2.93
logD(7.4) = -0.003
S(4.18) = 0.033 mg/mL
S(7.4) = 10.5 mg/mL



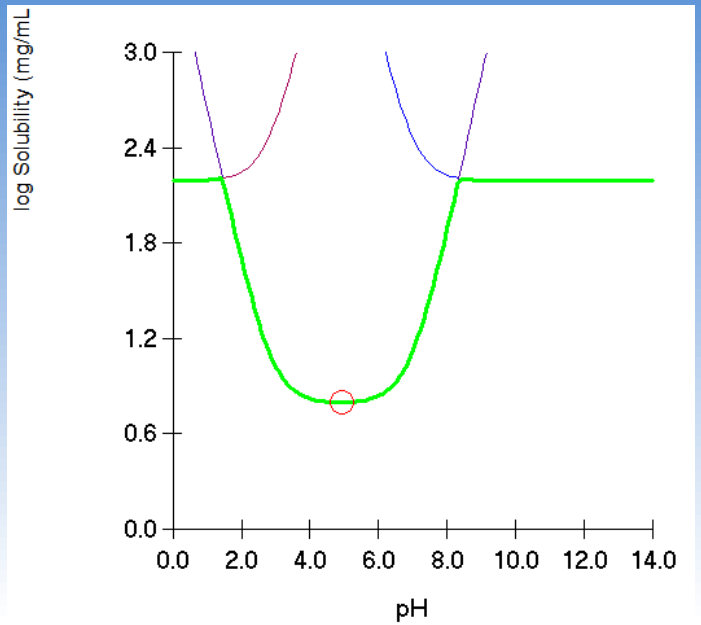


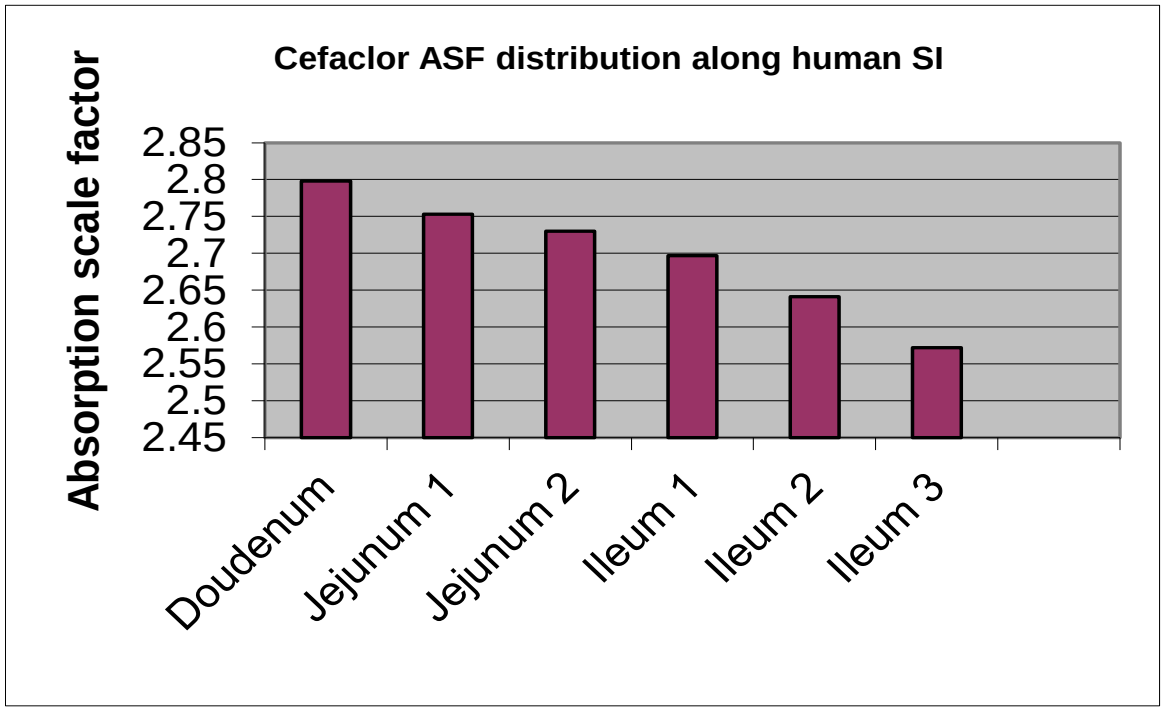


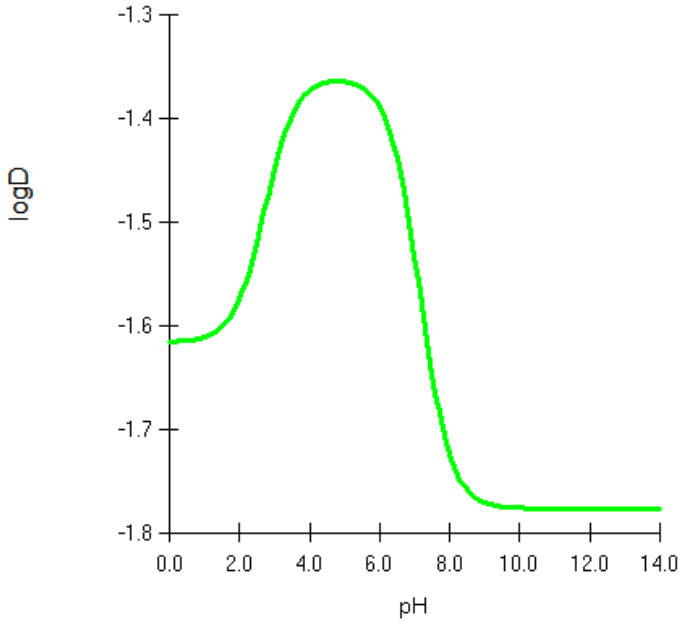
Cefaclor Profiles (zwitterion)



pK_a = 6.94
pK_a = 2.85
logP = -1.36
logD(7.4) = -1.62
S(4.92) = 6.29 mg/mL
S(7.4) = 24 mg/mL







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Questions?

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