SimulationsPlus

Fundamentals of Multiprotic Ionization and Ionization Modeling

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Simulations Plus, Inc.

The Ionization Prediction Summit

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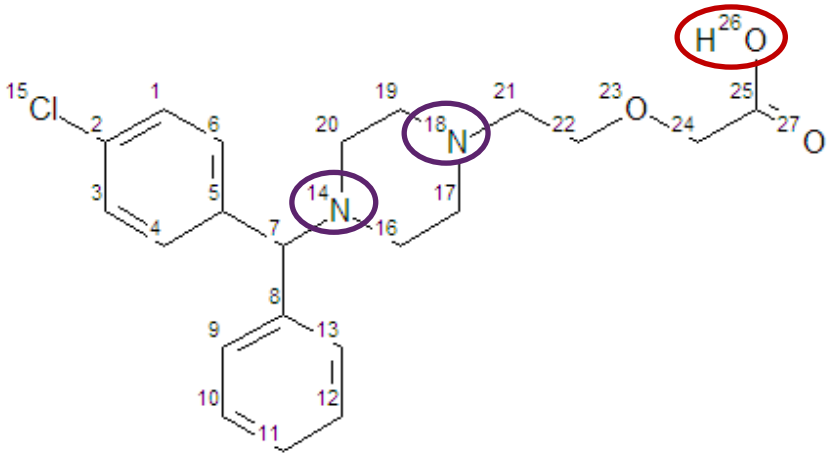
“You Must Unlearn What You Have Learned”:

“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.

Clearing Up Myths About Aqueous Ionization of Drugs

Myth #1: apparent pK_a can always be "assigned" to a functional group



2.10
3.01
8.17

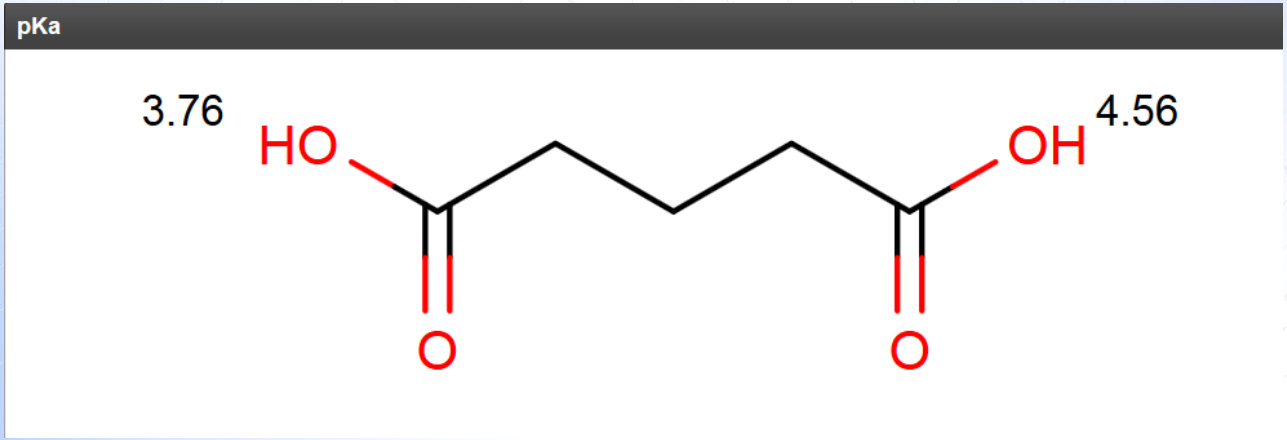
Marosi A, Kovacs Z, Beni S, Kokosi J and Noszal B. European Journal of Pharmaceutical Sciences, 37: 321-328, 2009.

Glutaric acid example

Measured apparent pK_a: 5.42, 4.35

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

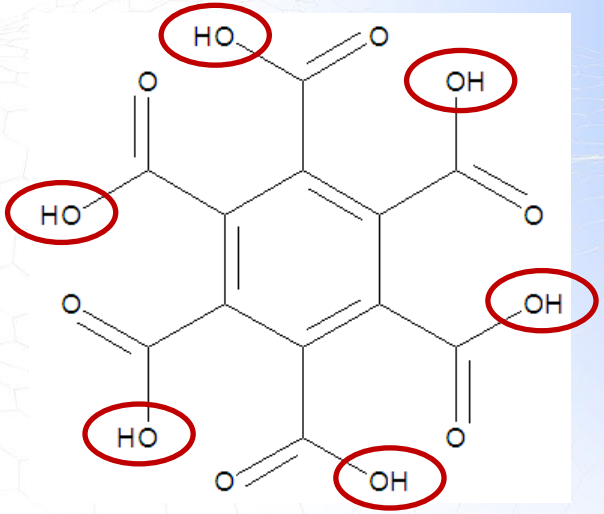
How one popular program predicts and reports pK_a for glutaric acid:



Futility of “assignments” – another example

Apparent pK_a

1.40
2.19
3.31
4.78
5.89
6.96

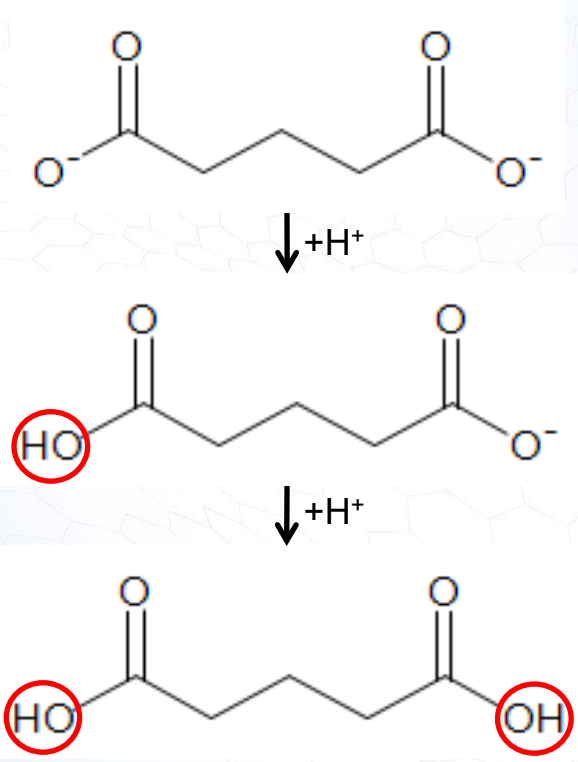


“Assign”? How?

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

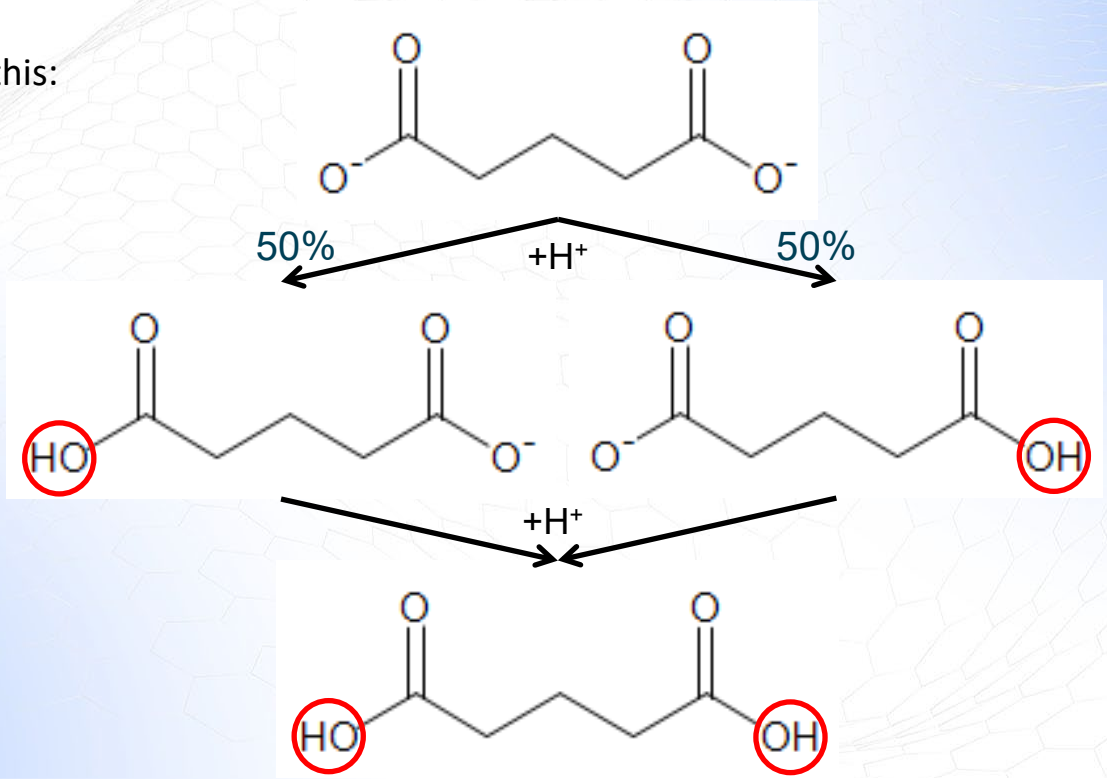
How do polyprotic molecules protonate?

Like this? :

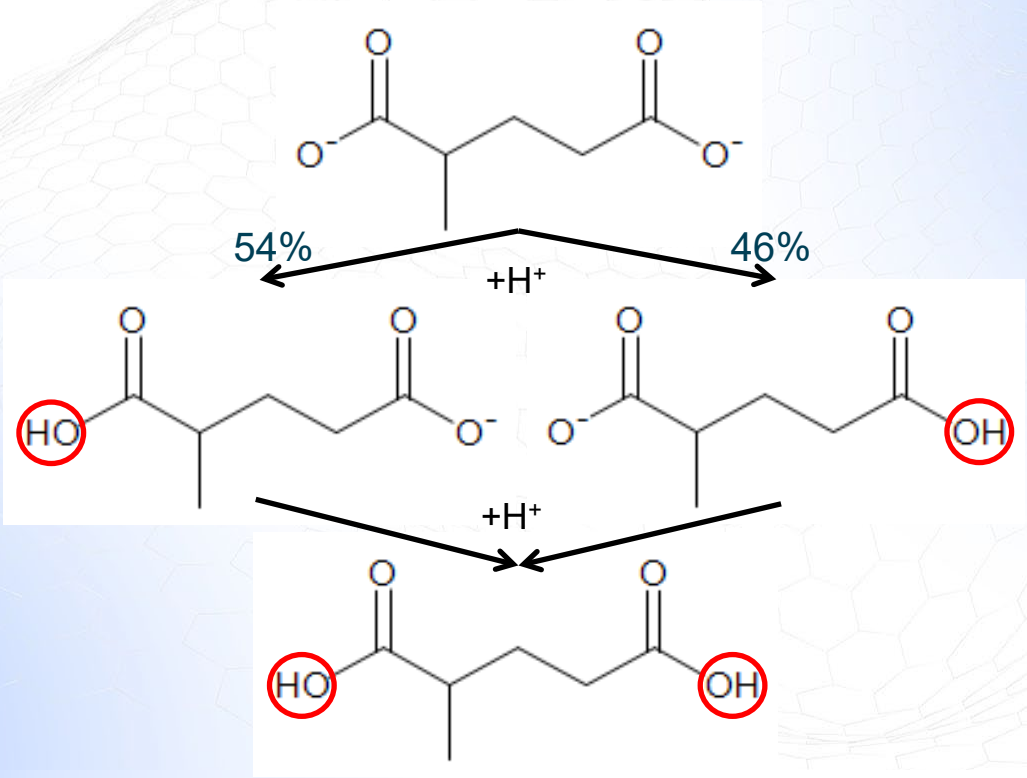


How do polyprotic molecules protonate?

No! Like this:

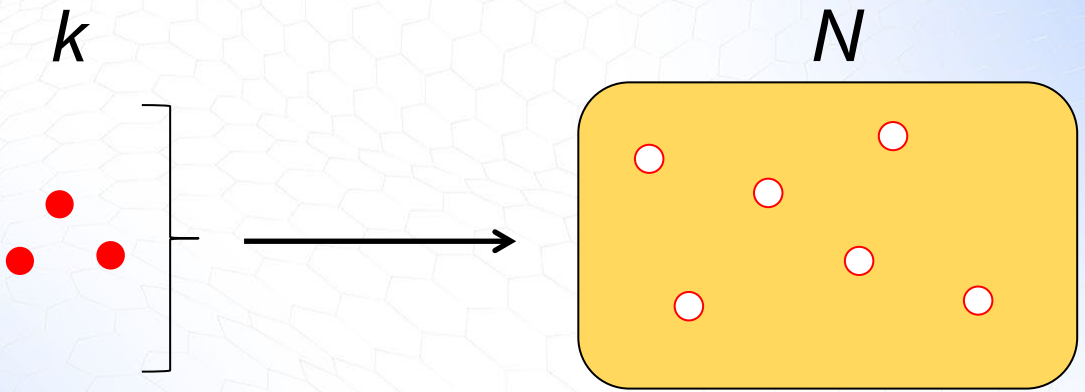


How do polyprotic molecules protonate?



It‘s a simple combinatorial problem

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



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

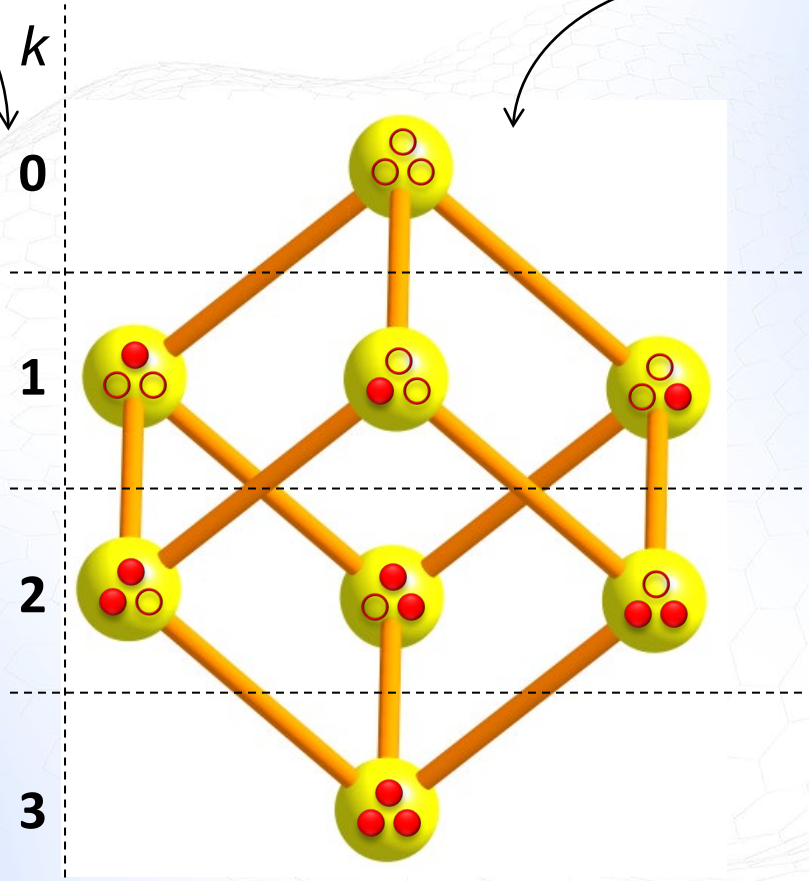
N=3

Macrostates:

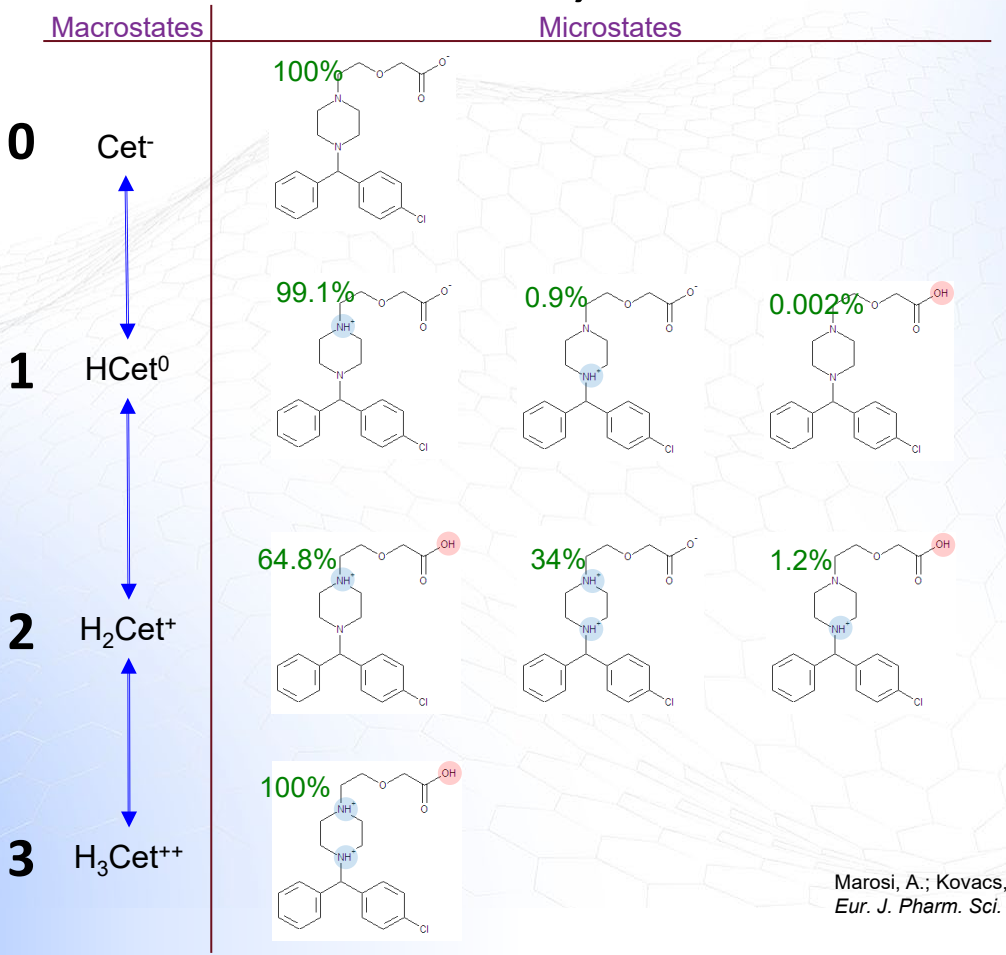
knowing there are *k* protons somewhere

Microstates:

knowing where the *k* protons exactly are

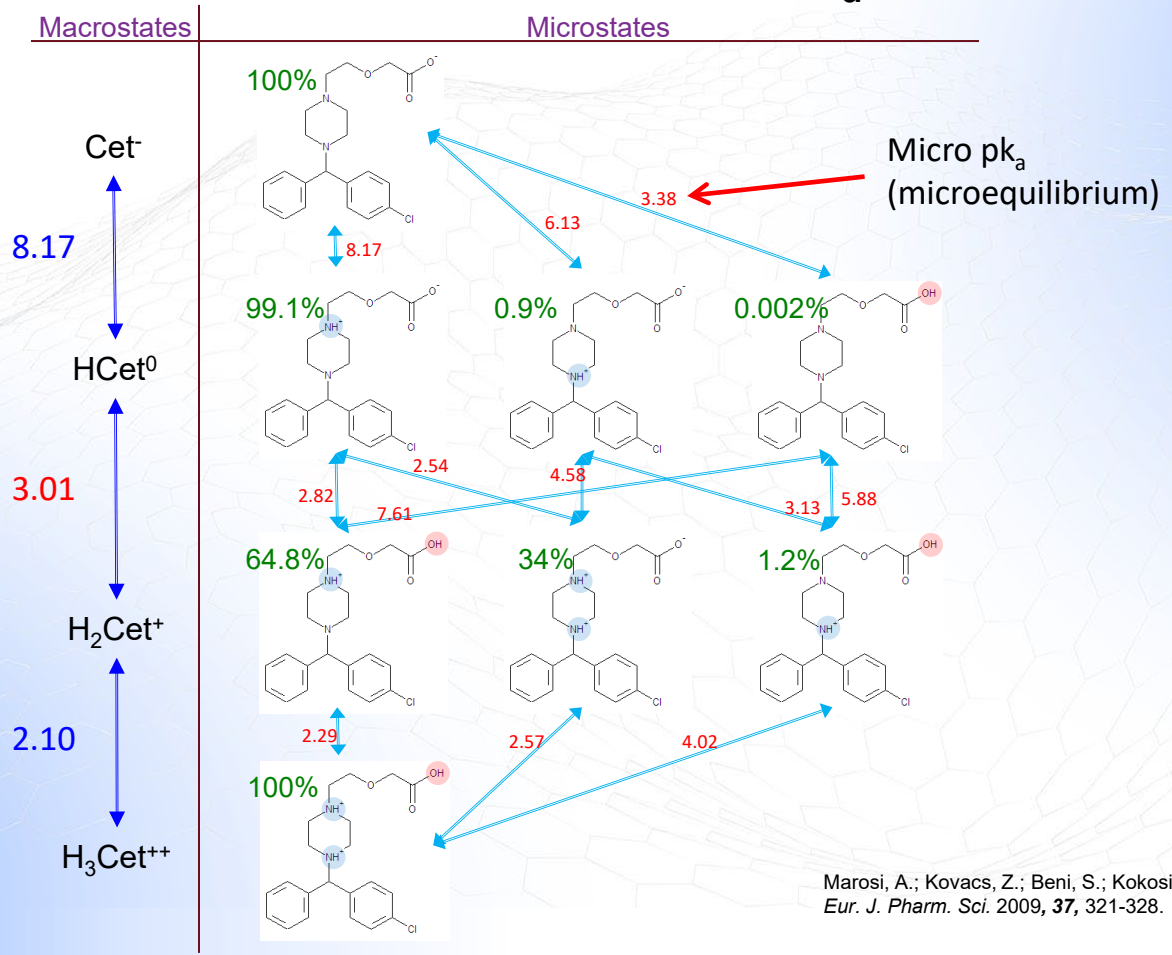


Cetirizine, N=3



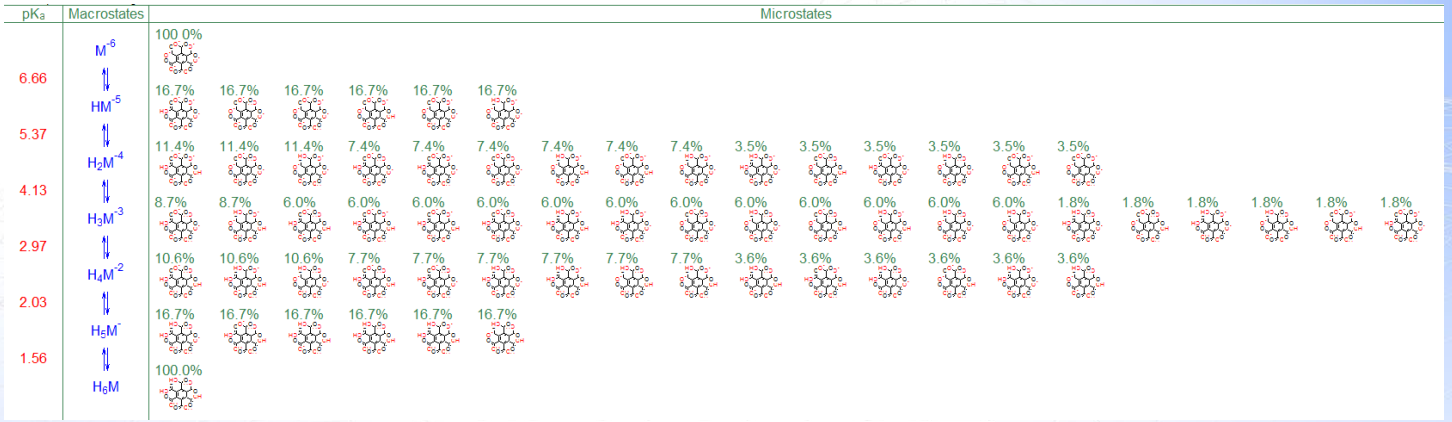
Marosi, A.; Kovacs, Z.; Beni, S.; Kokosi, J.; Noszal, B. *Eur. J. Pharm. Sci.* 2009, ***37,*** 321-328.

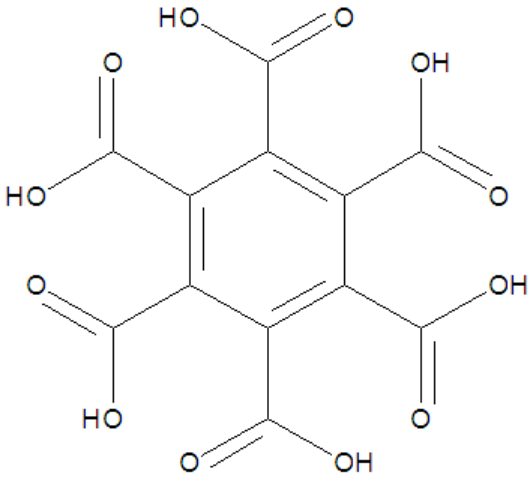
Cetirizine, N=3, with pK_a



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

Mellitic Acid, N=6

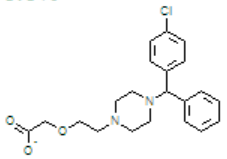
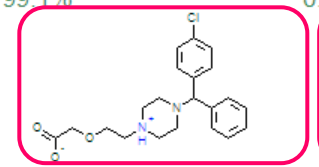
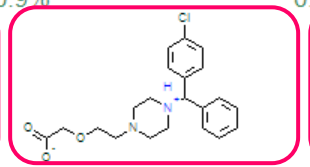
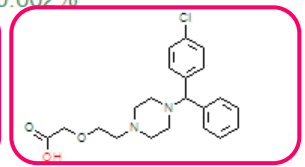
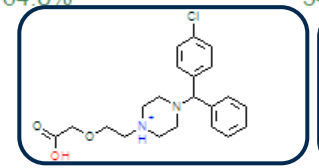
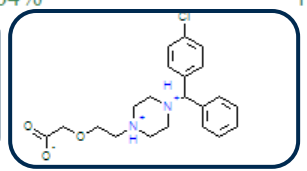
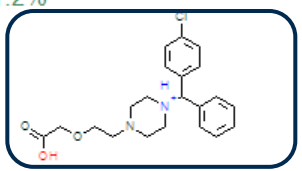
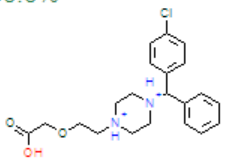




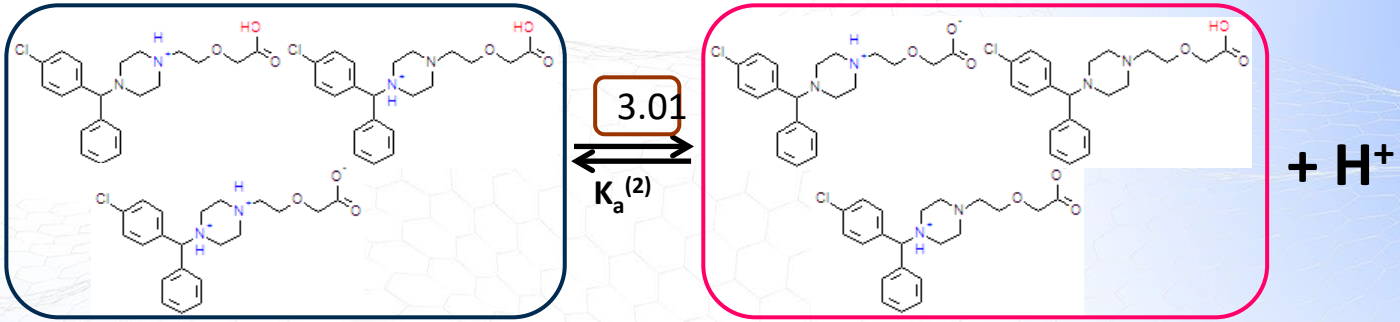
ADMET Predictor, v7.0

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

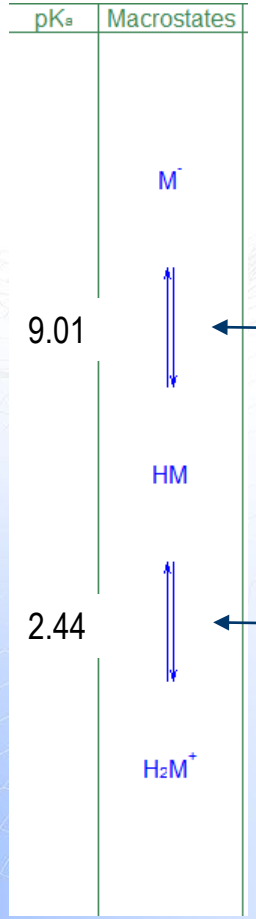


H_2M^+ HM

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

Clearing Up Myths About Aqueous Ionization of Drugs

Myth #2: apparent pK_a can unambiguously be labeled as either "acidic", or "basic" every time



A "physical chemist" point of view: focus on the whole molecule and its charge states (*macroscopic*)

Acid

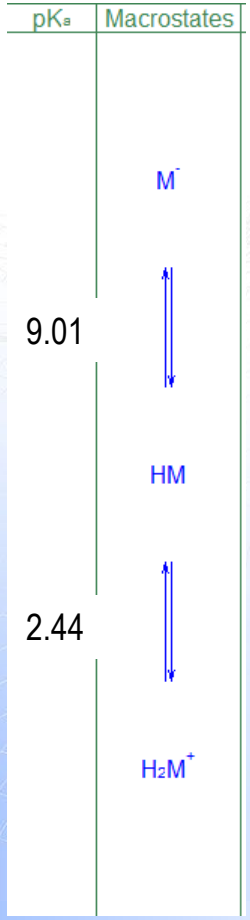
Proton loss = Acid

Base

Proton gain = Base

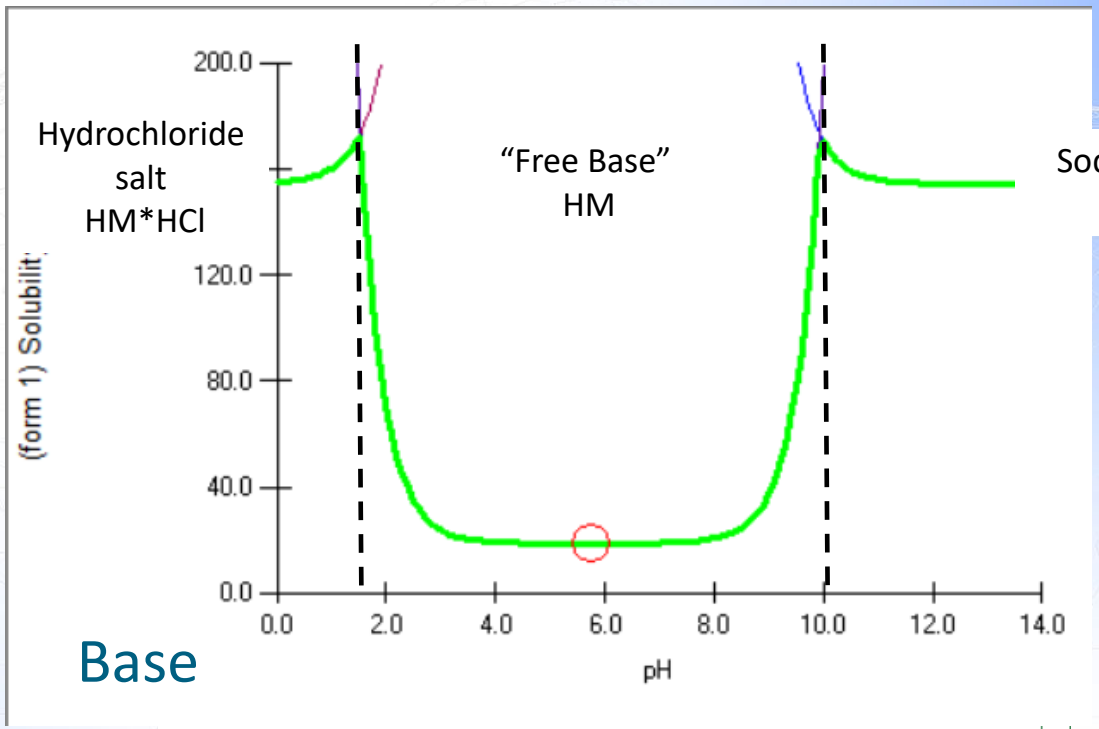
Simple, unambiguous, and accurate!

The physical chemist point of view is exactly reflected in, e.g., pH dependence of solubility



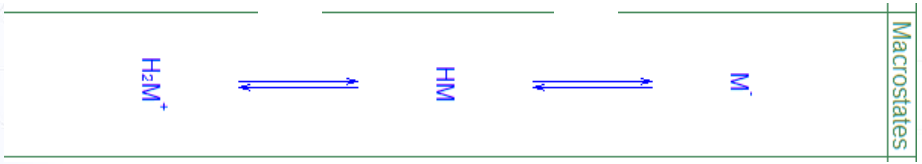
Acid

Base

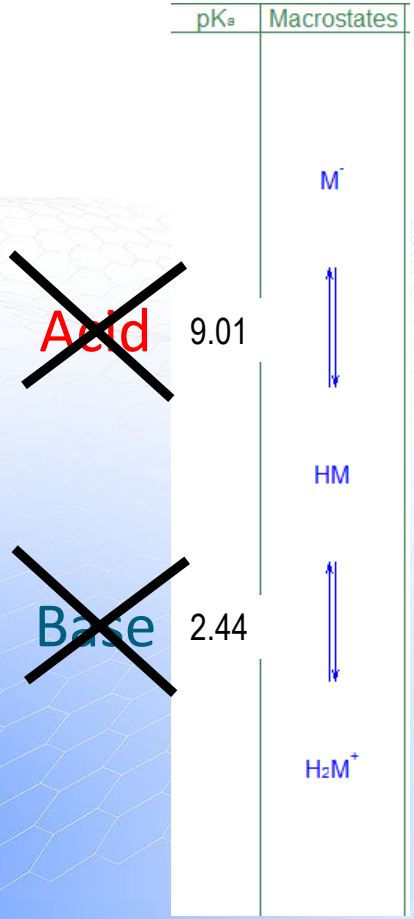


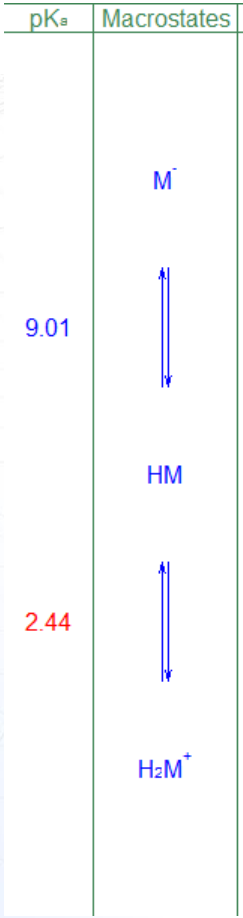
Base

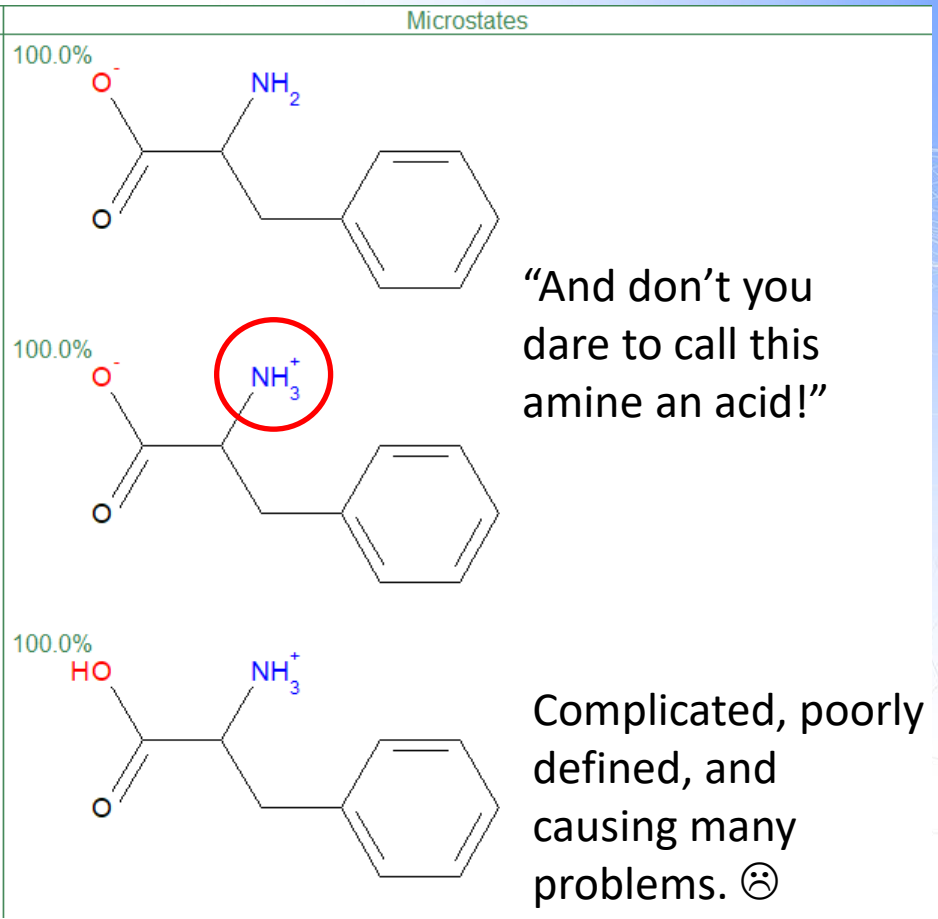
Acid



An "organic chemist" point of view: focus on individual functional groups (*microscopic*)

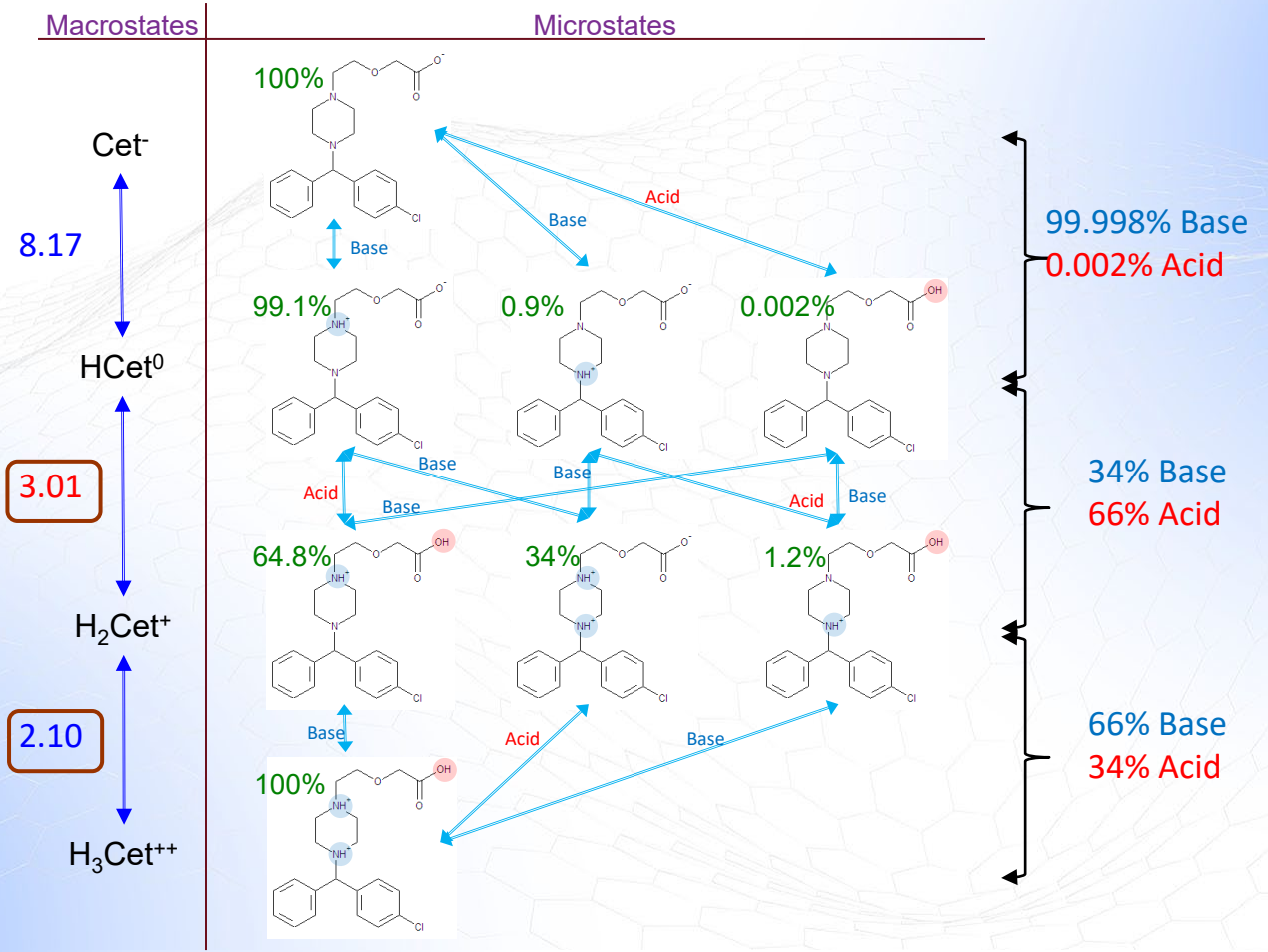






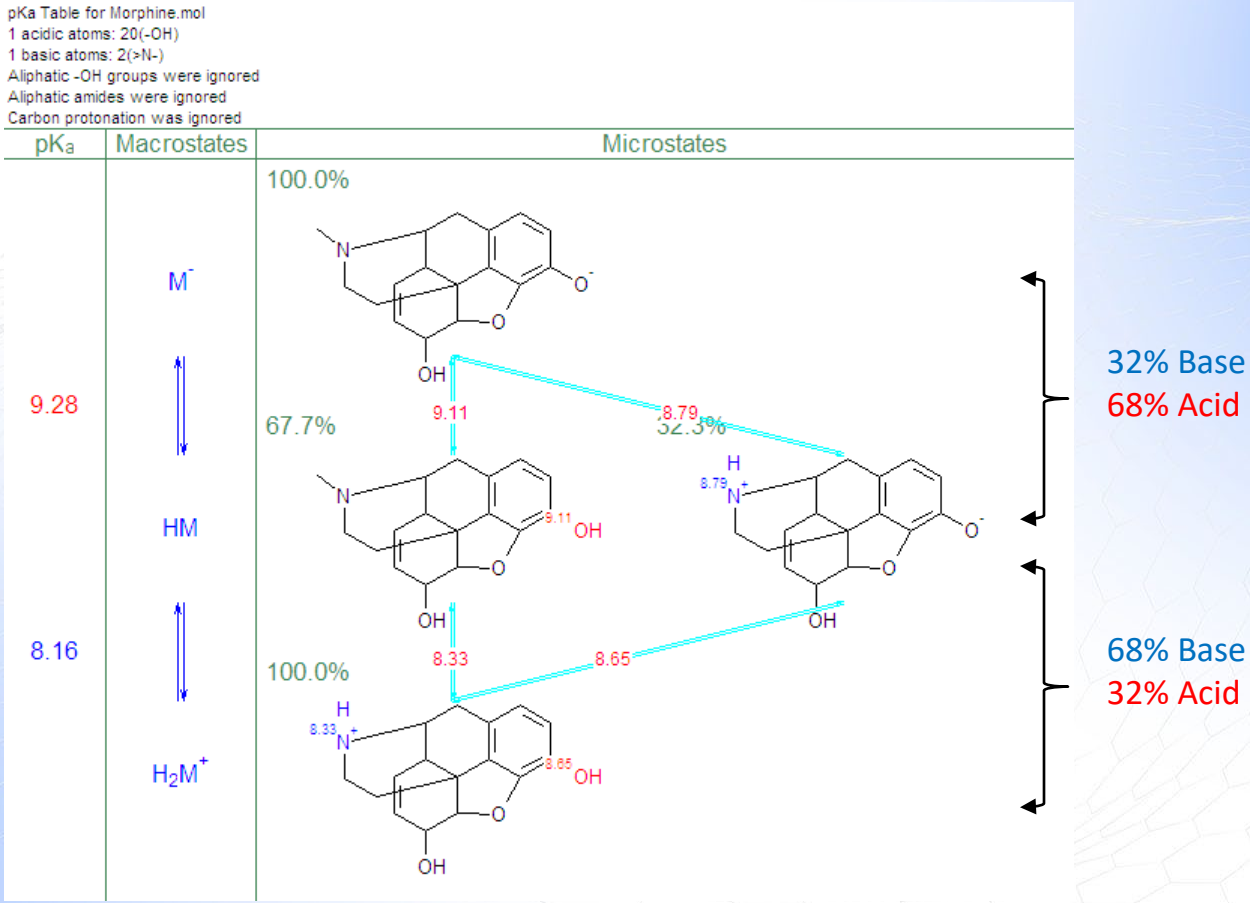
"And don't you dare to call this amine an acid!"

Complicated, poorly defined, and causing many problems. ☹



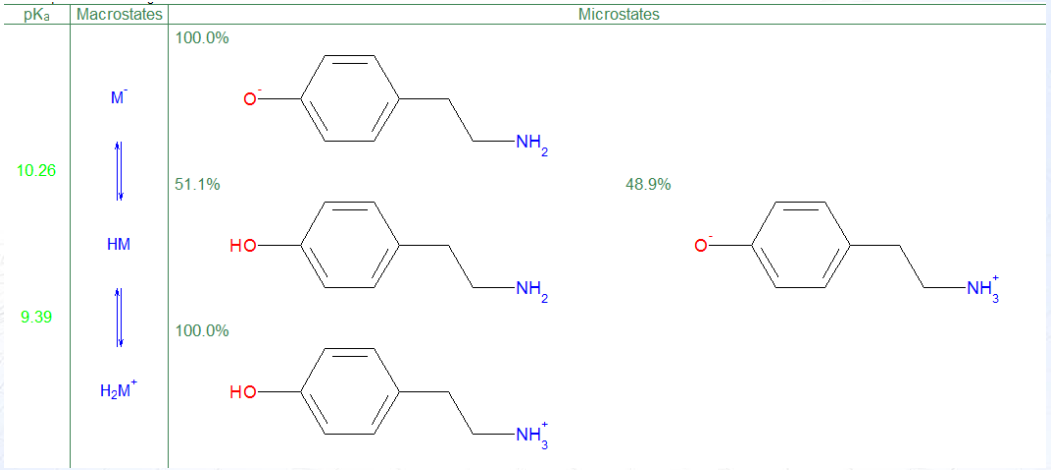
Marosi, A.; Kovacs, Z.; Beni, S.; Kokosi, J.; Noszal, B. *Eur. J. Pharm. Sci.* 2009**, *37,*** 321-328.

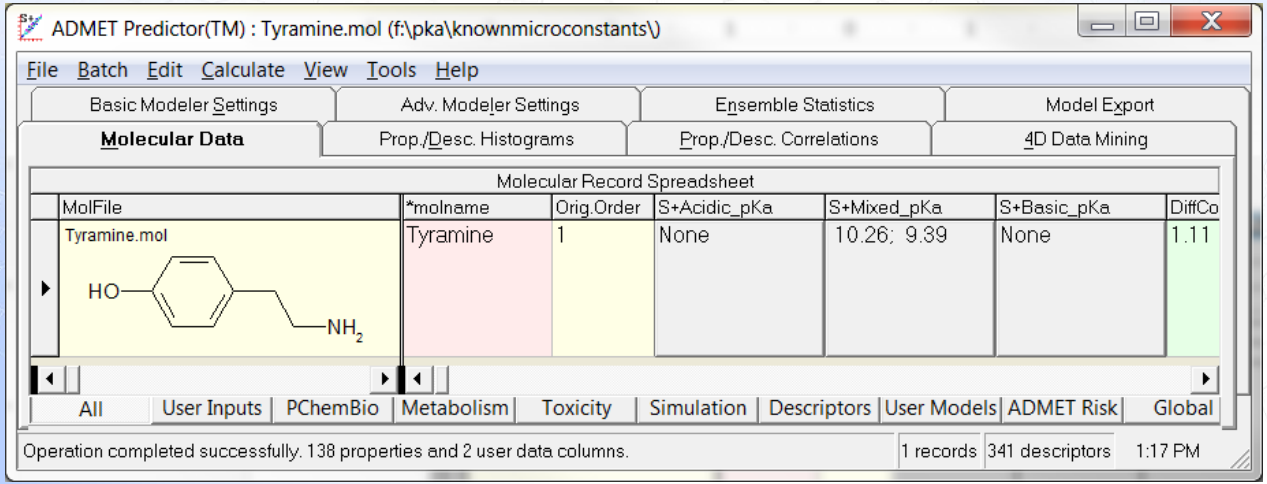
Apparent and microscopic pK_a for morphine



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

What is mixed pK_a?





Questions?