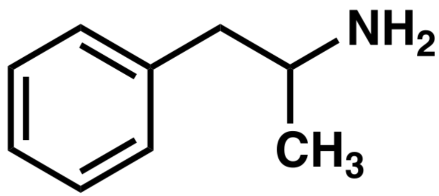
Week 8 problem solving

+ equations, + applications

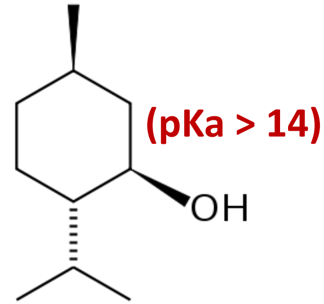
Ionization of acids and bases
LogD, pH of drug solutions,
Solubility, prodrugs

Find groups that can become **negatively** charged under physiological conditions (pH 2-7)

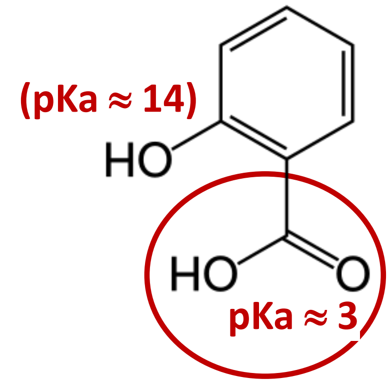
A. Amphetamine
B. Menthol
C. Salicylic acid
D. Clodronic acid
E. Aminohippuric acid
F. Guanadrel



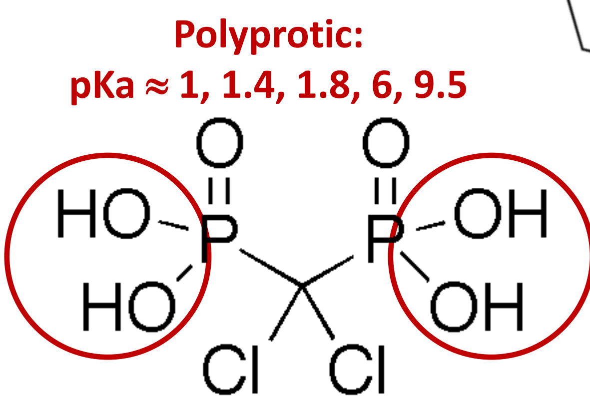
Amphetamine



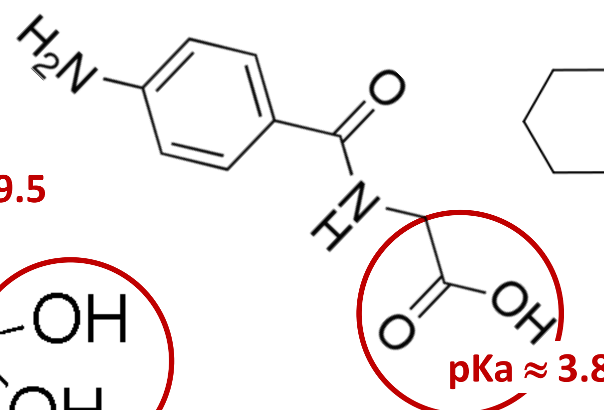
Menthol



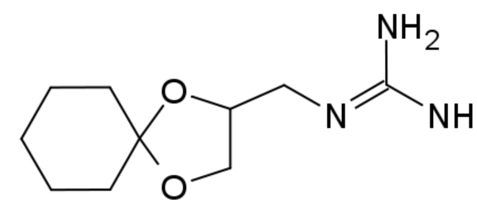
Salicylic acid



Clodronic acid



Aminohippuric acid



Guanadrel

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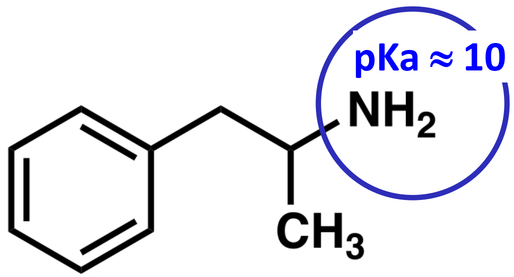
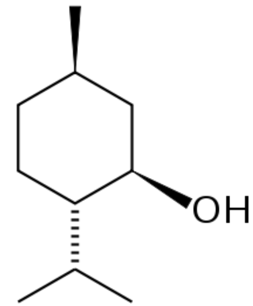
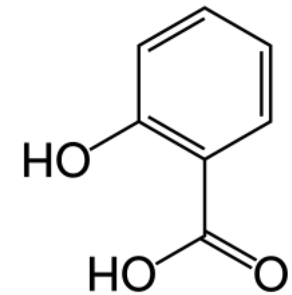


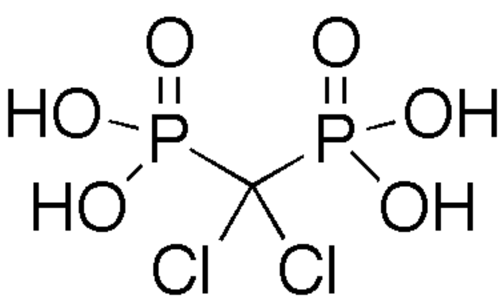
Amphetamine



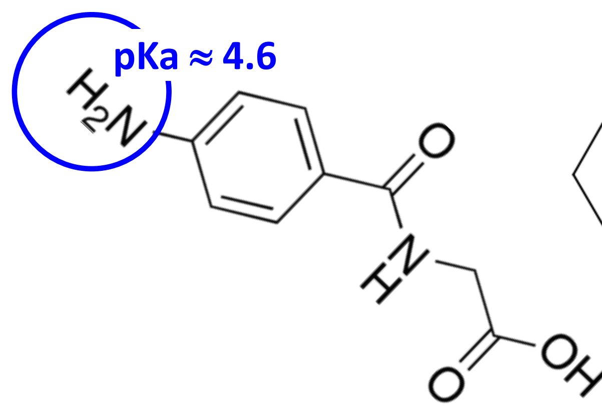
Menthol



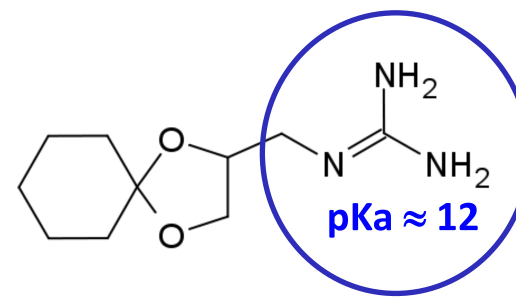
Salicylic acid



Clodronic acid (a 1st gen bisphosphonate)



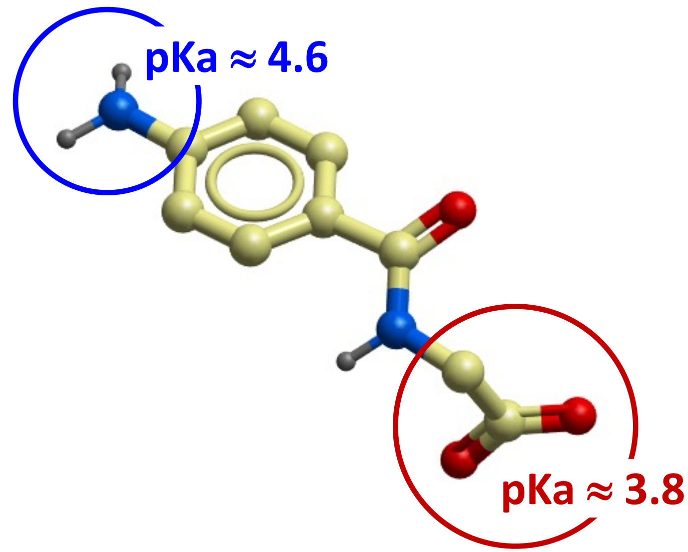
Aminohippuric acid (used as a diagnostic agent for renal plasma flow)



Guanadrel

Amphoteric or zwitterionic? Predominant species as pH increases?

- ***Problem***: Aminohippurate has a basic group with pKa of 4.6 and an acidic group with pKa of 3.8. What is the order or predominant species of aminohippurate in solution as the pH increases from 2 to 11?
  A. (+) → neutral → (-)
  B. (+) → zwitterion → (-)
  C. (+) → (-)
  D. (-) → neutral → (+)
  E. (-) → zwitterion → (+)
  F. (-) → (+)



- ***Solution***:

	pH < 3.8	3.8 ≤ pH ≤ 4.6	pH > 4.6
Amine	(+)	(+)	Neutral
Carboxylate	neutral	(-)	(-)

- ***Answer:*** (+) → zwitterion → (-)

Ratio vs fraction of negatively charge species vs neural (or total)

$[A^-]/[AH]$	$\%[A^-]$
$10^{-3} = 0.001$	0.001/(1+0.001) ~ 0.1%
$10^{-2} = 0.01$	0.01/(1+0.01) ~ 0. 99%
$10^{-1} = 0.1$	0.1/(1+0.1) ~ 9.09%
$10^{0} = 1$	1/(1+1) = 50%
$10^{1} = 10$	10/(10+1) ~ 90.91%
$10^{2} = 100$	100/(100+1) ~ 99.01 %
$10^{3} = 1000$	1000/(1000+1) ~ 99.9%

If **$[A^-]/[AH]$ = R** **then $\%[A^-]$ = R/(1+R)**

Henderson-Hasselbalch equation

- **Problem:** An acidic drug with pK_A of 3.5 is dissolved in stomach at pH=2. What fraction of the drug molecules is ionized/?
  A. 100%
  B. 66%
  C. 3%
  D. 0.0316%
- **Solution:** log([A-]/[AH]) = $pH - pK_A$ = -1.5
  [A-] = 0.0316[AH]
  fraction ionized is 0.0316/(1+0.0316) ~ 3%
- **Answer:** Only about 3% is ionized.
- **Bonus Q:** How and where will this drug absorb?

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Solubility of ionizable substances

Solubility at different pH: buffer

- In a **saturated** solution of an ionizable substance:

	Acid	Base
H.-H. equation	$\text{Log}([A^-]/[AH]) = pH - pK_A$	$\text{Log}([B]/[BH^+]) = pH - pK_A$
S_0: solubility of neutral form	$[AH] = S_0$	$[B] = S_0$
All ionized species are soluble	$[A^-] = S - S_0$	$[BH^+] = S - S_0$
	$\text{Log}((S-S_0)/S_0) = pH - pK_A$	$\text{Log}((S-S_0)/S_0) = pK_A - pH$
	$(S-S_0)/S_0 = 10^{pH-pK_A}$	$(S-S_0)/S_0 = 10^{pK_A-pH}$
	$S = S_0(1+10^{pH-pK_A})$	$S = S_0(1+10^{pK_A-pH})$

- Caution:
  - pH is affected by a high concentration of acid/base…
  - Approximation is only accurate for buffered solutions when $S - S_0 << \beta$ (buffer capacity)

Solubility at different pH

- **Problem:** The saturation solubility of a drug at different pH and T=300K are shown in the table. What type of compound is it and what is pK_A?
  A. Acid, pK_A of 3
  B. Acid, pK_A of 5
  C. Base, pK_A of 8
  D. Base, pK_A of 9

pH	Saturation solubility
7.4	205 μM
9	10 μM
10	5.5 μM
12	5 μM

- **Solution:** Solubility↓ with pH↑ ⇒ it is a **base**
  Solubility at pH = 12 is ~ S_0
  $pK_A = pH + \log (S - S_0)/S_0$
  When using S=205 μM at pH=7.4, $pK_A=7.4+\log 200/5 \sim 9$
  When using S=10 μM at pH=9, $pK_A=9+\log 5/5=9$

- **Answer**: Base, pKa of 9

Ionizable drugs are often formulated as salts

- Commonly used salts:
  - ❖ Weak acid / strong base
  - ❖ Weak base / strong acid
  - ❖ Weak acid / weak base
- *Salt formulations affect solubility*
  - ❖ *Salts deliver **ionized** components into the solution; the pH variations are favorable for dissolution*
  - ❖ ***Crystal state interactions** vary between salts and free form*

Drug	Acid	pK_A	Base	pK_A
Divalproex Sodium	Valproate $^{-}$	4.8	Na^{+}	–
Penicillin G Potassium	Penicillin G^{-}	2.7	K^{+}	–
Chlorpromazine HCl	Cl^{-}	–	Chlorpromazine H^{+}	9.3
Codeine Phosphate	PO_4^{-}	2.2,7.2,12.3	Codeine H^{+}	8.2
Dramamine	8-Chlorotheophylline^{-}	4.6	Diphenhydramine H^{+}	9.0

LogD

- **Problem:** Ibuprofen is a weak acid with pK_A of 4.91. The logP value for the neutral form of ibuprofen is 3.5. Calculate logD of ibuprofen at pH 3 in the stomach and pH 7 in the bloodstream.
  A. pH 3: logD = 3.5; pH 7: logD = 1.4
  B. pH 3: logD = 1.4; pH 7: logD = 3.5
  C. pH 3: logD = -1.4; pH 7: logD = 4.9
  D. pH 3: logD = -4.9; pH 7: logD = 7

- **Solution:**
  - ❖ Bloodstream: pH = 7 is greater than pKa + 1, therefore, the linear approximation **can** be used:
    - ❖ logD = logP - (pH - pKa) = 3.5 – (7 – 4.91) = 1.41
  - ❖ Stomach: pH = 3 is not greater than pKa + 1, the linear approximation **cannot** be used:
    - ❖ $\log D = \log P - \log(1 + 10^{pH - pK_A}) = 3.5 - \log(1 + 10^{-1.91}) = 3.495 \approx 3.5$

(optional, supplementary)

pH of a drug solution – practical, linear approximations

Weak Acid, e.g. carboxylic acid:

$$\mathbf{pH = \tfrac{1}{2}\,pK_A - \tfrac{1}{2}\log \mathit{c}}$$

Weak Base, e.g. amine

$$\mathbf{pH = 7 + \tfrac{1}{2}\,pK_A + \tfrac{1}{2}\log \mathit{c}}$$

pH of a drug solution: linear approximation

(optional, supplementary)

- **Problem:** calculate pH of 1 mM solution of ibuprofen in water (ibuprofen is a weak acid with pK_A of 4.91)
  A. 0.955
  B. 3.955
  C. 4.91
  D. 5.455

- **Solution:**
  - concentration is relatively high, acid is weak, try linear approximation
  - $pH = ½\, pK_A – ½ \log c = 4.91 / 2 + 3 / 2 = 3.955$
  - this pH is less than pK_A; likely accurate

- **Answer:** pH = 3.955