Kislost-bazičnost
Hammettove konstante

Izr. prof. dr. Marko Anderluh

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Vpliv kislinsko bazičnih lastnosti

- Vezava na tarčno mesto – farmakodinamsko delovanje
- Topnost/sproščanje
- Topnost/absorpcija
- Distribucija po telesu
- Izločanje

Kislost - bazičnost

$$HA + H_2O \rightleftharpoons A^- + H_3O^+$$

kislina

nedisociirana oblika

konjugirana baza

disociirana oblika

$$B + H_2O \rightleftharpoons {}^+BH + {}^-OH$$

baza

neprotonirana oblika

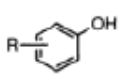
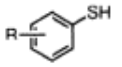
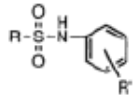
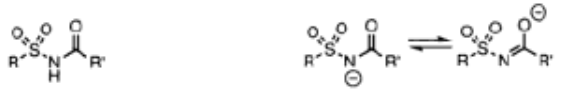
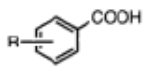
konjugirana kislina

protonirana oblika

Vezava na tarčno mesto - ionizacija

- Kisle skupine

Table 2.1. Common Acidic Organic Functional Groups and Their Ionized (Conjugate Base) Forms

Acids (pKa)		Conjugate Base
Phenol (9-11)		Phenolate
Sulfonamide (9-10)		Sulfonamidate
Imide (9-10)		Imidate
Alkylthiol (10-11)		Thiolate
Thiophenol (9-10)		Thiophenolate
N-Arylsulfon-amide (6-7)		N-Arylsulfon-amidate
Sulfonimide (5-6)		Sulfonimidate
Alkylcarboxylic acid (5-6)		Alkylcarboxylate
Arylcarboxylic acid (4-5)		Arylcarboxylate
Sulfonic acid (0-1)		Sulfonate

Acid strength usually increases as one moves down the table.

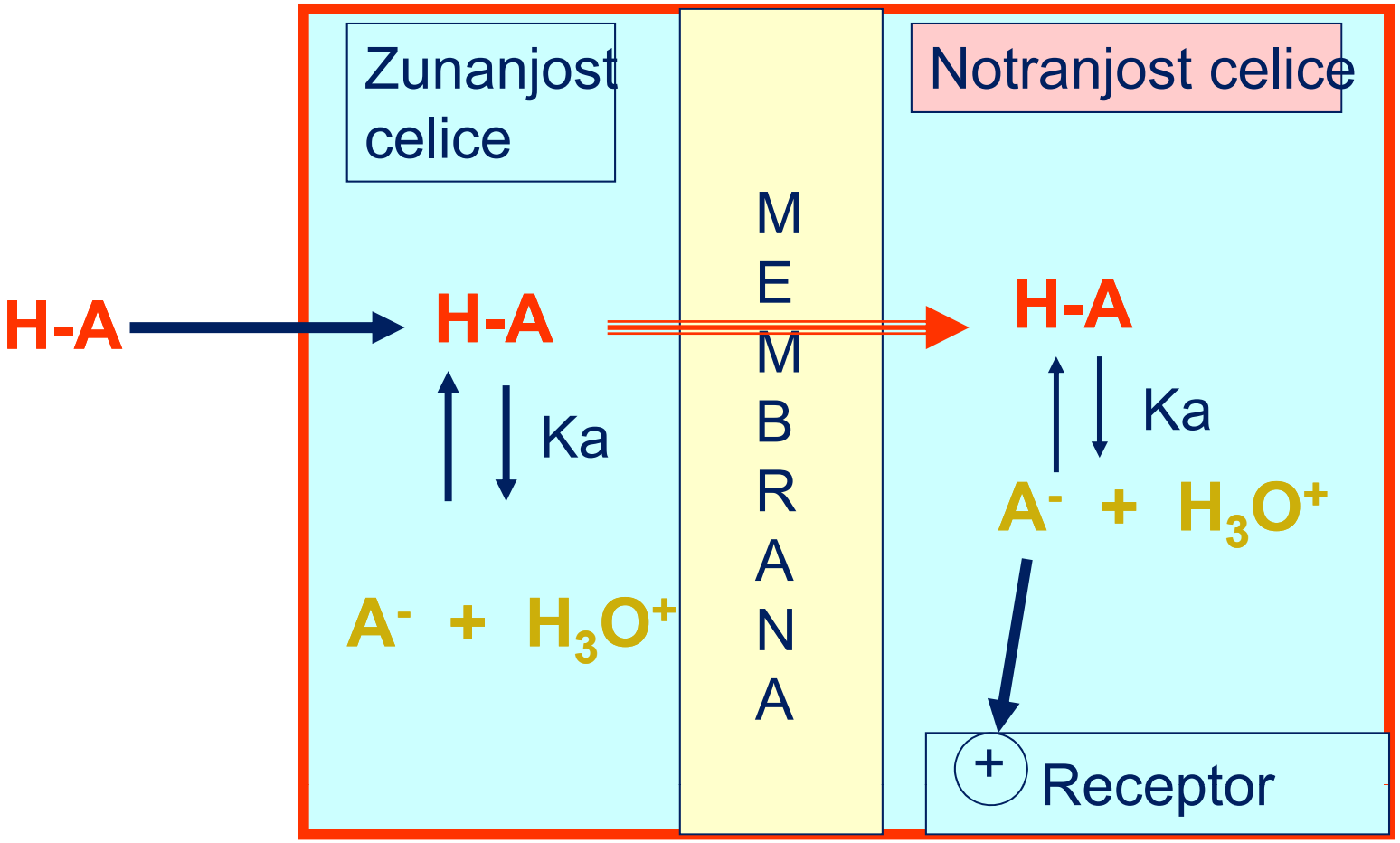
Vezava na tarčno mesto - ionizacija

- Bazične skupine

Table 2.2. Common Basic Organic Functional Groups and Their Ionized (Conjugate Acid) Forms

Base (pKa)		Conjugate Acid
Arylamine (9-11)		Arylammonium
Aromatic amine (5-6)		Aromatic ammonium
Imine (3-4)		Iminium
Alkylamines (2^0 - 10-11) (1^0 - 9-10)		Alkylammonium
Amidine (10-11)		Amidinium
Guanidine (12-13)		Guanidinium

Topnost – sproščanje, absorpcija



Ključna topnost/lipofilnost obenem!

Vpliv pKa na delovanje sulfonamidov

Učinkovina	**MIC x 10^{-6}**	**pK_a**	**α (%)**
Sulfanilamid	2500	10,5	0,03
Sulfapiridin	20	8,5	3,4
Sulfatiazol	4	6,8	61,4
Sulfadiazin	4	6,5	80,0

pH


Johnson's
pH
5.5
2 IN 1
BODY WASH


Johnson's
pH
5.5
FAIR
COMPLEXION
DAY CREAM
SPF 15
Johnson's
pH
5.5
FAIR
COMPLEXION
NIGHT
CREAM

pKa

- Kaj pa je pKa?
- Odvisnost pKa – ionizirana oblika?

Henderson-Hasselbalch

- pKa =?
- pH = ?

Universitas Labacensis
Faculty of pharmacy

Foye's Principles of MC

APPENDIX A. pK_a Values for Some Drugs and Miscellaneous Organic Acids and Bases

DAVID A. WILLIAMS

Table A.1. pK_a Values for Some Drugs and Miscellaneous Organic Acids and Bases

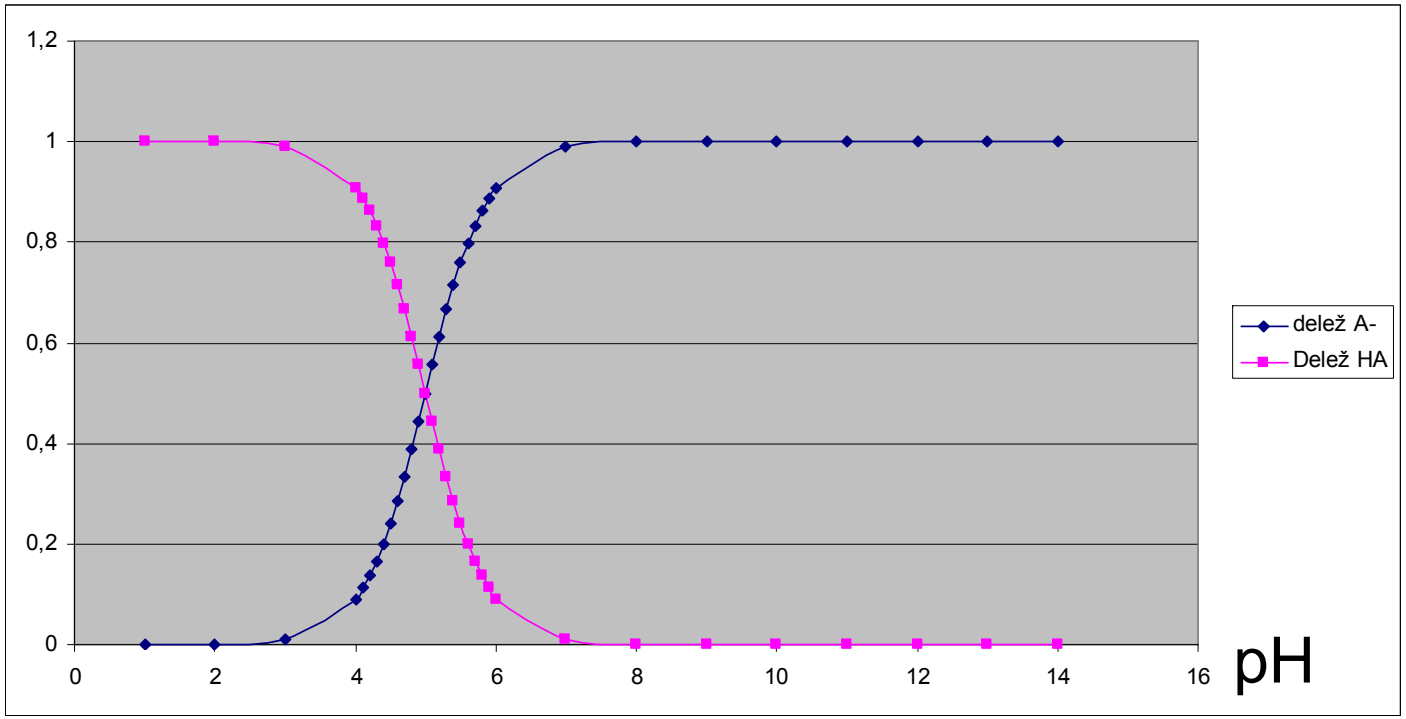
Drugs	pK_a Values HA	pK_a Values HB$^+$	Reference
Acebutolol		9.2	1
Acenocoumarol	4.7		1
Acetaminophen	9.7		1
Acetanilide		0.5	1
Acetazolamide	7.4, 9.1		3
Acetohydroxamic acid	9.4		1
α-Acetylmethadol		8.6	1
Acetylsalicylic acid	3.5		1
Acyclovir	9.3	2.3	1
Adriamycin		8.2	1
Ajameline		8.2	1
Albuterol	10.3	9.3	9
Alclofenac	4.3		1
Alfentanil		6.5	1
Allobarbital	7.8		1
Allopurinol	9.4		1,4
Alphaprodine		8.7	1
Alprenolol		9.7	1,5
Altretamine		10.3	1
Amantadine		9.0	1
Amidinocillin	3.4	8.9	1
Amiloride		8.7	1
Aminacrine		10.0	1
p-Aminobenzoic acid	4.9	2.5	1
Aminocaproic acid	4.4	10.8	1
Aminohippuric acid	3.8		1
Aminopterin	5.5		1
Aminopyrine		5.0	1
p-Aminosalicylic acid	3.6	1.8	1
Aminothiadiazole		3.2	1
Amiodarone		6.6	1
Amitriptyline		9.4	15
Amobarbital	7.8		1
Amoxapine		7.6	1,4
Amoxicillin	2.4	9.6	12
Amphetamine		10.0	1
Amphotericin B	5.5	10.0	11
Ampicillin	2.5	7.2	16
Anileridine		3.7, 7.5	1
Antazoline		2.5, 10.1	1
Antipyrine		1.5	1
Apomorphine	8.9	7.0	1
Aprobarbital	8.0		1
Ascorbic acid	4.2, 11.6		1
Atenolol		9.6	6
Atropine		9.8	1
Azatadine		9.3	1
Azathioprine	8.0		9
Azlocillin	2.8		1
Aztreonam	0.7, 2.9	3.9	1
Bacampicillin		6.8	1
Baclofen	5.4	9.5	1
Barbital	7.9		1
Bendroflumethiazide	8.5		5

(Continued)

pKa

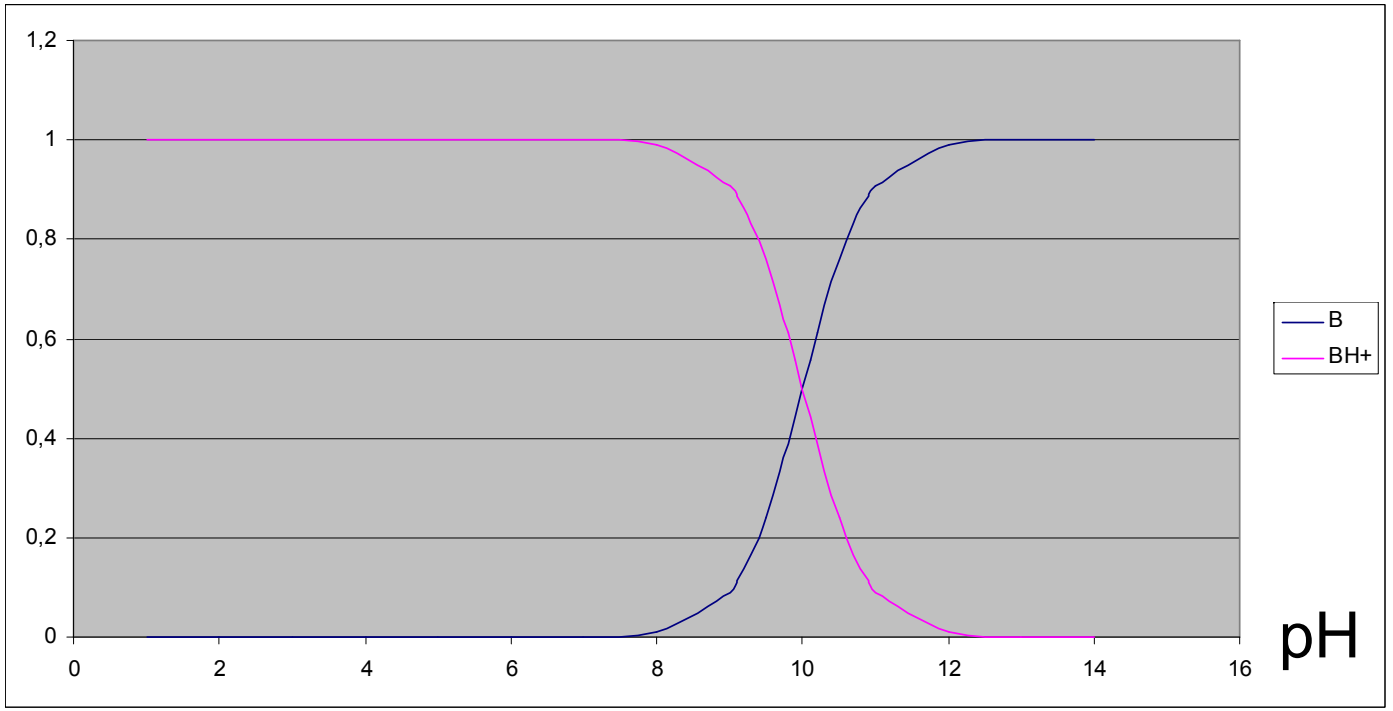
- Zakaj tako pri kislinah kot bazah operiramo s pKa?

pH!!!



Monoprotična kislina

pKa=5

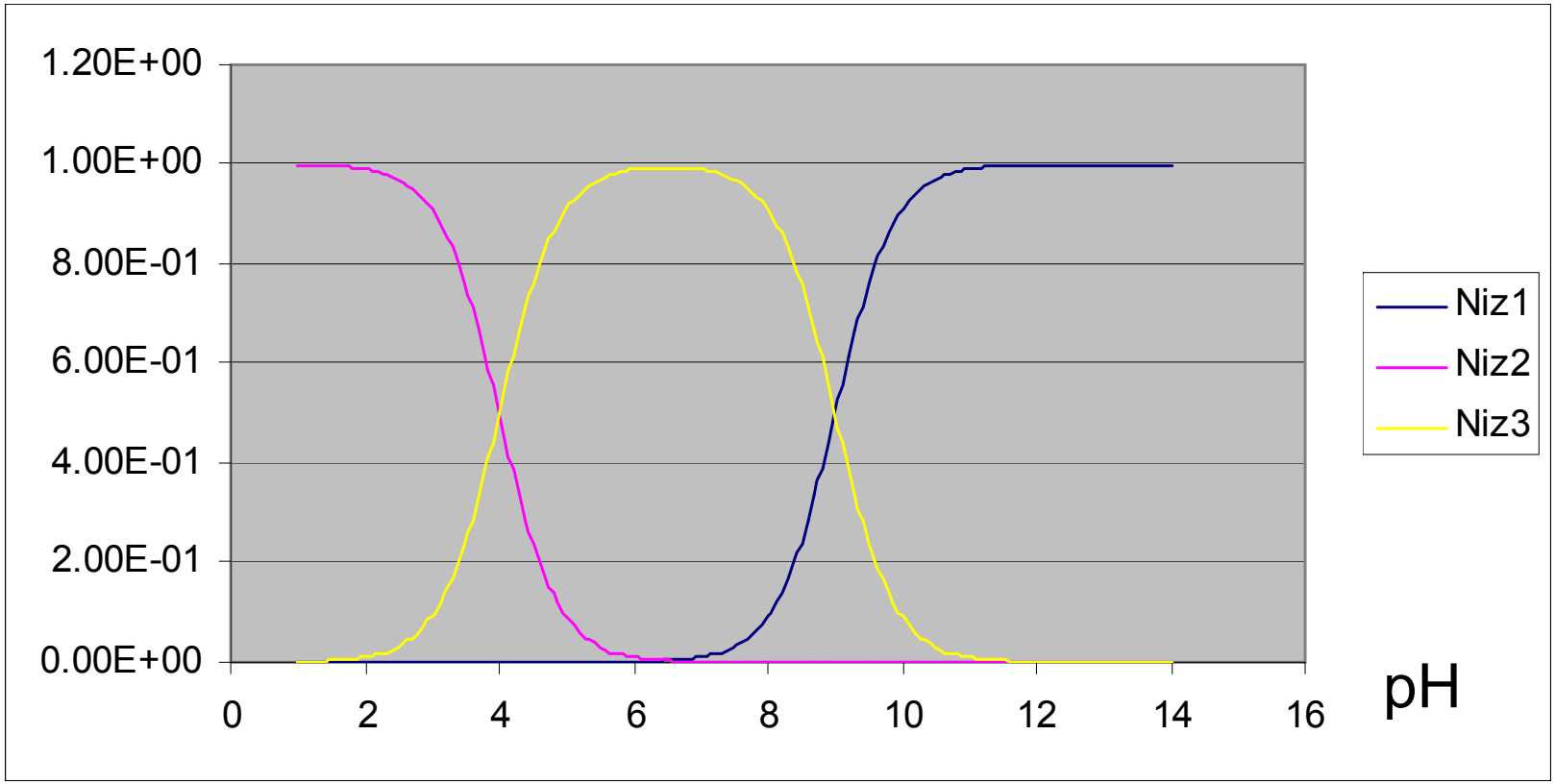


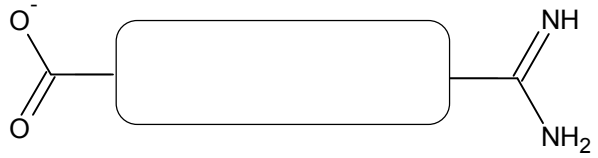
Monoprotična baza

pKb=4
pKa=10

Amfifilne molekule

- Kisle in bazične skupine se ne “čutijo”
- Neodvisna ionizacija skupin

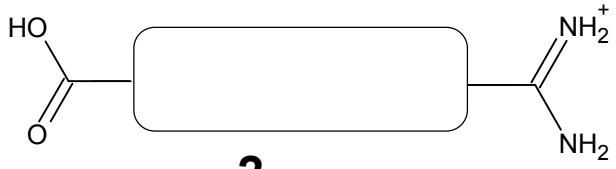




1

Amfoliti:

bazična skupina $pK_{a1}=9$
kisla skupina $pK_{a2}=4$



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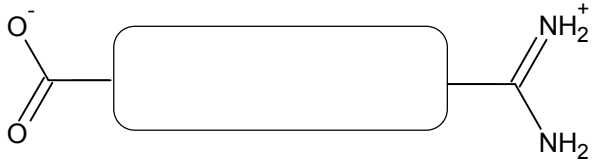

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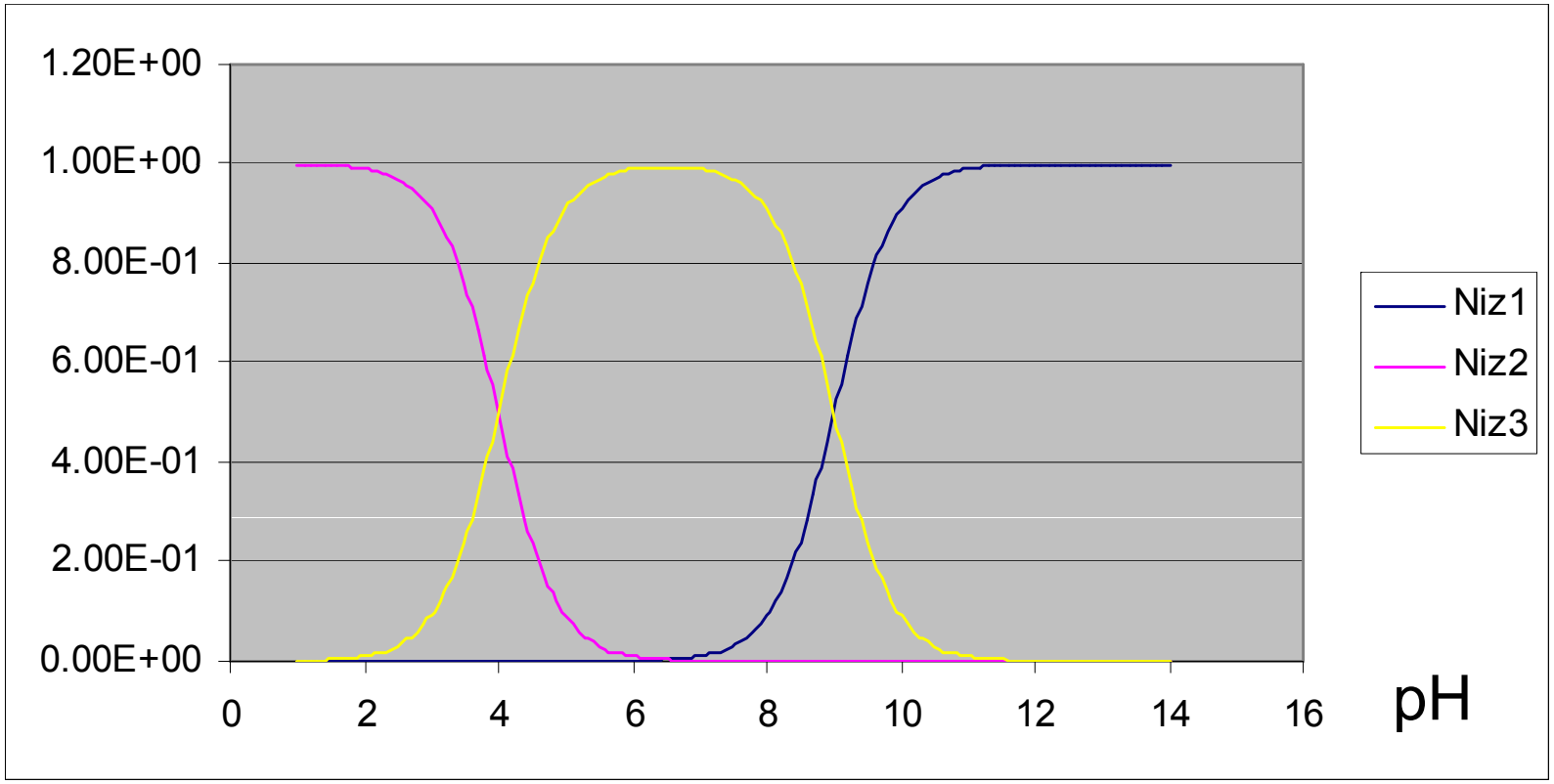
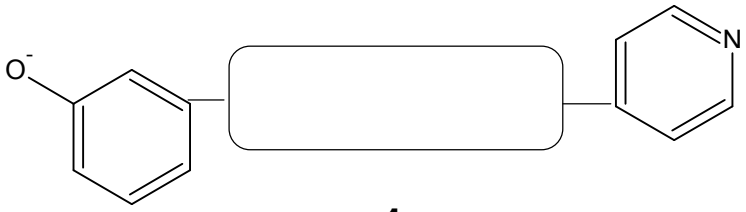
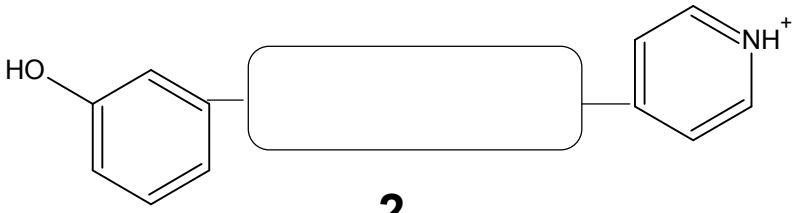


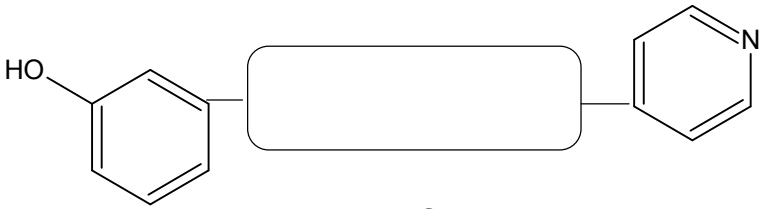


1



2

Amfoliti: bazična skupina $pK_{a1}=4$
kisla skupina $pK_{a2}=9$



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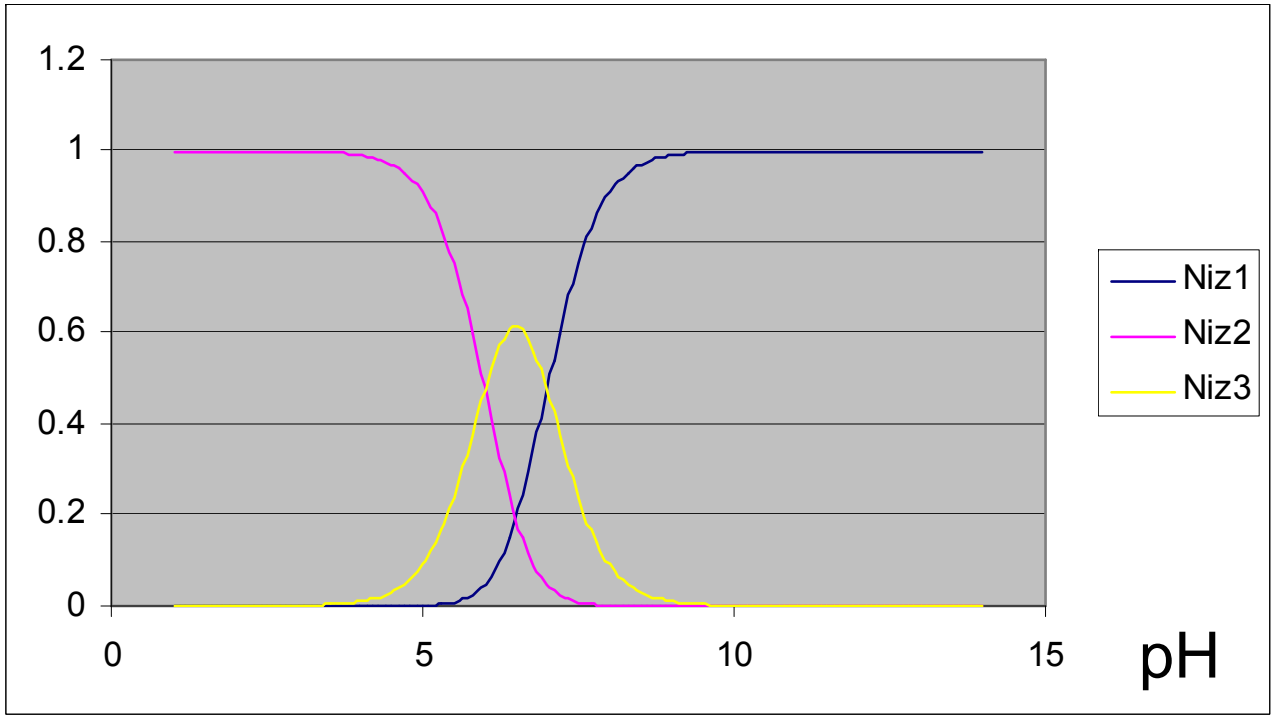
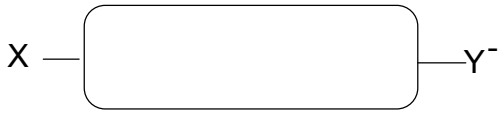


Amfoliti – ioni dvojčki
Majhna razlika v K_a

$pK_{a1}=6$
$pK_{a2}=7$



1

2

3

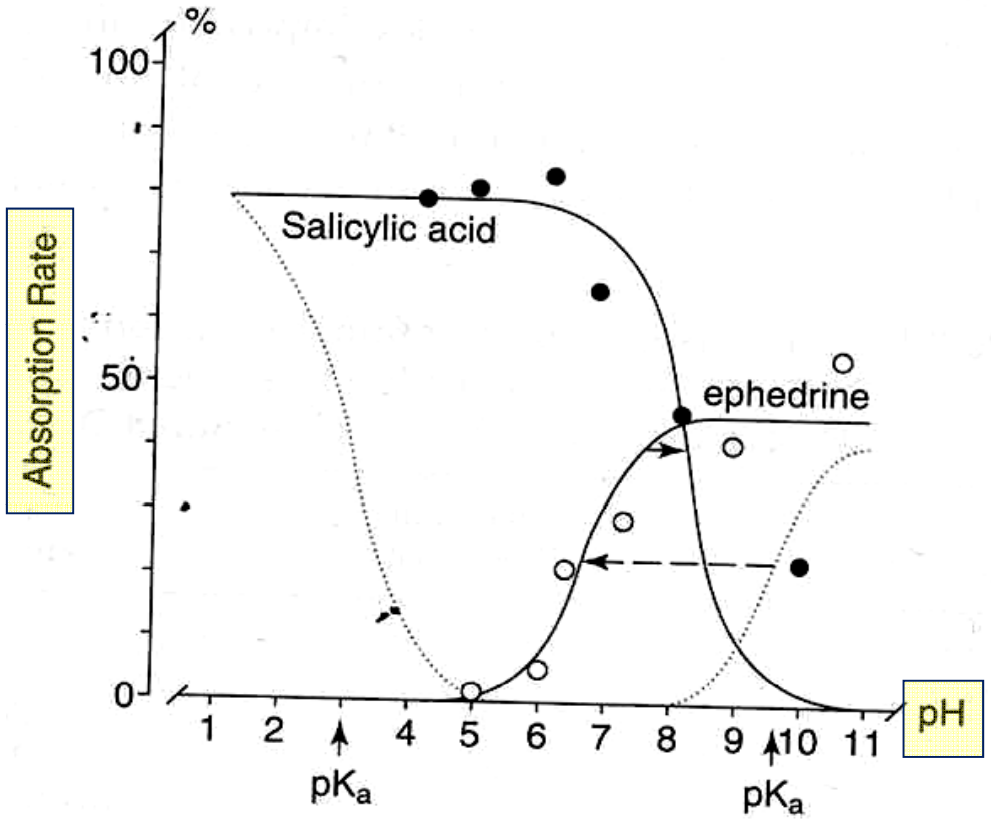
Topnostni profil – sproščanje/absorpcija

Kako pH odloča o absorpciji učinkovin?

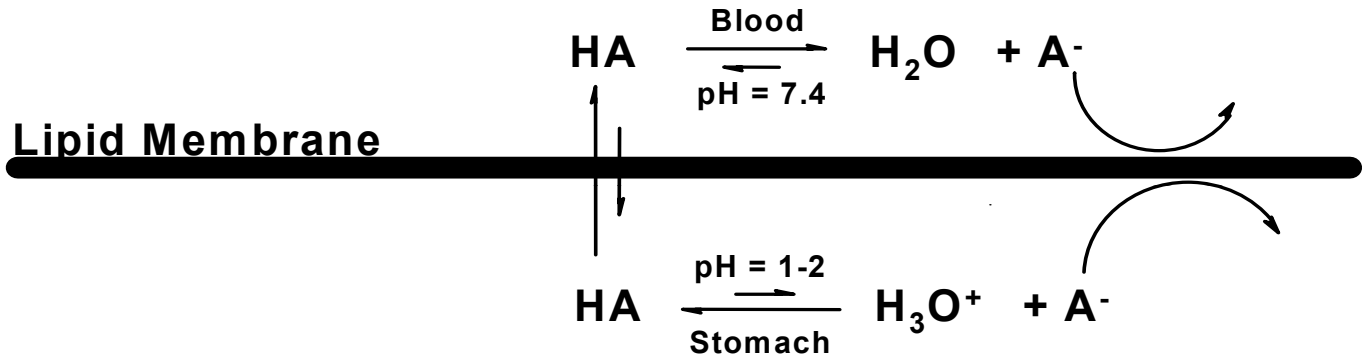
- **Kisline** - absorpcija v želodcu
- **Baze** - absorpcija v tankem črevesju
- Okoli 3/4 učinkovin šibke baze!

Topnostni profil – sproščanje/absorpcija

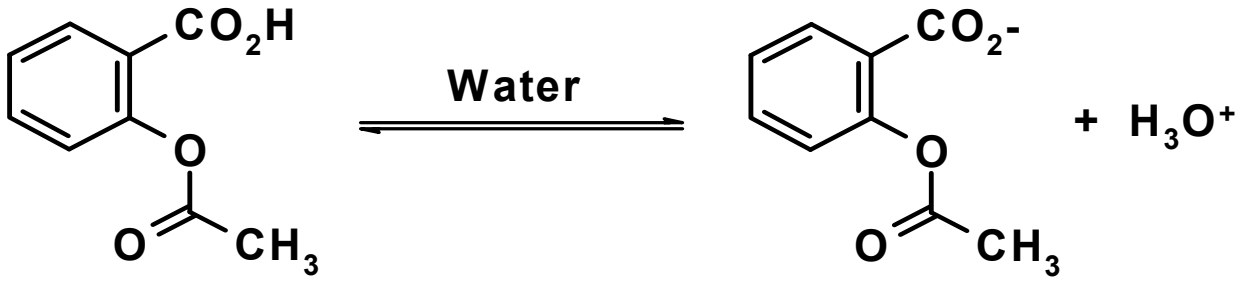
Primera



Acidic Drug "A" - Primary absorption in the stomach

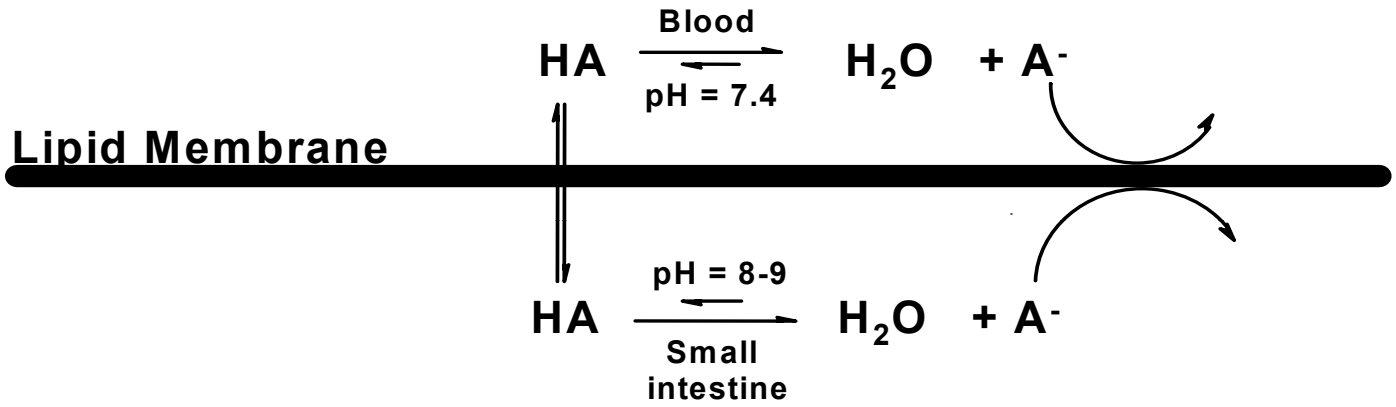


Example: Aspirin - Acetylsalicylic acid

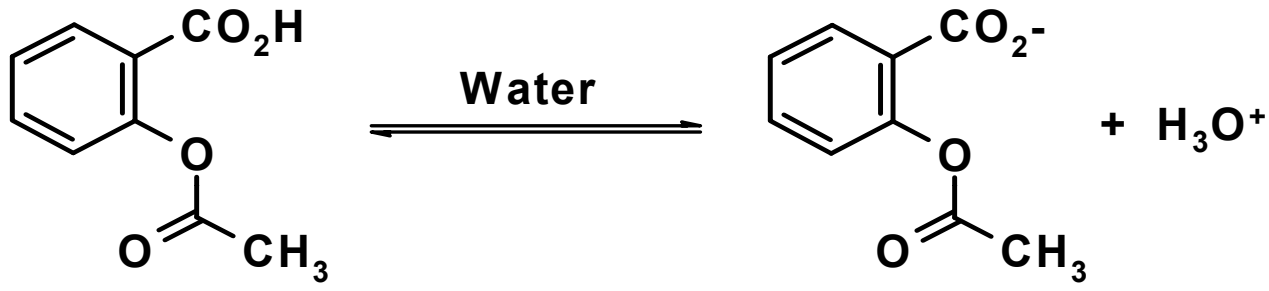


pKa = 3.5------The pH at which you have 50% unionized and 50% ionized forms of the molecule.

Acidic Drug "A" - Little absorption in the small intestine

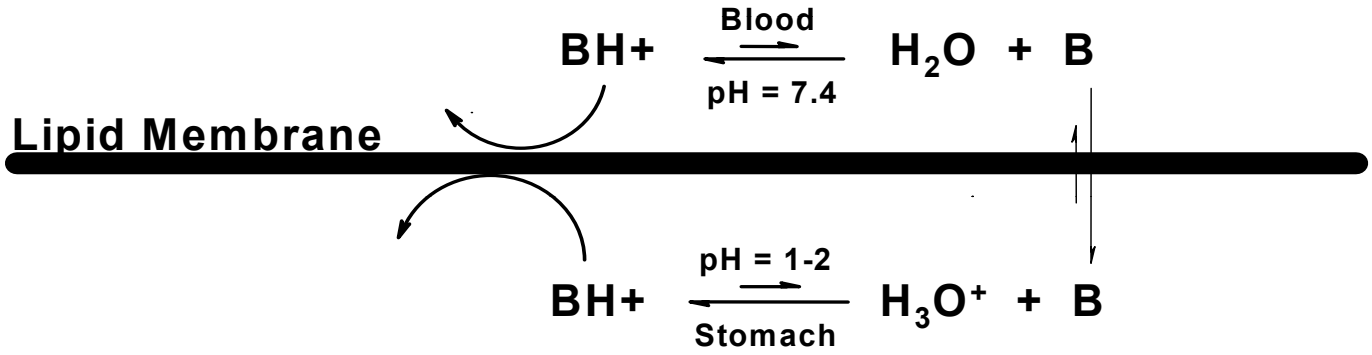


Example: Aspirin - Acetylsalicylic acid

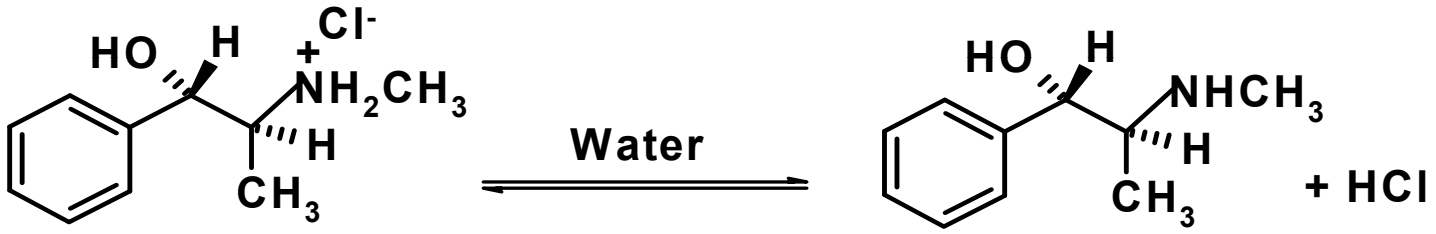


pKa = 3.5---------@ pH = 4.5 - 90.0% in ionized form
@ pH = 5.5 - 99.0% in ionized form

Basic Drug "B" - Little absorption in the stomach



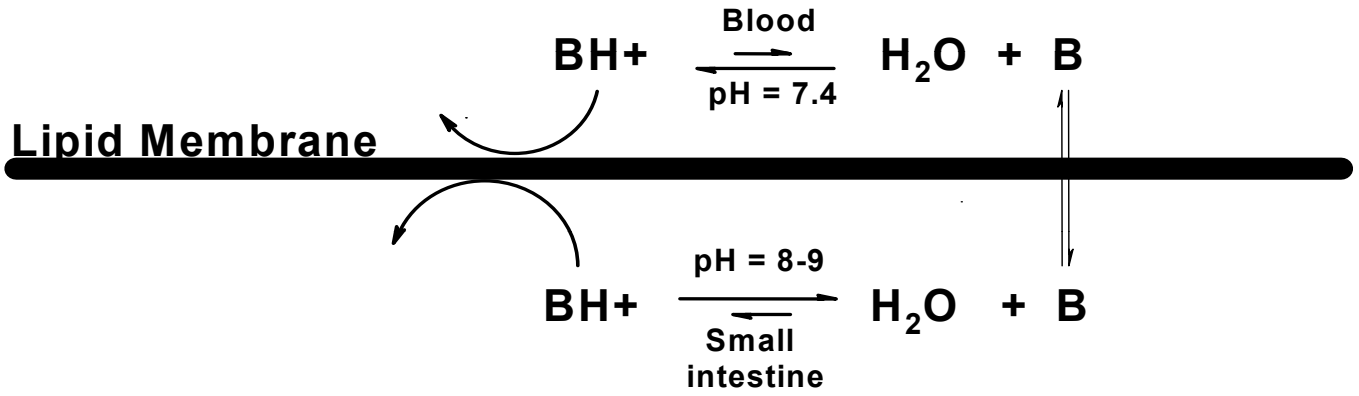
Example: Pseudoephedrine HCl



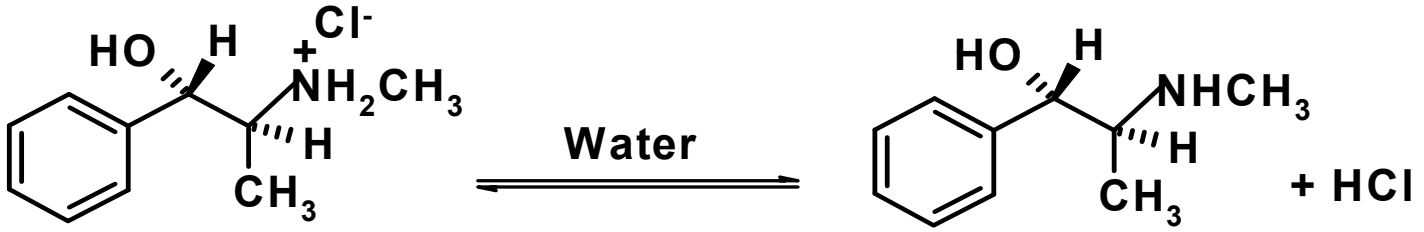
Pseudoephedrine HCl

pKa = 9.9------The pH at which you have 50% unionized and 50% ionized forms of the molecule.

Basic Drug "B" - Primary absorption in the small intestine



Example: Pseudoephedrine HCl



Pseudoephedrine HCl

pKa = 9.9---------@ pH = 8.9 - 90.0% in ionized form
@ pH = 7.9 - 99.0% in ionized form

Topnostni profil – sproščanje/absorpcija

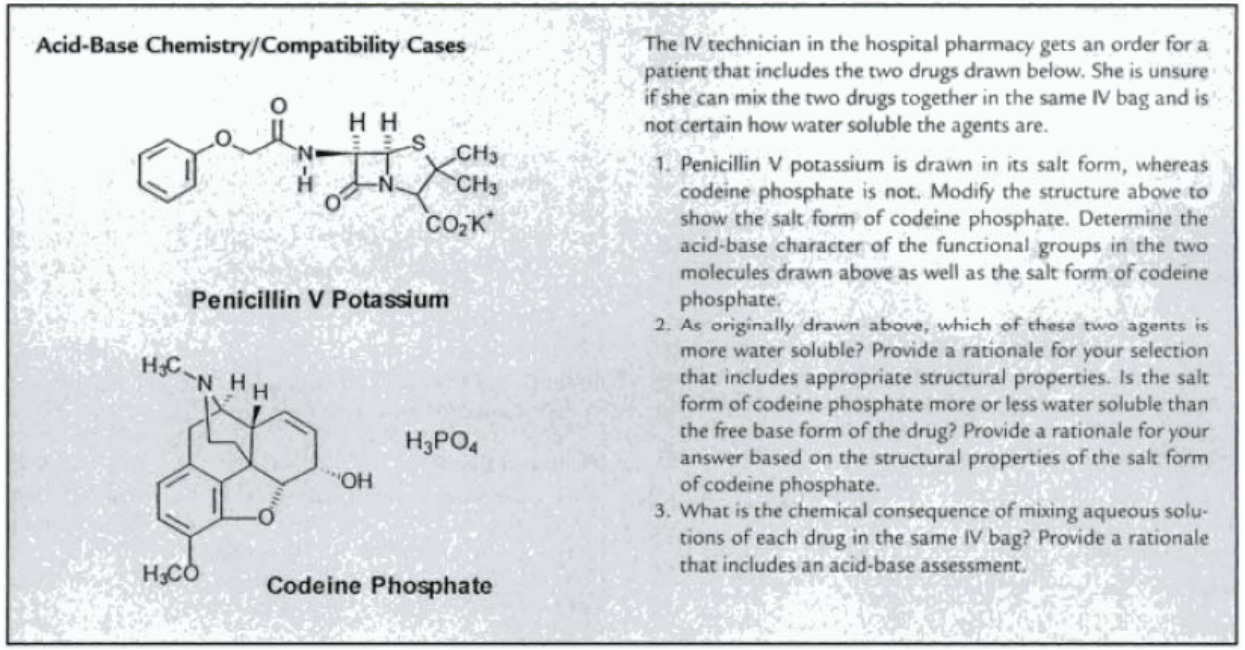
- Primer: ibuprofen
- pKa = 3,5, topnost (voda) = 0,049 mg/ml

Topnostni profil – sproščanje/absorpcija

- Primer: amoksicilin
- $pKa_1 = 2,6$; $pKa_2 = 9,6$
- Topnost (voda) = 3,40 g/L

Topnost - primer

- Penicilin V pKa = 2,7
- Kodein pKa = 8,2
- Stabilne soli – razlika vsaj 3 enote pKa



Acid-Base Chemistry/Compatibility Cases

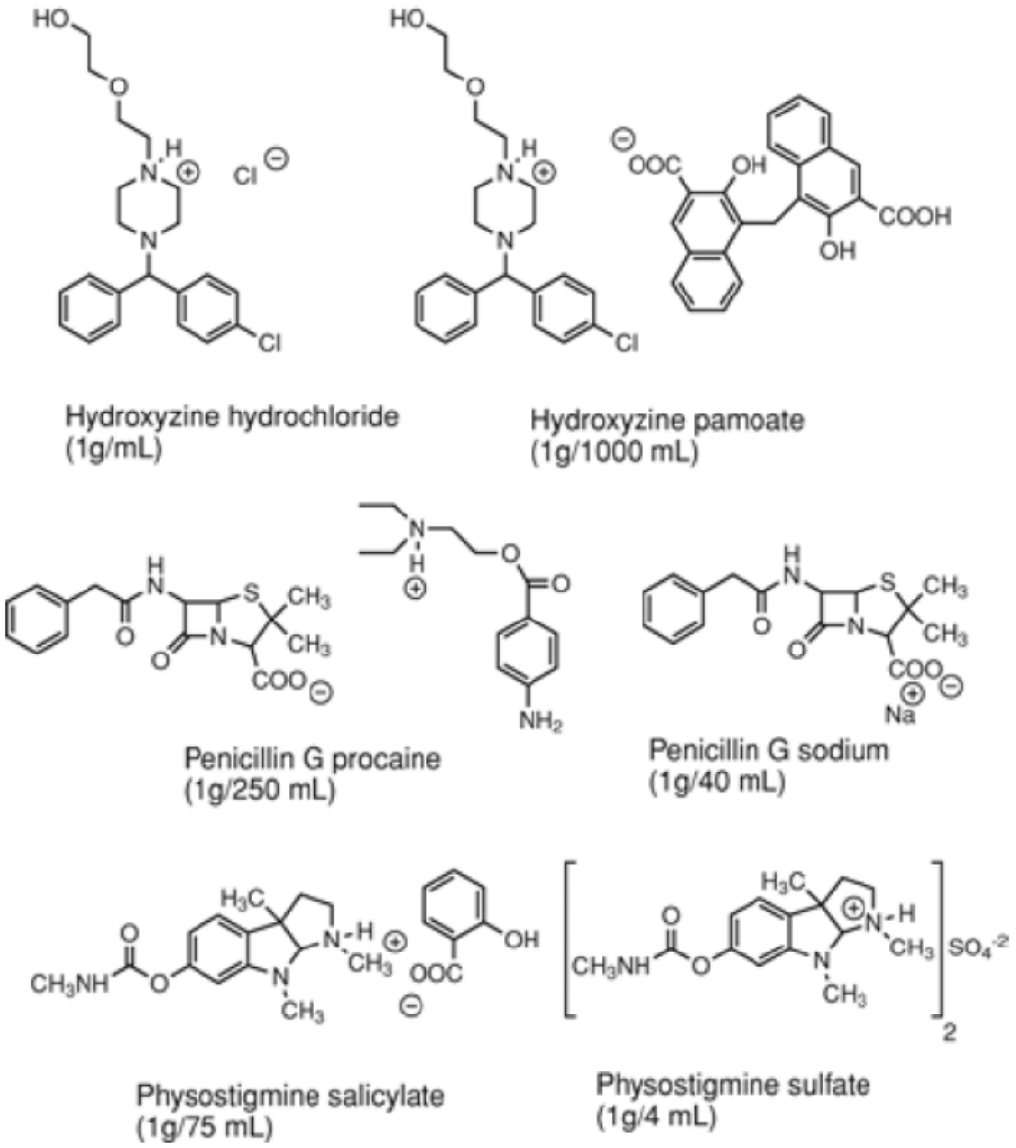
Penicillin V Potassium

Codeine Phosphate

The IV technician in the hospital pharmacy gets an order for a patient that includes the two drugs drawn below. She is unsure if she can mix the two drugs together in the same IV bag and is not certain how water soluble the agents are.

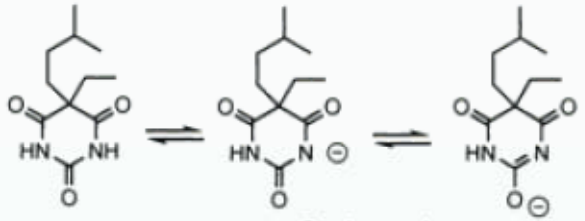
1. Penicillin V potassium is drawn in its salt form, whereas codeine phosphate is not. Modify the structure above to show the salt form of codeine phosphate. Determine the acid-base character of the functional groups in the two molecules drawn above as well as the salt form of codeine phosphate.
2. As originally drawn above, which of these two agents is more water soluble? Provide a rationale for your selection that includes appropriate structural properties. Is the salt form of codeine phosphate more or less water soluble than the free base form of the drug? Provide a rationale for your answer based on the structural properties of the salt form of codeine phosphate.
3. What is the chemical consequence of mixing aqueous solutions of each drug in the same IV bag? Provide a rationale that includes an acid-base assessment.

Ni tako preprosto...



Distribucija

- Primer: amobarbital



Acid form
pK_a 8.0

Conjugate base

Question: At a pH of 7.4, what is the percent ionization of amobarbital?

Answer:

$$8.0 = 7.4 + \log \frac{[\text{acid}]}{[\text{base}]}$$

$$0.6 = \log \frac{[\text{acid}]}{[\text{base}]}$$

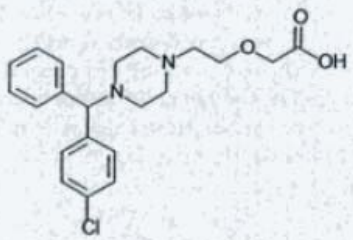
$$10^{0.6} = \frac{[\text{acid}]}{[\text{base}]} = \frac{3.98}{1}$$

$$\% \text{ acid form} = \frac{3.98 \times 100}{4.98} = 79.9\%$$

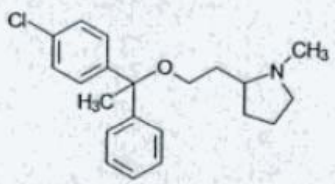
Fig. 2.6. Calculation of percentage ionization of amobarbital. Calculation indicates that 80% of the molecules are in the acid (or protonated) form, leaving 20% in the conjugate base (ionized) form.

Distribucija - primer

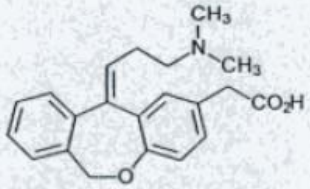
Absorption/Acid-Base Case



Cetirizine (Zyrtec)



Clemastine (Tavist)



Olopatadine (Patanol)

A long-distance truck driver comes into the pharmacy complaining of seasonal allergies. He asks you to recommend an agent that will act as an antihistamine but that will not cause drowsiness. He regularly takes TUMS for indigestion because of the bad food that he eats while on the road.

1. Identify the functional groups present in Zyrtec and Tavist, and evaluate the effect of each functional group on the ability of the drug to cross lipophilic membranes (e.g., blood-brain barrier). Based on your assessment of each agent's ability to cross the blood-brain barrier (and, therefore, potentially cause drowsiness), provide a rationale for whether the truck driver should be taking Zyrtec or Tavist.
2. Patanol is sold as an aqueous solution of the hydrochloride salt. Modify the structure above to show the appropriate salt form of this agent. This agent is applied to the eye to relieve itching associated with allergies. Describe why this agent is soluble in water and what properties make it able to be absorbed into the membranes that surround the eye.
3. Consider the structural features of Zyrtec and Tavist. In which compartment (stomach [pH 1] or intestine [pH 6–7]) will each of these two drugs be best absorbed?
4. TUMS neutralizes stomach acid to pH 3.5. Based on your answer to question 3, determine whether the truck driver will get the full antihistaminergic effect if he takes his antihistamine at the same time that he takes his TUMS. Provide a rationale for your answer.

Cetirizin pKa_1 = 2,2, pKa_2 = 2,9, pKa_3 = 8,3

Klemastin pKa ~ 8

Distribucija - primer

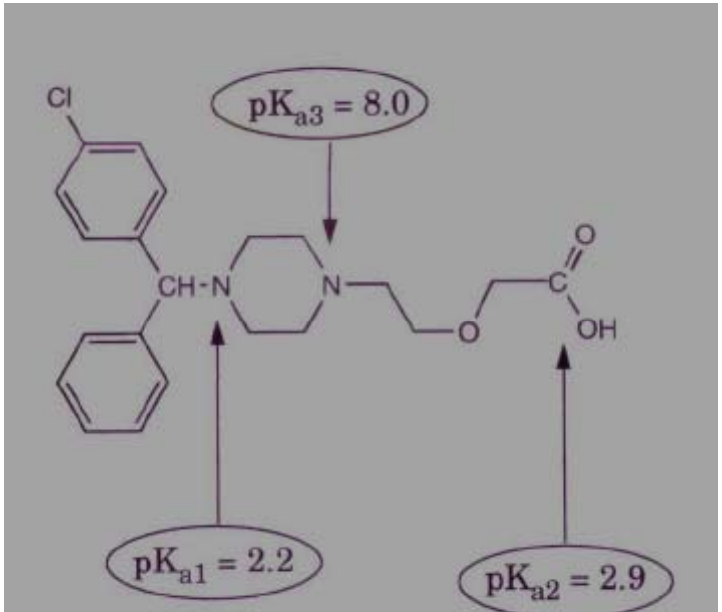


Fig. 1. The molecular structure and pKa values of cetirizine (Copyright Bernard Testa).

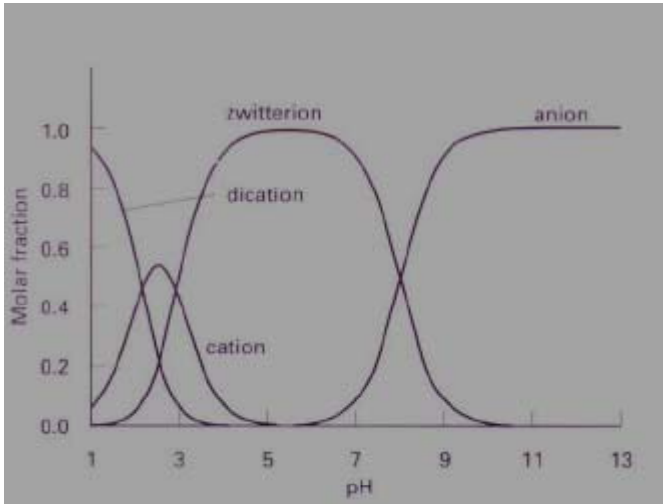


Fig. 3. Population of the electical species of cetirizine as a function of pH (Copyright Bernard Testa).

Distribucija

Plazemski proteini:

- Albumin (bazičen); vezava kislih spojin
- $\alpha 1$-kisli glikoprotein; vezava bazičnih spojin
- Vpliv na t1/2 in distribucijo

Distribucija - primer

učinkovina	% vezave na HSA	pKa
Acetilsalicilna kislina	99,8	3,5
Varfarin	97	4,8
Sulfametoksazol	70	6,1
Fenobarbital	20-45	7,4

Distribucija - primer

- Prime sočasne aplikacije 2 učinkovin

	Before Displacement	After Displacement	% increase in unbound fraction
Drug A			
% bound	95	90	
% unbound	5	10	+100
Drug B			
% bound	50	45	
% unbound	50	55	+10

Pri učinkovinah z visokim % vezane frakcije izjemno velike razlike!

Izločanje

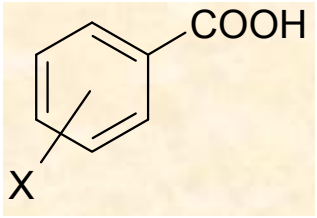
- Ionizacija – hidrofilne spojine – lažje izločanje v urin
- Vezava na plazemske proteine – izloča se le nevezana frakcija!

Predikcija kislinskih lastnosti

pK_a vrednosti alifatskih kislin

R	pK_a
CH_3-	4,74
CH_3CH_2-	4,77
CH_3OCH_2-	3,54
CH_2=$CHCH_2$-	4,35
HC≡CCH_2-	3,32
F-CH_2-	2,59
Cl-CH_2-	2,86
Br-CH_2-	2,90
NC-CH_2-	2,46
Cl_2-CH-	1,26
Cl_3C-	0,64
F_3C-	0,23

pK_a vrednosti kislin



X	pK_2(orto X)	pK_2(meta X)	pK_2(para X)
H	**4,20**	**4,20**	**4,20**
CH_3	**3,91**	**4,27**	**4,38**
CH_2CH_3	**3,79**	**4,27**	**4,35**
F	**3,27**	**3,86**	**4,14**
Cl	**2,92**	**3,83**	**3,97**
Br	**2,85**	**3,81**	**3,97**
CN	**3,14**	**3,64**	**3,55**
OH	**2,98**	**4,08**	**4,57**
OCH_3	**4,09**	**4,09**	**4,47**
NO_2	**4,09**	**4,09**	**4,47**

Hammettova enačba

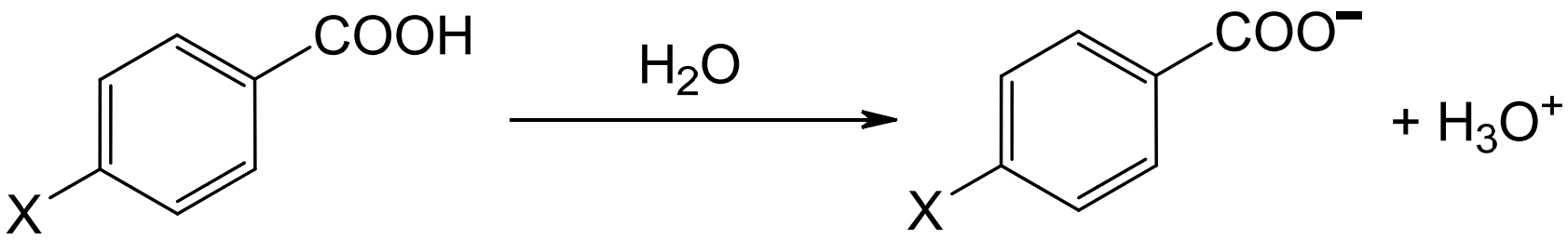
Hammett je opazil (1940) linearno povezanost med <u>prosto energijo</u> in:

- **<u>logaritmom relativne hitrostne konstante</u>** pri hidrolizi estrov
- **logaritmom ionizacijske ravnotežne konstante** substitutiranih benzojskih kislin

$$\log (k_x/k_H) = \log (K_x/K_H) = \rho\sigma$$

- Za ρ je arbitrarno določil, da je to reakcijska konstanta, ki ima za benzojsko kislino vrednost 1.

Disociacija benzojskih kislin



$pK_2(X=H) = 4,20$

$pK_2(X=CH_3) = 4,38$

$\Delta G^0 = -RT \log k_{rav} = RT\, pK_a$

$\Delta G^0(R\text{-}H) = -RT \log k_{rav}(R\text{-}H) = RT pK_a(R\text{-}H)$

$\Delta G^0(R\text{-}X) = -RT \log k_{rav}(R\text{-}X) = RT pK_a(R\text{-}X)$

$\log k(R\text{-}X) = \log k(R\text{-}H) + \sigma (X)$

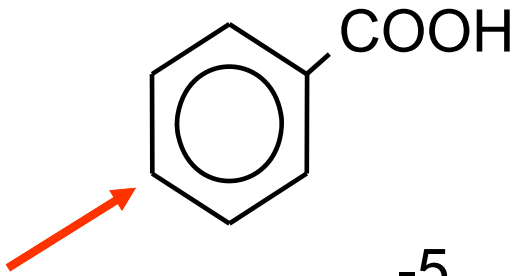
$pK_a (R\text{-}X) = pK_a (R\text{-}H) - \sigma (X)$

Prispevek skupine X

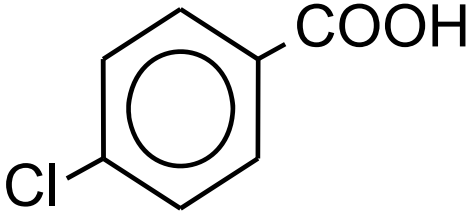
Sprememba pKa pri derivatizaciji benzojske kisline

$$\text{Log}\ \frac{K_X}{K_H} = \sigma_x$$

Primer:



$K_a = 6.25 \times 10^{-5}$



$K_a = 10.0 \times 10^{-5}$

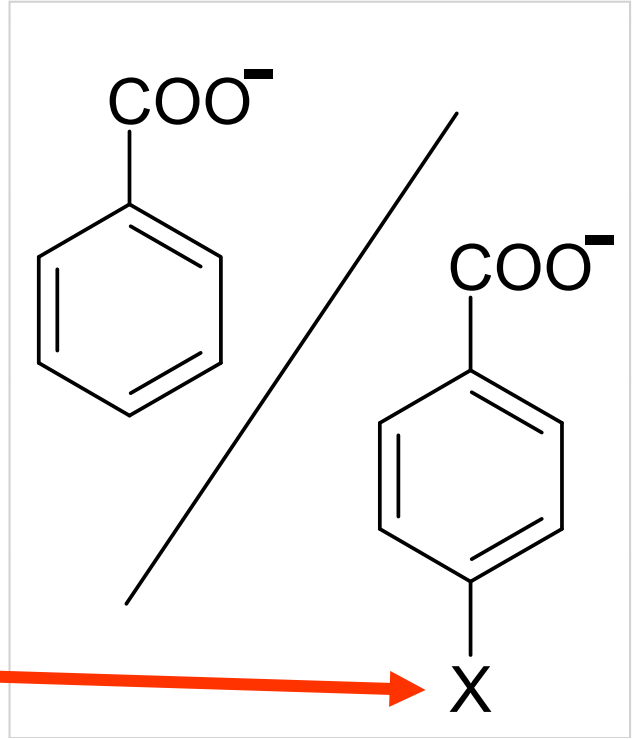
$$\text{Log}\ \frac{10.0 \times 10^{-5}}{6.25 \times 10^{-5}} = 0.204 = \sigma_p \text{ za Cl}$$

Hammettove konstante

- merilo resonančnih in induktivnih vplivov;
- vrednost σ je odvisna od vrste substituenta in od pozicije na aromatskem oboču: para ali meta mesto; pri orto mestu prevlada sterični vpliv
- Obstajajo ustrezne konstante tudi za alifatiske spojine.

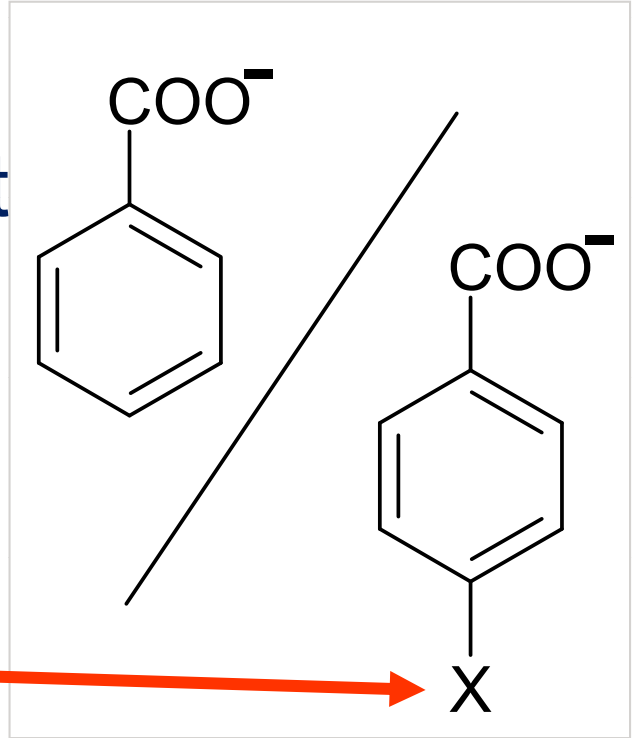
Hammettove konstante

- Elektron privlačne skupine: $K_x > K_{benzojska}$
- $\sigma_x = \log K_x - \log K_{benzojska} = \log (K_x/K_{benzojska})$
- σ ima **pozitivno** vrednost



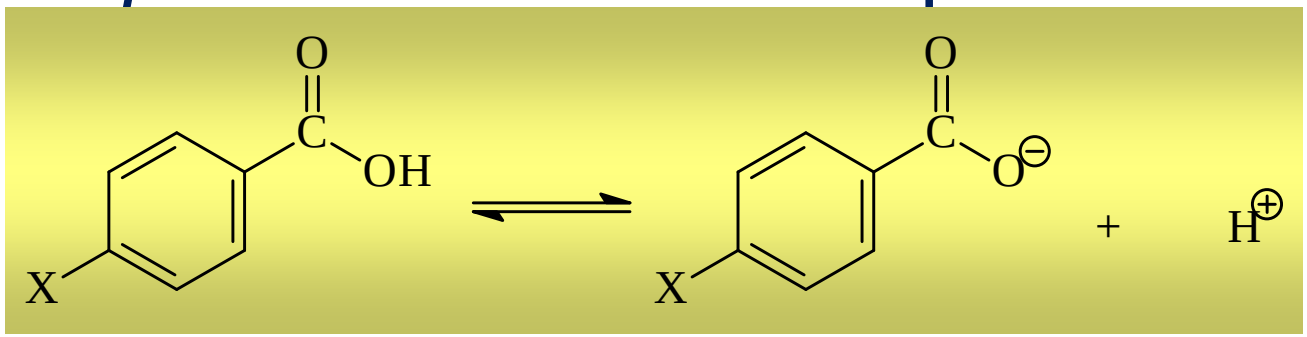
Hammettove konstante

- Elektron donorske skupine: $K_{benzojska} > K_x$
- $\sigma_x = \log K_x - \log K_{benzojska} = \log (K_x/K_{benzojska})$
- σ ima **<u>negativno</u>** vrednost

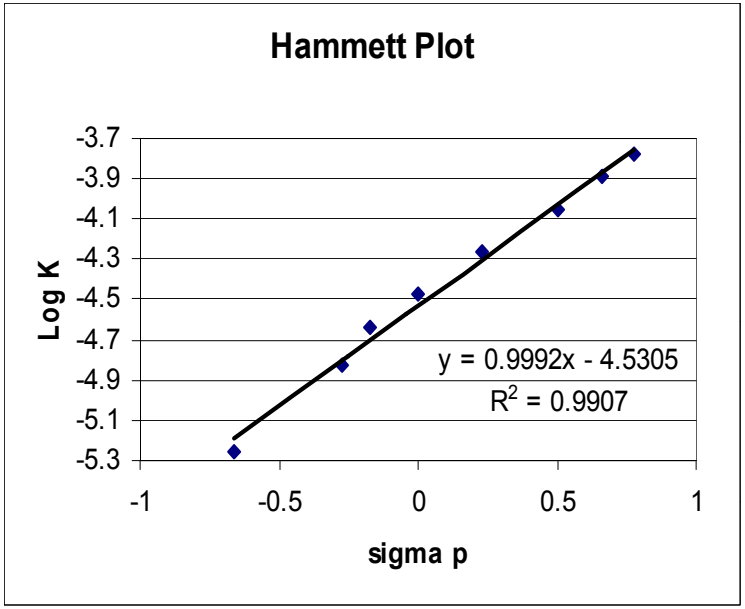


Hammettove konstante

- Vpliv *para* substituenta na pKa



substituent	σ_p	Eq. constant	log K
-NH2	-0.66	0.00000554	-5.25649
-OCH3	-0.27	0.000015	-4.82391
-CH3	-0.17	0.000023	-4.63827
-H	0.00	0.000034	-4.46852
-Cl	0.23	0.000055	-4.25964
-COCH3	0.5	0.000088	-4.05552
-CN	0.66	0.000128	-3.89279
-NO2	0.78	0.000166	-3.77989



Ko so $\sigma(x)$ vrednosti znane, se uporabijo za pridobivanje informacij o občutljivosti drugih reakcij na vplive X.

Hammettova enačba

$$\text{Log}\left(\frac{K_X}{K_H}\right) \quad \text{ali} \quad \text{Log}\left(\frac{k_X}{k_H}\right) = \rho\sigma_X$$

Pozitivna ρ vrednost pomeni reakcijo, kjer so elektroni odtegnjeni z mesta reakcije.

Negativne ρ vrednosti pomenijo reakcijo, kjer so elektroni usmerjeni k mestu reakcije.

Literatura predavanj

Foye's Principles of Medicinal Chemistry, 6. Ed. :

- 2. poglavje
- 9. poglavje

G. L. Patrick: An introduction to medicinal chemistry, 4. Ed. :

- 18. poglavje