



Metodologie di Sintesi e Sviluppo Farmaceutico

Synthesis and Development Pharmaceutical Methodologies

IV ed

Laurea Magistrale in Chimica a.a. 2018/2019



pK_a (*acidità e basicità*)

- Capacità di ipotizzare la presenza di gruppi **deprotonabili** in ambiente acquoso
 - Applicazione in Chimica Farmaceutica: concetto di *drugability*
- 
- 
- 
- 
- 

The chemio-physical constant

Some examples:

Melting point (mp),

Boiling point (bp)

Solubility



Sempre qui dobbiamo stare!!!

logP,

pK_a,

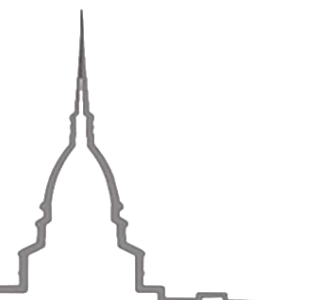
Density

Viscosity

Chromatografic retention time (Rf)

IR Vibration frequency,

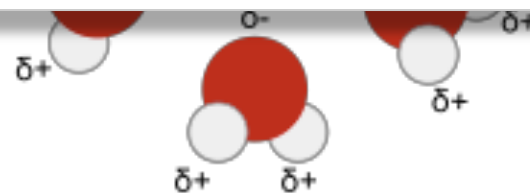
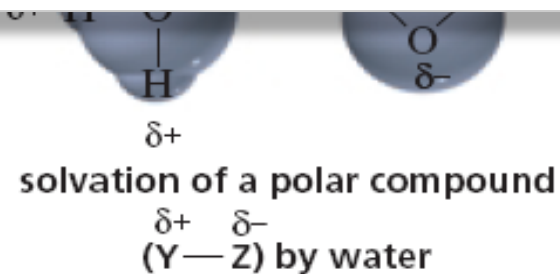
NMR *chemical shift*,



Solvation

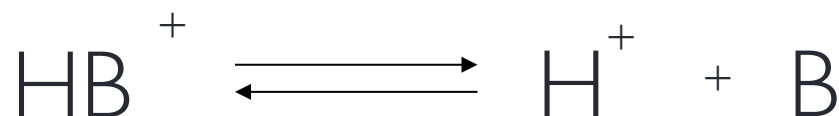
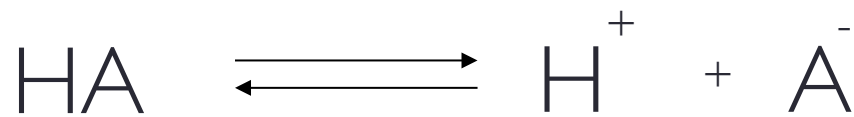
Solubility - definition#1:

Solubility is a phenomena strictly correlate to the intramolecular forces inside this equilibrium:

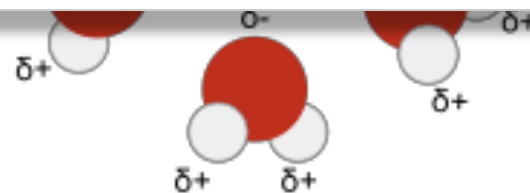
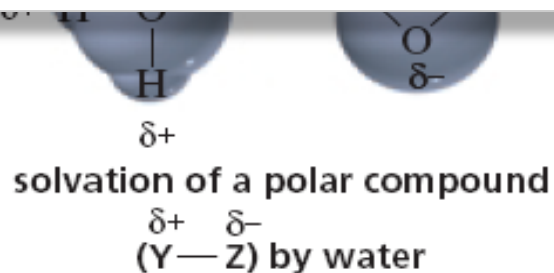


Solubility - definition#2:

When charged functional groups are present in the structure, the water solubility is strictly correlate to **the pKa the functional groups** and the **pH the water solvent**.

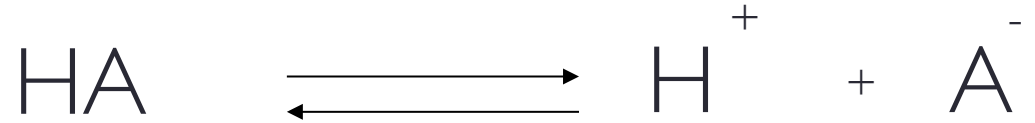
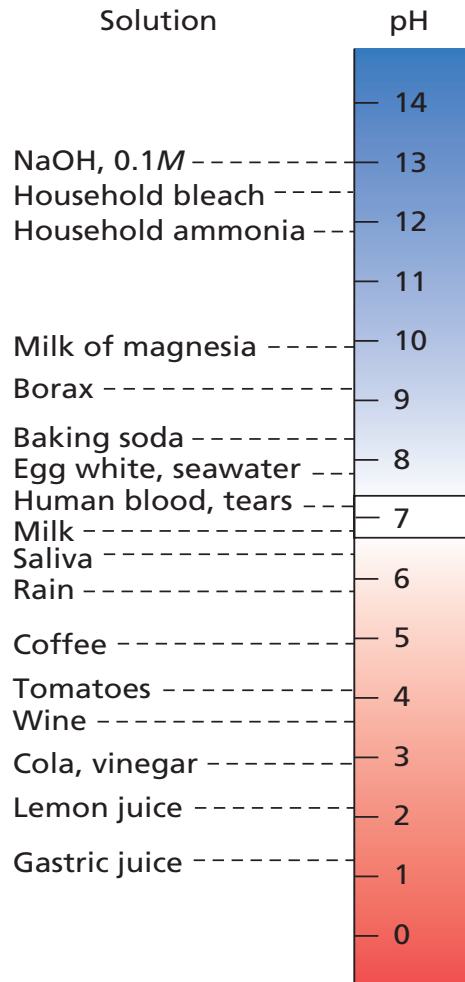


$$\text{pKa} = -\log K_a$$

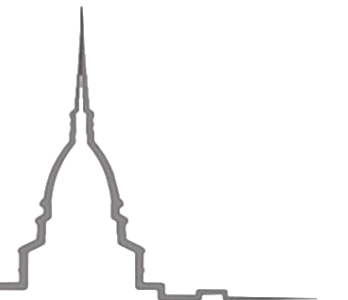


Dissociation constant (pK_a)

The stronger the acid, the smaller is its pK_a .

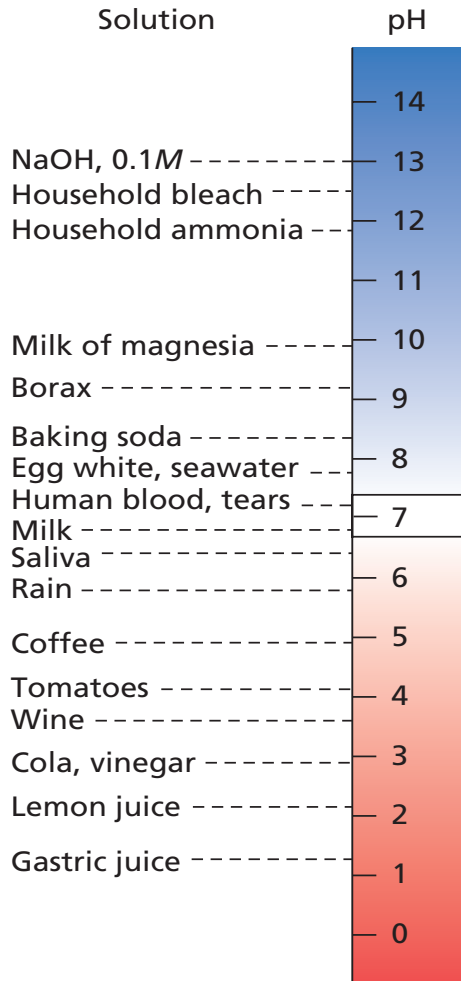


$$pK_a = -\log K_a$$



Dissociation constant (pK_a)

The stronger the acid, the smaller is its pK_a .



The dissociation constant (pK_a) chemiophysical constant influenced by few structural:

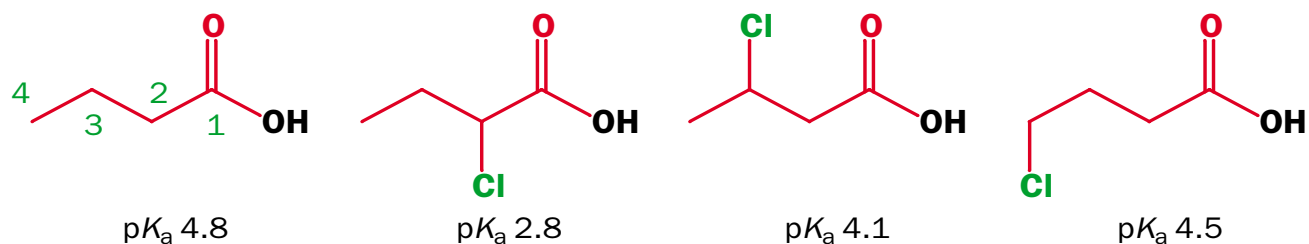
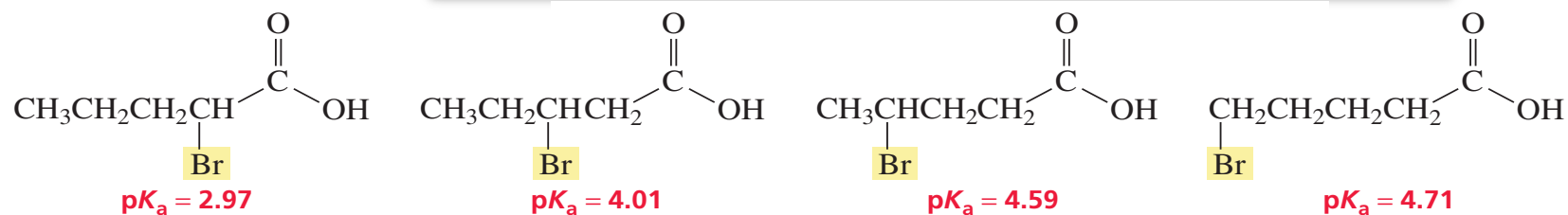
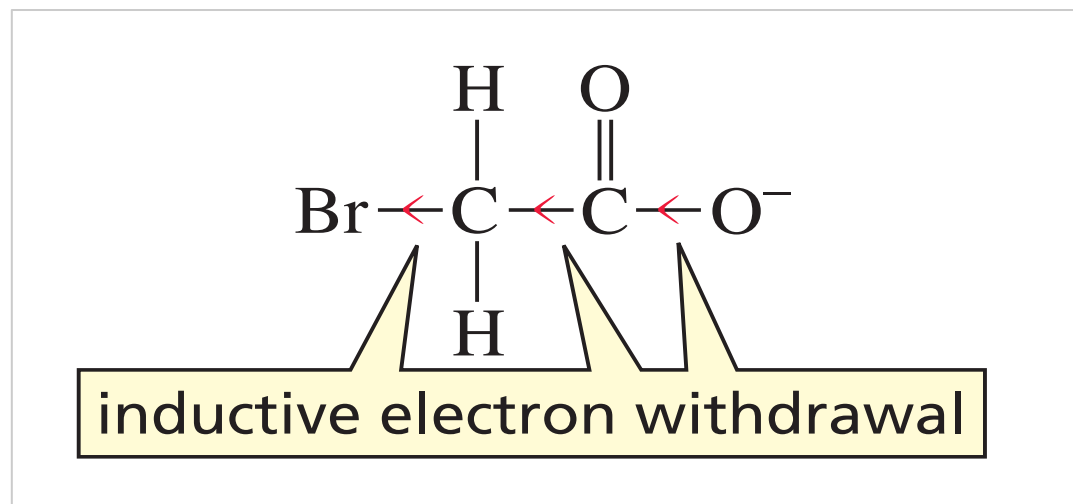
- * Inductive effects (+ I/- I)
- * Mesomeric effects (+ M/- M)
- * Steric effects

and environmental factors:

- * Solvent
- * Temperature

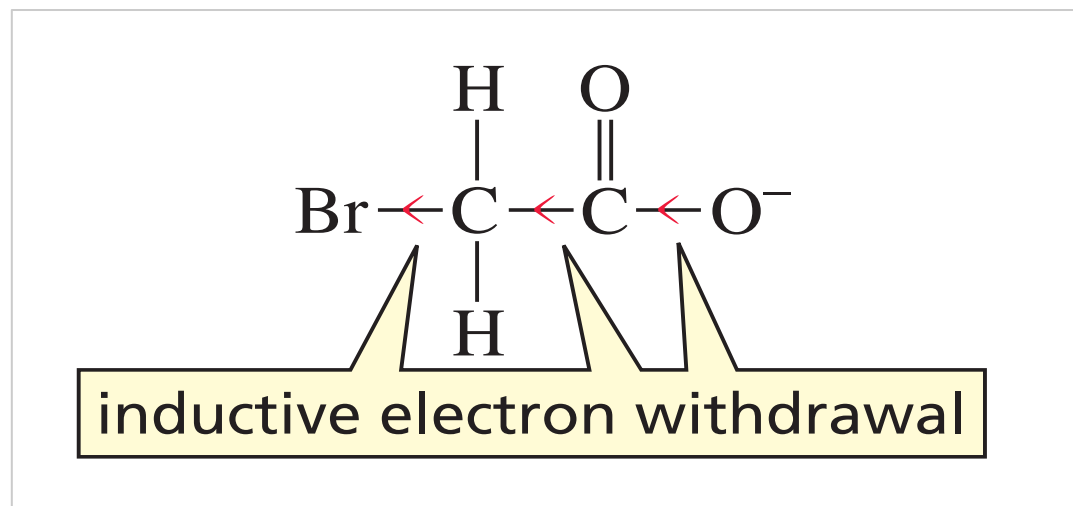
Inductive effect

pK_a
acidity

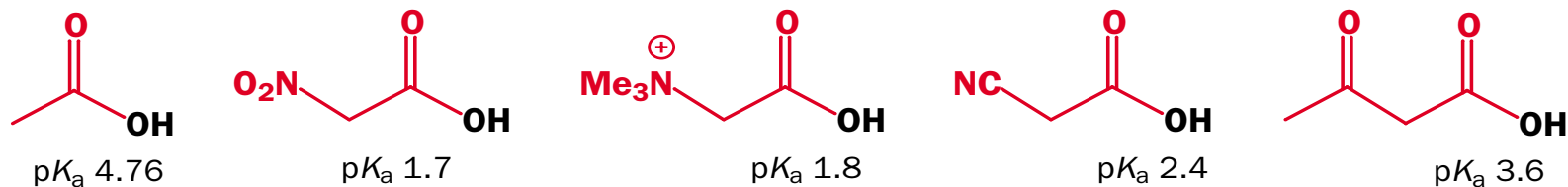


Inductive effect

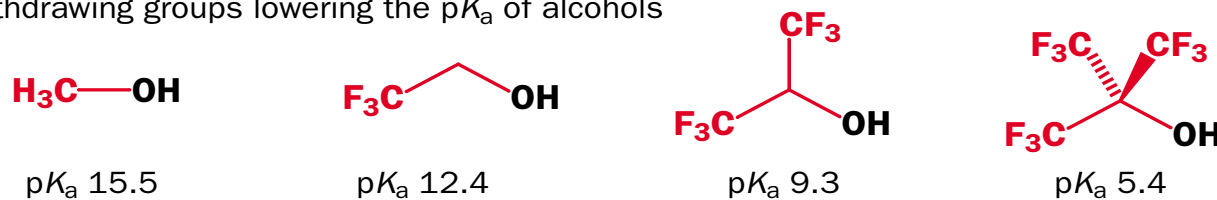
pK_a
acidity



electron-withdrawing groups lowering the pK_a of carboxylic acids



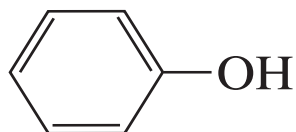
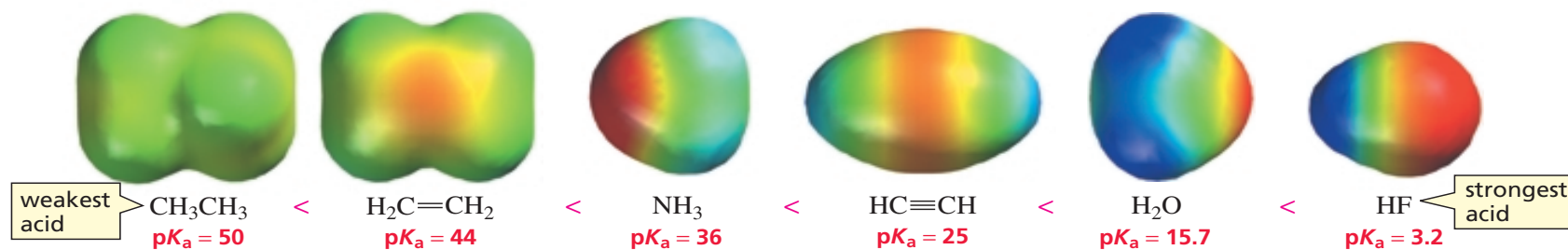
electron-withdrawing groups lowering the pK_a of alcohols



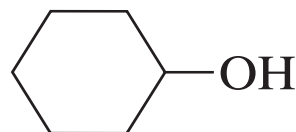
Inductive effect

pK_a
acidity

relative acid strengths



phenol
 $pK_a = 10$



cyclohexanol
 $pK_a = 16$



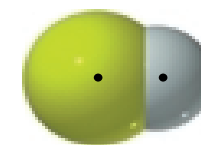
ethanol
 $pK_a = 16$

Inductive effect

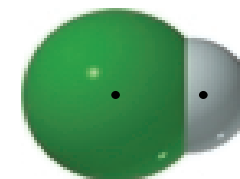
pK_a
acidity

Table 1.9 The pK_a Values of Some Simple Acids

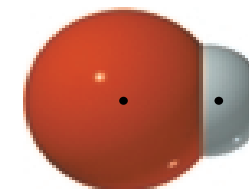
CH_4 $pK_a = 50$	NH_3 $pK_a = 36$	H_2O $pK_a = 15.7$	HF $pK_a = 3.2$
		H_2S $pK_a = 7.0$	HCl $pK_a = -7$
			HBr $pK_a = -9$
			HI $pK_a = -10$



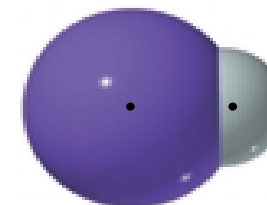
hydrogen fluoride



hydrogen chloride



hydrogen bromide



hydrogen iodide

Inductive effect

pK_a
acidity

relative electronegativities:



most
electronegative

largest

relative stabilities:

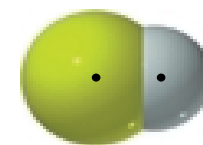


most
stable

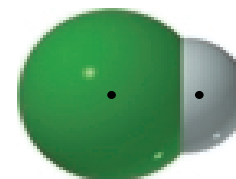
relative acidities:



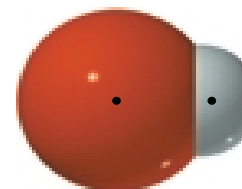
strongest
acid



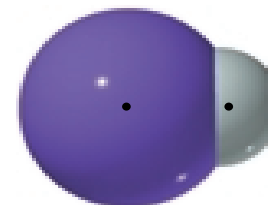
hydrogen fluoride



hydrogen chloride



hydrogen bromide

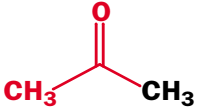
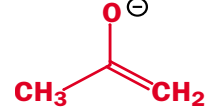


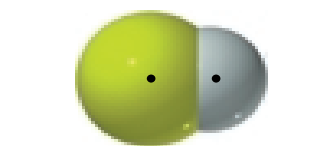
hydrogen iodide

Inductive effect

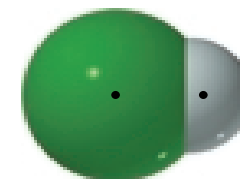
pK_a
acidity

Table 8.1 The pK_a value of some compounds

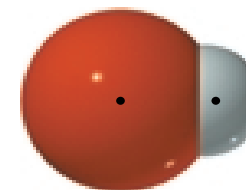
Acid	pK_a	Conjugate base
HI	ca. -10	I^-
HCl	ca. -7	Cl^-
H_2SO_4	ca. -3	HSO_4^-
HSO_4^-	2.0	SO_4^{2-}
CH_3COOH	4.8	CH_3COO^-
H_2S	7.0	HS^-
NH_4^+	9.2	NH_3
C_6H_5OH	10.0	$C_6H_5O^-$
CH_3OH	15.5	CH_3O^-
	20.0	
$CH\equiv C-H$	25	$CH\equiv C^-$
NH_3	33	NH_2^-
C_6H_6	ca. 43	$C_6H_5^-$
CH_4	ca. 48	CH_3^-



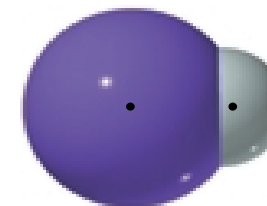
hydrogen fluoride



hydrogen chloride



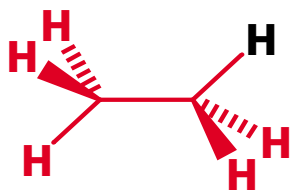
hydrogen bromide



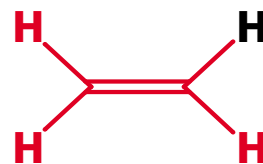
hydrogen iodide

Inductive effect

pK_a
acidity



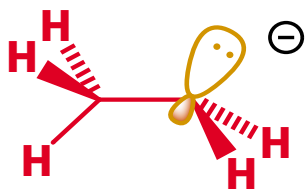
pK_a ca. 50



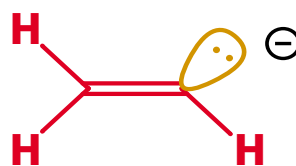
pK_a ca. 44



pK_a ca. 26



lone pair of CH_3CH_2^-
in sp^3 orbital



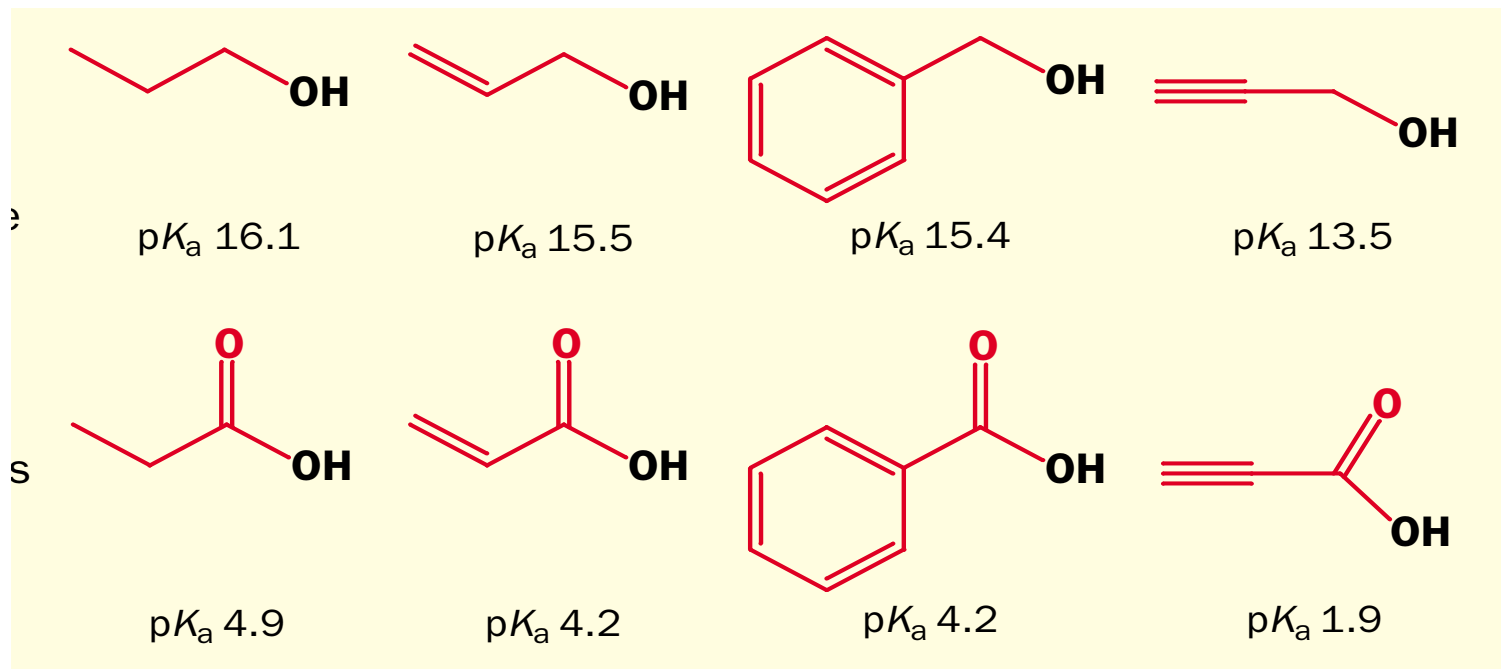
lone pair of $\text{CH}_2=\text{CH}^-$
in sp^2 orbital



lone pair of $\text{HC}\equiv\text{C}^-$
in sp orbital

Inductive effect

pK_a
acidity



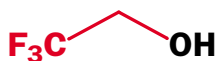
Inductive effect

pK_a
acidity

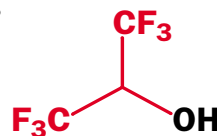
electron-withdrawing groups lowering the pK_a of alcohols



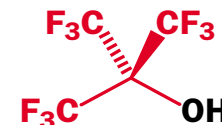
pK_a 15.5



pK_a 12.4

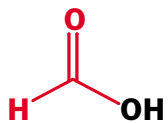


pK_a 9.3

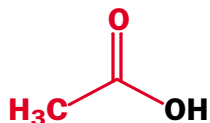


pK_a 5.4

Steric effect



formic (methanoic) acid
 pK_a 3.7



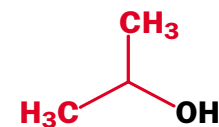
acetic (ethanoic) acid
 pK_a 4.8



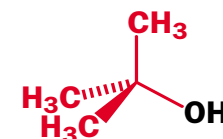
methanol
 pK_a 15.5



ethanol
 pK_a 16.0



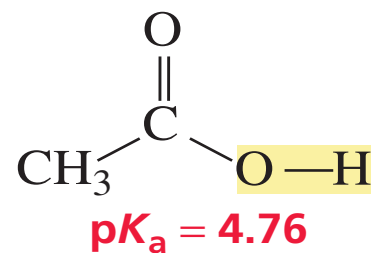
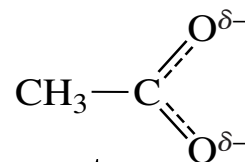
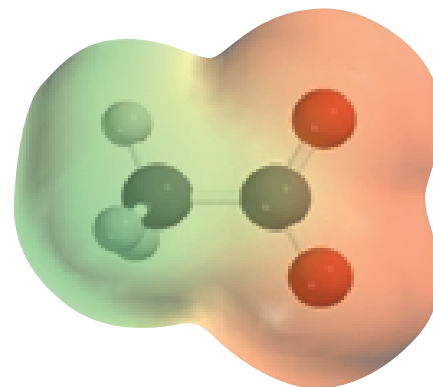
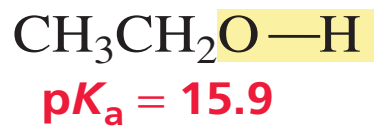
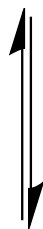
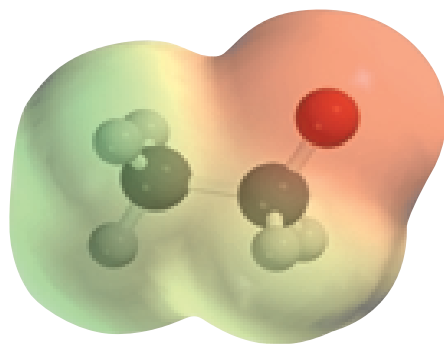
isopropyl alcohol
 pK_a 17.1



tert-butyl alcohol
 pK_a 19.2

Mesomeric effect

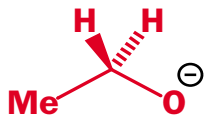
pK_a
acidity



Mesomeric effect

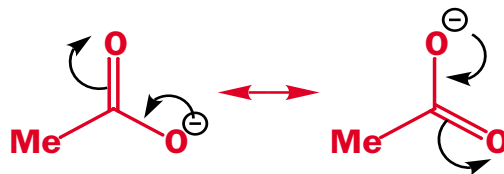
pK_a
acidity

ethoxide

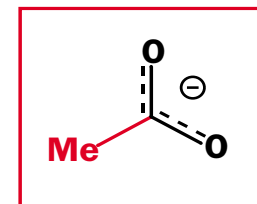


charge localized on one oxygen

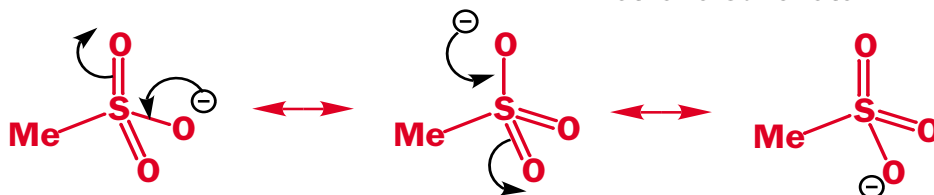
acetate



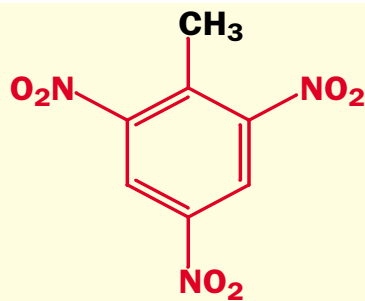
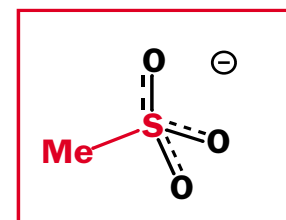
charge delocalized over two oxygens



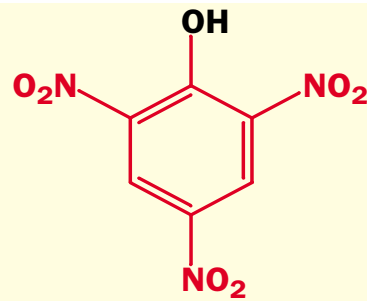
methane sulfonate



charge delocalized over three oxygens



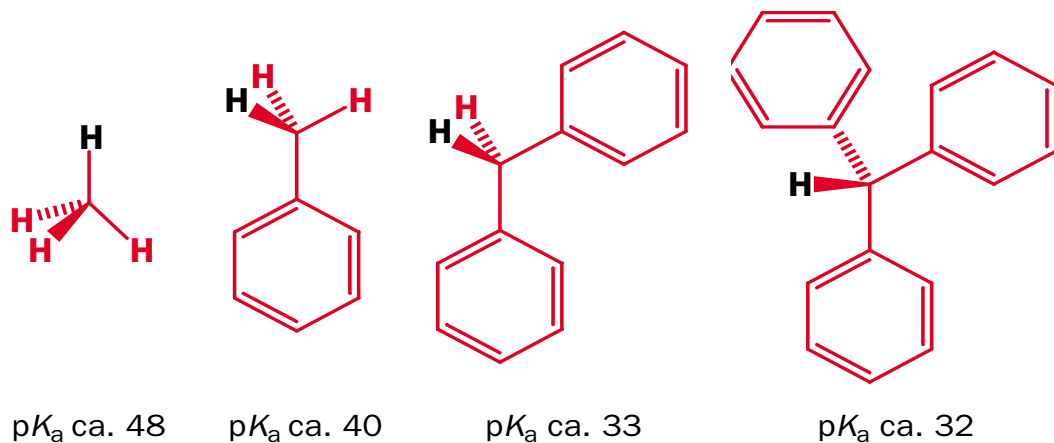
trinitrotoluene, TNT



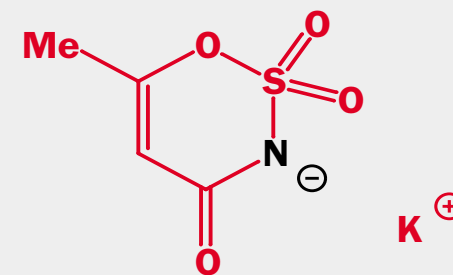
picric acid

Mesomeric effect

pK_a
acidity



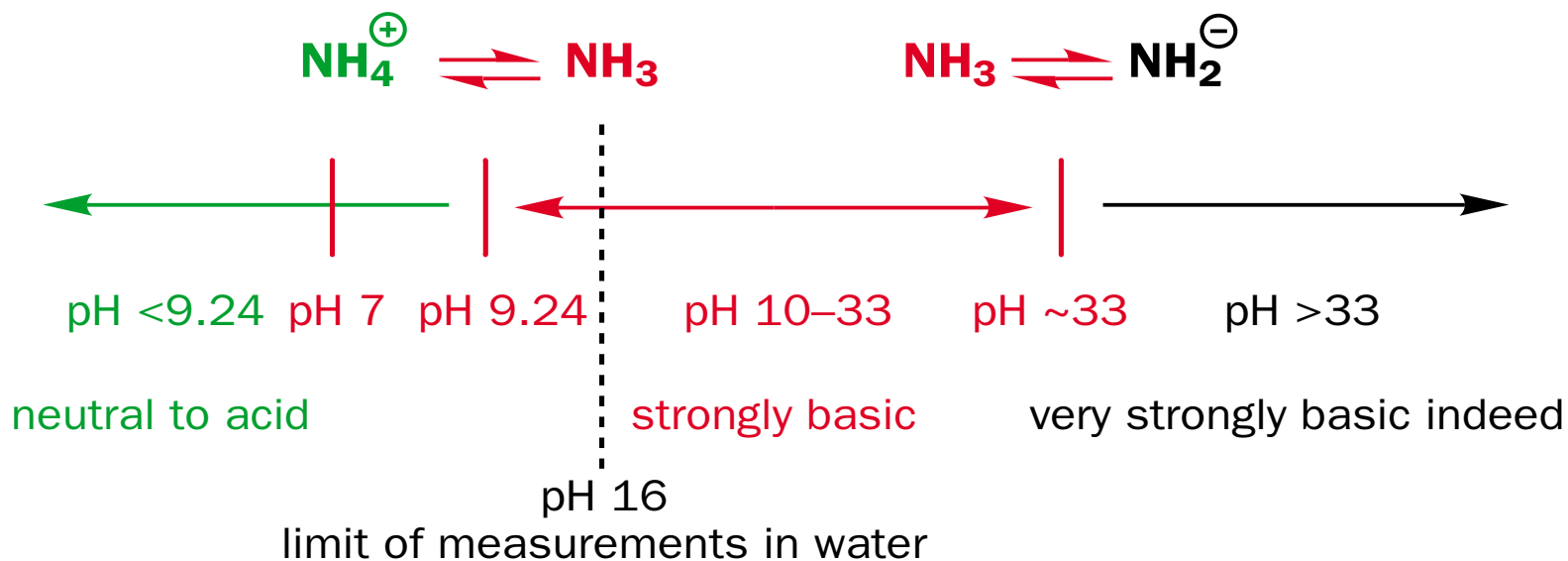
The potassium salt of 6-methyl-1,2,3-oxathiazin-4-one 2,2-dioxide known as acesulfame-K is used as an artificial sweetener (trade name Sunett). Here the negative charge is delocalized over both the carbonyl and the sulfone groups.



acesulfame-K

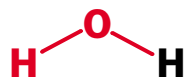
Basicity evaluation

pK_a
basicity

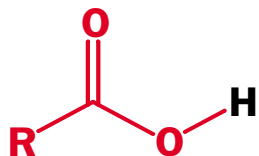


Basicity evaluation

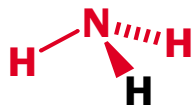
pK_a
basicity



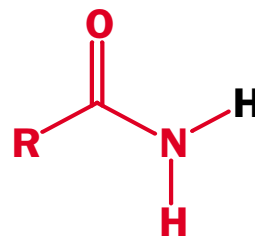
water
 pK_a 15.74



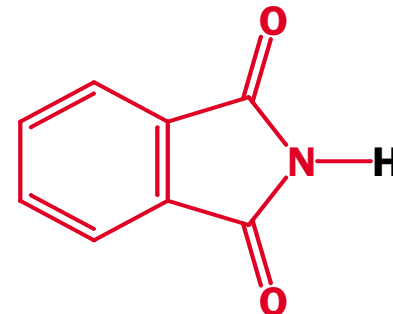
carboxylic acid
 pK_a ca. 5



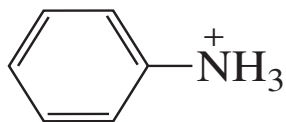
ammonia
 pK_a ca. 33



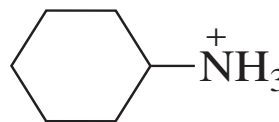
amide
 pK_a ca. 17



phthalimide
 pK_a 8.3



protonated aniline
 $pK_a = 4.60$



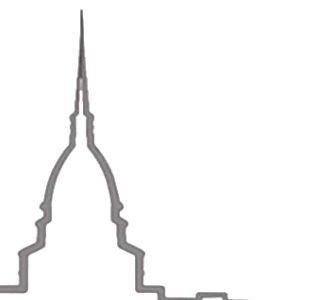
protonated cyclohexylamine
 $pK_a = 11.2$

Table 8.4 pK_{aH} values for primary, secondary, and tertiary amines

R	pK_{aH} RNH ₂	pK_{aH} R ₂ NH	pK_{aH} R ₃ N
Me	10.6	10.8	9.8
Et	10.7	11.0	10.8
<i>n</i> -Pr	10.7	11.0	10.3
<i>n</i> -Bu	10.7	11.3	9.9

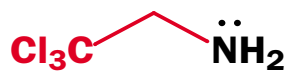
Table 8.5 pK_{aH} s of unsaturated primary, secondary, and tertiary amines

R	RNH ₂	R ₂ NH	R ₃ N
H₃C—CH₂—CH₂—	10.7	11.0	10.3
H₂C=CH—CH₂—	9.5	9.3	8.3
HC≡C—CH₂—	8.2	6.1	3.1



Basicity evaluation

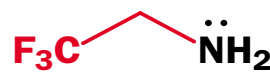
pK_a
basicity



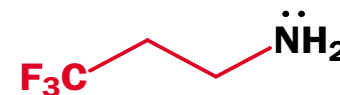
pK_{aH} 5.5



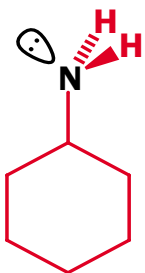
pK_{aH} 9.65



pK_{aH} 5.7

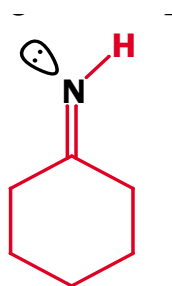


pK_{aH} 8.7



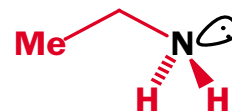
lone pair in sp^3 orbital

pK_{aH} 10.7



lone pair in sp^2 orbital

pK_{aH} 9.2



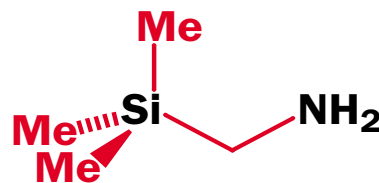
lone pair in sp^3 orbital

pK_{aH} 10.8



lone pair in sp orbital

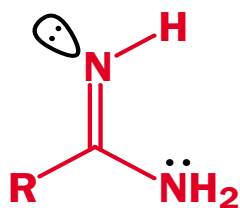
pK_{aH} ca. -10



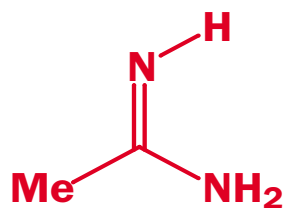
pK_{aH} 11.0

Basicity evaluation

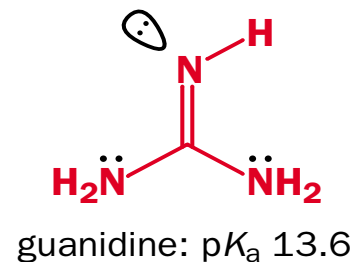
pK_a
basicity



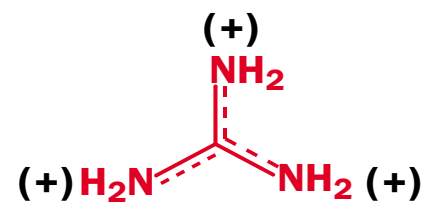
an amidine



pK_{aH} 12.4



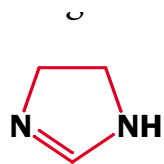
guanidine: pK_a 13.6



very stable guanidinium cation
each (+) is a third
of a positive charge

Basicity evaluation

pK_a
basicity

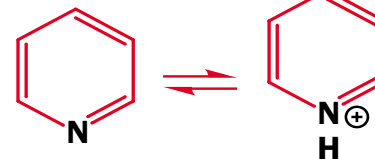


imidazoline
 pK_{aH} 11



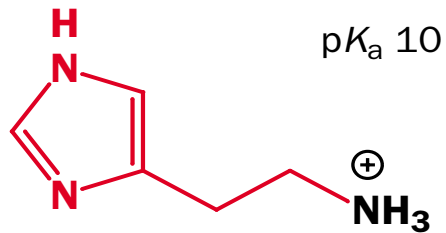
imidazole
 pK_{aH} 7.1

imidazolium
cation

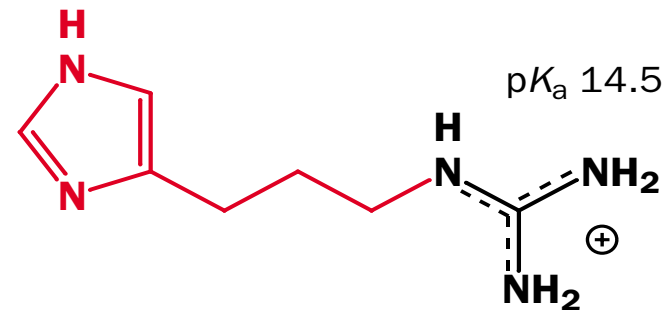


pyridine
 pK_{aH} 5.2

pyridinium
cation



the major form of histamine
at physiological pH (7.4)



the guanidine analogue
the extra carbon in the chain was found
to increase the efficacy of the drug

Henderson-Hasselbalch Equation

pK_a and Solubility

$$K_a = \frac{[A^-][H^+]}{[HA]} \quad \text{pH} = \text{p}K_a + \log \frac{[A^-]}{[HA]}$$

	2.8	3.8	4.8	5.8	6.8
HA	100	90	50	10	1
A ⁻	0	10	50	90	100

	2.8	3.8	4.8	5.8	6.8
BH ⁺	100	90	50	10	1
B	0	10	50	90	100

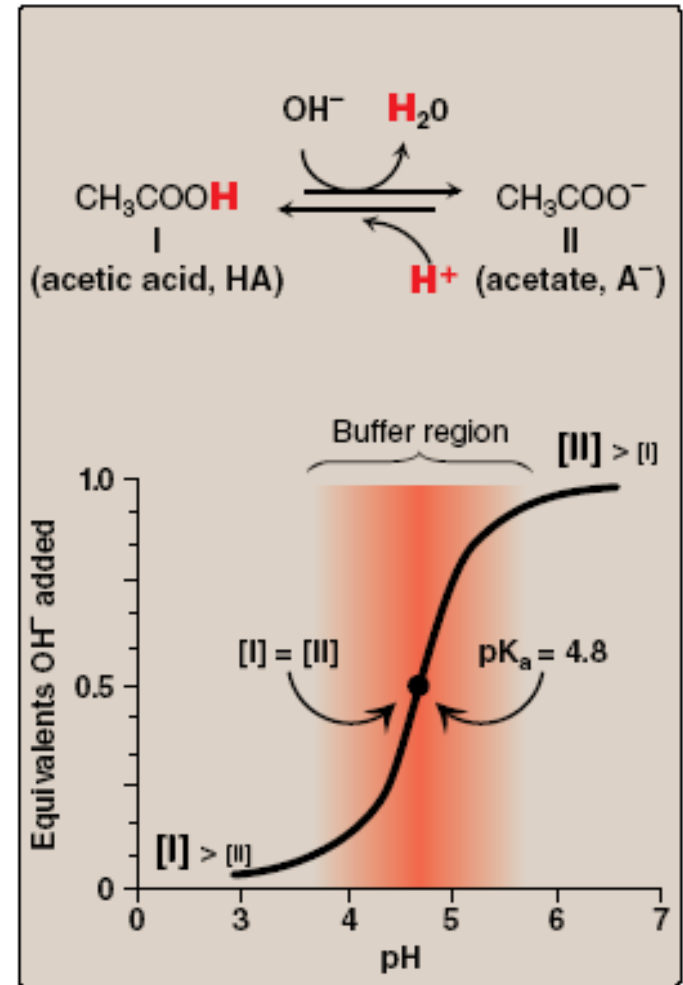
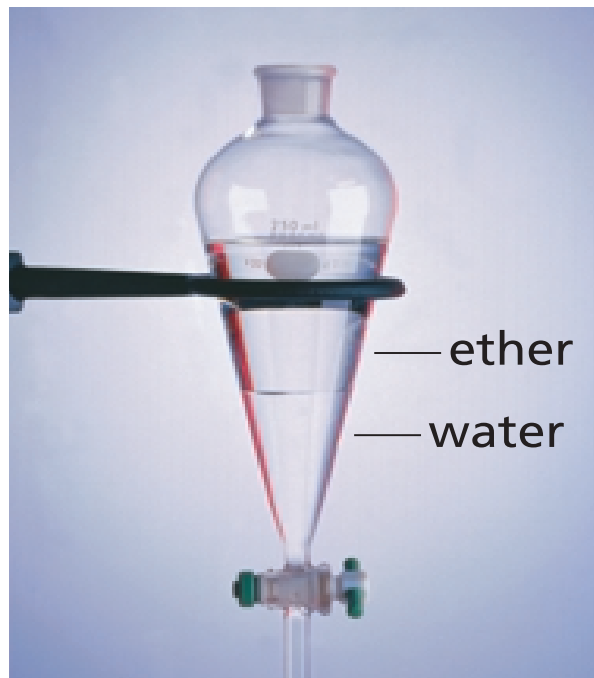


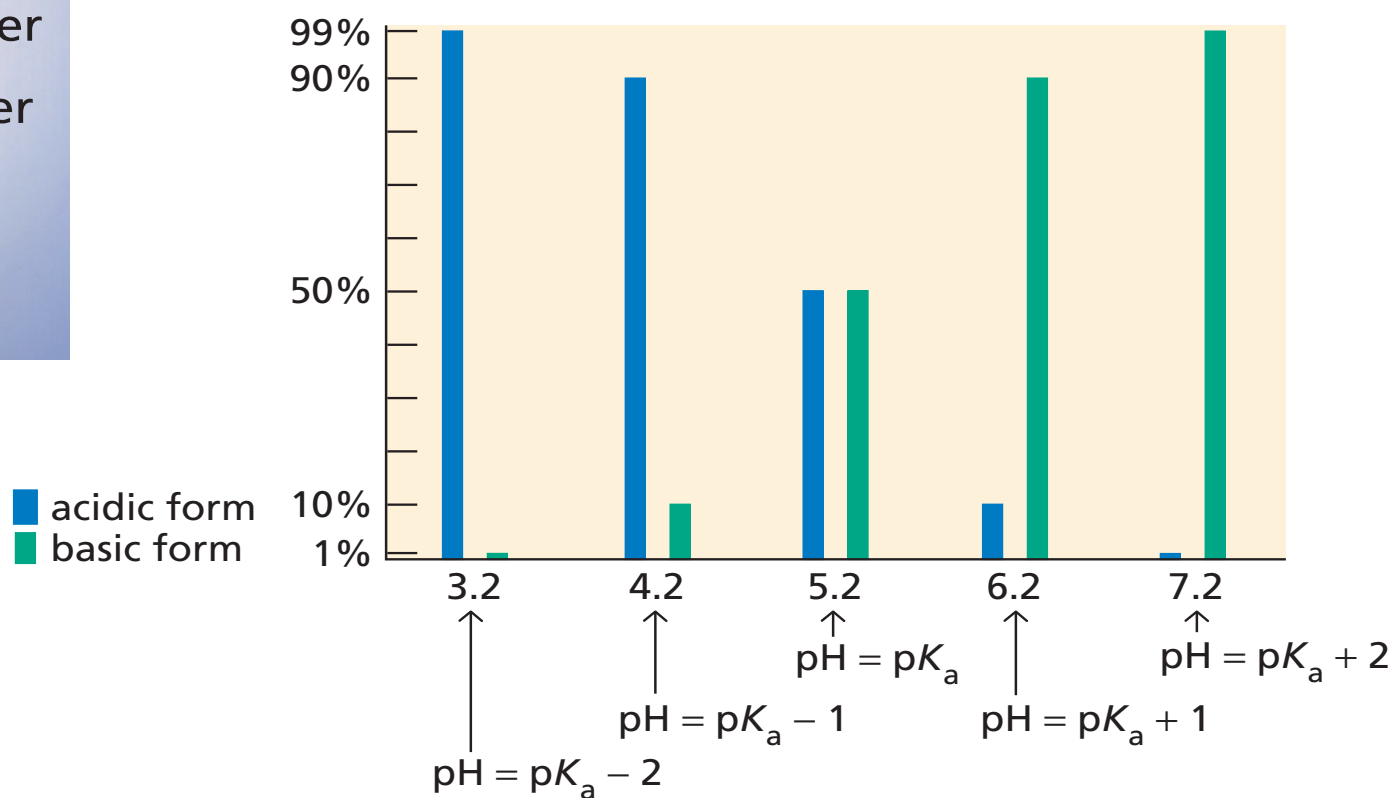
Figure 1.9
Titration curve of acetic acid.

pK_a and Solubility



acidic form

basic form



■ acidic form
■ basic form