

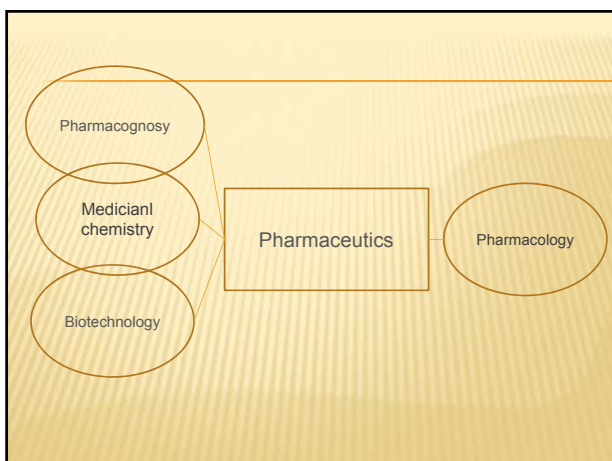
MEDICINAL CHEMISTRY I

Dr Sakhteman

MEDICINAL CHEMISTRY

× **Medicinal chemistry** and **pharmaceutical chemistry** are disciplines at the intersection of **chemistry**, especially synthetic organic chemistry, and **pharmacology** and various other biological specialties, where it is involved with **design**, **chemical synthesis** and development for market of **pharmaceutical agents (drugs)**.

(From Wikipeda)



x Medicinal chemistry : Relationship Between Molecular Structure and Biologic Activity
 x Crum Brown Fraser (1869)

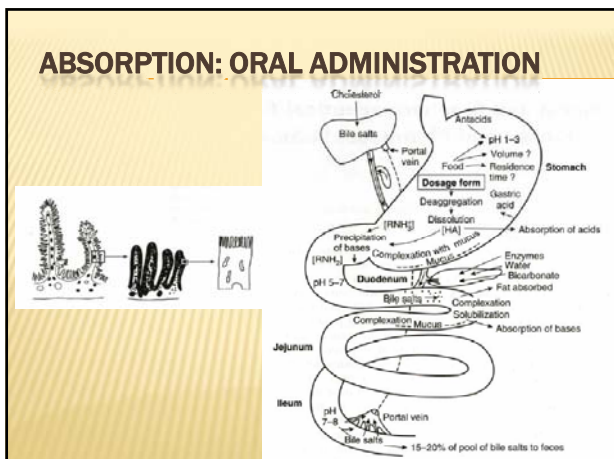
Morphine (analgesic) → N-Methylmorphine (muscle relaxant)
 Nicotine (insecticide) → N-Methylnicotine (muscle relaxant)
 Atropine (mydriatic) → N-Methylatropine (muscle relaxant)

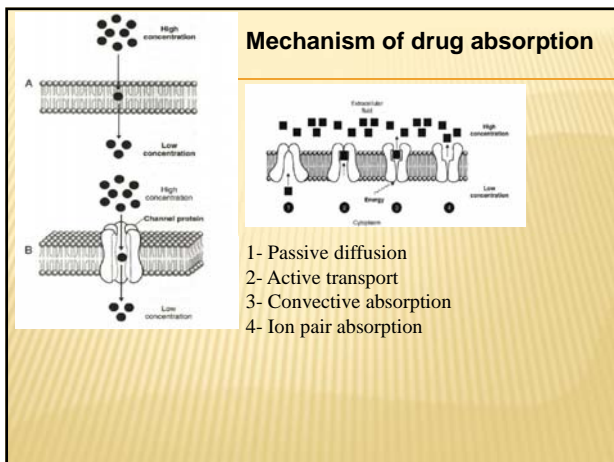
$D + R \rightleftharpoons D-R$: Pharmacodynamic

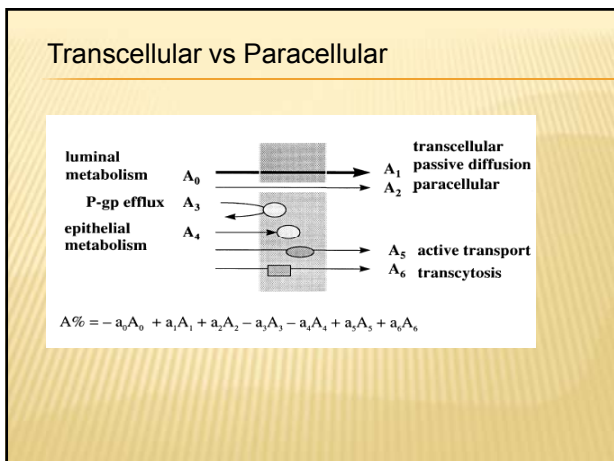
: Pharmacokinetic

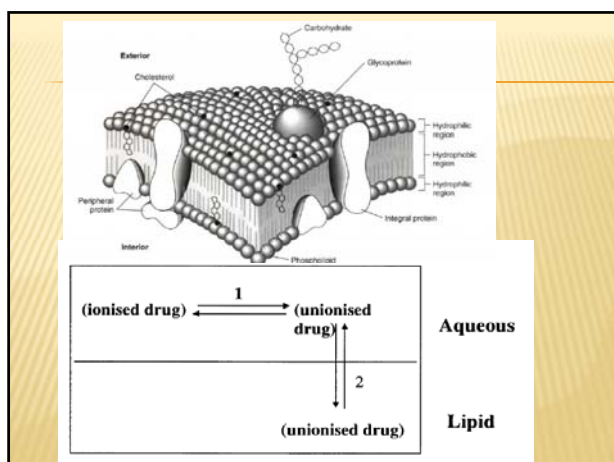
PHYSICO-CHEMICAL PROPERTIES

- x **physicochemical properties:** influence of the organic functional groups on acid/base properties, water solubility, partition coefficient, crystal structure, stereochemistry
- x All of these properties influence the absorption, distribution, metabolism and excretion (ADME) of the molecule









ACID/BASE PROPERTIES


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

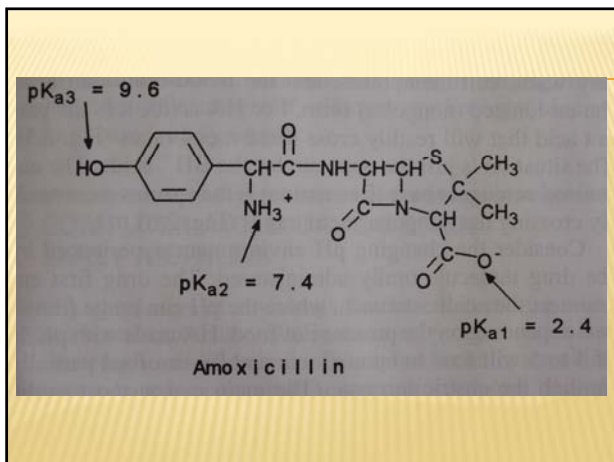
Acid	pKa	Chemical Structure	Chemical Structure	Conjugate Base
Phenol	9-11	<chem>c1ccc(O)cc1</chem>	<chem>c1ccc([O-])cc1</chem>	Phenoxide
Sulfonamide	9-10	<chem>NC(=O)S(=O)(=O)R</chem>	<chem>[O-]C(=O)S(=O)(=O)R</chem>	Sulfonamide
Imide	9-10	<chem>OC(=O)N(C)C(=O)R</chem>	<chem>[O-]C(=O)N(C)C(=O)R</chem>	Imide
Alkaloid	10-11	<chem>R-NH2</chem>	<chem>R-NH3+</chem>	Tritone
Thiourea	9-10	<chem>NC(=S)N</chem>	<chem>[O-]C(=S)N</chem>	Thiothiourea
N-alkylmorpholine	8-7	<chem>CN1CCOCC1</chem>	<chem>C[NH+]1CCOCC1</chem>	N-alkylmorpholinium
Sulfonamide	9-8	<chem>NC(=O)S(=O)(=O)R</chem>	<chem>[O-]C(=O)S(=O)(=O)R</chem>	Sulfonamide
Alkylcarboxylic acid	3-4	<chem>RCOOH</chem>	<chem>RCOO-</chem>	Alkylcarboxylate
Aromatic carboxylic acid	4-6	<chem>c1ccc(C(=O)O)cc1</chem>	<chem>c1ccc(C(=O)[O-])cc1</chem>	Aromatic carboxylate
Sulfonic acid	0-1	<chem>RSO3H</chem>	<chem>RSO3-</chem>	Sulfonate

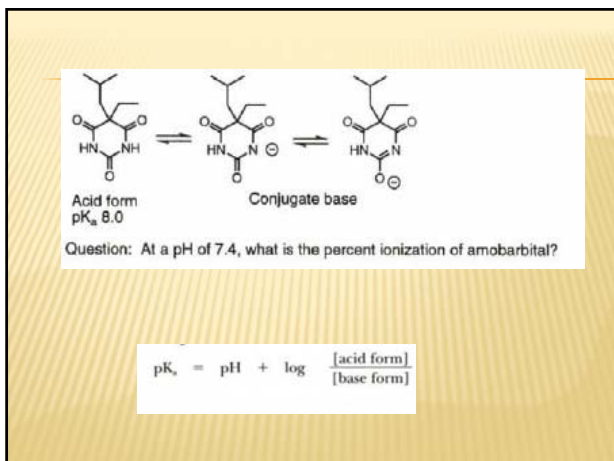
Table 2.2. Common Basic Organic Functional Groups and Their Ionized (Conjugate Acid) Forms

Base	pKa	Chemical Structure	Chemical Structure	Conjugate Acid
Arylamines	4-5	<chem>R-NH2</chem>	<chem>R-NH3+</chem>	Arylammonium
Aromatic amine	5-6	<chem>R-N</chem>	<chem>R-NH3+</chem>	Aromatic ammonium
Imine	3-4	<chem>R-C=NH</chem>	<chem>R-C=[NH2+]</chem>	Iminium
Alkylamines	10-11	<chem>R-NH2</chem>	<chem>R-NH3+</chem>	Alkylammonium
Amidine	10-11	<chem>R-C(=NH)NH2</chem>	<chem>R-C(=[NH2+])NH2</chem>	Amidinium
Guandine	10-11	<chem>R-C(=NH)NH2</chem>	<chem>R-C(=[NH2+])NH2</chem>	Guandinium

Table 2.3. Common Organic Functional Groups That Are Considered Neutral Under Physiologic Conditions

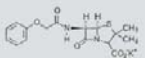
$R-CH_2-OH$ Alkyl alcohol	$R-O-R$ Ether	$R-C(=O)-O-R$ Ester	$R-SO_2-O-R$ Sulfonic acid ester
$R-C(=O)-NH_2$ Amide	 Diarylamine	$R-C\equiv N$ Nitrile	$R-N^+(R')_3$ Quaternary ammonium
$R-N(R')_2$ Amine oxide	$R-C(=O)-R$ Ketone & Aldehyde	$R-S-R$ Thioether	$R-S(=O)-R$ Sulfoxide $R-S(=O)_2-R$ Sulfone



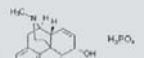


Acid Base Chemistry/Compatibility Cases

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 isn't sure how water-soluble either of the agents are.



Penicillin V Potassium



Codeine Phosphate

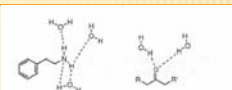
PH AT THE ABSORPTION SITE

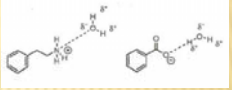
Table 72. Comparison of Intestinal Absorption of Acids and Bases in the Rat at Several pH Values (13)

	pK _a	Percent Absorbed from Rat Intestine			
		pH 4	pH 5	pH 7	pH 8
Acids					
5-Nitrosalicylic acid	2.3	40	27	0	0
Salicylic acid	3.0	64	35	30	10
Acetylsalicylic acid	3.5	41	27	—	—
Benzoic acid	4.2	62	36	35	5
Bases					
Aniline	4.6	40	48	58	61
Amiopyrine	5.0	21	35	48	52
p-Toluidine	5.3	30	42	65	64
Quinine	8.4	9	11	41	54

WATER SOLUBILITY

- ✦ Hydrogen bonds
- ✦ Ionization





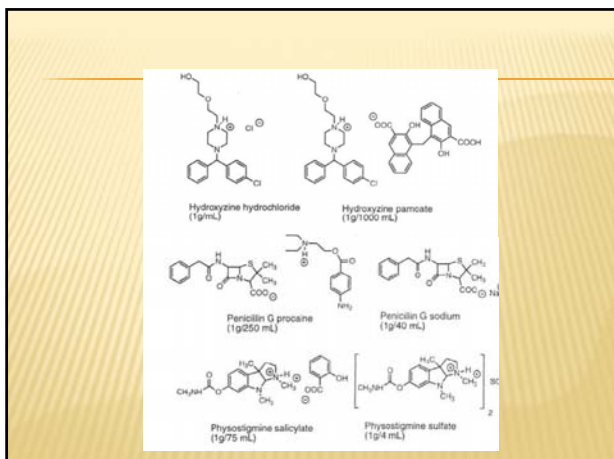
Dissolution

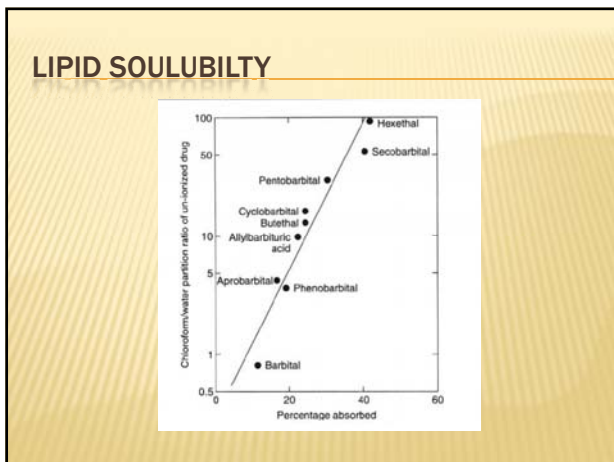
Dosage forms

Drug in solution

Absorption

Drug in general cyclization





PARTITION COEFFICIENT

$$P = \frac{[\text{drug}]_{\text{organic}}}{[\text{drug}]_{\text{aqueous}}}$$

1-octanol: common organic phase

$$D = \frac{[\text{HA}]_{\text{organic}}}{([\text{HA}]_{\text{aqueous}} + [\text{A}^-]_{\text{aqueous}})}$$

$$K_a = \frac{[\text{H}^+][\text{A}^-]}{[\text{HA}]} \longrightarrow \log D = \log P - \log(1 + 10^{\text{pH} - \text{p}K_a})$$

Limitations in the Use of 1-Octanol

- Octanol, contains 4% v/v water at equilibrium.
- Hydrogen bonding due to hydroxyl group

$$-\Delta \log P = \log P_{(\text{octanol})} - \log P_{(\text{cyclohexane})}$$

Octanol/Cyclohexane Ratio (H-bonding) →		
Alkyl Phenyl Halogen	Amine Ester Ether Ketone Nitrile Nitro	Sec Amide Amide Pri Amine Carboxylate Hydroxyl Sulphonamide Sulphone Sulphoxide

TRANSPORTATION RATE OF BASIC DRUGS ACROSS CACO-2 MONOLAYERS

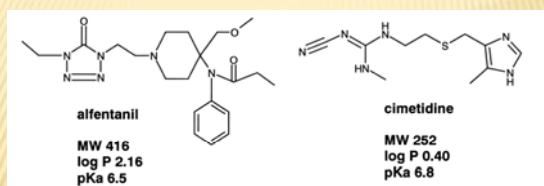
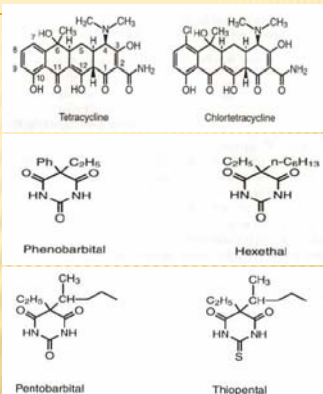


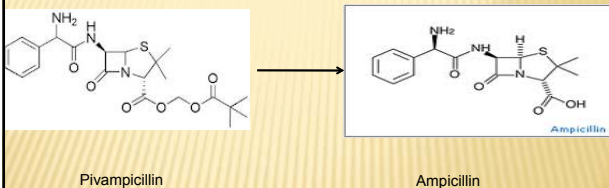
Table 73. Comparison of Barbiturate Absorption in Rat Colon and Partition Coefficient (Chloroform/Water) of Undissociated Drug

Barbiturate	Partition Coefficient	Percent Absorbed
Barbital	0.7	12
Apobarbital	4.9	17
Phenobarbital	4.8	20
Allylbarbital	10.5	23
Butethal	11.7	24
Cyclobarbital	13.9	24
Pentobarbital	28.0	30
Secobarbital	50.7	40
Hexethal	>100	44

Modification to improve absorption

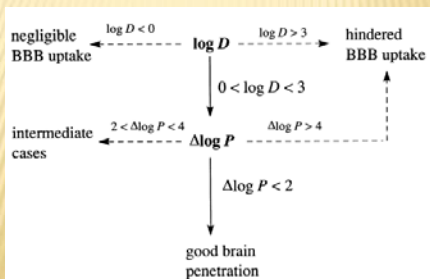


PRODRUGS: TO IMPROVE ABSORPTION

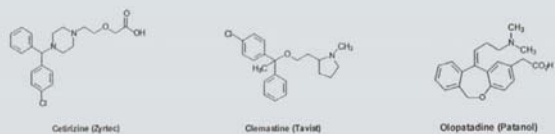


PERMEABILITY TO BBB

Decision tree for the design of non-sedative H1antihistaminics. Log *D* is measured at pH 7.4



Penetration to BBB



Antiepileptic agents

IC_{50} <i>in vivo</i>	0.11 mM active	0.1 mM inactive
p <i>K_a</i>	3.57/9.23	3.39/9.25
log <i>D_{oct}</i>	0.99	0.71
log <i>D_{mem}</i>	-0.43	-2.00
Δ log <i>D</i>	1.42	2.71

COMPUTAION OF LOGP

$LogP = \sum \pi$ (fragments)

EXPERIMENTAL CALCULATION OF LOGP

- Liquid-liquid partitioning
- RP-HPLC

PARAMETERS AFFECTING LOGP OR LOGD

$$\log P \text{ or } \log D = a \cdot V - \Lambda$$

- ✗ *V* : molar volume of the compound
- ✗ *Λ*: general polarity descriptor
- ✗ *a*: regression coefficient

BALANCE FOR HYDROPHILICITY LIPOPHILICITY

Lipinski rule of five:

- ✗ $M_w < 500$
- ✗ $\text{Log } P < 5$
- ✗ HB donors < 5
- ✗ HB acceptors < 10

End of session I : Any questions?
