PHYSICOCHEMICAL PROPERTIES OF DRUG ACTION

III Year B.Pharm I Sem

Subject: Medicinal Chemistry-I

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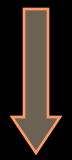
PHYSICOCHEMICAL PRINCIPLES OF DRUG ACTION

INTRODUCTION

Drug molecules interact with biological structures



drug effect

lipoproteins/enzymes

membranes

nucleic acids

DRUG EFFECT

Drug effect is preceded by drug transport

from site of application to site of action

and is dependent on

physicochemical properties

PHYSICOCHEMICAL PROPERTIES

Interatomic distances

Intermolecular forces

Stereochemistry

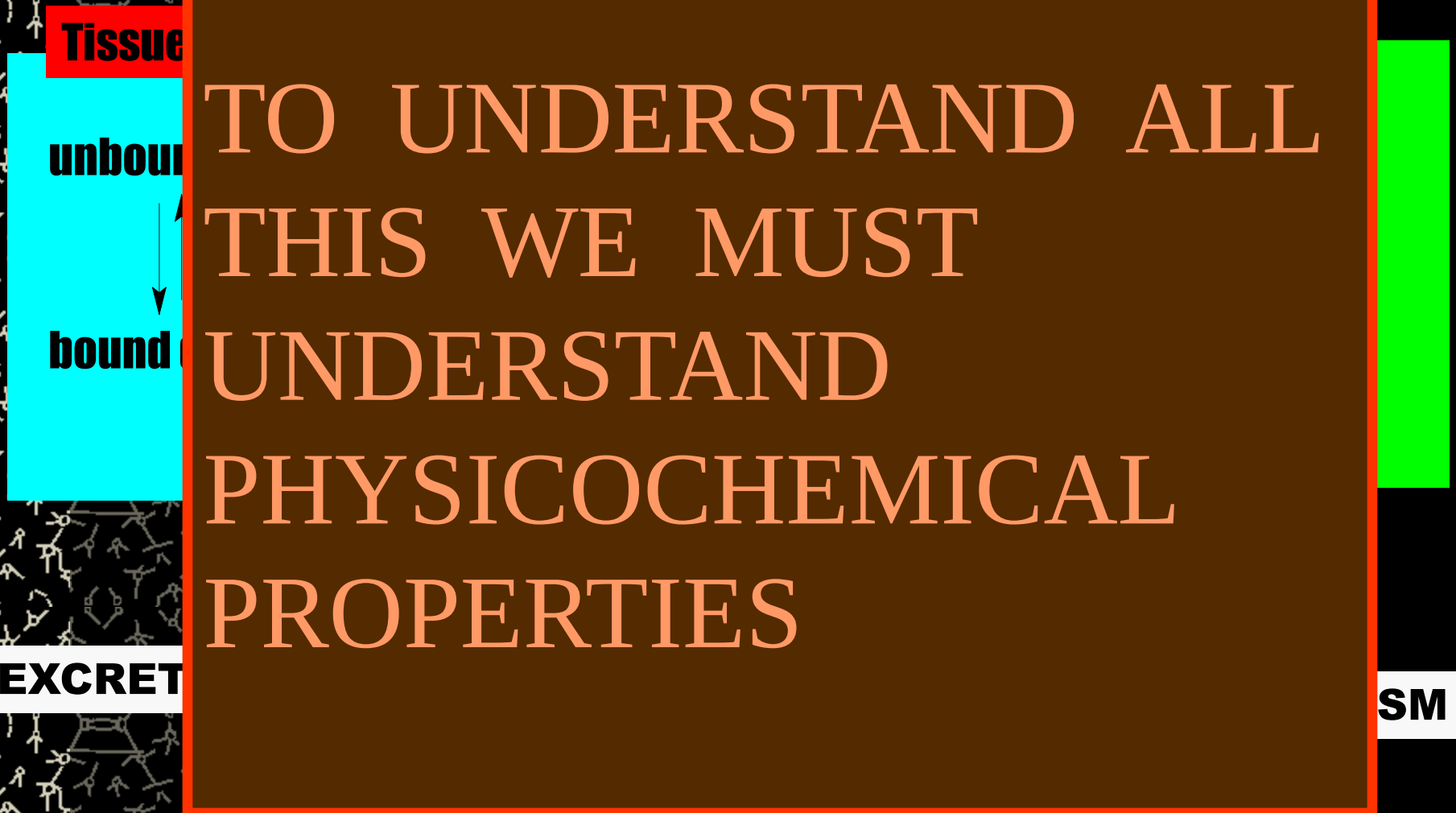
Partition coefficient

Solubility

Ionization

All affect pharmacokinetics

PHARMACOKINETICS



TO UNDERSTAND ALL THIS WE MUST UNDERSTAND PHYSICOCHEMICAL PROPERTIES

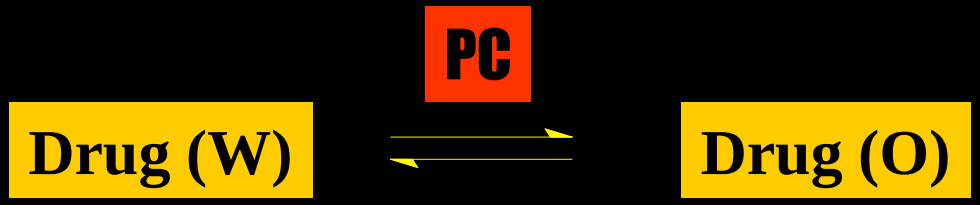
PHYSICOCHEMICAL PROPERTIES

- ✓ Interatomic distances
- ✓ Intermolecular forces
- ✓ Stereochemistry
- Partition coefficient
- Solubility
- Ionization

PARTITION COEFFICIENT

Hydrophobic bonding interactions are critical

Can be approximated by partition coefficient



$$PC = \frac{[drug]_O}{[drug]_W}$$

Thus, PC describes the entire drug.

PARTITION COEFFICIENT

Useful to know the hydrophobic bonding properties of substituent groups.

Hydrophobic bonding constant π for a substituent is obtained as a difference In log P.

$$\pi = \log P_X - \log P_H$$

P_X = PC for substituted compound

P_H = PC for parent compound

Thus, π describes the substituent.

REPRESENTATIVE π VALUES

Substituent	Aromatic	Aliphatic
C_6H_{11}	2.51	2.51
n-C_4H_9	2.00	2.00
Cl	0.76	0.39
H	0.00	0.00
NO_2	-0.28	-0.82
COOH	-0.28	-1.26
OH	-0.67	-1.16

SOLUBILITY

Drugs must be in solution to interact with receptors.

Drugs have some degree of solubility in both aqueous and lipid compartments (PC).

Solubility is a function of:

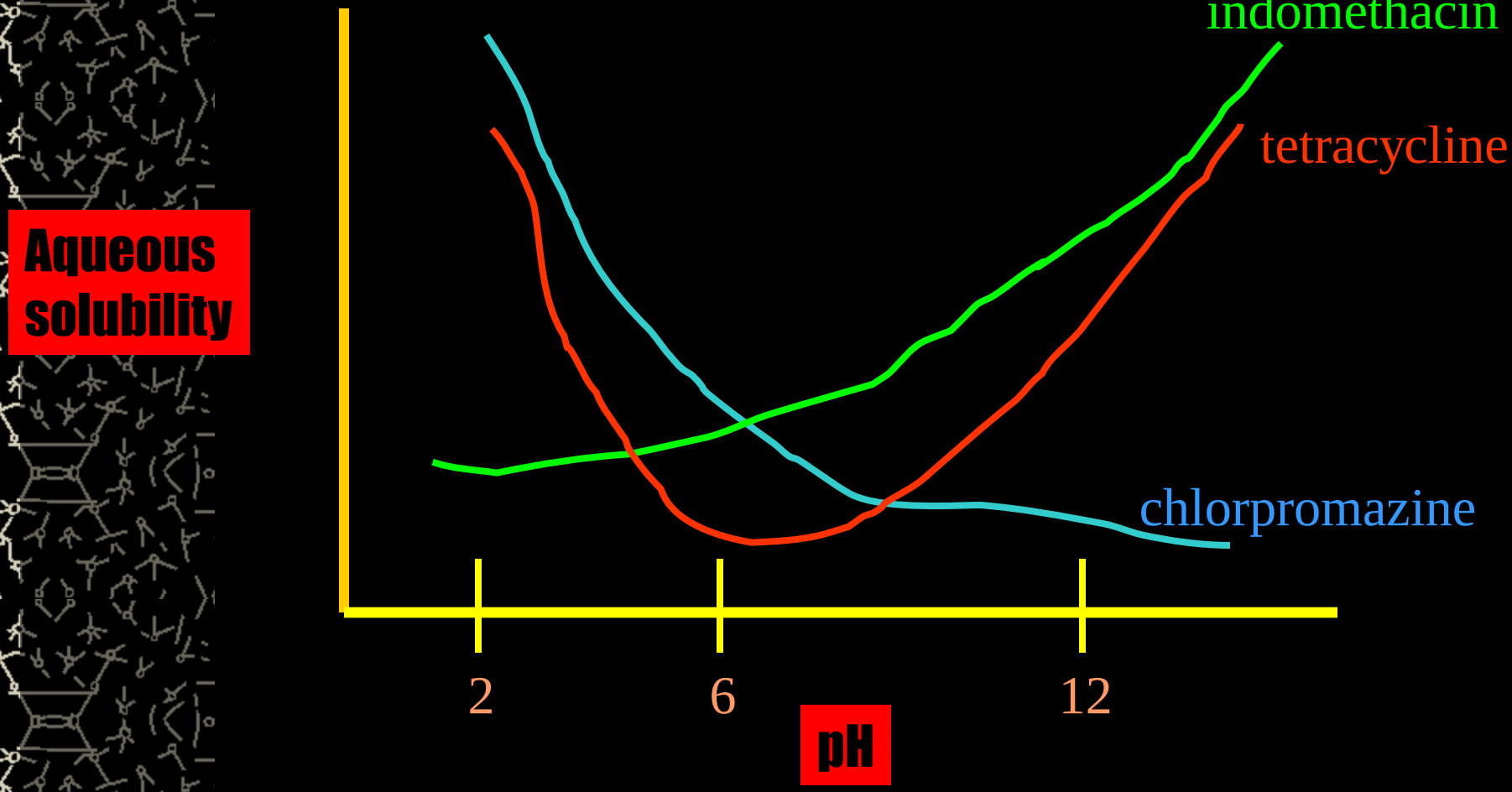
- ionization
- molecular structure
- molecular weight
- stereochemistry
- electronic structure

SOLUBILITY of WEAK ELECTROLYTES

Solubility will be affected by pH.

Acidic drugs	barbiturates, NSAIDs
Basic drugs	phenothiazines, β -blockers
Amphoterics	tetracyclines, ACEIs

SOLUBILITY of WEAK ELECTROLYTES



PREDICTING WATER SOLUBILITY

Empiric method

Analytic method

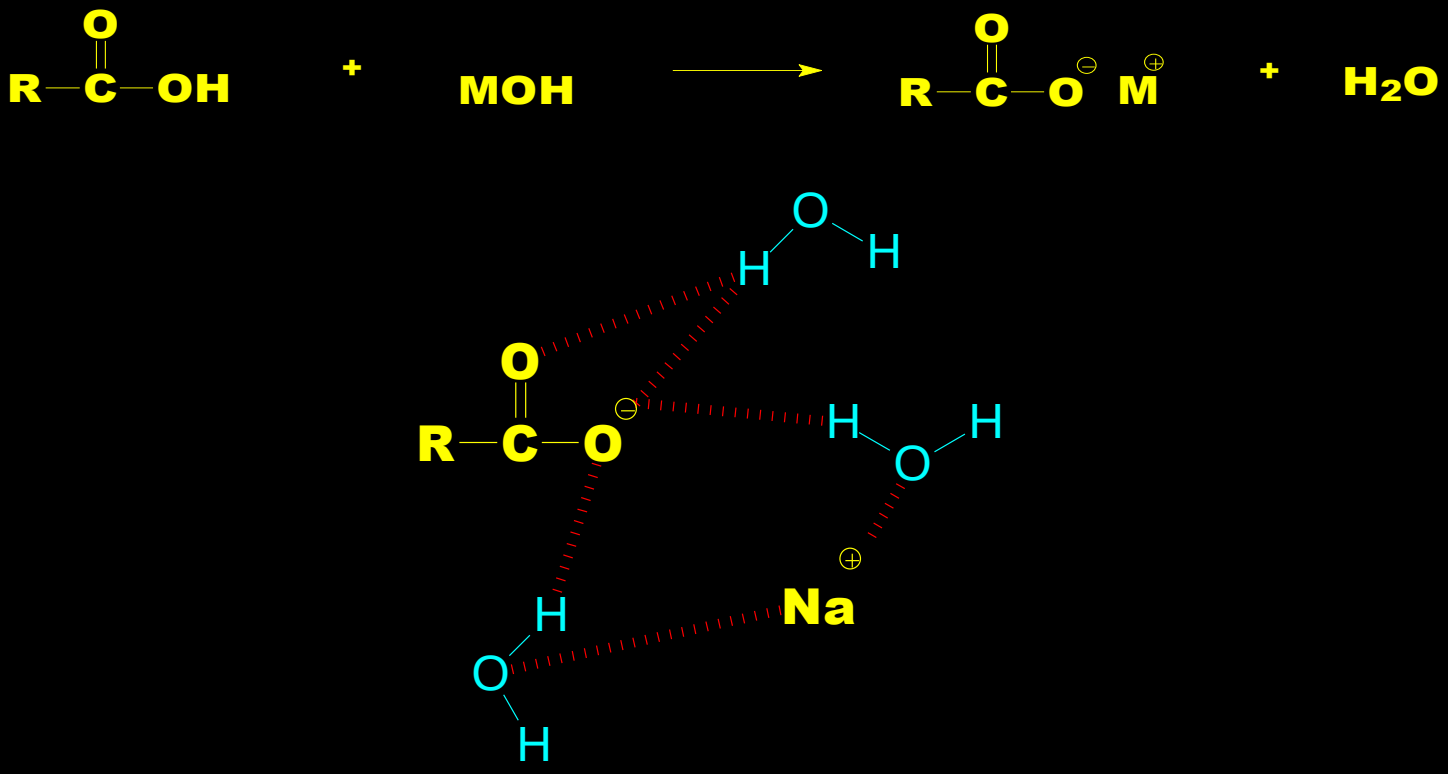
Solubility in water

ionic compounds, i.e. salts of WA, WB

polar compounds, i.e. those that H-bond

EMPIRIC METHOD

Solubility Properties of Na Salts of Common Organic Acids



EMPIRIC METHOD

Solubility Properties of Na Salts of Common Organic Acids

$RCOO^-Na^+$	Solubility (g/100g H2O)
C_6H_5	55.5
CH_3	125.0
CH_3CH_2	100.0
$CH_3(CH_2)_{16}$	10.0

H_2O solubility can be increased by salt formation

EMPIRIC METHOD

Solubility Properties of Common Organic Acids

RCOOH	Solubility (g/100g H2O)
$CH_3(CH_2)_2$	∞
$CH_3(CH_2)_4$	1.0
$CH_3(CH_2)_8$	0.015
$CH_3(CH_2)_{16}$	insoluble

COOH brings into solution 5 – 6 C's to extent of 1%

EMPIRIC METHOD

Solubility Properties of Common Alcohols

ROH	Solubility (g/100g H2O)
2-propanol	∞
1-butanol	7.9
2-butanol	12.5
1-pentanol	2.3

ROH brings into solution 5 – 6 C's to extent of 1%

EMPIRIC METHOD

Solubility Properties of Common Amines

$NR_1R_2R_3$			Solubility (g/100g H2O)
R1	R2	R3	
Me	H	H	very soluble
Me	Me	Me	91
Et	H	H	very soluble
Et	Et	Et	14
Ph	H	H	3.7
Ph	Me	Me	1.4

N brings into solution 6 – 7 C's to extent of 1%

EMPIRIC METHOD

Solubility Properties of Common Phenols

ArOH	Solubility (g/100g H2O)
cyclohexanol	3.6
phenol	9.3
p-cresol	2.3
m-chlorophenol	2.6
catechol	45.0

ArOH brings into solution 6 – 7 C's to extent of 1%

BASIS OF EMPIRIC METHOD

For monofunctional compounds a single functional group (capable of H-bonding) will bring into solution 5–7 carbons to the extent of 1%.

but

Drugs are usually not simply monofunctional.

Simple summation of "water-solubilizing" potential may not give accurate predictions.

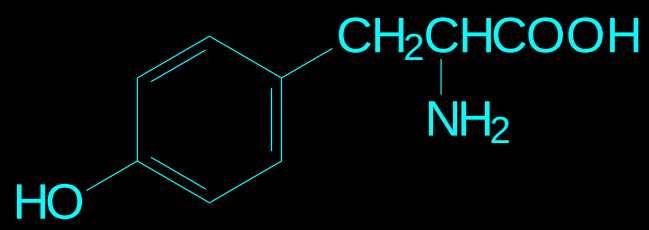
EMPIRIC METHOD

Water Solubilizing Potential of Functional Groups

Group	Mono	Poly
ROH	5-6 C	3-4 C
ArOH	6-7	3-4
ROR	4-5	2
RCHO	4-5	2
R_2CO	5-6	2
$N(R)_3$	6-7	3
RCOOH	5-6	3
RCOOR	6	3
RRNCOR	6	2-3
Urea, carbamate, etc		2

solubility defined as ≥ 1%

EMPIRIC METHOD



tyrosine

COOH	5 – 6 C
OH	6 – 7 C
NH_2	6 – 7 C

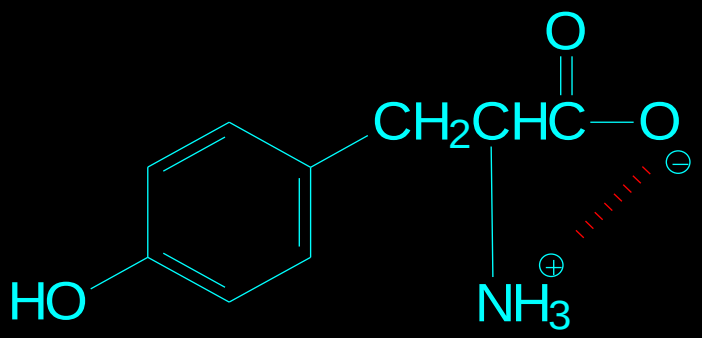
Prediction: 17 – 20 C should be brought into solution.

Only 9 C present, so should be >1% soluble.

Experimental Results: 0.045% solubility

WHY?

EMPIRIC METHOD



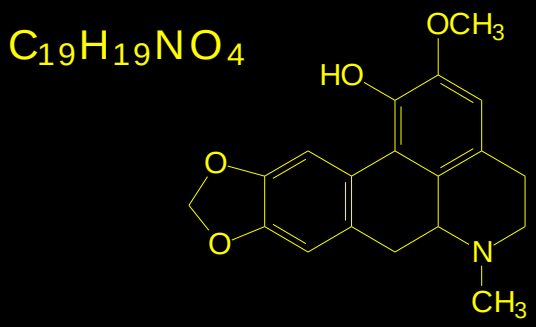
intramolecular ionic bonding reduces solubility

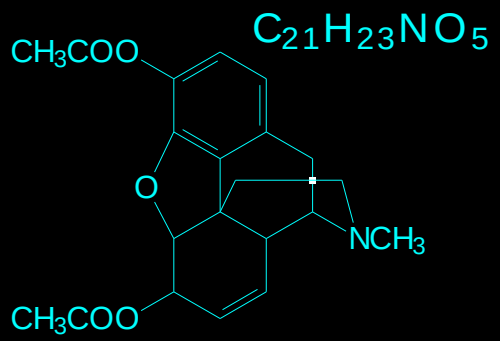
pH adjustment increases solubility

Polyfunctional data compensates for intra- and inter-molecular bonding.

Group	Mono	Poly
ROH	5-6 C	3-4 C
ArOH	6-7	3-4

EMPIRIC METHOD





Mono

$5 + 5 + 5 + 7 + 7 = 29$

soluble

$6 + 6 + 5 + 7 = 24$

soluble

Poly

$2 + 2 + 2 + 3 + 4 = 13$

insoluble

$3 + 3 + 2 + 3 = 11$

insoluble

ANALYTIC METHOD

$$\log P = \frac{[\text{drug}]_{\text{octanol}}}{[\text{drug}]_{\text{water}}}$$

log P is a measure of the solubility of the **whole** drug

π is the log P of the fragment

$$\log P_{\text{calc}} = \Sigma \pi_{\text{fragments}}$$

solubility defined as >3.3%

if calc. logP is **> +0.5** then compound is H_2O insoluble

if calc. logP is **< +0.5** then compound is H_2O soluble

ANALYTIC METHOD

π Values for Organic Fragments

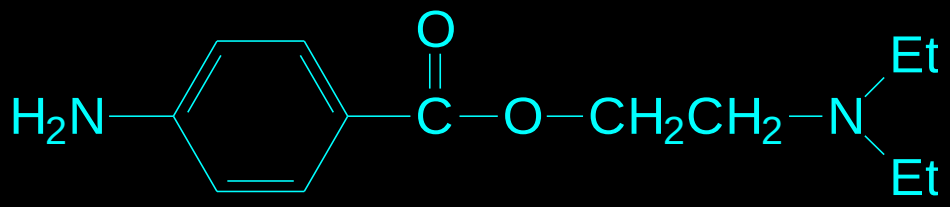
Fragment	π Value
C (aliphatic)	+0.5
phenyl	+2.0
Cl	+0.5
O_2NO (nitrate)	+0.2
IMHB	+ 0.65
S	0.0
OCO, OCN	-0.7
O, N	-1.0
O_2N (aliphatic)	-0.85
O_2N (aromatic)	-0.28

solubility defined as >3.3%

ANALYTIC METHOD

1. table is only a brief compilation
2. π values are approximations
3. π values depend on whether fragment aromatic or aliphatic
4. π values are obtained under nonionizing conditions
5. intramolecular H-bonding must be considered
6. values for heterocycles can be estimated

ANALYTIC METHOD



procaine

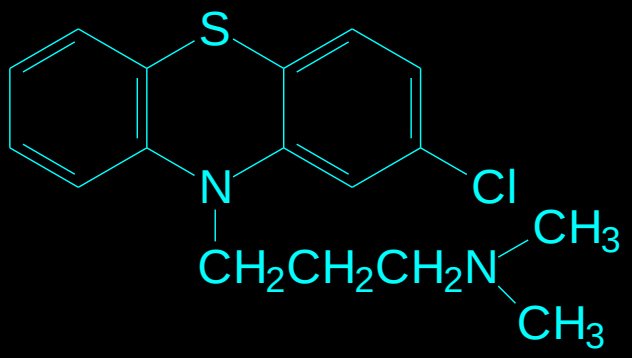
6 C @ +0.5	+3.0
phenyl	+2.0
2 N @ -1.0	-2.0
O=C-O	-0.7

+2.3

solubility defined as >3.3%

insoluble

ANALYTIC METHOD



chlorpromazine

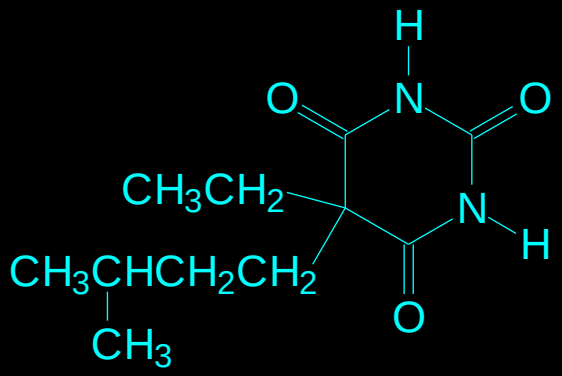
solubility defined as >3.3%

5C @ +0.5	+2.5
2 Ph @ +2	+4.0
Cl	+0.5
2 N @ -1	-2.0
S	0.0

Calc. +5.0

Exp. +5.3

ANALYTIC METHOD



amobarbital

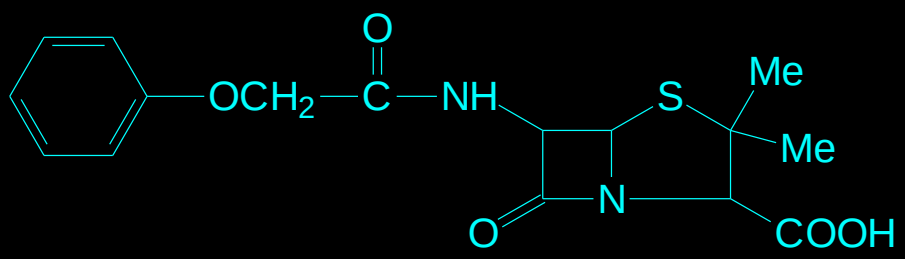
9C @ +0.5	+4.5
1 O @ -1	-1.0
2 OCN @ -0.7	-1.4

solubility defined as >3.3%

Exp. +2.1

Calc. +2.1

ANALYTIC METHOD



penicillin V

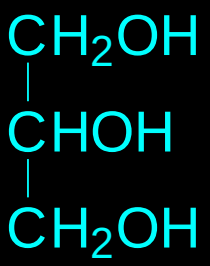
7C @ +0.5	+3.5
1 O @ -1	-1.0
3 OCN, OCO @ -0.7	-2.1
1 Ph @ +2	+2.0
S	0.0

Calc. +2.4

Exp. +2.1

solubility defined as >3.3%

ANALYTIC METHOD



glycerol

3C @ +0.5	+1.5
3 O @ -1	-3.0

solubility defined as >3.3%

Calc. -1.5

Exp. –1.7