



Metodologie di Sintesi e Sviluppo Farmaceutico

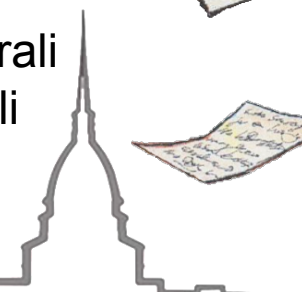
Synthesis and Development Pharmaceutical Methodologies

Laurea Magistrale in Chimica a.a. 2018/2019



MP, BP and Solubility, (*Druggability*)

- Capacità di giudicare una sostanza in termini di polarità/lipofilia
- Capacità di correlare lo stato fisico con la presenza di elementi strutturali
- Capacità di correlare la solubilità con la presenza di elementi strutturali
- Applicazione in Chimica Farmaceutica: concetto di *druggability*

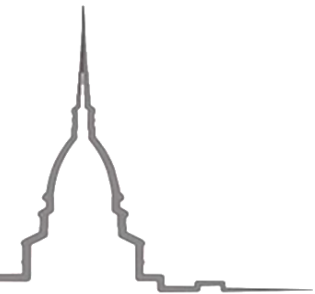


The chemio-physical constant

“A numeric value associated to a *measurable* property that became constant if the experimental conditions are determined and maintained.”

Associated to determine:

- Identity
- Purity



The chemio-physical constant

Some examples:

Melting point (mp),

Boiling point (bp)

Solubility

$\log P$,

pK_a ,

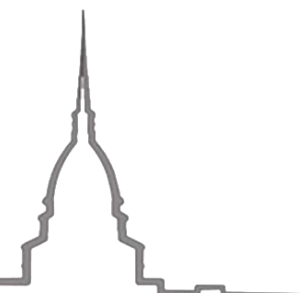
Density

Viscosity

Chromatografic retention time (Rf)

IR Vibration frequency,

NMR *chemical shift*,



The chemio-physical constant

Some examples:

Melting point (mp),

Boiling point (bp)

Solubility

logP,

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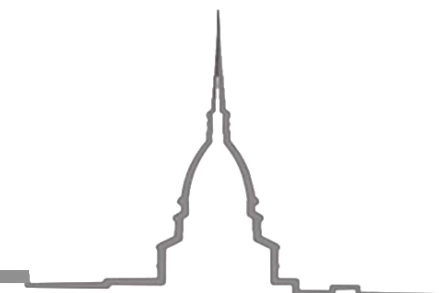
Density

Viscosity

Chromatografic retention time (Rf)

IR Vibration frequency,

NMR *chemical shift*,



Aggregation states

Matter can exist in three aggregate states, i.e., **solid**, **liquid** and **gas**. The passages from one state to another (by adding or removing heat) are known as **phase changes**.

S < --- > L

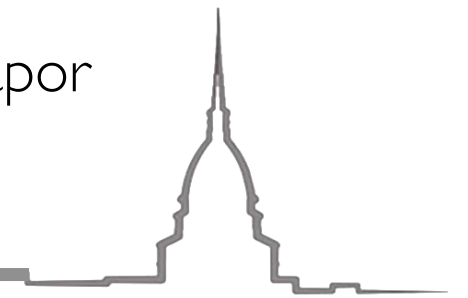
The transformation from the solid state to the liquid state is said **fusion** or melting, the inverse is said **solidification**.

L < --- > G

The transformation from the liquid state to the vapor state is said **vaporization**, the inverse is said **condensation**.

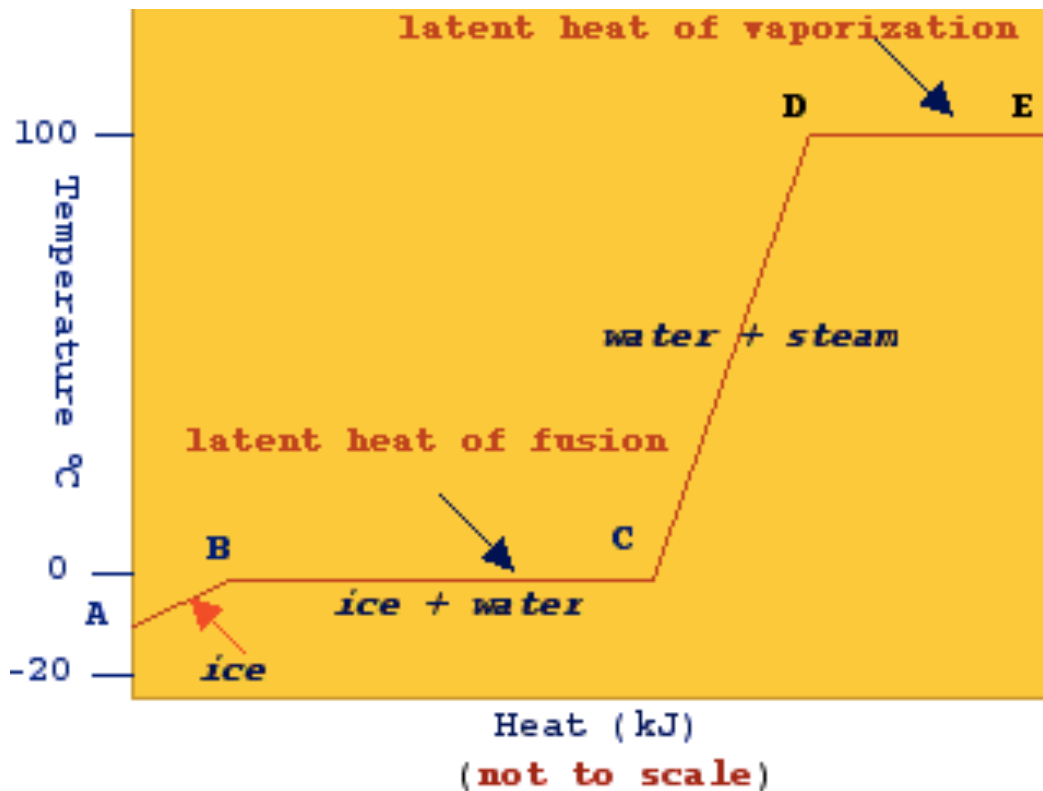
S < --- > G

The passage from the solid state directly to the vapor state (i.e., without passing from the liquid state) is said **sublimation**



The melting point

Fusion is the passage from the solid state to the liquid state and it requires heat (energy) to take place.



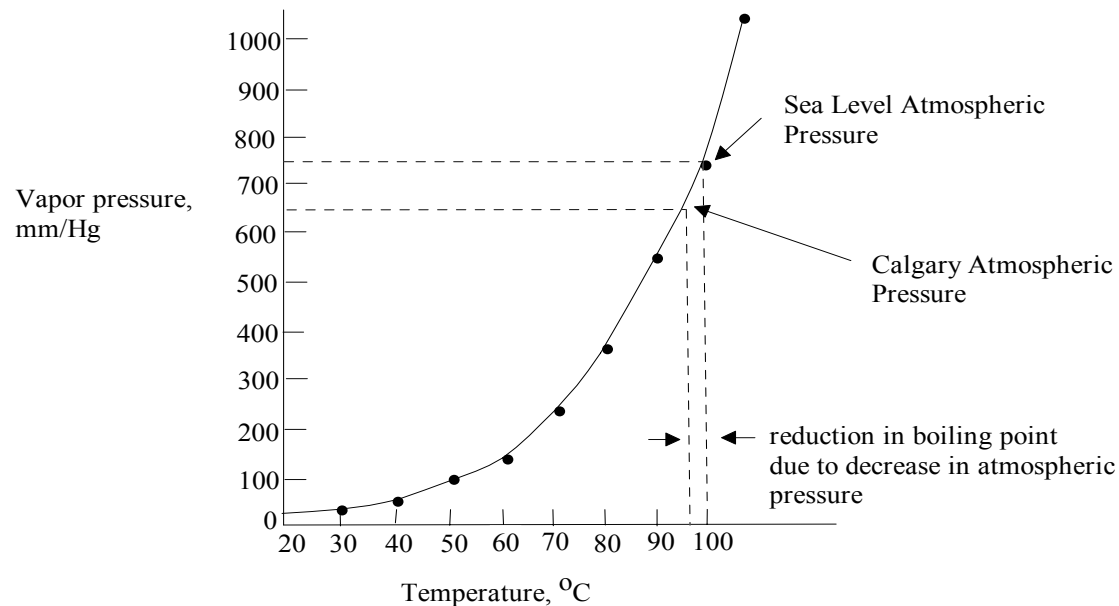
Def 1) The melting point is the temperature where both phases (S and L) are present

Def 2) The melting point is the temperature where both phases (S and L) own the same **vapour pressure**.

The **melting point** is a chemio-pysical constant that depend from the pressure

The boiling point

Vaporization is the passage from the liquid state to the vapour state and it requires heat (energy) to take place.



Vapour Pressure - Temperature Curve for Water

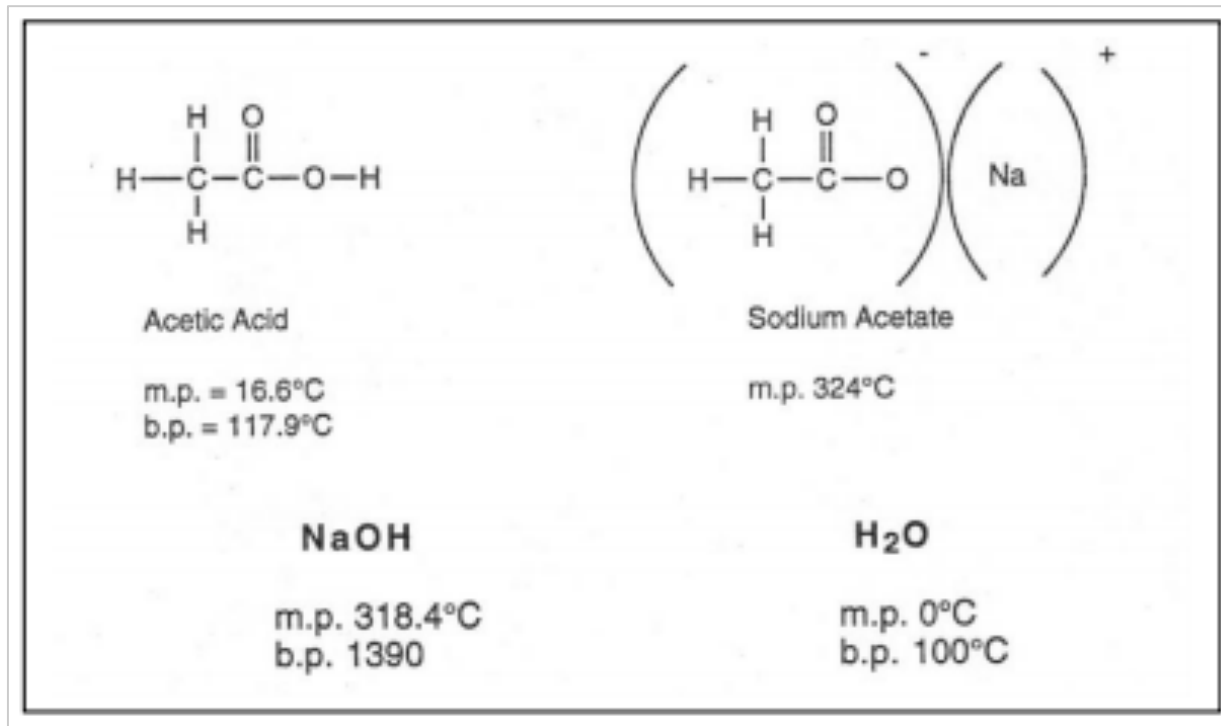
Def 1) The boiling point is the temperature where both phases (L and V) are present

Def 2) The boiling point is the temperature where both phases (L and V) own the same **vapour pressure**.

The **boiling point** is a chemio-pysical constant that **strictly** depend from the pressure

Melting/Boiling point and structural features

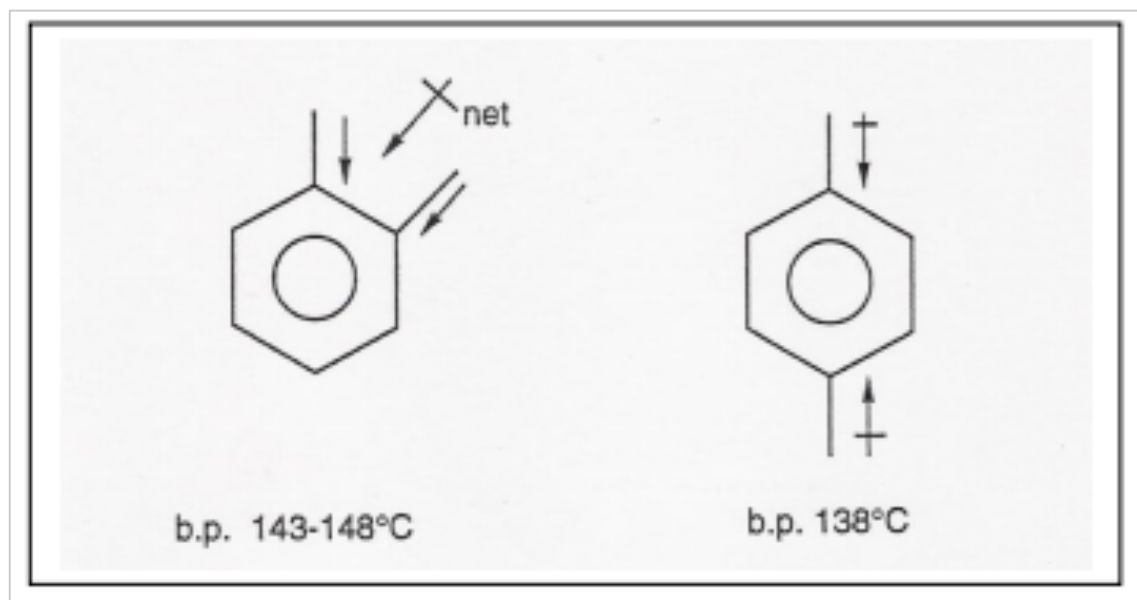
- Mp/bp values will be effected by which weak **Intermolecular interaction forces** (Ionic, HC, VdW) are involved.



- Columbian forces

Melting/Boiling point and structural features

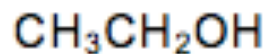
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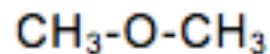
- Dipole-dipole

Melting/Boiling point and structural features

- Mp/bp values will be effected by which weak **Intermolecular interaction forces** (Ionic, HC, VdW) are involved.

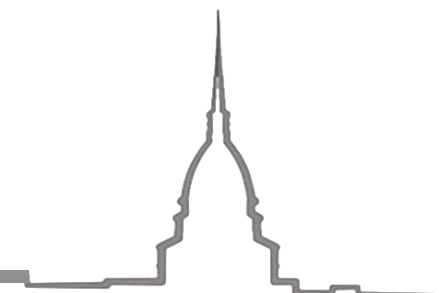


b.p. 78.3°C
ethanol



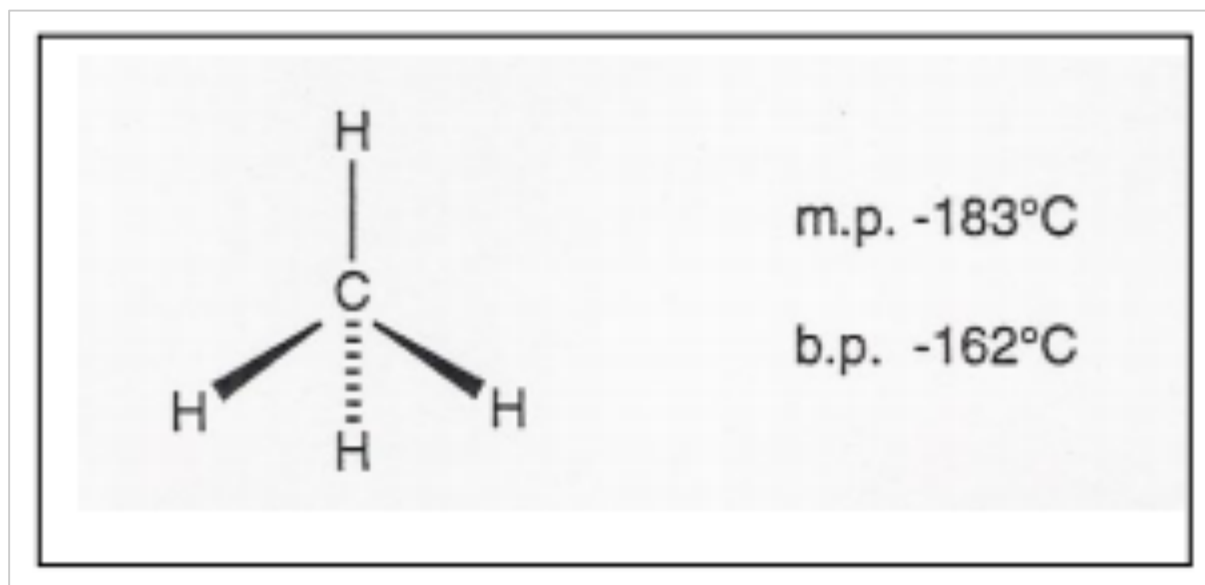
b.p. -25°C
dimethyl ether

- Hydrogen bonding



Melting/Boiling point and structural features

- Mp/bp values will be effected by which weak **Intermolecular interaction forces** (Ionic, HC, VdW) are involved.



- Van der Waals

Melting/Boiling point and structural features

Table 2.1 Nomenclature and Physical Properties of Straight-Chain Alkanes

Number of carbons	Molecular formula	Name	Condensed structure	Boiling point (°C)	Melting point (°C)	Density ^a (g/mL)
1	CH ₄	methane	CH ₄	-167.7	-182.5	
2	C ₂ H ₆	ethane	CH ₃ CH ₃	-88.6	-183.3	
3	C ₃ H ₈	propane	CH ₃ CH ₂ CH ₃	-42.1	-187.7	
4	C ₄ H ₁₀	butane	CH ₃ CH ₂ CH ₂ CH ₃	-0.5	-138.3	
5	C ₅ H ₁₂	pentane	CH ₃ (CH ₂) ₃ CH ₃	36.1	-129.8	0.5572
6	C ₆ H ₁₄	hexane	CH ₃ (CH ₂) ₄ CH ₃	68.7	-95.3	0.6603
7	C ₇ H ₁₆	heptane	CH ₃ (CH ₂) ₅ CH ₃	98.4	-90.6	0.6837
8	C ₈ H ₁₈	octane	CH ₃ (CH ₂) ₆ CH ₃	127.7	-56.8	0.7026
9	C ₉ H ₂₀	nonane	CH ₃ (CH ₂) ₇ CH ₃	150.8	-53.5	0.7177
10	C ₁₀ H ₂₂	decane	CH ₃ (CH ₂) ₈ CH ₃	174.0	-29.7	0.7299
11	C ₁₁ H ₂₄	undecane	CH ₃ (CH ₂) ₉ CH ₃	195.8	-25.6	0.7402
12	C ₁₂ H ₂₆	dodecane	CH ₃ (CH ₂) ₁₀ CH ₃	216.3	-9.6	0.7487
13	C ₁₃ H ₂₈	tridecane	CH ₃ (CH ₂) ₁₁ CH ₃	235.4	-5.5	0.7546
⋮	⋮	⋮	⋮	⋮	⋮	⋮
20	C ₂₀ H ₄₂	eicosane	CH ₃ (CH ₂) ₁₈ CH ₃	343.0	36.8	0.7886
21	C ₂₁ H ₄₄	heneicosane	CH ₃ (CH ₂) ₁₉ CH ₃	356.5	40.5	0.7917
⋮	⋮	⋮	⋮	⋮	⋮	⋮
30	C ₃₀ H ₆₂	triacontane	CH ₃ (CH ₂) ₂₈ CH ₃	449.7	65.8	0.8097

^a Density is temperature dependent. The densities given are those determined at 20 °C (*d*^{20°}).

Melting/Boiling point and structural features

Table 2.5 Comparative Boiling Points (°C)

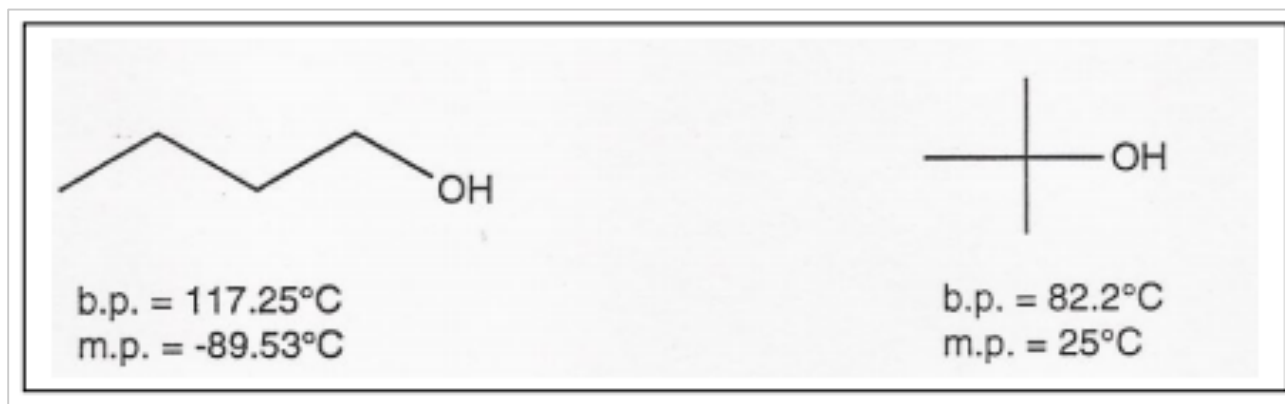
Alkanes	Ethers	Alcohols	Amines
CH ₃ CH ₂ CH ₃ -42.1	CH ₃ OCH ₃ -23.7	CH ₃ CH ₂ OH 78	CH ₃ CH ₂ NH ₂ 16.6
CH ₃ CH ₂ CH ₂ CH ₃ -0.5	CH ₃ OCH ₂ CH ₃ 10.8	CH ₃ CH ₂ CH ₂ OH 97.4	CH ₃ CH ₂ CH ₂ NH ₂ 47.8
CH ₃ CH ₂ CH ₂ CH ₂ CH ₃ 36.1	CH ₃ CH ₂ OCH ₂ CH ₃ 34.5	CH ₃ CH ₂ CH ₂ CH ₂ OH 117.3	CH ₃ CH ₂ CH ₂ CH ₂ NH ₂ 77.8

Table 2.6 Comparative Boiling Points of Alkanes and Alkyl Halides (°C)

	Y				
	H	F	Cl	Br	I
CH ₃ —Y	-161.7	-78.4	-24.2	3.6	42.4
CH ₃ CH ₂ —Y	-88.6	-37.7	12.3	38.4	72.3
CH ₃ CH ₂ CH ₂ —Y	-42.1	-2.5	46.6	71.0	102.5
CH ₃ CH ₂ CH ₂ CH ₂ —Y	-0.5	32.5	78.4	101.6	130.5
CH ₃ CH ₂ CH ₂ CH ₂ CH ₂ —Y	36.1	62.8	107.8	129.6	157.0

Melting/Boiling point and structural features

- Mp/bp values will be effected by which weak **Intermolecular interaction forces** (Ionic, HC, VdW) are involved.



- Molecular shape

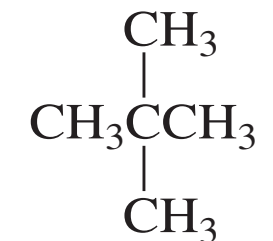
Melting/Boiling point and structural features



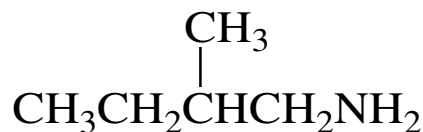
pentane
bp = 36.1 °C



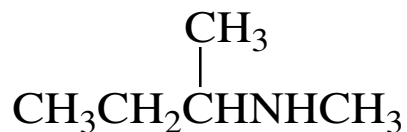
isopentane
bp = 27.9 °C



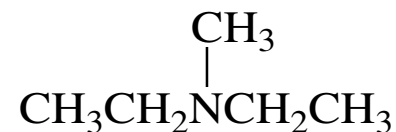
neopentane
bp = 9.5 °C



a primary amine
bp = 97 °C



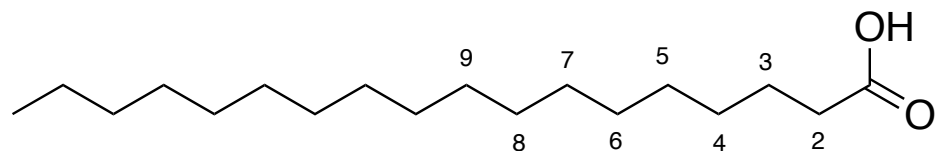
a secondary amine
bp = 84 °C



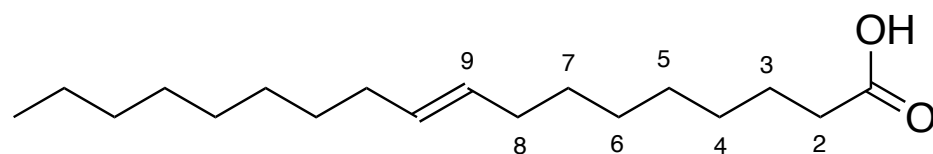
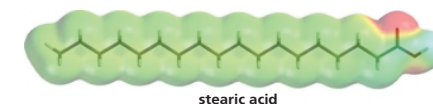
a tertiary amine
bp = 65 °C

Melting/Boiling point and structural features

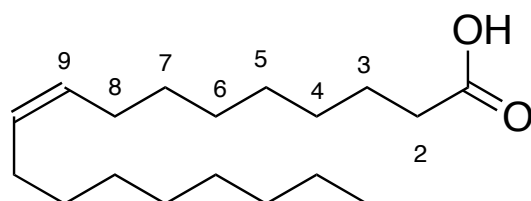
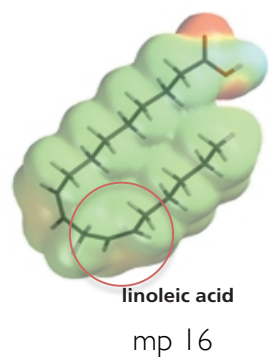
Molecular shape



Stearic acid
mp 69



Elaidinic acid (*trans* oleic acid)
mp 46



Oleic acid
mp 13



Melting/Boiling point and structural features

Table 26.1 Common Naturally Occurring Fatty Acids

Number of carbons	Common name	Systematic name	Structure	Melting point °C
Saturated				
12	lauric acid	dodecanoic acid		44
14	myristic acid	tetradecanoic acid		58
16	palmitic acid	hexadecanoic acid		63
18	stearic acid	octadecanoic acid		69
20	arachidic acid	eicosanoic acid		77
Unsaturated				
16	palmitoleic acid	(9Z)-hexadecenoic acid		0
18	oleic acid	(9Z)-octadecenoic acid		13
18	linoleic acid	(9Z,12Z)-octadecadienoic acid		-5
18	linolenic acid	(9Z,12Z,15Z)-octadecatrienoic acid		-11
20	arachidonic acid	(5Z,8Z,11Z,14Z)-eicosatetraenoic acid		-50
20	EPA	(5Z,8Z,11Z,14Z,17Z)-eicosapentaenoic acid		-50

Examples



The chemio-physical constant

Some examples:

Melting point (mp),

Boiling point (bp)

Solubility

$\log P$,

pK_a ,

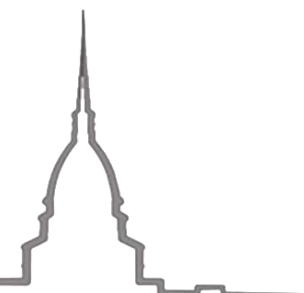
Density

Viscosity

Chromatografic retention time (Rf)

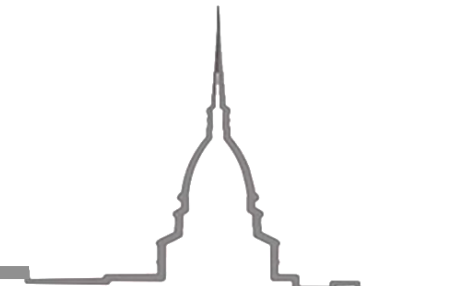
IR Vibration frequency,

NMR *chemical shift*,



What information can be obtained from Solubility??

- **Solubility** is chemio-physical constants.
- **Solubility** reflect the ways the molecule attract one another, both in the solute and in the solvent.
- it will be effected by which weak **Intermolecular interaction forces** (Ionic, HC, VdW) are involved.
- **Solubility** can be used used to determine:
 - **Identity** of substance
 - **Purity** of substance



The story of the Chemistry: **the alchemic times**



In absence of science rules, the solubility phenomena was absolutely **amazing!!!**

.....A mineral white powder, formed by evaporating seawater, resist to hot flames but disappear (transform) if water is added.....

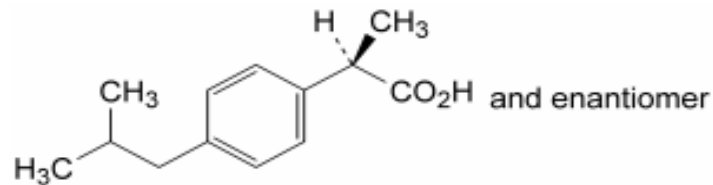
- Alkahest
- Similia similibus solvuntur

Solubility and European Pharmacopea

07/2002:0721 TESTS

IBUPROFEN

Ibuprofenum



$C_{13}H_{18}O_2$

M_r 206.3

DEFINITION

(2*RS*)-2-[4-(2-Methylpropyl)phenyl]propanoic acid.

Content: 98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white, crystalline powder or colourless crystals.

Solubility: practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates.

IDENTIFICATION

First identification: A, C

Solution S
with the s

Appearance
colourless

Angle of o
Dissolve 0
the same s

Related su
Test soluti
examined

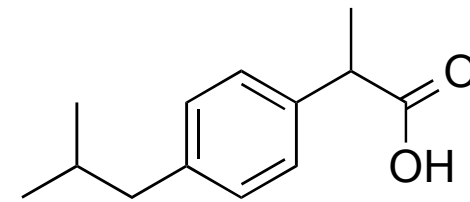
mobile phase

Reference sc
100.0 ml wit

Reference sc
2 ml of aceto

ibuprofen in
10.0 ml with

Column:



Ibuprofen

Solubility



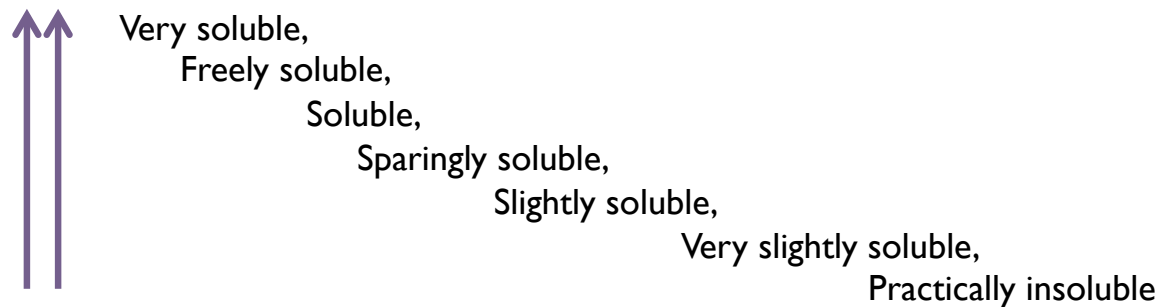
Farmacopea
Ufficiale
della
Repubblica
Italiana
X Edizione



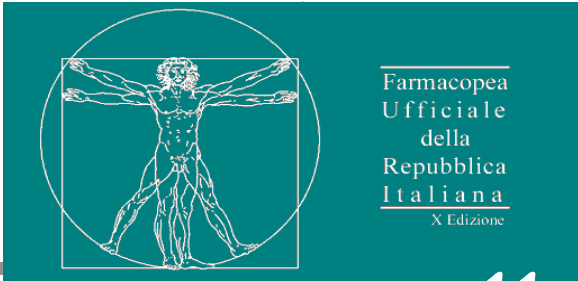
Solubility and European Pharmacopea

Descriptive term	Approximate volume of solvent in millilitres for 50 mg of solute			
<i>Very soluble</i>	less than	50 μ l	///	///
<i>Freely soluble</i>	from	50 μ l	to	500 μ l
<i>Soluble</i>	from	500 μ l	to	1.5 ml
<i>Sparingly soluble</i>	from	1.5 ml	to	5 ml
<i>Slightly soluble</i>	from	5 ml	to	50 ml
<i>Very slightly soluble</i>	from	50 ml	to	500 ml
<i>Practically insoluble</i>	more than		///	500 ml

In EP, the solubility is **not** expressed as usual (amount of solute in the solvent) but **use SIX intervals**. This approach reduce the possibility of making mistake and allows a more confortable judgement



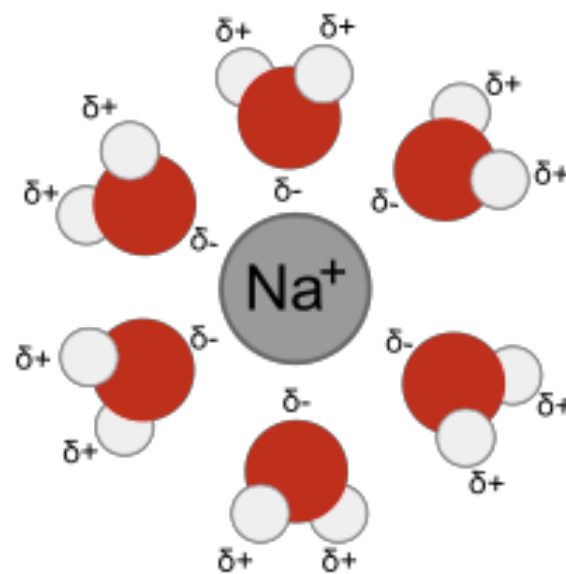
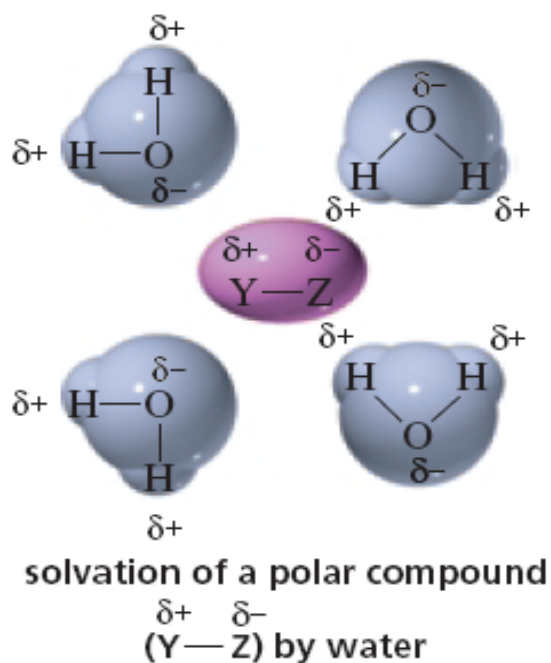
Solubility



Solvation

is an interaction of a **solute** with the **solvent**, which leads to stabilization of the solute species in the solution.

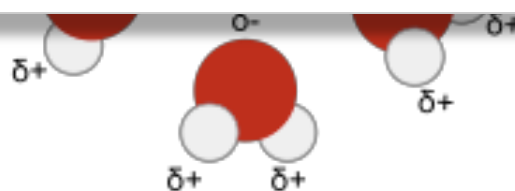
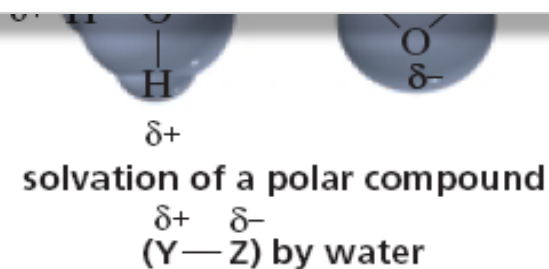
The **solvated state** is the stable state where an ion/molecule in a solution is surrounded or complexed by solvent molecules (*solvation shell*).



Solvation

Solubility - definition#1:

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



Dielectric constant

Dielectric constant or permittivity (ϵ) is an index of the ability of a substance to attenuate the transmission of an electrostatic force from one charged body to another. The lower the value, the greater the attenuation. The standard measurement apparatus utilises a vacuum whose dielectric constant is 1.

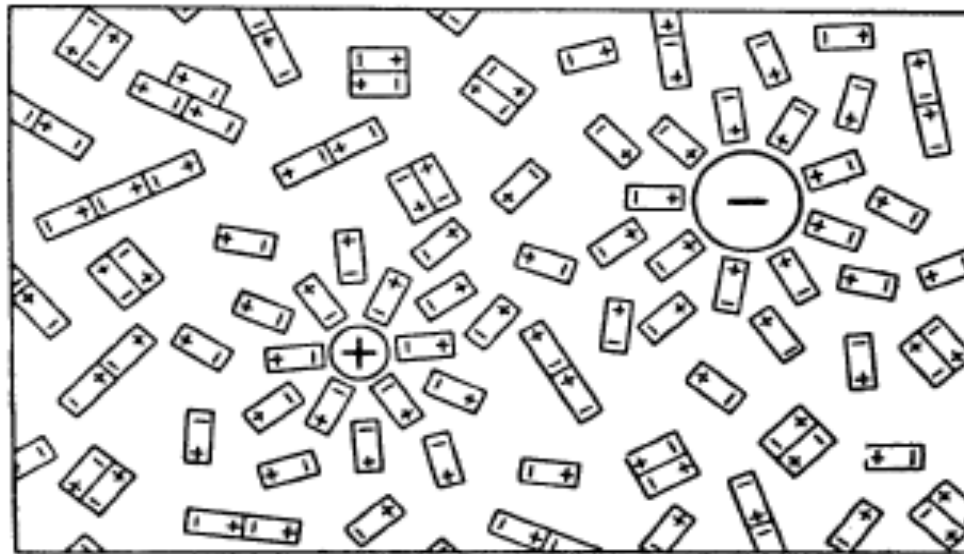


Fig. 2-7. Solvation of ions in a solvent consisting of dipolar molecules [99]. The charges of the dipolar molecules are in fact partial charges δ^+ and δ^- .

Solventi ordinati per Costante dielettrica

<i>Solvente</i>	<i>b.p. °C</i>	<i>m.p. °C</i>	<i>Densità</i>	<i>Costante dielettrica</i>	<i>Solubilità in acqua (g / 100 g)</i>	<i>TLV (ppm)</i>
Acqua	100	0	1,00	80,2	---	----
Dimetilsolfossido (DMSO)	189	18	1,10	46,7	25,3	-----
Acido trifluoroacetico	72	-15	1,49	39,5	∞	----
Acetonitrile	82	-44	0,78	37,5	∞	40
Dimetilformammide (DMF)	153	-60	0,95	36,7	∞	10
Metanolo	65	-98	0,79	32,7	∞	200
Glicoldietilenico	245	-7	1,11	31,7	∞	-----
Etanolo	78	-114	0,79	24,6	∞	1000
Acetone	56	-95	0,79	20,7	∞	1000
1-propanolo	97	-126	0,80	20,3	∞	200
2-propanolo	82	-88	0,79	19,9	∞	---
Terz-Butanolo	82	26	0,78	12,5	∞	100
Piridina	115	-42	0,98	12,4	∞	5
Diclorometano	40	-95	1,33	8,9	1,30	250
Tetraidrofurano (THF)	66	-109	0,89	7,6	∞	200
Acetato d'etile	77	-84	0,9	6,0	8,1	400
Clorobenzene	132	-46	1,11	5,6	0,05	75
Cloroformio	61	-64	1,49	4,8	0,82	25
Etere	35	-116	0,71	4,3	6,0	400
Etere dibutilico	142	-95	0,77	3,1	0,03	---
Solfuro di carbonio	46	-111	1,26	2,6	0,29	20
Benzene	80	5,5	0,88	2,3	0,18	25
CCL ₄	77	-23	1,59	2,2	0,08	10
Cicloesano	81	6,5	0,78	2,0	0,01	300
Esano	69	-95	0,66	1,9	Insolubile	500
Pentano	36	-130	0,63	1,8	Insolubile	500

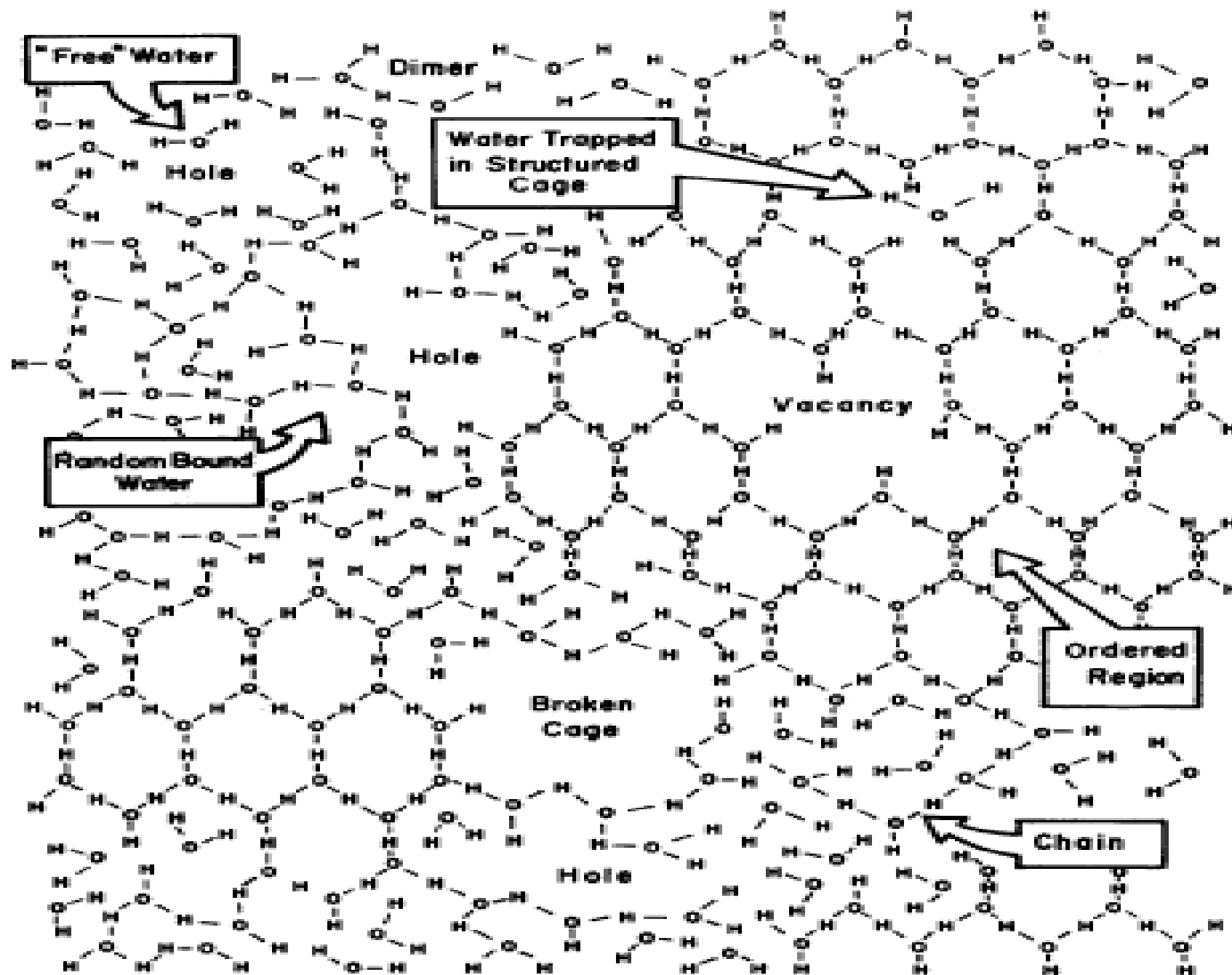


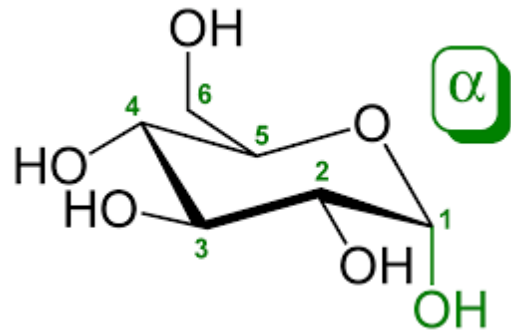
Fig. 2-1. Two-dimensional schematic diagram of the three-dimensional structure of liquid water

Solventi ordinati per Solubilità Acquosa

<i>Solvente</i>	<i>b.p. °C</i>	<i>m.p. °C</i>	<i>Densità</i>	<i>Costante dielettrica</i>	<i>Solubilità in acqua (g / 100 g)</i>	<i>TLV (ppm)</i>
Acqua	100	0	1,00	80,2	---	----
Acido trifluoroacetico	72	-15	1,49	39,5	∞	----
Acetonitrile	82	-44	0,78	37,5	∞	40
Dimetilformamide (DMF)	153	-60	0,95	36,7	∞	10
Metanolo	65	-98	0,79	32,7	∞	200
Glicoldietilenico	245	-7	1,11	31,7	∞	-----
Etanolo	78	-114	0,79	24,6	∞	1000
Acetone	56	-95	0,79	20,7	∞	1000
1-propanolo	97	-126	0,80	20,3	∞	200
2-propanolo	82	-88	0,79	19,9	∞	---
Terz-Butanolo	82	26	0,78	12,5	∞	100
Piridina	115	-42	0,98	12,4	∞	5
Tetraidrofurano (THF)	66	-109	0,89	7,6	∞	200
Dimetilsolfossido (DMSO)	189	18	1,10	46,7	25,3	-----
Acetato d'etile	77	-84	0,9	6,0	8,1	400
Etere	35	-116	0,71	4,3	6,0	400
Diclorometano	40	-95	1,33	8,9	1,30	250
Cloroformio	61	-64	1,49	4,8	0,82	25
Solfuro di carbonio	46	-111	1,26	2,6	0,29	20
Benzene	80	5,5	0,88	2,3	0,18	25
CCL ₄	77	-23	1,59	2,2	0,08	10
Clorobenzene	132	-46	1,11	5,6	0,05	75
Etere dibutilico	142	-95	0,77	3,1	0,03	---
Cicloesano	81	6,5	0,78	2,0	0,01	300
Esano	69	-95	0,66	1,9	Insolubile	500
Pentano	36	-130	0,63	1,8	Insolubile	500

Solubility and structural features

- Solubility values will be effected by the **Molecular weight**.



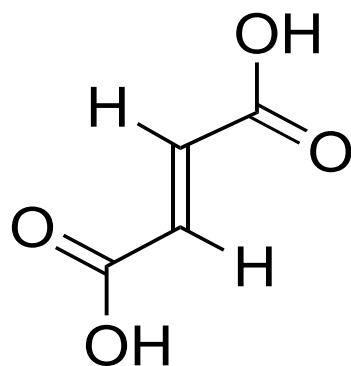
Glucose



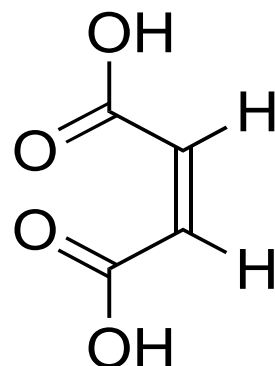
Paper

Solubility and structural features

- Solubility values will be effected by the mp/bp



Ac. Fumarico
sublima 200 C
Insolubile in acqua

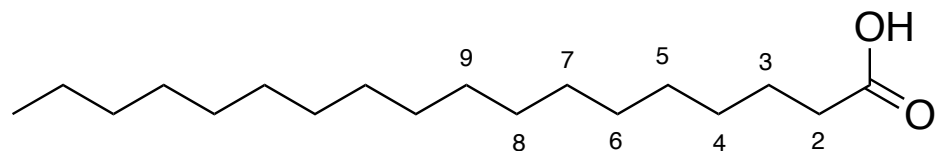


Ac. Maleico
fonde a 130 C
Solubile in acqua

- Melting point

Melting/Boiling point and structural features

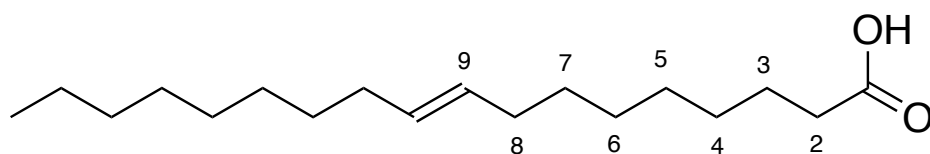
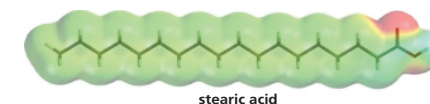
Molecular shape



Stearic acid

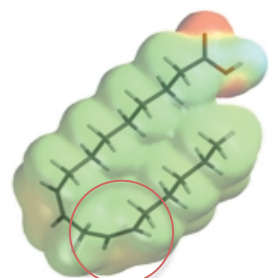
mp 69

0.00029 g/100 g (20 °C)

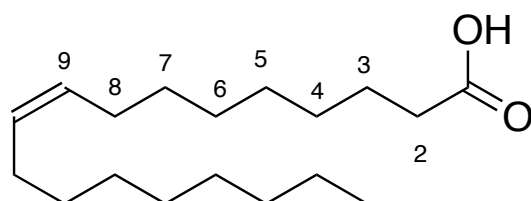


Elaidinic acid (*trans* oleic acid)

mp 46

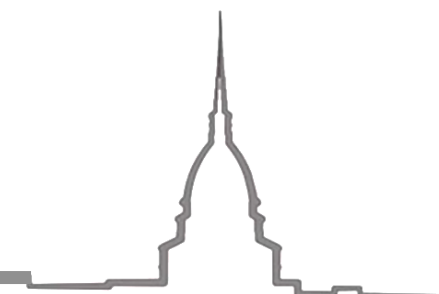


mp 16



Oleic acid

mp 13



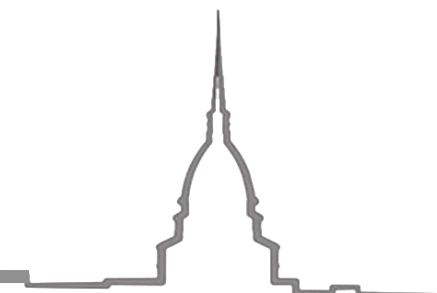
Solubility and structural features

- Solubility values will be effected by the % hydrocarbon present in the structure

Table 2.7 Solubilities of Ethers in Water

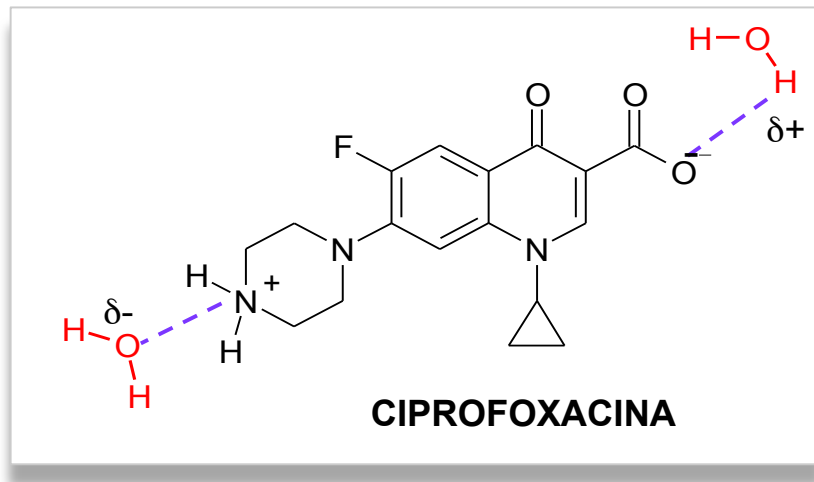
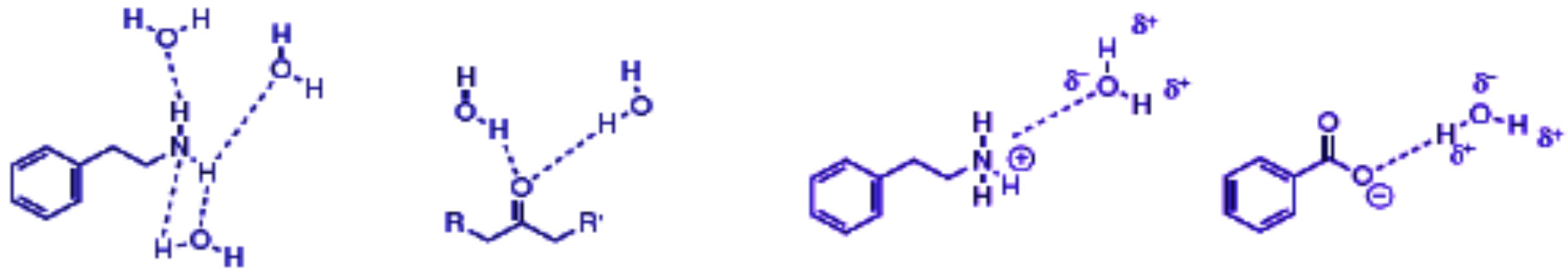
2 C's	CH_3OCH_3	soluble
3 C's	$\text{CH}_3\text{OCH}_2\text{CH}_3$	soluble
4 C's	$\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$	slightly soluble (10 g/100 g H_2O)
5 C's	$\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_3$	minimally soluble (1.0 g/100 g H_2O)
6 C's	$\text{CH}_3\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_3$	insoluble (0.25 g/100 g H_2O)

- Hydrocarbon %



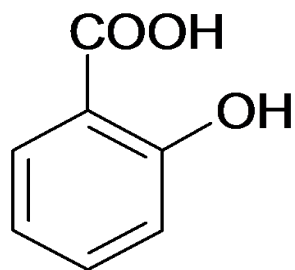
Solubility and structural features

- Solubility values will be effected by the **HBA/HBD**



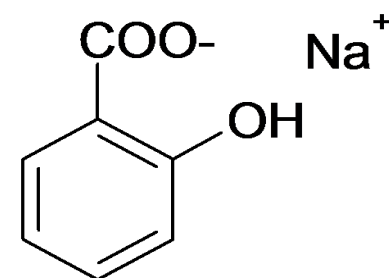
- HAD/HDB

Solubility and salts



$$S = 0.2 \% \text{ p/v}$$

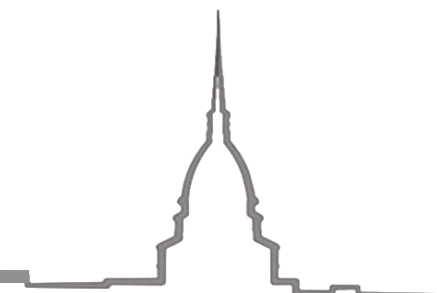
A white, crystalline powder or white or colourless, acicular crystals, slightly soluble in water, freely soluble in alcohol and in ether, sparingly soluble in methylene chloride



$$S = 125 \% \text{ p/v}$$

A white, crystalline powder or small, colourless crystals or shiny flakes, freely soluble in water, sparingly soluble in alcohol.

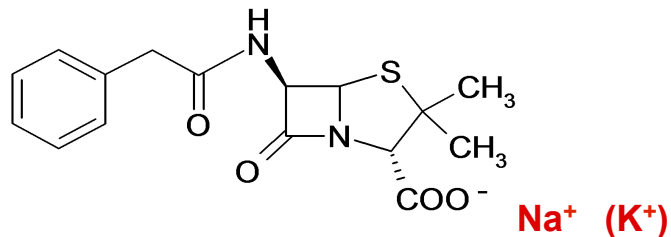
Solubilità acquosa del sale incrementa di almeno di 2 ordini di grandezza



Solubility and salts

NON tutti i sali sono dotati di elevata solubilità acquosa

Benzilpenicillina: Penicillina G sale sodico o potassico



MOLTO SOLUBILE (> 10 % p/v)

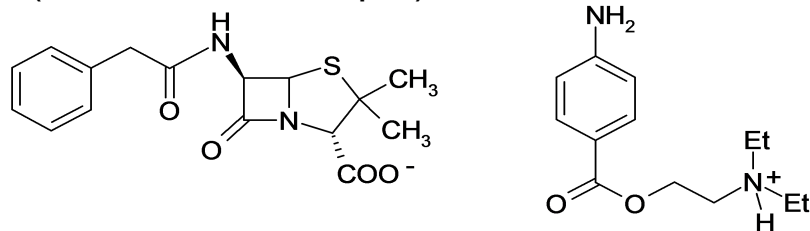
iniettata per via i.m. o e.v. trattamento di **infezioni acute** (intervallo posologico: 6 h)

Soluzione estemporanea preparata con H₂O per preparazioni iniettabili



Benzilpenicillina Procaina:

forma ritardo della benzilpenicillina somministrata per **via intramuscolare** come **sospensione** (solubilità = 0.4% p/v)



Forma ritardo ⇒ **assorbimento lento e prolungato**

trattamento di infezioni croniche (intervalli di somministrazione: da **1 volta alla settimana** ad **1 volta al mese**)



Solubility and salts

Il farmaco NON deve precipitare dopo essere stato iniettato in vena o instillato come collirio

