Chimie organique bioorientée

Luc Patiny

https://biooriented.cheminfo.org

Introduction

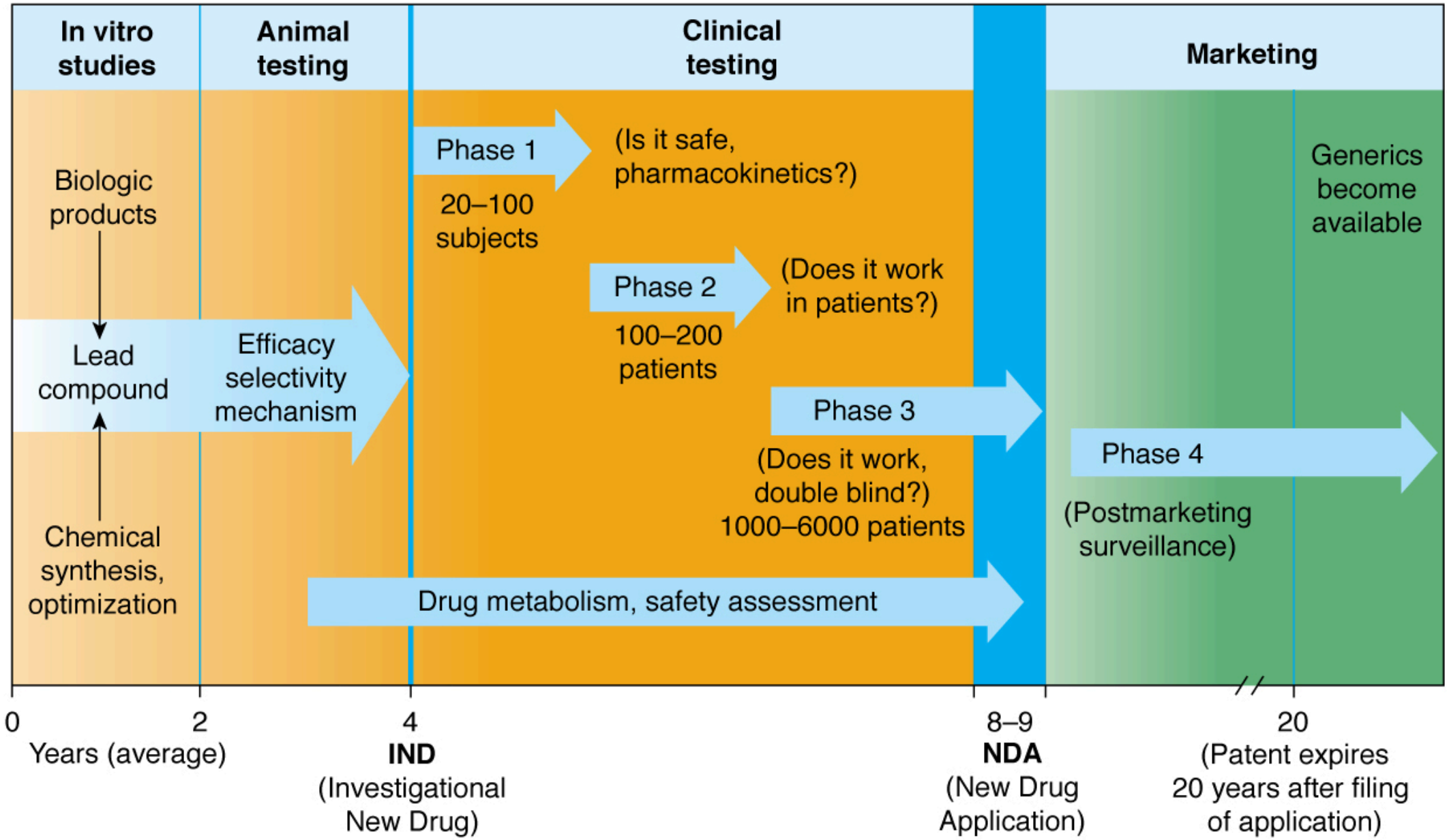
En 2020, l’industrie chimique et pharmaceutique a contribué à hauteur de 6,3% au produit intérieur brut. Elle se place ainsi juste derrière l’industrie des machines, mais est en tête pour les exportations. Chaque année des produits chimiques et pharmaceutiques d’une valeur de plus de 116 milliards de francs sont vendus à l’étranger, ce qui représente près de 52% des exportations totales. En 2020, cette industrie employait environ 74’000 personnes en Suisse et plus de 338’000 à l’étranger.

https://www.eda.admin.ch/aboutswitzerland/fr/home/wirtschaft/taetigkeitsgebiete/chemie-und-pharma.html

Productivité exceptionnelle en comparaison de branches

Les nouvelles données font encore mieux apparaître l'avance de productivité de l'industrie pharmaceutique. Avec une valeur ajoutée de 332 francs suisses par heure de travail ou 627 000 francs par poste de travail en 2014, la productivité horaire de l'industrie pharmaceutique était environ quatre fois supérieure à celle de l'économie globale et 3,5 fois supérieure à celle de l'ensemble de l'industrie.

Recherche d'un médicament



Plan du cours

- **Introduction**
- **Analyse structurale**
  - Spectrométrie de masse
  - Degré d’insaturation
  - Spectrométrie infrarouge
  - Résonance Magnétique Nucléaire
- **Acides aminés, peptides et protéines**
  - Acides aminés
  - Synthèse peptidique
  - Protéine et JsMol
- **Conclusions**
  - Interaction protéine / inhibiteur
  - Exemple avec la 'peptide deformylase'

Organisation pratique

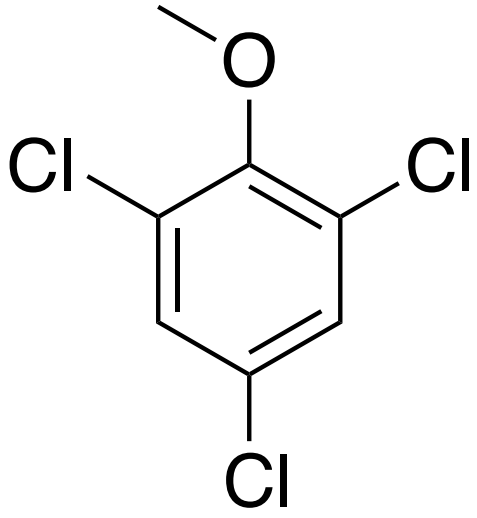
- **Cours théorique toutes les 2 semaines**
- **Exercices pratiques toutes les semaines**
- **Assistant:**
  - Shubhanga Balla - shubhanga.ballal@epfl.ch
- **Contrôle continu:**
  - 2/6: travail JsMol (présentation le 12 ou 19 décembre)
  - 4/6: test écrit (12 décembre)

Support

- https://moodle.epfl.ch/course/view.php?id=16403
- https://biooriented.cheminfo.org

Analyse structurale

Détermination de la structure d'un produit inconnu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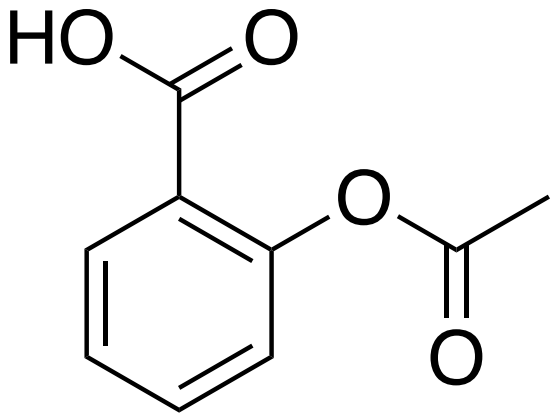
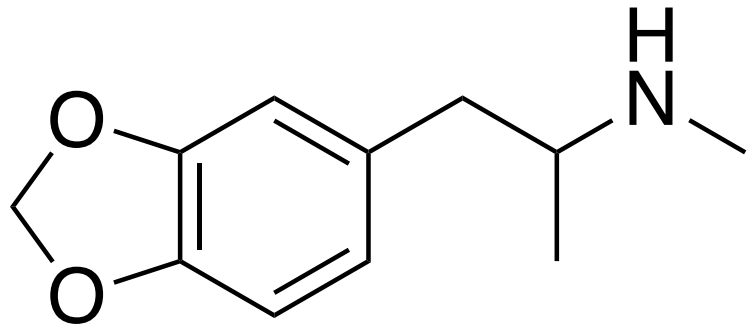
Cl
Cl
Cl


HO
O
O
O


H
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O
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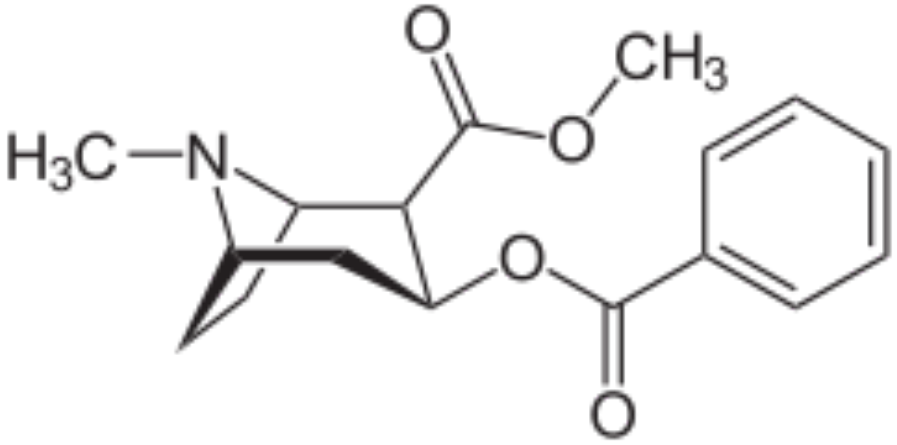
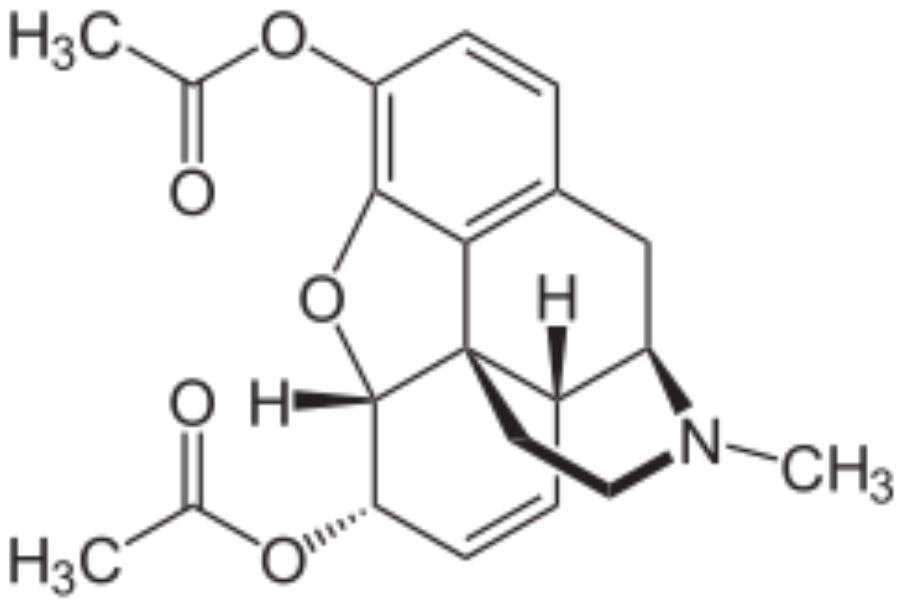
O


H3C
N
O
CH3
O
O


H3C
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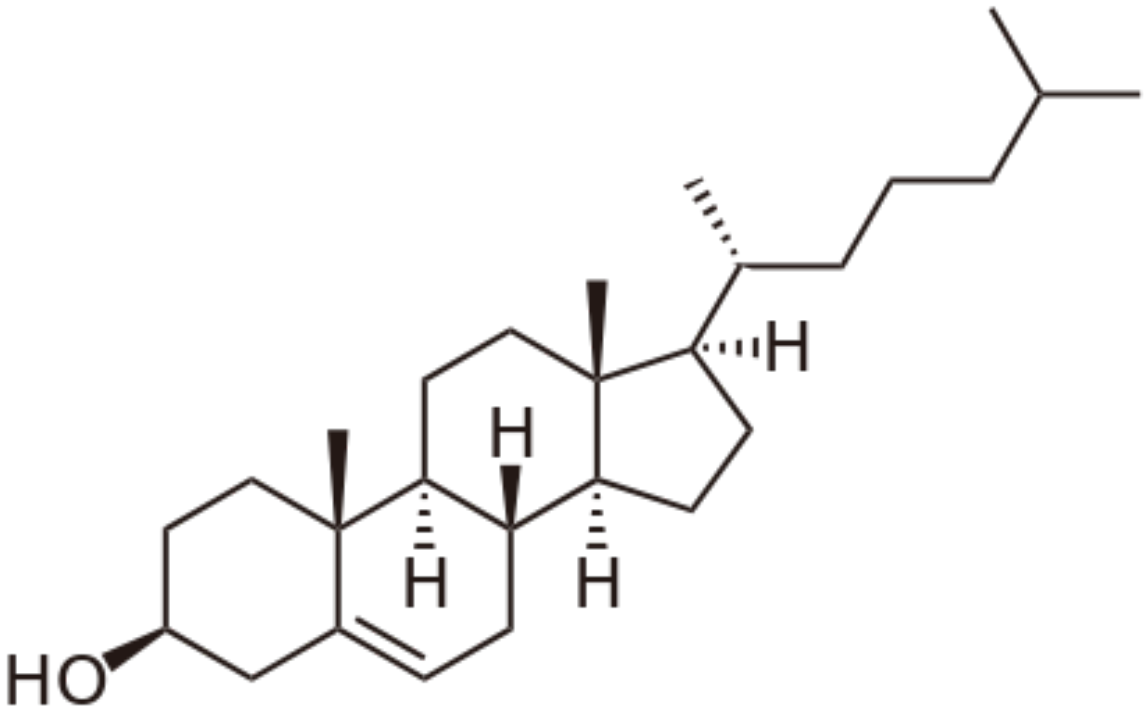
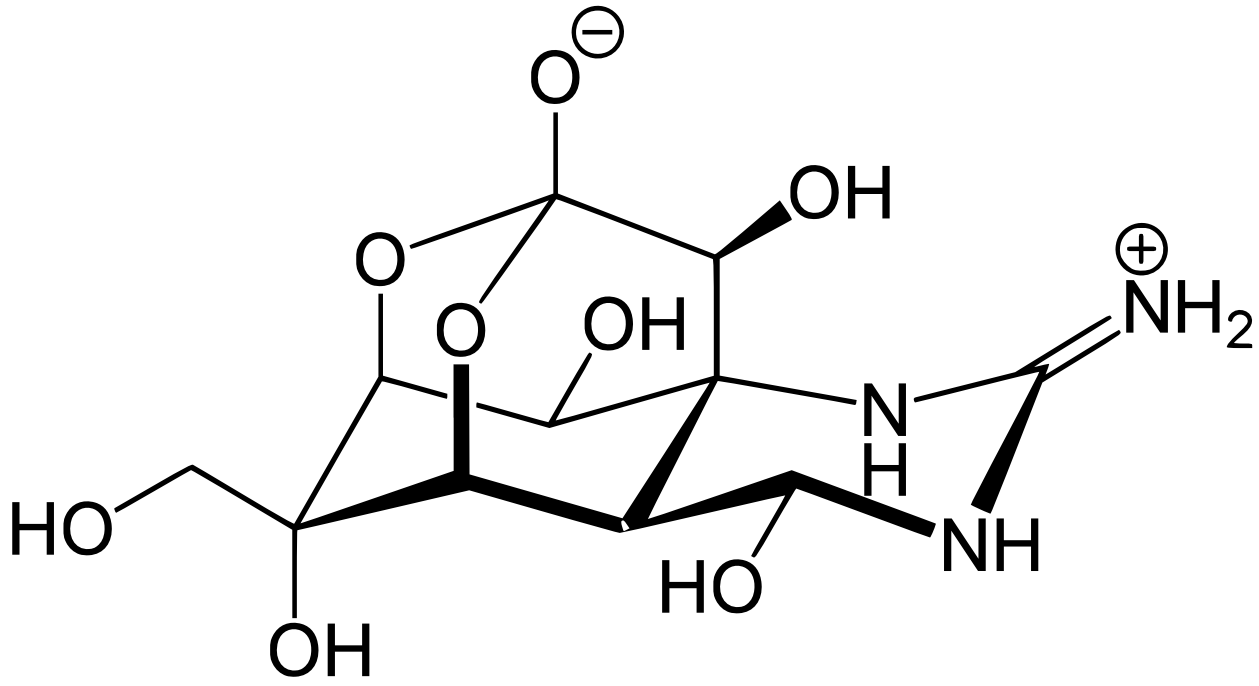
H
H
O
N
CH3
H3C
O


H
H
H
H
HO


O
OH
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OH
NH2
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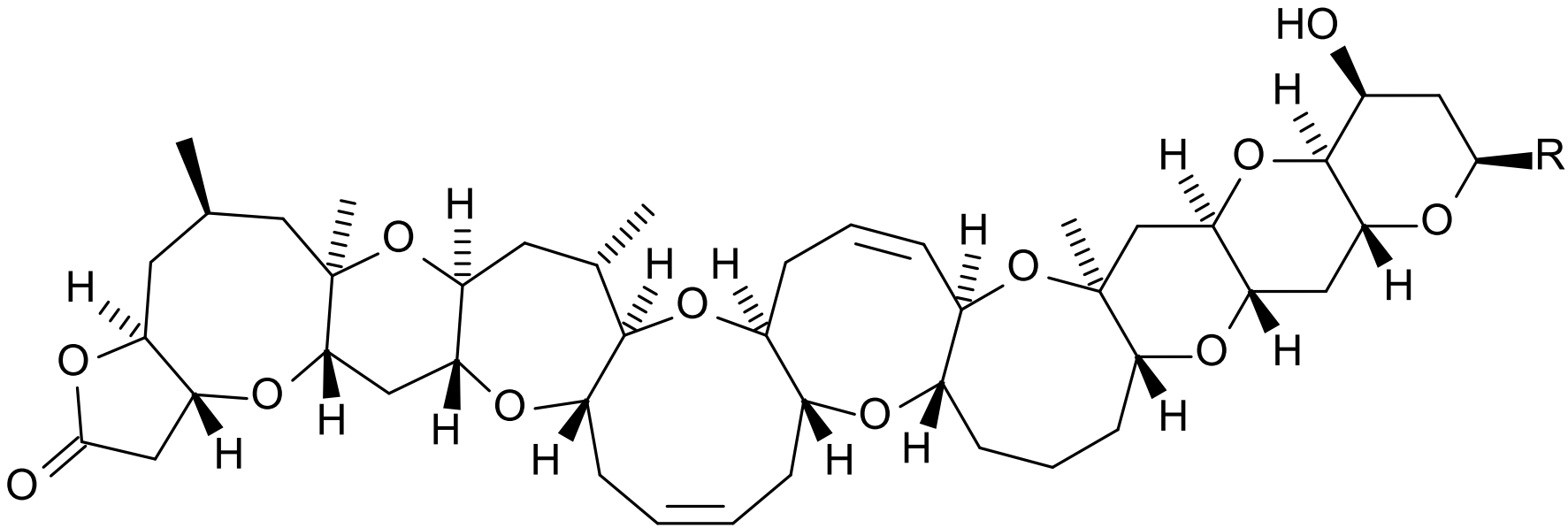
HO
NH
HO
OH


HO
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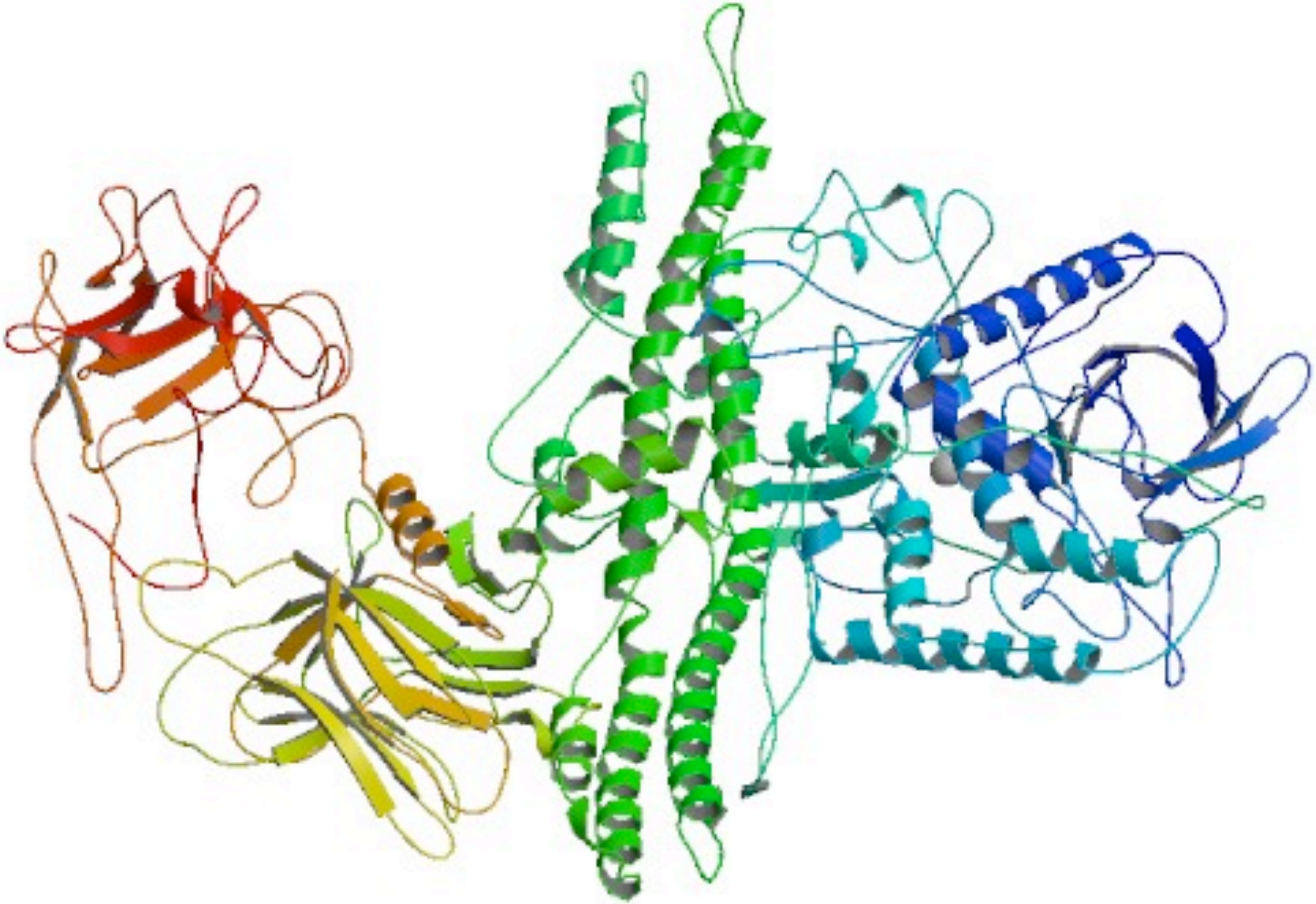
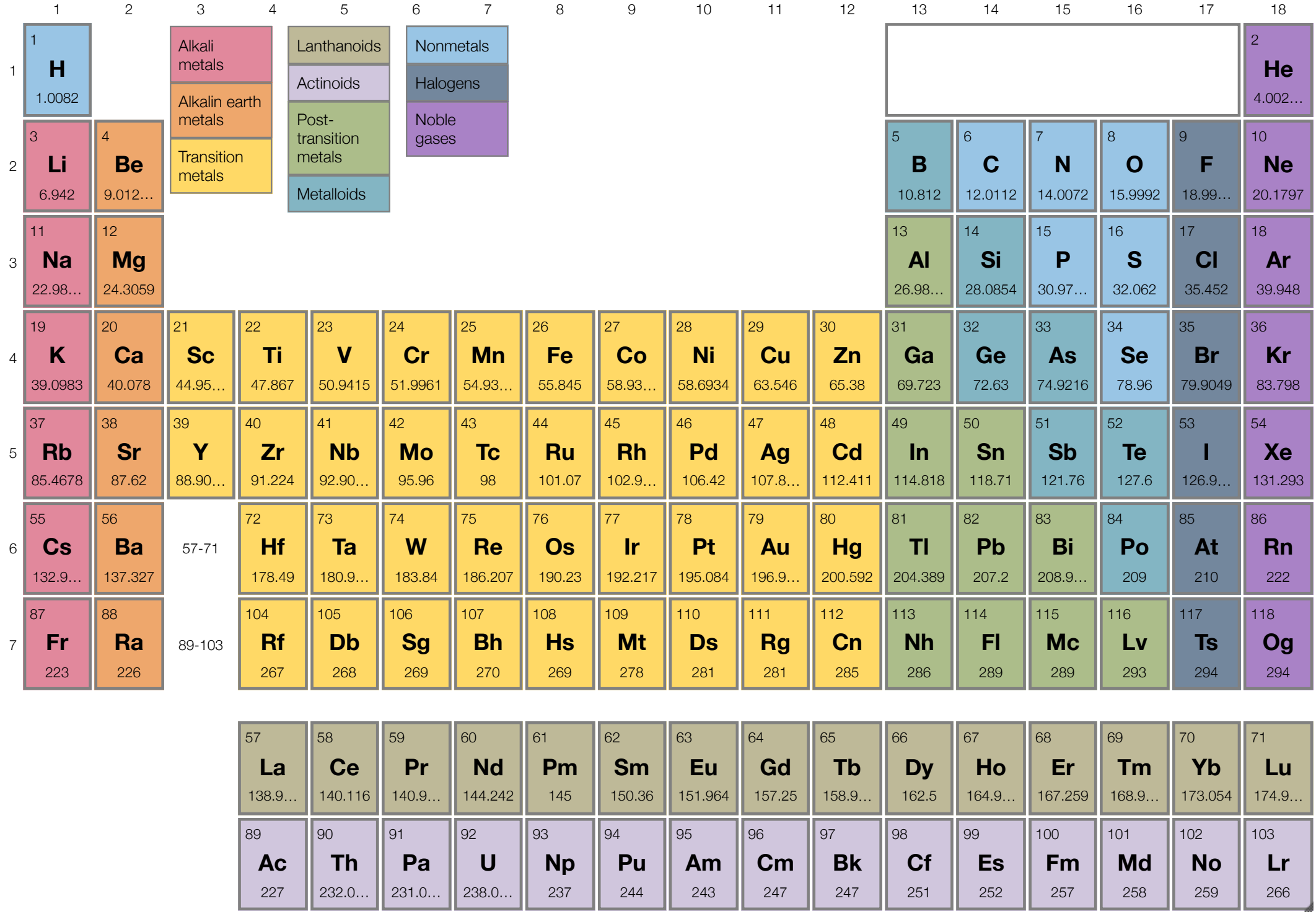


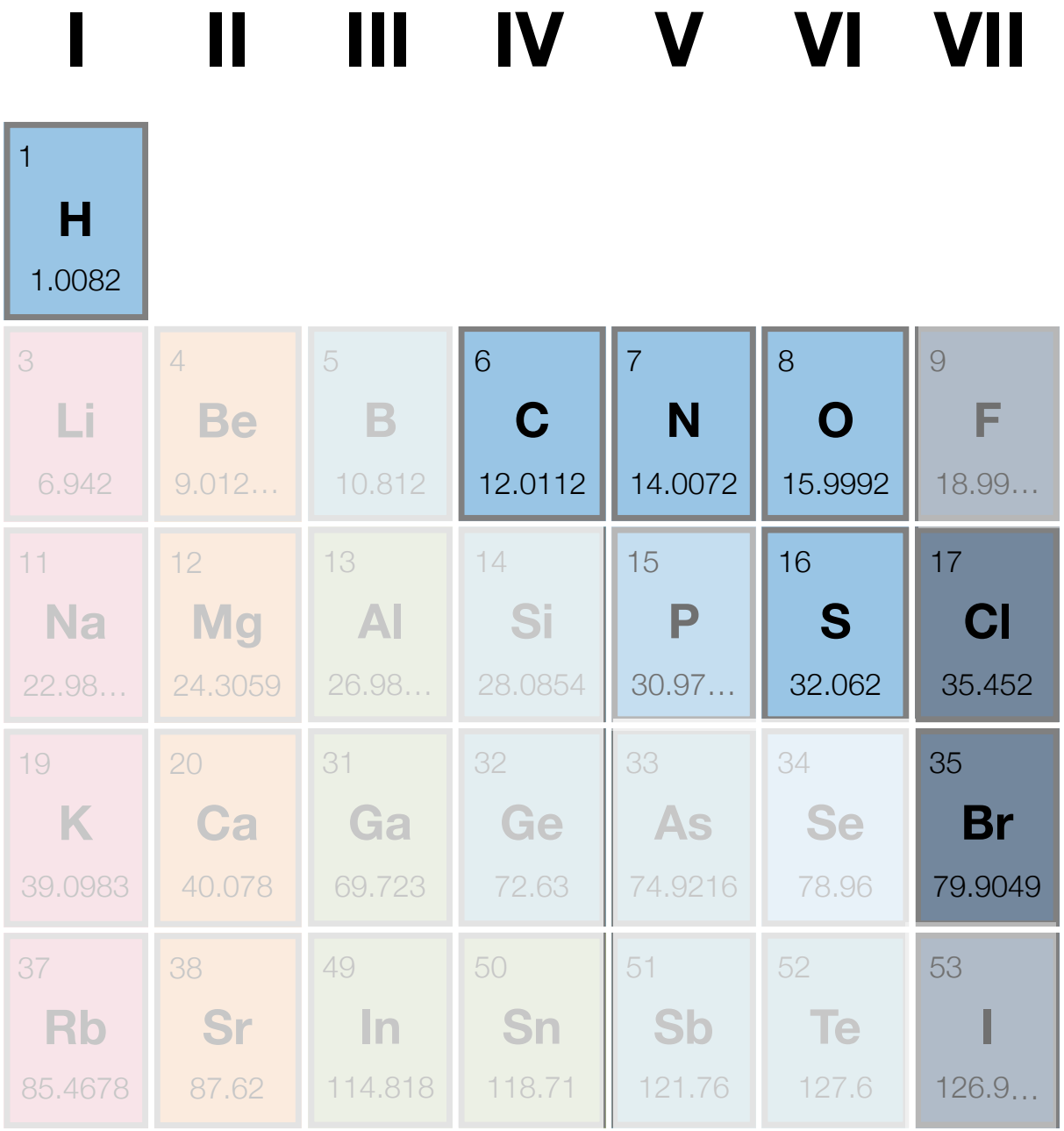
DOUZE CAS, UN MORT... CE QUE L'ON SAIT SUR LES CAS DE BOTULISME DÉTECTÉS EN FRANCE

Sophie Cazaux Le 13/09/2023 à 11:47

12 cas de botulisme ont été identifiés en France ces derniers jours, liés à des sardines servies dans un restaurant de Bordeaux. Un décès a été recensé en Île-de-France. En raison du délai d'incubation de la maladie, les autorités s'attendent à détecter des cas jusqu'à ce week-end.

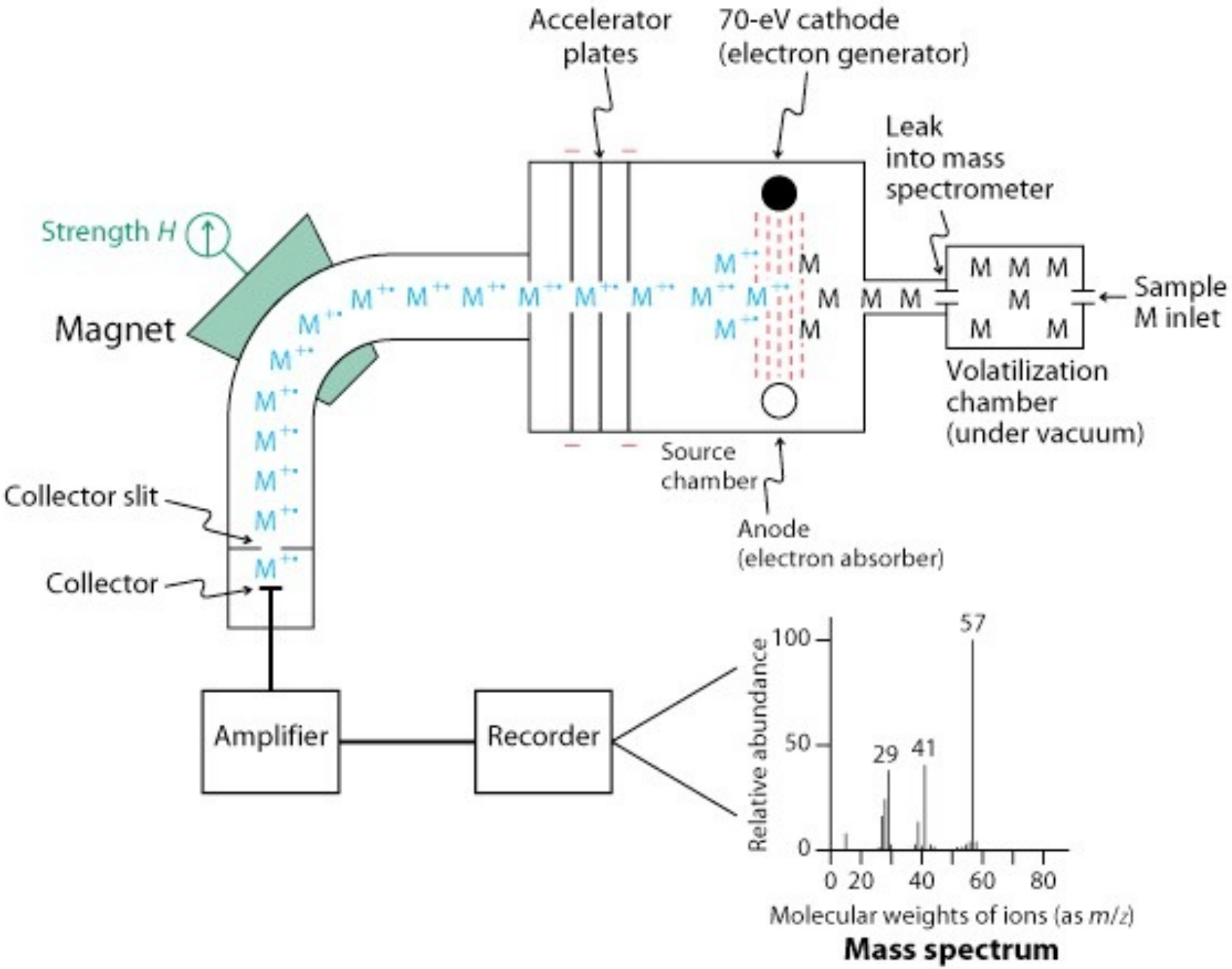
Link


1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Alkali metals
Alkalin earth metals
Transition metals
Lanthanoids
Actinoids
Post-transition metals
Metalloids
Nonmetals
Halogens
Noble gases
1 H 1.0082
2 He 4.002…
3 Li 6.942
4 Be 9.012…
5 B 10.812
6 C 12.0112
7 N 14.0072
8 O 15.9992
9 F 18.99…
10 Ne 20.1797
11 Na 22.98…
12 Mg 24.3059
13 Al 26.98…
14 Si 28.0854
15 P 30.97…
16 S 32.062
17 Cl 35.452
18 Ar 39.948
19 K 39.0983
20 Ca 40.078
21 Sc 44.95…
22 Ti 47.867
23 V 50.9415
24 Cr 51.9961
25 Mn 54.93…
26 Fe 55.845
27 Co 58.93…
28 Ni 58.6934
29 Cu 63.546
30 Zn 65.38
31 Ga 69.723
32 Ge 72.63
33 As 74.9216
34 Se 78.96
35 Br 79.9049
36 Kr 83.798
37 Rb 85.4678
38 Sr 87.62
39 Y 88.90…
40 Zr 91.224
41 Nb 92.90…
42 Mo 95.96
43 Tc 98
44 Ru 101.07
45 Rh 102.9…
46 Pd 106.42
47 Ag 107.8…
48 Cd 112.411
49 In 114.818
50 Sn 118.71
51 Sb 121.76
52 Te 127.6
53 I 126.9…
54 Xe 131.293
55 Cs 132.9…
56 Ba 137.327
57-71
72 Hf 178.49
73 Ta 180.9…
74 W 183.84
75 Re 186.207
76 Os 190.23
77 Ir 192.217
78 Pt 195.084
79 Au 196.9…
80 Hg 200.592
81 Tl 204.389
82 Pb 207.2
83 Bi 208.9…
84 Po 209
85 At 210
86 Rn 222
87 Fr 223
88 Ra 226
89-103
104 Rf 267
105 Db 268
106 Sg 269
107 Bh 270
108 Hs 269
109 Mt 278
110 Ds 281
111 Rg 281
112 Cn 285
113 Nh 286
114 Fl 289
115 Mc 289
116 Lv 293
117 Ts 294
118 Og 294
57 La 138.9…
58 Ce 140.116
59 Pr 140.9…
60 Nd 144.242
61 Pm 145
62 Sm 150.36
63 Eu 151.964
64 Gd 157.25
65 Tb 158.9…
66 Dy 162.5
67 Ho 164.9…
68 Er 167.259
69 Tm 168.9…
70 Yb 173.054
71 Lu 174.9…
89 Ac 227
90 Th 232.0…
91 Pa 231.0…
92 U 238.0…
93 Np 237
94 Pu 244
95 Am 243
96 Cm 247
97 Bk 247
98 Cf 251
99 Es 252
100 Fm 257
101 Md 258
102 No 259
103 Lr 266


I
II
III
IV
V
VI
VII
1
H
1.0082
3
Li
6.942
4
Be
9.012…
5
B
10.812
6
C
12.0112
7
N
14.0072
8
O
15.9992
9
F
18.99…
11
Na
22.98…
12
Mg
24.3059
13
Al
26.98…
14
Si
28.0854
15
P
30.97…
16
S
32.062
17
Cl
35.452
19
K
39.0983
20
Ca
40.078
31
Ga
69.723
32
Ge
72.63
33
As
74.9216
34
Se
78.96
35
Br
79.9049
37
Rb
85.4678
38
Sr
87.62
49
In
114.818
50
Sn
118.71
51
Sb
121.76
52
Te
127.6
53
I
126.9…

Stratégie

Spectrométrie de masse


Accelerator plates
70-eV cathode (electron generator)
Leak into mass spectrometer
Strength H
Magnet
Sample M inlet
Volatilization chamber (under vacuum)
Source chamber
Anode (electron absorber)
Collector slit
Collector
Amplifier
Recorder
Relative abundance
100
50
0
57
29
41
0 20 40 60 80
Molecular weights of ions (as m/z)
Mass spectrum

https://forms.gle/edM9eWG49uRh59GQ9

Signal correspondant à un carbone chargé positivement en spectrométrie de masse

1 carbone

- ◯ < 12u
- ◯ = 12u
- ◯ > 12u
- ◯ Impossible d'être certain

Answer

	Isotope	Abondance (%)	Masse isotopique [u]
H	1	99.99	1.0078
	2	0.01	2.0141
C	12	98.93	12.0000
	13	1.07	13.0033
N	14	99.64	14.0030
	15	0.36	15.0001
O	16	99.76	15.9949
	17	0.04	16.9991
	18	0.20	17.9991

Electron: 0.0005

Exercice

- **Dessiner le spectre de masse théorique de C_2^{++}**

	Isotope	Abondance (%)	Masse isotopique [u]
H	1	99.99	1.0078
	2	0.01	2.0141
C	12	98.93	12.0000
	13	1.07	13.0033
			Electron: 0.0005

https://www.cheminfo.org/flavor/biooriented

https://biooriented.cheminfo.org

Exercice pour déterminer la charge de la molécule observée en masse

	Isotope	Abondance (%)	Masse isotopique [u]
H	1	99.99	1.0078
	2	0.01	2.0141
C	12	98.93	12.0000
	13	1.07	13.0033
N	14	99.64	14.0030
	15	0.36	15.0001
O	16	99.76	15.9949
	17	0.04	16.9991
	18	0.20	17.9991

Electron: 0.0005

Définitions

Unité de masse atomique unifiée

Unité égale à (quasi *) 1/12 de la masse
d'un isotope 12 du carbone
=
$1.660539\ 10^{-27}$ kg

Unité: Da (dalton) ou u

* exactement jusqu'au 20 mai 2019

	Isotope	Abondance (%)	Masse isotopique [u]
H	1	99.99	1.0078
	2	0.01	2.0141
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	15	0.36	15.0001
O	16	99.76	15.9949
	17	0.04	16.9991
	18	0.20	17.9991

Electron: 0.0005

Masse atomique

Moyenne pondérée des masses des isotopes naturels stables d’un élément donné

	Isotope	Abondance (%)	Masse isotopique [u]
H	1	99.99	1.0078
	2	0.01	2.0141
C	12	98.93	12.0000
	13	1.07	13.0033

Electron: 0.0005

Masse moléculaire

Masse calculée en utilisant la masse atomique de chaque élément.

Masse nominale

Masse calculée en utilisant la masse entière de l’isotope majoritaire de chaque élément.

	Isotope	Abondance (%)	Masse isotopique [u]
H	1	99.99	1.0078
	2	0.01	2.0141
C	12	98.93	12.0000
	13	1.07	13.0033
N	14	99.64	14.0030
	15	0.36	15.0001
O	16	99.76	15.9949
	17	0.04	16.9991
	18	0.20	17.9991

Masse isotopique

Masse calculée en utilisant les masses exactes des isotopes considérés

Masse monoisotopique

Masse calculée en utilisant les masses exactes des isotopes majoritaires de chaque élément

Les chimistes organiciens appellent parfois cela "masse exacte"

	Masse nominale	Abondance relative (%)	Abondance (%)	Masse isotopique [u]	Masse atomique
H	1 2	100 0.01	99.99 0.01	1.007825 2.014101	1.008
C	12 13	100 1.08	98.93 1.07	12.000000 13.003354	12.011
N	14 15	100 0.37	99.64 0.36	14.003074 15.000108	14.007
O	16 17 18	100 0.04 0.20	99.76 0.04 0.20	15.994914 16.999131 17.999161	15.999
P	31	100	100	30.973761	30.974
S	32 33 34 36	100 0.79 4.47 0.01	94.99 0.75 4.25 0.01	31.972071 32.971458 33.967866 35.967080	32.065
F	19	100	100	18.998403	18.998
Cl	35 37	100 32.00	75.76 24.24	34.968852 36.965902	35.453
Br	79 81	100 97.28	50.69 49.31	78.918337 80.916290	79.903
I	127	100	100	126.904473	126.904

Electron: 0.00054858

https://biooriented.cheminfo.org

Déterminer la masse monoisotopique de la molécule non ionisée

https://forms.gle/ps6voMgXnJkzmvNT6

Quelle formule brute correspond le mieux à une molécule mono chargée positivement dont la masse observée est 30.0450

30.0450

- ◯ CH2O
- ◯ C2H6
- ◯ NO

Answer

pe	Abondance (%)	Masse isotopique [u]
	1	99.99	1.0078
	2	0.01	2.0141
C	12	98.93	12.0000
	13	1.07	13.0033
N	14	99.64	14.0030
	15	0.36	15.0001
O	16	99.76	15.9949
	17	0.04	16.9991
	18	0.20	17.9991

Electron: 0.0005

Distribution isotopique
1 seul atome

Exercice

- **Dessinez le spectre de masse de :**
  - $C^{+\bullet}$
  - $Cl^{+\bullet}$
  - $Br^{+\bullet}$
  - $S^{+\bullet}$

$C^{+\bullet}$ - $Cl^{+\bullet}$ - $Br^{+\bullet}$ - $S^{+\bullet}$

	Masse nominale	Abondance relative (%)	Abondance (%)	Masse isotopique [u]	Masse atomique
H	1	100	99.99	1.007825	1.008
	2	0.01	0.01	2.014101	
C	12	100	98.93	12.000000	12.011
	13	1.08	1.07	13.003354	
N	14	100	99.64	14.003074	14.007
	15	0.37	0.36	15.000108	
O	16	100	99.76	15.994914	15.999
	17	0.04	0.04	16.999131	
	18	0.20	0.20	17.999161	
P	31	100	100	30.973761	30.974
S	32	100	94.99	31.972071	32.065
	33	0.79	0.75	32.971458	
	34	4.47	4.25	33.967866	
	36	0.01	0.01	35.967080	
F	19	100	100	18.998403	18.998
Cl	35	100	75.76	34.968852	35.453
	37	32.00	24.24	36.965902	
Br	79	100	50.69	78.918337	79.903
	81	97.28	49.31	80.916290	

Electron: 0.00054858

Element	A (masse)	A (%)	A+1 (masse)	A+1 (%)	A+2 (masse)	A+2 (%)	A+4 (masse)	A+4 (%)
H	1	100	2	0.01				
C	12	100	13	1.08				
N	14	100	15	0.37				
O	16	100	17	0.04	18	0.20		
P	31	100						
S	32	100	33	0.79	34	4.47	36	0.01
F	19	100						
Cl	35	100			37	32.00		
Br	79	100			81	97.28		
I	127	100						

Elem	A	A	A+1	A+1	A+2	A+2	A+4	A+4
H	1	100	2	0.01				
C	12	100	13	1.08				
N	14	100	15	0.37				
O	16	100	17	0.04	18	0.20		
P	31	100						
S	32	100	33	0.79	34	4.47	36	0.01
F	19	100						
Cl	35	100			37	32.00		
Br	79	100			81	97.28		
I	127	100						

Distribution isotopique - plusieurs atomes

Isotopomères

2 molécules ayant le même nombre de chacun des isotopes à des positions différentes.

Isotopologues

2 molécules différents uniquement par leur composition isotopique

Isotopologue majoritaire

Composition isotopique la plus abondante.

Distribution isotopique

Ensemble des isotopologues avec leur masse et intensité relative respective

https://www.chemcalc.org

Exercice

- **Dessiner la distribution isotopique de:**
  - $C_2^{+\bullet}$
  - $Cl_2^{+\bullet}$
  - $Br_2^{+\bullet}$

Elem	A	A	A+1	A+1	A+2	A+2	A+4	A+4
H	1	100	2	0.01				
C	12	100	13	1.08				
N	14	100	15	0.37				
O	16	100	17	0.04	18	0.20		
P	31	100						
S	32	100	33	0.79	34	4.47	36	0.01
F	19	100						
Cl	35	100			37	32.00		
Br	79	100			81	97.28		
I	127	100						

https://biooriented.cheminfo.org

Trouver la MF au départ de la distribution isotopique

Autres exercices sur https://www.chemcalc.org

	Masse nominale	Abondance relative (%)	Abondance (%)	Masse isotopique [u]	Masse atomique
H	1 2	100 0.01	99.99 0.01	1.007825 2.014101	1.008
C	12 13	100 1.08	98.93 1.07	12.000000 13.003354	12.011
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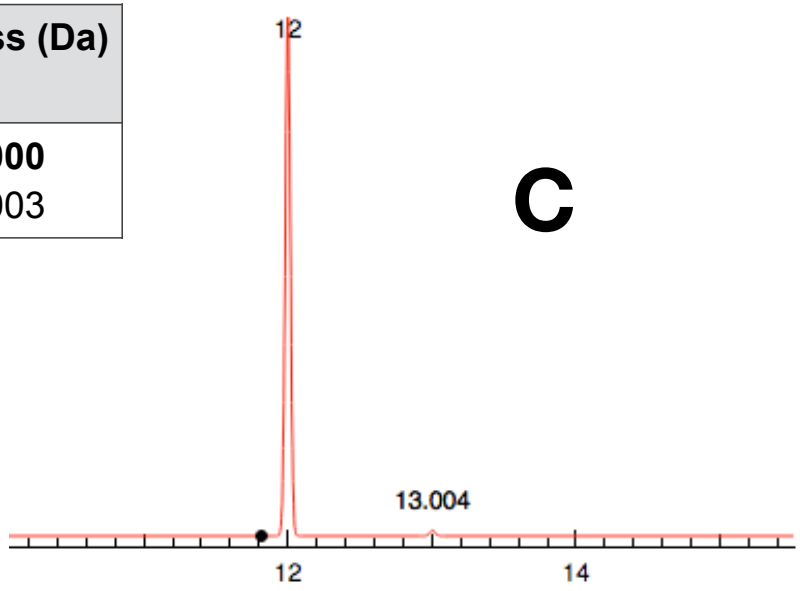
Br	79 81	100 97.28	50.69 49.31	78.918337 80.916290	79.903
I	127	100	100	126.904473	126.904

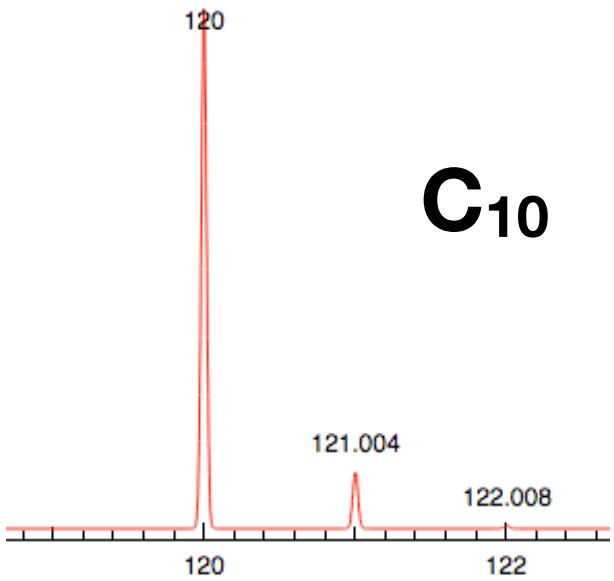
Electron: 0.00054858

Plusieurs carbones

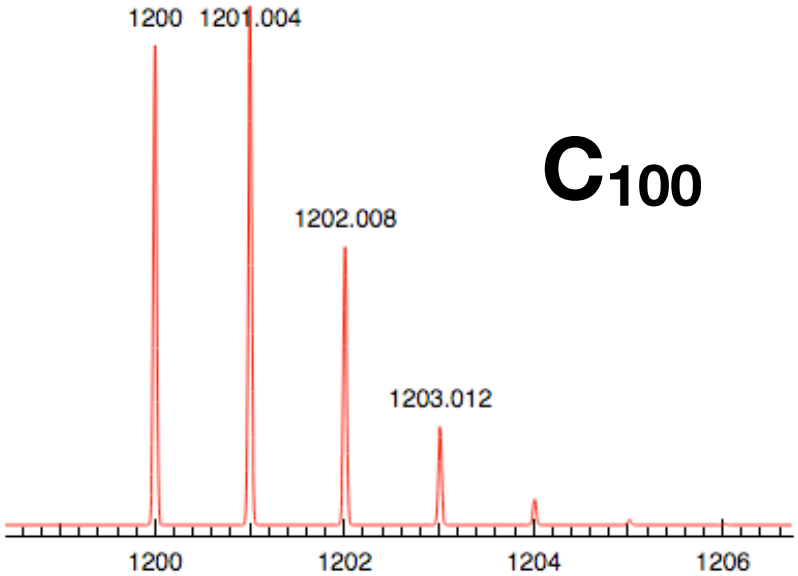
	Nominal mass	Abundance (%)	Mass (Da)
C	**12**	**98.93**	**12.000**
	13	1.07	13.003



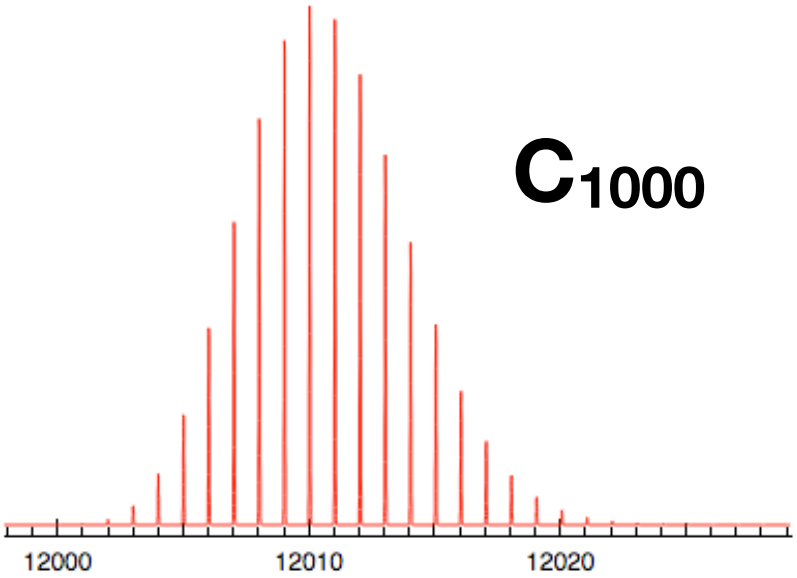
C



C_{10}

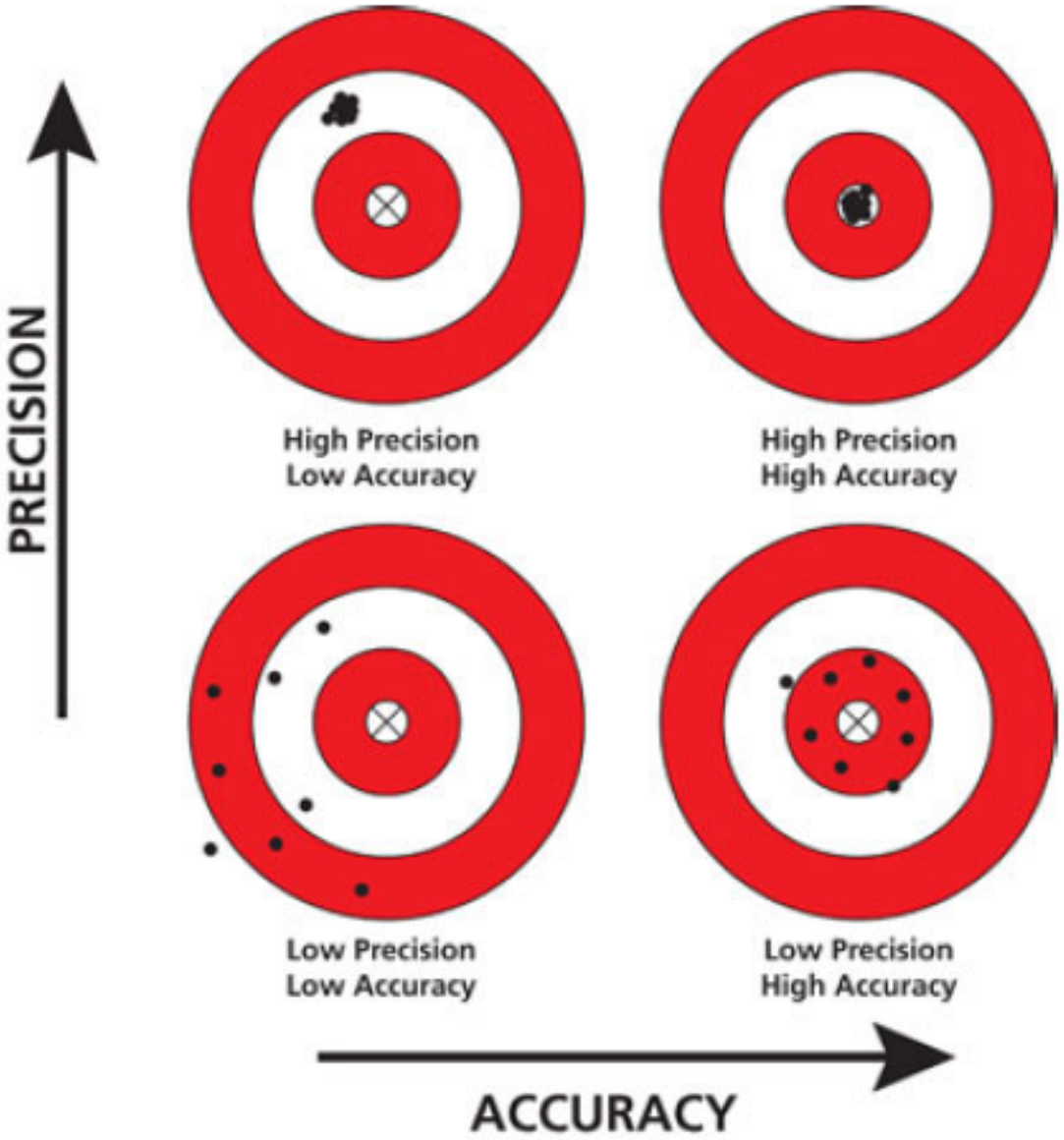


C_{100}



C_{1000}

Répétabilité / Exactitude



Répétabilité

=

precision

Exactitude

=

accuracy

Exactitude (accuracy)

$$Exactitude = Mass\ accuracy = \frac{m_{experimental} - m_{theory}}{m_{theory}} * 10^6 ppm$$

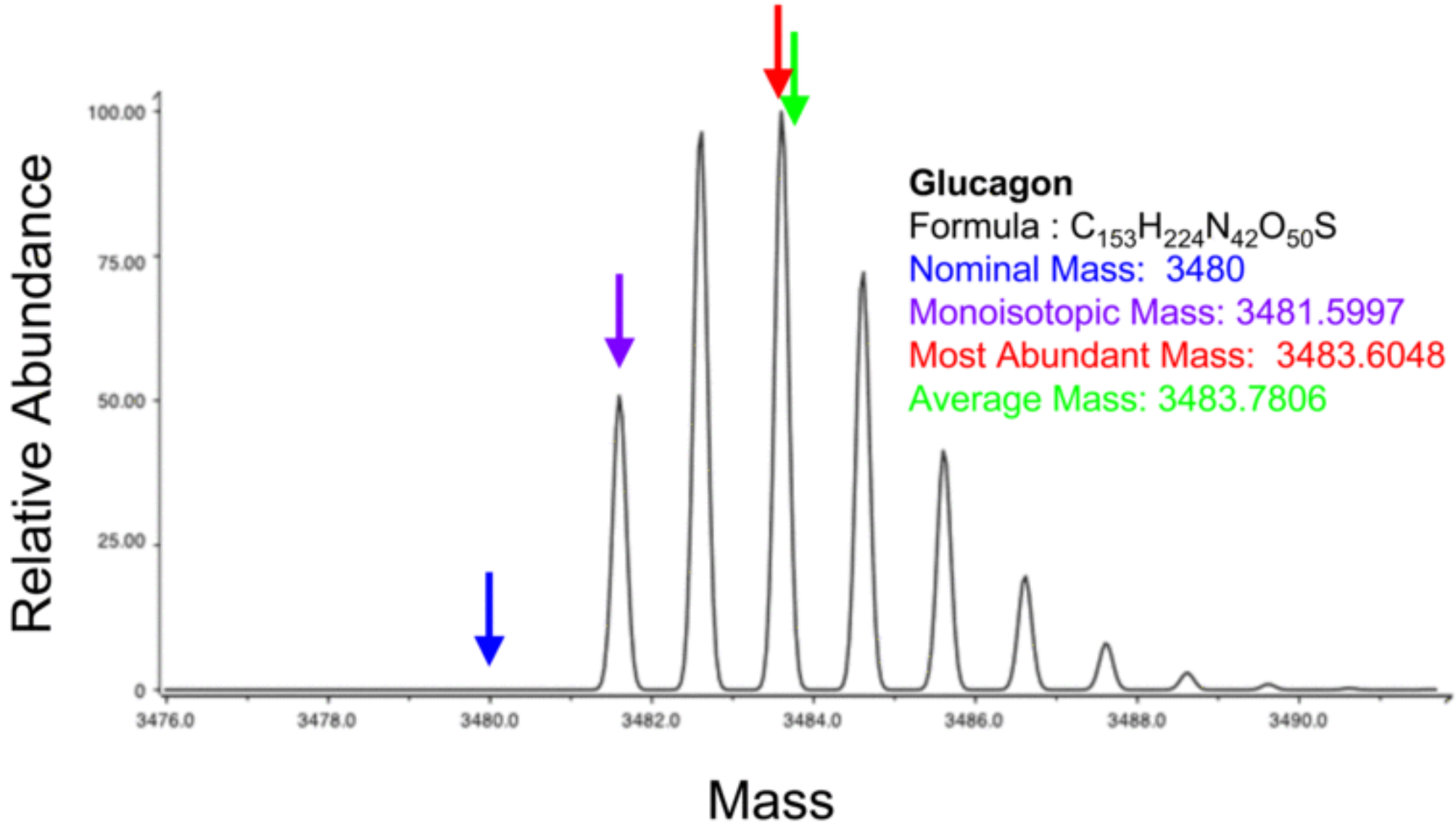
Mass defect

	Isotope	Abondance (%)	Masse isotopique [u]
H	1	99.99	1.008
	2	0.01	2.014
C	12	98.93	12.000
	13	1.07	13.003
N	14	99.64	14.003
	15	0.36	15.000
O	16	99.76	15.995
	17	0.04	16.999
	18	0.20	17.999
S	32	94.99	31.972
	33	0.75	32.971
	34	4.25	33.968
	36	0.01	35.967

SCN^-

Masse majoritaire

Masse correspondante au pic majoritaire observé dans le spectre de masse
Dépend de la largeur des pics (résolution)

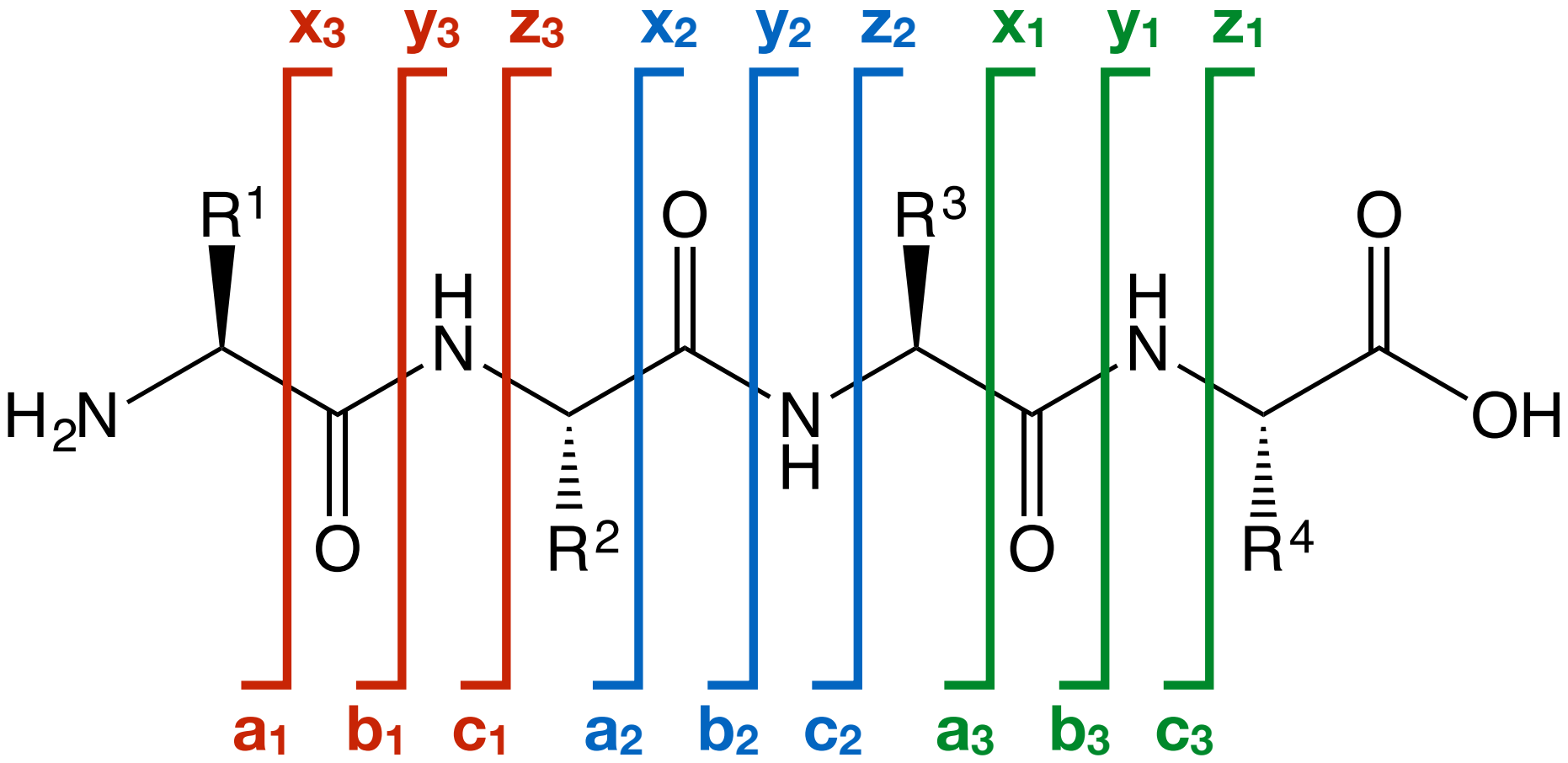

Relative Abundance
100.00
75.00
50.00
25.00
0
3476.0
3478.0
3480.0
3482.0
3484.0
3486.0
3488.0
3490.0
Mass
Glucagon
Formula : $C_{153}H_{224}N_{42}O_{50}S$
Nominal Mass: 3480
Monoisotopic Mass: 3481.5997
Most Abundant Mass: 3483.6048
Average Mass: 3483.7806

Cys100

Exercices intégrés

Exo

Peptide fragmentation



Demo

Proteomics

Protein digestion

ASP GLU ILE LYS ILE VAL LYS TYR PRO ASP PRO ILE LEU
ARG ARG ARG SER GLU VAL THR ASN PHE ASP ASP ASN LEU
LYS ARG VAL VAL ARG LYS MSE PHE ASP ILE MSE TYR GLU
SER LYS GLY ILE GLY LEU SER ALA PRO GLN VAL ASN ILE
SER LYS ARG ILE ILE VAL TRP ASN ALA LEU TYR GLU LYS
ARG LYS GLU GLU ASN GLU ARG ILE PHE ILE ASN PRO SER
ILE VAL GLU GLN SER LEU VAL LYS LEU LYS LEU ILE GLU
GLY CYS LEU SER PHE GLY ILE GLU GLY LYS VAL GLU ARG
PRO SER ILE VAL SER ILE SER TYR TYR ASP ILE ASN GLY
TYR LYS HIS LEU LYS ILE LEU LYS GLY ILE HIS SER ARG
ILE PHE GLN HIS GLU PHE ASP HIS LEU ASN GLY THR LEU
PHE ILE ASP LYS MSE THR GLN VAL ASP LYS LYS LYS VAL
ARG PRO LYS LEU ASN GLU LEU ILE ARG ASP TYR LYS ALA
THR HIS SER GLU GLU PRO LEU GLU HIS HIS HIS HIS HIS
HIS

Example: digestion of peptide deformylase by chymotrypsin

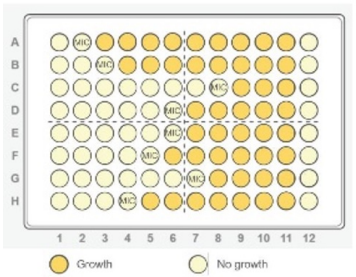
Déréplication

https://octochemdb.cheminfo.org

Natural product: dereplication

Natural product extraction

Fractionation



Biological testing

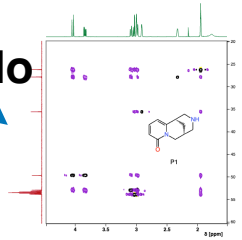
HRMS

Dereplication

Known product ?

Yes

No



Searching for existing information

LOTUS

Natural products : 276 K

COCONUT

COllection of Open Natural ProdUcts

Natural Products: 407 K

GNPS

Spectra : 410 K

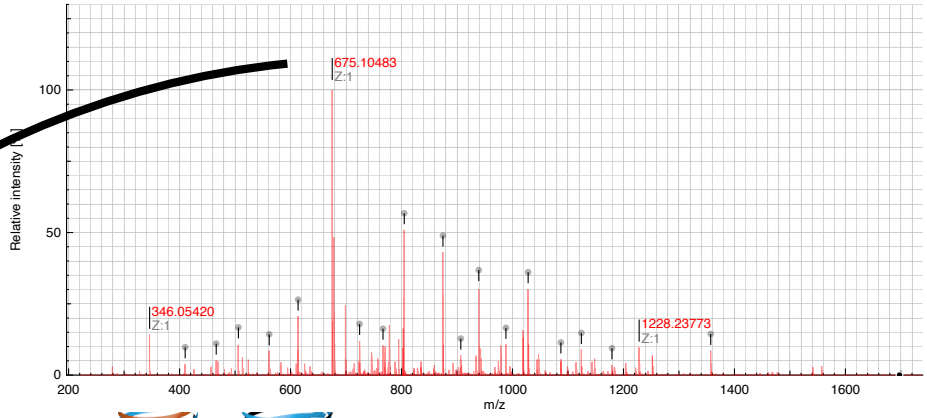
PubChem

Compounds : 112 M

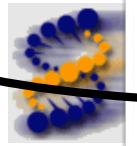
PubMed

Articles : 34 M

octochemdb

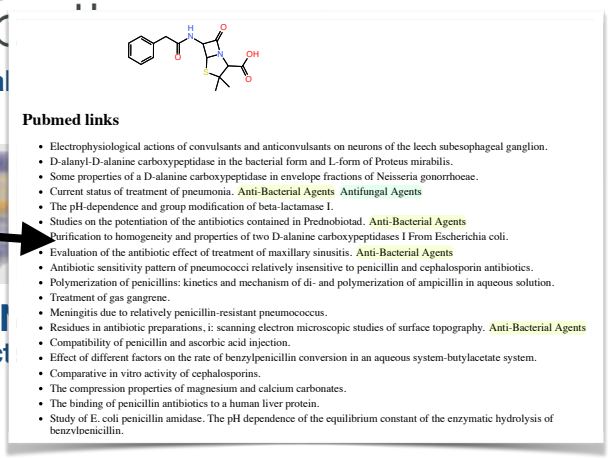


Natural



BIDD Group

Natural Product



Pubmed links

- Electrophysiological actions of convulsants and anticonvulsants on neurons of the leech subesophageal ganglion.
- D-alanyl-D-alanine carboxypeptidase in the bacterial form and L-form of Proteus mirabilis.
- Some properties of a D-alanine carboxypeptidase in envelope fractions of Neisseria gonorrhoeae.
- Current status of treatment of pneumonia. Anti-Bacterial Agents Antifungal Agents
- The pH-dependence and group modification of beta-lactamase I.
- Studies on the potentiation of the antibiotics contained in Prednobiotad. Anti-Bacterial Agents
- Purification to homogeneity and properties of two D-alanine carboxypeptidases I From Escherichia coli.
- Evaluation of the antibiotic effect of treatment of maxillary sinusitis. Anti-Bacterial Agents
- Antibiotic sensitivity pattern of pneumococci relatively insensitive to penicillin and cephalosporin antibiotics.
- Polymerization of penicillins: kinetics and mechanism of di- and polymerization of ampicillin in aqueous solution.
- Treatment of gas gangrene.
- Meningitis due to relatively penicillin-resistant pneumococcus.
- Residues in antibiotic preparations, i: scanning electron microscopic studies of surface topography. Anti-Bacterial Agents
- Compatibility of penicillin and ascorbic acid injection.
- Effect of different factors on the rate of benzylpenicillin conversion in an aqueous system-butylacetate system.
- Comparative in vitro activity of cephalosporins.
- The compression properties of magnesium and calcium carbonates.
- The binding of penicillin antibiotics to a human liver protein.
- Study of E. coli penicillin amidase. The pH dependence of the equilibrium constant of the enzymatic hydrolysis of benzylpenicillin.

NCBI Taxonomy

Taxonomies : 2.5 M

PubChem Bioassay

Bioassay results : 5.9 M

https://octochemdb.cheminfo.org

Degré d’insaturation

Exercice

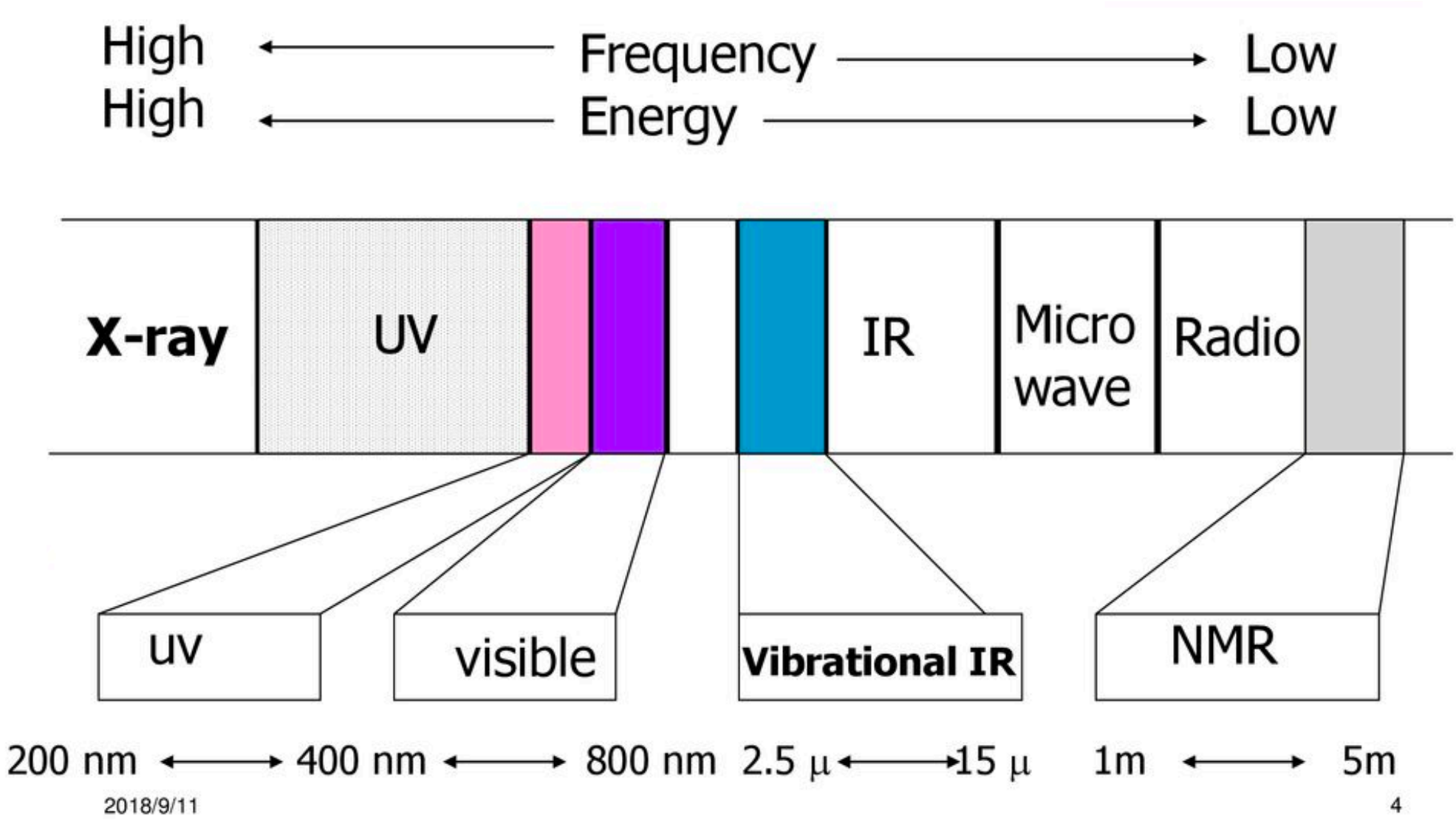
Isomères de structure

C_3H_7N

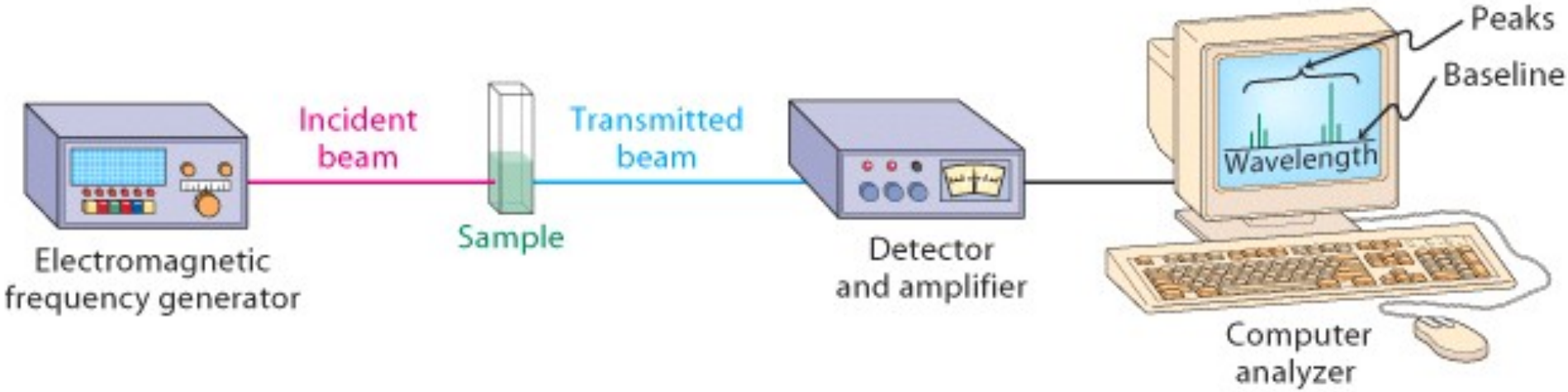
Demo

Spectroscopie infrarouge

Electromagnetic spectrum

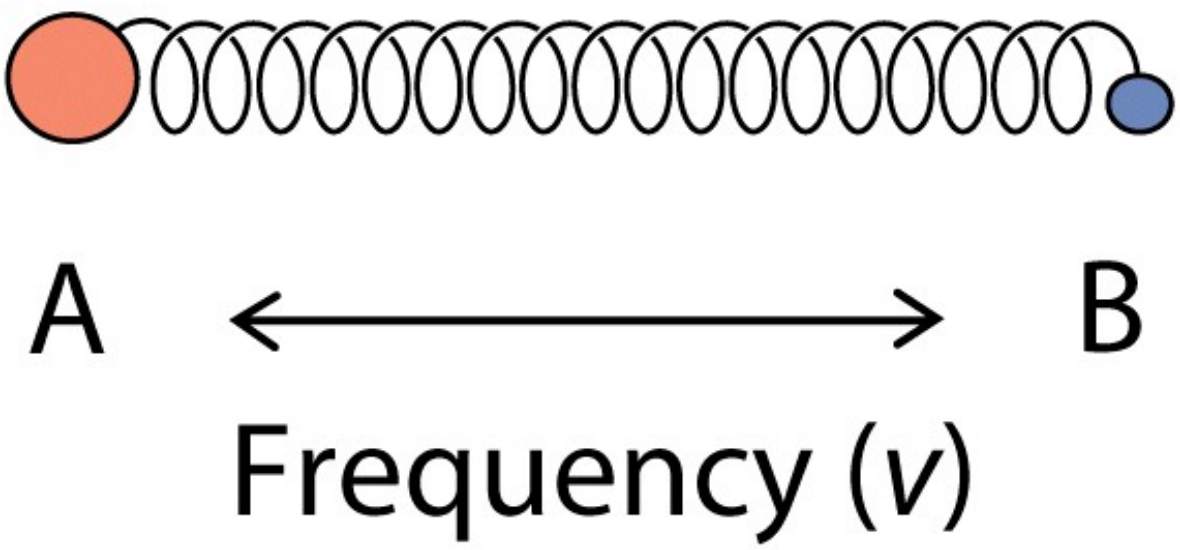


IR spectrophotometer



IR of ethylbenzene

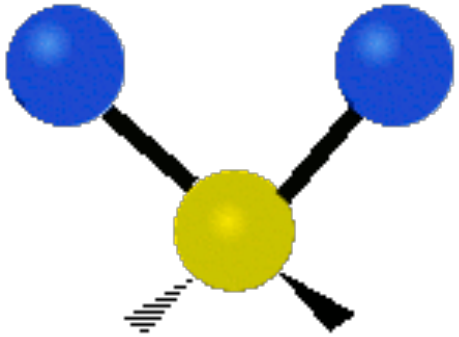
Loi de Hooke



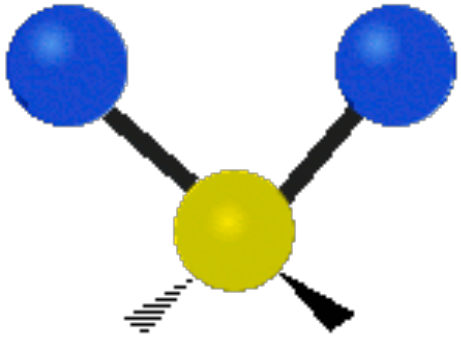
$$\bar{v} = k\sqrt{f\frac{m_1 + m_2}{m_1 m_2}}$$

$$\overline{v} = k\sqrt{f\frac{m_1 + m_2}{m_1 m_2}}$$

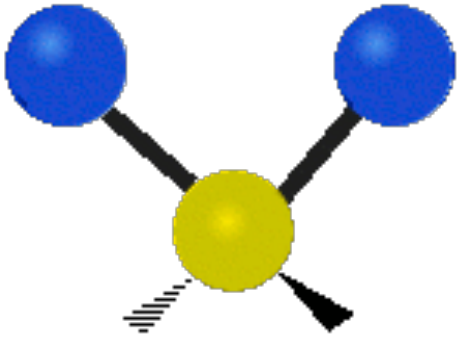
Vibrations moléculaires



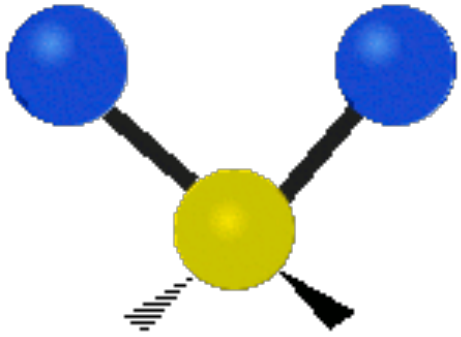
Symmetrical stretching



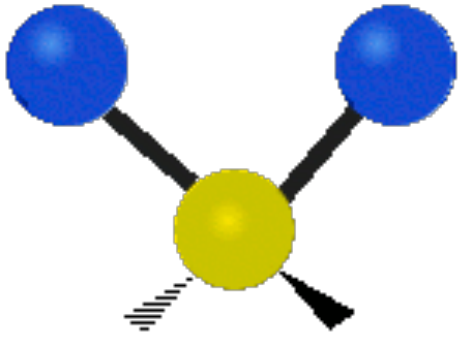
Scissoring



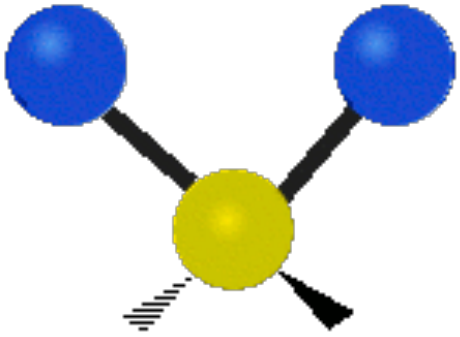
Wagging



Asymmetrical stretching



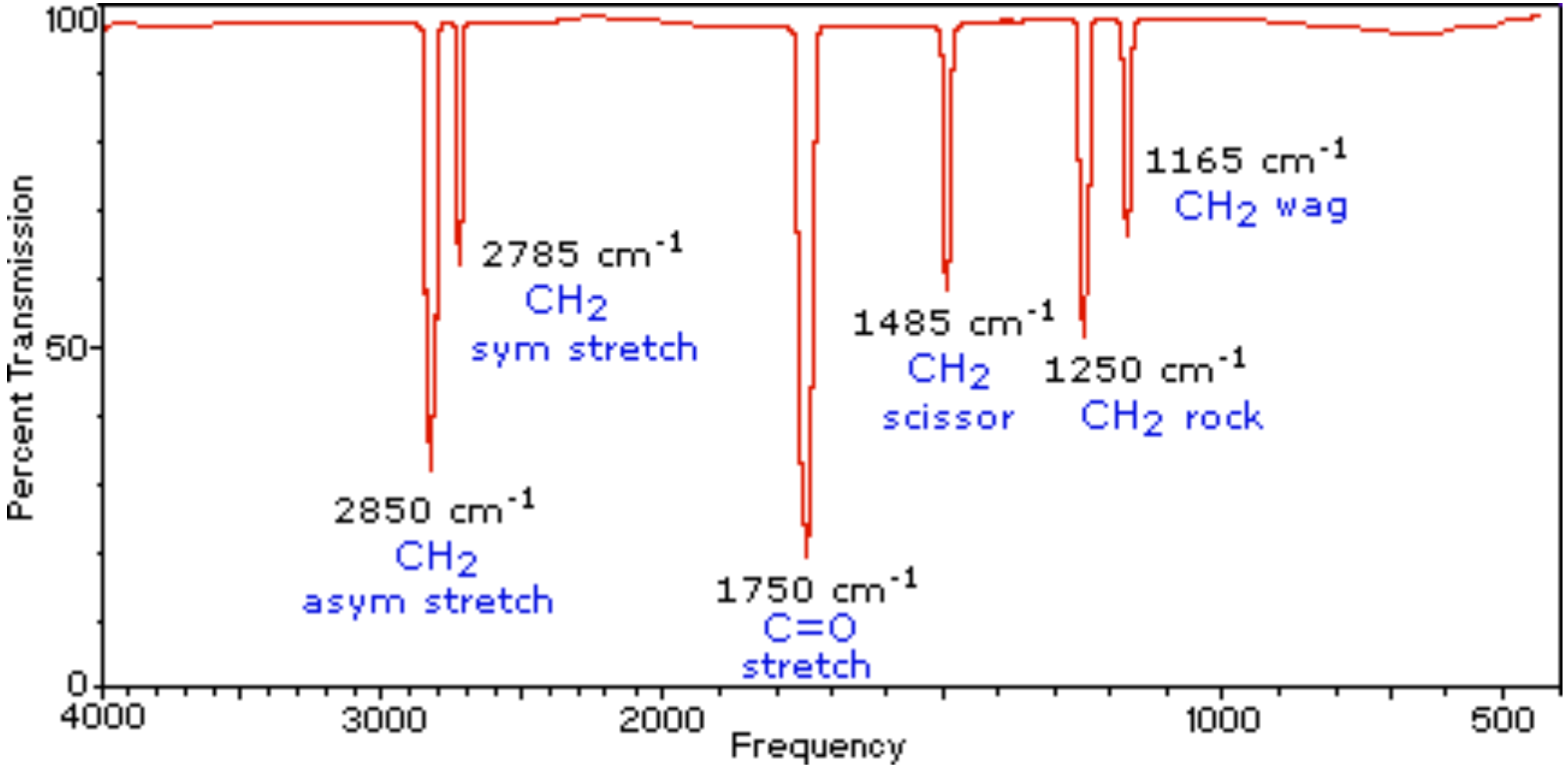
Rocking



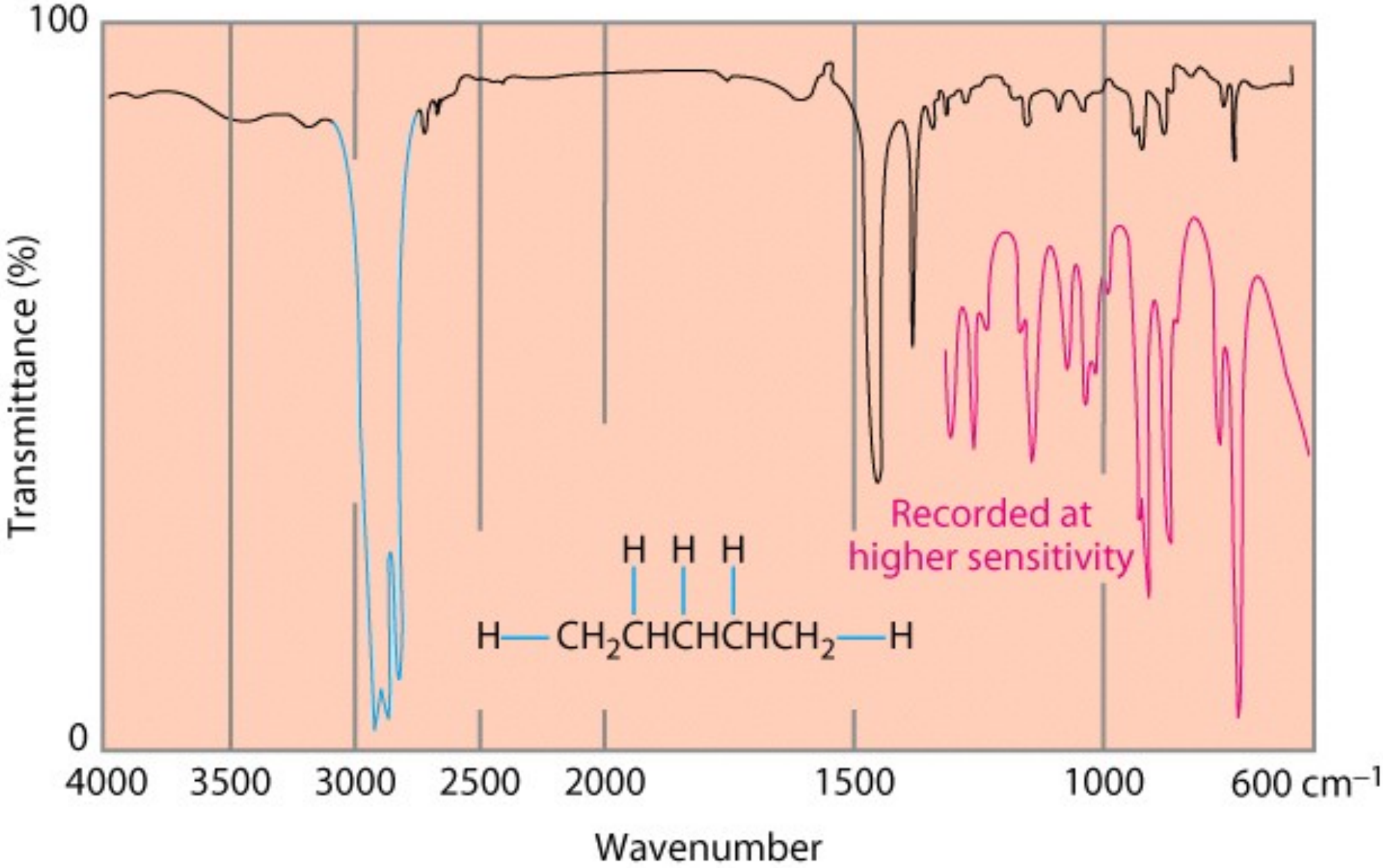
Twisting

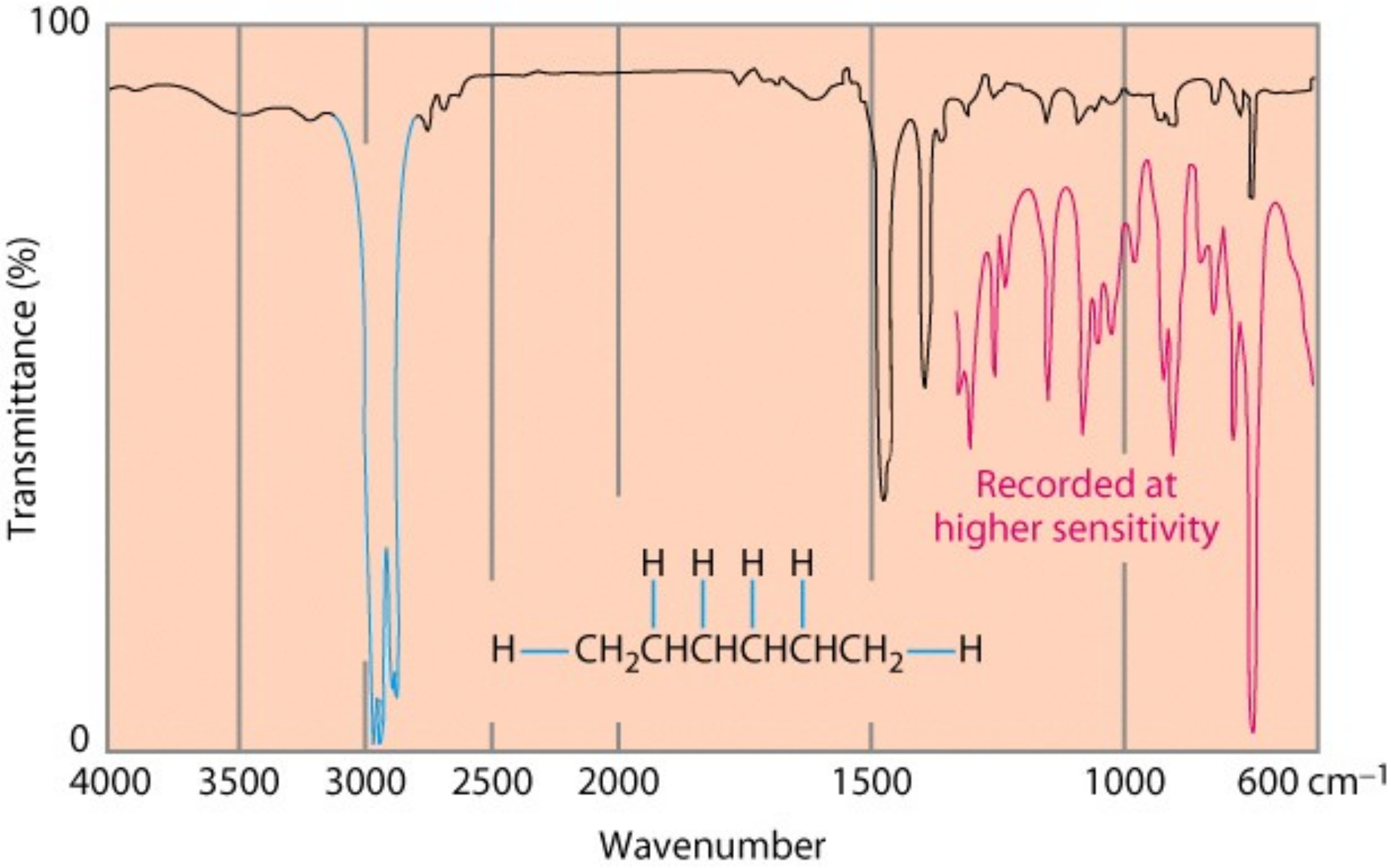
Images from wikipedia

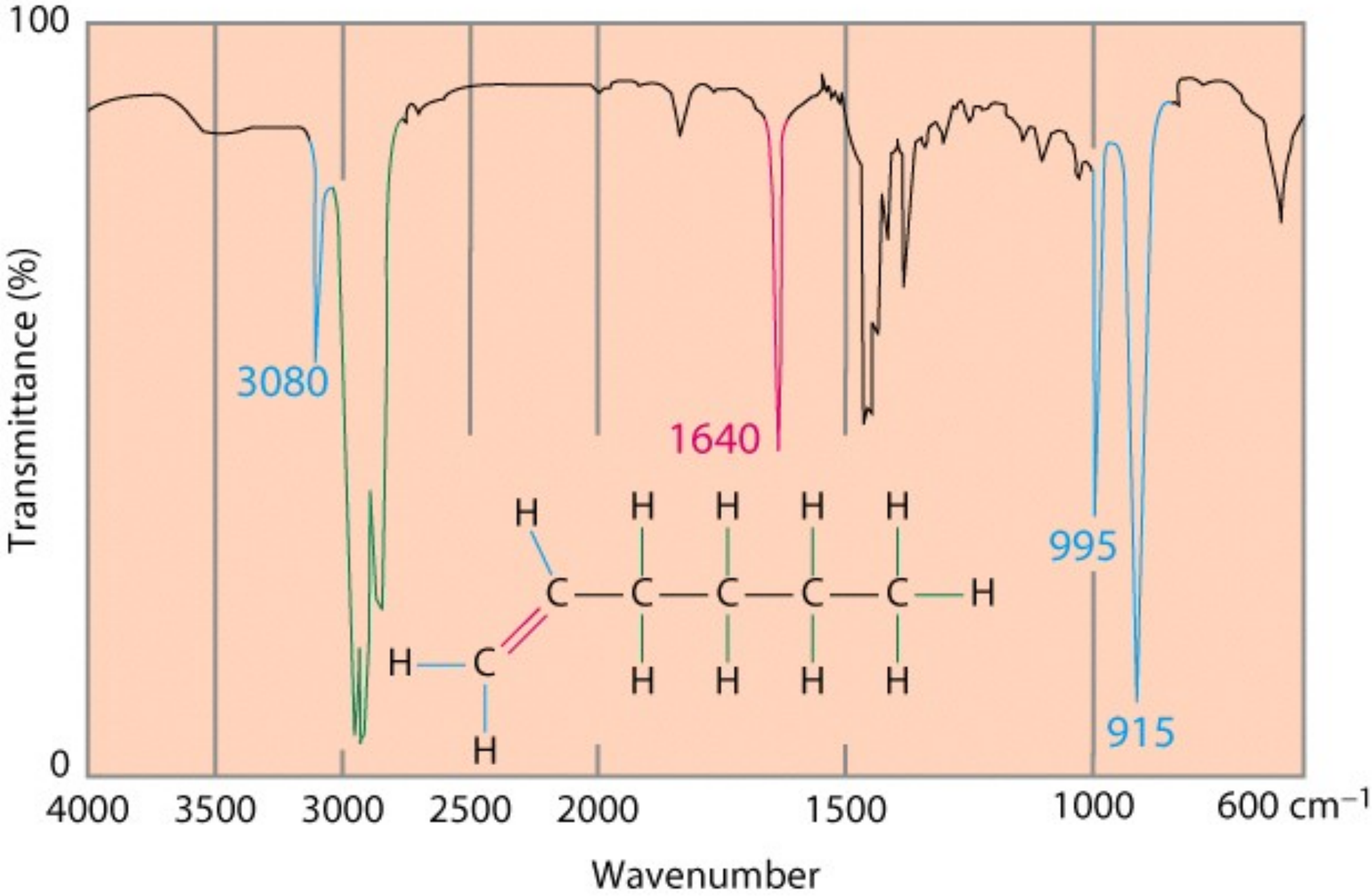
Formaldehyde

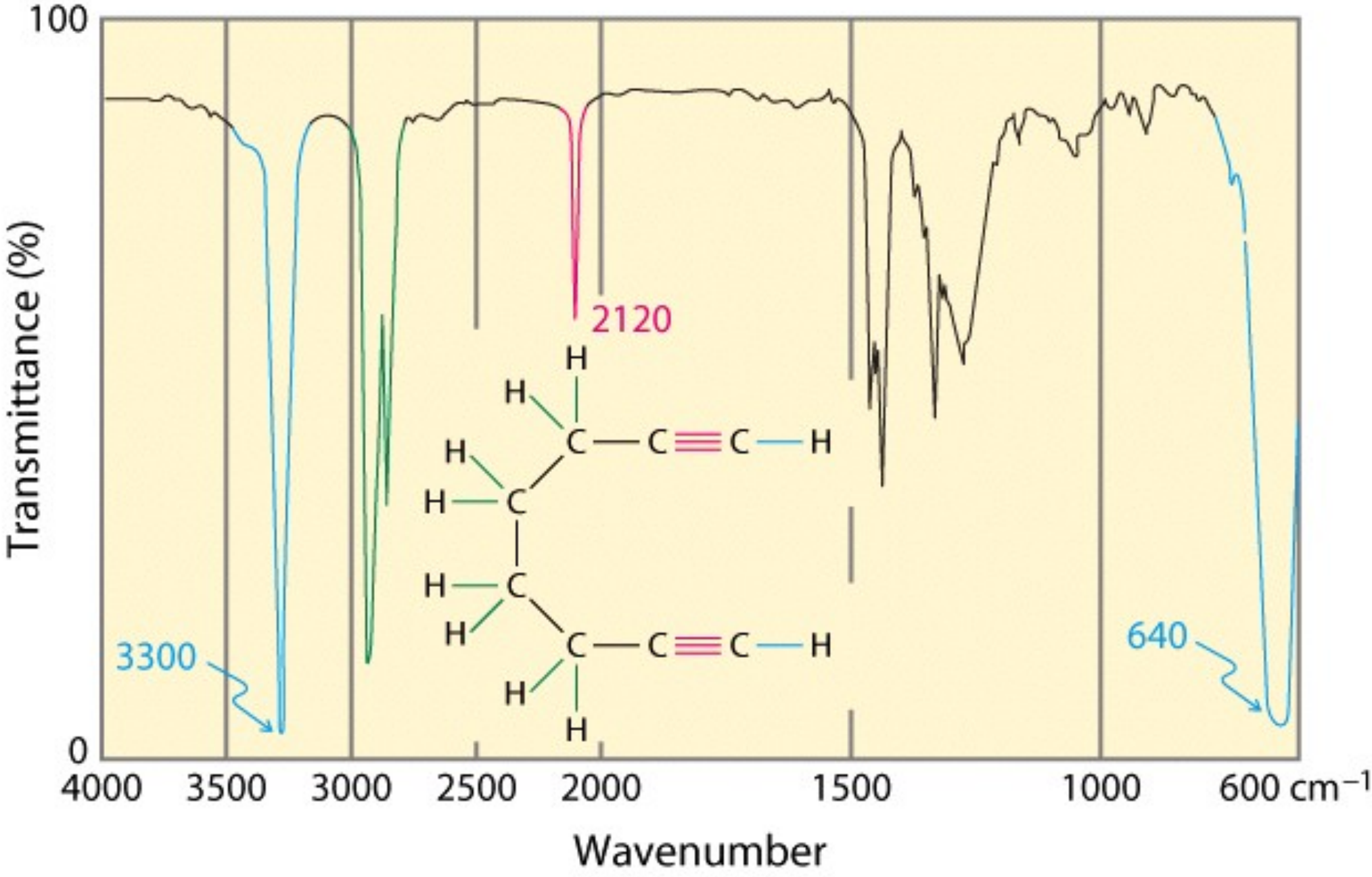


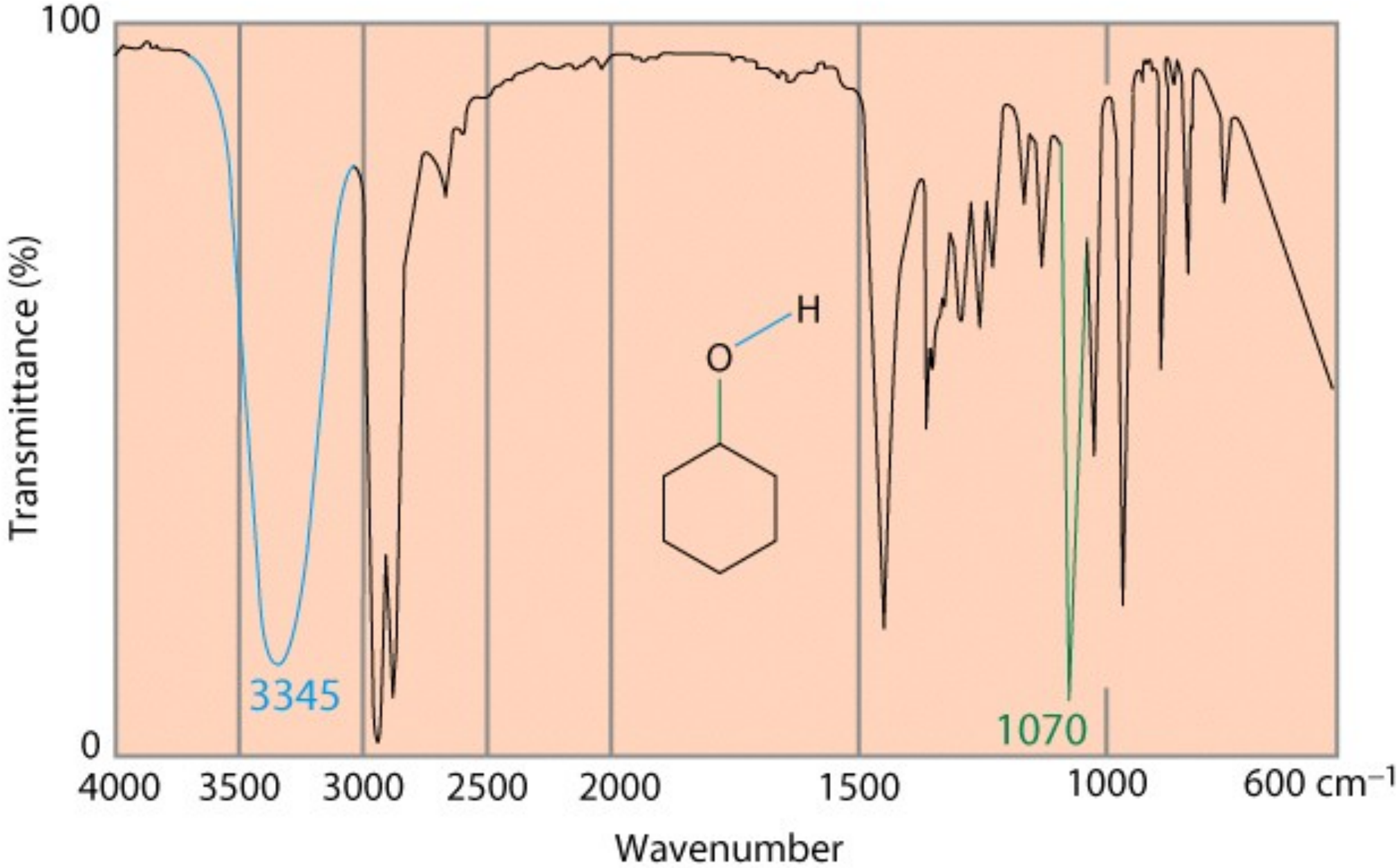
Demo

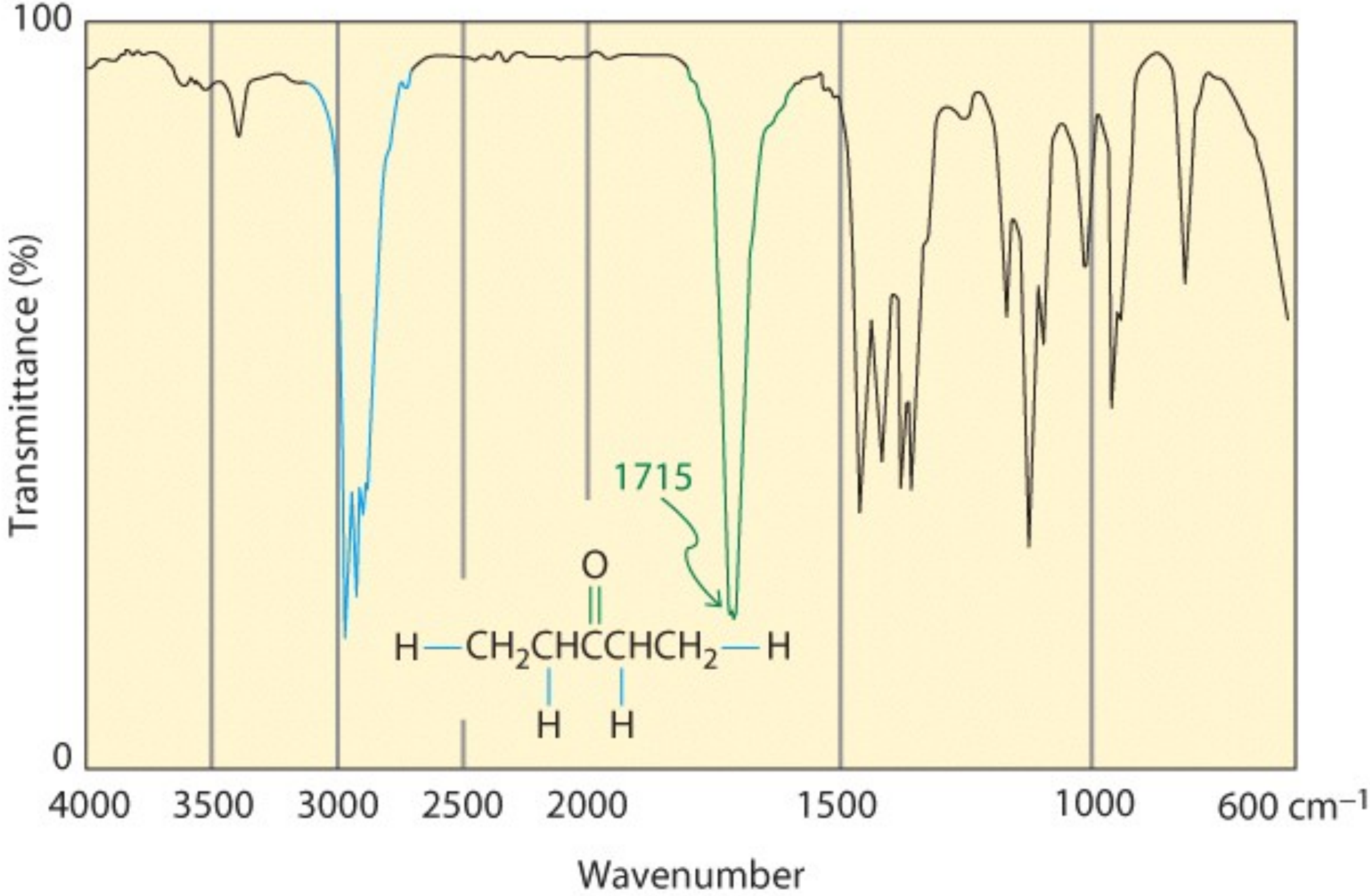

100
Transmittance (%)
0
Recorded at
higher sensitivity
H H H
H— $CH_2CHCHCHCH_2$ —H
4000
3500
3000
2500
2000
1500
1000
600 cm^{-1}
Wavenumber

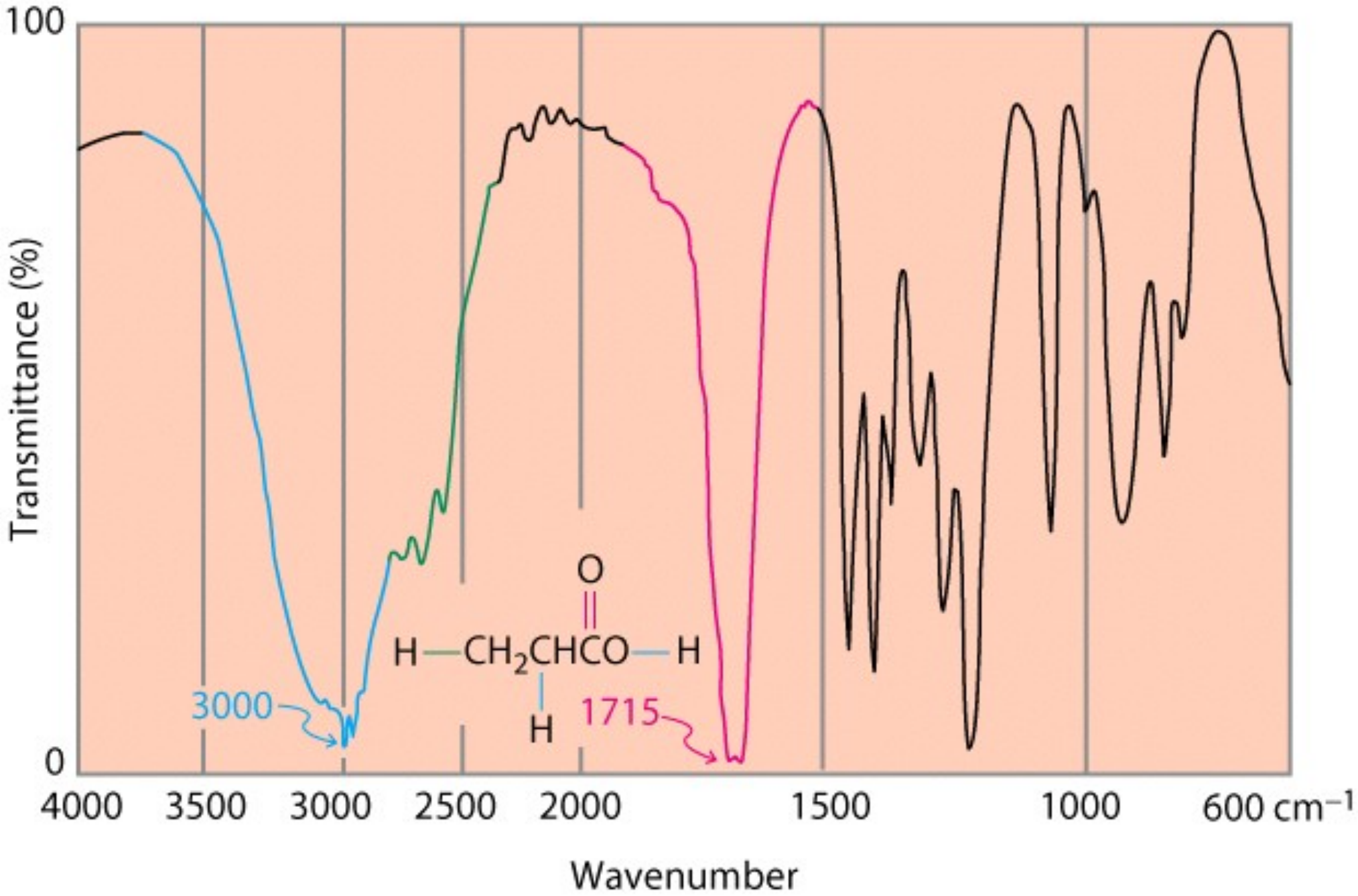

100
Transmittance (%)
0
Recorded at
higher sensitivity
H H H H
H—CH2CHCHCHCHCH2—H
4000
3500
3000
2500
2000
1500
1000
600 cm−1
Wavenumber

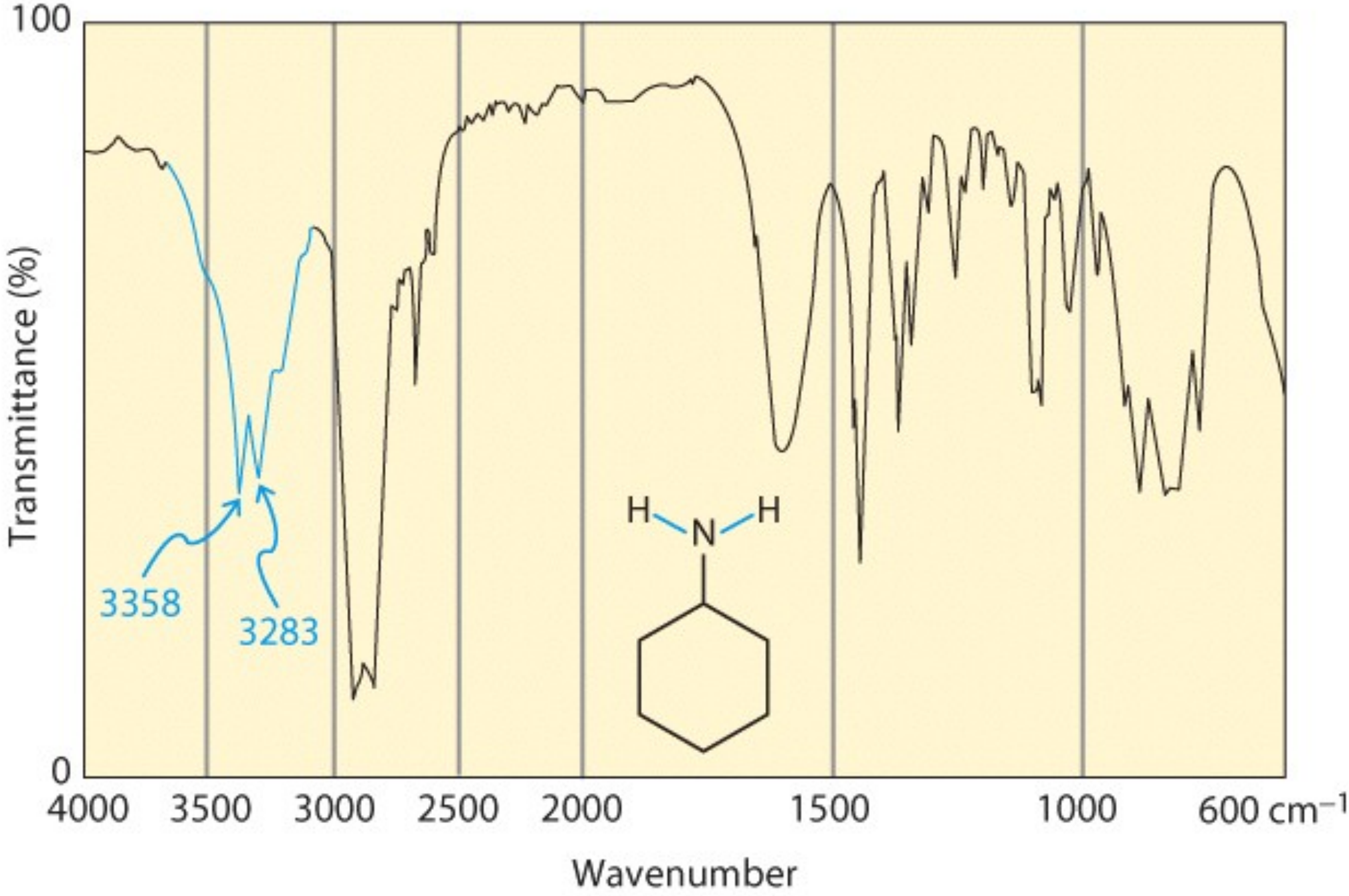

100
Transmittance (%)
0
3080
1640
995
915
4000
3500
3000
2500
2000
1500
1000
600 cm⁻¹
Wavenumber


100
Transmittance (%)
0
2120
3300
640
4000
3500
3000
2500
2000
1500
1000
600 cm⁻¹
Wavenumber


100
Transmittance (%)
0
3345
1070
O
H
4000
3500
3000
2500
2000
1500
1000
600 cm⁻¹
Wavenumber


100
Transmittance (%)
0
1715
O
H—CH2CHCCHCH2—H
H H
4000
3500
3000
2500
2000
1500
1000
600 cm−1
Wavenumber


100
Transmittance (%)
0
3000
1715
O
H—CH2CHCO—H
H
4000
3500
3000
2500
2000
1500
1000
600 cm−1
Wavenumber


100
Transmittance (%)
0
3358
3283
H
N
H
4000
3500
3000
2500
2000
1500
1000
600 cm⁻¹
Wavenumber

https://biooriented.cheminfo.org

Structure du produit inconnu au départ du spectre IR

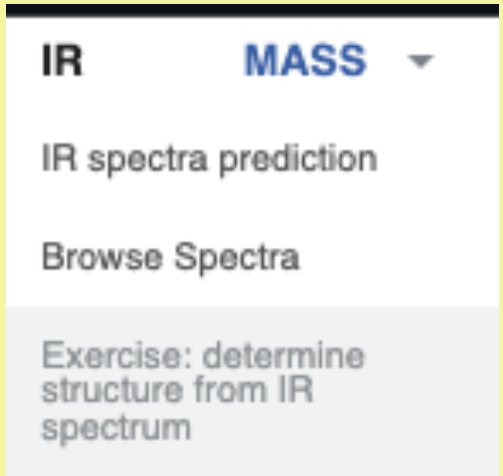
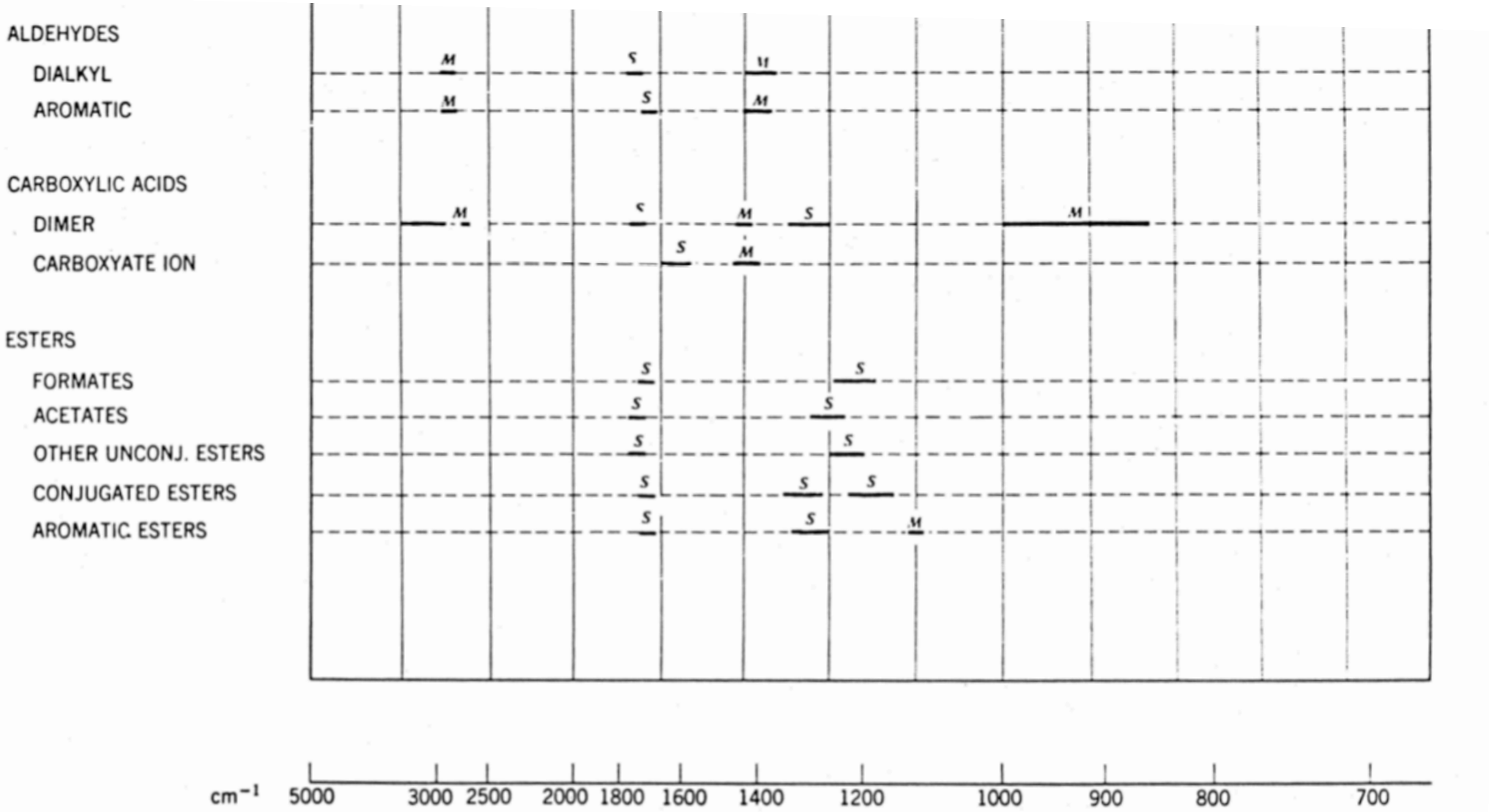


TABLE 11-4 Characteristic Infrared Stretching Wavenumber Ranges of Organic Molecules

Bond or functional group	$\tilde{\nu}$ (cm^{-1})	Bond or functional group	$\tilde{\nu}$ (cm^{-1})
RO—H (alcohols)	3200–3650	RC≡N (nitriles)	2220–2260
RCO—H (carboxylic acids)	2500–3300	RCH, RCR′ (aldehydes, ketones)	1690–1750
R_2N—H (amines)	3250–3500	RCOR′ (esters)	1735–1750
RC≡C—H (alkynes)	3260–3330	RCOH (carboxylic acids)	1710–1760
C=C, H (alkenes)	3050–3150	C=C (alkenes)	1620–1680
—C—H (alkanes)	2840–3000	RC—OR′ (alcohols, ethers)	1000–1260
RC≡CH (alkynes)	2100–2260		



*Three bands, sometimes a fourth band for ketals and a fifth band for acetals.

Atomes “équivalents”

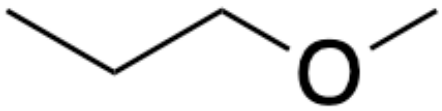
diethyl ether

Combien d'hydrogènes différents ?

- 1
- 2
- 3
- 4
- 5
- 10

Answer

methyl propyl ether

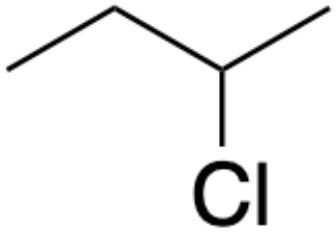


Combien d'hydrogènes différents ?

- 1
- 2
- 3
- 4
- 5
- 10

Answer

2-chlorobutane

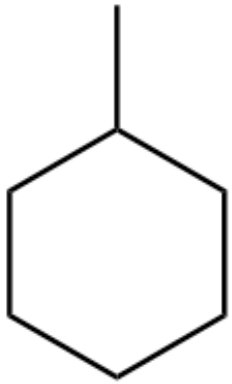


Combien d'hydrogènes différents ?

- 1
- 2
- 3
- 4
- 5
- 9

Answer

methylcyclohexane

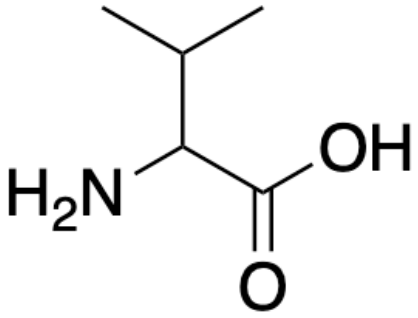


How many kind of protons

- 5
- 6
- 7
- 8
- 9
- 10

Answer

valine



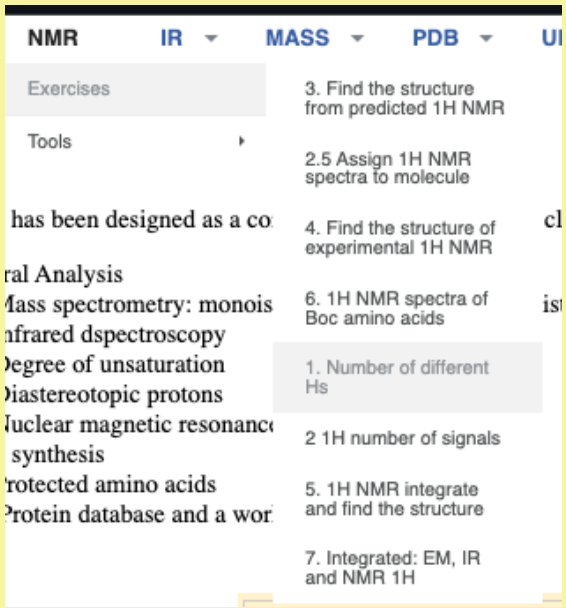
Combien d'hydrogènes différents ?

- 1
- 2
- 3
- 4
- 5
- 6
- 7

Answer

https://biooriented.cheminfo.org

Nombre d'hydrogènes différents

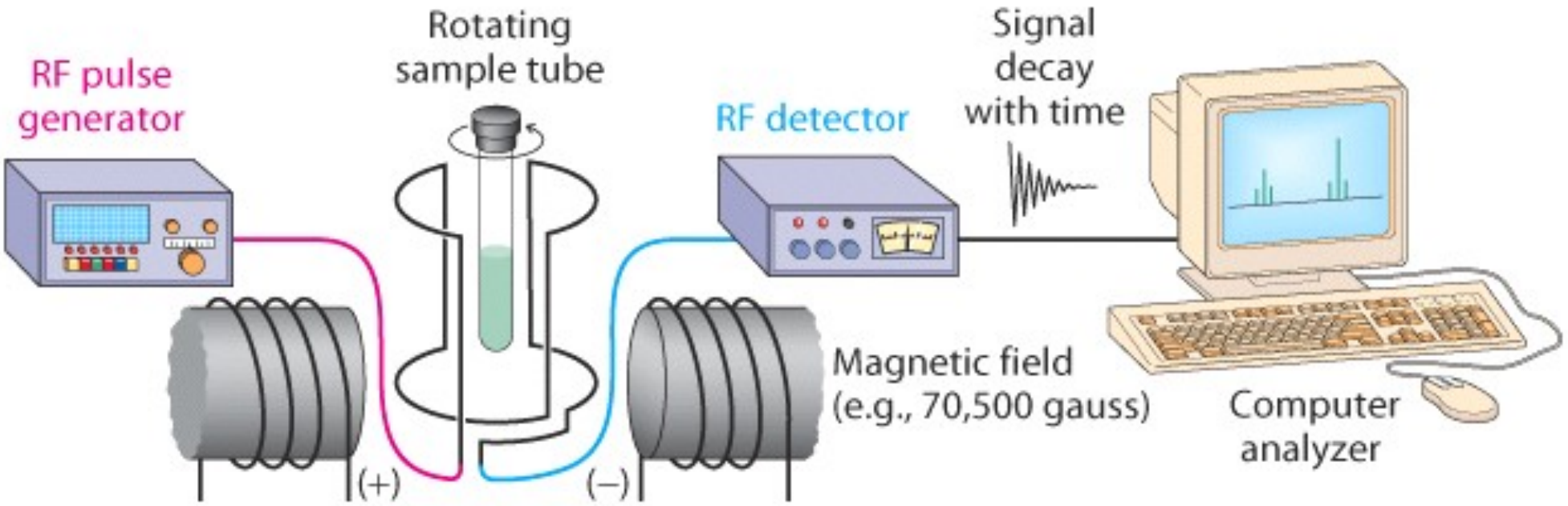


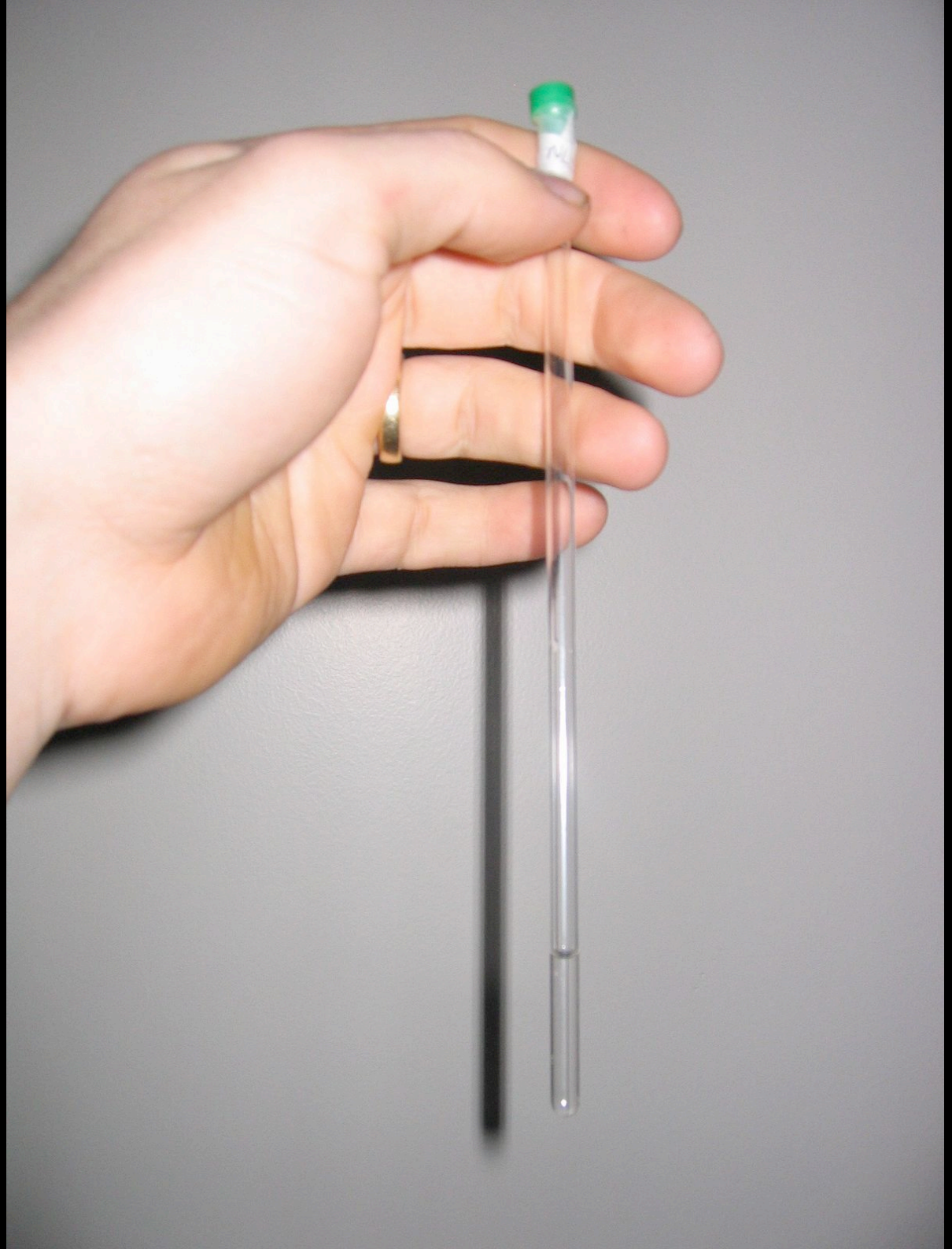
RMN

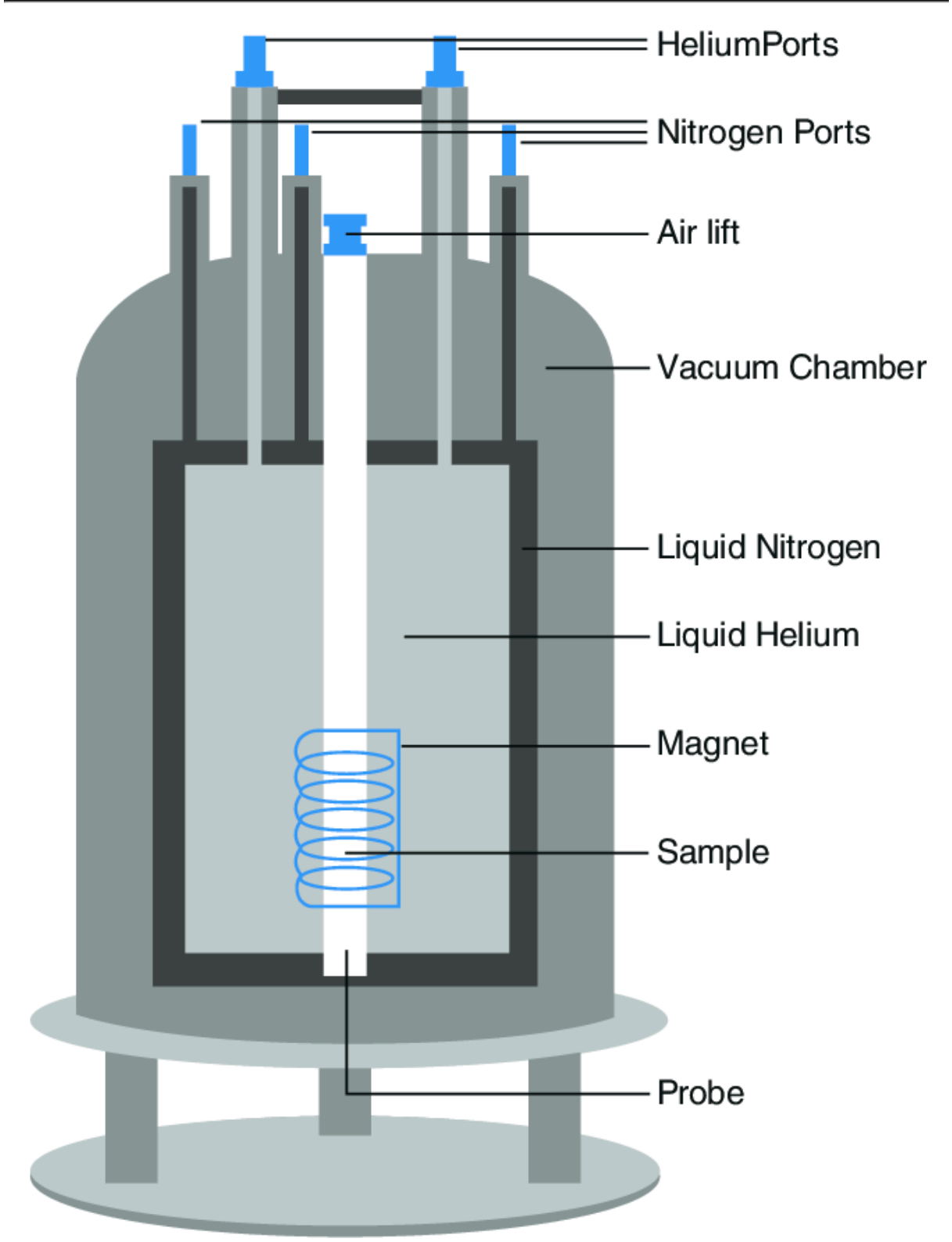
Résonance Magnétique Nucléaire

Prix Nobel:
- 1991 Richard Ernst
- 2002 Kurt Wüthrich

NMR spectroscopy

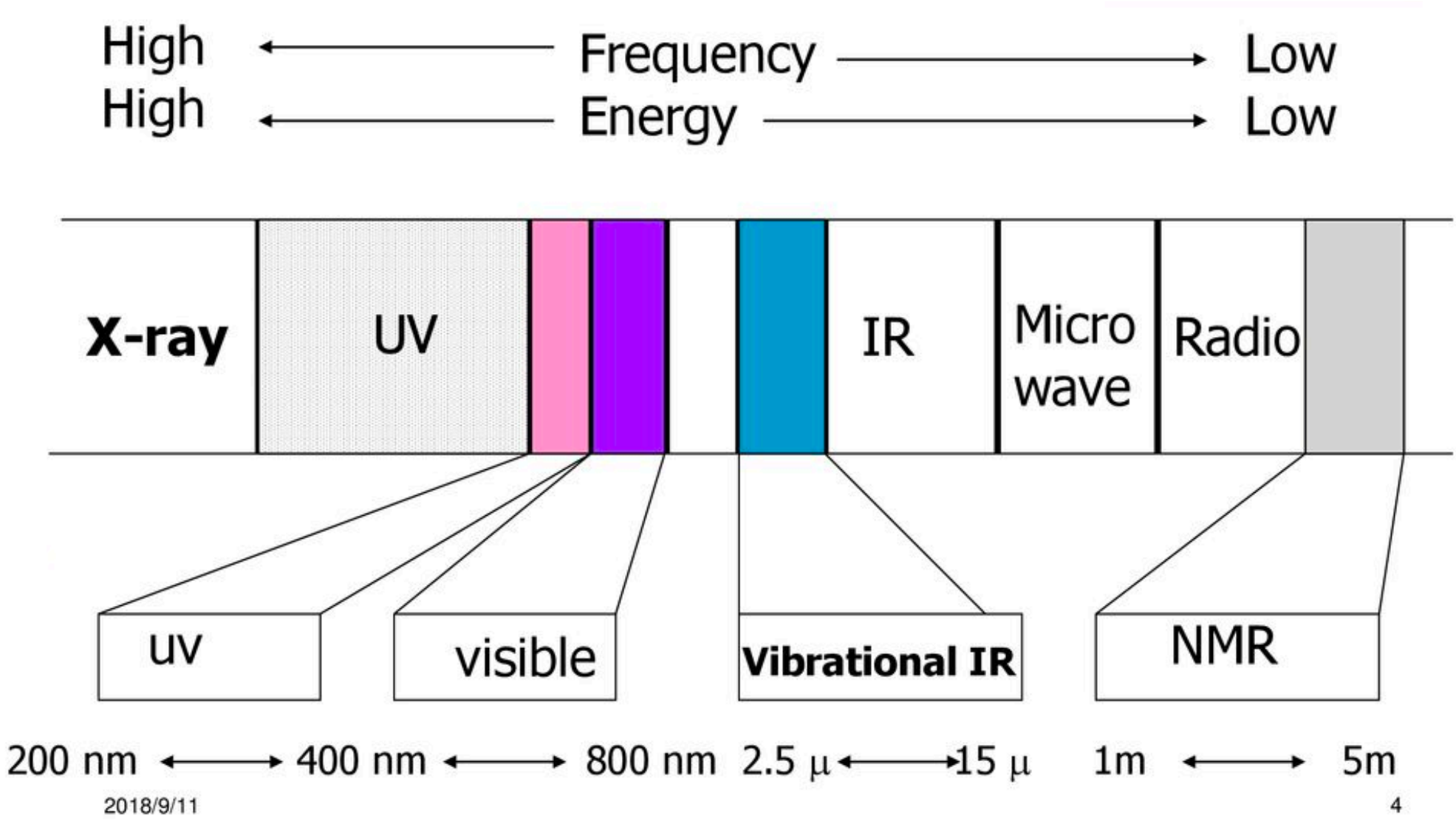





HeliumPorts
Nitrogen Ports
Air lift
Vacuum Chamber
Liquid Nitrogen
Liquid Helium
Magnet
Sample
Probe


BRUKER
Ascend™ 600
BRUKER
AVANCE III 600

Electromagnetic spectrum



United Kingdom

- 380–399.9 MHz: Terrestrial Trunked Radio (TETRA) service for emergency use
- 430–440 MHz: Amateur radio (70 cm band)
- 446.0–446.2 MHz : European unlicensed PMR service => PMR446
- 457–464 MHz: Scanning telemetry and telecontrol, assigned mostly to the water, gas, and electricity industries
- 606–614 MHz: Radio microphones and radio-astronomy
- 470–862 MHz: Previously used for analogue TV channels 21–69 (until 2012).
  - Currently channels 21–37 and 39–48 are used for Freeview digital TV.[6] Channels 55-56 were previously used by temporary muxes COM7 and COM8, channel 38 was used for radio astronomy but has been cleared to allow PMSE users access on a licensed, shared basis.
  - 694-790 MHz:[7] i.e. Channels 49-60 have been cleared, to allow these channels to be allocated for 5G cellular communication.
  - 791–862 MHz,[8] i.e. channels 61–69 inclusive were previously used for licensed and shared wireless microphones (channel 69 only), has since been allocated to 4G cellular communications.
- 863–865 MHz: Used for licence-exempt wireless systems.
- 863–870 MHz: Short range devices, LPWAN IoT devices such as NarrowBand-IoT.
- 870–960 MHz: Cellular communications (GSM900 - Vodafone and O2 only) including GSM-R and future TETRA
- 1240–1325 MHz: Amateur radio (23 cm band)

Source: https://en.wikipedia.org/wiki/Ultra_high_frequency

Caractéristiques des principaux noyaux

Noyau	Spin I	Abondance naturelle (%)	υ obs. (MHz) (B_0=2.3488 T)	Rapport gyromagnétique γ [10^7 rad T^{-1} s^{-1}]	Relative sensibility
^{1}H	1/2	99.98	100	26.7519	100
^{2}H	1	0.016	15.3	4.1066	0.96
^{10}B	3	19.58	10.7	2.8746	1.99
^{11}B	3/2	80.42	32.0	8.5843	16.5
^{12}C	0	98.9	–	–	–
^{13}C	1/2	1.108	25.1	6.7283	1.59
^{14}N	1	99.63	7.2	1.9338	0.10
^{15}N	1/2	0.37	10.1	–2.712	0.10
^{16}O	0	99.96	–	–	–
^{17}O	5/2	0.037	13.6	-3.6279	2.91
^{19}F	1/2	100	97.1	25.181	83.3
^{29}Si	1/2	4.70	19.9	–5.3188	0.78
^{31}P	1/2	100	40.4	10.841	6.63

ethyl acetate

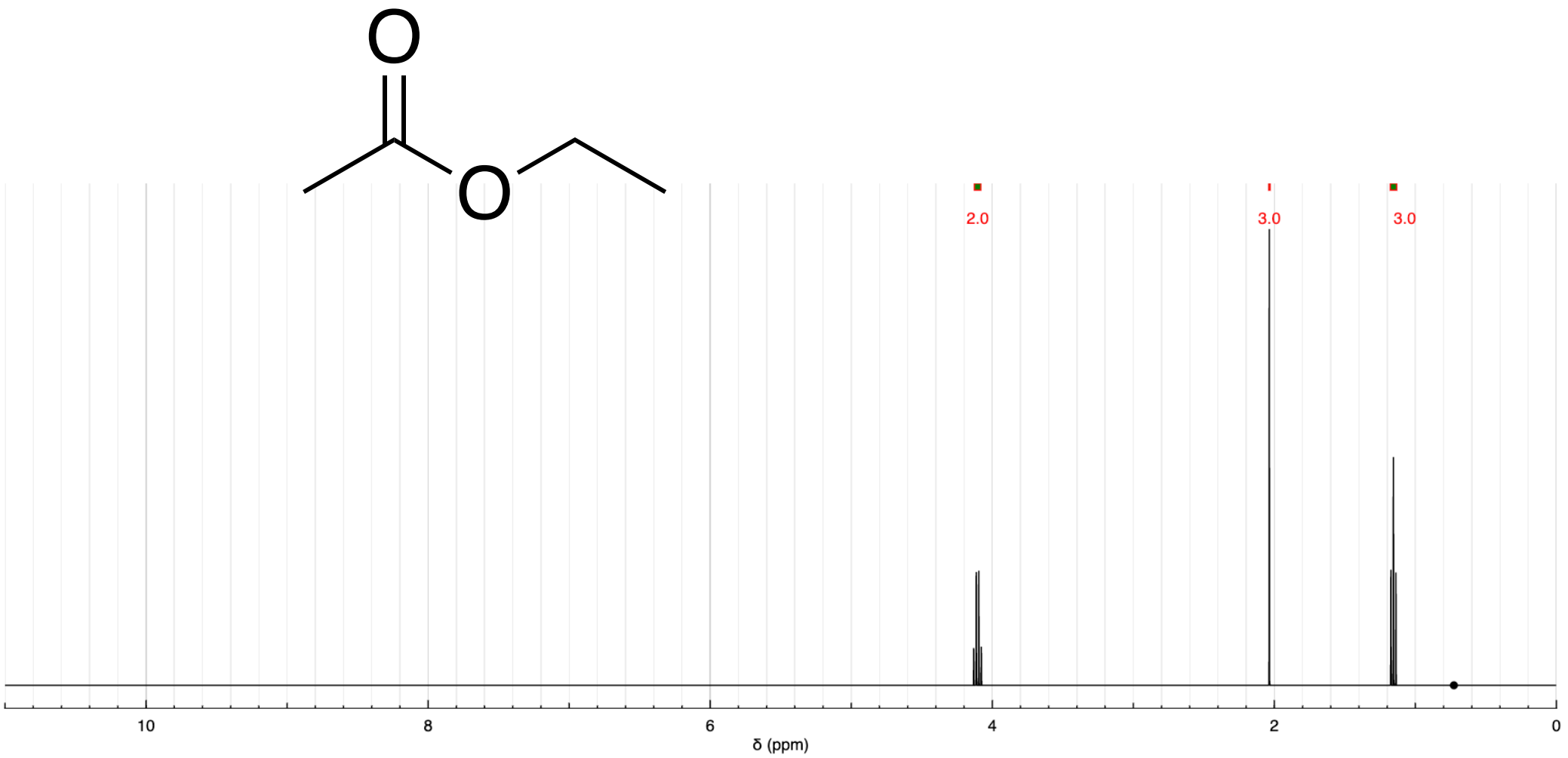
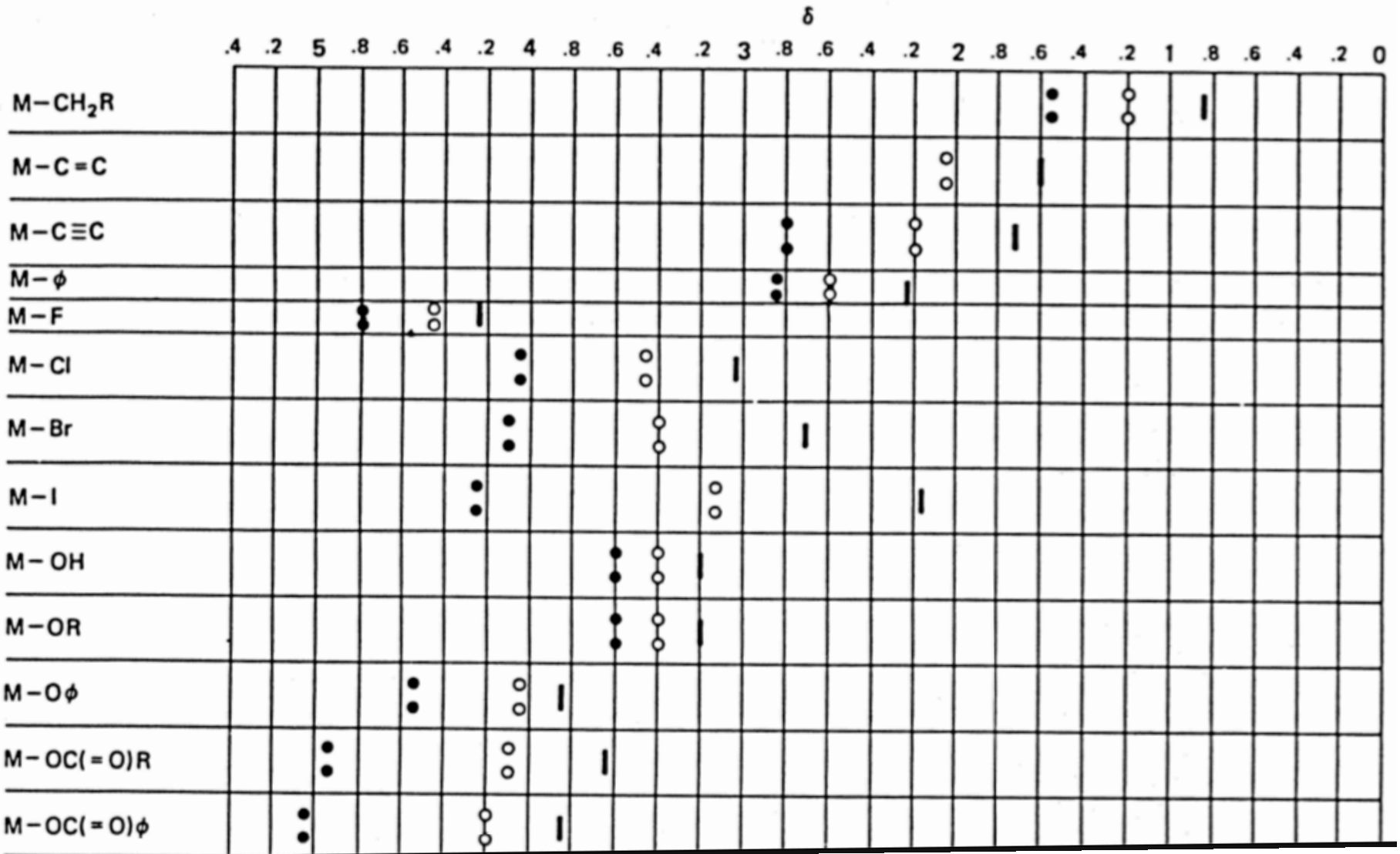


CHART 1. CHEMICAL SHIFTS OF PROTONS ON A CARBON ATOM ADJACENT (α - POSITION) TO A FUNCTIONAL GROUP IN ALIPHATIC COMPOUNDS (M—Y).

▮	M = methyl
⁘	M = methylene
⋮	M = methine

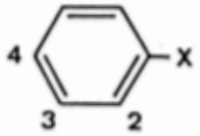


$$\delta_{CH_2R_1R_2} = 1.25 + \sum_{1}^{2} z_i \qquad \delta_{CHR_1R_2R_3} = 1.50 + \sum_{1}^{3} z_i$$

	Substituent	z_i
C	-alkyl	0.0
	-C=C-	0.8
	-C≡C-	0.9
	-phenyl	1.3
HAL	-Cl	2.0
	-Br	1.9
	-I	1.4
O	-OH	1.7
	-O-alkyl	1.5
	-O-phenyl	2.3
	-OCO-alkyl	2.7
	-OCO-phenyl	2.9
N	$-NH_2$	1.0
	$-N\text{-alkyl}_2$	1.0
	$-NO_2$	3.0
S	-S-alkyl	1.0
O ‖ C / \	-CHO	1.2
	-CO-alkyl	1.2
	-COOH	0.8
	-COO-alkyl	0.7
	-CN	1.2

$$\delta_{CH_2R_1R_2} = 0.23 + Z_{R_1} + Z_{R_2}$$

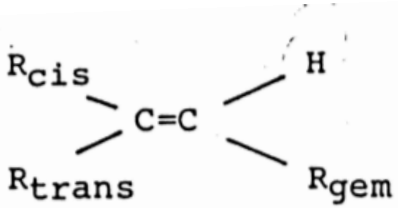
	Substituent R	Z_R	
	-alkyl	see p. H17	
	-C=C-	1.33	
C	-C≡CH	1.52	
	-C≡Calkyl	1.52	
	-C≡Cphenyl	1.77	
	-phenyl	1.85	
H	-F	3.15	
A	-Cl	2.48	
L	-Br	2.29	
	-OH	2.46	
	-Oalkyl	2.27	
O	-Ophenyl	2.89	
	-OCOalkyl	2.98	
	-OCOphenyl	3.23	
	$-NH_2$	1.69	
	-NHalkyl	1.60	
	$-N(alkyl)_2$	1.41	
	$-NH^{+}phenyl_2$	2.15	
N	-N(alkyl)phenyl	2.39	
	$-NH_3^{+}$	2.31	
	$-NH_2^{+}$alkyl	2.31	for D_2O a)
	$-NH^{+}(alkyl)_2$	2.46	
	$-N^{+}(alkyl)_3$	2.56	for D_2O b)
	-NHCOalkyl	2.23	
	-N(alkyl)COalkyl	2.23	
	-NHCOphenyl	2.33	
	-SH	1.63	
S	-Salkyl	1.63	
	-Sphenyl	1.92	
	-COalkyl	1.58	
	-COphenyl	2.08	
O	-COOH	1.49	
‖	-COOalkyl	1.49	
C	-COOphenyl	1.74	
/\	$-CONH_2$	1.39	
	$-CON(alkyl)_2$	1.39	
	-CONHphenyl	1.59	
	-C≡N	1.73	



$$\delta_{H_i} = 7.26 + z_i$$

	Substituent X	z_2	z_3	z_4
	-H	0	0	0
	$-CH_3$	-0.20	-0.12	-0.22
	$-CH_2CH_3$	-0.14	-0.06	-0.17
	$-CH(CH_3)_2$	-0.13	-0.08	-0.18
	$-C(CH_3)_3$	0.02	-0.08	-0.21
	$-CH_2Cl$	0.00	0.00	0.00
	$-CF_3$	0.32	0.14	0.20
C	$-CCl_3$	0.64	0.13	0.10
	$-CH_2OH$	-0.07	-0.07	-0.07
	$-CH=CH_2$	0.06	-0.03	-0.10
	-CH=CH-phenyl	0.15	-0.01	-0.16
	$-C\equiv CH$	0.15	-0.02	-0.01
	$-C\equiv C$-phenyl	0.19	0.02	0.00
	-phenyl	0.37	0.20	0.10
H	-F	-0.26	0.00	-0.20
A	-Cl	0.03	-0.02	-0.09
L	-Br	0.18	-0.08	-0.04
	-I	0.39	-0.21	0.00
	-OH	-0.56	-0.12	-0.45
	$-OCH_3$	-0.48	-0.09	-0.44
	$-OCH_2CH_3$	-0.46	-0.10	-0.43
O	-O-phenyl	-0.29	-0.05	-0.23
	$-OCOCH_3$	-0.25	0.03	-0.13
	-OCO-phenyl	-0.09	0.09	-0.08
	$-OSO_2CH_3$	-0.05	0.07	-0.01

$$\delta_{C=CH} = 5.25 + Z_{gem} + Z_{cis} + Z_{trans}$$



	Substituent R	Z_{gem}	Z_{cis}	Z_{trans}
C	-H	0	0	0
	-alkyl	0.45	-0.22	-0.28
	-alkyl ring[1)]	0.69	-0.25	-0.28
	$-CH_2$-aromatic	1.05	-0.29	-0.32
	$-CH_2X$, X: F, Cl, Br	0.70	0.11	-0.04
	$-CHF_2$	0.66	0.32	0.21
	$-CF_3$	0.66	0.61	0.32
	$-CH_2O$	0.64	-0.01	-0.02
	$-CH_2N$	0.58	-0.10	-0.08
	$-CH_2S$	0.71	-0.13	-0.22
	$-CH_2CO$, CH_2CN	0.69	-0.08	-0.06
	-C=C isolated	1.00	-0.09	-0.23
	-C=C conjugated[2)]	1.24	0.02	-0.05
	-C≡C	0.47	0.38	0.12
	-aromatic free rotation	1.38	0.36	-0.07
	-aromatic fixed[3)]	1.60	-	-0.05
	-aromatic o-substituted	1.65	0.19	0.09
H	-F	1.54	-0.40	-1.02
A	-Cl	1.08	0.18	0.13
L	-Br	1.07	0.45	0.55
	-I	1.14	0.81	0.88

https://moodle.epfl.ch/course/view.php?id=16403

Exemple avec les solvents

Couplage spin-spin

https://www.cheminfo.org/flavor/biooriented

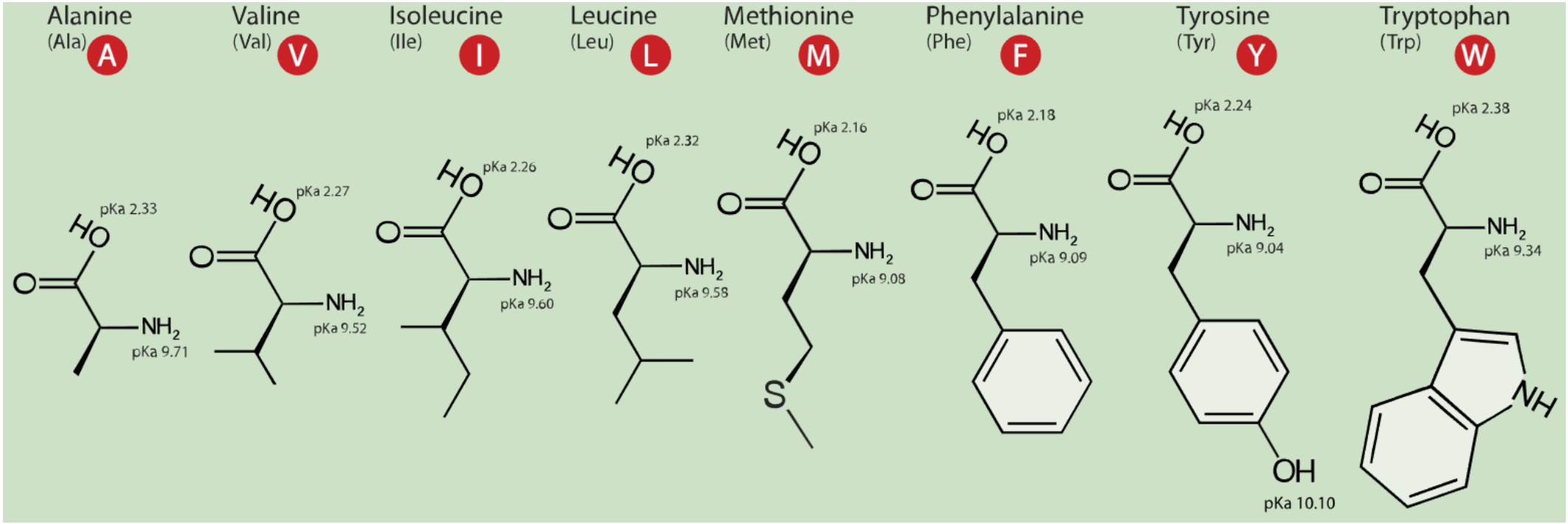
Second order effect

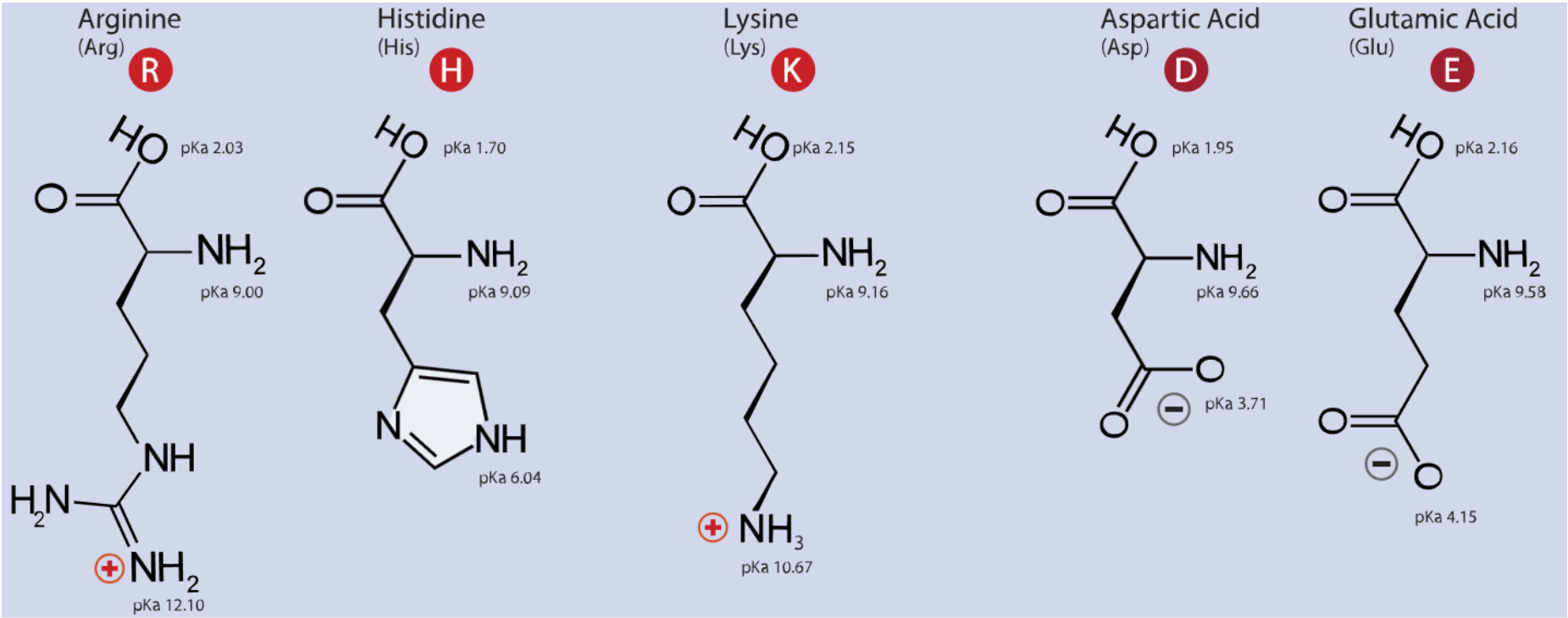
https://www.cheminfo.org/flavor/biooriented

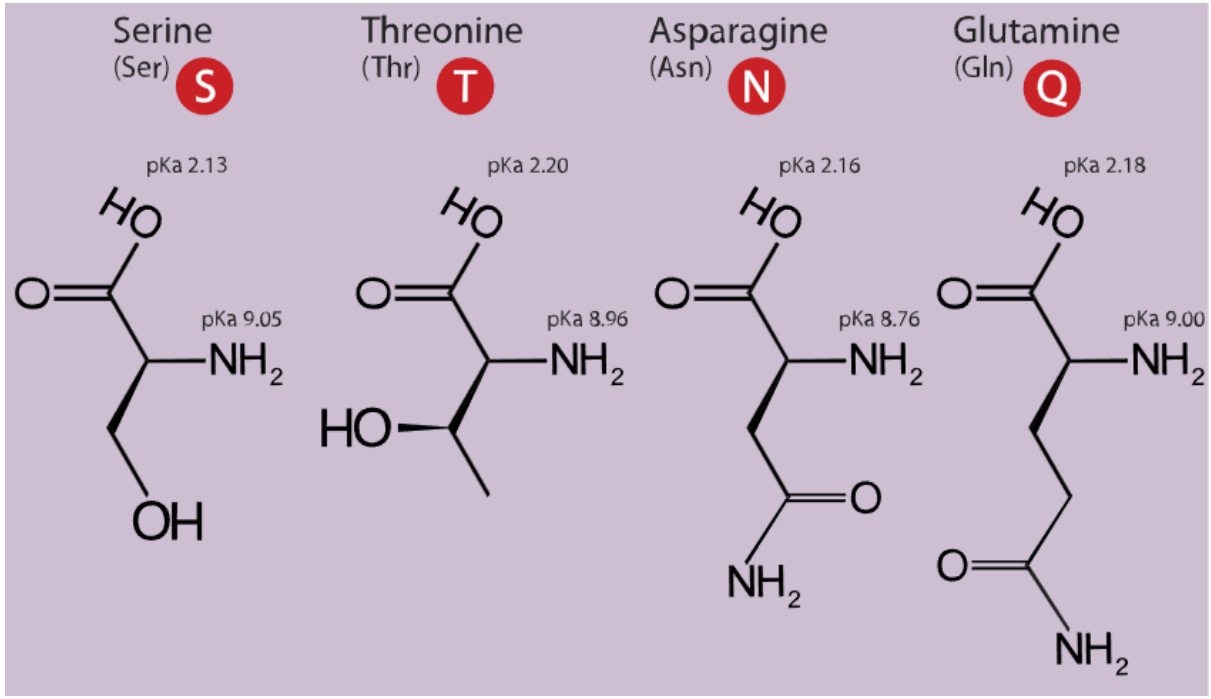
NMR

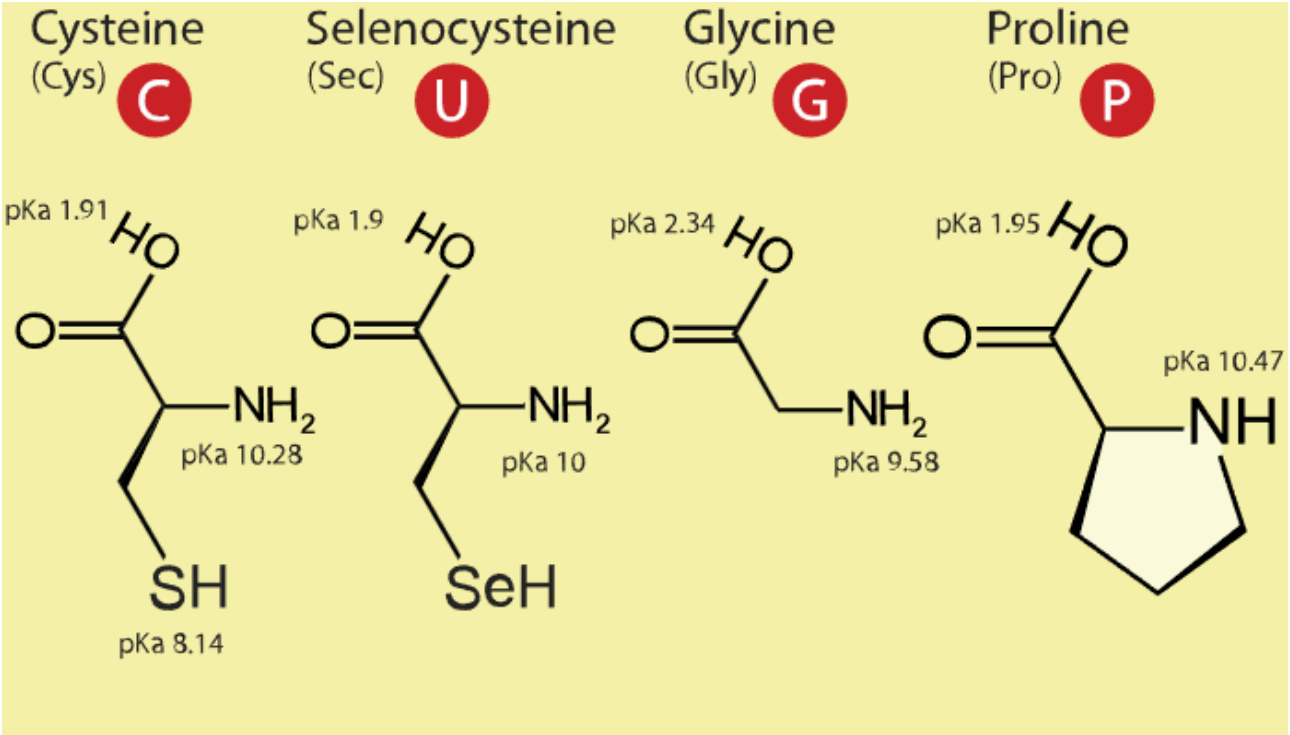
Boc protected amino-acids

Exercices Boc


Alanine
(Ala)
A
pKa 2.33
pKa 9.71
Valine
(Val)
V
pKa 2.27
pKa 9.52
Isoleucine
(Ile)
I
pKa 2.26
pKa 9.60
Leucine
(Leu)
L
pKa 2.32
pKa 9.58
Methionine
(Met)
M
pKa 2.16
pKa 9.08
Phenylalanine
(Phe)
F
pKa 2.18
pKa 9.09
Tyrosine
(Tyr)
Y
pKa 2.24
pKa 9.04
pKa 10.10
Tryptophan
(Trp)
W
pKa 2.38
pKa 9.34


Arginine
(Arg)
R
pKa 2.03
pKa 9.00
pKa 12.10
Histidine
(His)
H
pKa 1.70
pKa 9.09
pKa 6.04
Lysine
(Lys)
K
pKa 2.15
pKa 9.16
pKa 10.67
Aspartic Acid
(Asp)
D
pKa 1.95
pKa 9.66
pKa 3.71
Glutamic Acid
(Glu)
E
pKa 2.16
pKa 9.58
pKa 4.15


Serine
(Ser) S
pKa 2.13
pKa 9.05
Threonine
(Thr) T
pKa 2.20
pKa 8.96
Asparagine
(Asn) N
pKa 2.16
pKa 8.76
Glutamine
(Gln) Q
pKa 2.18
pKa 9.00


Cysteine
(Cys) C
pKa 1.91
pKa 10.28
pKa 8.14
Selenocysteine
(Sec) U
pKa 1.9
pKa 10
Glycine
(Gly) G
pKa 2.34
pKa 9.58
Proline
(Pro) P
pKa 1.95
pKa 10.47

Exercices intégrés

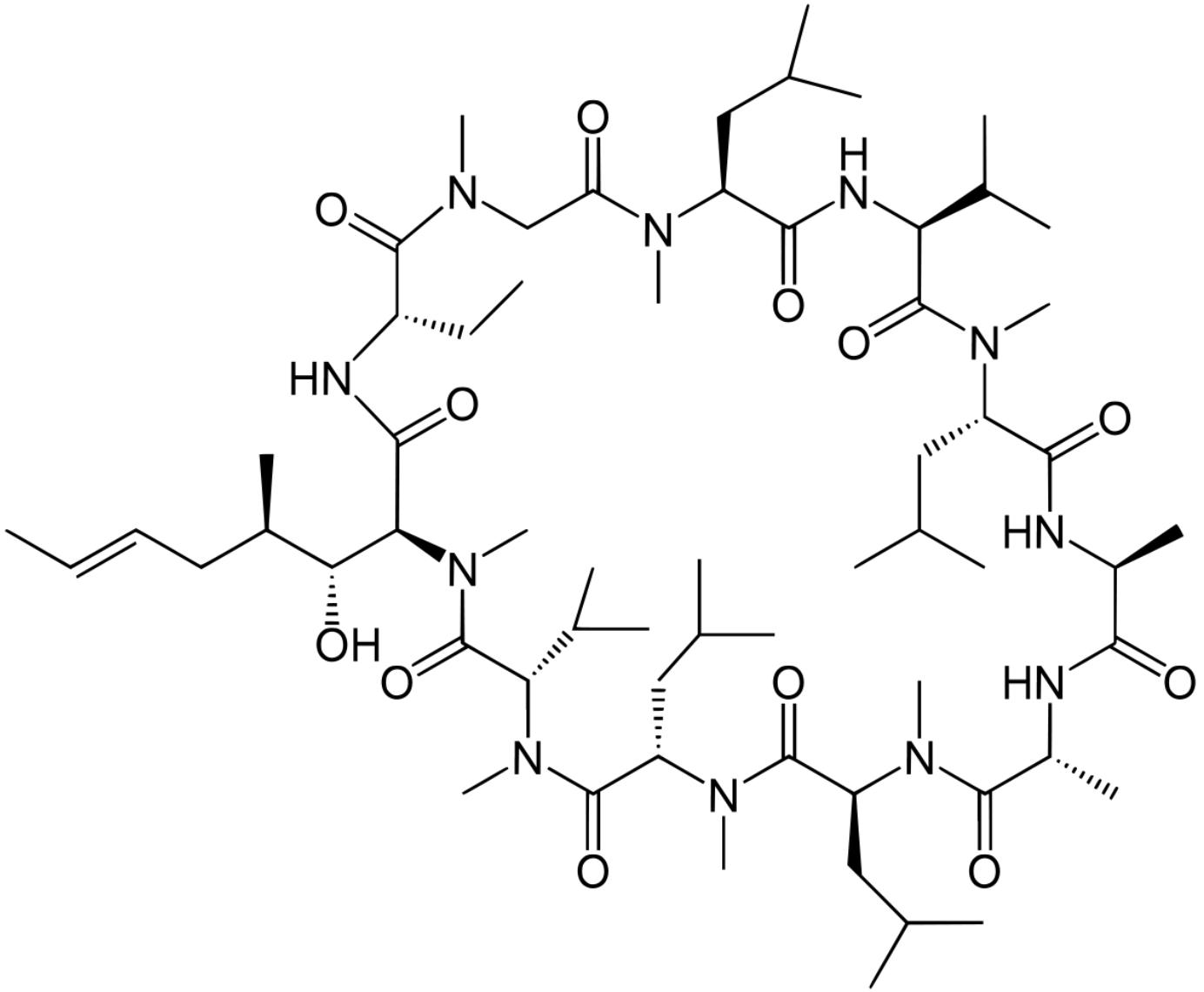
Acides aminés, peptides, protéines

Acides aminés

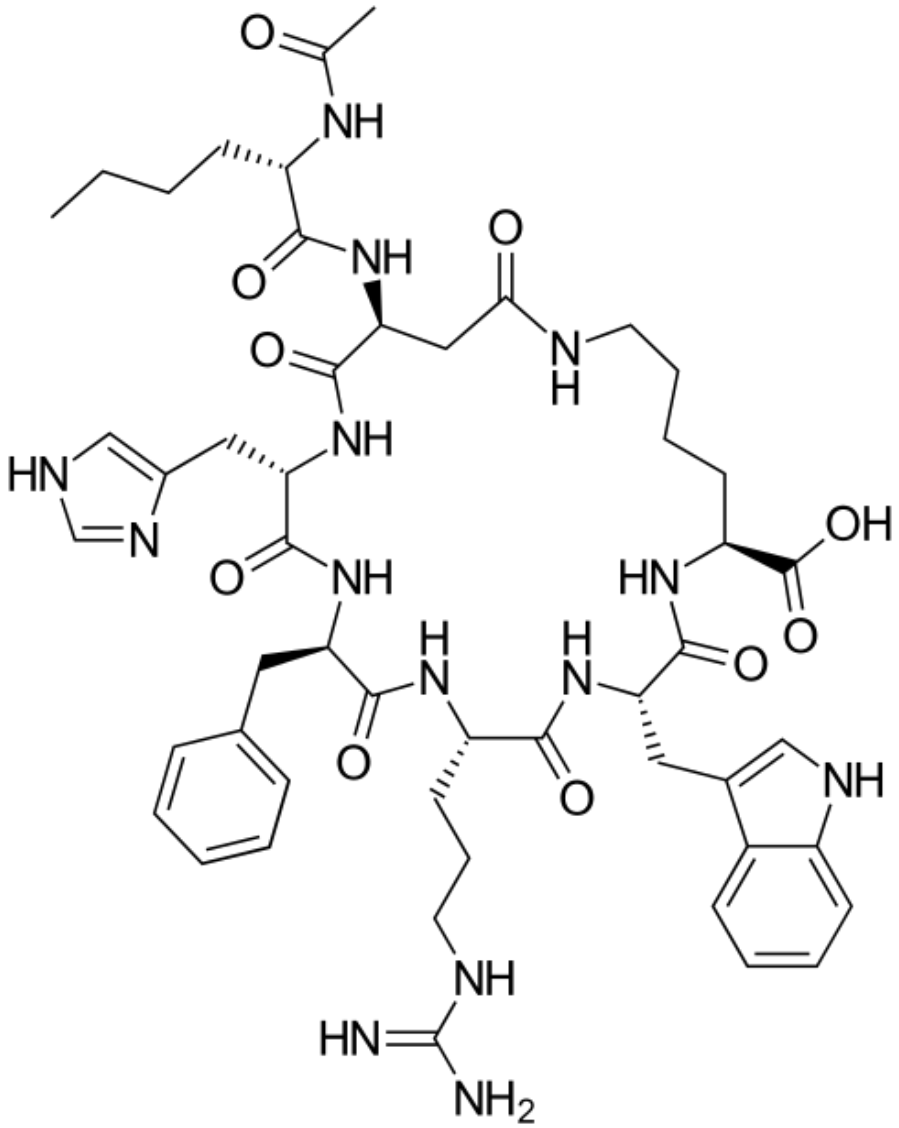
Codification IUPAC des atomes

Synthèse peptique

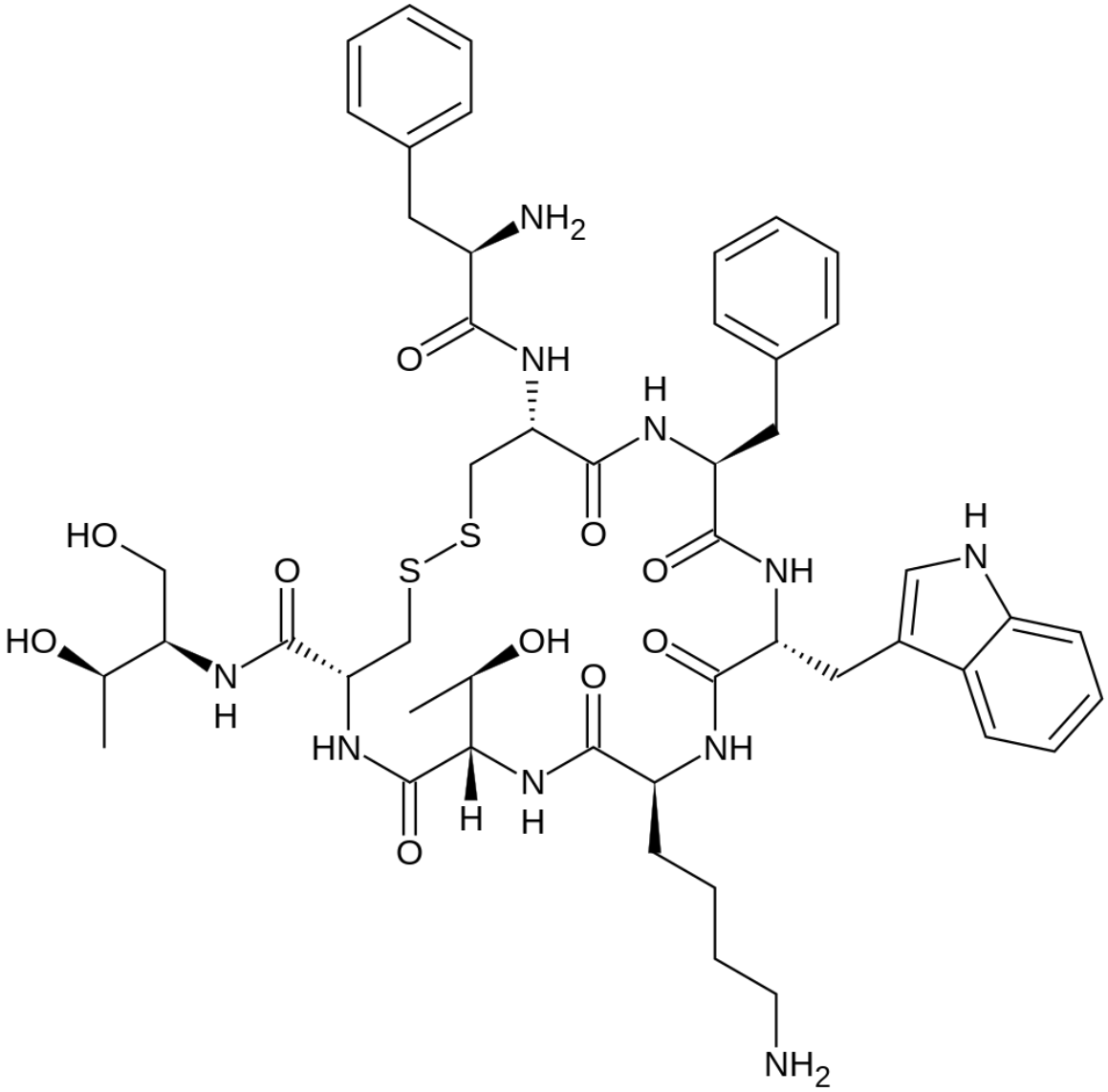
Cyclosporine



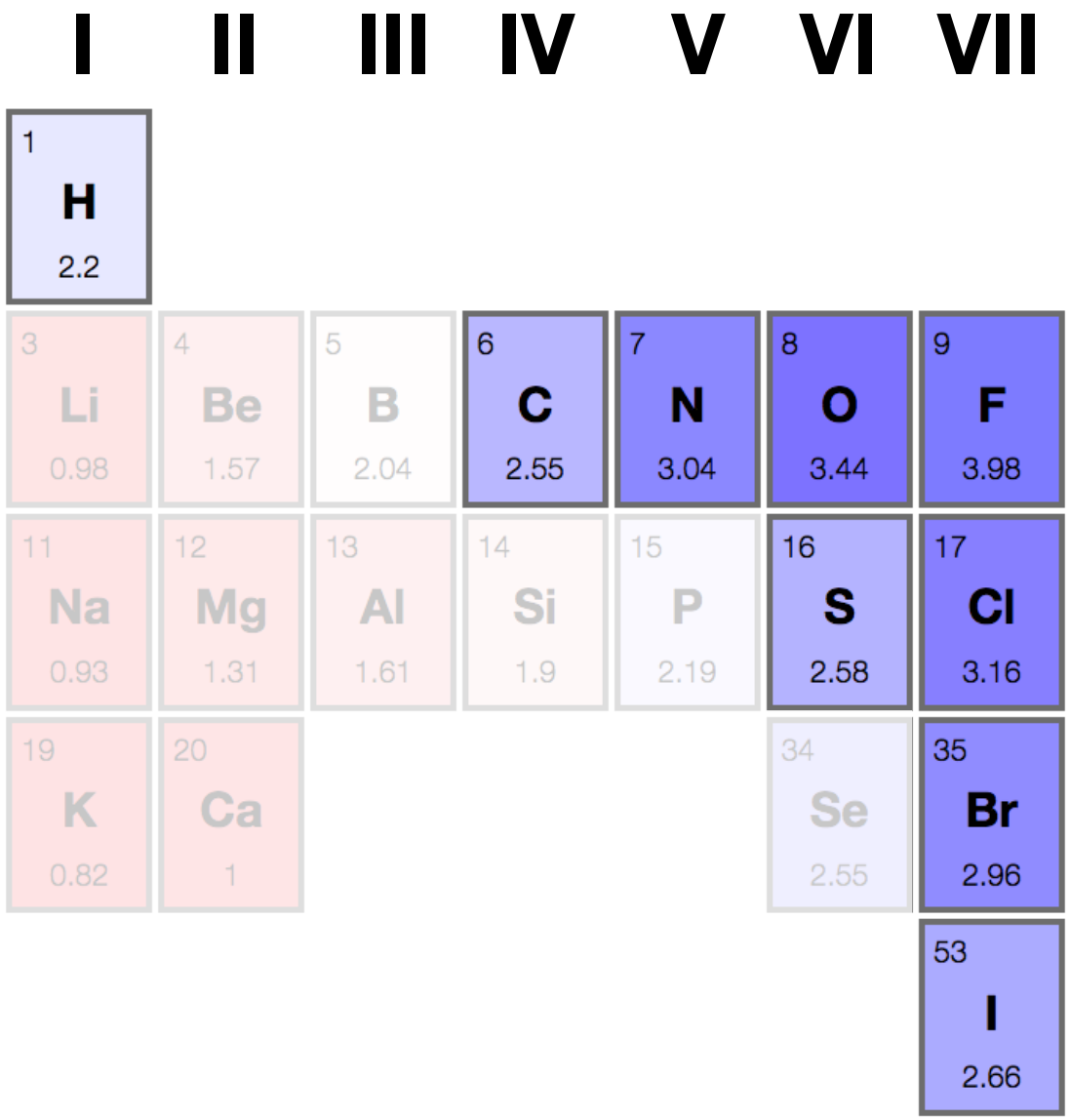
Bremelanotide



Octreotide



Electronegativity



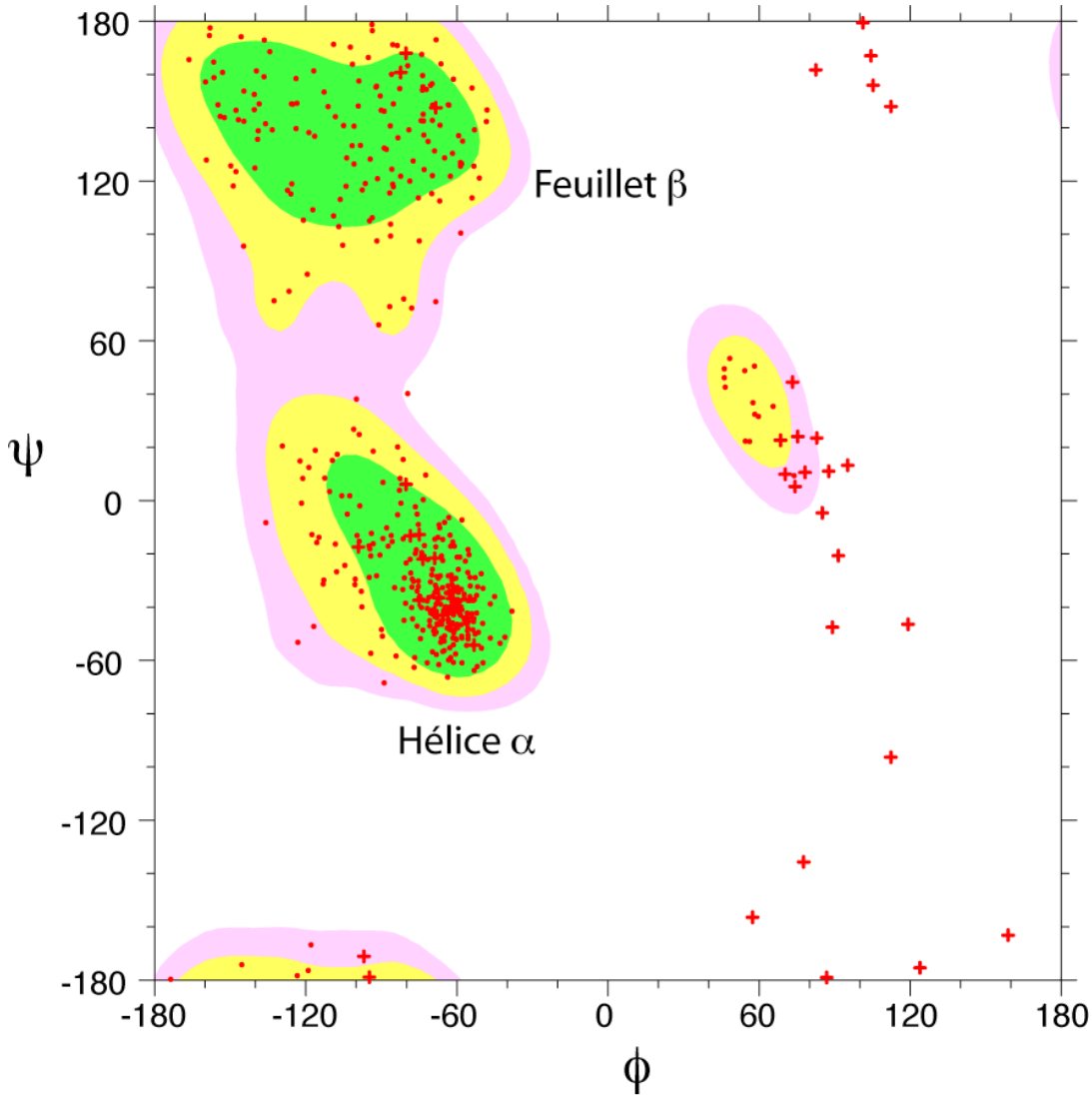
	acide	base conjuguée		pKa
acide très fort	HI	I^-	base très faible	-5.2
	HBr	Br^-		-4.7
	HCl	Cl^-		-2.2
acide le + fort dans l'eau	H_3O^+	H_2O		-1.7
	CF_3COOH	CF_3COO^-		0.2
	HF	F^-		3.2
	CH_3COOH	CH_3COO^-		4.7
	H2S	HS^-		7.0
	HCN	CN^-		9.2
	Me_3N^+H	Me_3N		9.8
	C_6H_5OH	$C_6H_5O^-$		10.0
	EtSH	EtS^-		10.6
	H_2O	HO^-	base la plus + dans l'eau	15.7
	EtOH	EtO^-		15.9
	CH_3COOEt	$^-CH_2COOEt$		24.5
	HCCH	HCC^-		25
acide très faible	$C_2H_5NH_2$	$C_2H_5NH^-$	base très forte	35

Protéine

Feuillet Beta

Diagramme de Ramachandran

Diagramme de Ramachandran



PDB format

- https://www.rcsb.org/


IBM 29
INTRODUCTION TO
STRUCTURED
FORTRAN

Protein Data Bank Contents Guide:

Atomic Coordinate Entry Format Description

Version 2.3, July 9, 1998

https://www.rcsb.org/structure/1CWA

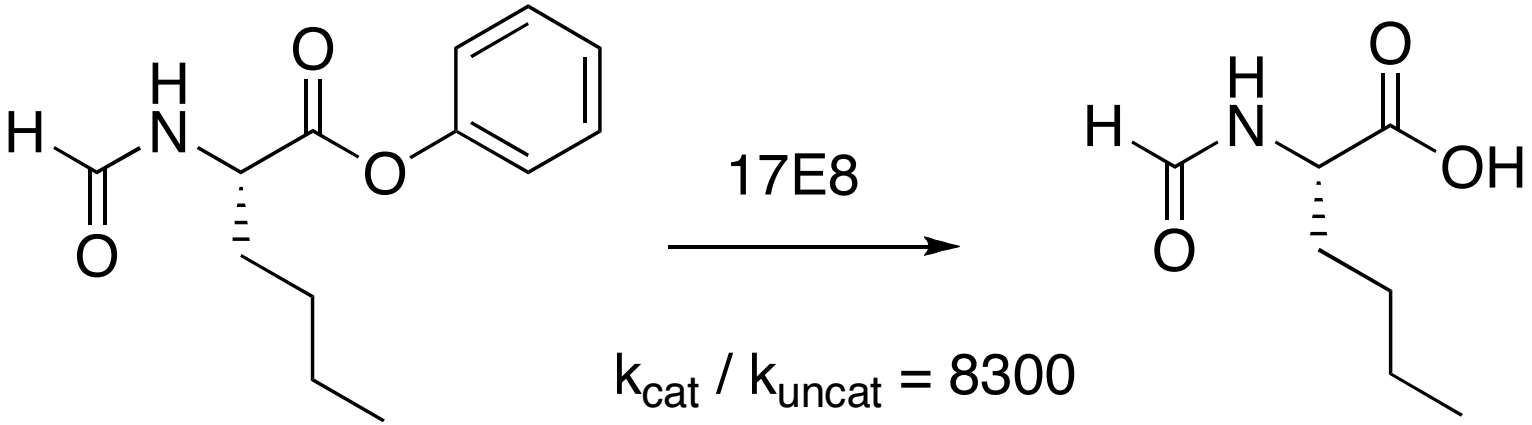
Protéine et travail JSMol

Travail JSMol

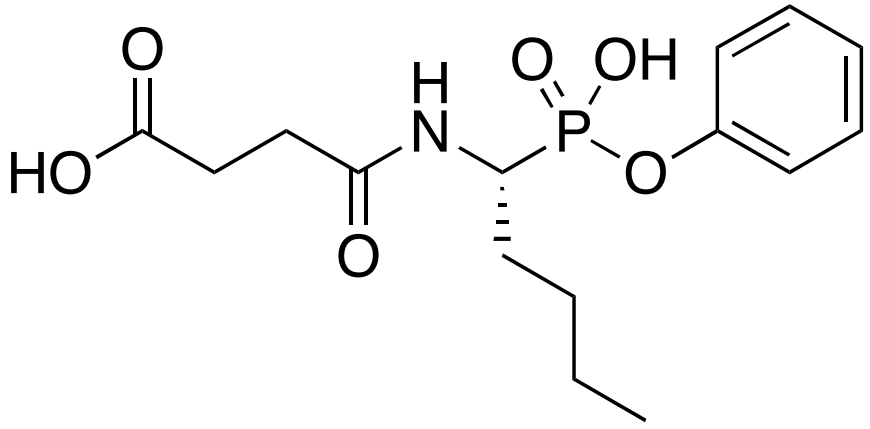
- Choisir une protéine
- Effectuer le travail JSMol

Réactions bio compatibles

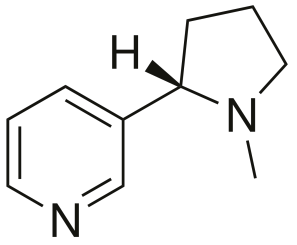
Catalyseur



Hapten:



Vaccin antinicotine



ONKOLOGIE

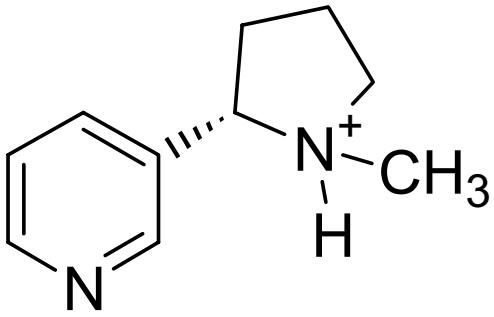
Focus: Nicotine and Tobacco · Original Article

Onkologie 2002;25:406–411

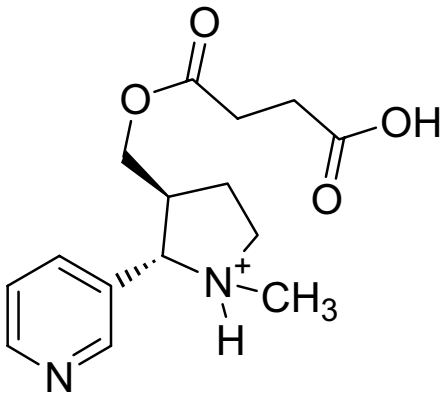
Preclinical Development of a Vaccine 'Against Smoking'

E. H. Cerny[a] R. Lévy[a] J. Mauel[b] M. Mpandi[c] M. Mutter[d] C. Henzelin-Nkubana[d] L. Patiny[d] G. Tuchscherer[d] T. Cerny[e]

[a] Chilka Ltd., Lausanne
[b] Institut de Biochemie, ISREC, Epalinges
[c] Serolab SA, Remaufens
[d] Institut of Molecular and Biological Chemistry, Swiss Federal Institute of Technology, Lausanne
[e] Department of Oncology/Haematology, Cantonal Hospital St. Gall



nicotine



hapten

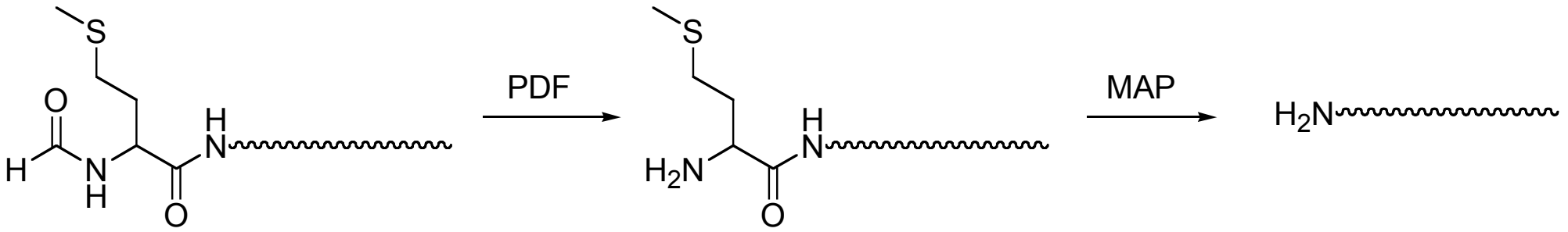
Réactions sur NH2

Réactions sur SH

Bioconjugaison

Peptide deformylase

PDF and MAP

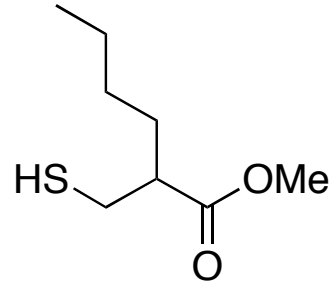
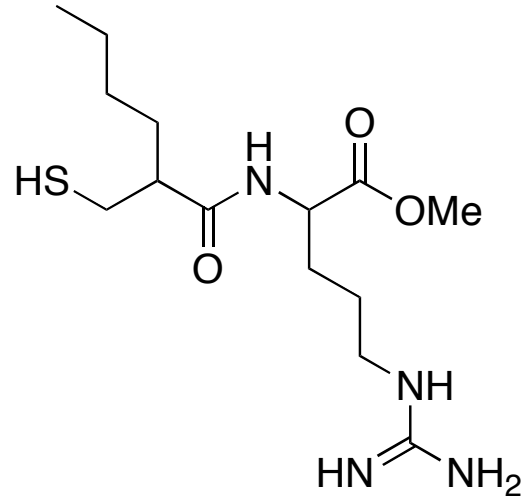
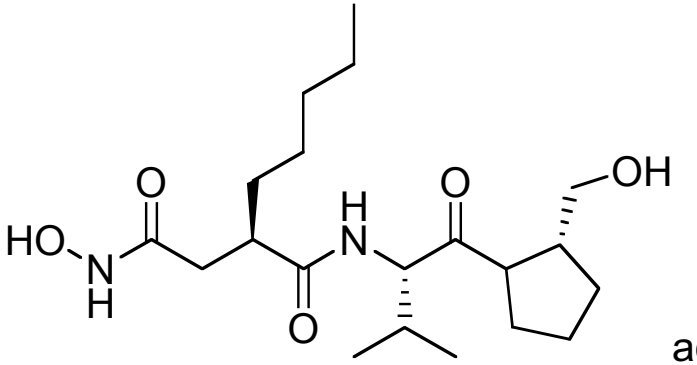


Recherche d’un inhibiteur

But: Structure 3D protéine / inhibiteur

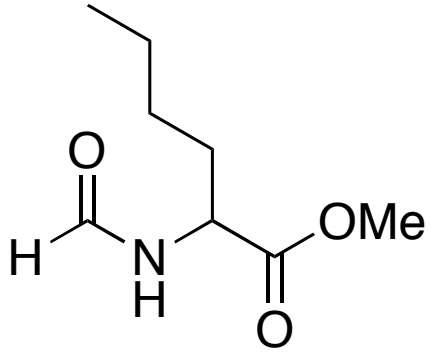
Substrat minimal

Peptide	vitesse relative
Fo-Ala-Ala-Ala-OH	0.20
Fo-Met-Ala-Ser-OH	100
Fo-Nle-Ala-Ser-OH	115
Fo-Leu-Ala-Ser-OH	11
Fo-Met-OMe	27
Fo-Nle-OMe	59
Fo-Met-OH	0.16
Fo-Leu-Ala-OMe	267
Fo-Nle-Arg-NH_2	839

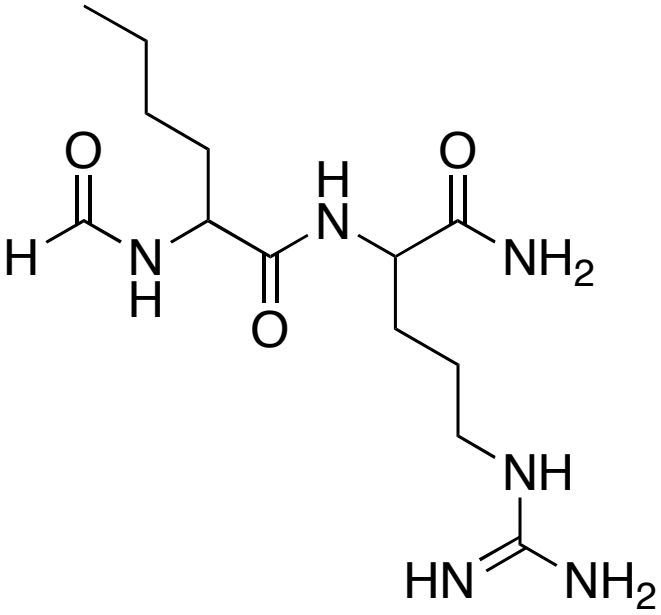
Peptide	K_i (μM)
H-Met-Ala-Ser-OH	53000
H-Met-Arg.OH	3800
$HS\text{-}CH_2\text{-}CH_2\text{-}OH$	10000
	52
	2.5
 actinonine*	64

* Antimicrobial Agents and Chemotherapy 2001, 563-570.

substrats

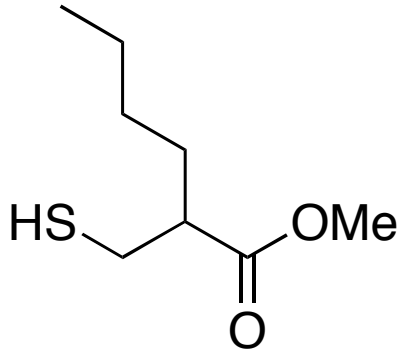


k_{rel}=59

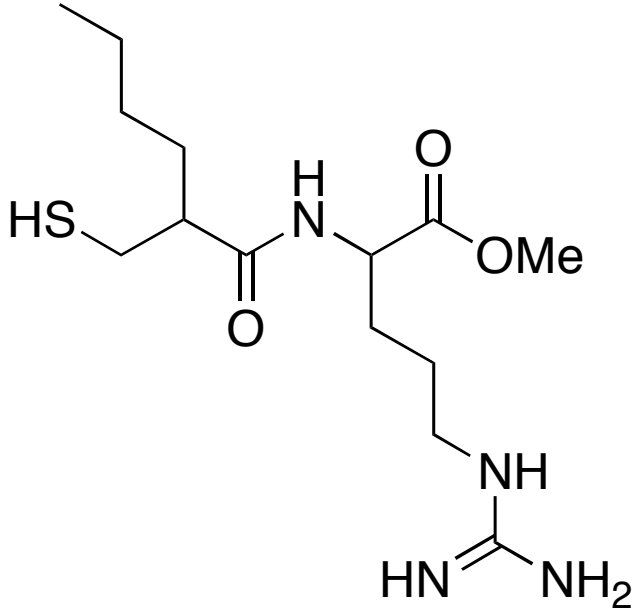


k_{rel}=839

inhibiteurs



Ki (μM)=52



Ki (μM)=2.5

Design and Synthesis of Substrate Analogue Inhibitors of Peptide Deformylase[†]

Thierry Meinnel,*[,‡] Luc Patiny,[§] Stéphane Ragusa,[‡] and Sylvain Blanquet[‡]

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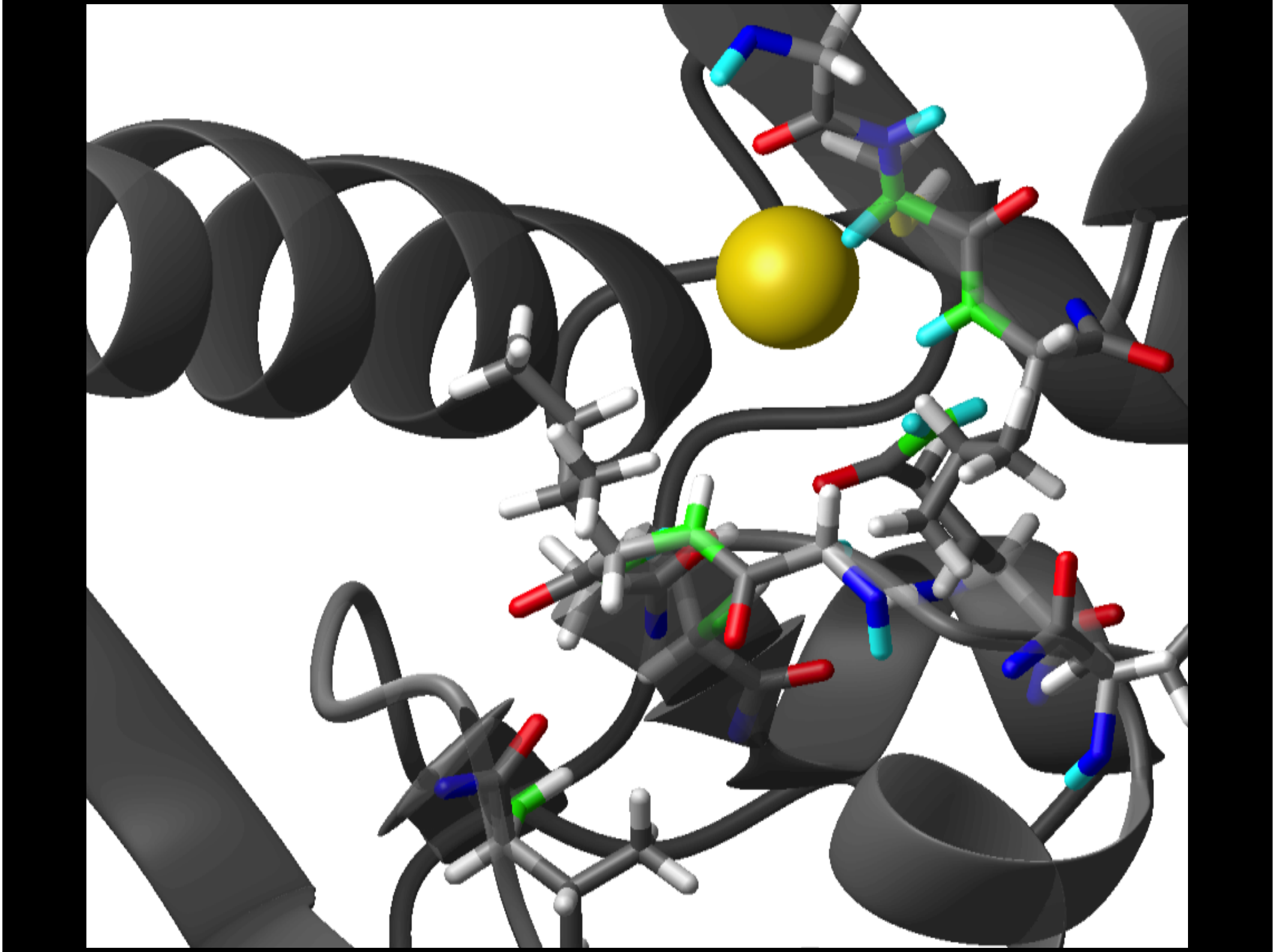
ABSTRACT: Series of substrates derivatives of peptide deformylase were systematically synthesized and studied for their capacities to undergo hydrolysis. Data analysis indicated the requirement for a hydrophobic first side chain and for at least two main chain carbonyl groups in the substrate. For instance, Fo-Met-OCH_3 and Fo-Nle-OCH_3 were the minimal substrates of peptide deformylase obtained in this study, while positively charged Fo-Nle-ArgNH_2 was the most efficient substrate ($k_{cat}/K_m = 4.5 \times 10^5$ $M^{-1}\cdot s^{-1}$). On the basis of this knowledge, 3-mercapto-2-benzylpropanoylglycine (thiorphan), a known inhibitor of thermolysin, could be predicted and further shown to inhibit the deformylation reaction. The inhibition by this compound was competitive and proved to depend on the hydrophobicity at the P_1' position. Spectroscopic evidence that the sulfur group of thiorphan binds next to the active site metal ion on the enzyme could be obtained. Consequently, a small thiopseudopeptide derived from Fo-Nle-OCH_3 was designed and synthesized. This compound behaved as a competitive inhibitor of peptide deformylase with $K_I = 52 \pm 5$ μM. Introduction of a positive charge to this thiopeptide via addition of an arginine at P_2' improved the inhibition constant up to 2.5 ± 0.5 μM, a value 4 orders of magnitude smaller than that of the starting inhibitors. Evidence that this inhibitor, imino[(5-methoxy-5-oxo-4-[[2-(sulfanylmethyl)-hexanoyl]amino]pentyl)amino]methanamine, binds inside the active site cavity of peptide deformylase, while keeping intact the 3D fold of the protein, was provided by NMR. A fingerprint of the interaction of the inhibitor with the residues of the enzyme was obtained.

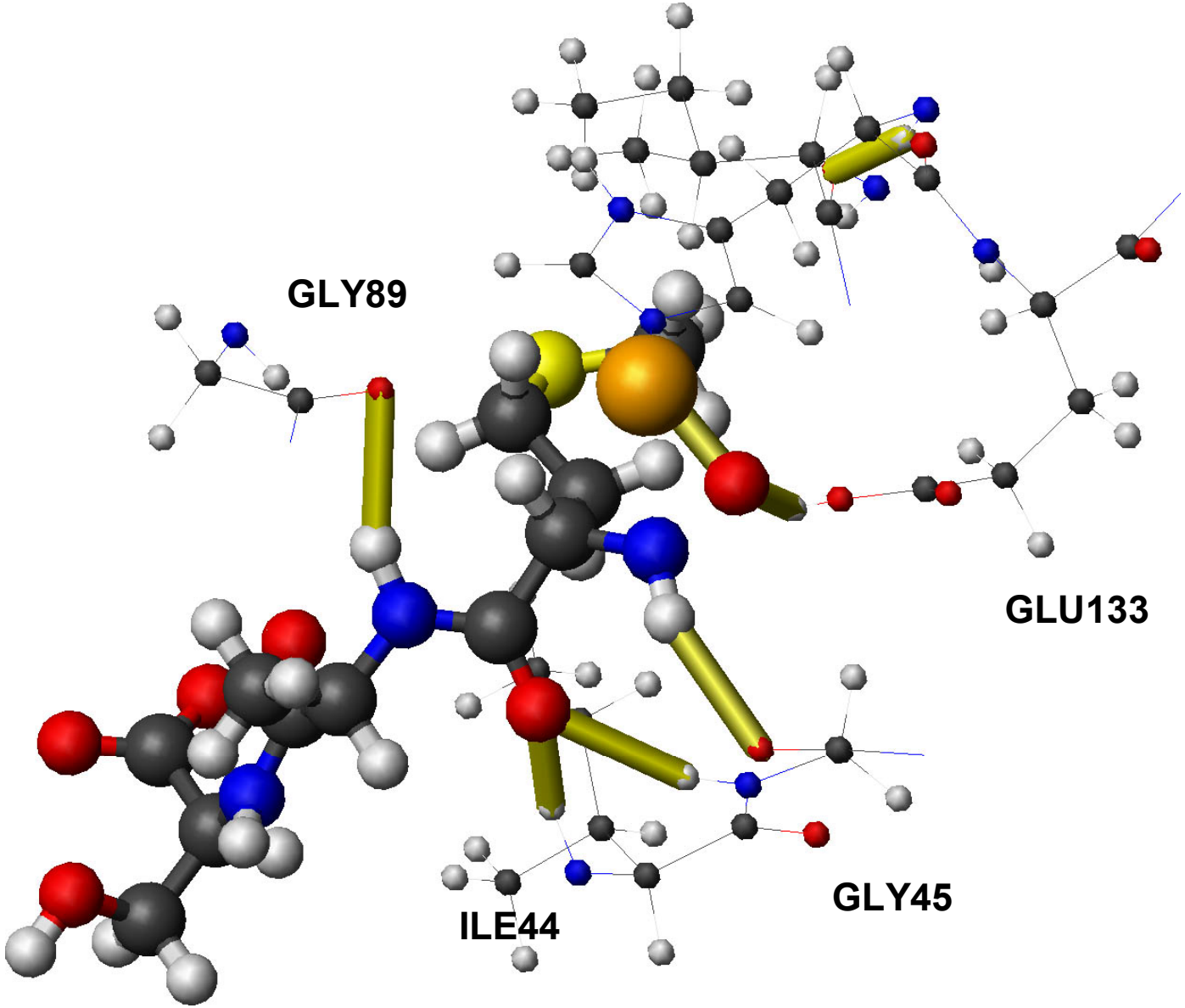
RMN PDF et PDF / inhibiteur

Atom	$\Delta\delta$ ^{15}N or ^{13}C (ppm)	Atom	$\Delta\delta$ ^{1}H (ppm)
C90 CA	7.2	C90 HA	1.32
Q50 NE2	5.5	Q50 HE21	0.92
L91 N	4.5	L91 HN	0.83
V59 N	3.0	H7 HN	0.57
I86 N	2.0	G89 HN	0.53
I44 N	1.5	Q50 HNE2	0.51
G45 N	1.5	G43 HA1	0.45
A47 N	1.5	E41 HN	0.40
		G45 HN	0.35
		C90 HN	0.34
		G43 HN	0.31

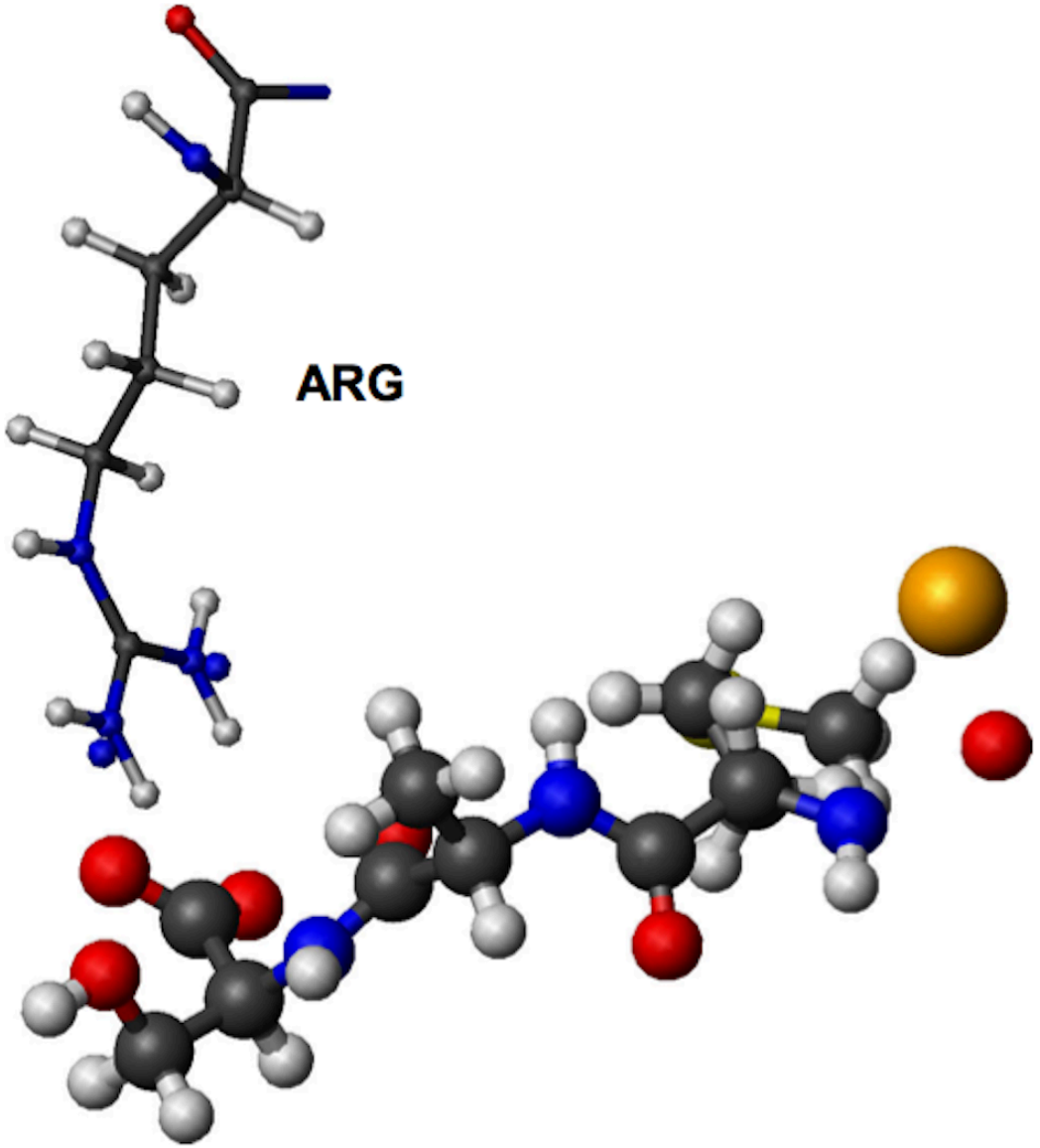


Stabilisation inhibiteur

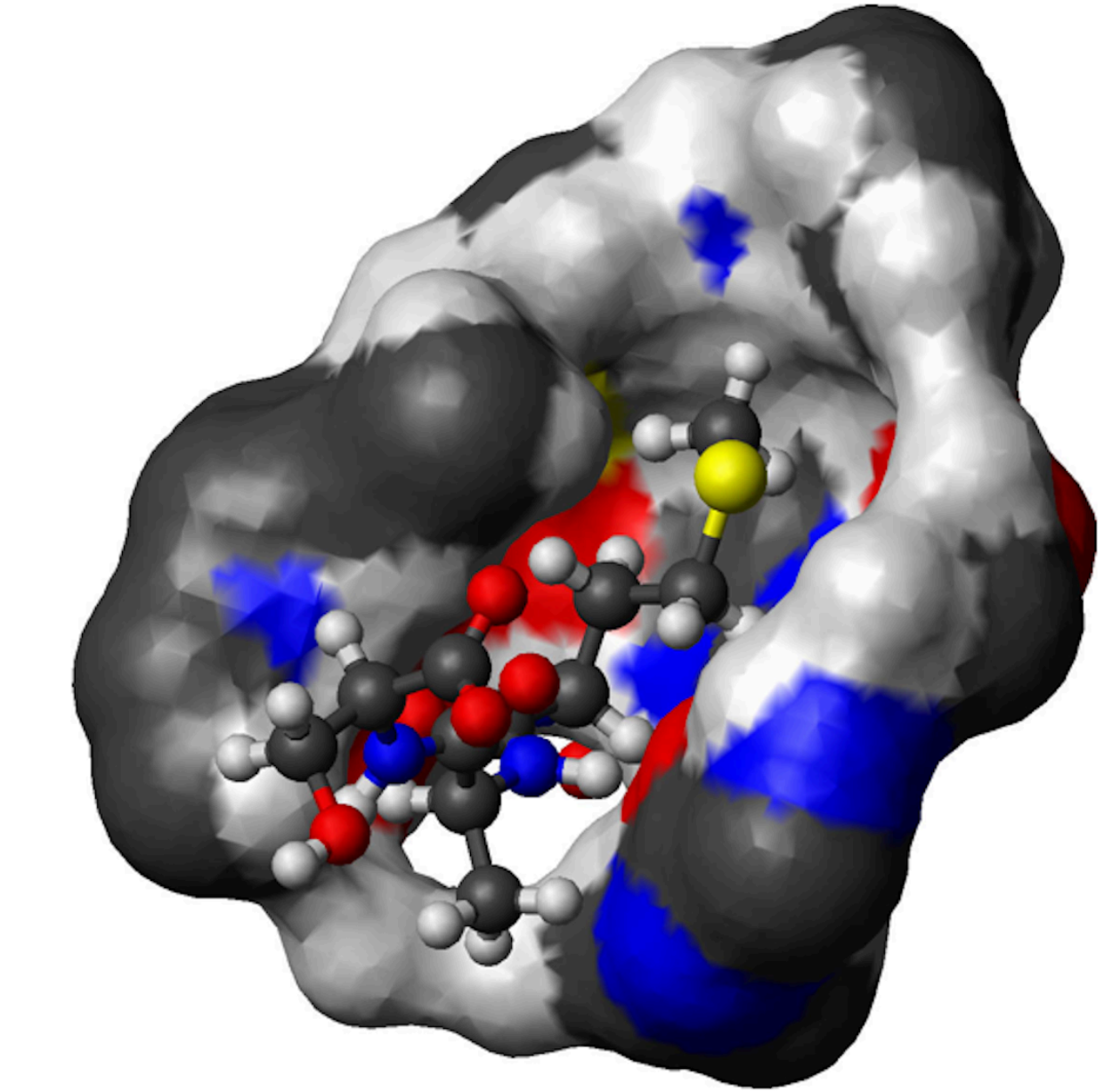
Ponts hydrogènes



Effets électrostatiques

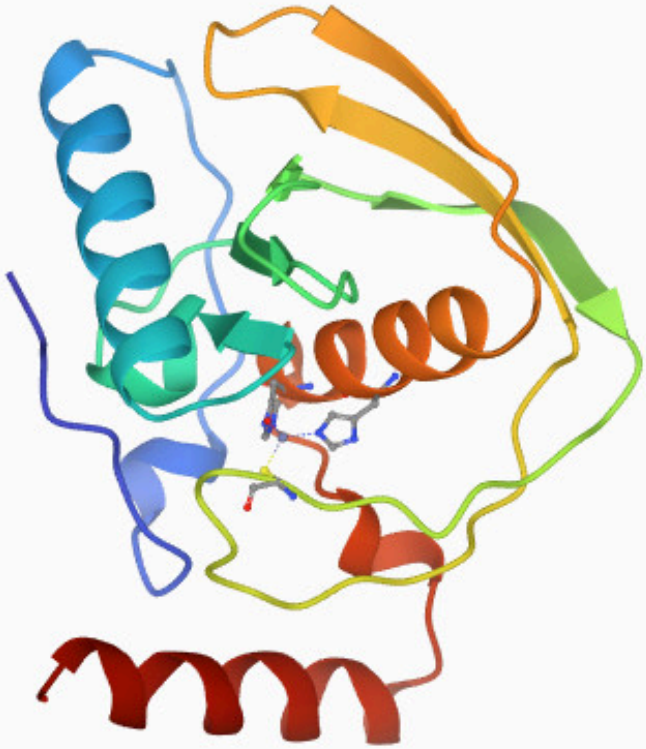


Effets hydrophobes

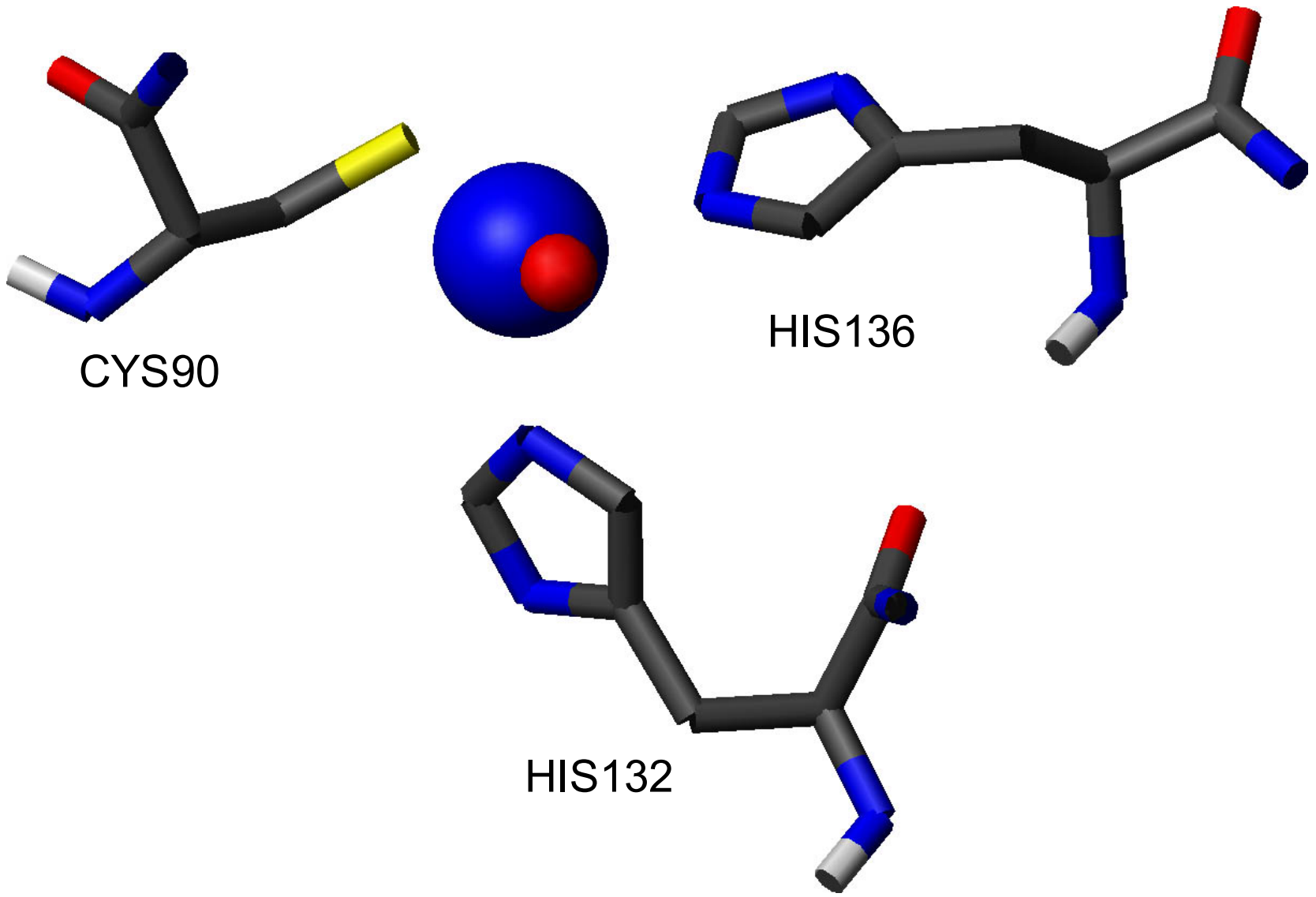


3D structure

1DEF



1DFF


CYS90
HIS136
HIS132

Conclusions

Conclusions

- **RMN / Mass / IR:**
  - Déterminer la structure de petites molécules
  - Déterminer la structure de protéines ou l'interaction en inhibiteur et protéine
- **Importance de la structure de la protéine:**
  - Déterminer le site catalytique
  - Comprendre le mécanisme de la réaction (par exemple hydrolase)
  - Améliorer un inhibiteur (charge, poche hydrophobe, ...)
- **Réactions chimiques:**
  - Problème des groupes protecteurs
  - Possibilité de faire des réactions chimiosélective / biocompatible