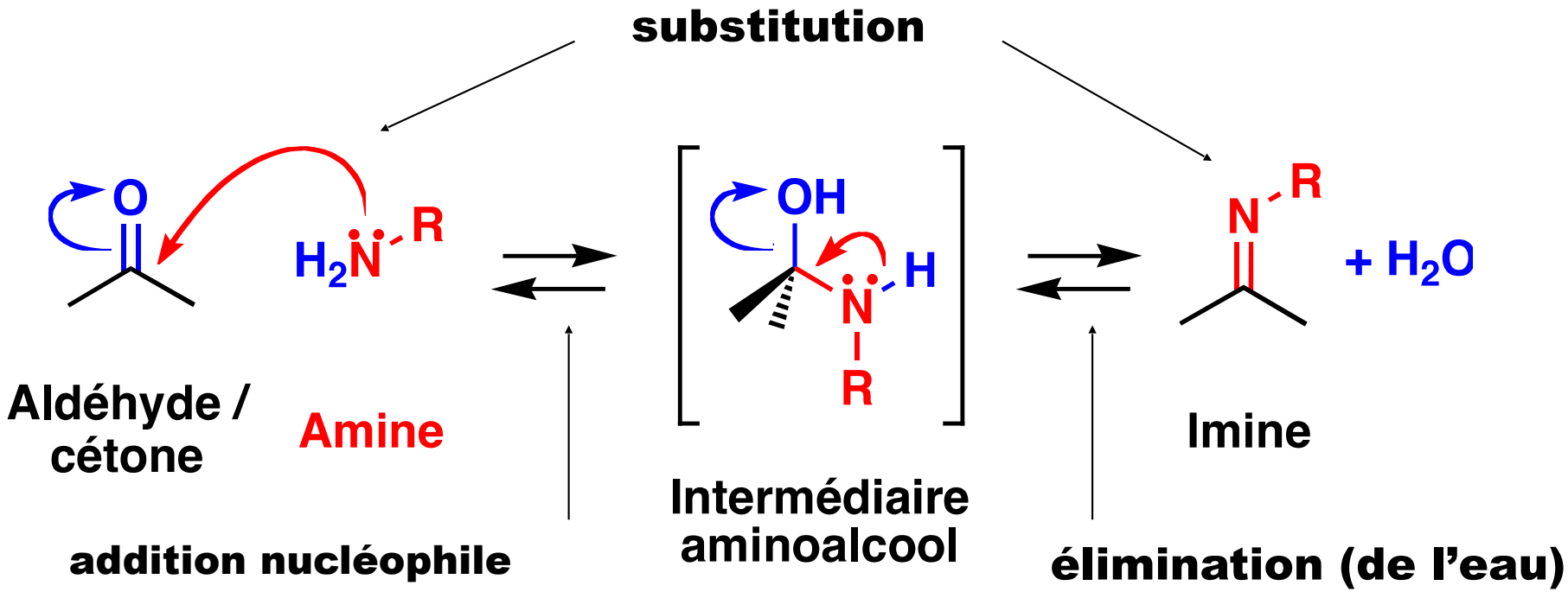
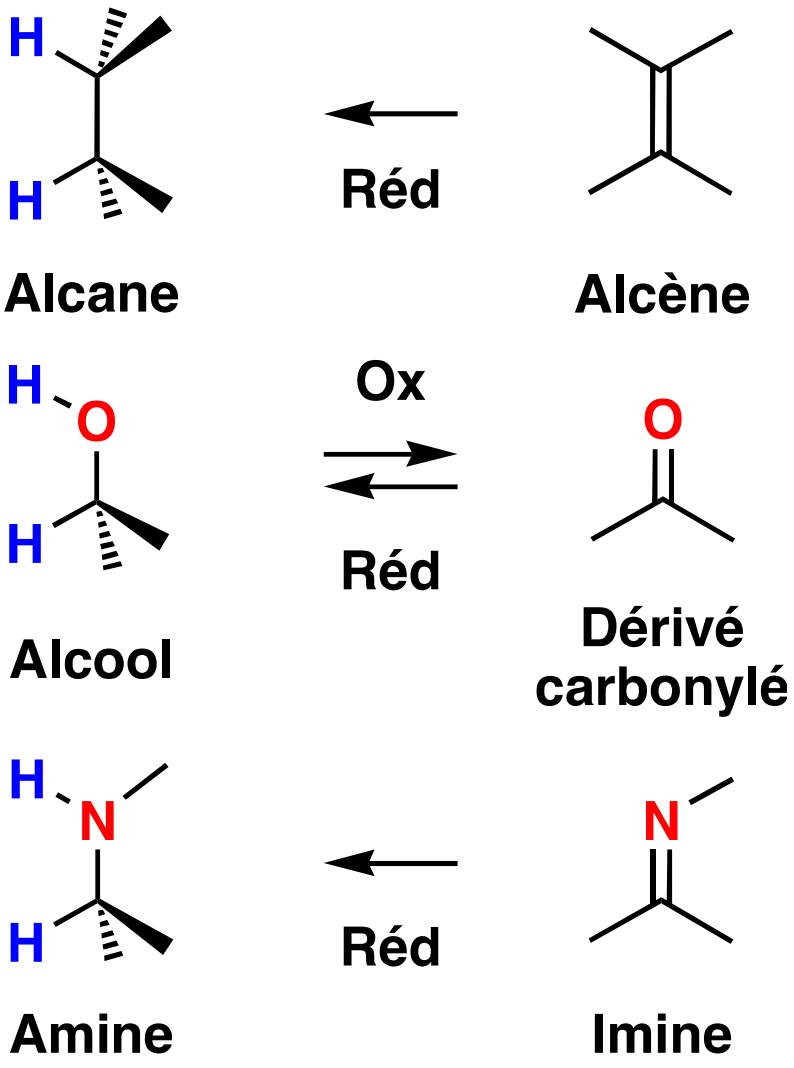
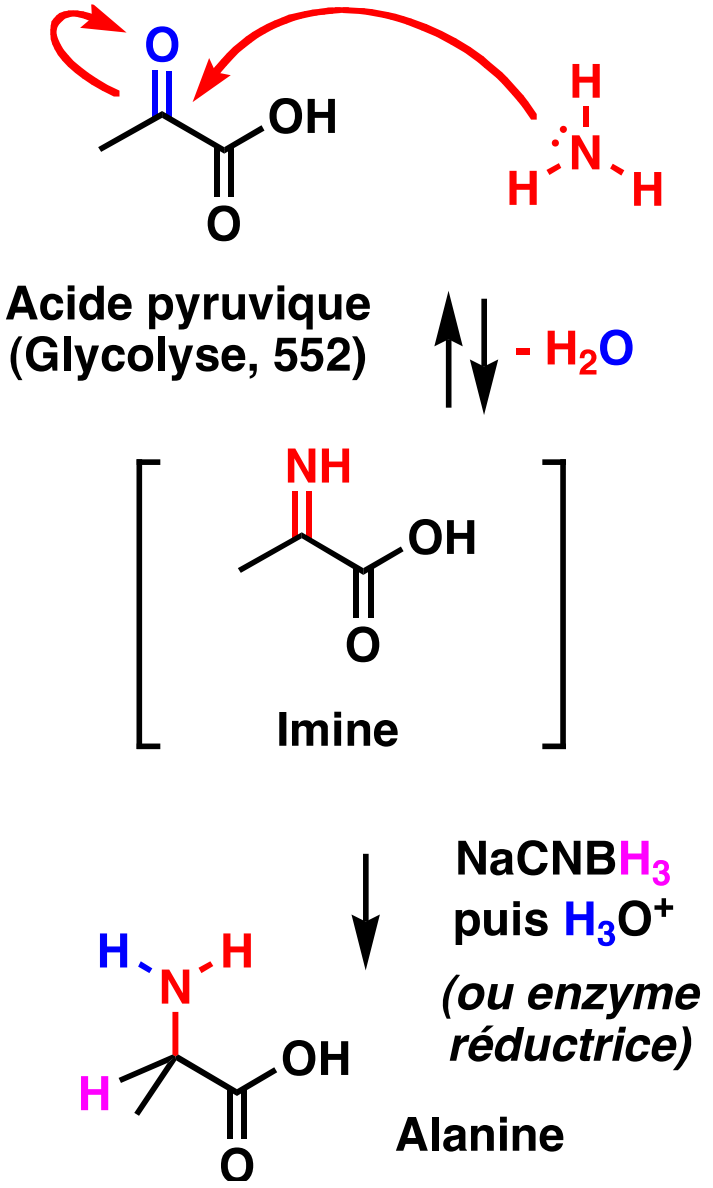
Substitution Nucléophile : Imines

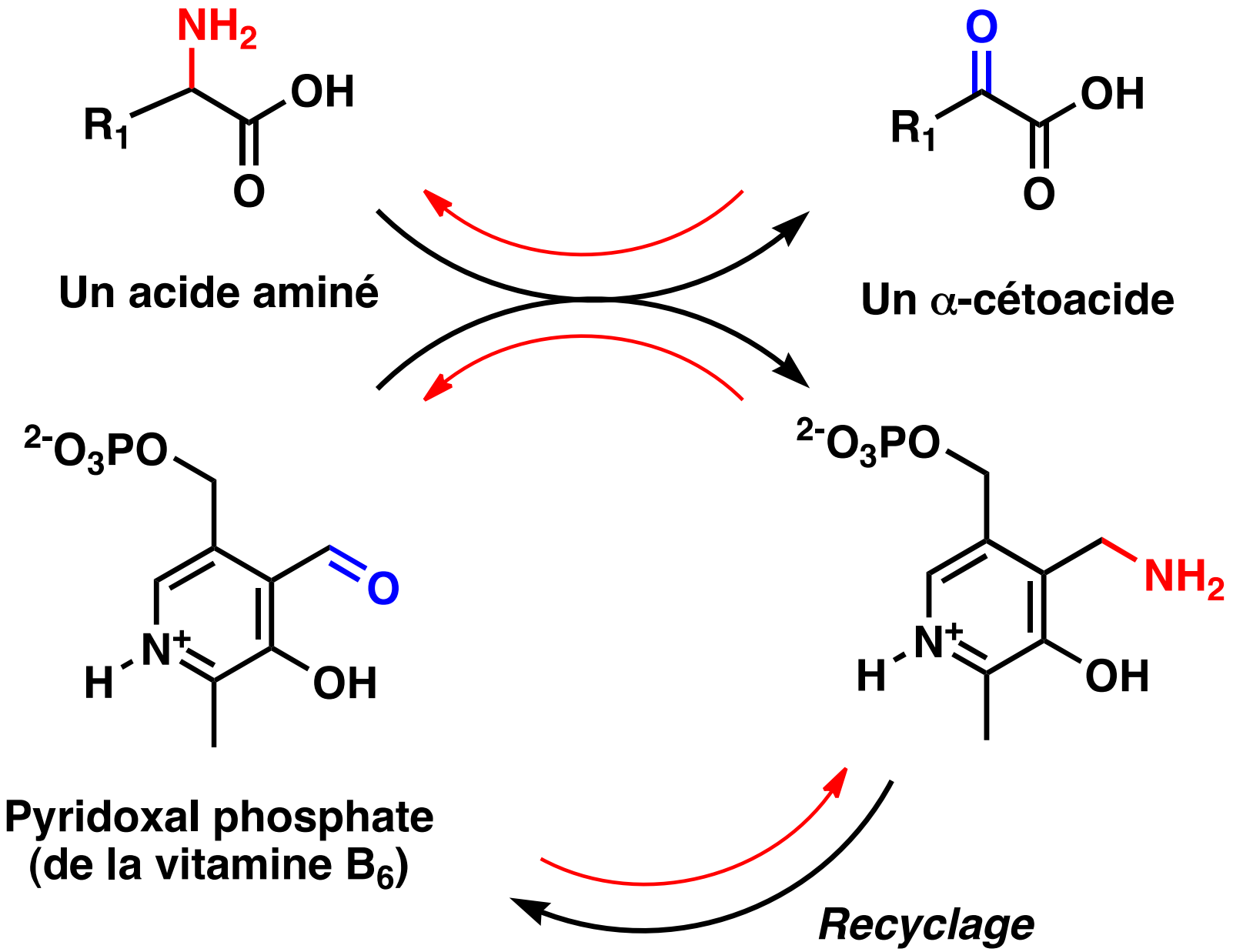


Imines : Réduction





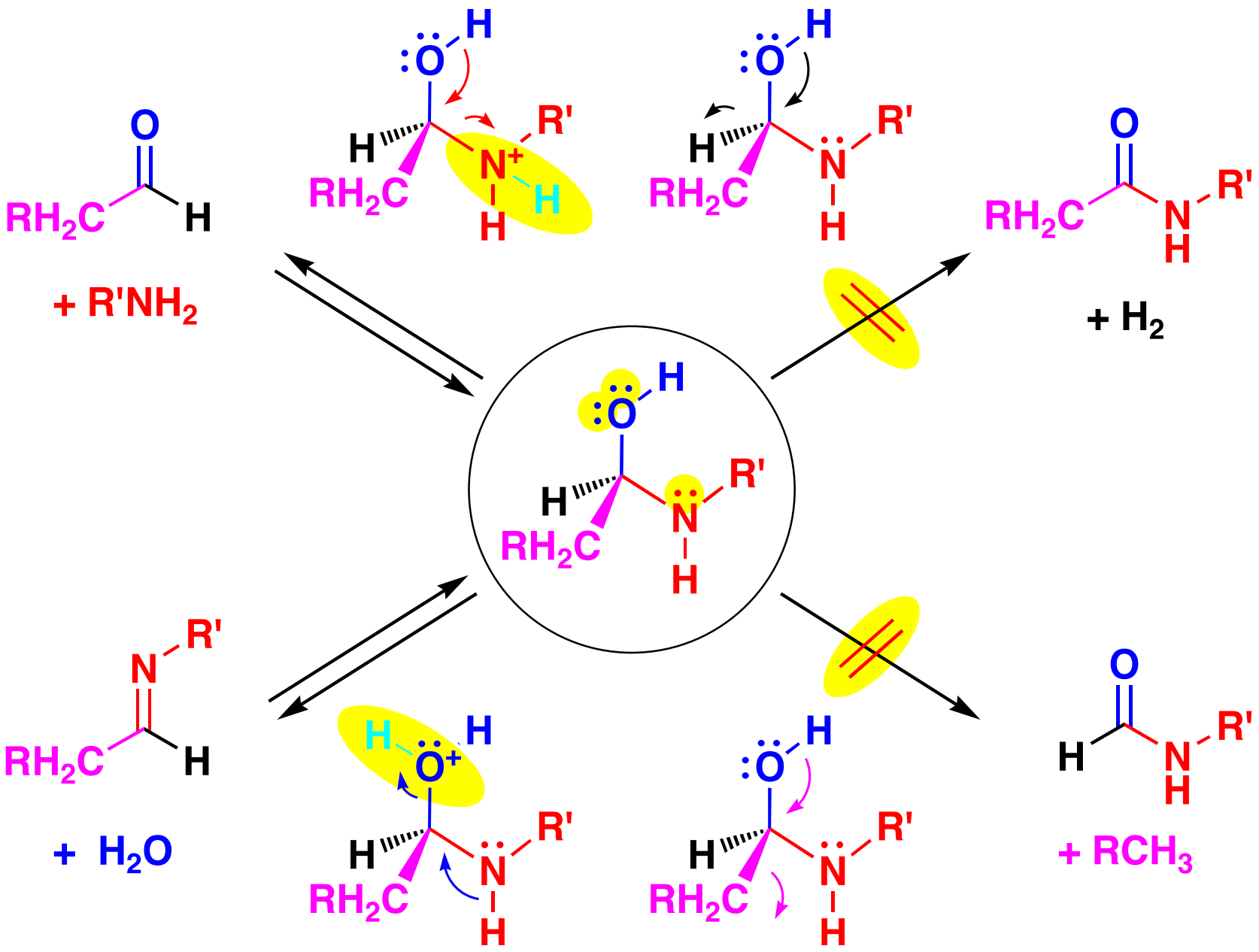
Imines : Transamination



Substitution nucléophile et groupes partants

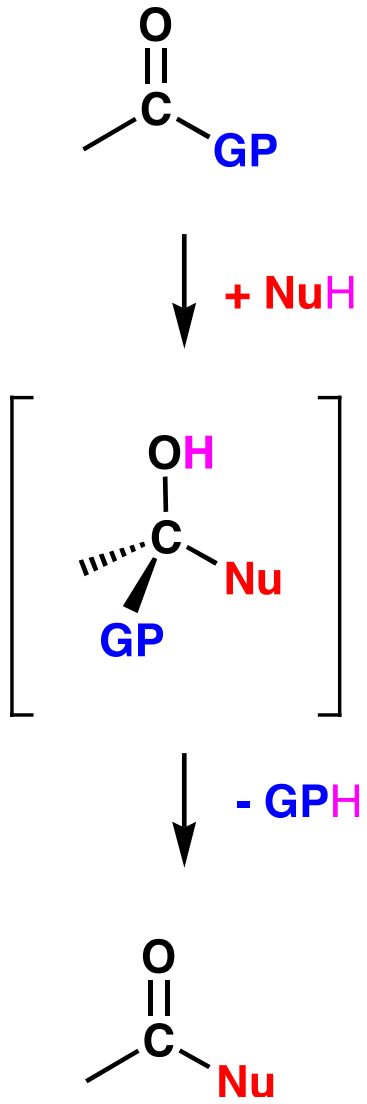
222, 227, 231

(226, 232, 236)



Sélectivité

Groupes partants (groupes sortants, nucléofuges)

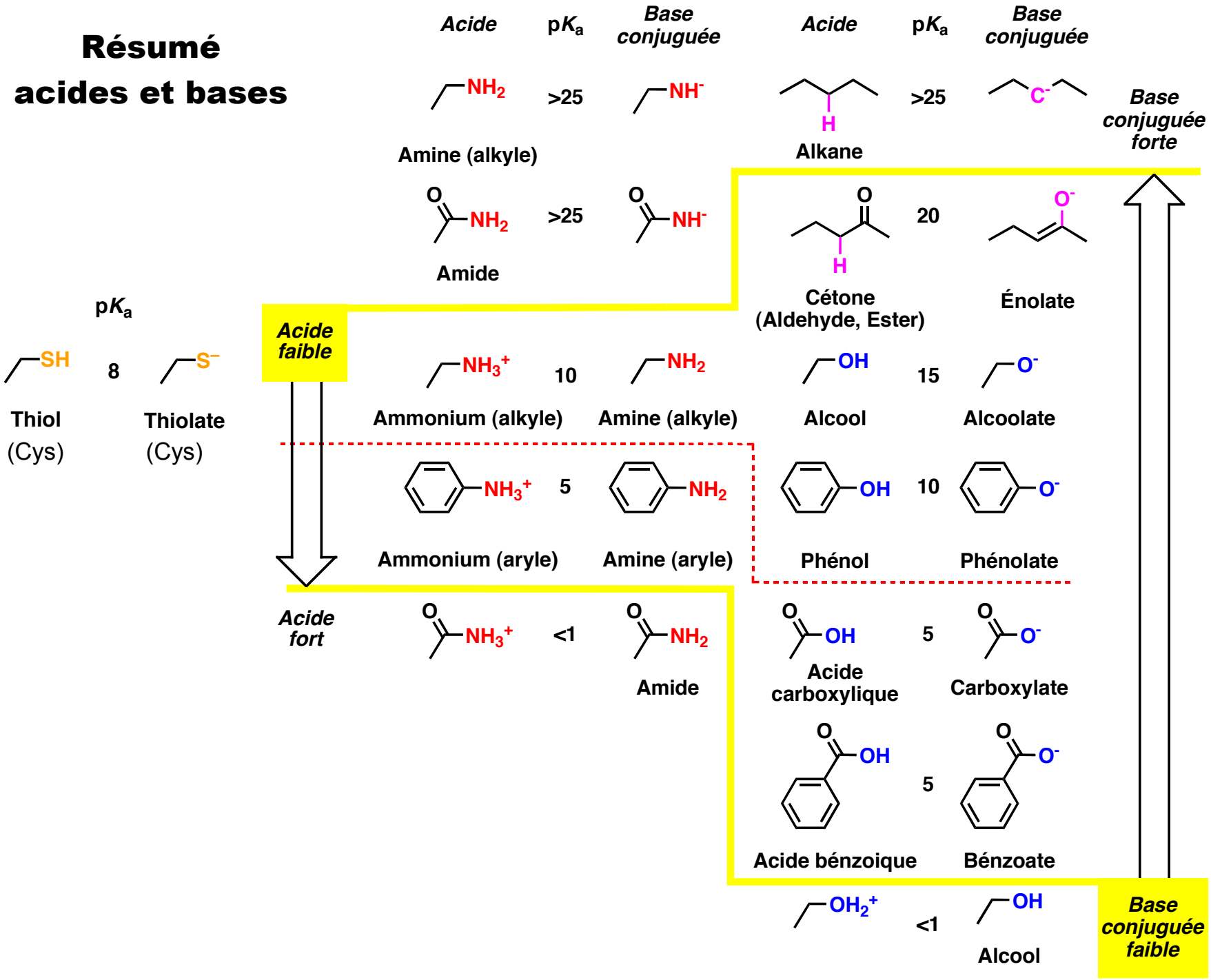


Groupe partant			*Acide conjuguée*	pK_a
I	→	I^-	HI	-5,2
Br	→	Br^-	HBr	-5,0
Cl	→	Cl^-	HCl	-2,2
OH_2^+	→	H_2O	H_3O^+	-1,7
NH_3^+	→	NH_3	NH_4^+	9,3
OCH_3	→	CH_3O^-	CH_3OH	15,5
OH	→	OH^-	H_2O	15,7
NH_2	→	NH_2^-	NH_3	35
H	→	H^-	H_2	35
CH_3	→	CH_3^-	CH_4	~50
O^-	→	O^{2-}	OH^-	?

Bon groupe partant

Mauvais groupe partant

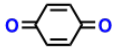
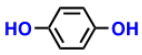
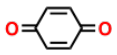
Résumé
acides et bases

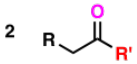
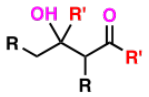
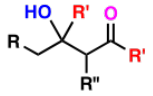
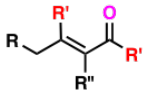
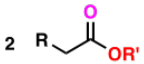
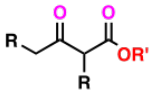
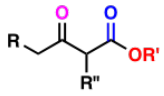
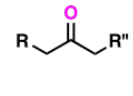
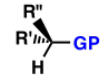


Résumé 5 (Glucides – aldéhydes - cétones - imines -)

- réactions :
  - addition - élimination - substitution - diagramme d'énergie -
  - état de transition - intermédiaire réactionnel - mécanisme -
  - nucléophile - électrophile – catalyse - groupes protecteurs - groupes partants
- addition nucléophile : aldéhyde / cétone +
  - H_2O : hydrate; alcool : hémiacétal
- substitution nucléophile : aldéhyde / cétone +
  - 2 x alcool : acétal
- glucides : aldose - cétose - hexose - pentose - pyranose -
  furanose - projection de Haworth - anomère – glycoside
- intermédiaires réactionnels : médicaments antiviraux, antidiabétiques
- substitution nucléophile : aldéhyde / cétone +
  - amines : imines - réduction - transamination - pyridoxal phosphate -
    chimie de la vision

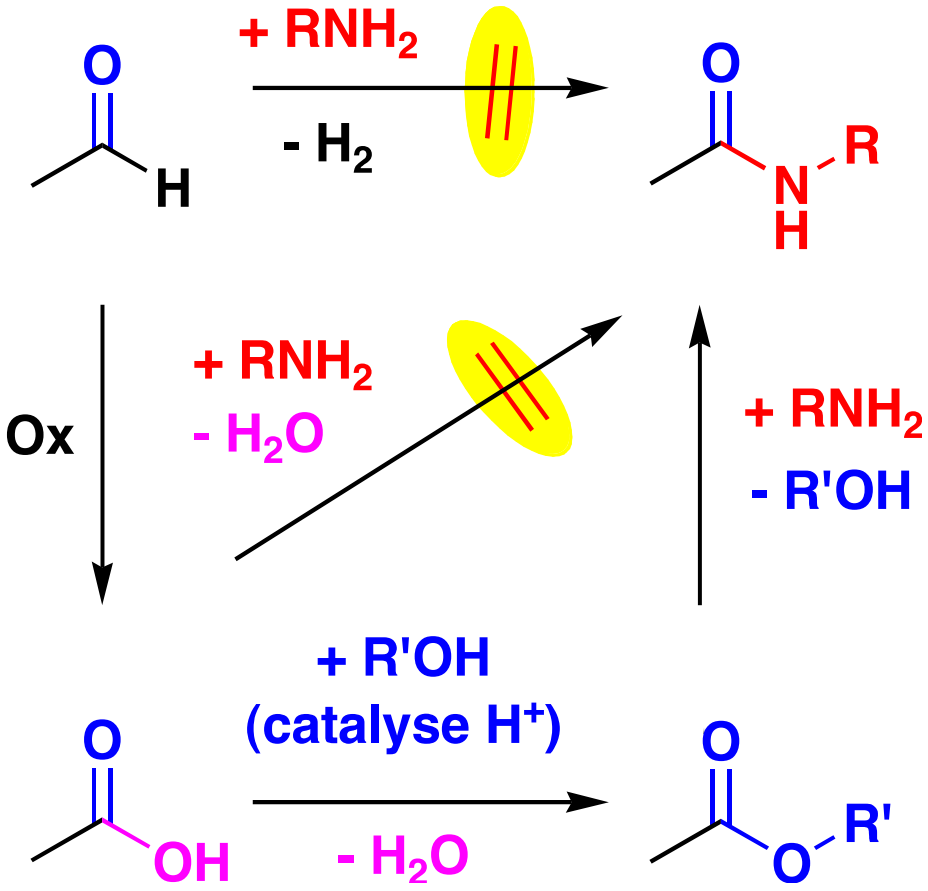
Résumé des réactions

			2007	2003
 Alcène	H_2, catalyseur	 Alcane	4.6	4.6
 Alcool primaire	CrO_3, H_3O^+ ⇌ $LiAlH_4$, puis H_3O^+	 Acide carboxylique	8.5 8.4	8.7 8.5
 Alcool secondaire	$Na_2Cr_2O_7$, H_3O^+ ⇌ $NaBH_4$, puis H_3O^+	 Cétone	8.5 8.4	8.7 8.5
 Alcool primaire	PCC ⇌ $NaBH_4$, puis H_3O^+	 Aldéhyde	8.5 8.4	8.7 8.5
 Phénol	$Na_2Cr_2O_7$, H_3O^+	 Benzoquinone	8.6	8.8
 Hydroquinone	$Na_2Cr_2O_7$, H_3O^+ ⇌ $NaBH_4$, puis H_3O^+	 Benzoquinone	8.6	8.8
 Aldéhyde / cétone + H_2O	⇌	 Hydrate	9.7	9.7
 Aldéhyde / cétone + ROH	⇌	 Hémiacétal	9.8 9.9 14.5 14.6	9.8 14.5 14.6
 Aldéhyde / cétone + 2 ROH Alcool	Catalyseur (H_3O^+) ⇌	 Acétal + H_2O	9.8 9.9 14.7	9.8 14.8
 Aldéhyde / cétone + RNH_2 Amine	⇌	 Imine + H_2O	9.10	9.9

			2007	2003
 Acide carboxylique + ROH Alcool	Catalyseur (H_3O^+) ⇌ Catalyseur (OH^- ou H_3O^+)	 Ester + H_2O	10.8 10.11	10.6 10.9
 Ester + $R'NH_2$ Amine	⇌ Chauffage, catalyseur (OH^- ou H_3O^+)	 Amide + ROH Alcool	16.13 10.10	10.9 10.10
 Ester	$LiAlH_4$, puis H_3O^+	 Alcool primaire + ROH Alcool	10.11 8.4	10.9 8.5
2  Aldéhyde / cétone	Catalyseur (OH^-) ⇌	 β-Hydroxycétone	11.9	11.8
 β-Hydroxycétone	Catalyseur (OH^- ou H_3O^+) ⇌	 Énone conjuguée + H_2O	11.10	11.9
2  Ester	Catalyseur (NaOR') ⇌	 β-Cétoester + R'OH Alcool	11.11	11.10
 β-Cétoester	Chauffage, catalyseur (OH^- ou H_3O^+) →	 Cétone + R'OH + CO_2	17.4	17.4
RNH_2 +  Amine GP = groupe partant	→	 Alkylamine + HGP^+	12.4 7.5	12.4 7.7 8.11
 Imine	$NaCNBH_3$, puis H_3O^+ →	 Amine	9.10	9.11

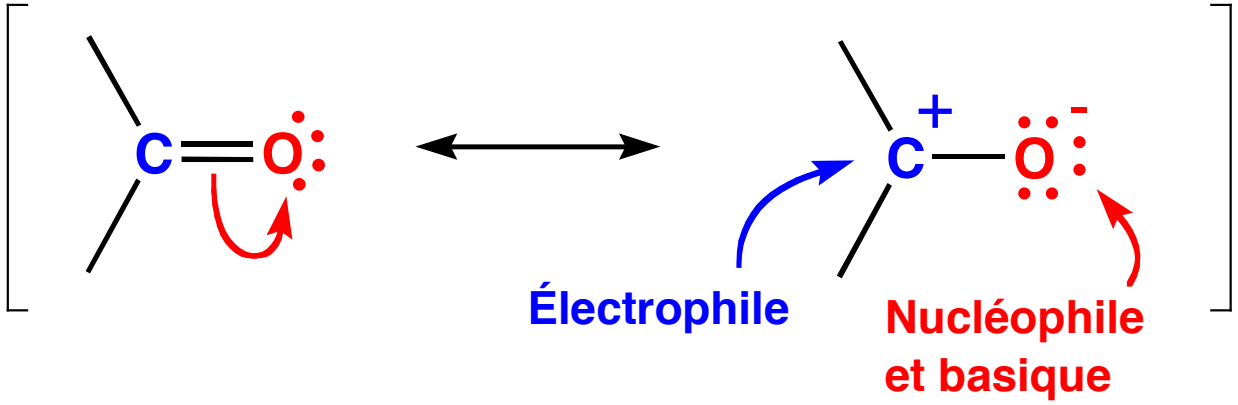
CONTENU	McMurry
1. Généralités	(1, 2, 15)
2. Lipides - stéroïdes - alcanes - alcènes - arènes -	(2 - 5, 16)
3. Glucides - stéréochimie -	(6, 14)
4. Alcools - éthers – phénols - hydroquinones - thiols - disulfures	(8, 16)
5. Glucides - aldéhydes - cétones - imines -	(9, 14)
6. Protéines - lipides - acides - esters - amides -	(10, 11, 15, 16)
7. Acides nucléiques - amines -	(12, 16)

Synthèse des protéines

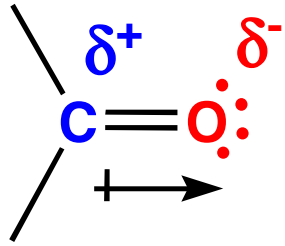


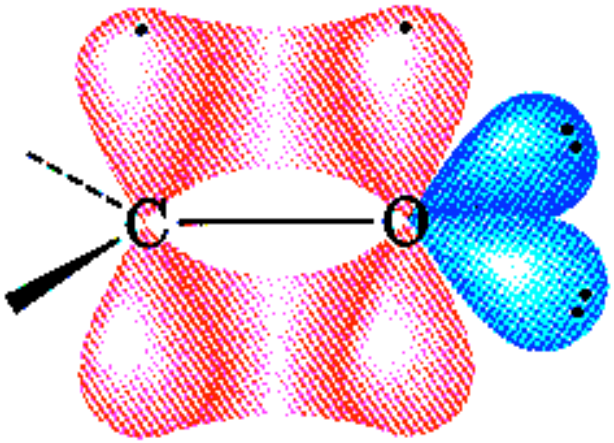
Erythropoietin
(EPO, hormone, anemia)

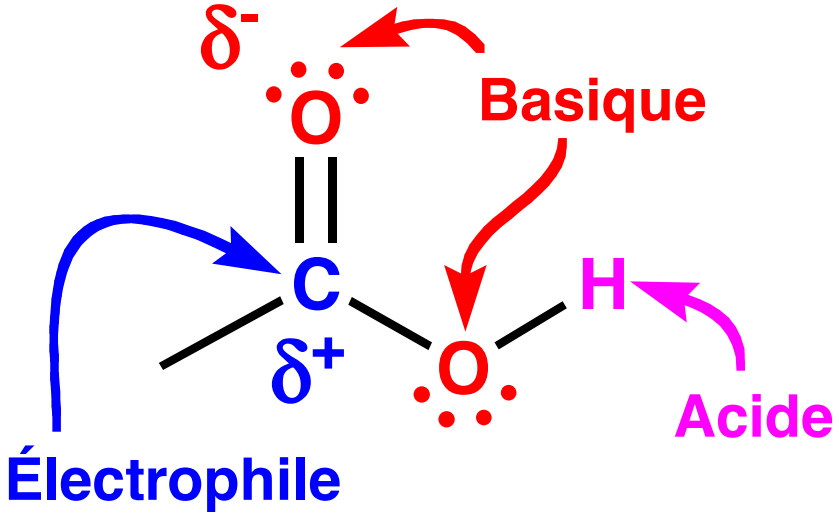
Acide carboxylique



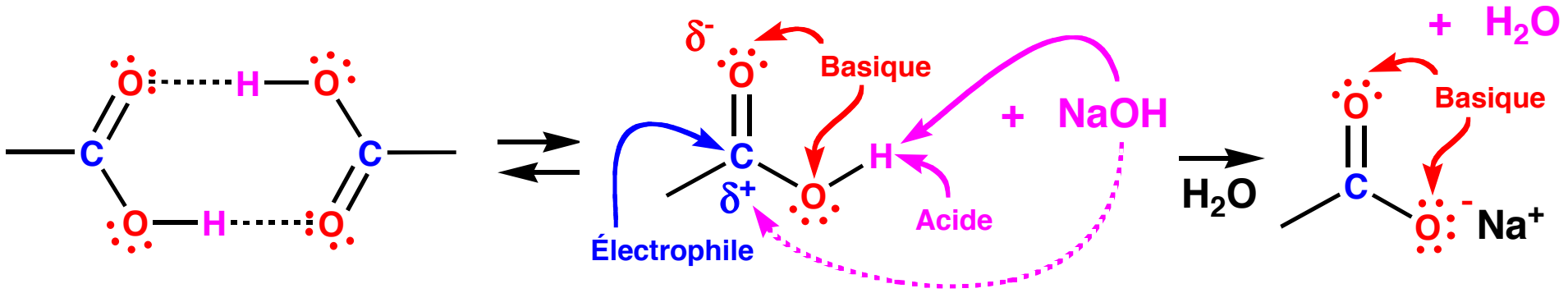
ou







Liaisons hydrogènes et solubilité



dimère d'un acide carboxylique

acide carboxylique

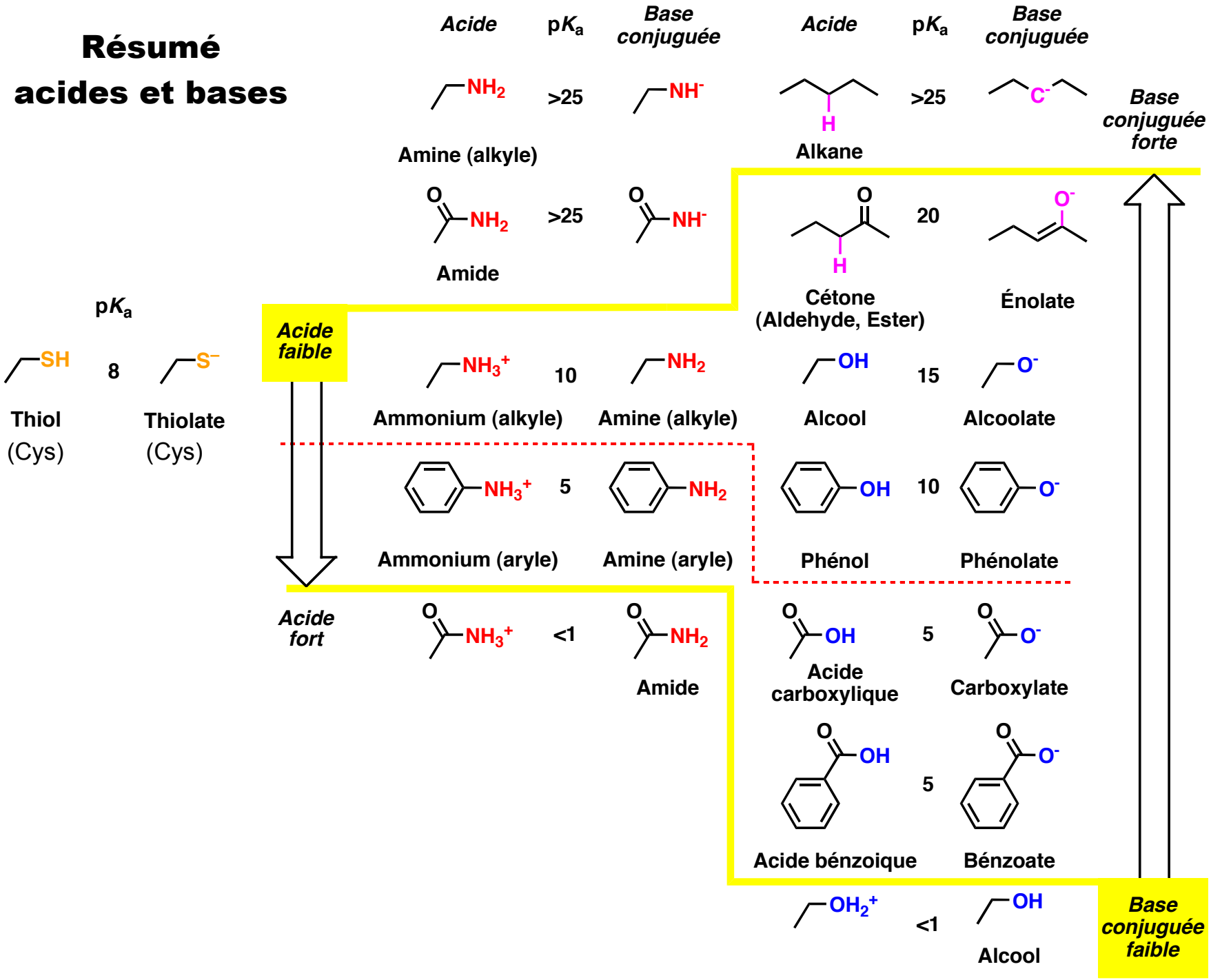
sel de l'ion carboxylate

acide acétique : Eb =118 °C

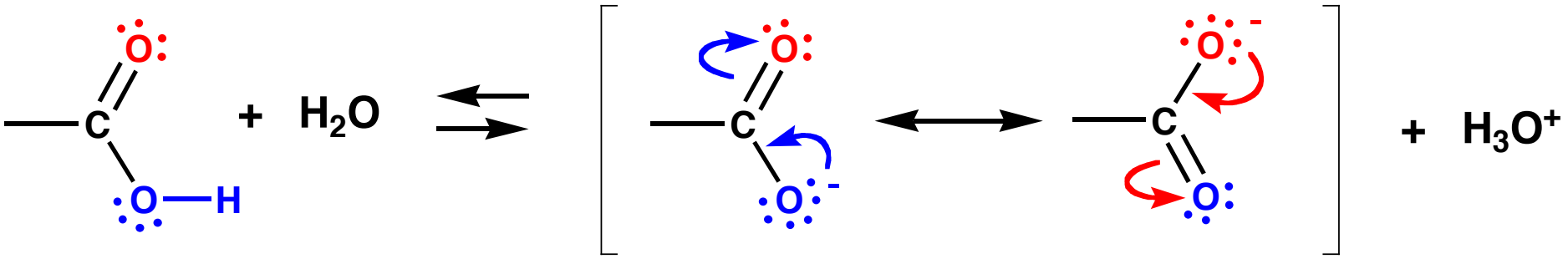
insoluble dans l'eau

soluble dans l'eau

Résumé
acides et bases



Acidité et résonance

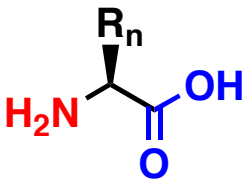


acide carboxylique

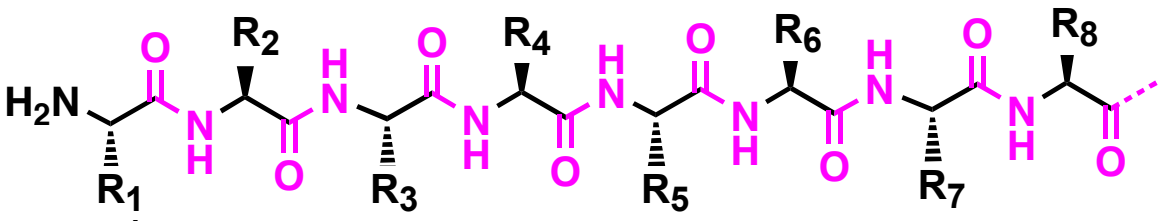
ion carboxylate stabilisé par résonance
(deux mésomères équivalents)

pK_a ~ 5	pK_a ~ 10	pK_a ~ 15	

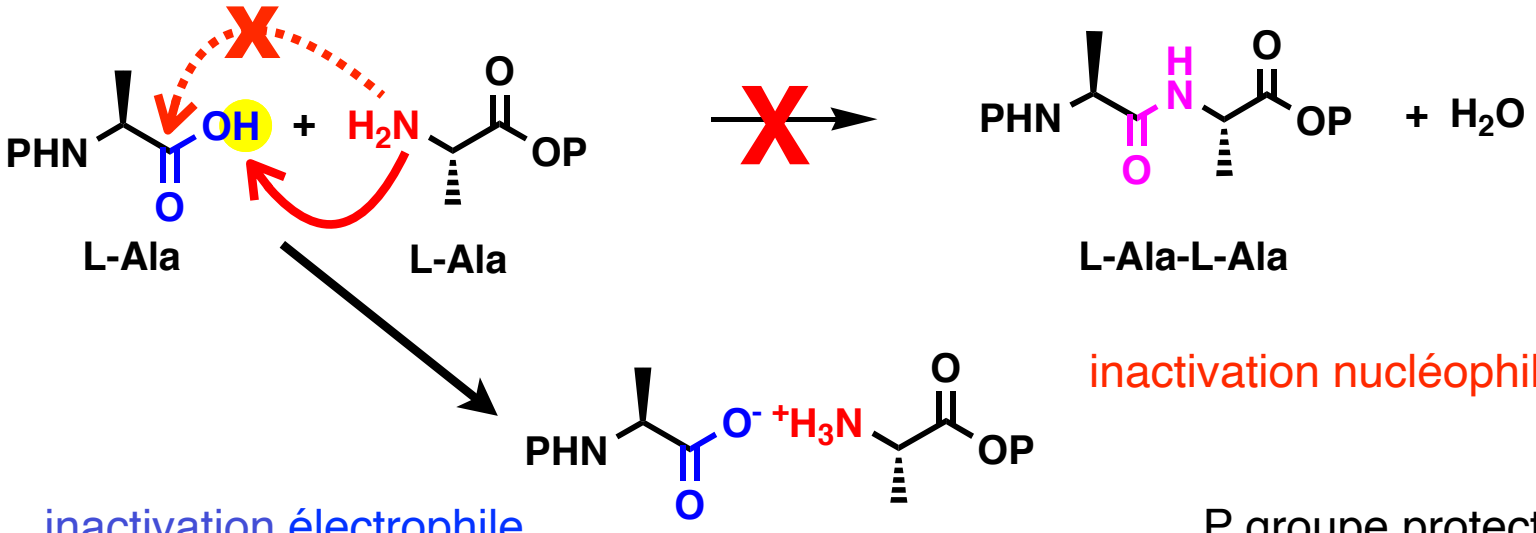
Synthèse des protéines



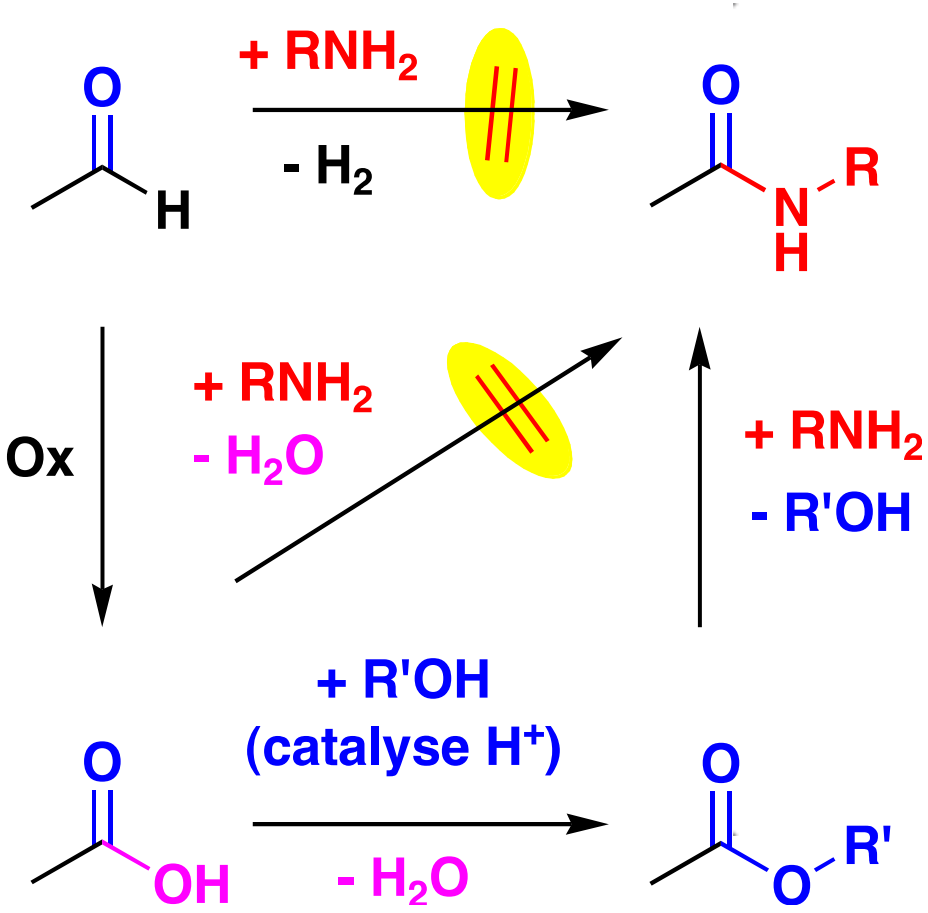
Plusieurs acides aminés

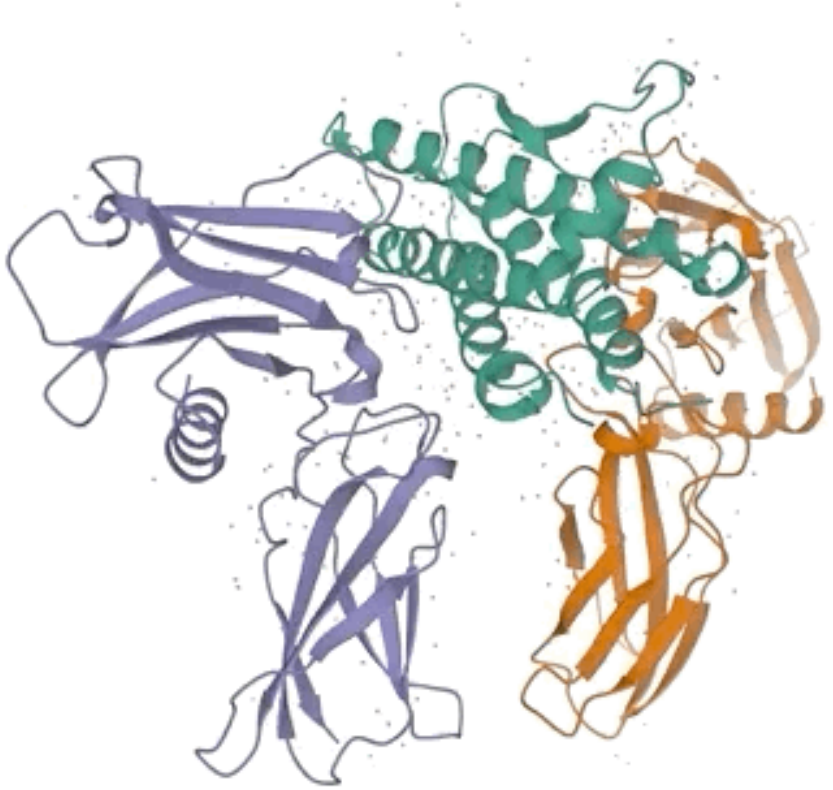


Polypeptide (plusieurs liaisons amide)

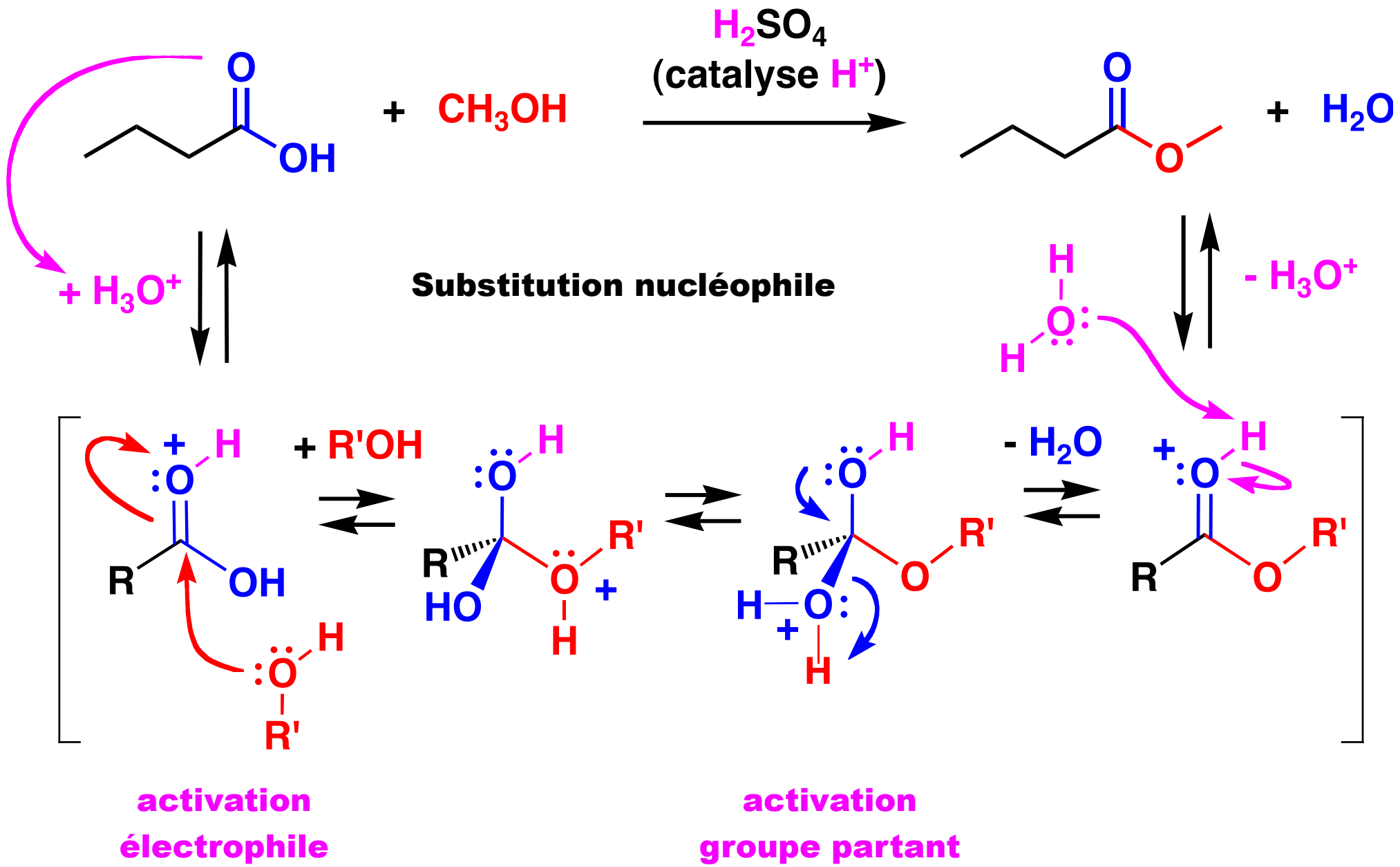


Synthèse des protéines

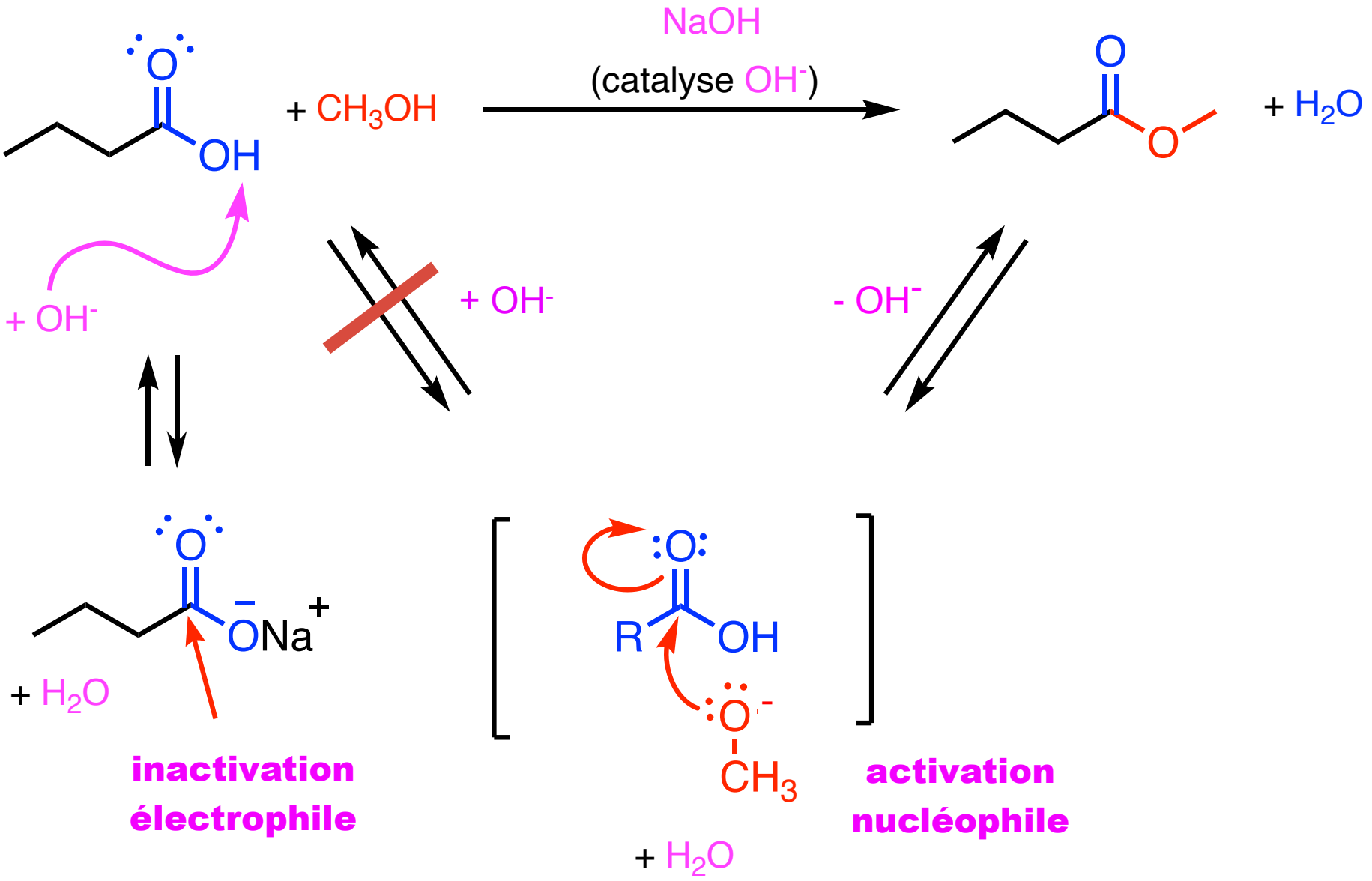




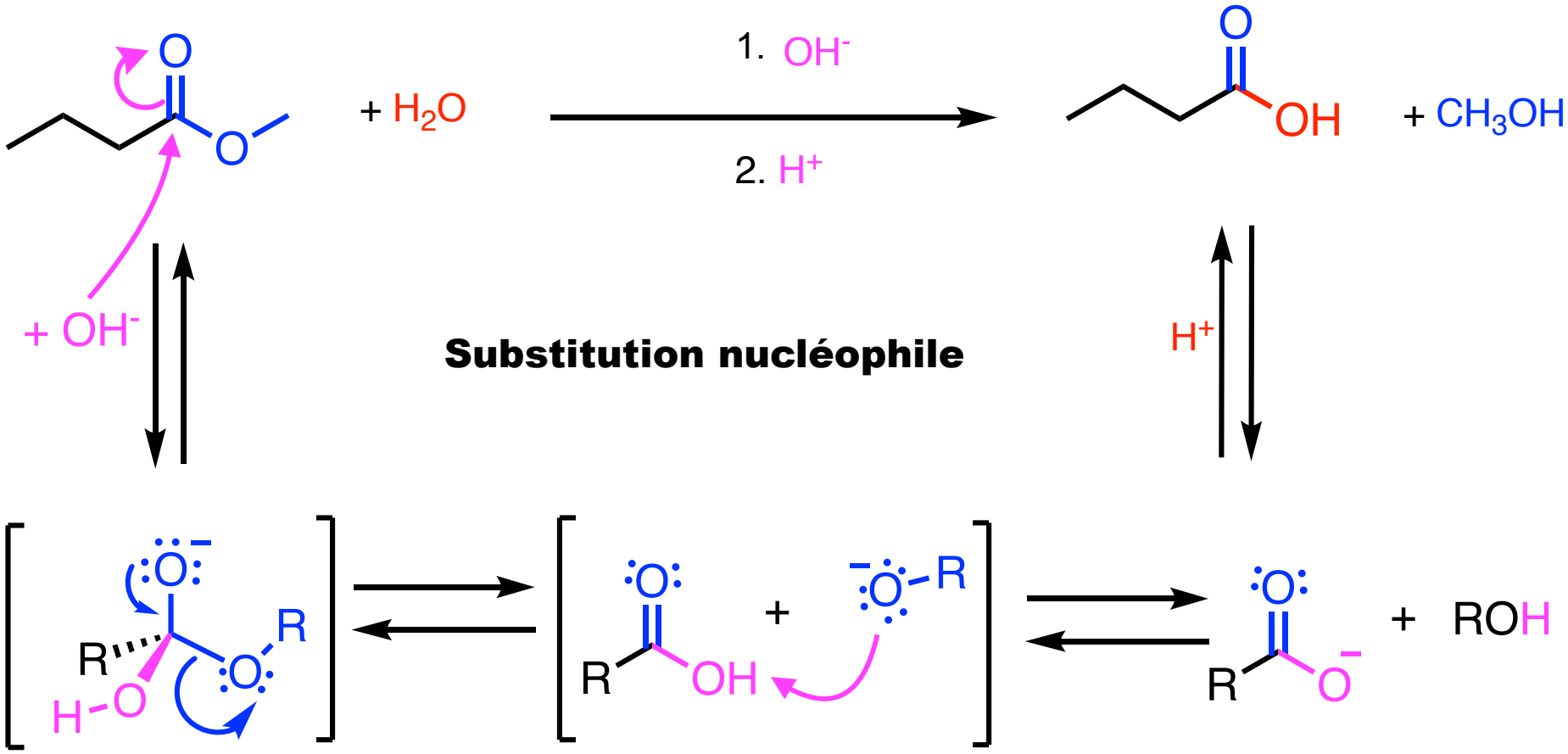
L'estérification de Fischer - catalyse acide



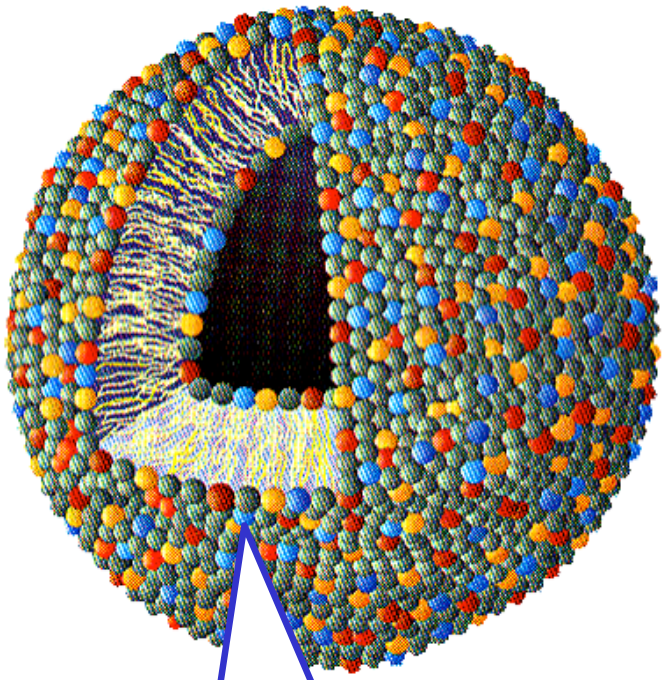
Estérification de Fischer - ~~catalyse basique~~

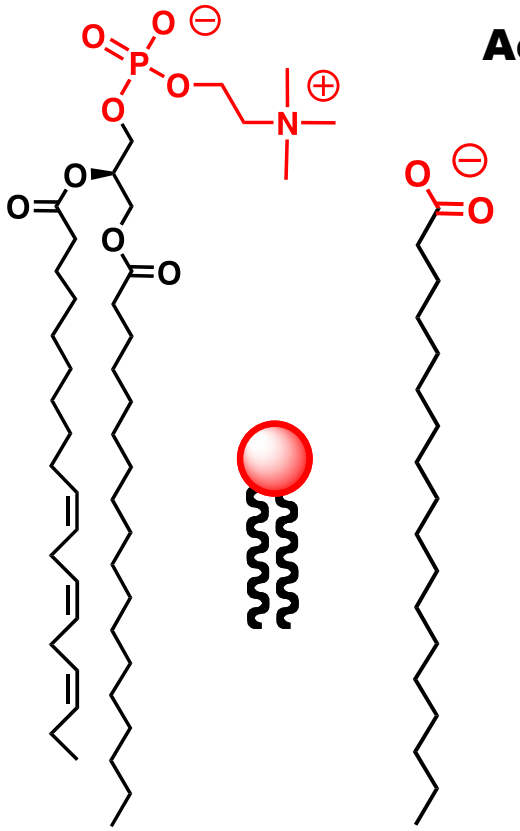


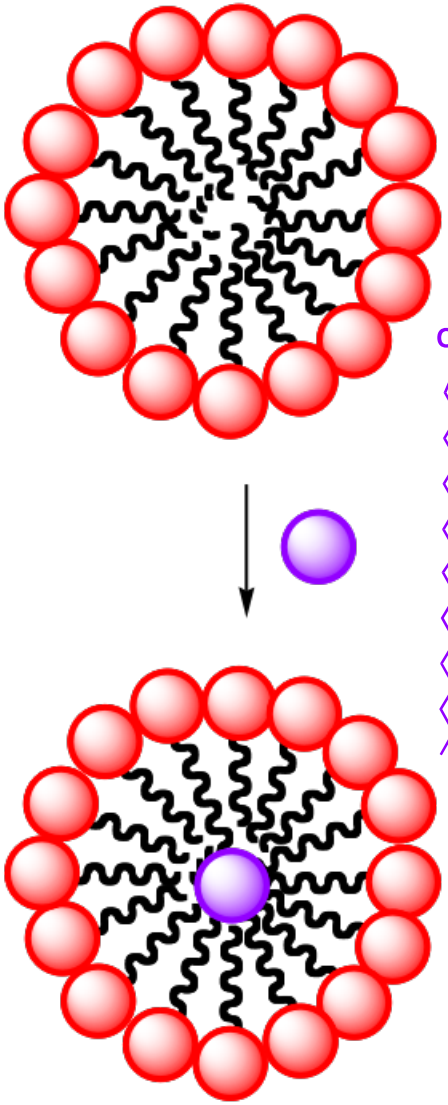
Hydrolyse des esters - conditions basique (saponification)

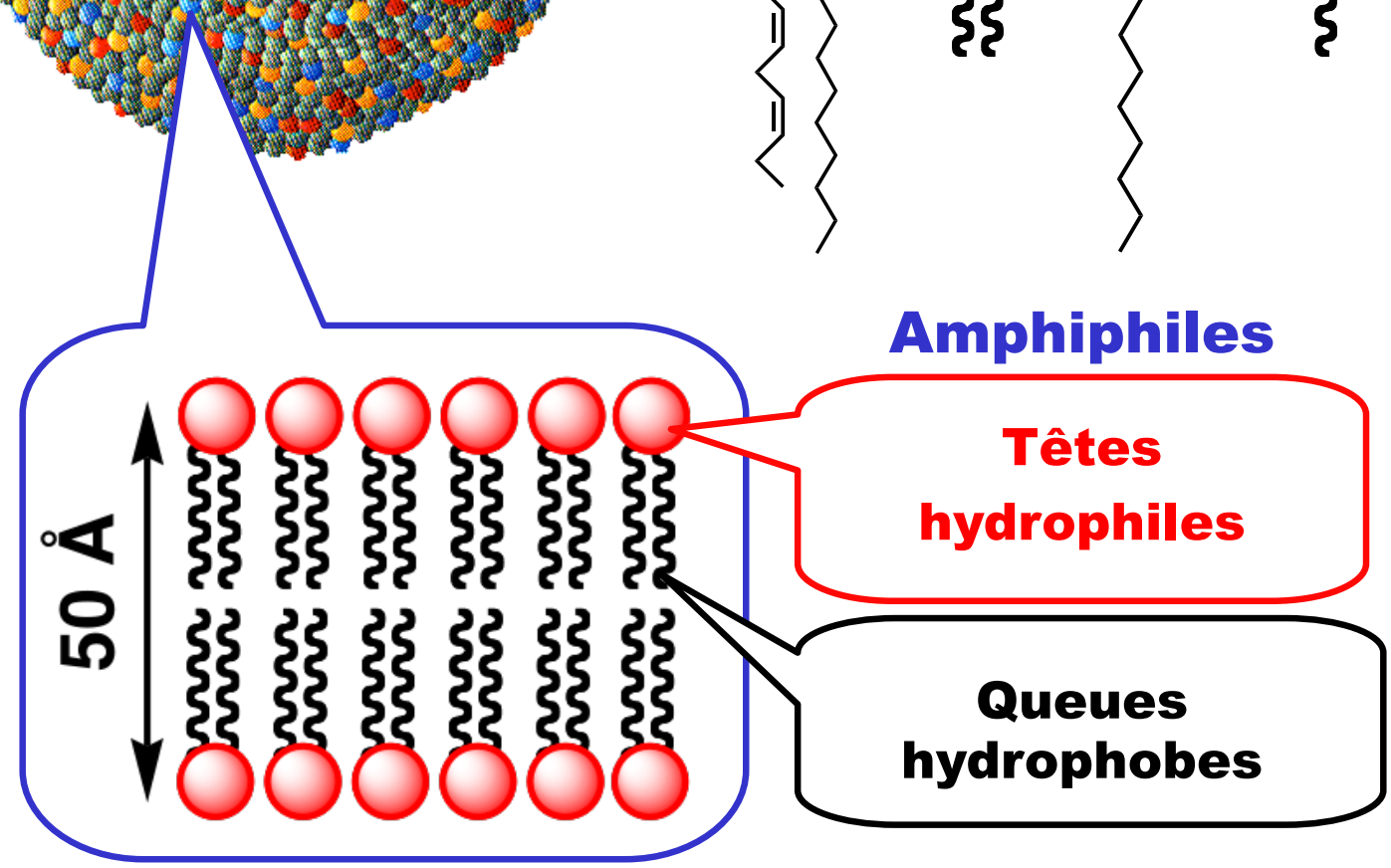


Acides gras et phospholipides
micelles et biomembranes
savon et cellules









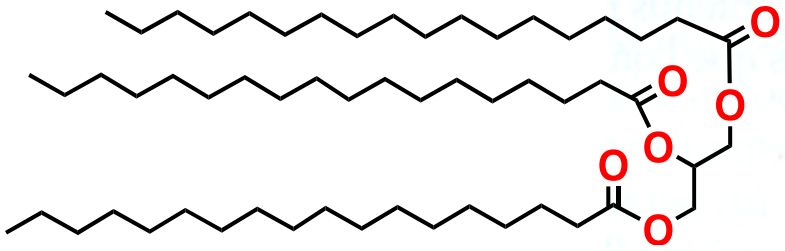
Sélectivité

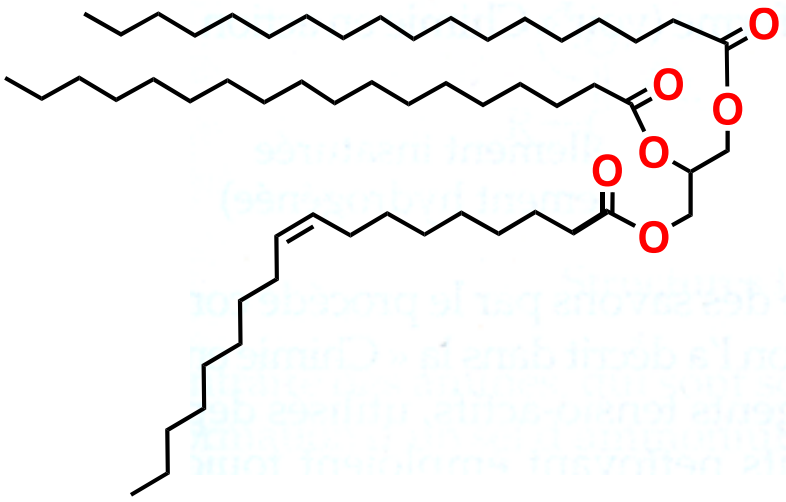
A $LiAlH_4$, puis H_3O^+

B H_2, catalyseur

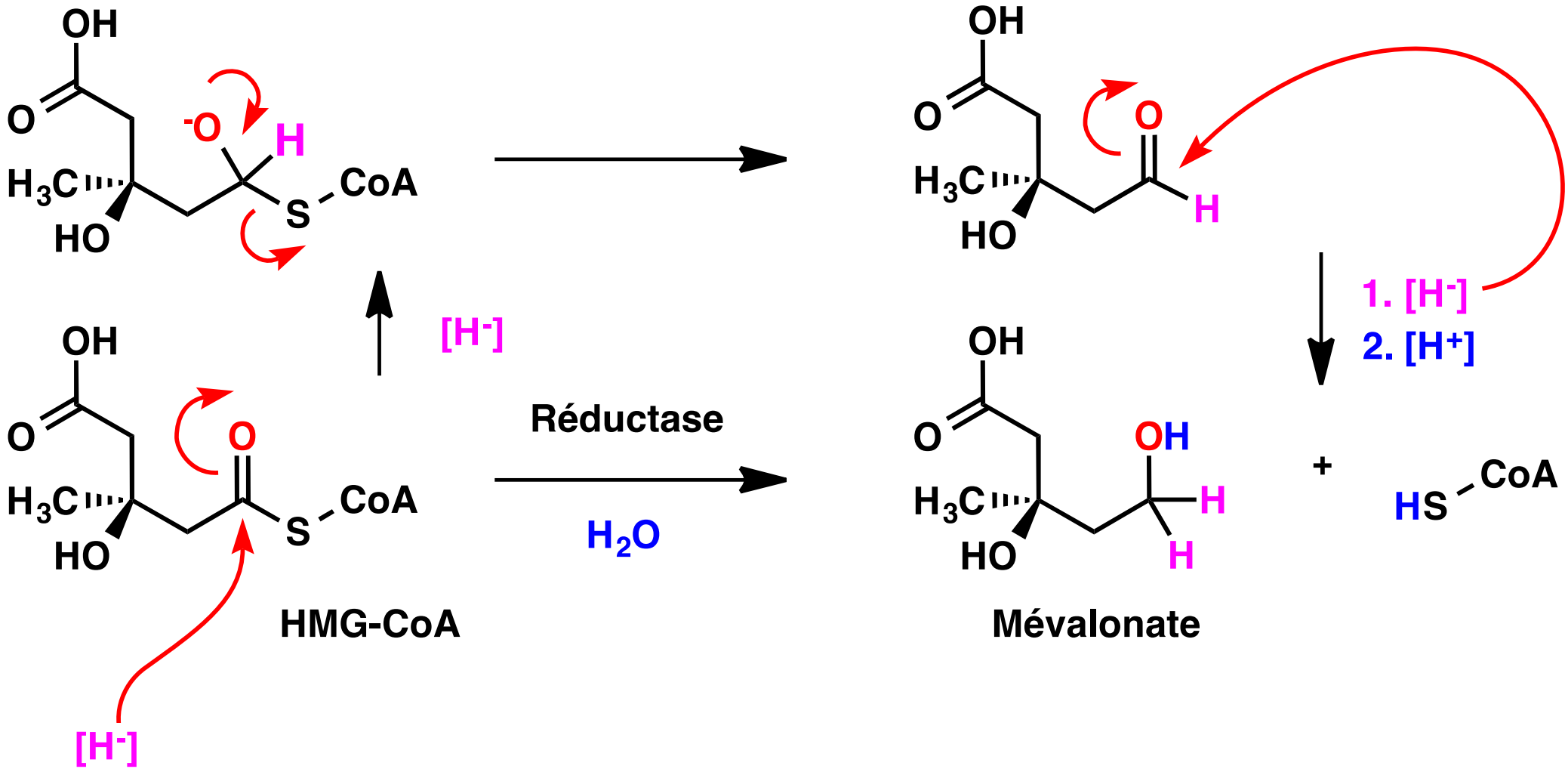
C H_2O, cat H^+ ou OH^-

A, B ou C?

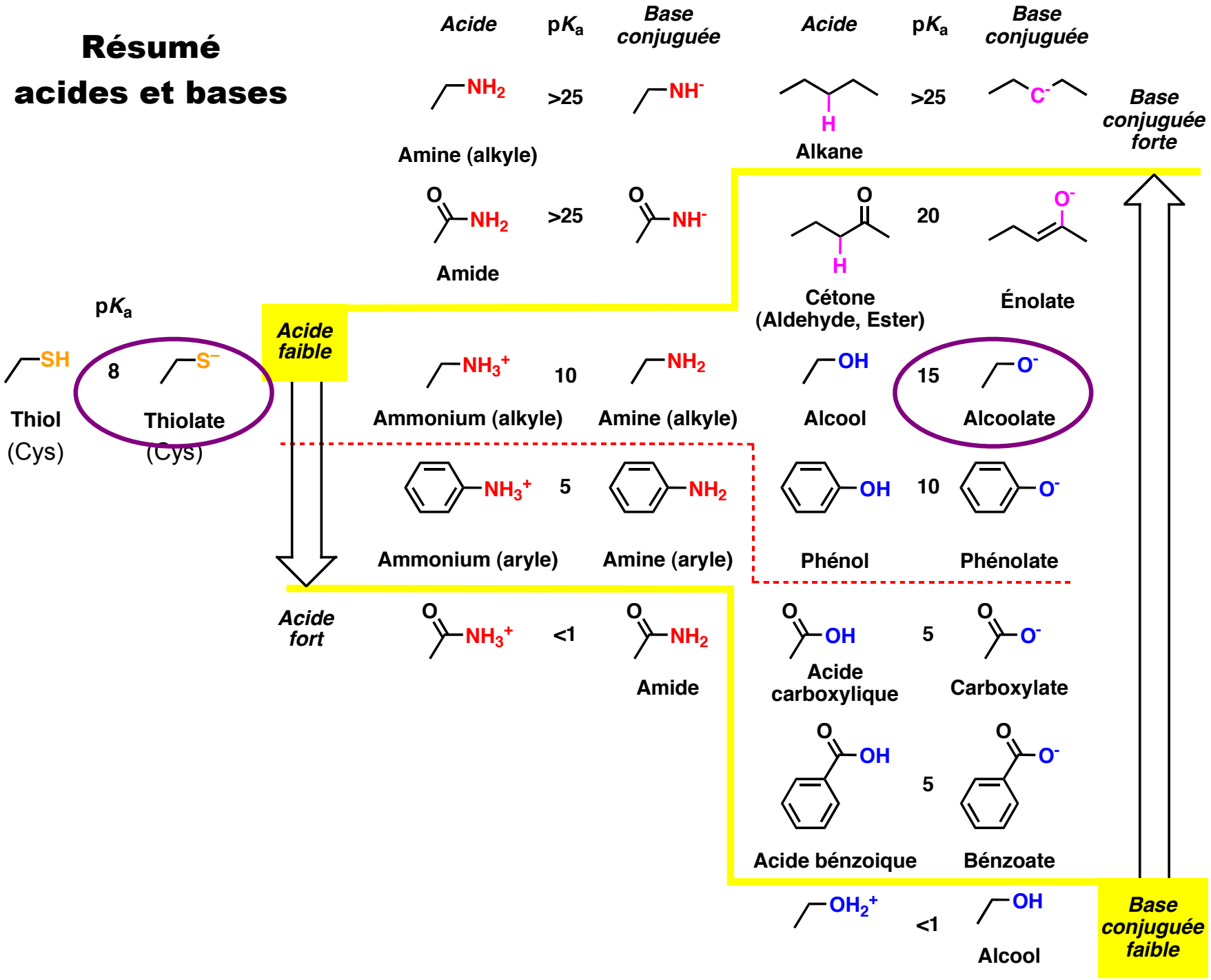




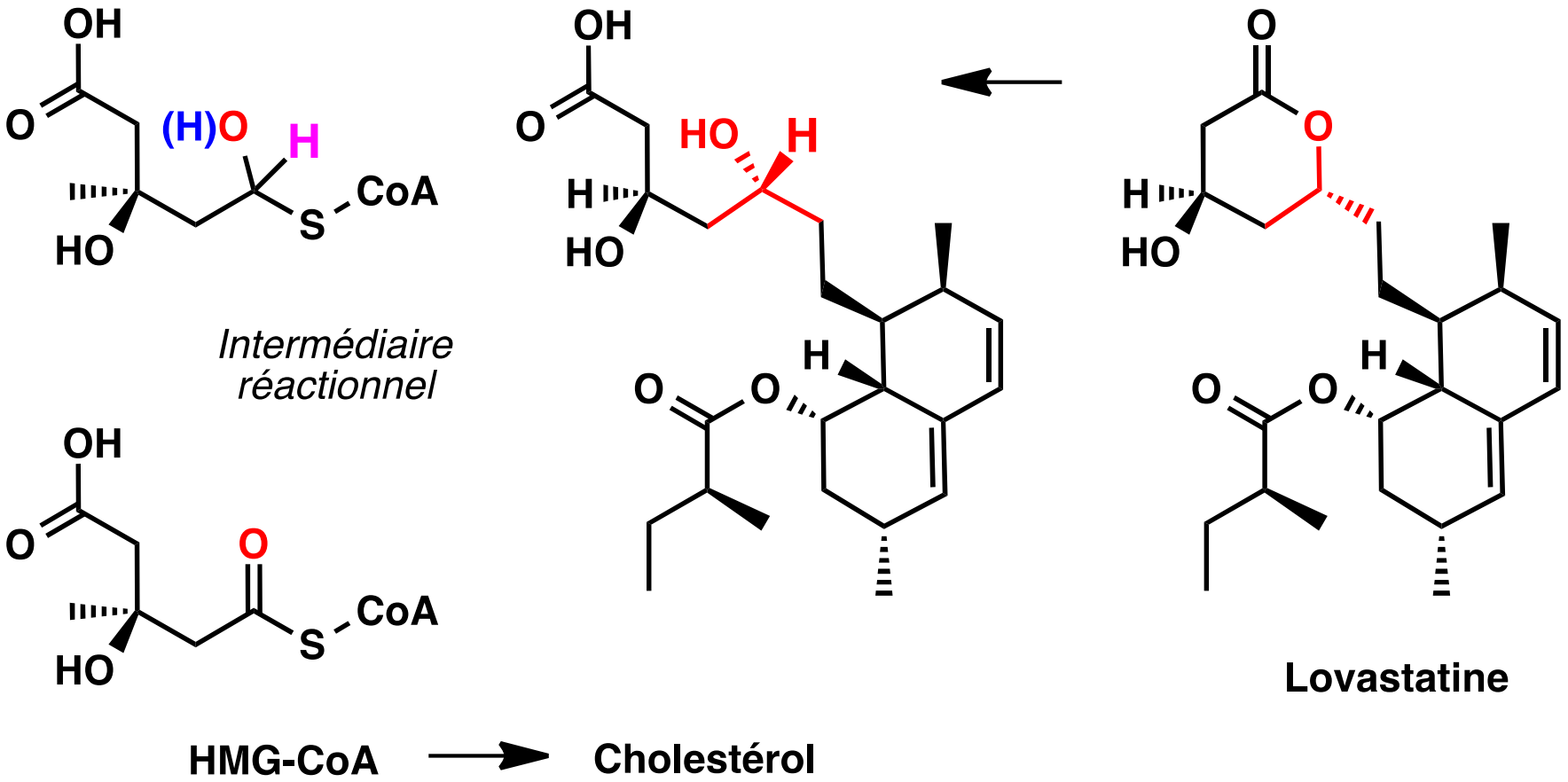
Réduction des (thio)esters : addition nucléophile d'hydrures



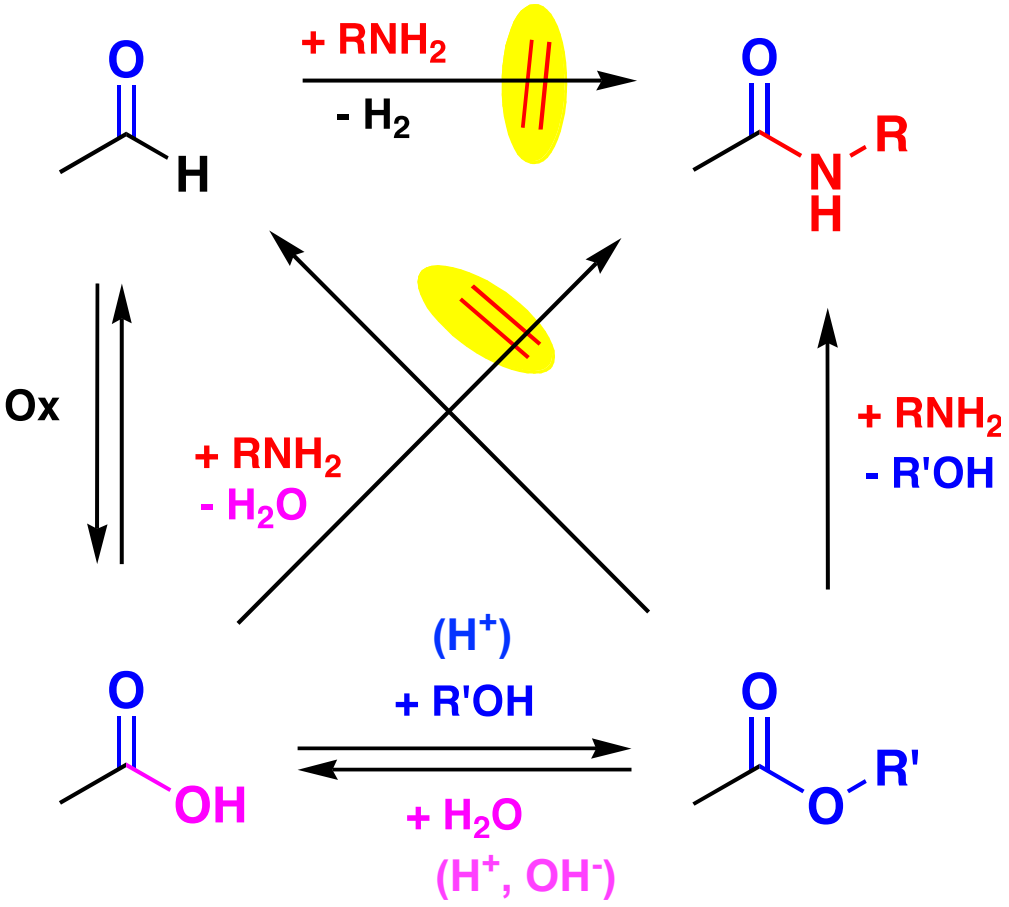
Résumé
acides et bases

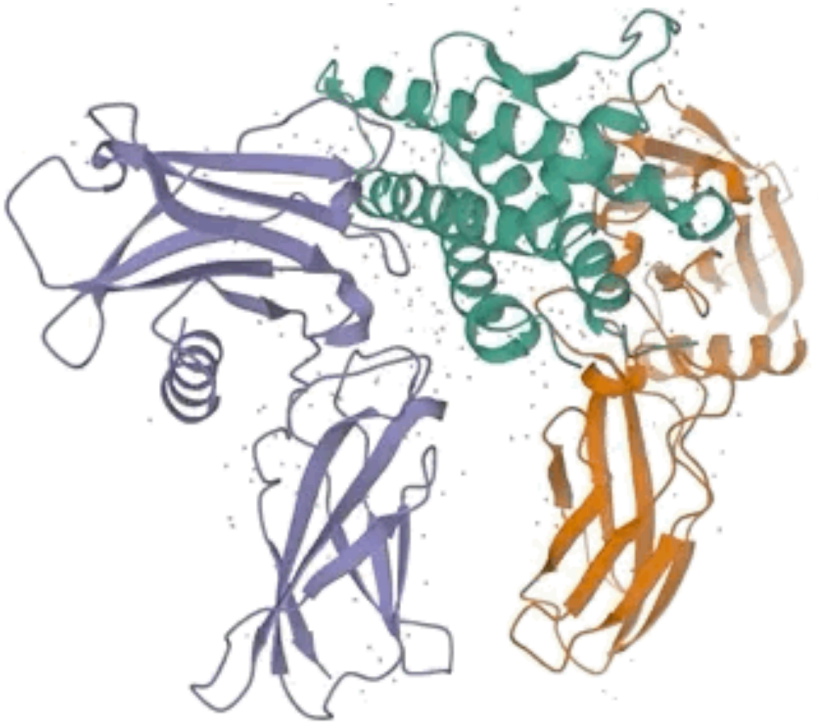


Hydrolyse des lactones (médicaments anti-cholestérol)

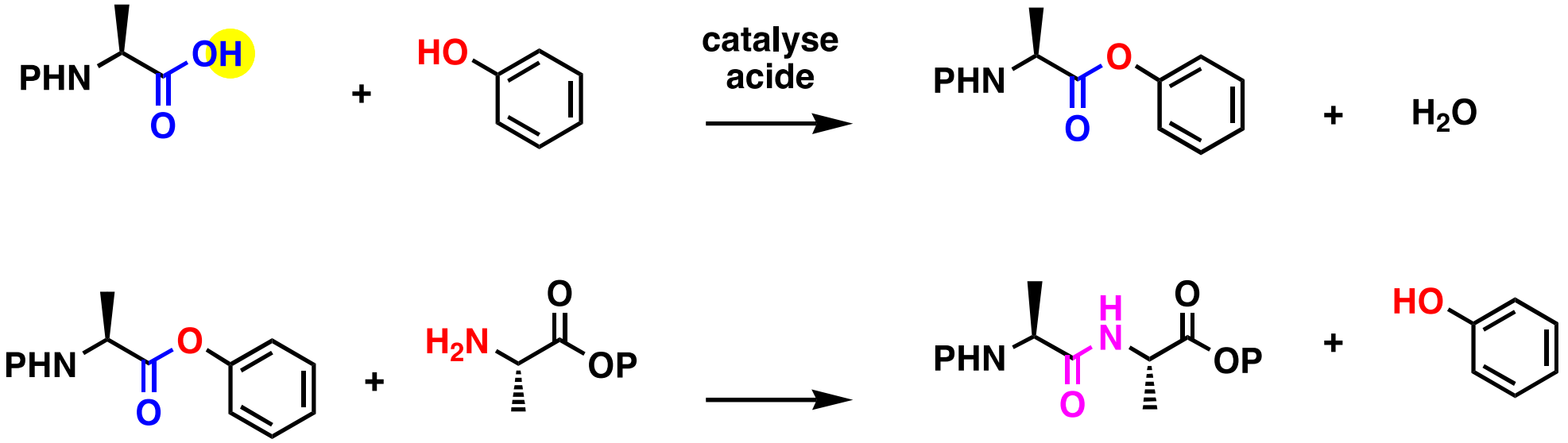


Synthèse des protéines



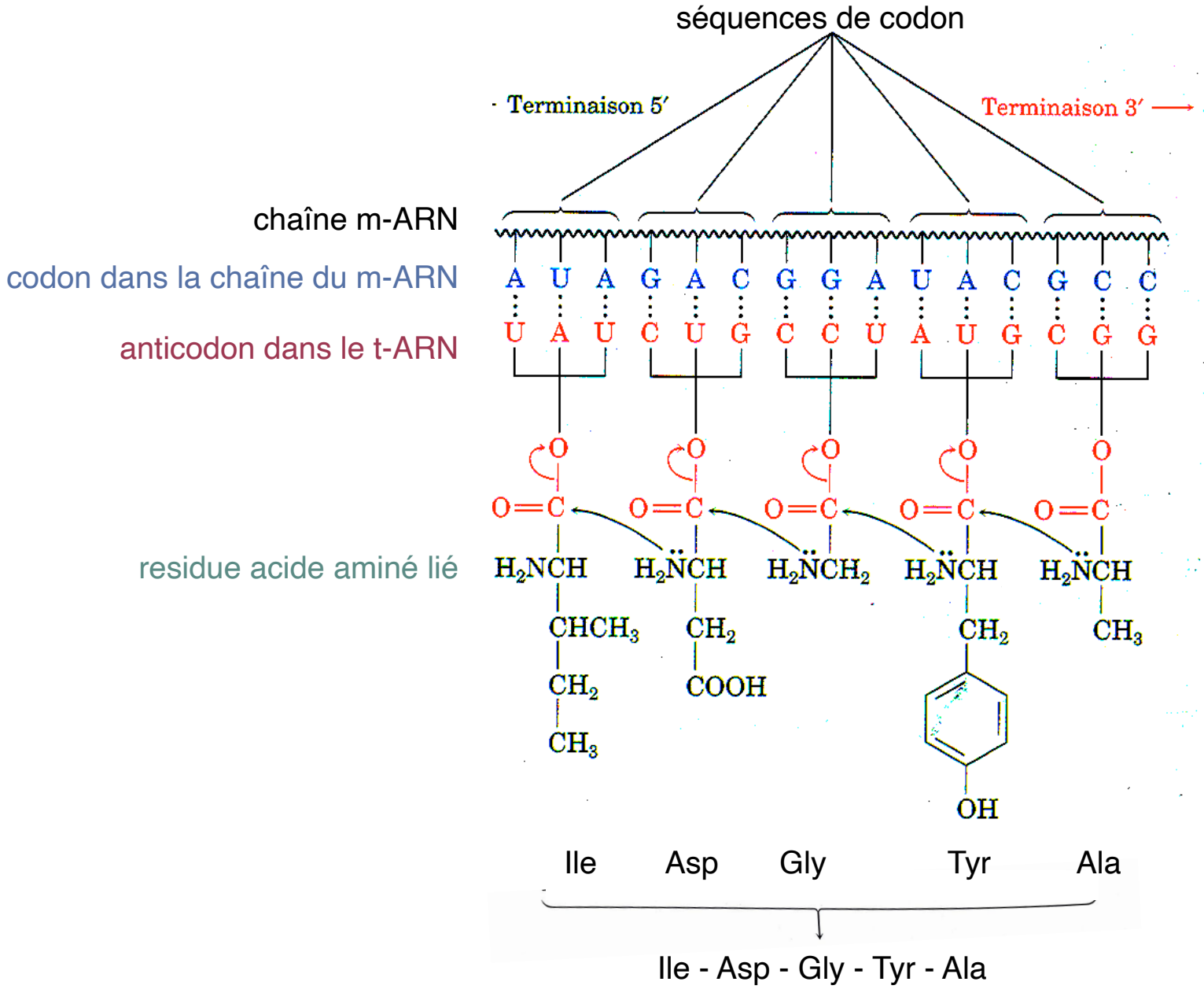


Synthèse des protéines

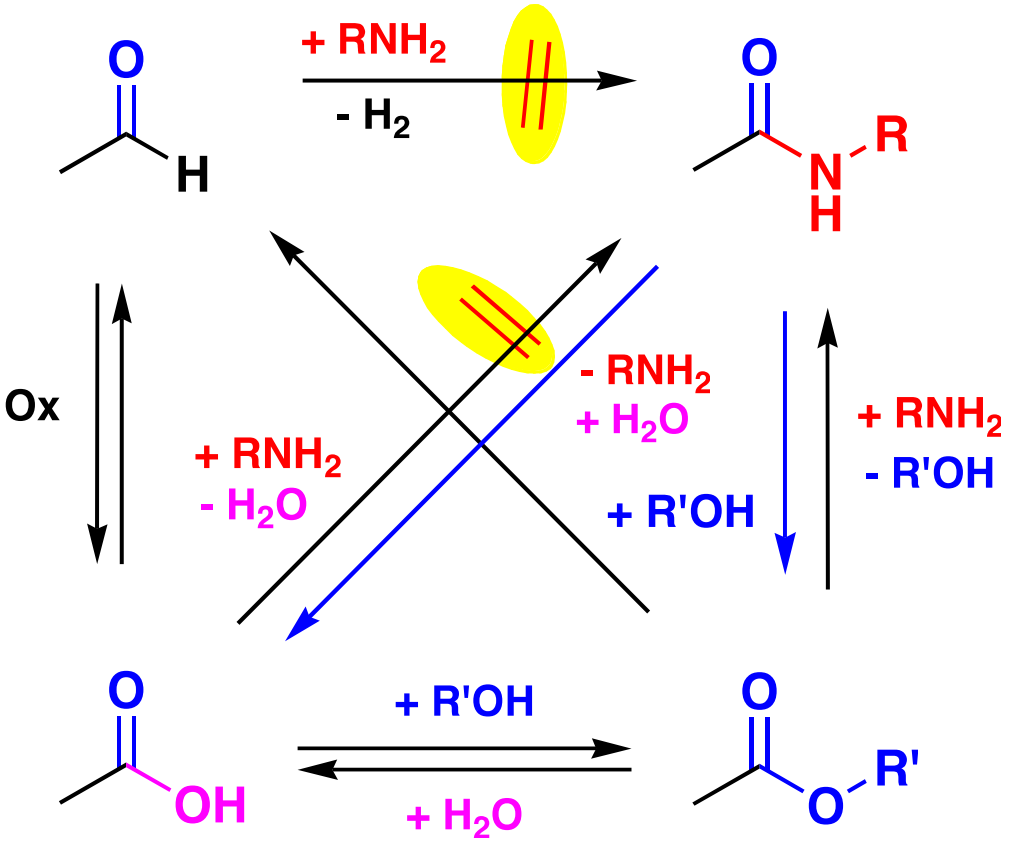


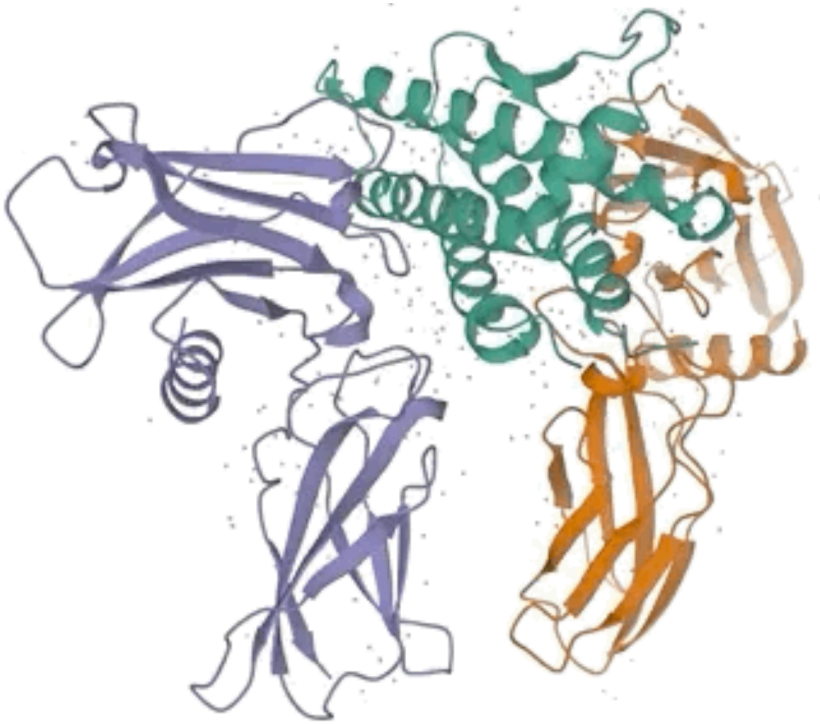
P groupe protecteur

Synthèse des protéines

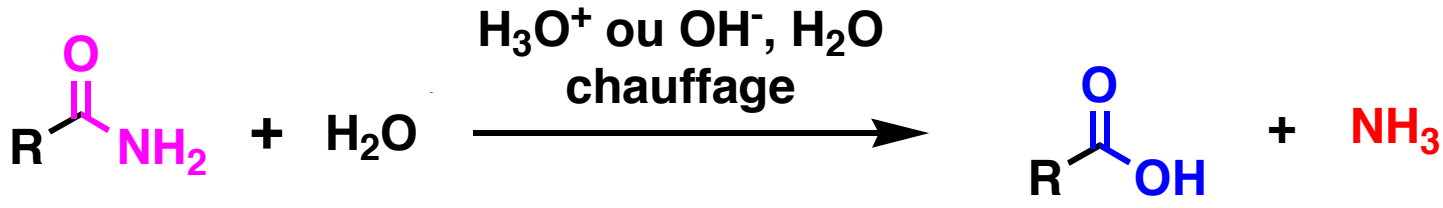


Synthèse des protéines



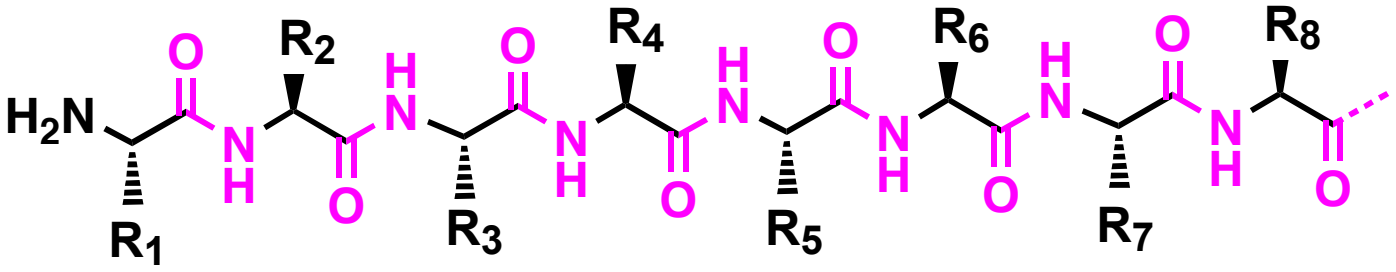


Hydrolyse des amides - enzymes



Amide

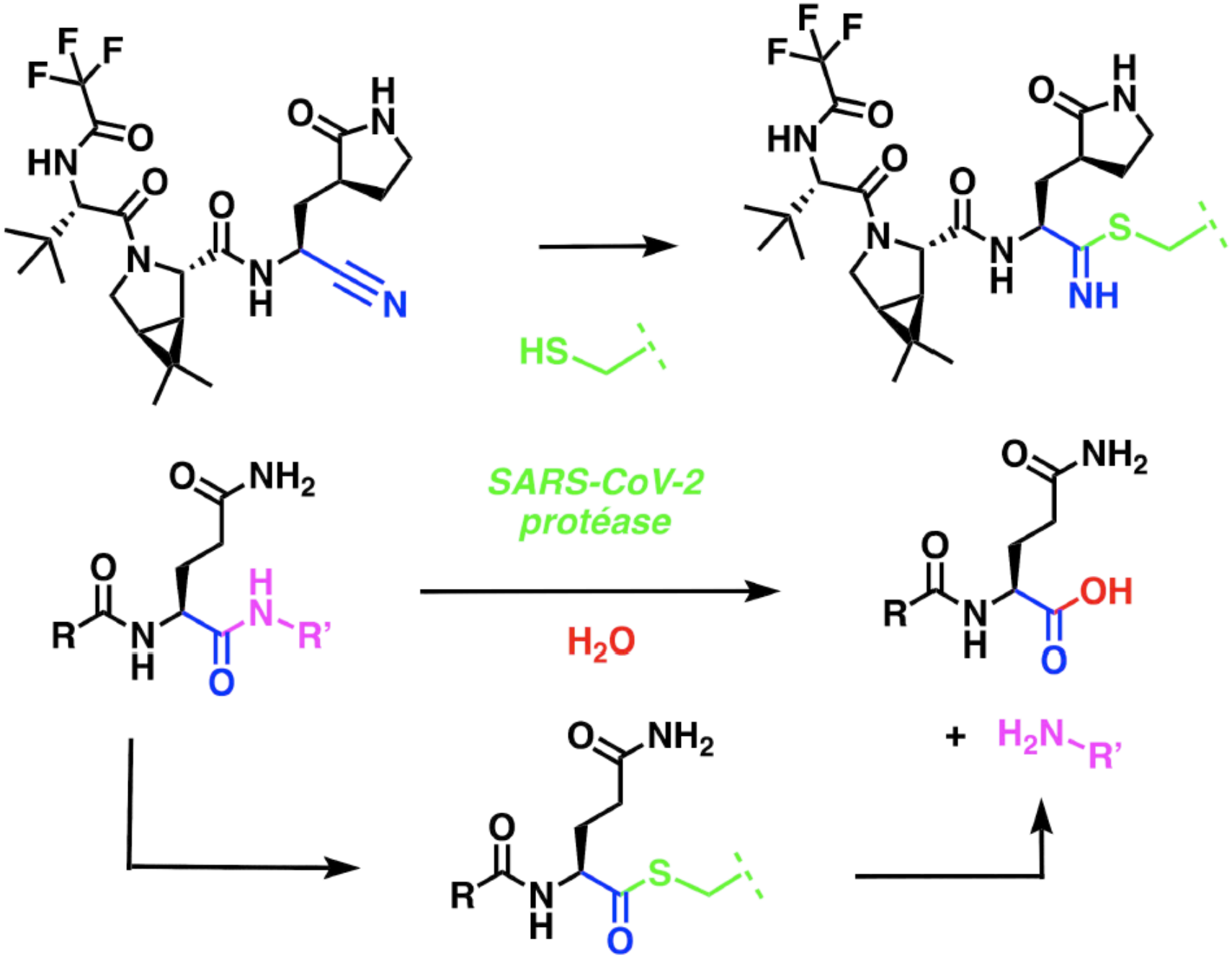
Acide



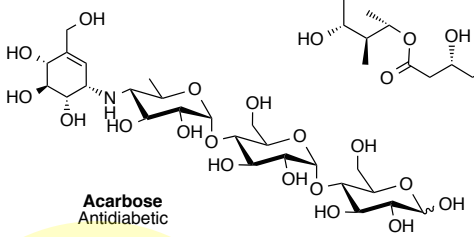
Polypeptide (plusieurs liaisons amide)

Plusieurs

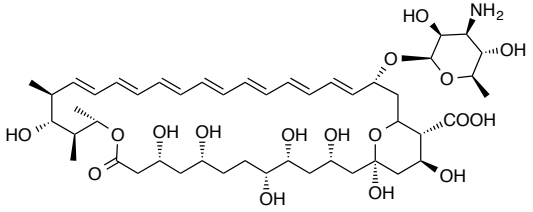
Paxlovid



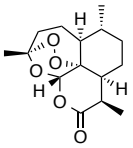
Molécules qui ont changé notre monde...



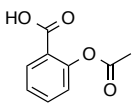
Acarbose
Antidiabetic



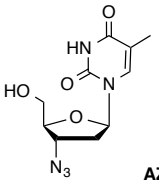
Amphotericin B
Antifungal



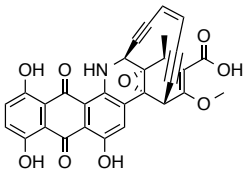
Artemisinin
Antimalarial



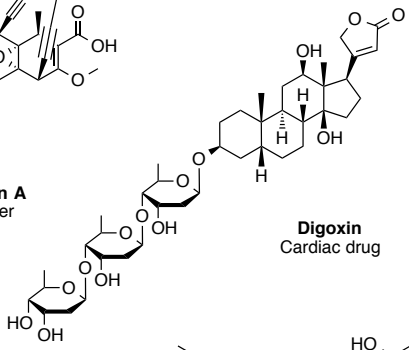
Aspirin
Analgesic



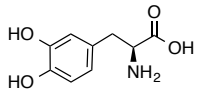
AZT
Antiviral (AIDS)



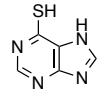
Dynemicin A
Anticancer



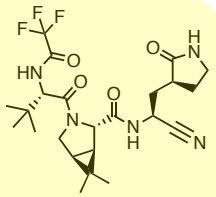
Digoxin
Cardiac drug



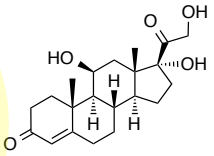
L-Dopa
Antiparkinson



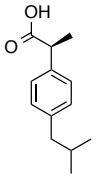
6-Mercaptopurine
Anticancer



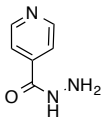
Paxlovid
Antiviral
(SARS-CoV-2)



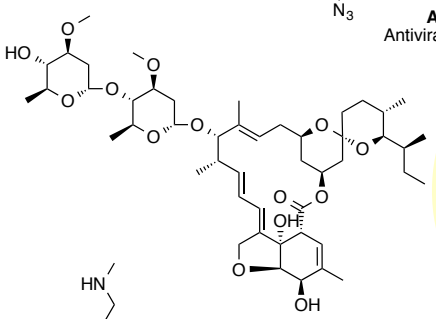
Hydrocortisone
Hormone



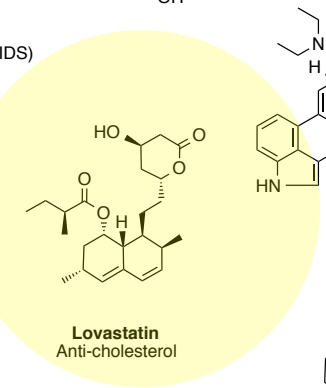
Ibuprofen
Analgesic



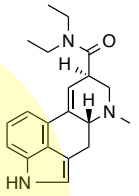
Isoniacid
Antibacterial
(Tuberculosis)



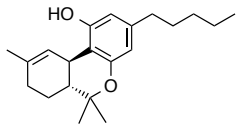
Ivermectin
Antiparasitic
(Onchocerciasis)



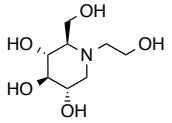
Lovastatin
Anti-cholesterol



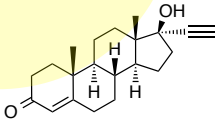
LSD
Psychedelic



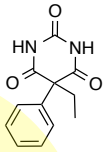
Marijuana
Antiemetic



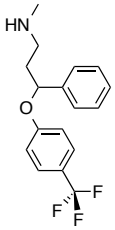
Miglitol
Antidiabetic



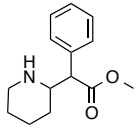
Norethindrone
Hormone
(oral contraceptive)



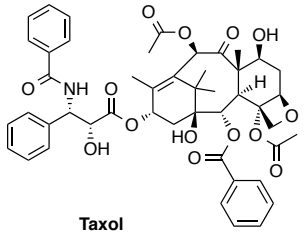
Phenobarbital
Anticonvulsant



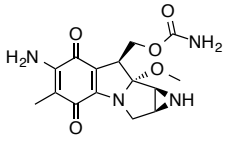
Prozac
Antidepressant



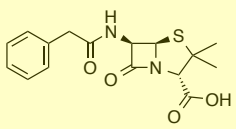
Ritalin
Stimulant



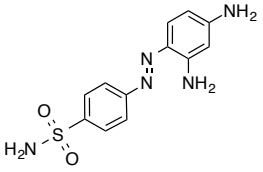
Taxol
Anticancer



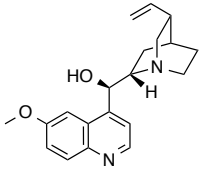
Mitomycin C
Anticancer



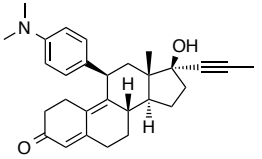
Penicillin
Antibacterial



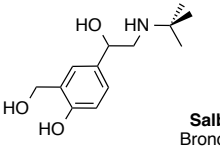
Prontosil
Antibacterial



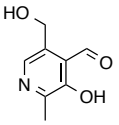
Quinine
Antimalarial



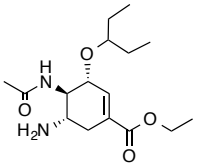
RU-486
Hormone
("abortion pill")



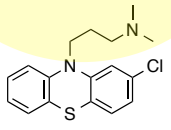
Salbutamol
Bronchodilator
(Asthma)



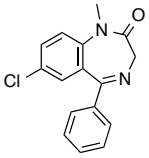
Vitamin B_6
Nutrient



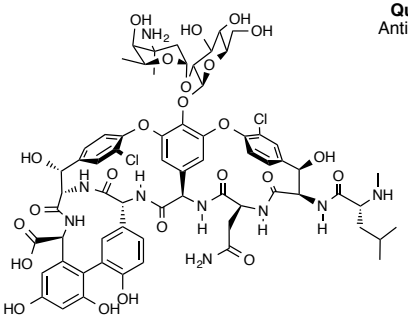
Tamiflu
Antiviral



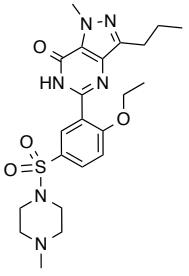
Thorazine
Antipsychotic
(Schizophrenia)



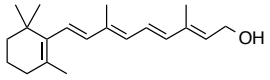
Valium
Tranquilizer



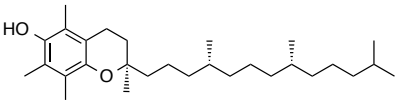
Vancomycin
Antibacterial



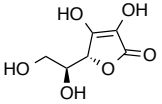
Viagra
Vasodilator



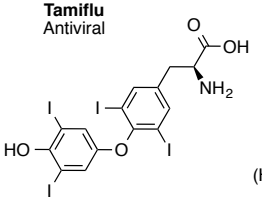
Vitamin A
Nutrient



Vitamin E
Nutrient

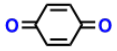
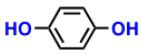
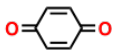


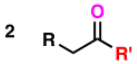
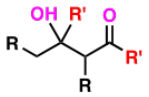
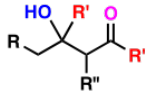
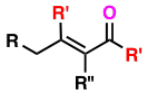
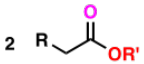
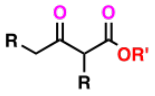
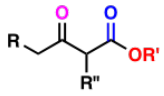
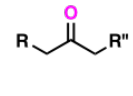
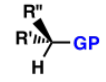
Vitamin C
Nutrient



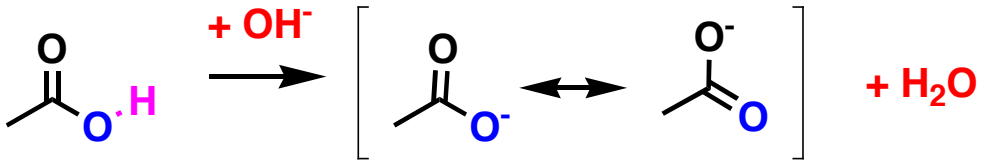
Thyroxine
Hormone
(Hypothyroidism)

Résumé des réactions

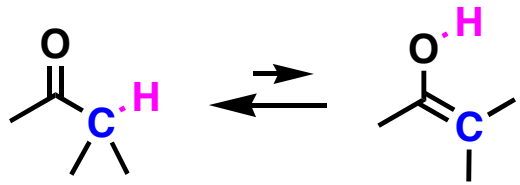
			2007	2003
 Alcène	H_2, catalyseur	 Alcane	4.6	4.6
 Alcool primaire	CrO_3, H_3O^+ ⇌ $LiAlH_4$, puis H_3O^+	 Acide carboxylique	8.5 8.4	8.7 8.5
 Alcool secondaire	$Na_2Cr_2O_7$, H_3O^+ ⇌ $NaBH_4$, puis H_3O^+	 Cétone	8.5 8.4	8.7 8.5
 Alcool primaire	PCC ⇌ $NaBH_4$, puis H_3O^+	 Aldéhyde	8.5 8.4	8.7 8.5
 Phénol	$Na_2Cr_2O_7$, H_3O^+	 Benzoquinone	8.6	8.8
 Hydroquinone	$Na_2Cr_2O_7$, H_3O^+ ⇌ $NaBH_4$, puis H_3O^+	 Benzoquinone	8.6	8.8
 Aldéhyde / cétone + H_2O	⇌	 Hydrate	9.7	9.7
 Aldéhyde / cétone + ROH	⇌	 Hémiacétal	9.8 9.9 14.5 14.6	9.8 14.5 14.6
 Aldéhyde / cétone + 2 ROH Alcool	Catalyseur (H_3O^+) ⇌	 Acétal + H_2O	9.8 9.9 14.7	9.8 14.8
 Aldéhyde / cétone + RNH_2 Amine	⇌	 Imine + H_2O	9.10	9.9

			2007	2003
 Acide carboxylique + ROH Alcool	Catalyseur (H_3O^+) ⇌ Catalyseur (OH^- ou H_3O^+)	 Ester + H_2O	10.8 10.11	10.6 10.9
 Ester + $R'NH_2$ Amine	⇌ Chauffage, catalyseur (OH^- ou H_3O^+)	 Amide + ROH Alcool	16.13 10.10	10.9 10.10
 Ester	$LiAlH_4$, puis H_3O^+	 Alcool primaire + ROH Alcool	10.11 8.4	10.9 8.5
2  Aldéhyde / cétone	Catalyseur (OH^-) ⇌	 β-Hydroxycétone	11.9	11.8
 β-Hydroxycétone	Catalyseur (OH^- ou H_3O^+) ⇌	 Énone conjuguée + H_2O	11.10	11.9
2  Ester	Catalyseur (NaOR') ⇌	 β-Cétoester + R'OH Alcool	11.11	11.10
 β-Cétoester	Chauffage, catalyseur (OH^- ou H_3O^+) →	 Cétone + R'OH + CO_2	17.4	17.4
RNH_2 +  Amine GP = groupe partant	→	 Alkylamine + HGP^+	12.4 7.5	12.4 7.7 8.11
 Imine	$NaCNBH_3$, puis H_3O^+ →	 Amine	9.10	9.11

Tautomérie céto-énolique

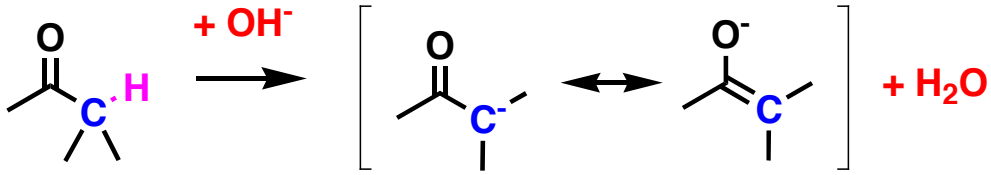


Mésomères

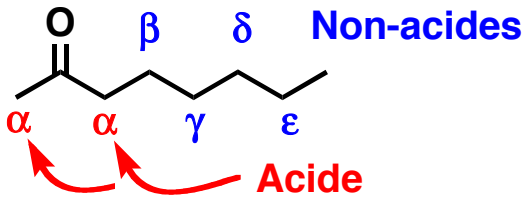


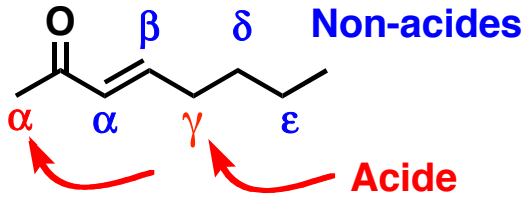
Cétone Énol

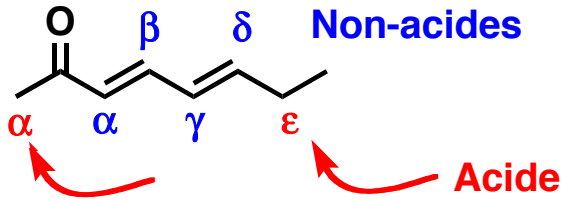
Tautomères

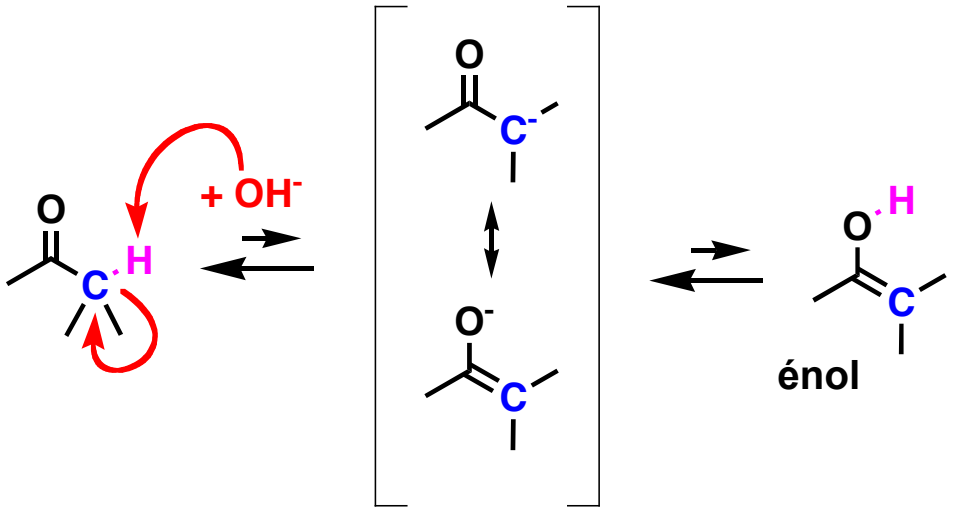


Ion énolate









énol

conjugaison

(576)

Tautomères

A

Alternance de liaisons simples et multiples avec recouvrement des orbitales *p*

B

Anion d'un enol ; carbanion alpha-cétonique stabilisé par résonance

C

Représentations d'une molécule ne différant que par la position des électrons de liaison

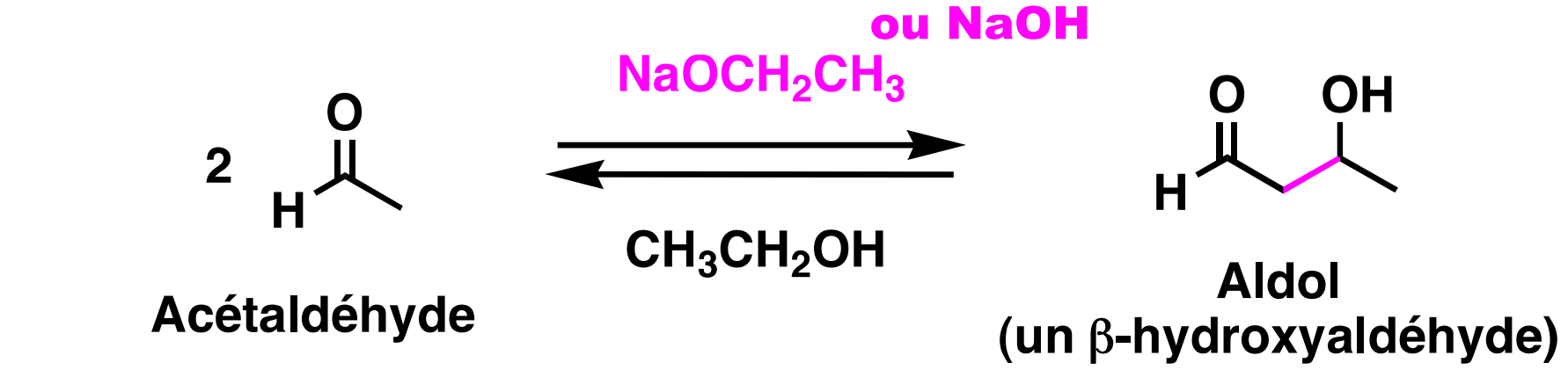
D

molécules avec même formule moléculaire, mais d'arrangements des atomes différents

E

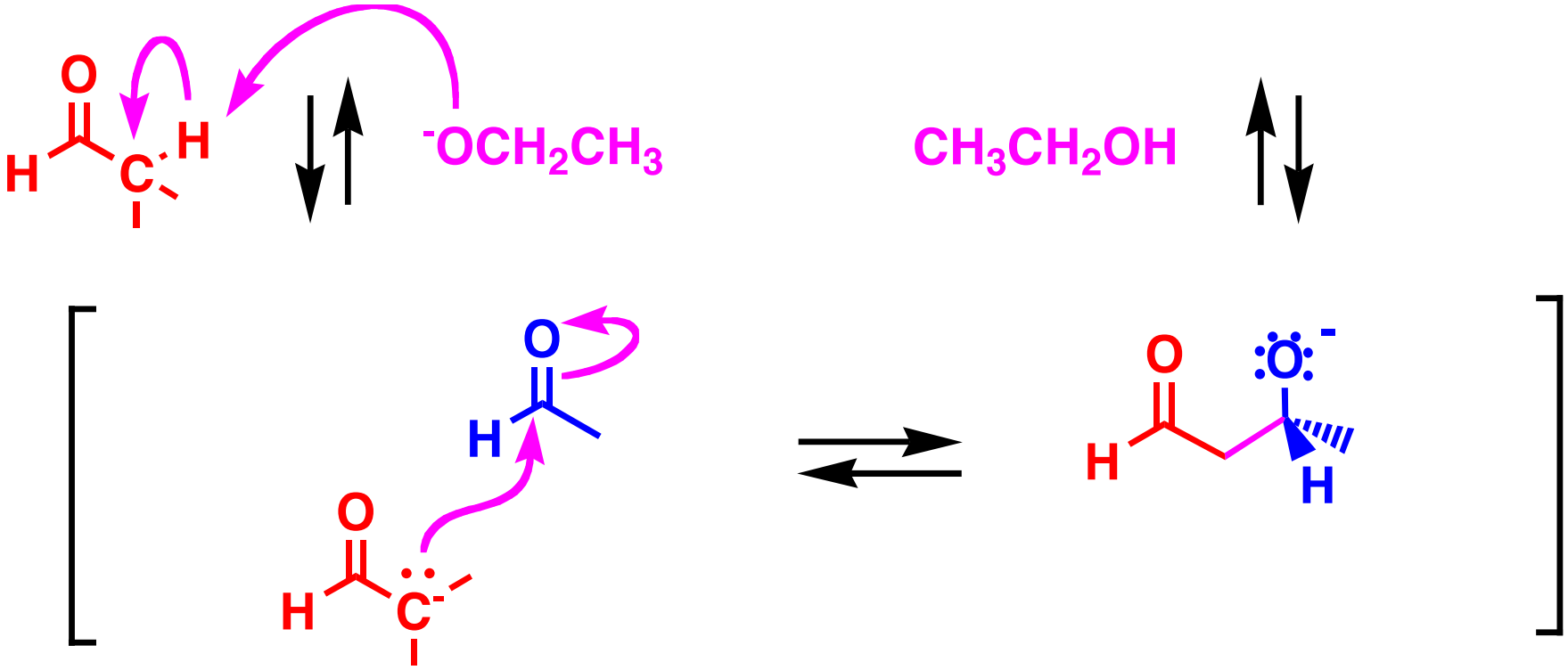
Isomères qui s'interconvertissent rapidement

L'aldolisation



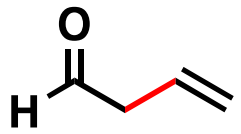
Acétaldéhyde

Aldol
(un β-hydroxyaldéhyde)

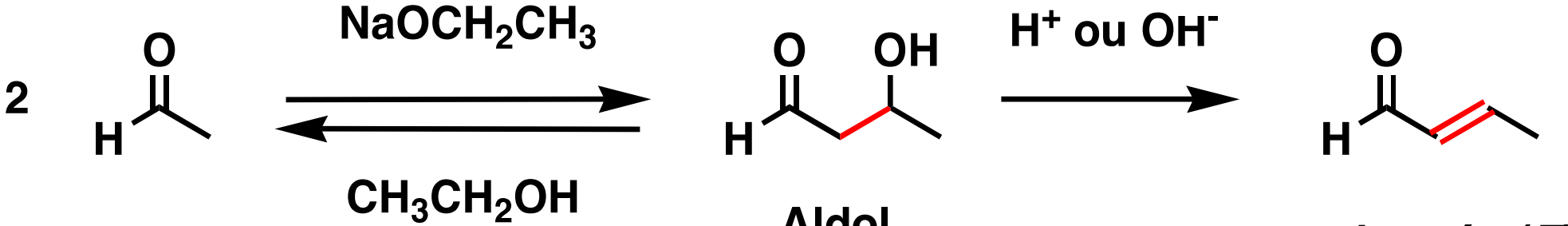


addition nucléophile

Déshydratation



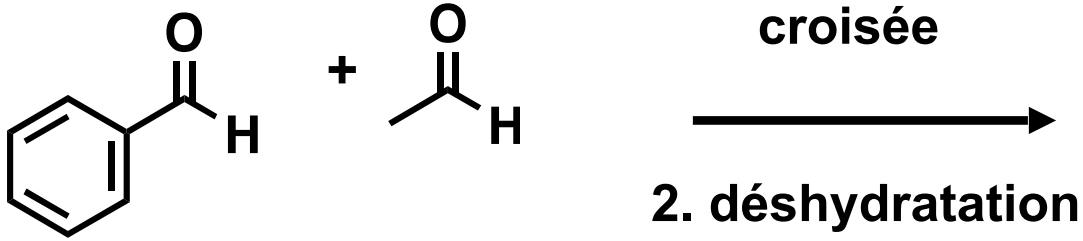
non-conjuguée
(moins stable)



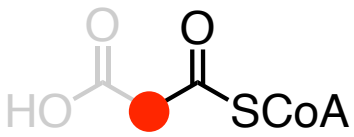
Aldéhyde

Aldol
(un β-hydroxyaldéhyde)

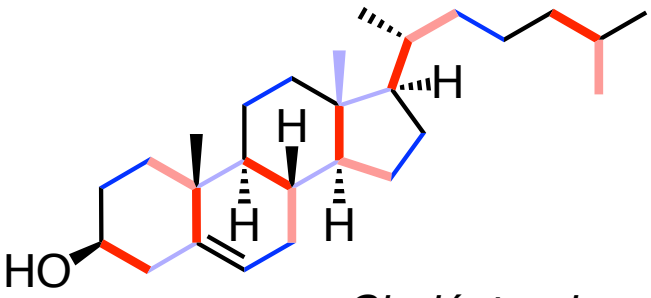
conjuguée (*E*)



Condensation de Claisen

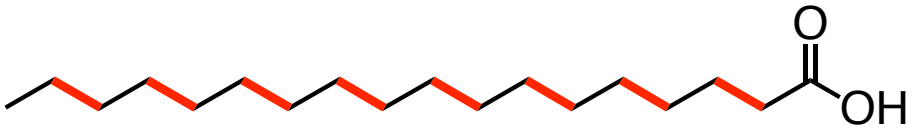


Aldolisation *Condensation de Claisen*



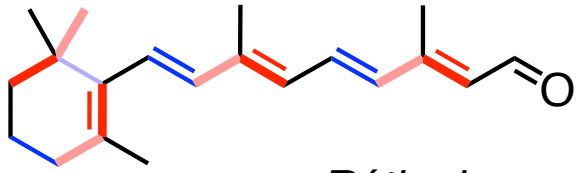
Cholésterol

52%



Acide stéarique

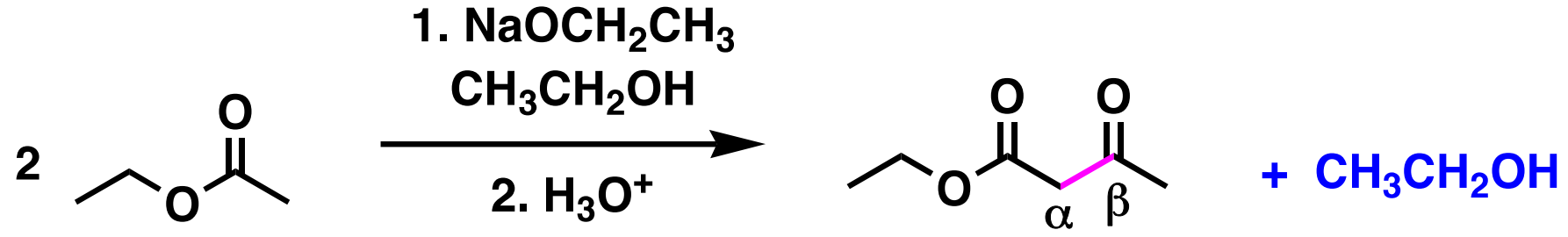
100%



Rétinal

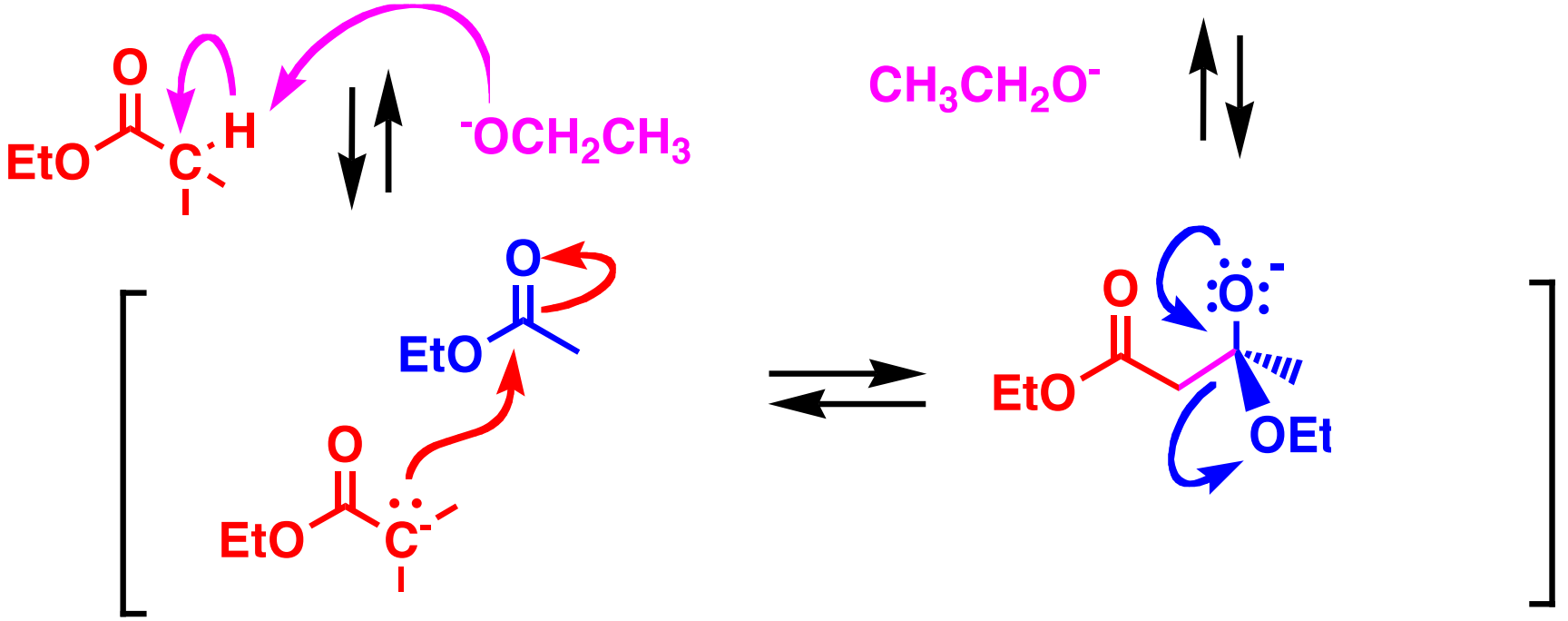
67%

Condensation de Claisen



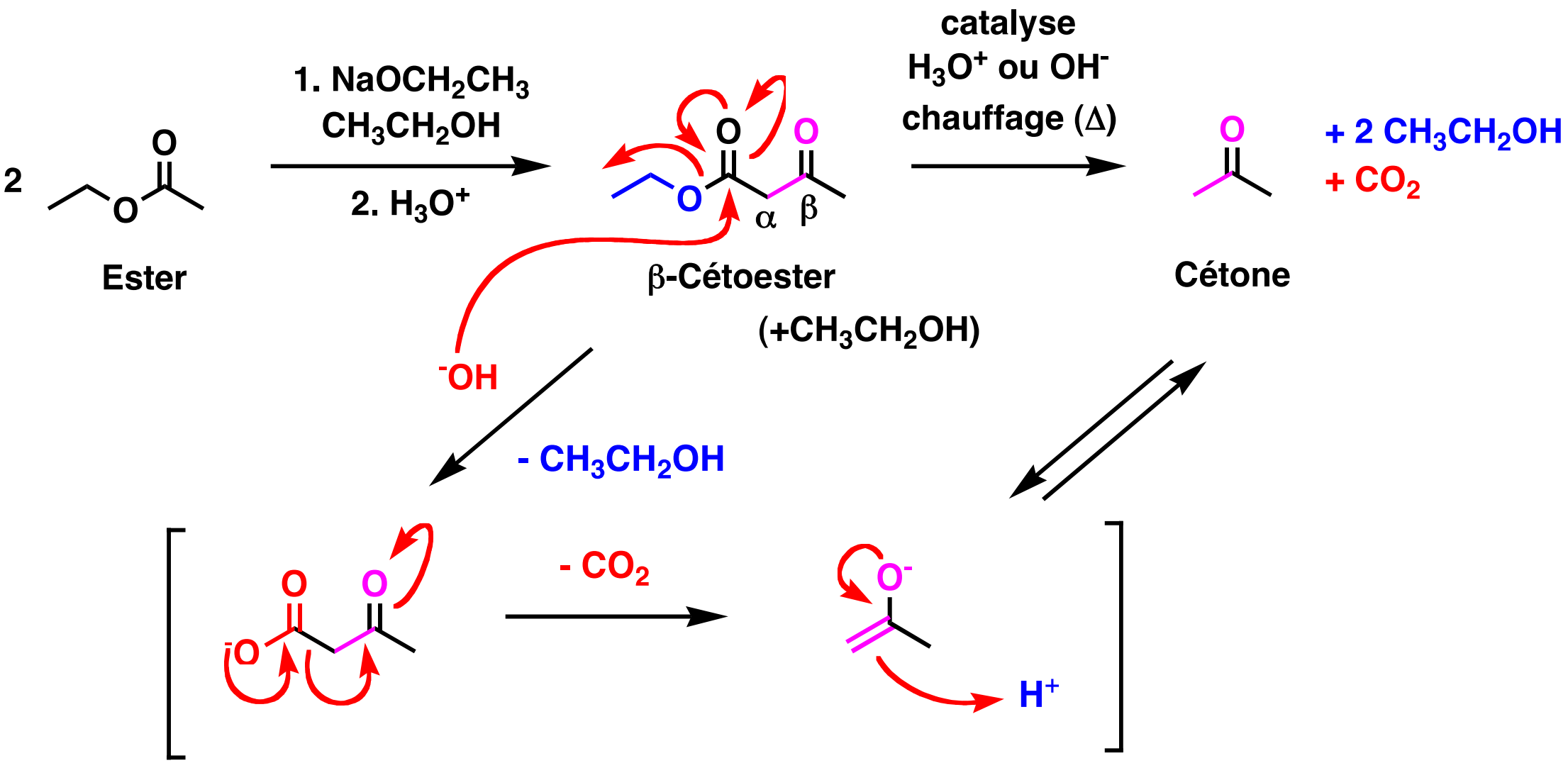
Ester

Un β-cétoester



substitution nucléophile

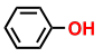
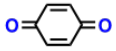
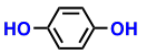
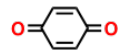
Décarboxylation

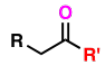
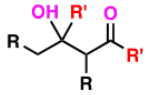
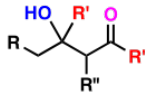
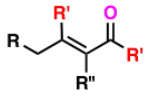
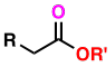
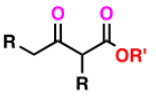
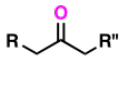
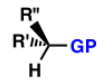


Résumé 6 (Acides - Esters - Amides - Protéines -)

- synthèse et dégradation des protéines, liaisons C-C, médicaments
- acides et bases : acidité et résonance (alcools - acides) - énolate
- tautomère (enol) / mésomère / conjugaison / chiralité
- substitution (addition) nucléophile :
  - acide + alcool : ester + H_2O (Fischer, catalyse acide)
  - ester + H_2O : acide + alcool (saponification ; thioester : thiol; lactone, médicaments)
  - ester + amine : amide + alcool (protéines ; acide + amine : x)
  - amide + H_2O : acide + amine (médicaments ; alcool : ester ; lactame, médicaments)
  - réduction ester / acide : alcool primaire (thioester : thiol, médicaments)
  - 2 x aldéhyde / cétone : aldol (aldolisation) / énone conjuguée (déshydratation)
  - 2 x ester : β-cétoester (condensation de Claisen) / cétone (décarboxylation)

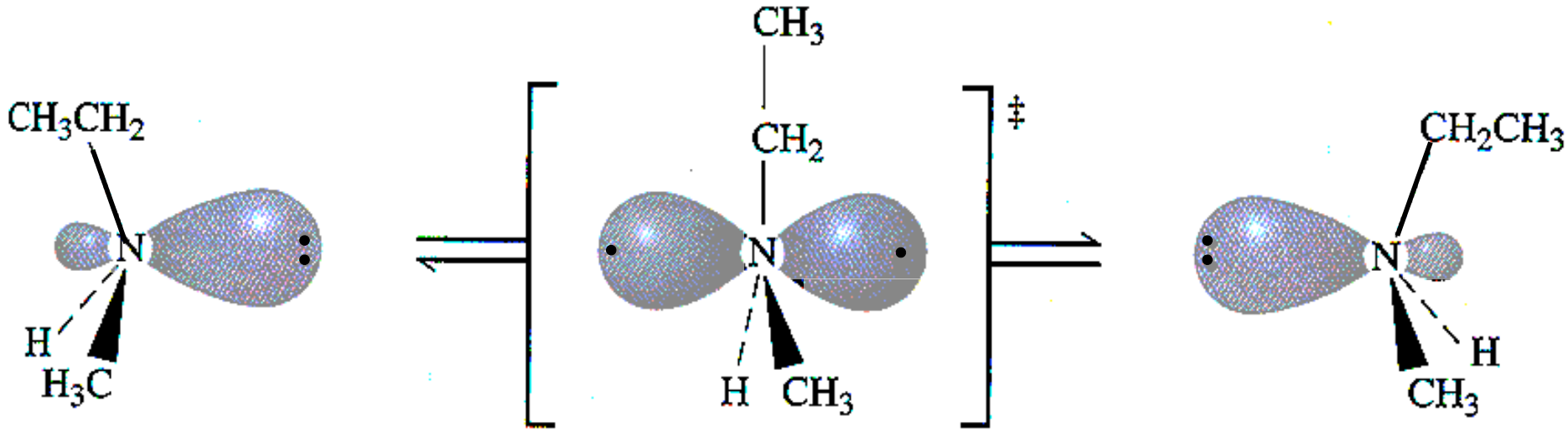
Résumé des réactions

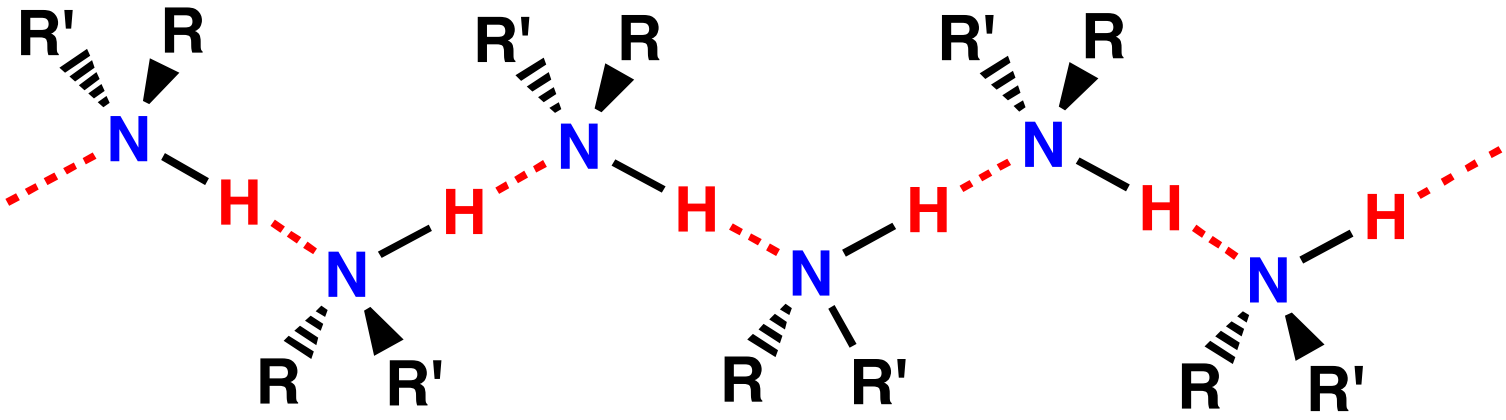
			2007	2003
 Alcène	H_2, catalyseur	 Alcane	4.6	4.6
 Alcool primaire	CrO_3, H_3O^+ ⇌ $LiAlH_4$, puis H_3O^+	 Acide carboxylique	8.5 8.4	8.7 8.5
 Alcool secondaire	$Na_2Cr_2O_7$, H_3O^+ ⇌ $NaBH_4$, puis H_3O^+	 Cétone	8.5 8.4	8.7 8.5
 Alcool primaire	PCC ⇌ $NaBH_4$, puis H_3O^+	 Aldéhyde	8.5 8.4	8.7 8.5
 Phénol	$Na_2Cr_2O_7$, H_3O^+	 Benzoquinone	8.6	8.8
 Hydroquinone	$Na_2Cr_2O_7$, H_3O^+ ⇌ $NaBH_4$, puis H_3O^+	 Benzoquinone	8.6	8.8
 Aldéhyde / cétone + H_2O	⇌	 Hydrate	9.7	9.7
 Aldéhyde / cétone + ROH Alcool	⇌	 Hémiacétal	9.8 9.9 14.5 14.6	9.8 14.5 14.6
 Aldéhyde / cétone + 2 ROH Alcool	Catalyseur (H_3O^+) ⇌ + H_2O	 Acétal	9.8 9.9 14.7	9.8 14.8
 Aldéhyde / cétone + RNH_2 Amine	⇌	 Imine + H_2O	9.10	9.9

				2007	2003
 Acide carboxylique + ROH Alcool	Catalyseur (H_3O^+) ⇌ Catalyseur (OH^- ou H_3O^+)	 Ester	+ H_2O	10.8 10.11	10.6 10.9
 Ester + $R'NH_2$ Amine	⇌ Chauffage, catalyseur (OH^- ou H_3O^+)	 Amide	+ ROH Alcool	16.13 10.10	10.9 10.10
 Ester	$LiAlH_4$, puis H_3O^+	 Alcool primaire	+ ROH Alcool	10.11 8.4	10.9 8.5
2  Aldéhyde / cétone	Catalyseur (OH^-) ⇌	 β-Hydroxycétone		11.9	11.8
 β-Hydroxycétone	Catalyseur (OH^- ou H_3O^+) ⇌	 Énone conjuguée	+ H_2O	11.10	11.9
2  Ester	Catalyseur ($NaOR'$) ⇌	 β-Cétoester	+ R'OH Alcool	11.11	11.10
 β-Cétoester	Chauffage, catalyseur (OH^- ou H_3O^+) ⇌	 Cétone	+ R'OH + CO_2	17.4	17.4
RNH_2 +  Amine GP = groupe partant	⇌	 Alkylamine	+ HGP^+	12.4 7.5	12.4 7.7 8.11
 Imine	$NaCNBH_3$, puis H_3O^+ ⇌	 Amine		9.10	9.11

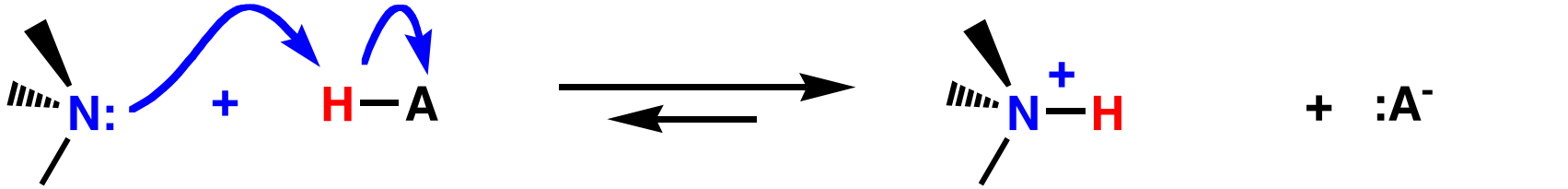
CONTENU	McMurry
1. Généralités	(1, 2, 15)
2. Lipides - stéroïdes - alcanes - alcènes - arènes -	(2 - 5, 16)
3. Glucides - stéréochimie -	(6, 14)
4. Alcools - éthers – phénols - hydroquinones - thiols - disulfures	(8, 16)
5. Glucides - aldéhydes - cétones - imines -	(9, 14)
6. Protéines - lipides - acides - esters - amides -	(10, 11, 15, 16)
7. Acides nucléiques - amines -	(12, 16)

« L'azote sp³ »



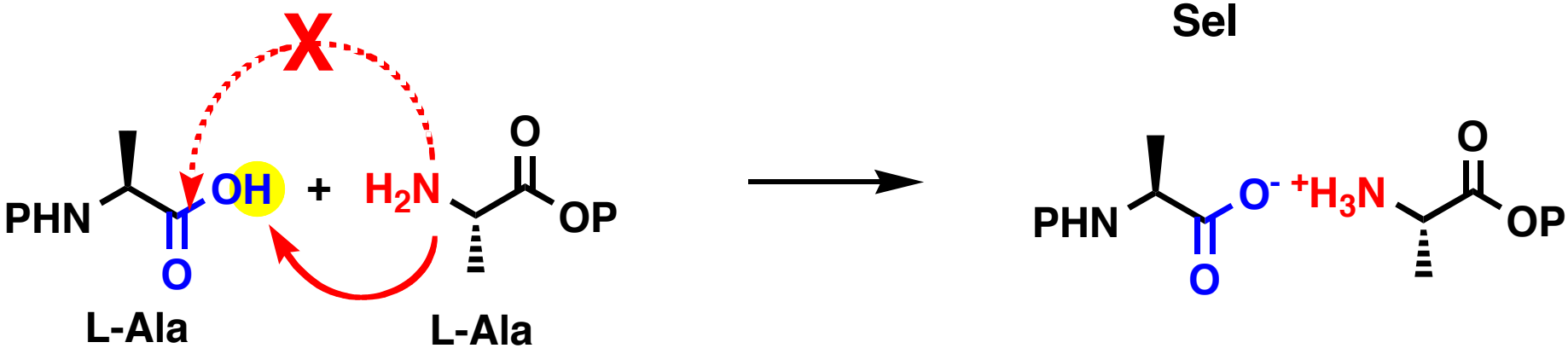


« L'azote sp³ »



Alkylamine (base forte) — **Acide** — **Ion ammonium (acide conjugué faible - pK_a ~10)** — **Base conjuguée**

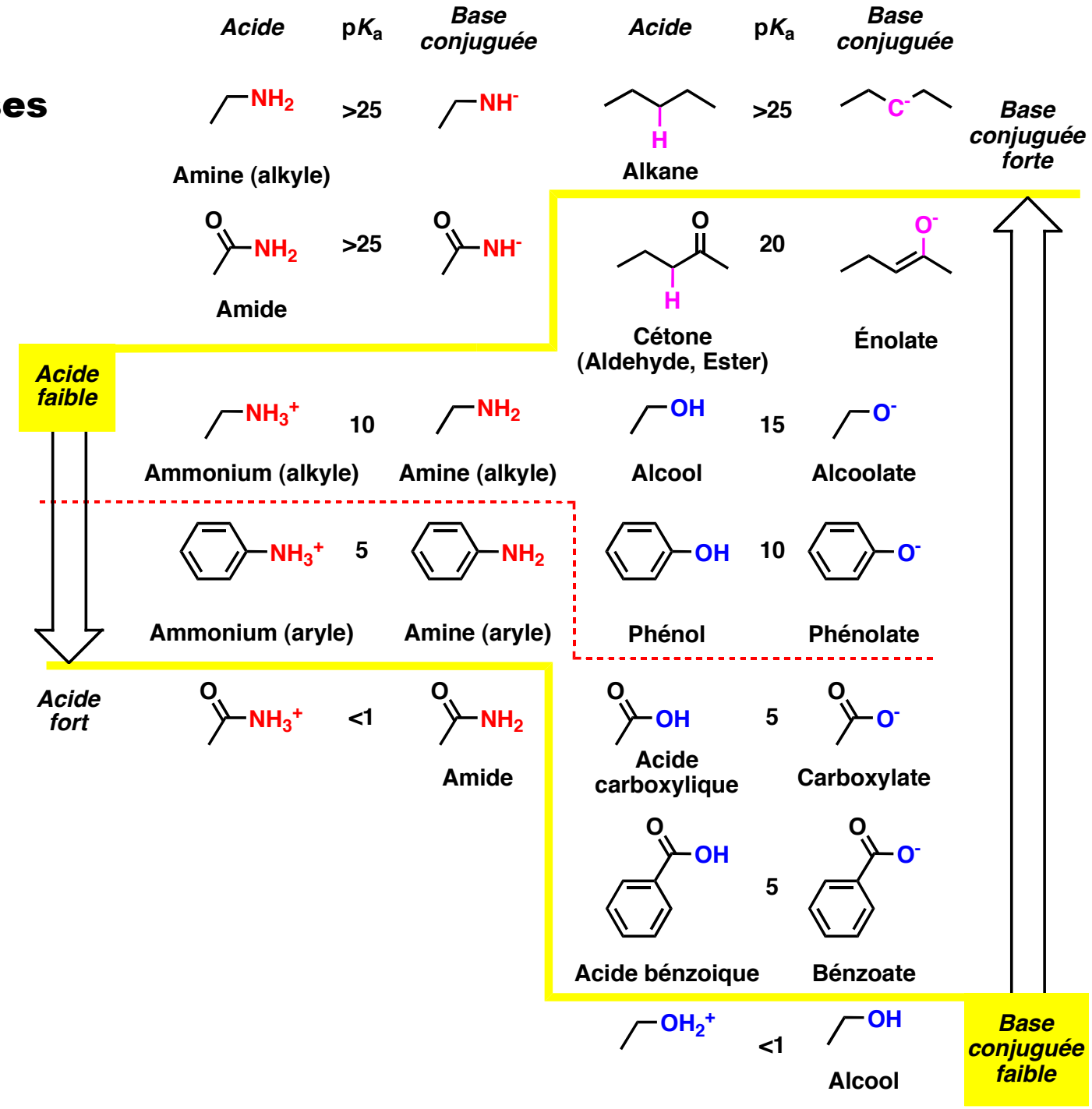
Sel



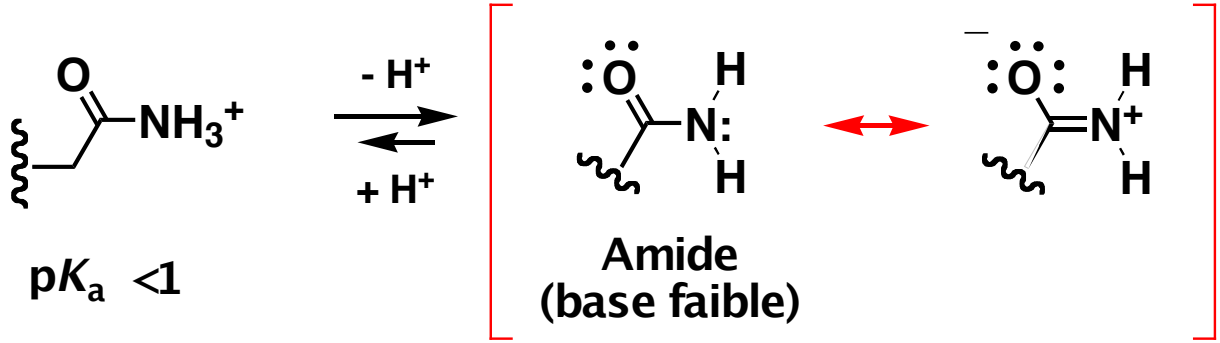
L-Ala — **L-Ala**

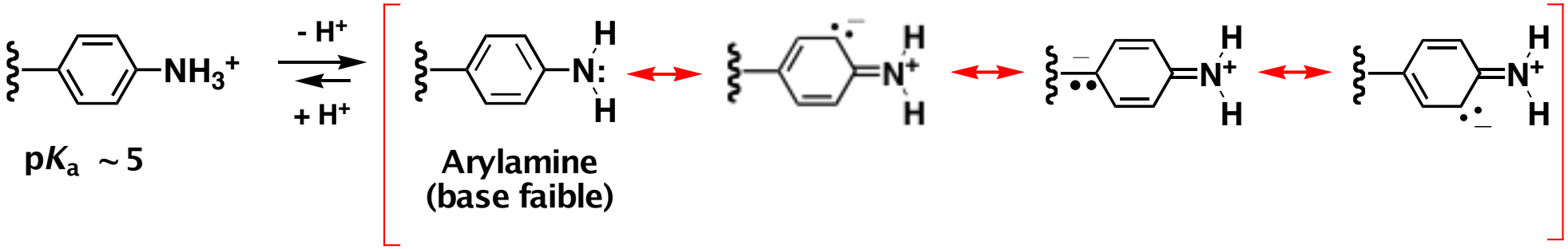
P = Groupes protecteurs

Résumé
acides et bases

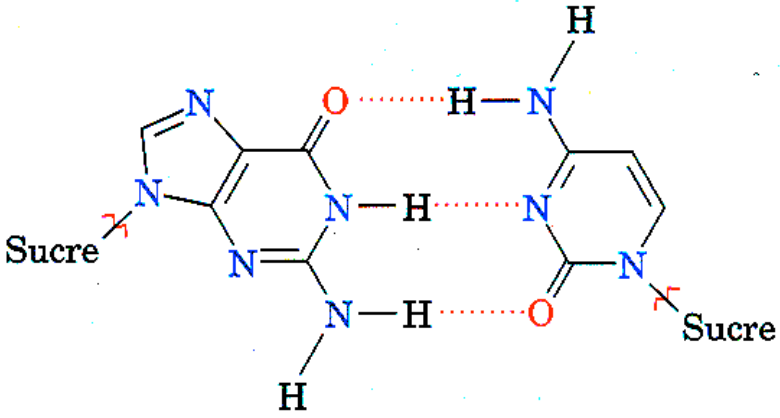


« L'azote sp² »

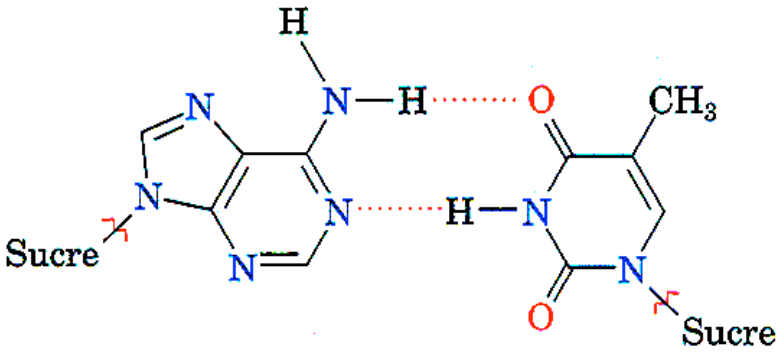

O
NH3+
- H+
+ H+
pKa <1
Amide
(base faible)


NH3+
- H+
+ H+
pKa ~5
Arylamine
(base faible)

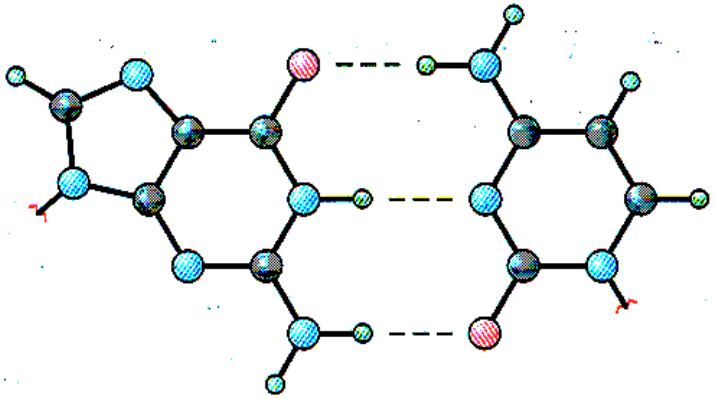
Arylamines et le code génétique

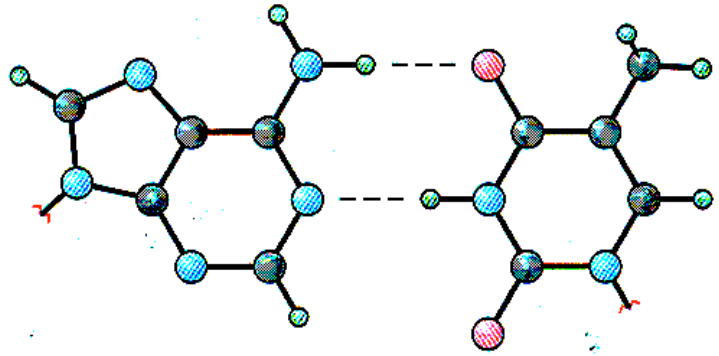


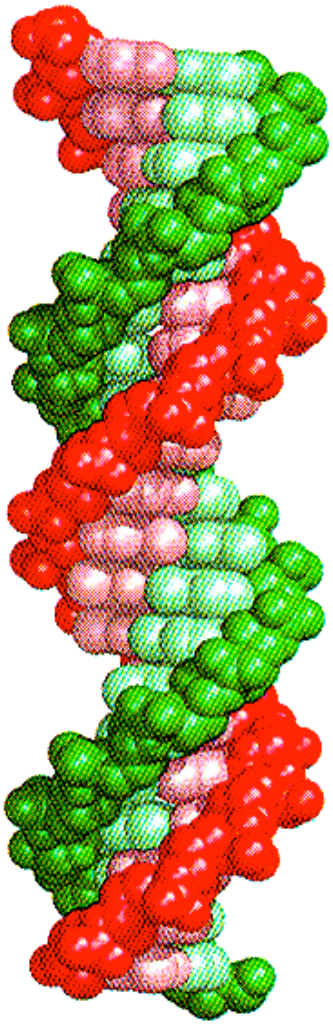
(Guanine) G ⋮⋮⋮⋮⋮⋮ C (Cytosine)



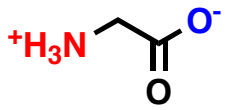
(Adénine) A ⋮⋮⋮⋮⋮⋮ T (Thymine)



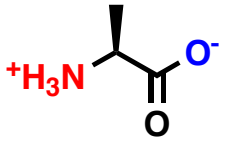




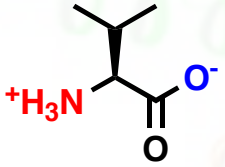
Les acides aminés (pH = 7)



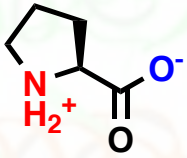
Glycine
(Gly, G)



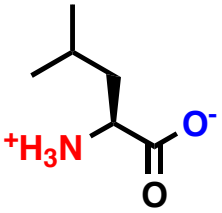
Alanine
(Ala, A)



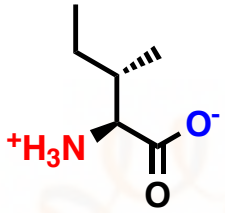
Valine
(Val, V)



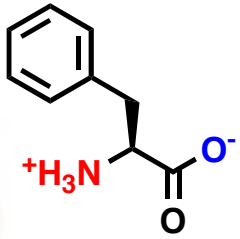
Proline
(Pro, P)



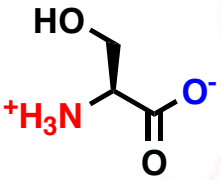
Leucine
(Leu, L)



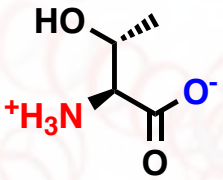
Isoleucine
(Ile, I)



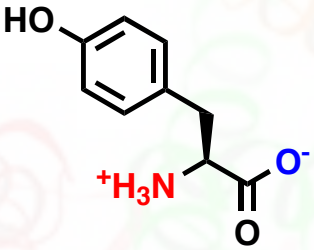
Phénylalanine
(Phe, F)



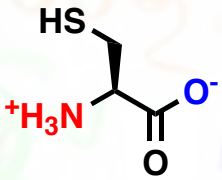
Sérine
(Ser, S)



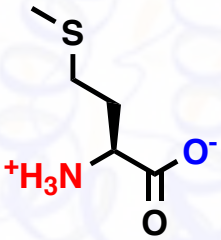
Thréonine
(Thr, T)



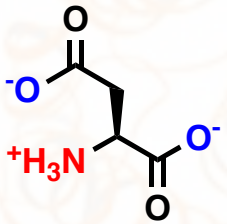
Tyrosine
(Tyr, Y)



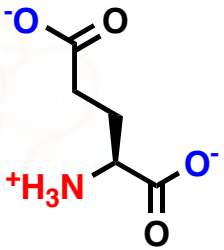
Cystéine
(Cys, C)



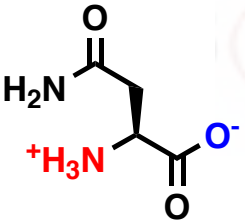
Méthionine
(Met, M)



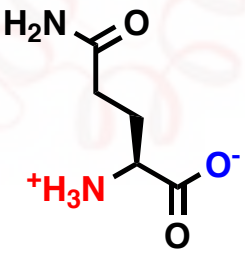
Acide aspartique
(Asp, D)



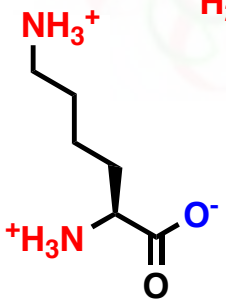
Acide glutamique
(Glu, E)



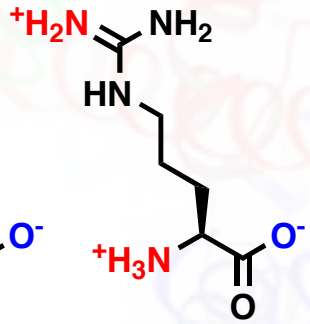
Asparagine
(Asn, N)



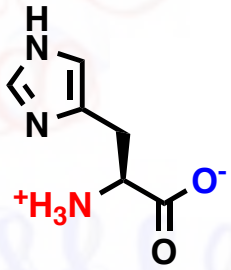
Glutamine
(Gln, Q)



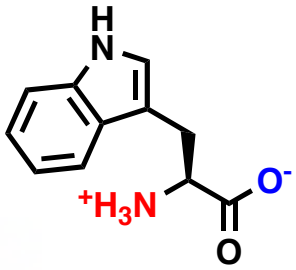
Lysine
(Lys, K)



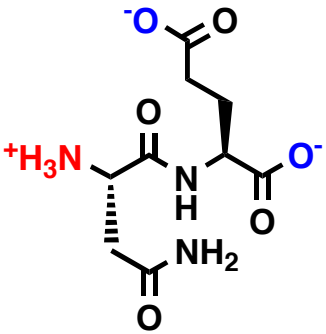
Arginine
(Arg, R)



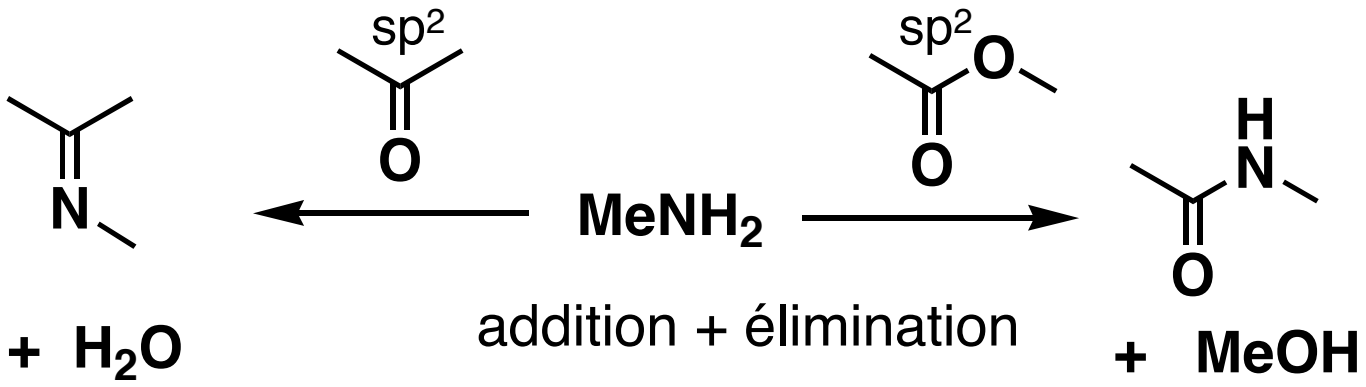
Histidine
(His, H)



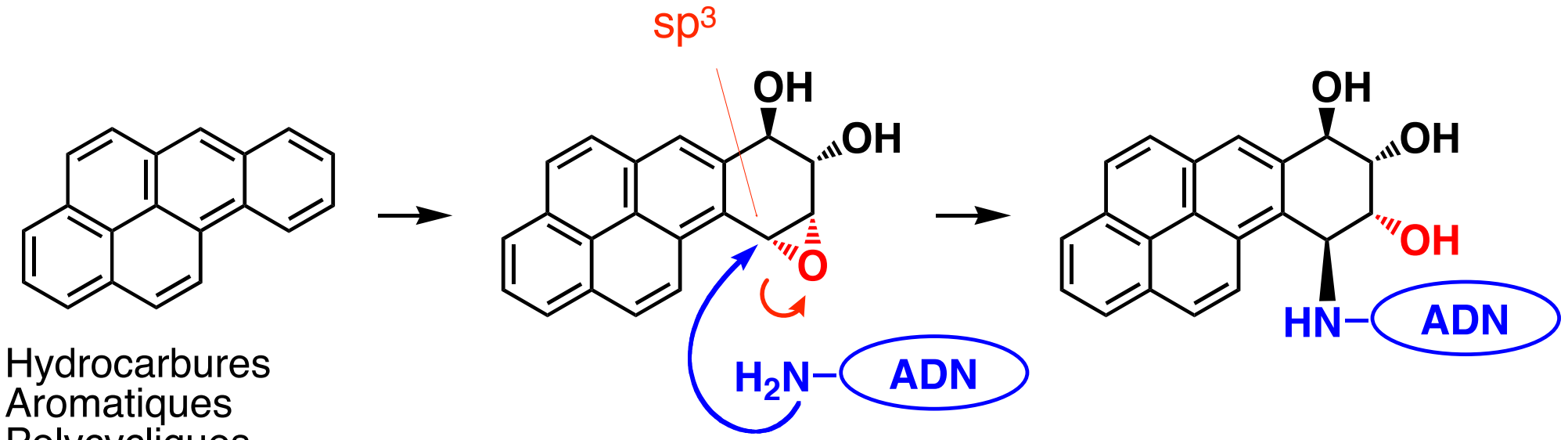
Tryptophane
(Trp, W)



Nucléophile



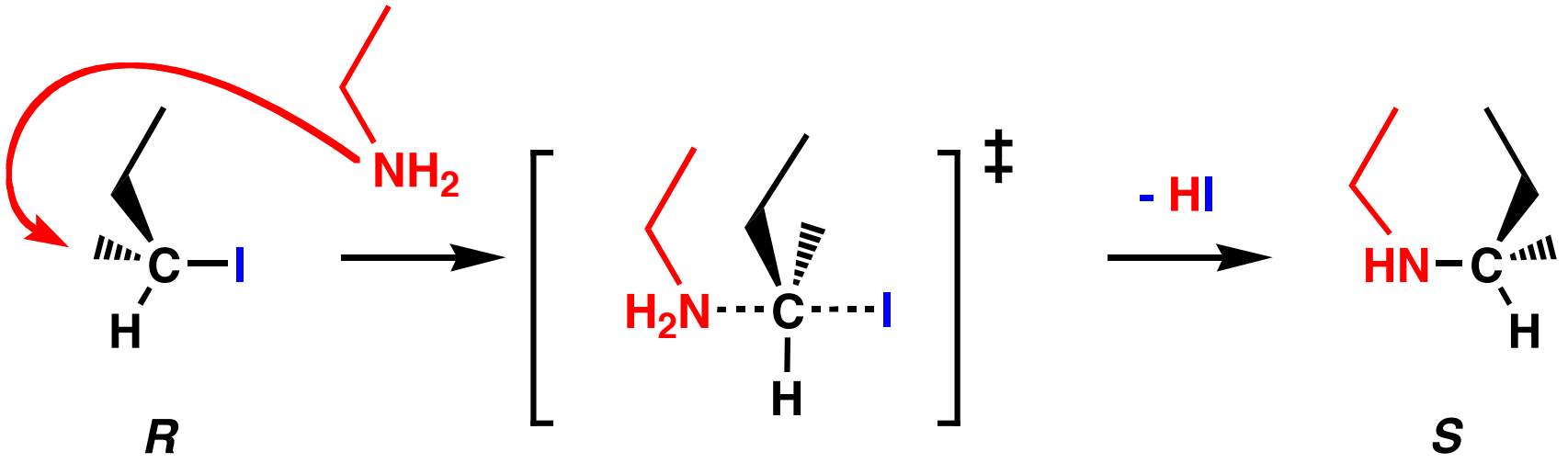
S_N2

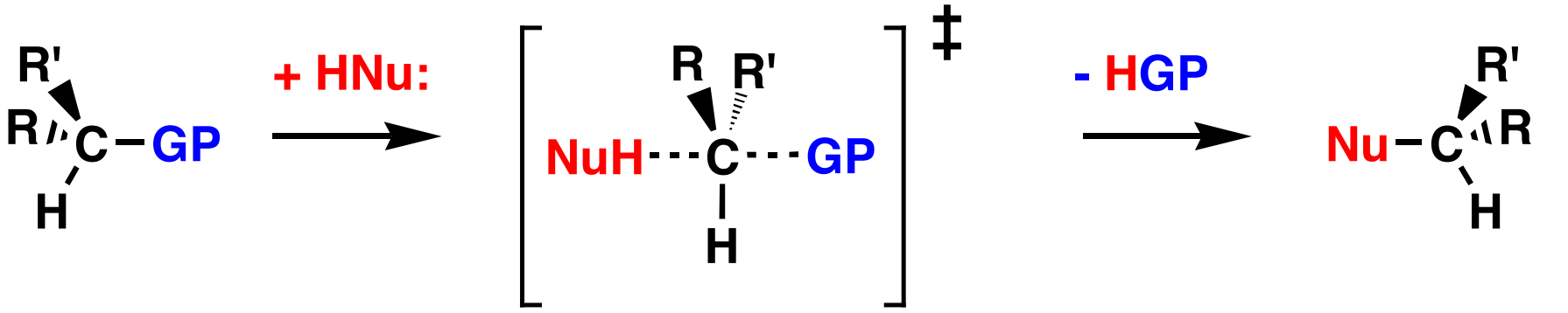


Hydrocarbures
Aromatiques
Polycycliques

substitution nucléophile bimoléculaire - S_N2

S_N2



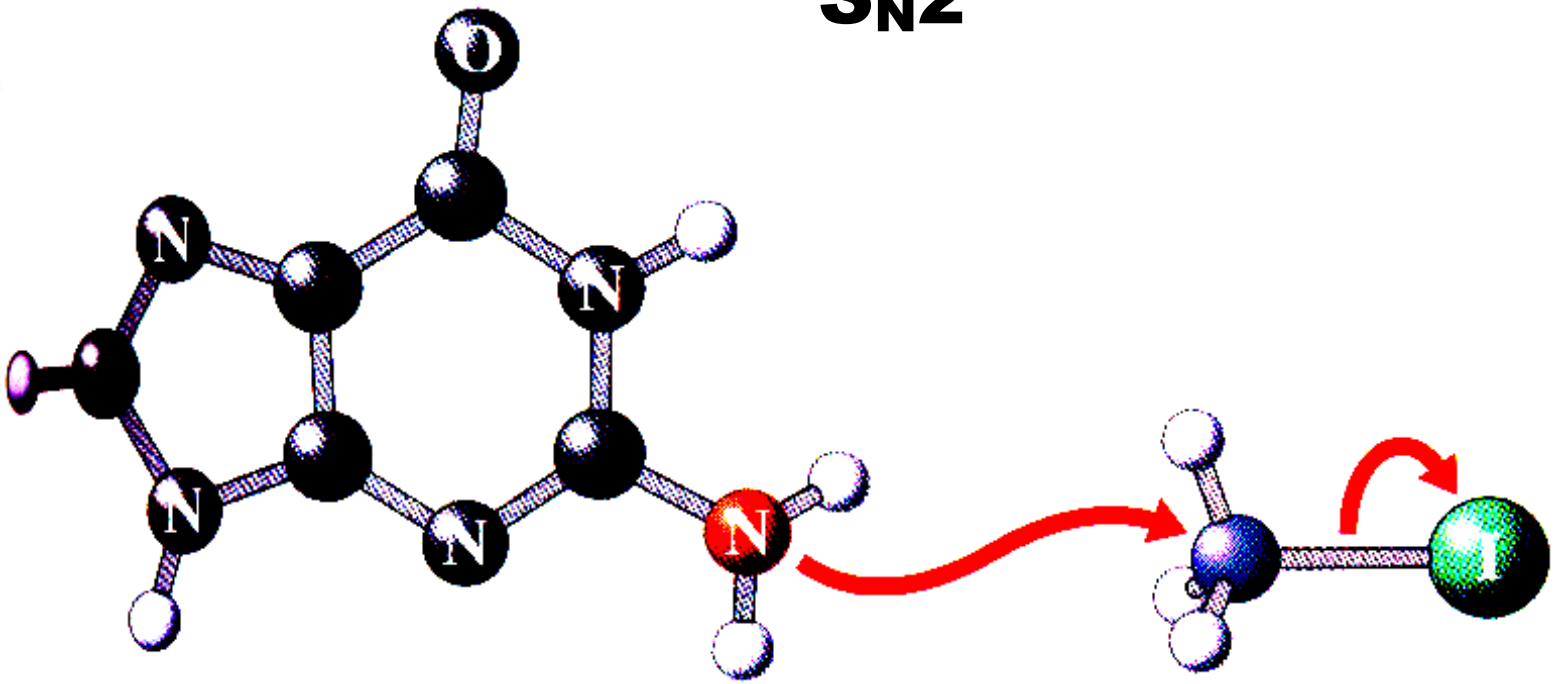


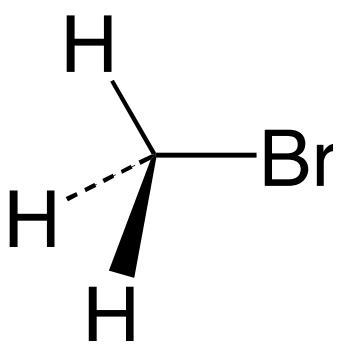
groupe partant

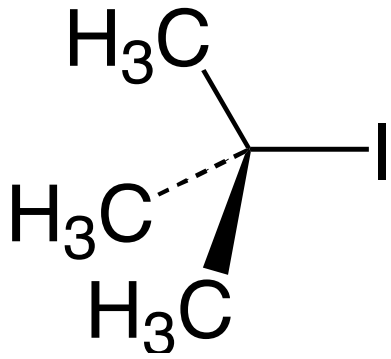
inversion de configuration

(226-32)

S_N2







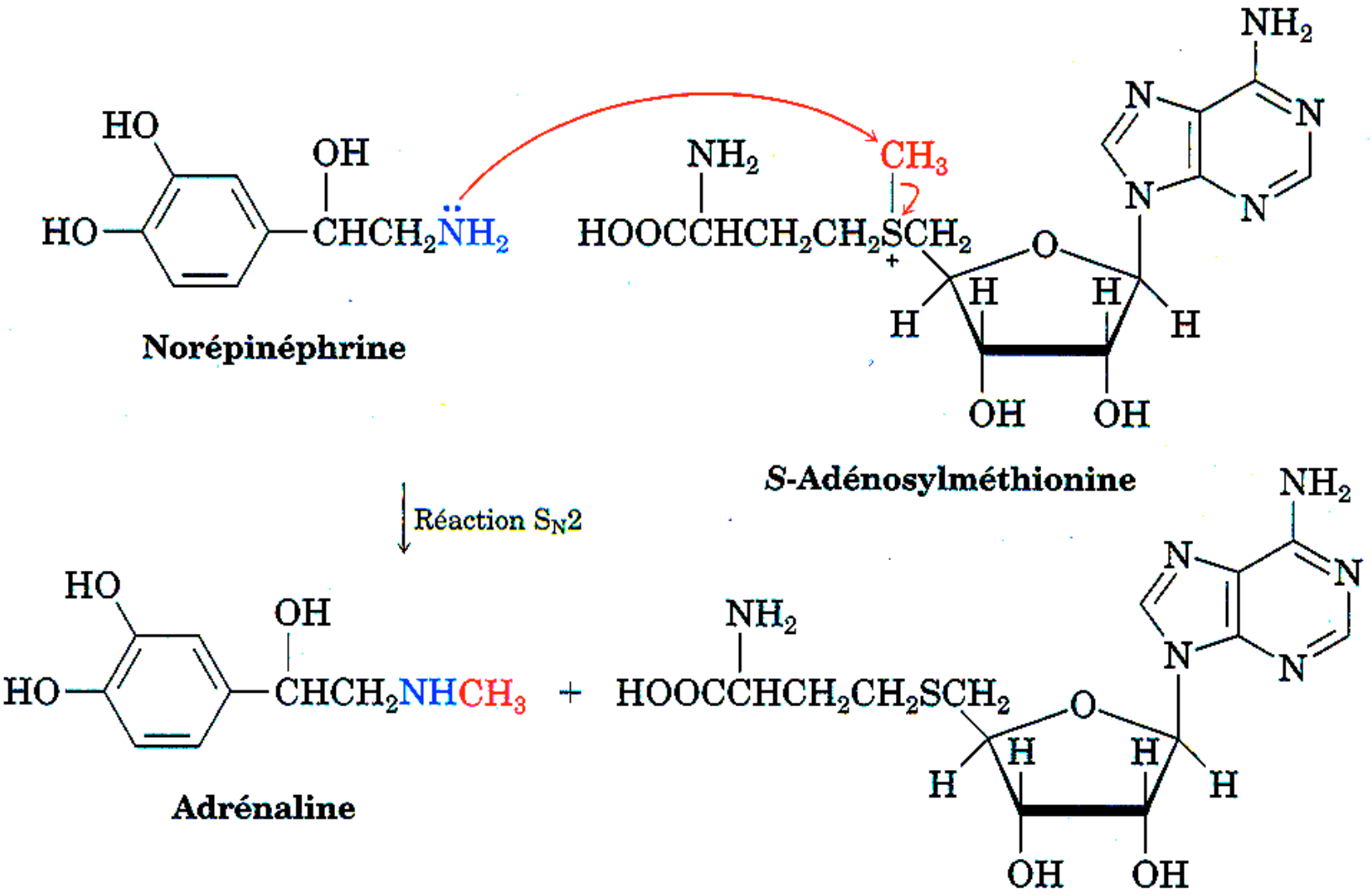
(groupes partants)

(232)

(effet stérique)

(230)

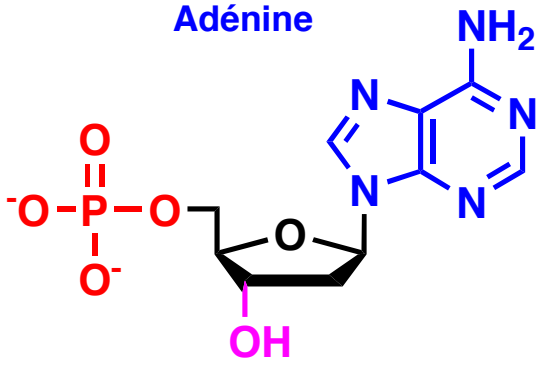
S_N2


HO
HO
OH
CHCH2NH2
Norépinéphrine
NH2
HOOCCHCH2CH2SCH2
CH3
S-Adénosylméthionine
Réaction SN2
HO
HO
OH
CHCH2NHCH3
Adrénaline
+
NH2
HOOCCHCH2CH2SCH2

Hétérocycles aromatiques, nucléotides et le code génétique

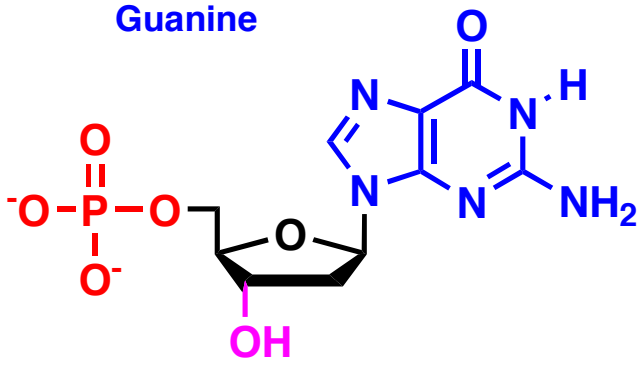
Désoxyribonucléotides

Adénine



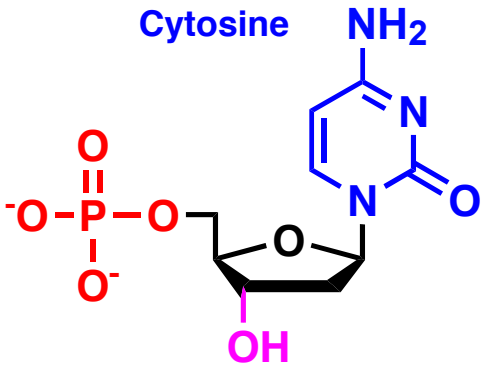
2'-Désoxyadénosine 5'-phosphate

Guanine



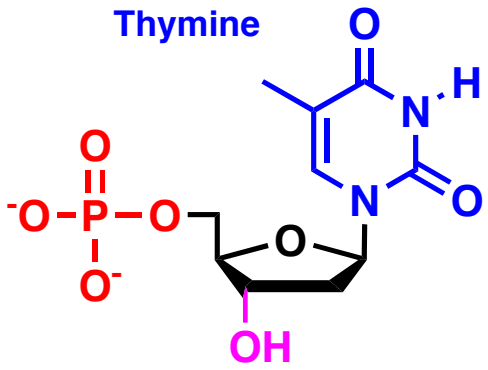
2'-Désoxyguanosine 5'-phosphate

Cytosine

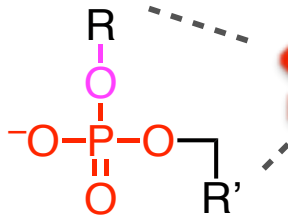


2'-Désoxycytidine 5'-phosphate

Thymine



2'-Désoxythymidine 5'-phosphate



Aromaticité

A
Alternance de liaisons simples et multiples avec recouvrement des orbitales *p*

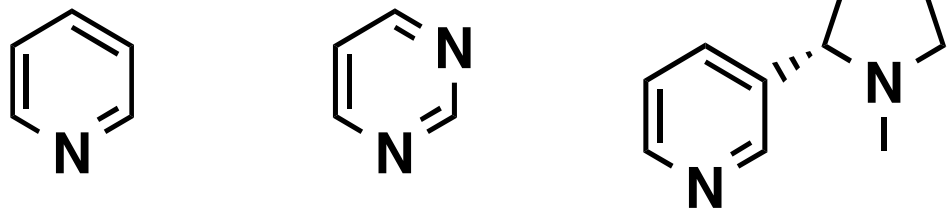
B
Délocalisation d'électrons dans des molécules représenté par une combinaison virtuelle de structures aux électrons localisées différemment

C
Un cycle d'atomes avec une orbitale *p* et 4*n* + 2 électrons délocalisés
(= système *π* conjugué formé de liaisons doubles et de doublets non-liants)

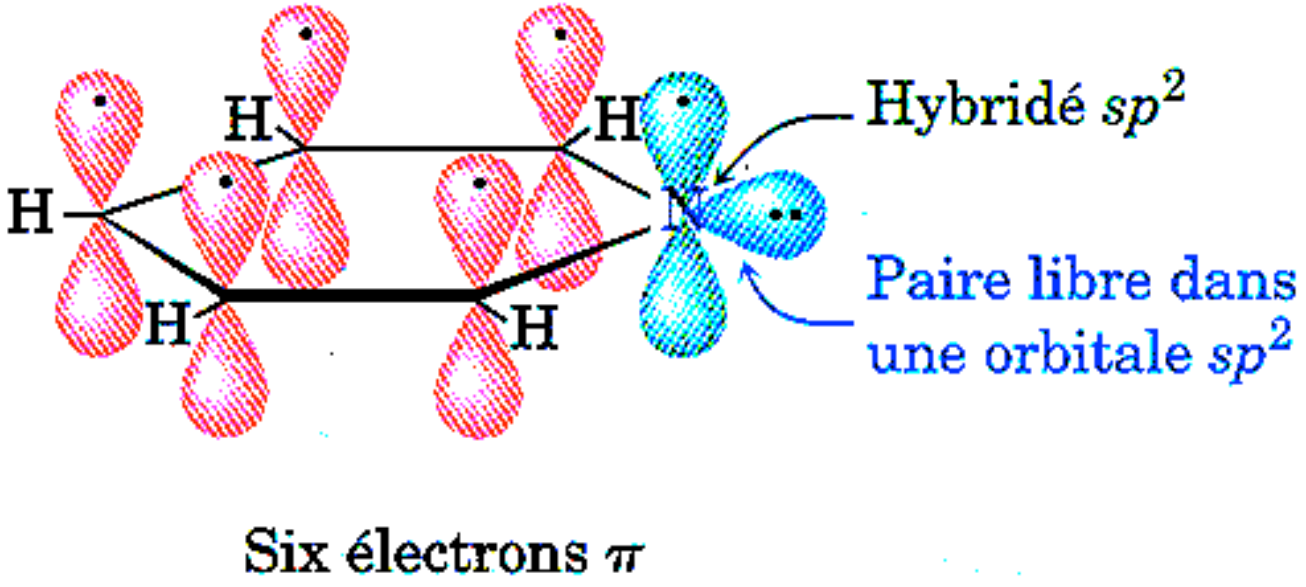
D
Représentations d'une molécule ne différant que par la position des électrons de liaison

E
Stéréoisomères qui diffèrent par leur stéréochimie au niveau d'une double liaison ou d'un cycle

« L'azote sp² » hétérocyclique

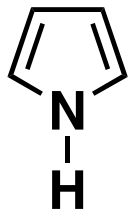


Pyridine Pyrimidine

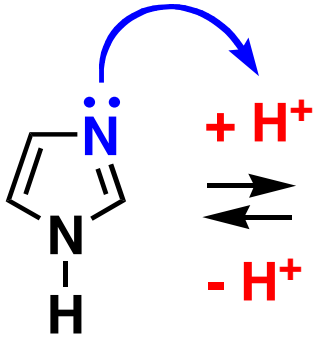


Six électrons π

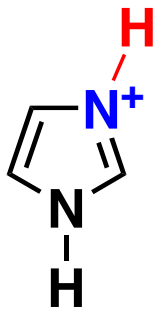
« L'azote sp² » hétérocyclique



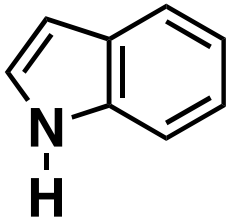
Pyrrole



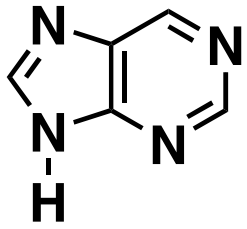
Imidazole



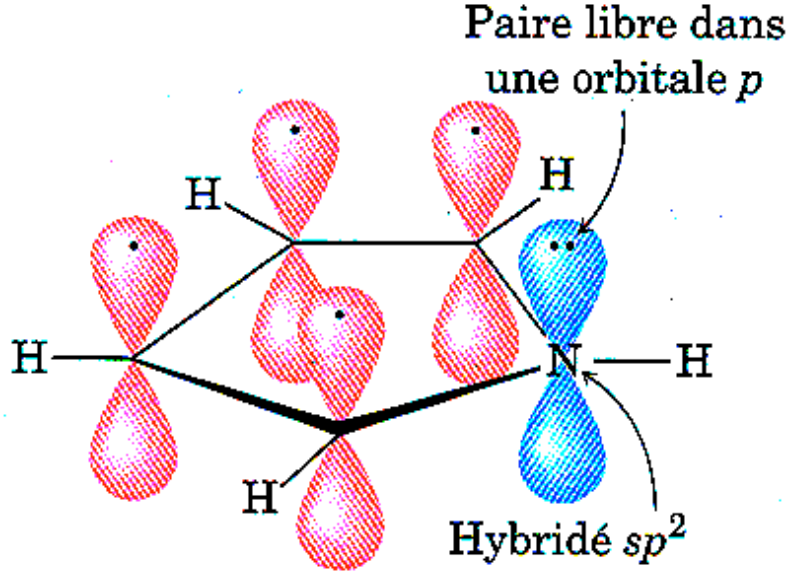
pK_a ~6



Indole

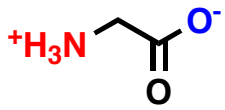


Purine

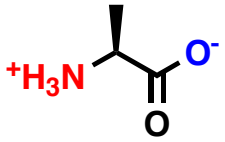


Six électrons π

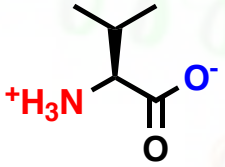
Les acides aminés (pH = 7)



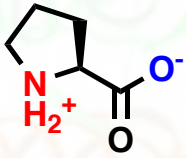
Glycine
(Gly, G)



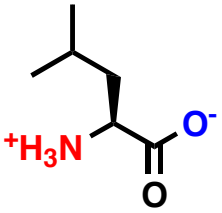
Alanine
(Ala, A)



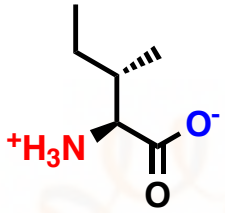
Valine
(Val, V)



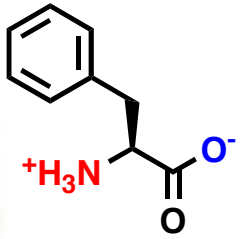
Proline
(Pro, P)



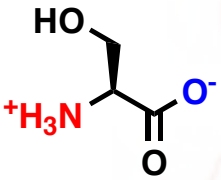
Leucine
(Leu, L)



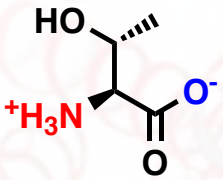
Isoleucine
(Ile, I)



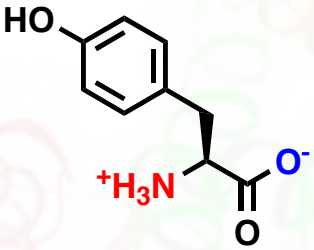
Phénylalanine
(Phe, F)



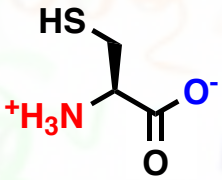
Sérine
(Ser, S)



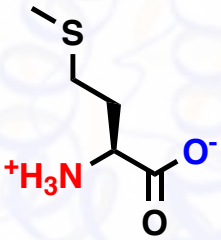
Thréonine
(Thr, T)



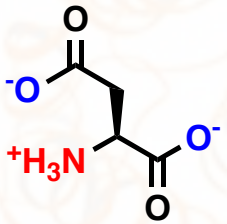
Tyrosine
(Tyr, Y)



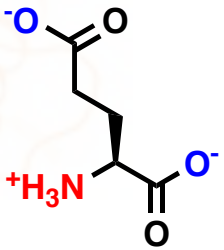
Cystéine
(Cys, C)



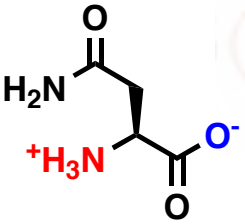
Méthionine
(Met, M)



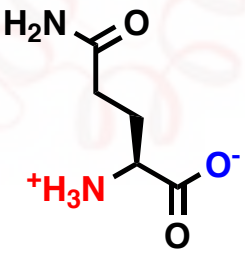
Acide aspartique
(Asp, D)



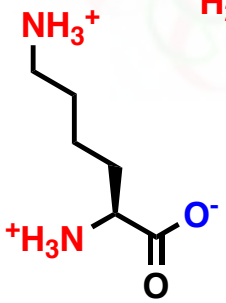
Acide glutamique
(Glu, E)



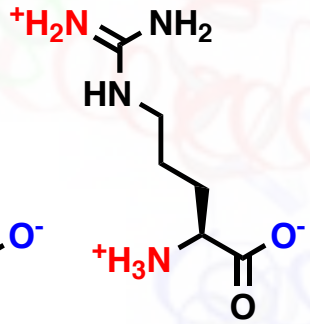
Asparagine
(Asn, N)



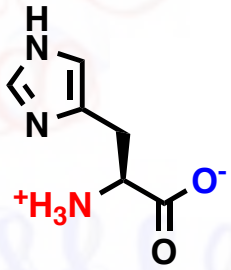
Glutamine
(Gln, Q)



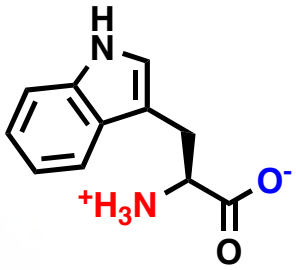
Lysine
(Lys, K)



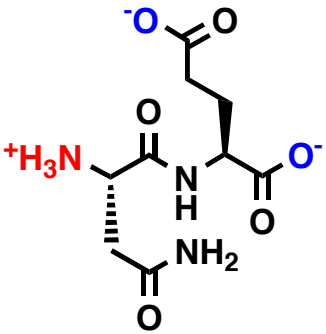
Arginine
(Arg, R)



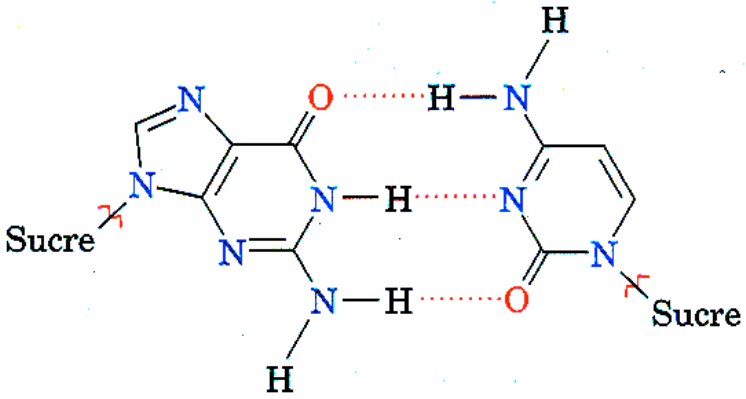
Histidine
(His, H)



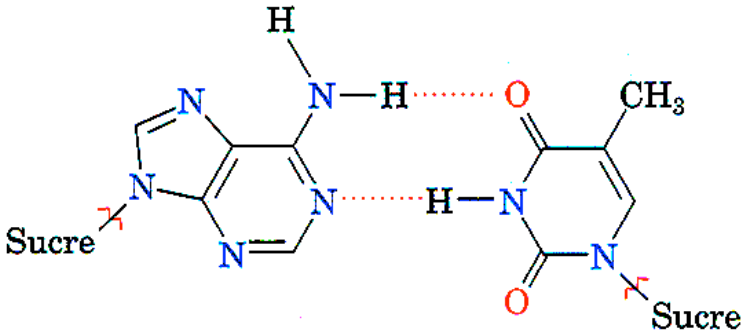
Tryptophane
(Trp, W)



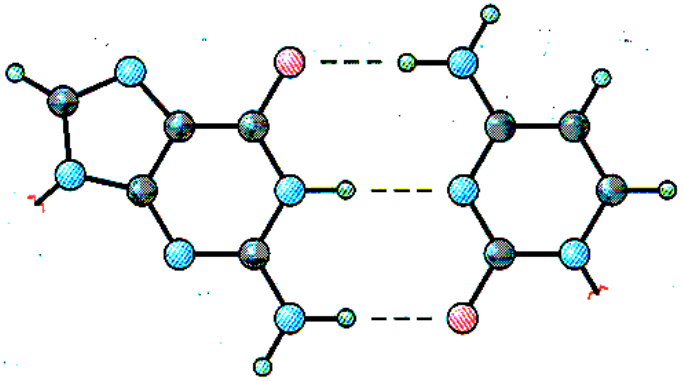
Hétérocycles aromatiques et le code génétique

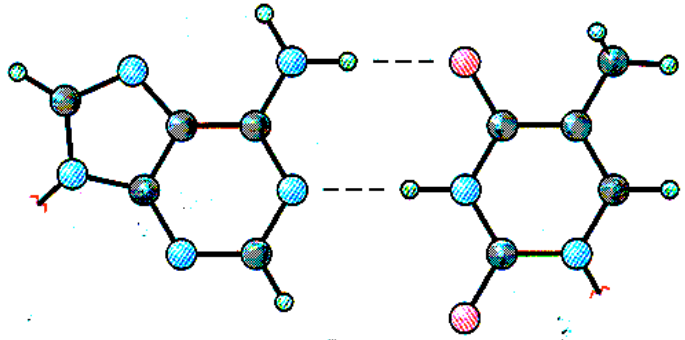


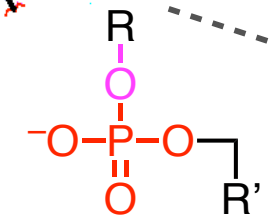
(Guanine) G ⋮⋮⋮⋮⋮ C (Cytosine)

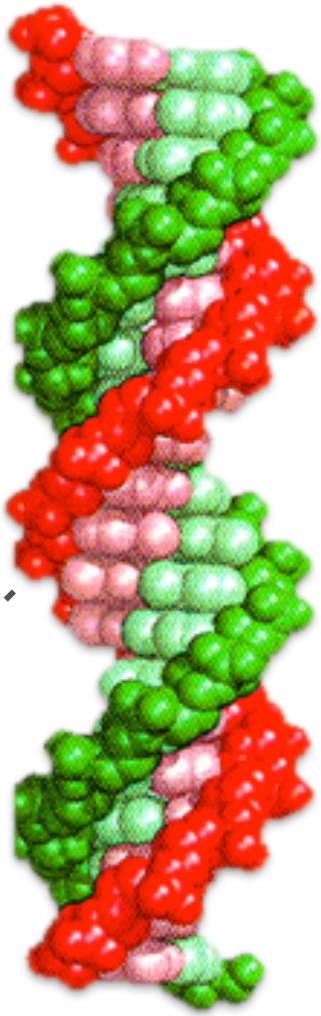


(Adénine) A ⋮⋮⋮⋮⋮ T (Thymine)

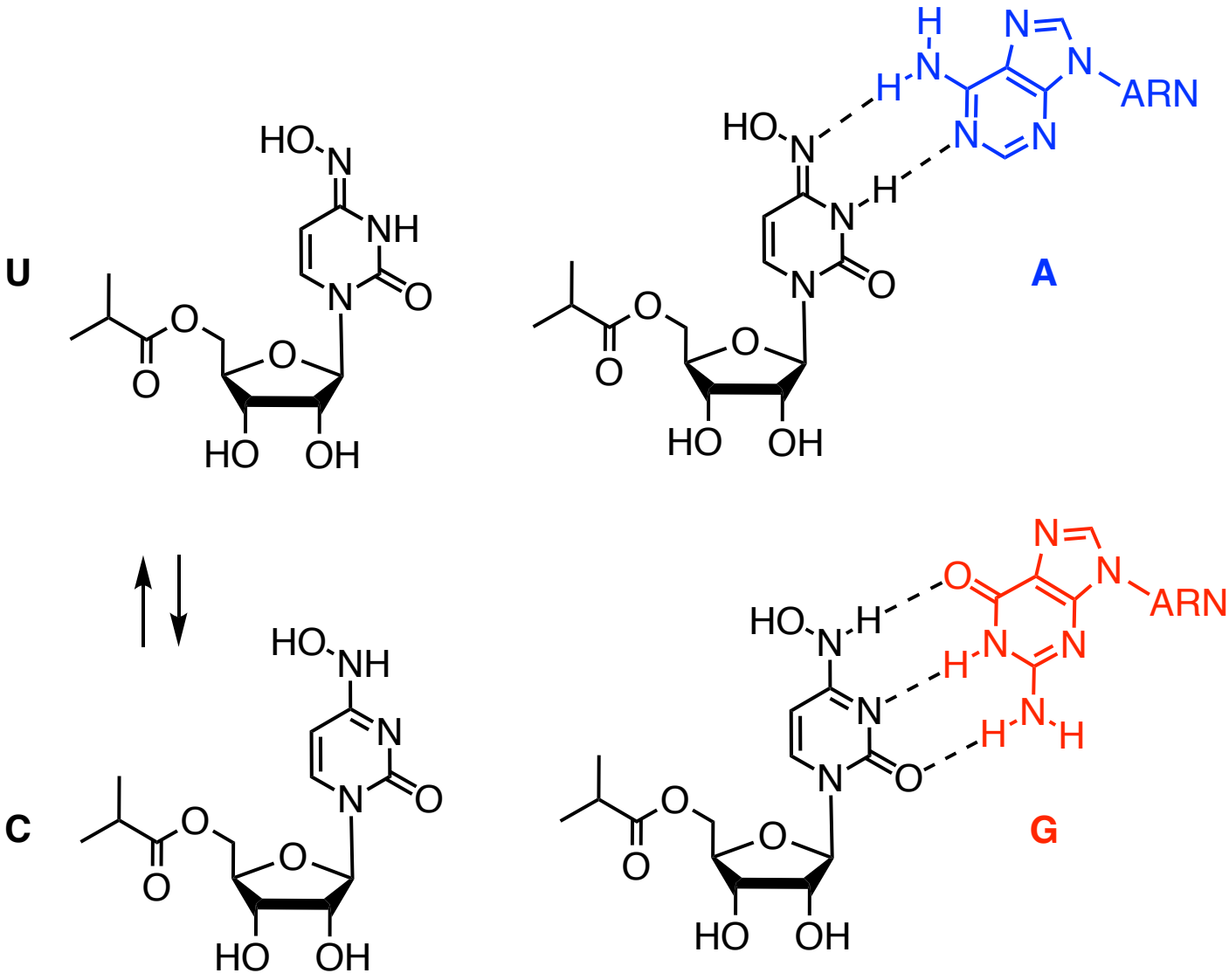








Molnupiravir



Résumé 7 (Acides nucléiques - amines)

- amine, ammonium (N sp^3)
- hétérocycles aromatiques (N sp^2) : pyridine, pyrrole, imidazole, indole (protéines), pyrimidine, purine (ADN)
- liaison hydrogène (code génétique)
- acidité, résonance, aromaticité :
    - alkylamines (protéines) - arylamines (ADN, code génétique)
    - amide (protéines)
    - hétérocycles aromatiques (ADN, protéines)
- substitution nucléophile S_N2 : C sp^3 électrophile, sans intermédiaire réactionnel (cigarettes, adrénaline)